Mechanism of Action of Atracurium on Airways

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Histamine-releasing drugs may produce significant effects on airways in high-risk populations. To determine if clinically relevant doses of atracurium produce adverse effects on airways, we measured changes in airway resistance in the lung periphery of anesthetized Basenji-Greyhound dogs before and after intravenous (iv) administration of atracurium. A wedged bronchoscopy technique was used to measure collateral system resistance (Rc). After a stable baseline was obtained, atracurium (1.2 or 0.5 mg/kg) or histamine (200 μg) were administered as an iv bolus, and percent increase in Rc was calculated. On separate days dogs were pretreated with the histamine, receptor antagonist, chlorpheniramine (0.2 mg/kg iv), with or without atropine (0.2 mg/kg iv) and ranitidine (0.75 mg/kg iv) and the experiment repeated. Histamine (200 μg) increased Rc 97 ± 24% at 30 ± 8 sublobar segments, whereas a second dose increased Rc 77 ± 15%. Pretreatment with chlorpheniramine (0.2 mg/kg iv) totally prevented increases in Rc (9 sublobar segments). Atracurium (1.2 mg/kg) increased Rc to 174 ± 55% at 3 min (14 sublobar segments), whereas 0.5 mg/kg had little effect (10 sublobar segments). A second bolus of atracurium (1.2 mg/kg) increased Rc only 54 ± 14% (P < 0.01). Chlorpheniramine pretreatment (0.2 mg/kg iv) reduced the response to the initial dose of atracurium to only 26 ± 14% (10 sublobar segments). Pretreatment with a combination of atropine and chlorpheniramine (4 sublobar segments) or ranitidine and chlorpheniramine (5 sublobar segments) did not attenuate the increase in Rc significantly more than chlorpheniramine pretreatment alone. We conclude that atracurium produces airway constriction in Basenji-Greyhound dogs and that release of histamine acting on histamine receptors in the airways is important for this effect. (Key words: Antagonists, histamine: chlorpheniramine; ranitidine. Bronchoconstriction: drug effects. Neuromuscular relaxant: atracurium.)

Neuromuscular blocking drugs possess two characteristics which can, at least theoretically, alter airway tone. They are capable of inducing release of histamine from mast cells lining the vessels into which they are injected. In addition, in order to interact with receptors at the neuromuscular junction, these drugs must structurally resemble acetylcholine. Thus, it is possible that they may bind to muscarinic receptors on airway smooth muscle, leading to constriction.

Both d-tubocurarine and atracurium cause release of histamine from human mast cell preparations. Intra-

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Materials and Methods

These studies were approved by the Animal Research Committee of The Johns Hopkins University. Eight Basenji-Greyhound (BG) dogs (weight = 18.5 ± 0.7 kg) were anesthetized with intravenous (iv) sodium thiopental (17 mg/kg). Maintenance anesthesia consisted of a continuous infusion of sodium thiopental (7–10 mg·kg⁻¹·h⁻¹), with supplemental doses of fentanyl citrate (25–50 μg) administered every 10–30 min. The dogs were not paralyzed. A Harvard constant-volume ventilator (Millis, MA) was used to ventilate the lungs with room air via an endotracheal tube. Tidal volume was set at 17 ml/kg, and respiratory rate was adjusted to maintain an end-tidal carbon dioxide concentration of 4.5%. Rectal temperature was monitored and maintained within 1°C of the initial temperature. The electrocardiogram was monitored continuously (Tektronics, Beaverton, OR). Neuromuscular blockade was evaluated by stimulation of the posterior tibial nerve (Neurotechnology, Houston, TX) and assessment of visible dorsiflexion of the animal’s hind limb. Blood pressure was measured either noninvasively (Data-
scope, Paramus, NJ) every 2.5 min or via a 20-G percutaneous femoral arterial catheter connected to a pressure transducer. Anesthetic depth was assessed by canthral reflex, presence of spontaneous movement, breathing, heart rate, and blood pressure.

