Canine model of nasal congestion and allergic rhinitis

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Tiniakov, Ruslan L., Olga P. Tiniakova, Robbie L. McLeod, John A. Hey, and Donovan B. Yeates. Canine model of nasal congestion and allergic rhinitis. J Appl Physiol 94: 1821–1828, 2003.—The ragweed- and histamine-induced decreases in nasal patency in cohorts of ragweed-sensitized and nonsensitized dogs were assessed. The volume of nasal airways (VNA) was assessed by acoustic rhinometry and resistance to airflow (RNA) by anterior rhinomanometry. Histamine delivered to the nasal passages of five dogs caused a rapid and prolonged increase in RNA from 0.16 ± 0.02 to 0.53 ± 0.07 cmH2O·l−1·min, an effect that was reversed by intranasal delivery of aerosolized phenylephrine. Ragweed challenge in five ragweed-sensitized dogs increased RNA from 0.16 ± 0.02 to 0.53 ± 0.07 cmH2O·l−1·min and decreased VNA from 12.5 ± 1.9 to 3.9 ± 0.3 cm3, whereas administration of saline aerosol neither increased RNA nor decreased VNA. Prior administration of D-pseudoephedrine (30 mg po) attenuated the ragweed-induced increase in RNA and decrease in VNA. Ragweed challenge changed neither RNA nor VNA in four nonsensitized dogs. Mediator-induced nasal congestion and allergen-induced allergic rhinitis in ragweed-sensitized dogs, which exhibit symptoms similar to human disease, can be used in the evaluation of safety and efficacy of antiallergic activity of potential drugs.

Ragweed; Histamine; α-adrenergic agonist; Nasal resistance; Acoustic rhinometry

inhaling airborne allergens, in persons with allergic rhinitis, results in congestion of the nasal passages that causes difficulty of nasal breathing and often complete nasal obstruction (23). Persons with allergies are often hypersensitive to other irritants such as nitrates and sulfur oxides, airborne particles, and ammonia (13, 19). In addition, coexposure to air pollutants and allergens may lead to synergistic responses (8, 22). Although histamine contributes to the responses, other mediators and neural pathways are undoubtedly involved. The delineation of these irritant-induced and allergen-induced cascades of reactions (24) in the nasal passages should provide novel targets, pathophysiologically relevant to treatment of allergic rhinitis and prevention of nasal congestion. A suitable animal model is required both for the delineation of novel target sites and for the testing of the potential efficacy as well as the toxicity of new chemical entities before their evaluation in human clinical trials.

Several animal models of rhinitis have been described. However, many of them are based on nonsurvival techniques performed in small animals (9, 16) that are often inappropriate for use in larger animals. The differences in basic nasal anatomy, physiology, and pharmacological sensitivity between humans and small animals like guinea pigs (18) or rabbits make the extrapolation of experimental data to humans less than ideal. In this aspect, the canine experimental model of allergic rhinitis provides an important advantage because the autonomic control of nasal resistance, an arterial supply, venous drainage, and collateral blood flow in canine nasal cavity are well established (10–12). Additionally, dogs are extensively used in preclinical studies and in the determination of the safety profiles of new therapeutic agents. Some of the dog models described use very invasive techniques (12). In other models, nasal congestion is induced pharmacologically by the application of vasodilators (11, 20, 25) or by mast cell mediator-releasing agents (7, 14, 15). The application of vasodilators, however, fails to induce the full range of pathophysiological events characteristic for allergic rhinitis. A more relevant model includes the administration of a specific allergen to large animals whose induced allergic responses were verified (4). Development of therapeutic treatments for rhinitis can be enhanced by the use of an animal model that 1) closely resembles the pathophysiology of human allergic rhinitis, 2) enables the use of experimental techniques that are similar to those used for the assessment of nasal passages in humans, and 3) allows multiple experiments in the same cohort of animals.

