Reduction in airway hyperresponsiveness to methacholine by the application of RF energy in dogs

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AIRWAY SMOOTH MUSCLE (ASM) contraction is known to cause airway narrowing in mammalian species. In humans with asthma, this may be associated with morbidity and, at times, mortality (7). Accordingly, blockade of ASM contractility is a primary target of therapy with short- and long-acting bronchodilator medications (7, 13). However, the ability to block airway narrowing in human subjects with asthma is not always satisfactory, exacerbations are largely unpredictable (17), and excessive airway narrowing that is not responsive to conventional medications occurs. A therapy that directly and persistently reduces the ability of the airways to narrow would address a major component of asthma exacerbations. This study was undertaken in dogs to determine the effect of temperature-controlled radio frequency (RF) treatment (Alair System; Asthmatax, Mountain View, CA) on the ability of airways to narrow in response to methacholine chloride (MCh).

We hypothesized that we could determine a dose of temperature-controlled RF energy capable of reducing the amount of functional ASM in the airway wall, with limited persistent changes to other airway tissues, and thereby attenuate the responsiveness of airways to a known bronchoconstrictor (MCh). Therapeutic RF energy is used in a number of treatment modalities, such as in the treatment of cardiac conduction defects in electrophysiology (16). High-energy RF technology has been employed in the lung as an ablative treatment for cancer (1). However, there has been no information available regarding the effect of the much lower energy RF treatment presented here on the bronchoconstrictor response of airways. In these studies, we examined specifically the effects of transient application of relatively low thermal energy to determine whether ASM could be blocked selectively without significant alteration of adjacent airway tissues.

This study examined the short- and long-term effects of the application of RF energy to the airways at three different temperature settings in healthy mongrel dogs. Parameters measured included the extent of altered ASM (as a percent of the airway circumference) present in the airway wall (as determined through histology) and the responsiveness of treated and control airways to local MCh challenge (as determined by bronchoscopic measurement). The data show that temperature-controlled RF treatment of the airways can reduce both the amount of functional ASM in the airway wall and the responsiveness of the airways to local MCh challenge and that these two effects are correlated.

MATERIALS AND METHODS

This study, using 11 healthy mongrel dogs at the University of Utah Animal Resource Center, followed an Institutional Animal Care and Use Committee-approved protocol. For all treatment and follow-up bronchoscopies, anesthesia was induced to effect by thiopental so-
dium (~25 mg/kg iv) and was maintained to effect by isofluorane (1–3%) administered during mechanical ventilation. Before baseline bronchoscopy, a physical examination and thoracic radiographs (lateral and dorsal/ventral views by computed tomography scout films) were performed on each dog. RF energy was delivered bronchoscopically to the airways >24 h after baseline MCh challenge and within 1 wk after the radiographs.

Physical examinations including auscultation were performed daily for the first 6 wk posttreatment and weekly thereafter. Bronchoscopic observations, measurements of resting airway diameters, and airway responsiveness to local MCh challenge were performed before treatment (baseline) and at 1, 6, 12, 30, 40, 58, 105, 128, and 157 wk posttreatment. Dogs were killed for necropsy and histology according to prospective randomization: two dogs at 1 wk, and three dogs at each of the 6-, 12-, and 157-wk time points. Thoracic radiographs were repeated before death. Observers remained blinded to treatment/control group assignments throughout follow-up bronchoscopies, at necropsy, and for internal histological analysis.

Resting airway diameter and airway responsiveness to local MCh challenge were measured at discrete sites within the bronchial tree, which were carefully mapped and recorded. These mapped, recorded sites served as both baseline and posttreatment follow-up sites for the duration of the study and were later excised for histological analysis. Mapping sites involved the counting of side branch/daughter airways and, where necessary, annotated diagrams of the bronchoscopic view. Before MCh challenge, the resting airway diameter was measured using the application catheter as a visual reference (18). The application catheter is 1.1 mm in diameter, with six radial holes at the distal tip, similar to that described by Brown and Mitzner (2). The mean error of this measurement technique in tubes of known diameter and in the size range of the airways examined in this study (1–6.6 mm) over 84 blinded measurements by four operators was 8.5 ± 2.0% (mean ± SE). The corresponding coefficient of variation for this technique is 22%.