One or two fiberoptic bronchoscopes (5.5 mm OD) were visually guided through the endotracheal tube, and the tip(s) were lodged in a sublobar airway. A double-lumen catheter (5-Fr) was threaded through the suction port of the bronchoscope. Through one lumen, 5% carbon dioxide in air was delivered to the obstructed segment. A constant flow rate of 200 ml/min \( (V_{coll}) \) approximating the resting ventilation to the area subtended by the bronchoscope, was maintained throughout the experiment. The other lumen of the double-lumen catheter was connected to a transducer to measure the pressure \( (P_b) \) at the tip of the bronchoscope. Collateral systemic resistance \( (R_{coll}) \) was determined by stopping the ventilator to allow the dog to exhale to functional residual capacity. At this point \( P_b \) reached a plateau, and the pressure in the surrounding unobstructed lung \( (P_{a0}) \) equaled zero. \( R_{coll} \) (cmH₂O·cm⁻¹·s⁻¹) was calculated as follows: 

\[
R_{coll} = \frac{P_b - P_{a0}}{V_{coll}}
\]

Data are presented as percent increase in \( R_{coll} \): \% \( R_{coll} = \frac{(R_{coll} - R_{coll} B)}{R_{coll} B} \cdot 100 \), where \( R_{coll} A \) is \( R_{coll} \) measured 30 s or 3 min after an iv challenge, and \( R_{coll} \) B is the average of three measurements of \( R_{coll} \) just before each challenge.

At the end of the experiment, neostigmine (50 µg/kg) and atropine (25 µg/kg) were administered every 30 min until full strength had returned. The dogs were monitored continuously until they were fully awake.

**Experimental Protocol**

**Effect of Histamine**

Repeated Doses: Four BG dogs were anesthetized, and two fiberoptic bronchoscope tips were wedged in sublobar segments (four right middle and four left middle lobes). In each sublobar segment, \( R_{coll} \) was measured every 5 min until a stable baseline was established for three consecutive readings. Histamine (200 µg) was then given as an iv bolus, and \( R_{coll} \) subsequently measured 30 s, 2, 5, and 10 min after the bolus. Thereafter, \( R_{coll} \) was measured every 5 min until it stabilized for three consecutive readings. A second dose of histamine (200 µg iv) was then administered and \( R_{coll} \) measured as described above. This dose of histamine was selected based on preliminary experiments that showed that histamine (200 µg iv) produced an increase in \( R_{coll} \) similar to that of atracurium (1.2 mg/kg) used in subsequent experiments.

Chlorpheniramine: The effect of a H₁ antagonist, chlorpheniramine, was studied in five BG dogs. Two fiberoptic bronchoscope tips were inserted into four dogs (four right middle lobes, four left middle lobes), and one bronchoscope was inserted into one dog (left middle lobe). The protocol was identical to that described above, except that chlorpheniramine (0.2 mg/kg iv) was administered between the two histamine challenges.

**Effect of Atracurium**

Repeated doses: Seven BG dogs (seven right middle lobes, seven left middle lobes) were studied. \( R_{coll} \) was measured every 5 min until a stable baseline was established for three consecutive readings. Atracurium (1.2 mg/kg iv) was administered, and \( R_{coll} \) was measured 1, 2, 3, 4, 5, 10, and 15 min after the bolus. When \( R_{coll} \) returned to the original baseline, a second dose of atracurium (1.2 mg/kg iv) was administered and \( R_{coll} \) measured as described above.

To determine whether a smaller dose of atracurium increased collateral resistance, six BG dogs were studied on a separate occasion. Two fiberoptic bronchoscopes were inserted into four dogs (four right middle lobes, four left middle lobes), and one bronchoscope was inserted into two dogs (one right middle lobe, one left middle lobe). After a stable baseline \( R_{coll} \) was established, atracurium (0.5 mg/kg iv) was administered and \( R_{coll} \) measured as described above.