In a cohort of beagle dogs that were neonatally sensitized to ragweed allergen, inhalation of the ragweed extract into the lower respiratory tract induced a complex systemic anaphylactic response that manifested in bronchoconstriction, alteration of a breathing pattern, increase in bronchial mucociliary clearance, and temporary cardiovascular depression (27). We hypothesized that, in these dogs, exclusive exposure of the upper respiratory tract to the same ragweed allergen would precipitate the development of allergic rhinitis.
that was responsive to treatment with α-adrenergic agonists. To test this hypothesis, we evaluated the degree of nasal congestion induced by ragweed and histamine in cohorts of ragweed-sensitized, sham-sensitized, and nonsensitized dogs. Nasal congestion was assessed by the measurement of 1) the resistance to conducting air, i.e., nasal airway resistance (R_{NA}) and 2) the relative cross-sectional areas (CSAs) and the volume of nasal passages.

**METHODS**

**Description of animals and their history.** Three series of experiments were conducted on subgroups selected from 14 adult beagle dogs (Covance) of both sexes, weighing 9.5–14.5 kg. Five dogs were neonatally sensitized to ragweed, three were their sham-sensitized littermates, and six dogs were nonsensitized. The method used to sensitize the dogs (27) was adapted from the method described by Becker et al. (2).

Briefly, newborn dogs received intraperitoneal injections containing 200 μg of aluminum hydroxide (gel USP, Roxane Laboratories) within 24 h of birth. Injections were repeated weekly for 6 wk and biweekly until 16 wk of age. In the sham-sensitized animals, only the aluminum hydroxide in saline was injected. Five-milliliter samples of venous blood were drawn from each dog beginning at 4 mo of age and thereafter four times per year to measure serum IgE levels. The protocols for animal use in these experiments were approved by the institutional Animal Care Committees.

These sensitization and sham sensitization procedures were conducted in November 1992 (2 dogs), July 1993 (3 dogs), and December 1993 to January 1994 (3 dogs). The ragweed-sensitized dogs previously exhibited an anaphylactic reaction on inhalation of ragweed extract, whereas their sham-sensitized littermates did not (27). The lungs of the ragweed-sensitized dogs and the sham-sensitized dogs were challenged with ragweed extract in a series of experiments conducted in 1994 and 1995 (17, 26, 27). They were not challenged with ragweed extract between those experiments and the experiments described herein, which were conducted in 2001. The nonsensitized dogs were used previously for other experiments, but these did not include challenges with ragweed allergens.

**Protocols.** The first series of experiments was designed to show, using a new method of anterior constant-flow nasal rhinomanometry, that a mediator of allergen-induced rhinitis, histamine, induced nasal congestion that was alleviated by the local administration of an α-adrenergic agonist. This series was conducted in five nonsensitized dogs. The nasal resistance was measured in both left and right nasal passages simultaneously. Nasal congestion was induced with 5% histamine (163 mM solution in saline) delivered for 1 min by aerosol to both nasal passages. Twenty minutes after the histamine challenge, 0.1% phenylephrine (4.9 mM solution in saline) was administered for 1 min by aerosol to each nasopharynx. Aerosols with particles of 1–2 μm in diameter were produced by an AeroTech II atomizer (Model CA-1200C, CIS-US, Bedford, MA) at 10 l/min and delivered at the rate of 5 l/min into each nasal passage.

The second series of experiments was designed to determine, by using our method for R_{NA} measurement in combination with acoustic rhinometry, whether any ragweed-induced nasal congestion in ragweed-sensitized, sham-sensitized, and nonsensitized dogs was immunologically induced and whether these responses were reversible by topically administered D-pseudoephedrine. This series was conducted in five ragweed-sensitized, three sham-sensitized, and two nonsensitized dogs. R_{NA} was measured in the left nasal airway, and geometric parameters of the right nasal airway were measured with the acoustic rhinometer simultaneously.

Ragweed extract was delivered to both nasal passages by use of a Micro Sprayer catheter (Penn Century, Philadelphia, PA). A volume of 0.25 ml of saline containing 0.525 units of ragweed extract (Greer Laboratories) was sprayed into each nasal passage to induce its congestion. Twenty minutes after the ragweed challenge, 12.4 μM of D-pseudoephedrine [(+)-pseudoephedrine, 0.25 ml of 1% solution] or equal volumes of isotonic saline were administered into each nasal passage. The order in which the experiments were conducted was randomized.