After resting airway diameter measurement, MCh (Provocholine from Methapharm, Brantford, Ontario, Canada) was sprayed onto the airway site (0.025 mg/ml in sterile normal saline, 15-μl volume). Approximately 90 s after challenge, the airway diameter was measured a second time. Airway responsiveness was defined as the percentage change in airway diameter after MCh challenge compared with the prechallenge diameter: [diameter pre-MCh - diameter post-MCh]/diameter pre-MCh]. Sites with baseline airway responsiveness >60% were selected as follow-up sites for the study of hyperresponsiveness. These airways comprised ~85% of the sites initially examined during baseline bronchoscopy.

In all dogs, the lungs were divided into four regions: upper left, lower left, upper right, and lower right. Three of these regions received treatment at 55, 65, or 75°C, and the remaining region was not treated. The treatment temperatures chosen were in the range used in RF electrosurgical tissue coagulation (22). The treatment and control regions for the dogs were assigned so that there were equal distributions of treatment groups (control, 55°C, 65°C, and 75°C) between upper and lower and between left and right regions among the dogs. Acceptable combinations of treatment and control groups among lung regions were prospectively identified for the cohort. These combinations were then randomized among the dogs.

Treatment of each dog was performed in a single bronchoscopic session. All accessible intraparenchymal airways in treated regions ≥3 mm in diameter and distal to the carina (as distal as the 6th generation) were treated with contiguous activations of the Alair System. The system consisted of a 460-kHz, low-power, monopolar RF generator (model ATS 115X1) and a four-electrode basket catheter (model ATS 2-5X1). The RF generator is equipped with numerous monitoring algorithms and designed to ensure precisely controlled energy delivery. The catheter contains a thermocouple located on the electrode for temperature-controlled energy delivery. The catheter was introduced into the lungs using a standard 5-mm bronchoscope (Pentax model FB-15P). The electrode basket was expanded to contact the airway wall (Fig. 1). The RF generator was then activated, supplying controlled RF energy to the airway wall for 10 s. Immediately after each RF generator activation, the catheter was repositioned adjacent to the previous treatment site for the next activation. This process of treating and repositioning the catheter was repeated to produce contiguous treatment of all targeted airways. Applying contiguous local treatments throughout all accessible airways produced, as closely as possible, treatment of the entire bronchial tree having airways ≥3 mm in diameter.

Dogs were killed for histology according to the protocol’s randomization schedule at 1, 6, 12, and 157 wk. A veterinarian who was blinded to treatment assignments of the lungs performed thorough gross examinations of the postmortem lung specimens. The lungs were then fixed in 10% formalin solution at an inflation pressure of ~40 cm H2O for ≥12 h. Previously identified baseline/follow-up sites were mapped and identified by bronchoscopy of the inflated, explanted lung and excised for histology. Transverse sections of each baseline/follow-up site were prepared with hematoxylin and eosin. These slides were examined by at least two respiratory pathologists who were blinded to treatment group. A third veterinary respiratory pathologist read a sample of 25% of both control and treated sites from each death time. Data from slides of treated regions that had no observable changes in any airway structure were omitted from the analysis because they are believed to be the result of the misidentification of sites during excision. Omission of these sites did not affect the conclusions of this study.

For the purpose of this study, altered ASM was defined as portions of ASM that were degenerative, absent, or replaced by plump, spindle-shaped fibroblasts. For each site, the pathologist, on an enlarged print of the slide, indicated the airway circumference containing altered ASM as observed with light microscopy. From this annotated enlarged print, the percent of altered ASM in each slide was estimated.

An analysis of variance (20) was used to establish the statistical significance of the variation in resting airway diameters (airway diameters while not under MCh) over the course of the study. The responsiveness of airways to local MCh challenge was evaluated by analysis of covariance with baseline responsiveness measurements as a covariate (20). Each of these analyses identified time points when statistically significant results were obtained but did not identify which treatment/control groups differed. At time points with signifi-

Fig. 1. Sketch of the radio frequency (RF) catheter deployed in an airway.
Fig. 2. Mean airway responsiveness (percent change in diameter after local methacholine (MCh) challenge) in dogs treated at various temperatures. Control airways show a stable response to MCh over the course of the 3-yr study. The 55°C treated airways also show a stable response to MCh over the course of the study and show a statistically significant difference from the control airways at only 1 of 9 posttreatment follow-up times ($P \neq 0.001$). Alternatively, 65°C treated airways show a statistically significant reduction in response to MCh with respect to control airways at 8 of 9 posttreatment follow-up times ($P \leq 0.039$ except 12 wk ($P \neq 0.001$)), whereas 75°C treated airways show a statistically significant reduction in response to MCh at all posttreatment follow-up times ($P \leq 0.001$).