Chlorpheniramine: Five BG dogs were pretreated with chlorpheniramine (0.2 mg/kg iv) after the induction of anesthesia. Two bronchoscope tips were wedged in sublobar segments (five right middle lobes, five left middle lobes). \( R_{coll} \) was measured every 5 min until it stabilized for three consecutive readings. Atracurium (1.2 mg/kg iv) was administered within 11 min of the dose of chlorpheniramine, and \( R_{coll} \) was measured.

This study was repeated using high-dose chlorpheniramine (5 mg/kg iv) in five dogs (one dog was studied twice). Two bronchoscope tips were wedged in sublobar segments (six right middle lobes, six left middle lobes).

Chlorpheniramine and Atropine: Two BG dogs were pretreated with atropine (0.2 mg/kg iv) and then chlorpheniramine (0.2 mg/kg iv) after the induction of anesthesia. The tips of two bronchoscopes were wedged in sublobar segments (two right middle lobes, two left middle lobes). \( R_{coll} \) was measured every 5 min until it stabilized for three consecutive readings. Atracurium (1.2 mg/kg iv) was administered with 17 min of the atropine and within 13 min of the chlorpheniramine, and \( R_{coll} \) was measured.

Chlorpheniramine and Ranitidine: Three BG dogs were pretreated with chlorpheniramine (0.2 mg/kg iv) and then ranitidine (0.75 mg/kg iv) after the induction of anesthesia. Two fiberoptic bronchoscopes were inserted into each of two dogs (two right middle lobes, two left middle lobes), and one bronchoscope was inserted into
one dog (right middle lobe). Rca was measured every 5 min until it stabilized for three consecutive readings. Atracurium (1.2 mg/kg iv) was administered within 26 min of the chlorpheniramine and within 20 min of the ranitidine, and Rca was measured.

STATISTICAL ANALYSIS

Analysis of variance and Fisher multiple comparison tests were used to analyze mean differences of Rca within sublobar segments, and blood pressure and heart rate responses within animals. T tests were used to analyze mean differences of Rca between sublobar segments. Raw data were used for all statistical analyses. We used P < 0.05 to indicate statistical significance. Data are expressed as mean ± standard error.

Results

EFFECT OF HISTAMINE

Repeated Doses

Histamine (200 μg iv) increased Rca, decreased systolic blood pressure, and increased heart rate (fig. 1). Baseline Rca before the first dose of histamine (200 μg iv) was 0.38 ± 0.09 cmH2O·ml⁻¹·s⁻¹ (n = 8 sublobar segments). Histamine increased Rca to 0.68 ± 0.14, a 97 ± 24% (P < 0.01) increase above baseline at 30 s (fig. 1). Rca returned to baseline by 10 min. Baseline Rca before the second dose of histamine was 0.37 ± 0.09 cmH2O·ml⁻¹·s⁻¹, which was not significantly different from the first baseline Rca. After the second dose of histamine, Rca increased to 0.66 ± 0.18 cmH2O·ml⁻¹·s⁻¹, a 77 ± 15% increase above the initial baseline at 30 s. Rca after the second dose of histamine was not significantly different from Rca after the first dose. Reductions in blood pressure and increases in heart rate were similar after the two doses of histamine (fig. 1).

Chlorpheniramine

Chlorpheniramine (0.2 mg/kg) totally prevented the histamine-induced increase in airway tone (fig. 2). Baseline Rca was 0.40 ± 0.08 cmH2O·ml⁻¹·s⁻¹ (n = 9 sublobar segments). Histamine (200 μg iv) increased Rca to 0.62 ± 0.10 cmH2O·ml⁻¹·s⁻¹, or 65 ± 16% increase above baseline at 30 s (fig. 2). After the administration of chlorpheniramine, baseline Rca (0.41 ± 0.07 cmH2O·ml⁻¹·s⁻¹) was not significantly different from baseline Rca in the absence of chlorpheniramine. In the presence of chlorpheniramine, histamine did not significantly increase Rca.

