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No influence of airway heat flux on airflow-induced bronchospasm

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ABSTRACT: We used a canine model of airway reactivity to examine the role of airway heat flux in the response to dry air challenge. Airflow-induced bronchospasm (AIB) was assessed by measuring collateral system resistance (Rcs) with a wedged bronchoscope technique in anaesthetized mechanically ventilated dogs. We manipulate post-challenge airway heat flux by exposing peripheral airways to cool dry air (23.9±0.3°C, 0.8±0.2 $mgH_2O \cdot l^{-1}$), cool humid air (24.2±0.2°C, 21.5±0.3 $mgH_2O \cdot l^{-1}$), or warm humid air (35.3±0.4°C, 40.6±0.3 $mgH_2O \cdot l^{-1}$) during the recovery period (n=14) following a high flow challenge (1,500 $ml \cdot min^{-1}$ for 2 min) with cool dry air. In a second series of experiments (n=6), we attempted to further exaggerate airway heat flux during challenge by exposing peripheral airways to warm humid air during both baseline and recovery periods.

In comparison to control (*i.e.* treatment with cool dry air before and after challenge), treatment with warm humid air during recovery period produced a small but significant attenuation ($p<0.01$) in Rcs. Cool humid air during recovery had no affect on Rcs following challenge. Warm humid air during both baseline and recovery tended to attenuate Rcs after challenge ($p<0.05$).

We conclude that airway heat flux in itself has no significant physiological affect on AIB in the canine lung periphery.

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Airflow-induced bronchospasm (AIB) in canine peripheral airways is analogous to hyperventilation- and exercise-induced bronchospasm in asthmatic individuals [1–5]. These similarities include: a) a similar time course of bronchoconstriction after exposure to cool dry air [1, 6] including a dose-response relationship [1, 7]; b) the attenuation of AIB when warm humid air is substituted for cool dry air [1, 4, 8]; c) bronchoconstriction in response to hypertonic aerosol challenge [9, 10]; d) the attenuation of AIB after pretreatment with atropine [4, 11], albuterol [12, 13], and aminophylline [12, 14]; and e) detection of mediators in bronchoalveolar lavage fluid immediately after AIB [3]. Considering these similarities, we believe that data from this model can provide considerable insight into the mechanisms involved in exercise-induced asthma.

The primary trigger for AIB in our canine model, and in humans who experience exercise-induced asthma, is unknown. Most investigators believe that either airway cooling [8], or drying [15], due to evaporative water loss, initiates AIB. Inhalation of warm humid air during recovery from exercise was reported to exacerbate AIB in some adult asthmatic subjects [16, 17]. It was suggested that rapid rewarming of airways during recovery enhanced AIB *via* a reactive hyperaemia of the bronchial vasculature and the subsequent formation of mucosal oedema [16]. However, insufficient data exists to support this hypothesis in general, and data concerning the exacerbation of AIB with warm humid air have not been reproduced in asthmatic children [18].

We used a canine peripheral airway model to examine the hypothesis that exposure to warm humid air during recovery from challenge with dry air exacerbates AIB. We hypothesized that recovery with warm humid air should produce a greater response than that seen during recovery with either cool humid or cool dry air. In addition, we attempted to increase airway heat influx by exposing canine peripheral airways to warm humid air both before and after dry air challenge. We hypothesized that if this manoeuvre increases airway heat flux, greater bronchoconstriction should result than when the airways are exposed to warm humid air during recovery only. We have demonstrated that our attempts to manipulate airway heat flux in this fashion have no significant physiological effect on either the time course or the magnitude of AIB in the canine lung periphery.