Results

All results are presented as means ± SE.

A total of 11 dogs were treated according to the study protocol. In the study of a 12th dog, an RF generator malfunction at the time of treatment prevented completion of the protocol. All data from this dog were excluded. In total, over 300 individual airway sites in 11 dogs were examined, and over 900 total examinations were made during the course of this 3-yr study.

Airway responsiveness to MCh was measured at all posttreatment follow-up times (Fig. 2). Airways with a prechallenge resting diameter of <2 mm were not subjected to MCh challenge. Airway responsiveness to MCh of the 55°C treatment group was not significantly different from the control group at any time point with the exception of week 1, where the 55°C treatment group showed significantly less responsiveness ($P = 0.001$). The 65°C treatment group showed significantly less airway responsiveness than the control group at eight of nine posttreatment follow-up times (weeks 1, 6, 30, 40, 58, 105, 128, and 157; $P \leq 0.039$). Only at week 12 did the airway responsiveness in the 65°C treatment group fail to show a statistically significant difference from the control group. The 75°C treatment group was significantly less responsive to local MCh challenge than the control group at all posttreatment follow-up times ($P \leq 0.001$). Table 1 gives a summary of the mean airway responsiveness data for all treatment groups and the control group over the course of the study.

Significant reductions in airway responsiveness after local MCh challenge over the last 2.5 yr of the study (30-, 40-, 58-, 105-, 128-, and 157-wk follow-ups) are shown in the groups treated at 65 and 75°C with respect to the control group ($P \leq 0.001$). No significant difference was detected between the control group and the 55°C treated group (Fig. 3).

On histological examination, untreated control airways showed distinct ASM with no evidence of altered ASM (de-

Table 1. Airway responsiveness results for each treatment and control group over the course of the study

<table>
<thead>
<tr>
<th>Follow-Up Time, wk</th>
<th>Control</th>
<th>55°C</th>
<th>65°C</th>
<th>75°C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Means ± SE, %</td>
<td>n</td>
<td>Means ± SE, %</td>
<td>n</td>
</tr>
<tr>
<td>Baseline</td>
<td>89±2</td>
<td>77</td>
<td>93±2</td>
<td>67</td>
</tr>
<tr>
<td>1</td>
<td>79±3</td>
<td>71</td>
<td>62±3</td>
<td>66</td>
</tr>
<tr>
<td>6</td>
<td>64±4</td>
<td>59</td>
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<td>12</td>
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<td>58</td>
<td>65±6</td>
<td>20</td>
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<td>105</td>
<td>85±4</td>
<td>20</td>
<td>79±7</td>
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<td>128</td>
<td>76±5</td>
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<td>18</td>
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<tr>
<td>157</td>
<td>87±4</td>
<td>21</td>
<td>84±5</td>
<td>18</td>
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Values of airway responsiveness [percent reduction in airway diameter after local methacholine chloride (MCh) challenge compared with the pre-MCh challenge diameter] are means ± SE. The number (n) of observations made at each follow-up time is shown for each treatment/control group. The decline in the numbers of observations over the course of the study is a result of death for histology.
vascularized connective tissue. Figure 4A shows an untreated airway. Persistent changes to ASM were observed in the treated groups. Altered ASM was present as early as 1 wk in all treated groups. At 12 wk posttreatment, regions containing altered ASM were accompanied by a slight increase in immature vascularized connective tissue. Figure 4B shows a 65°C treated airway from the same dog presented in Fig. 4A with ASM absent. At 3 yr posttreatment, in 75°C sites, ASM was replaced by a thin layer of mature collagen. At no time point during the study was there evidence of ASM regeneration.

The extent of the treatment effect on ASM was estimated on the basis of the percentage of the overall airway perimeter containing altered ASM. The effect of treatment was confined to the airway wall, and the immediate peribronchial region was circumferential in nature and was not generally localized to the points of contact of the electrode basket, i.e., localized areas of treatment patterned to the catheter geometry were not seen. The percent circumference of the airway with altered ASM generally increased as the treatment temperature increased (Table 2). This trend was observed at all histological time points.