The third series of experiments was designed to demonstrate the utility of this model in estimation of decongestive activity of orally administered α-adrenoceptor agonist, D-pseudoephedrine. This series was conducted in five ragweed-sensitized and four nonsensitized dogs. Either ragweed extract or a saline control was administered into both nasal passages by using the Micro Sprayer catheter technique as described above. R_{NA} in the left nasal airway and geometric parameters of the right nasal airway were measured simultaneously. Each sensitized dog underwent three experiments in randomized order: 1) a placebo (plain gelatin capsule) was given perorally 30 min prior to the ragweed challenge; 2) D-pseudoephedrine [30 mg (0.15 mM) in gelatin capsule] was given perorally 30 min before the ragweed challenge; and 3) a placebo (plain gelatin capsule) was given perorally 30 min before a saline challenge. The order in which the experiments were conducted was randomized. Each nonsensitized dog underwent only one experiment in which a placebo was administered before the ragweed challenge, because our preliminary experiments have shown no significant changes in either parameter measured in these dogs after the administration of either saline or D-pseudoephedrine.

**Animal preparation.** Before each experiment, dogs were fasted overnight but allowed water ad libitum. Each dog was anesthetized with a combination of propofol (450–550 μg·kg⁻¹·min⁻¹; Zeneca Pharmaceuticals, Wilmington, DE) and etomidate (5 μg·kg⁻¹·min⁻¹; Abbott Laboratories, North Chicago, IL) administered intravenously. The dog was intubated and secured in upright position in a sling. The depth of anesthesia was adjusted to the presence of palpebral reflex and adequate spontaneous respiration. Nasal catheters were placed in each nostril to facilitate the measurement of R_{NA}. To maintain the rectal temperature at 37.0 ± 0.5°C, a water-heated pad was placed under the dog and a blanket was placed over it. Physiological monitoring included ECG, respirometry by a pneumotachograph, arterial blood pressure by use of a pressure cuff on the foreleg, hemoglobin oxygen saturation by using a pulse oximeter with a sensor placed on the dog’s tongue, and rectal temperature. Nasal secretions were estimated qualitatively by visual observations of the open nostril and the posterior oropharynx. The presence of secretions in the nasal passages was also indicated by audible sounds as well as by perturbations in the pressure tracings. Dogs were allowed to recuperate for 2 wk between experiments.

**Measurement of R_{NA}.** R_{NA} was determined by measuring the air pressure required to achieve a constant predetermined flow through the nasal passage. The air was humidified in a pressurized (410 cmH₂O) modified Bird (3M) humidifier at room temperature (Fig. 1). The air output of the humidifier was controlled by a critical-flow orifice. This con-
constant airflow was delivered to the nasal passage through a nasal catheter (modified rubber cuffed endotracheal tube, ID 3.5 mm; Rusch, Duluth, GA) coupled to a pressure transducer (model 4423; Endevco, San Juan Capistrano, CA). The nasal catheter was snugly placed into the nostril, and the cuff was inflated to form a seal. The resistance to airflow in the nasal catheter was negligible. In the first series of experiments, in which the R\textsubscript{NA} was measured in both airways simultaneously, an airflow of 3.0 l/min through each nasal passage was used. In the second and third series of experiments, in which R\textsubscript{NA} in the left nasal passage was measured, an airflow of 4.9 l/min was used. The relatively small changes in endonasal pressure (<10.0 cmH\textsubscript{2}O) do not change the flow through the critical-flow orifice, thus the measured pressure changes directly reflect changes in R\textsubscript{NA}. Acoustic rhinometry was performed simultaneously in the right nasal passage. The ECG and respiratory flow as well as the analog signal from pressure transducers were recorded continuously on a multichannel Y-time recorder (Hewlett-Packard 7754A). R\textsubscript{NA} (cmH\textsubscript{2}O·l\textsuperscript{-1}·min\textsuperscript{-1}) was defined as the pressure differential between the input air pressure and atmospheric pressure divided by the airflow.