Methods

Male mongrel dogs (mean±SD weight 19.74±1.24 kg, range 16.0–27.7 kg, n=12) were anaesthetized with thiopental (25 mg·kg^{-1} *i.v.*), and supplemental anaesthesia was provide by continuous *i.v.* infusion of thiopental and by bolus injection of fentanyl (25 μg) every 15–30 min. Dogs were placed in the supine position, transorally intubated with a dual port endotracheal tube, and ventilated with a Harvard constant volume ventilator. Frequency was adjusted to maintain an end-expired CO_2 concentration of approximately 4.5% (Beckman LB-2). Body temperature was monitored and maintained throughout the experiment with a warming pad. Two bronchoscopes were inserted through airtight portals of the endotracheal tube and visually guided until the tip (5.5 mm o.d.) obstructed sublobar bronchi in opposite lungs. Ventilation of the obstructed segments by the surrounding lobes could then occur only through collateral airways [19]. Pressure at the tip of the bronchoscope (Pb) was measured with one lumen of a dual lumen catheter, threaded through the suction port of a bronchoscope. The other lumen of the catheter was used for infusion of a constant flow ($\dot{V}$=200 ml·min^{-1}) of 5% CO_2 in air into the wedged segments. When the ventilator was stopped at end-expiration (functional residual capacity (FRC)), resistance through collateral airways was calculated as Rcs=Pb/$\dot{V}$.

Measurement of the response of the collateral system to dry air challenge

Baseline Rcs was considered stable when measurements recorded every 5 min over a 15 min period were unchanged. A cool dry air challenge was then performed by abruptly increasing $\dot{V}$ using room temperature dry 5% CO_2 in air from 200 to 1,500 ml·min^{-1} for 2 min following which $\dot{V}$ was returned to 200 ml·min^{-1} until the next challenge. After the challenge, Rcs was recorded at 30 s and 2, 5, 10 and 15 min and every 5 min thereafter until it returned to baseline.

Experimental protocol

In all experiments, cool dry air challenge was performed as described above. Experiments for which cool dry air flowed into the segment during baseline, challenge and recovery periods were designated as controls. Responses from control trials were compared to responses from trials in which cool humid or warm humid air flowed into the segment only during the recovery period (protocol no.1) and cool humid or warm humid air flowed into the segment during both baseline and recovery periods (protocol no.2) (table 1). A separate control trial was performed for each cool humid or warm humid trial, and the order of the cool humid and warm humid trials was randomized with respect to the control trial.

The temperature (Ti) and relative humidity of the cool dry, cool humid, and warm humid inspired air were measured with a hygrometer containing a temperature probe. The water content of these inspired gases (Wi) was calculated using standard tables.

The Ti and Wi of the air delivered to the bronchoscope was determined following each experiment. The whole lung was ventilated with room air, the Ti and Wi of which were constant throughout the experiment. Thus, it was the Ti and Wi of the 5% CO_2 in air delivered only into wedged sublobar segments that were controlled. The Ti and Wi of air entering the peripheral airways was estimated by measuring the Ti and Wi of gas flowing from the tip of a bronchoscope submerged in a 38°C water bath, mimicking *in vivo* conditions [4].

Statistics

Treatments *vs* control Rcs data were compared using a two-way ANOVA, and Duncan's multiple range test was used to compare the means. Student's paired t-test was used to compare differences in the time to peak response to dry air challenge. Responses typically peak at either 2 or 5 min post-challenge. Note that the calculation of the average peak response based on each dog's maximum change in Rcs regardless of

Table 1. – Protocols

	Baseline	Challenge	Recovery	Trials (dogs) n	Lobes*
Protocol 1	Cool dry Cool dry	Cool dry Cool dry	Cool dry Cool humid	7(5)	1^2, 2^2, 5^1, 6^2
	Cool dry Cool dry	Cool dry Cool dry	Cool dry Warm humid	7(6)	1^1, 2^3, 4^1, 6^2
Protocol 2	Cool dry Cool humid	Cool dry Cool dry	Cool dry Cool humid	6(5)	1^1, 2^2, 5^3
	Cool dry Warm humid	Cool dry Cool dry	Cool dry Warm humid	6(4)	1^1, 2^3, 6^2

* 1: right upper lobe; 2: right middle lobe; 3: right lower lobe; 4: left upper lobe; 5: left middle lobe; 6: left lower lobe. Superscripted numbers indicate the number of times each lobe was used (the same lobe was not used twice in the same protocol). n: number of trials.

time, yields values similar to the time-dependent maximum response reported for each experiment in this study.