In the presence of chlorpheniramine, histamine decreased systolic blood pressure from 156 ± 19 mmHg to 139 ± 24 mmHg at 30 s (fig. 2). This reduction was not significantly different from the reduction in blood pressure in the absence of chlorpheniramine. In the presence of chlorpheniramine, histamine increased heart rate from 74 ± 9 beats per min to 109 ± 14 beats per min at 30 s. Maximum heart rate was significantly less in the presence of chlorpheniramine (P < 0.05).

Effect of Atracurium

Repeated Doses

Atracurium produced significant effects on both airways and the cardiovascular system. Atracurium (1.2 mg/kg) produced an increase in Rca, a decrease in systolic blood pressure, and an increase in heart rate (fig. 3). Before the first dose of atracurium (1.2 mg/kg), baseline Rca was 0.23 ± 0.04 cmH2O·ml⁻¹·s⁻¹ (n = 14 sublobar segments). Peak response to atracurium occurred 3 min after the bolus (fig. 3), at which time Rca increased to 0.67 ± 0.16 cmH2O·ml⁻¹·s⁻¹, or 174 ± 35% above the baseline. By 10 min, Rca had returned to baseline. Before the second dose of atracurium, baseline Rca was 0.22 ± 0.04
Varying Doses

Atracurium (0.5 mg/kg) did not significantly increase $R_\infty$: $R_\infty$ was $0.24 \pm 0.05$ and $0.25 \pm 0.05 \text{ cmH}_2\text{O} \cdot \text{m}^{-1} \cdot \text{s}^{-1}$ ($n = 10$ sublobar segments) before and 3 min after atracurium, respectively ($P = 0.48$).

Chlorpheniramine

Chlorpheniramine significantly attenuated but did not abolish the increase in $R_\infty$. Baseline $R_\infty$ in dogs pretreated with low-dose chlorpheniramine (0.2 mg/kg) was $0.37 \pm 0.08 \text{ cmH}_2\text{O} \cdot \text{m}^{-1} \cdot \text{s}^{-1}$ ($n = 10$ sublobar segments). Atracurium given within 11 min of the chlorpheniramine dose produced a significant increase in $R_\infty$ (fig. 3) ($P = 0.0001$). In the presence of chlorpheniramine, atracurium increased peak $R_\infty$ to $0.52 \pm 0.13 \text{ cmH}_2\text{O} \cdot \text{m}^{-1} \cdot \text{s}^{-1}$ or only $26 \pm 14\%$ above baseline at 3 min. Baseline systolic blood pressure decreased from 144 cmH$_2$O $\cdot$ ml$^{-1} \cdot $s$^{-1}$, which was not significantly different from the baseline before the first dose. A second dose of atracurium, administered 19–43 min after the first dose, increased $R_\infty$ to only $0.38 \pm 0.09 \text{ cmH}_2\text{O} \cdot \text{m}^{-1} \cdot \text{s}^{-1}$, or $54 \pm 14\%$ above baseline at 3 min. Thus, peak $R_\infty$ was significantly less than peak $R_\infty$ following the first dose of atracurium ($P < 0.01$).

Systolic blood pressure before the first dose of atracurium was $142 \pm 5$ mmHg and decreased to $81 \pm 8$ mmHg at 3 min (fig. 3). Before the second dose of atracurium, systolic blood pressure was $145 \pm 7$ mmHg and decreased to $112 \pm 10$ mmHg after the second dose of atracurium. The lowest systolic blood pressure was significantly different between the first and second doses ($P < 0.01$). Atracurium increased heart rate from $101 \pm 5$ beats per min to $155 \pm 7$ beats per min after the first dose (fig. 3) and from $134 \pm 7$ beats per min to $143 \pm 11$ beats per min after the second dose. The peak heart rate after the second dose of atracurium was not significantly different from the peak heart rate after the first dose.