Acoustic rhinometry. Changes in the geometry of the nasal cavity were estimated by using the Eccovision acoustic rhinometry system (Hood Laboratories, Pembroke, MA). The procedure for use of the Eccovision required the system to be calibrated every time it is turned on. The calibration was conducted by using a calibration tube provided by the manufacturer. The acoustic wave tube was fitted with a handmade plastic tip (ID 5.0 mm) designed to match the shape of the dog’s nostrils. Acoustic measurements of the geometric parameters of the right nasal passage were performed four times during each experiment: 1–2 min before the ragweed challenge, 5 min after the ragweed extract was deposited in nasal passages, 20 min after the ragweed challenge, and 40 min after the ragweed challenge. Volume of the right nasal airway (V\textsubscript{NA}) and CSAs of right nasal cavity at the levels of a nasal valve, anterior and posterior regions of maxilloturbinates, and ethmoturbinates were calculated by using acoustic rhinometry. These anatomical structures correspond to a nasal valve, frontal and rear regions of anterior turbinates, and posterior turbinates in humans, respectively. These regions were determined by comparing the form of the acoustic rhinogram with the visually identified anatomical structures on the sagittal section of a canine head after scaling for the size of the beagles studied herein. The terminology used herein is adopted from Schreider (21). The calibration of the acoustic rhinometer with the handmade plastic tip attached was checked by using a variety of volumetric flasks. Under these conditions, the tip on the acoustic wave tube caused overestimations of the volume and CSAs of a nasal cavity. Thus a correction factor (k = 0.8) was used to convert the values derived by an acoustic rhinometer into standard units (cm\textsuperscript{3} and cm\textsuperscript{2}, respectively).

Data processing. The heart rates, respiratory rates, and R\textsubscript{NAS} were derived from the chart recording of analog signals. Statistical significance was determined by using the standard accessories of Microsoft Excel: two-way ANOVA and Student’s t-test, as appropriate. All the data herein are expressed as means ± SE.

RESULTS

In the first series of experiments, histamine delivered to the nasal passages of five dogs caused rapid increase in R\textsubscript{NA} from 0.75 ± 0.26 to a maximum of 3.56 ± 0.50 cmH\textsubscript{2}O·l\textsuperscript{-1}·min\textsuperscript{-1} within the first 5 min. The R\textsubscript{NA} in these dogs remained above the baseline (P < 0.05) for the next 40 min (Fig. 2). The histamine-induced increase in R\textsubscript{NA} was almost completely reversed (P < 0.05) by the administration of aerosolized 0.1% phenylephrine to the nasal passages (Fig. 2). The

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**Fig. 1.** Schematic of the system used for measurements of nasal airway resistance (R\textsubscript{NA}). Compressed air (1) from the gas cylinder (not shown) is delivered to humidifier (2). By use of the gauge (3), the air pressure in the humidifier is set to 300 Torr. The airflow at the output of humidifier is controlled by a critical flow orifice (4). Humidified air is delivered to dogs through the modified rubber endotracheal tube (5), which has a cuff (6). The air pressure at the end of this endonasal tube is measured with a pressure sensor (7) connected to amplifier (8) and registered on a Y-time recorder (9) together with other parameters.

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**Fig. 2.** Histamine-induced increases in R\textsubscript{NA} in nonsensitized dogs lasted over 40 min. Administration of phenylephrine caused rapid relief of the nasal congestion, with R\textsubscript{NA} returning to the prechallenge level. Single and double arrows show the time that histamine and phenylephrine, respectively, were administered. "J Appl Physiol • VOL 94 • MAY 2003 • www.jap.org"
responses to histamine and phenylephrine in both the left and right nasal passages were similar. Any changes in heart rate and blood pressure due to histamine administration and subsequent administration of phenylephrine were unremarkable. However, histamine provoked an immediate increase in respiratory rate from 17 ± 2 to 30 ± 6 breaths/min (P < 0.05) that was not reversed by phenylephrine.