Estimates of the extent of altered ASM through histology and corresponding bronchoscopic measurements of airway responsiveness to local MCh challenge measured immediately before death were available for 175 follow-up sites mapped at baseline. There was a statistically significant inverse correlation between airway responsiveness and the percentage of ASM circumference containing altered ASM (n = 175, r = −0.54, P < 0.001). These data are shown, averaged by treatment or control group and follow-up time point (Fig. 5).

Figure 5 illustrates clearly the inverse correlation between the mean airway responsiveness and the mean percentage of altered ASM (n = 16, r = −0.72, P < 0.001).

The resting airway diameter was measured at baseline and at each posttreatment time point for all follow-up sites. The mean change in resting airway diameter for sites in each treatment group and the control group, expressed as percent change from baseline diameter, is shown in Fig. 6. No airway was found narrowed to closure while not under MCh challenge at any time point during the study. There also was no observable trend for narrowing over time in any airway, and the range of changes in resting airway diameters for treated sites was within that of untreated sites.

There were no statistically significant differences between the resting airway diameters of the 55°C treatment sites and the untreated control sites at any posttreatment follow-up times.

<table>
<thead>
<tr>
<th>Table 2. Percent of airway circumference with altered ASM in each treatment/control group over the course of the study</th>
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<tr>
<td><strong>Average Percent of Airway Circumference with Altered ASM at Follow-Up Time Points, %</strong></td>
</tr>
<tr>
<td>Treatment Group</td>
</tr>
<tr>
<td>Control</td>
</tr>
<tr>
<td>55°C</td>
</tr>
<tr>
<td>65°C</td>
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<tr>
<td>75°C</td>
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</table>

Values of percent of airway circumference with altered airway smooth muscle (ASM) are means ± SE. Altered ASM is defined as ASM that is degenerative, absent, or replaced by plump, spindle-shaped fibroblasts.
Significant differences between the resting diameters of the 65°C treatment sites and control sites were identified at two of nine posttreatment follow-up times (weeks 1 and 58; \( P \leq 0.005 \)), and significant differences between the resting diameters of the 75°C treatment sites and control sites were identified at only one of nine posttreatment follow-up times (week 1; \( P \leq 0.001 \)).

Physical examinations of the dogs included breath sounds, respiratory status, oxygen saturation, and arterial blood gas data. Physical examination revealed a minor unproductive cough in two dogs and a productive cough in two others. These findings were accompanied by adventitious breath sounds and resolved within 1 wk after the RF treatment. Laboratory tests, including examination of the arterial blood gases, remained in the normal range. No clinically significant observations were noted during the study, and all dogs were in good health.

Thickening of bronchial walls was noted in the computed tomography radiographs of one of the dogs killed for evaluation at 1 wk. Histological observations of these airways suggest that this thickening resulted from inflammatory edema in the airway wall at the treatment site. No significant pulmonary alveolar edema was observed. No additional remarkable radiographic observations were made in any dogs.

Variable amounts of blanching (whitening) of the surface of the airway wall at the point of catheter contact, including some cases of circumferential blanching, were observed immediately after treatment. There was a clear trend toward greater amounts of tissue blanching with higher treatment temperature settings. We observed occasional residual blanching and erythema during the 1-wk bronchoscopic follow-up. At 6 wk and beyond, all airways appeared normal, and the treatment or control history of all airways was indistinguishable to blinded operators performing bronchoscopic follow-up.

There were isolated instances of retained mucus at follow-up sites that were not easily removed by suction. At the week 1 follow-up time, four dogs had a single 75°C treated airway with retained mucus and one dog had a single 65°C treated airway with retained mucus. There were no occurrences of retained mucus in any airway at any treatment temperature at the 6-wk follow-up time or later, with the exception of one instance of retained mucus at 157 wk, which was observed in a 75°C treated airway. There were no occurrences of retained mucus at 55°C or control sites.

**DISCUSSION**

The objective of this investigation was to determine the effect of the application of temperature-controlled RF energy to the airways of dogs. We also tested the hypothesis that reductions in ASM caused by RF energy delivery would correlate inversely to the magnitude of airway responsiveness to local MCh challenge. In this investigation, we found that reduction in ASM was related directly to reduction in airway responsiveness to MCh (Fig. 5).