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**Fig. 2.** Airway resistance ($R_\infty$), blood pressure, and heart rate in response to two sequential iv bolus doses of histamine (200 μg iv) in the presence and absence of chlorpheniramine (0.2 mg/kg iv) in Basenji-Greyhound dogs. $n = 9$ sublobar segments.

**Fig. 3.** Airway resistance ($R_\infty$), blood pressure, and heart rate in response to atracurium (1.2 mg/kg iv bolus) with and without chlorpheniramine (0.2 mg/kg iv) pretreatment in Basenji-Greyhound dogs. $n = 14$ sublobar segments without chlorpheniramine; $n = 10$ sublobar segments with chlorpheniramine.
± 4 mmHg to 82 ± 14 mmHg postchallenge (fig. 3). Baseline heart rate increased from 81 ± 10 beats per min to 132 ± 14 beats per min postchallenge (fig. 3).

In animals pretreated with high-dose chlorpheniramine (5 mg/kg), atracurium (1.2 mg/kg) did not significantly increase $R_{ca}$ during the 10-min period of observation ($n = 12$ sublobar segments). Baseline $R_{ca}$ following pretreatment with chlorpheniramine (5 mg/kg) was $0.17 ± 0.03$ cmH$_2$O·ml$^{-1}$·s$^{-1}$ (table 1). Atracurium (1.2 mg/kg) did not significantly increase $R_{ca}$. In fact, a small reduction in $R_{ca}$ to 0.14 ± 0.03 cmH$_2$O·ml$^{-1}$·s$^{-1}$ was observed ($P = 0.023$).

Chlorpheniramine and Atropine

The combination of atropine and chlorpheniramine was no more protective than chlorpheniramine alone. Baseline $R_{ca}$ after pretreatment with both chlorpheniramine (0.2 mg/kg iv) and atropine (0.2 mg/kg iv) was $0.36 ± 0.11$ cmH$_2$O·ml$^{-1}$·s$^{-1}$ ($n = 4$ sublobar segments) (table 1). $R_{ca}$ increased to $0.53 ± 0.17$ cmH$_2$O·ml$^{-1}$·s$^{-1}$, a 45 ± 12% increase, after the administration of atracurium. Peak $R_{ca}$ was not significantly different from peak $R_{ca} (0.52 ± 0.13$ cmH$_2$O·ml$^{-1}$·s$^{-1}$) following pretreatment with chlorpheniramine alone ($P = 0.98$). Baseline systolic blood pressure after chlorpheniramine and atro- pine pretreatment was $151 ± 1$ mmHg and decreased to $44 ± 6$ postchallenge ($P < 0.01$). Baseline heart rate after chlorpheniramine and atropine pretreatment was $169 ± 5$ beats per min, which did not significantly change after administration of atracurium.

Chlorpheniramine and Ranitidine

The addition of ranitidine did not increase the protection afforded by chlorpheniramine alone. Baseline $R_{ca}$ in dogs pretreated with chlorpheniramine (0.2 mg/kg iv) and ranitidine concurrently (0.75 mg/kg iv) was $0.32 ± 0.08$ cmH$_2$O·ml$^{-1}$·s$^{-1}$ ($n = 5$ sublobar segments) (table 1). $R_{ca}$ increased to $0.46 ± 0.12$ cmH$_2$O·ml$^{-1}$·s$^{-1}$, 47 ± 29% above baseline, 3 min after atracurium (table 1). Peak $R_{ca}$ was not significantly different from peak $R_{ca}$ following pretreatment with chlorpheniramine alone ($P = 0.74$). Systolic blood pressure, after pretreatment with chlorpheniramine and ranitidine, was $143 ± 4$ mmHg and did not decrease after atracurium challenge. Baseline heart rate after chlorpheniramine and ranitidine was $95 ± 21$ beats per min, which did not significantly change after administration of atracurium.