In the second series of experiments, administration of the ragweed extract into the nasal passages of five ragweed-sensitized dogs caused R\textsubscript{NA} to increase over a period of 20 min from 0.25 ± 0.01 to a maximum of 1.98 ± 0.84 cm\textsubscript{H2O}·l\textsuperscript{-1}·min (P < 0.05) (Fig. 3A). Administration of aerosolized saline to these dogs caused a further increase in R\textsubscript{NA} to 2.52 ± 0.77 cm\textsubscript{H2O}·l\textsuperscript{-1}·min. These ragweed-induced changes in R\textsubscript{NA} in ragweed-sensitized dogs observed 20 min after ragweed challenge were almost completely reversed by 12.4 µM of \textit{d}-pseudoephedrine sprayed into each nasal passage (Fig. 3A). Unexpectedly, all three sham-sensitized dogs also demonstrated signs of sensitivity to ragweed challenge (Fig. 3B). However, the increase in R\textsubscript{NA} in these sham-sensitized dogs was less pronounced than in ragweed-sensitized dogs (P < 0.05). Any increases in R\textsubscript{NA} caused by the ragweed extract in two nonsensitized dogs were small compared with the responses in the ragweed-sensitized and sham-sensitized dogs (Fig. 3B). In sensitized dogs, the increases in R\textsubscript{NA} in left nasal passage were coincident with decreases in V\textsubscript{NA} of the right nasal cavity (Fig. 4A), whereas in sham-sensitized and nonsensitized dogs, analogous to the measurements of R\textsubscript{NA} in these dogs, any changes in V\textsubscript{NA} caused by ragweed were small (Fig. 4B). In sensitized dogs, ragweed extract induced a marked increase in nasal secretion. Somewhat lower secretory responses were observed in ragweed-challenged sham-sensitized dogs, and no observable secretions were induced by ragweed in nonsensitized dogs. No significant changes in heart rate, respiratory rate, or blood pressure could be ascribed to the administration of either ragweed or \textit{d}-pseudoephedrine.

In the third series of experiments, 30–40 min after the intranasal delivery of aerosolized ragweed extract, signs of severe nasal congestion were observed in four of five sensitized dogs that received placebo 30 min before the ragweed challenge. One dog demonstrated relatively low responses to ragweed. The mean R\textsubscript{NA} in these dogs increased from 0.16 ± 0.02 to 0.53 ± 0.07 cm\textsubscript{H2O}·l\textsuperscript{-1}·min (P < 0.05) (Fig. 5), and V\textsubscript{NA} decreased from 12.5 ± 1.9 to 3.9 ± 0.3 cm\textsuperscript{3} (P < 0.05) (Fig. 6), coincident with the observed increase in mucus secretion. The acoustic measurements of CSAs of the right nasal passage revealed a gradual reduction of the airway lumen throughout the 40-min postchallenge observation period. These changes were most evident in the anterior region of maxilloturbinates as well as in the region of the ethmoturbinates (Fig. 7A). Under the same conditions, an equal volume of aerosolized saline administered to the nasal passages neither increased R\textsubscript{NA} (Fig. 5) nor decreased V\textsubscript{NA} (Fig. 6A) or CSAs in these dogs (Fig. 7B). The 30 mg of \textit{d}-pseudoephedrine given per os, 30 min before the ragweed challenge, markedly reduced the ragweed-induced responses in sensitized dogs. In these five experiments, the tendency of R\textsubscript{NA} to increase (from 0.13 ± 0.03 to 0.25 ± 0.03 cm\textsubscript{H2O}·l\textsuperscript{-1}·min; Fig. 5) and the tendency of V\textsubscript{NA} to decrease (from 13.7 ± 1.9 to 10.7 ± 2.2 cm\textsuperscript{3}; Fig. 6B) were not statistically significant. The nonsensitized dogs, which received the placebo perorally 30 min before ragweed challenge, did not demonstrate any signs of nasal congestion. Changes in R\textsubscript{NA} (0.13 ± 0.03 vs. 0.18 ± 0.02 cm\textsubscript{H2O}·l\textsuperscript{-1}·min; Fig. 5) and V\textsubscript{NA} (12.1 ± 1.4 vs. 11.0 ± 1.6 cm\textsuperscript{3}; Fig. 6B) as well as
changes in values of CSAs of right nasal passage (Fig. 7D) in nonsensitized dogs after intranasal ragweed delivery were statistically insignificant. It is notable that, despite the decongestive action of orally administered D-pseudoephedrine, no significant changes in arterial blood pressure or heart rate were registered.