Results

The Ti's and Wi's of gas delivered through the bronchoscope under experimental conditions are shown in table 2. Under simulated conditions, the Ti of warm humid gas passing through the bronchoscope decreased 7°C (from 39 to 32°C), and Wi decreased 14.9 $mgH_2O \cdot l^{-1}$ (from 48.7 to 33.8 $mgH_2O \cdot l^{-1}$). The Ti of the cool humid gas decreased only 1°C (from 23 to 22°C), and Wi increased as the cool dry gas passed through the bronchoscope by 1.1 $mgH_2O \cdot l^{-1}$ (from 1.5 to 2.6 $mgH_2O \cdot l^{-1}$).

Table 2. – Temperature (Ti) and water content (Wi) of air flowing into the bronchoscope

	Ti °C	Wi $mgH_2O \cdot l^{-1}$
Protocol 1		
Cool dry	23.9±0.3	0.8±0.2
Cool humid	24.0±0.2	21.5±0.3
Cool dry	23.3±0.3	1.2±0.1
Warm humid	35.3±1.4	40.6±3.0
Protocol 2		
Cool dry	24.2±0.3	1.2±0.4
Warm humid	36.8±2.75	43.4±6.20

Values represent the mean±SE.

During warm humid air recovery (protocol 1) (n=7) the peak increase in Rcs occurred 2 min post challenge and was 56±25% greater than baseline ($p<0.05$), where as 5 min post challenge Rcs increased only 37±18% greater than baseline ($p<0.05$, fig. 1). During recovery with cool dry air (protocol 1) (control), the peak increase in Rcs occurred 5 min post dry air challenge and was 65±18% (n=7) greater than baseline ($p<0.05$). Note that cool dry air was used during baseline for both trials. The attenuation in Rcs 5 min post-challenge during warm humid air recovery was significant ($p<0.01$) when compared to cool dry air recovery at 5 min, but no differences between these two trials were evident at any other time during baseline or recovery.

During cool humid air recovery (protocol 1), the peak increase in Rcs occurred 2 min post challenge and was 66±8% greater than baseline ($p<0.05$, n=7) (fig. 2). During cool dry air recovery (protocol 1), the peak increase in Rcs also occurred 2 min post-challenge and was 56±9% greater than baseline ($p<0.05$, n=7). There were no significant differences at any time point during baseline or recovery between the two trials.

For trials in which peripheral airways were exposed to warm humid air during baseline and recovery periods (protocol 2), peak Rcs occurred 2 min post challenge and was 29±12% greater than baseline ($p<0.05$) (fig. 3). When dry air challenge was preceded and followed by cool dry air (protocol 2), peak Rcs occurred 2 min post challenge and was 50±12% greater than baseline ($p<0.05$, n=6). Although not statistically significant, responses under warm humid conditions tended to be less than those recorded under cool dry conditions.

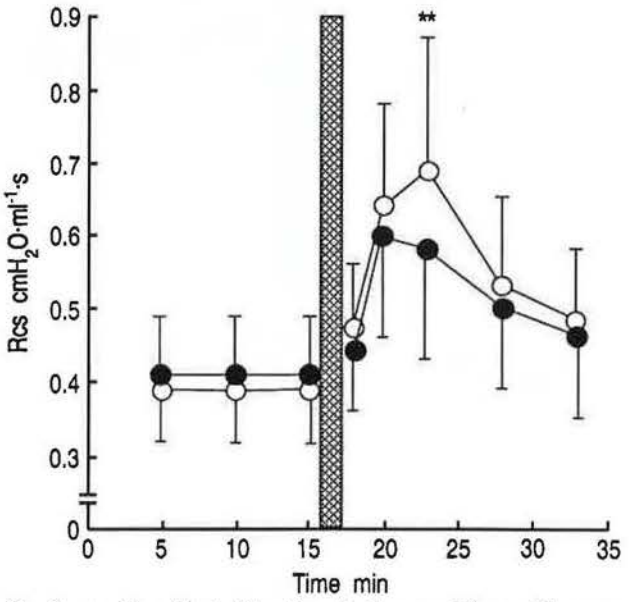

Fig. 1. – The effect of treating the lung periphery with warm humid air during recovery only (n=7). Cool dry air was used during baseline for warm humid trial (●) as well as during baseline and recovery for the control trial (○). Values represent mean±SE. The cross hatched bars indicate the challenge period. **: statistically significant difference between the warm humid trial and control ($p<0.01$). Rcs: collateral system resistance.