Discussion

The present study demonstrates that atracurium produces significant effects on the airways as well as on the cardiovascular system. The airway effects are short-lived, are dose-related, are qualitatively similar to an iv bolus of histamine, and are markedly attenuated by pretreatment with a H$_1$ receptor antagonist.

Crago et al.,$^{10}$ Simpson et al.,$^3$ and Gerbershagen and Bergman$^8$ failed to find significant increases in airway tone after administration of $d$-tubocurarine to humans with normal lung function. However, Crago et al.$^{10}$ did find greater increases in airway resistance in subjects with preexisting lung disease paralyzed with $d$-tubocurarine, than with pancuronium, but did not follow up this observation with histamine receptor antagonist studies.

We are aware of only one study in humans that examined changes in airway tone after atracurium.$^9$ Simpson et al.$^9$ found a significant decrease in specific airways conductance at only one time point, 6 min after administration of a 0.5-mg/kg dose to humans. Our results differ from those of Simpson et al.$^9$ in that the peak effect on airways occurred 3 min after administration of an even higher dose of drug. A maximal effect at 3 min, not 6 min, agrees with the study of Moss et al.,$^5$ who showed that, for $d$-tubocurarine, maximal plasma histamine concentrations were attained at 2 min and that by 5 min,

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Baseline</th>
<th>Peak $R_{ca}$</th>
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<tbody>
<tr>
<td>Histamine 200-μg iv bolus</td>
<td></td>
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<tr>
<td>First dose</td>
<td>0.38 ± 0.09</td>
<td>0.68 ± 0.14</td>
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<tr>
<td>Second dose</td>
<td>0.37 ± 0.09</td>
<td>0.66 ± 0.18</td>
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<tr>
<td>Chlorpheniramine 0.2-mg/kg pretreatment</td>
<td>0.41 ± 0.07</td>
<td>0.41 ± 0.07</td>
</tr>
<tr>
<td>Atracurium 1.2-mg/kg iv bolus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First dose</td>
<td>0.23 ± 0.04</td>
<td>0.67 ± 0.16</td>
</tr>
<tr>
<td>Second dose</td>
<td>0.22 ± 0.04</td>
<td>0.58 ± 0.09</td>
</tr>
<tr>
<td>Chlorpheniramine 0.2-mg/kg pretreatment</td>
<td>0.37 ± 0.08</td>
<td>0.62 ± 0.13</td>
</tr>
<tr>
<td>Chlorpheniramine 0.2-mg/kg and atropine 0.2-mg/kg pretreatment</td>
<td>0.17 ± 0.03</td>
<td>0.17 ± 0.03</td>
</tr>
<tr>
<td>Chlorpheniramine 0.2-mg/kg and ranitidine 0.75-mg/kg pretreatment</td>
<td>0.36 ± 0.11</td>
<td>0.53 ± 0.17</td>
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<tr>
<td>Atracurium 0.5-mg/kg iv bolus</td>
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</tr>
<tr>
<td>One dose</td>
<td>0.32 ± 0.08</td>
<td>0.46 ± 0.12</td>
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<tr>
<td></td>
<td>0.24 ± 0.05</td>
<td>0.25 ± 0.05</td>
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histamine concentrations had returned to control values. Clinically significant effects on both the airways and the cardiovascular system were not seen in our study with the lower dose (0.5 mg/kg) of atracurium. This agrees with a study in humans\textsuperscript{25} that showed that significant increases in heart rate and decreases in mean arterial blood pressure occurred after a bolus of a higher dose than 0.5 mg/kg of atracurium. A steep dose–response relationship for histamine release by atracurium from human mast cells has also been demonstrated.\textsuperscript{5,4}

Plasma histamine concentrations were not measured in this study because it was unclear to us at which site they should be measured. Measured plasma levels of histamine only roughly reflect histamine release from tissue but do not presumably account for the large amount of histamine metabolized or taken up within various tissue beds. Instead, we elected to inject into the systemic circulation a bolus dose of histamine that produced a similar airway constrictor response to atracurium 1.2 mg/kg. Two differences were seen between histamine and atracurium. Atracurium induced peak effects on airways at 3 min, whereas peak effects of histamine were seen at 30 s. Moreover, the airways exhibited reduced responsiveness to a second dose of atracurium but not to histamine, presumably reflecting depleted histamine stores in the mast cells, not rapid desensitization of the airways to circulating histamine.