DISCUSSION

As hypothesized, the nasal passages of ragweed-sensitized dogs demonstrated clear signs of hyperreactivity to the ragweed allergen, resulting in the development of severe nasal congestion. This nasal congestion was evidenced by the characteristic changes in RNA and nasal luminal geometry. In sensitized dogs, nasal congestion appeared to be immunologically precipitated because it was never observed in nonsensitized dogs challenged with the same ragweed allergen. Local vasodilatation and consequent mucosal edema play key roles in development of the observed nasal congestion given that both the histamine-induced congestion in nonsensitized dogs and the ragweed-induced changes in sensitized dogs were susceptible to the treatment with α-adrenomimetics.

Anterior constant-flow rhinomanometry, as described herein, has some specific features that make the measurements physiologically relevant, sensitive, reliable, and easy to perform. The upstream air was humidified at room temperature to avert drying and subsequent irritation of the nasal mucosa. The method is simple and requires only the measurement of pressure at the entrance of the nasal passage. The downstream pressure is assumed to be atmospheric pressure. This assumption is valid provided that the soft palate does not obstruct the output airflow from the

Fig. 4. In 5 ragweed-sensitized dogs, intranasal ragweed challenge caused dramatic decrease in nasal airway volume (VNA) of the right nasal airway; this effect was reversed by D-pseudoephedrine but not by saline administered intranasally 20 min after ragweed challenge (A). Neither in 3 sham-sensitized nor in 2 nonsensitized dogs were significant changes in VNA observed after ragweed challenge followed by saline in 20 min (B). *P < 0.05 compared with baseline value; #P < 0.05 compared with value at 20 min after ragweed challenge.

Fig. 5. Orally administered D-pseudoephedrine, but not placebo pretreatment, prevented a development of severe nasal congestion after intranasal antigen delivery to ragweed-sensitized dogs. In sensitized dogs, however, $R_{NA}$ did not change significantly after saline challenge. In placebo-pretreated nonsensitized dogs, intranasal ragweed challenge failed to produce any significant congestion. Arrow marks the time that ragweed extract or saline was administered intranasally. *P < 0.05 compared with the sensitized dogs: D-pseudoephedrine + ragweed group; #P < 0.05 compared with the nonsensitized dogs: placebo + ragweed group; **P < 0.05 compared with the sensitized dogs: placebo + saline group.
The increase in $R_{\text{NA}}$ revealed significant nasal congestion in sham-sensitized dogs, whereas acoustic rhinometry showed no significant changes in the geometrical parameters of nasal lumen in these dogs. The ability to detect changes in $R_{\text{NA}}$ when changes in acoustic rhinometry may not be evident could be related to the fact that the resistance is proportional to the fourth power of the radius of an airway, whereas the CSA increases with the square of this dimension. The acoustic rhinometry measurements suggest that, although the nasal valve represents the area of highest resistance to airflow, the main site of airway constriction caused the observed increases in $R_{\text{NA}}$ and was located within the region of the maxilloturbinates. In our preparation, any influence of the nasal valve on $R_{\text{NA}}$ was excluded by the presence of the endonasal tube, the open end of which protruded a few millimeters beyond the nasal valve. It is notable that the acoustic measurements conducted in the contralateral nasal passage also revealed no significant changes in CSAs of the nasal valve throughout the study. This can be ascribed to the fact that ragweed was administered to the nasal passage through the Micro Sprayer catheter, the tip of which was inserted through the nasal valve to a position of 2.0–2.5 cm distal to the naris. Thus, by using this technique, ragweed was delivered distally to the nasal valve with the result that the CSA of the nasal valve remained essentially unchanged throughout the experiments.

All the ragweed-sensitized dogs previously demonstrated anaphylactic responses to ragweed challenge to the lungs, whereas the sham-sensitized dogs demonstrated little, if any, responses to these doses of ragweed extract (27). It is notable that, despite the lack of ragweed challenges for 5–6 yr, there were marked ragweed-induced increases in $R_{\text{NA}}$ obtained in four of five sensitized dogs. This confirms the general nature and long duration of the allergic sensitivity induced in this model. That sham-sensitized dogs responded to the intranasal application of ragweed antigen with a marked increase in $R_{\text{NA}}$ was unexpected. The responses in the sham-sensitized dogs were likely due to the adjuvant-induced increase in nonspecific hyperreactivity and/or due to some degree of specific hypersensitivity developed after multiple exposures of their lungs to ragweed challenge. Thus these dogs could not serve an appropriate immunonegative control to demonstrate the immune nature of responses to ragweed. The nasal passages of nonsensitized dogs previously unexposed to any specific antigen, however, did not respond to ragweed challenge. Thus we conclude that the ragweed-induced responses in the sensitized dogs occurred as a result of the activation of immune mechanism(s). Other investigators have described the development of allergic sensitivity of the nasal mucosa to ragweed after neonatal intraperitoneal sensitization procedures similar to those performed in the ragweed-sensitized dogs used herein (4).