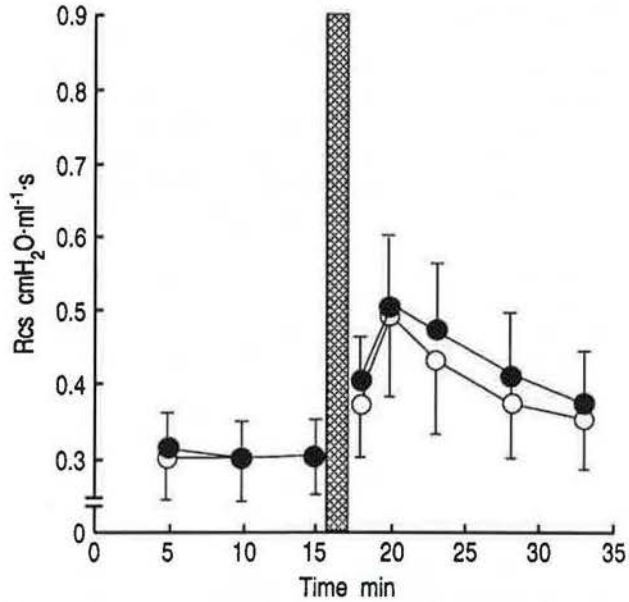

Fig. 2. – The effect of treating the lung periphery with cool humid air during recovery only (n=7), Cool dry air was used during baseline for the cool humid trial (●) as well as during baseline and recovery for the control trial (○). Values represent mean±SE. The cross hatched bars indicate the challenge period. Rcs: collateral system resistance.

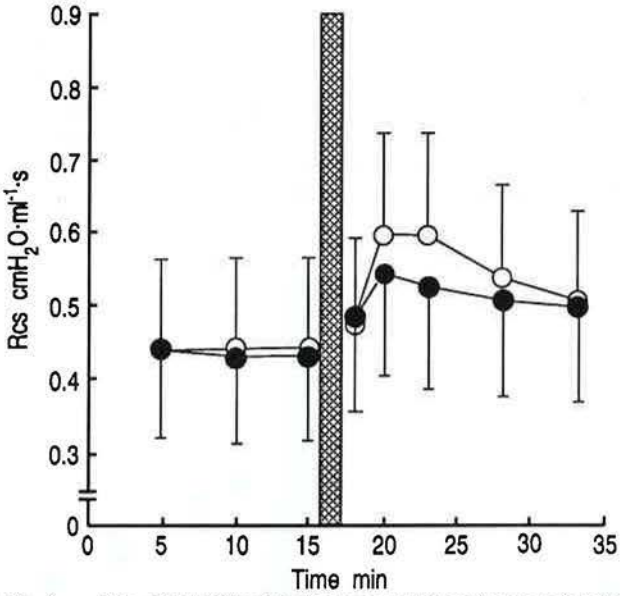

Fig. 3. – The effect of treating the lung periphery to warm humid air (●) during both baseline and recovery periods (n=6). Cool dry air was used during both baseline and recovery for the control trial (○). Values represent mean±SE. The cross hatched bars ndicate the challenge period. Rcs: collateral system resistance

Discussion

Dry airflow-induced changes in Rcs of canine peripheral airways are not enhanced by exposure to warm humid air during either the recovery or baseline and recovery periods (figs 1 and 3). In fact, during recovery with warm humid air, a small but significant attenuation of the peak increase in Rcs was observed (fig. 1). Exposure of peripheral airways to cool humid air during recovery also failed to affect AIB (fig. 2). These results are similar to those reported in asthmatic children in which SMITH *et al.* [18] failed to enhance AIB with rapid airway rewarming. However, our results are in contrast to other human studies in which MCFADDEN *et al.* [16] and MIHALYKA *et al.* [17] demonstrated an exaggerated fall in FEV_1 in asthmatic adults recovering from exercise only when breathing warm humid air.