Both vascular and airway smooth muscle contain H\textsubscript{1} and H\textsubscript{2} receptors. Histamine induces dilatation of resistance vessels by stimulation of both H\textsubscript{1} and H\textsubscript{2} receptors. H\textsubscript{1} receptors are believed to mediate the immediate response, whereas H\textsubscript{2} receptors are believed to mediate the more sustained response.\textsuperscript{21} In contrast, histamine produces constriction of airway smooth muscle of many species including the human and the dog, mediated by H\textsubscript{1} receptors.\textsuperscript{22} However, in the presence of H\textsubscript{1} blockade histamine can induce bronchodilation mediated by H\textsubscript{2} receptors.\textsuperscript{23} Our results are consistent with these theories. A combination of H\textsubscript{1} and H\textsubscript{2} receptor blockade significantly attenuated the cardiovascular effects of atracurium. Moreover, H\textsubscript{1} receptor blockade totally abolished histamine-induced airway constriction and markedly attenuated atracurium-induced airway constriction. It is unlikely that the small residual constriction provoked by atracurium in the presence of H\textsubscript{1} receptor blockade was due to stimulation of muscarinic cholinergic receptors,\textsuperscript{2} since atropine in concentrations known to block airway muscarinic receptors\textsuperscript{25} failed to modify this response. A combination of H\textsubscript{1} and H\textsubscript{2} receptor blockade also failed to abolish the small residual constriction provoked by atracurium. It is possible that H\textsubscript{2} receptor-induced dilatation is not important in this model. It is also possible that H\textsubscript{2} antagonists could have concurrently increased histamine release from mast cells, since histamine acting via H\textsubscript{2} receptors has been shown to inhibit histamine release from basophils.\textsuperscript{24} A more likely possibility is that the small residual constriction reflects the presence in the airways of other bronchoactive inflammatory mediators released along with histamine.

One additional explanation for the residual airway constriction is prejunctional activity of atracurium. One study in dogs showed that atracurium increased total pulmonary resistance during vagal stimulation.\textsuperscript{25} The authors hypothesized that this could be due to blockade of prejunctional muscarinic receptors (M2) that inhibit vagally mediated increases in pulmonary resistance.

In this study, we assessed the effects of atracurium on peripheral airway resistance. We suspected that if atracurium released histamine, then changes in airway resistance would be most easily detected in the lung periphery, the predominant site of histamine-induced airway constriction in the dog.\textsuperscript{26} Peripheral airway caliber was determined by assessing changes in R\textsubscript{8}. In the past, pathways for collateral flow were believed to be comprised of pores of Kohn, bronchoalveolar channels of Lambert, and interbromchiolar channels of Martin.\textsuperscript{27,28} Recent evidence, however, has demonstrated that the predominant pathway for collateral flow is through interbromchiolar channels of Martin, so that R\textsubscript{8} primarily reflects resistance at the level of the alveolar duct.\textsuperscript{19} In addition, collateral system responses are very similar to those of other normal small airways.\textsuperscript{29,30} Thus, it appears likely that atracurium-induced changes in R\textsubscript{8} in this study truly reflect constriction of peripheral airways.

In summary, atracurium constricts peripheral airways in doses that produce significant cardiovascular effects. Release of histamine acting on H\textsubscript{1} receptors is important for this effect. Our study suggests that airway constrictor effects of atracurium can largely be prevented in high-risk populations by using low drug doses, divided doses, and H\textsubscript{1} receptor antagonists.

References