Persistent reductions in ASM were observed as a result of treatment. Altered ASM was present as early as 1 wk in all treatment groups, and the extent of airway circumference containing altered ASM increased at all time points as the treatment temperature increased from 55 to 75°C. The decrease in airway responsiveness to local MCh challenge was also dependent on treatment temperature. Airway responsiveness was significantly decreased at eight of nine time points after treatment at 65°C and at all time points after treatment at 75°C, whereas treatment at 55°C caused a significant decrease at only one of nine time points (week 1; Fig. 2). The reductions in airway responsiveness observed in the 65 and 75°C treated airways persisted to 3 yr after treatment (Figs. 2 and 3).

The inverse correlation between the amount of altered ASM and the airway responsiveness to local MCh challenge does not by itself indicate causation. We suggest that the reduction in the amount of normal ASM observed histologically may result from thermal denaturation of ASM proteins, their subsequent necrosis, and replacement with a thin layer of collagen matrix. Because ASM contraction is known to directly cause airway...
narrowing, we conclude that the reduction in ASM resulting from treatment likely leads to the observed reduction in airway responsiveness.

By analyzing the data with and without sites identified as mismapped, we found that the conclusion of a statistically significant correlation between the reduction in ASM and responsiveness holds regardless of the treatment of these sites in the analysis. Because omission of the mismapped sites has not affected the statistical significance of the results and because of a high degree of confidence in our ability to identify mismapped sites, we have presented only the data from the excised sites that we believe to have been accurately identified during excision.

Although the observed reduction in airway responsiveness resulting from treatment could depend solely on the reduction in amount of ASM, it is possible that subtle changes to ASM may also contribute to the benefit seen. Perhaps the contractile response of the remaining ASM is altered as a result of treatment or loss of continuity of muscle bands inhibits bronchoconstriction. Alternatively, the extracellular collagen matrix seen around ASM after the application of RF energy to the airways may serve to constrain the ASM and prevent its full contraction. It is also possible that stiffening of the airway wall as a result of limited fibrosis could contribute to a reduction in bronchoconstriction. These possibilities were not examined here and remain to be investigated. We observed no other histological changes plausibly linked to the reduction in airway responsiveness that persisted to the 3-yr (157 wk) follow-up. There was no histological or bronchoscopic evidence indicating a negative functional effect (i.e., constriction, dilation, or distortion of the airway lumen) resulting from the treatment. In addition to measuring the responsiveness of airways to local MCh challenge before and after treatment, the variability in resting airway diameters over time was measured and compared with pretreatment/baseline resting airway diameters (while not under MCh challenge). The variability from baseline in the resting diameters of untreated control airways is consistent with the long-term variability reported by Brown and Mitzner in dogs (2). However, the variability from baseline in the resting diameters of treated airways measured here varied within a range that is less than the variability seen in untreated, control airways.

One potential source of variability in measures of airway responsiveness to local MCh challenge and resting airway diameter over time could be that we did not use the atropine-relaxed state as our reference airway dimension. The atropine-relaxed state has previously been shown in dogs to reduce the variability in airway size owing to baseline tone (2). Another potential source of variability could be the measurement technique used. Airway diameter measurements were made bronchoscopically using a catheter as visual reference.

Although it is possible that we may remove some of the observed variability in airway diameters by using the atropine-relaxed state to determine the prechallenge airway size or by using other techniques such as computed tomography to measure airway sizes, both of these add operational challenges when the large number of measurements performed here are taken. Nonetheless, the treatment effect size observed here was sufficient to conclude through comparison of blinded observations of treated and untreated airways that the reduced airway responsiveness to local MCh challenge after treatment was statistically significant.

Dogs tolerated the treatment well. There were no adverse physiological or clinical observations made, and the stability of airway diameter and maintenance of airway patency was supported by the >900 blinded bronchoscopic observations made over the course of the 3-yr study. One dog in a separate study was euthanized more than 2 yr postprocedure because of acute bronchopneumonia. An extensive pathological examination established that this was an acute event caused by a β-hemolytic streptococcal infection. Evidence of this infection was found in four additional dogs in the colony. All of these dogs were successfully treated with antibiotics. The wide separation in time between the procedure and the pneumonia strongly suggests that these two events were unrelated.