Enhanced bronchoconstriction during warm humid air recovery [16, 17] may result from condensation of inspired water vapour on cooled airways and a concomitant reduction in airway fluid osmolality [20]. Although the mechanism by which condensation would cause such bronchoconstriction is difficult to envisage, studies have shown that asthmatic individuals bronchoconstrict in response to a hypertonic aerosol challenge that theoretically alters airway fluid osmolality [21]. However, condensation may not be equivalent to challenge with hypertonic aerosol. In fact, if AIB is stimulated by increases in airway fluid osmolality, then condensation may act to diminish a hyperosmolar stimulus. Thus, condensation may reduce, rather than enhance, the stimulus for bronchoconstriction and may account for the attenuated response as seen in figure 1.

It is possible that asthmatic subjects experience greater degrees of airway heat flux [16] than those that occur in the canine peripheral airways during and after dry air challenge. However, our data suggest that this is unlikely. We assume that heat flux is, at least in part, related to the change in airstream temperature during the transition from exercise (or dry air challenge in the dog) to recovery, and that this change is in turn related to the Ti and Wi during both of these periods. The Ti in a right lower lobe (RLL) subsegmental bronchus of asthmatic subjects breathing subfreezing air falls from approximately 35°C at rest to 29.7°C during exercise. Expiratory temperatures are several degrees higher [9]. Although the Wi in the RLL was understandably not measured [9], the relative humidity in this location was probably quite high. In comparison, the Ti and Wi in a subsegmental bronchus in the current experiments fell to 23.3°C and 1.2 mg·dl^{-1}, respectively, throughout the entire dry air challenge and increased to 35.5°C and 40.1 mg·dl^{-1}, respectively, during recovery. Although measurements of canine peripheral airway wall temperature during challenge [4] are significantly warmer than Ti, these data suggest that heat flux may be greater in the dog than in the human. Our failure to demonstrate enhanced bronchoconstriction under changes of heat flux similar to or greater than those experienced by human subjects suggests that thermal changes are unlikely to be a primary stimulus for AIB in the dog lung.

Airway cooling and rewarming were hypothesized to increase bronchial blood flow in humans after exercise, resulting in oedema and the subsequent airway obstruction that characterizes exercise-induced asthma [16]. Indeed, it is proposed that the magnitude of the change in airway temperature that occurs during recovery determines the severity of the obstruction, and it is this increased temperature gradient that accounts for the exaggerated fall in FEV_1 in asthmatics recovering from exercise when breathing warm humid air [16]. However, analogous experiments in humans [16] and dogs [2] indicate that prolonged airway cooling antagonizes AIB. The use of invasive techniques enabled us to clearly demonstrate that extreme transient changes in airway temperature neither initiate nor enhance airway obstruction in our canine model [2]. In our current study, increasing airway heat flux in a manner comparable to that performed in humans had no significant physiological effect on AIB. In addition, experiments in sheep failed to demonstrate any affect of bronchial blood flow on airway resistance, even when increased for 3 h to 300% above the baseline blood flow rate [22]. Thus, no direct evidence exists, either in the dog and sheep animal models or in humans which demonstrates a cause and effect relationship between changes in airway temperature, rebound hyperaemia and oedema, and the acute reversible airway obstruction that characterizes AIB.

In summary, manipulation of thermal gradients in canine peripheral airways has little effect on the bronchoconstriction resulting from dry air challenge.

AIB in the canine lung periphery is attenuated, not enhanced, by treatment with warm humid air during the recovery period. We speculate that this is due to a reduced osmotic stimulus [15, 20] resulting from a more rapid rehydration of airways that were dried during dry air challenge. To the extent that AIB results from similar mechanisms in human and canine lungs, we conclude that pre-and postexertional variation in airway heat flux play an insignificant role in the production of AIB.

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