The absolute values of $R_{\text{NA}}$ measured under the basal conditions by use of our method ($7.8 \pm 1.8 \text{ cmH}_2\text{O} \cdot \text{L}^{-1} \cdot \text{s}$) are lower than those reported by Lung et al. (10).
for sodium pentobarbital-anesthetized greyhounds and mongrel dogs (23.4 ± 1.6 cmH$_2$O·l$^{-1}$·s$^{-1}$). This fact could be ascribed to methodological differences between our studies: 1) the use of different anesthetics and 2) active anterior rhinomanometry (in our study) vs. posterior rhinomanometry (in Ref. 10). Not surprisingly, our values of unilaterally measured $R_{NA}$ in beagle dogs are somewhat higher than those reported for humans by Davies and Eccles (5) (from 3.25 ± 0.25 to 9.96 ± 1.44 cmH$_2$O·l$^{-1}$·s$^{-1}$) and Birchall et al. (3), who have shown that, in humans, topical administration of histamine causes an increase in $R_{NA}$ from the basal level of 3.1 ± 0.52 to 8.81 ± 2.09 cmH$_2$O·l$^{-1}$·s$^{-1}$.

The acoustic rhinometry measurements of $V_{NA}$ (12.4 ± 1.9 cm$^3$) in our 9.5–14.5 kg dogs compare favorably with the $V_{NA}$ of 13.5 ± 1.0 cm$^3$ measured in 9.0–11.0 kg conscious dogs by Koss et al. (7) rather than with the 7.2 ± 0.5 cm$^3$ measured when these dogs were anesthetized with thiopental. The anesthetic regime (propofol + etomidate, iv) used herein likely maintains sympathetic vasomotor tone better than the barbiturate used in aforementioned work. Propofol is about twofold less a potent inhibitor of sympathetic mechanisms and cardiovascular function than thiopental (1). Introduction of etomidate (5 µg·kg$^{-1}$·min$^{-1}$ iv) in the anesthetic regime enabled the reduction in the dose of propofol to 450–550 µg·kg$^{-1}$·min$^{-1}$. Etomidate is known to maintain hemodynamic stability through the preservation of both sympathetic outflow and autonomic reflexes (6). Aono et al. (1) have reported that etomidate stimulates the carotid bodies as well as the sympathetic nervous system. Thus the anesthetic regime described herein could provide better vasomotor control and thus reduce the substantial decreases in $V_{NA}$ observed in barbiturate-anesthetized dogs.

The measurement of $R_{NA}$ using our modification of anterior constant-flow rhinomanometry appears to be a simple, practical, and sensitive method for assessment of nasal airway patency. The method is relatively noninvasive and allows multiple experiments in the same cohort of dogs. In our modification, rhinomanometry can be easily combined with other diagnostic methods (i.e., acoustic rhinometry, nasal lavage, etc.). This provides more detailed information about the present condition of nasal passages. Our model of allergic rhinitis described herein is relevant to human disease (27) and thus can be successfully used in the exploration of a wide range of research tasks, particularly in the identification of novel therapeutic target sites and the pharmacological screening of newly developed topically or systemically administered antiallergic drugs.

Fig. 7. Temporal changes in cross-sectional areas of right nasal airway in placebo-pretreated ragweed-sensitized dogs after ragweed challenge (A); placebo-pretreated ragweed-sensitized dogs after saline challenge (B); D-pseudoephedrine-pretreated ragweed-sensitized dogs after ragweed challenge (C); and placebo-pretreated nonsensitized dogs after ragweed challenge (D).
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