It is important to consider the limitations of our findings. This study was performed in dogs, which did not have and do not develop bronchial asthma. ASM was reduced in these dogs without evidence of regeneration, but the degree to which human ASM can regenerate is unknown. We note that RF alteration of ASM was inversely correlated with bronchial hyperresponsiveness, an effect that persisted for up to 3 yr (Figs. 2 and 3). A goal of these early investigations is to determine the potential applicability of these findings to therapy for human asthma. Three specific issues underlie the potential applicability of these findings to a human study: 1) asthma must involve significant ASM contraction in larger (>3 mm) airways of the lung; 2) the potential role of inflammation, especially in small airways that were not treated in this study, must be considered; and 3) ASM must not play a fundamental or necessary homeostatic role in the regulation of airway function, such that attenuation of its function might cause predisposition to other problems not immediately anticipated from the data obtained in these studies.

There is considerable evidence that ASM in the larger (>3 mm) airways of the lung is involved substantially in asthmatic bronchoconstriction. Ingram and McFadden (12) have reviewed the literature and have implicated larger airways as the source of acute bronchoconstriction and subsequent dilation in the remission of asthma in humans. The theoretical underpinnings for these data are based on the classical work of Pedley et al. (23), who demonstrated by exquisite technology and mathematical analysis that 75% of the postnasal resistance to airflow in the human bronchial tree occurs within the first six to eight generations of airways (>3 mm). Drazen et al. (4) demonstrated, by using gases of different densities, that the predominant site of airflow obstruction in asthma could be determined. This principle was previously applied by Hutchison et al. (10) in smokers assumed to have mildly abnormal lung function to demonstrate that chronic obstructive pulmonary disease is likely a disease of the smaller airways of the lung. Data were validated plethysmographically to account for gas compression according to the method of Habib and Engel (8).

In contrast to the studies of Hutchison et al., Fairrhter and Wilson (6) demonstrated by the same technique that the predominant sites of bronchodilation causing improvement of airflow in asthmatic humans to be the central airways of the lung (proximal to bronchioles). Because the larger airways are in series with the smaller airways of the lung, it is expected that the ability to attenuate narrowing in larger airways will, in any
The classical physiological data designating larger airways as the exclusive site of airflow obstruction in human asthma have recently been challenged by the demonstrated persistence of intermittent airway obstruction even of intermittent asthmatic subjects between active asthma events. Recent reports (15) using monoclonal antibodies directed against interleukin-5 have questioned the importance of eosinophilic inflammation in mediating asthmatic bronchoconstriction. Similar studies using soluble receptor antagonist against interleukin-4 have been shown not to be efficacious in preventing asthma exacerbations (11). Thus the role and site of inflammation and its importance in contributing to narrowing remain to be elucidated. This elucidation will require empirical demonstration of efficacy of interventions targeted specifically at small airways, large airways, and inflammatory processes. In this paper, we have examined a hypothesis directed at a classical site of airway constriction, the central airways (>3 mm). Further studies are required to determine whether the attenuation of responsiveness demonstrated in these studies can be applied more generally to alleviate bronchoconstriction in humans.

A final question is the potential role of ASM in homeostasis of lung function. To date, no specific role for ASM has been demonstrated. Preliminary data (3) have not demonstrated problems in humans with global RF treatment (all lobes except the right middle lobe were treated). Mitzner (19), in an extensive review of ASM function, has argued for a total vestigial function of ASM in humans. Because these studies merely establish parameters for approaching such studies in humans, further consideration is beyond the scope of the data presented here. Although inflammation and mucus secretion clearly play a large role in asthma (21, 26), bronchial hyperresponsiveness is another important pathological feature of the disease (25). Accordingly, the ability to attenuate airway hyperresponsiveness in humans could improve the control of asthma. Such treatment could be of particular benefit to patients with moderate to severe asthma.

In summary, our data indicate that applying temperature-controlled RF energy to the conducting airways of the lung reduces canine ASM and that the extent of this reduction in ASM correlates inversely to the bronchoconstrictor response to MCh. Although it is not possible to extrapolate these findings directly to human asthma, our data suggest a potential approach for the development of a treatment for asthma.

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DISCLOSURES

The authors have financial interests in the form of consultancies or primary employment.

REFERENCES


