

Association of expiratory airway dysfunction with marked obesity in healthy adult dogs

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Objective—To evaluate the effects of obesity on pulmonary function in healthy adult dogs.

Animals—36 Retrievers without cardiopulmonary disease.

Procedures—Dogs were assigned to 1 of 3 groups on the basis of body condition score (1 through 9): nonobese (score, 4.5 to 5.5), moderately obese (score, 6.0 to 6.5), and markedly obese (score, 7.0 to 9.0). Pulmonary function tests performed in conscious dogs included spirometry and measurement of inspiratory and expiratory airway resistance (R_{aw}) and specific R_{aw} (sR_{aw}) during normal breathing and during hyperpnea via head-out whole-body plethysmography. Functional residual capacity (FRC; measured by use of helium dilution), diffusion capacity of lungs for carbon monoxide (DLCO), and arterial blood gas variables (P_{aO_2} , P_{aCO_2} , and alveolar-arterial gradient) were assessed.

Results—During normal breathing, body condition score did not influence airway function, DLCO, or arterial blood gas variables. During hyperpnea, expiratory sR_{aw} was significantly greater in markedly obese dogs than nonobese dogs and R_{aw} was significantly greater in markedly obese dogs, compared with nonobese and moderately obese dogs. Although not significantly different, markedly obese dogs had a somewhat lower FRC, compared with other dogs.

Conclusions and Clinical Relevance—In dogs, obesity appeared to cause airflow limitation during the expiratory phase of breathing, but this was only evident during hyperpnea. This suggests that flow limitation is dynamic and likely occurs in the distal (rather than proximal) portions of the airways. Further studies are warranted to localize the flow-limited segment and understand whether obesity is linked to exercise intolerance via airway dysfunction in dogs. (*Am J Vet Res* 2007;68:670–675)

Obesity is widely recognized as the most prevalent nutritional disease in dogs, for which the reported incidence is 21.4% to 28.0%.¹⁻³ Research studies⁴⁻⁶ have revealed a variety of deleterious effects of obesity in dogs, including increased incidence of orthopedic disease, shortened lifespan, and risk of death as a result of pancreatitis. Dogs of all breeds can become obese, but there is the clinical impression that some breeds are at higher risk, including Retriever breeds.

Obesity is also common in humans, and the incidence has risen dramatically over the past 20 years.⁷ Obesity increases the risk of death from all causes, is linked to increased risk of development of hypertension and type 2 diabetes mellitus,⁷ and negatively impacts cardiovascular^{8,9} and pulmonary functions.¹⁰⁻¹²

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ABBREVIATIONS

FRC	Functional residual capacity
R_{aw}	Airway resistance
BCS	Body condition score
sR_{aw}	Specific airway resistance
TV	Tidal volume
PIF	Peak inspiratory flow
PEF	Peak expiratory flow
DLCO	Diffusion capacity of lungs for carbon monoxide
A-a	Alveolar-arterial
MV	Minute ventilation

Specifically, obesity in people results in decreased FRC, increased R_{aw} , decreased lung compliance, and hypoxemia at rest.¹³ Additionally, obstructive sleep apnea occurs more frequently with obesity because obesity is associated with increased pharyngeal fat deposits that cause airflow limitation during sleep.¹⁴

To our knowledge, the specific effects of obesity on the respiratory system in dogs have not been described, although it has been reported^{3,a} that weight loss is associated with improved respiratory function in obese dogs. Further insight into the effects of obesity on pulmonary mechanics and gas exchange is needed and may provide an impetus for weight loss. The purpose of the study reported here was to evaluate the effects of

obesity on pulmonary function in healthy adult dogs. Our hypothesis was that obesity in Retriever breeds causes mechanical dysfunction of the airways and, in particular, that obesity results in increased R_{aw} during both inspiration and expiration in the absence of ventilatory limitations or hypoxemia.

Materials and Methods

The project was approved by the Institutional Animal Care and Use Committee of the Cummings School of Veterinary Medicine at Tufts University. Informed consent was obtained from owners prior to enrollment of dogs in the study.

Dogs—Privately owned Retrievers (Labrador, Golden, Flat-Coated, Chesapeake Bay, or Curly Coated Retrievers) were eligible for recruitment. Retriever breeds were selected because of their similarities in size, body conformation, and good nature. Additionally, they are popular pets among students and staff at Tufts University, which was considered helpful in recruiting dogs for the study. Inclusion criteria included age > 1 year, no abnormalities detected via physical examination, and a cooperative nature. Two orthogonal thoracic radiographic views were obtained to exclude occult pulmonary or cardiac disease. Exclusion criteria included historical or physical evidence of cardiopulmonary disease, audible upper airway noise at rest or during exercise as reported by owner, or any abnormal thoracic radiographic findings. Eligible dogs were weighed, and their BCS was evaluated by use of a scale of 1 through 9¹⁵ by one of the authors (DLC), who had no knowledge of pulmonary function data for any dog. Dogs were grouped on the basis of their BCS as nonobese (score, 4.5 to 5.5), moderately obese (score, 6.0 to 6.5), or markedly obese (score, 7.0 to 9.0).

Pulmonary function tests—Pulmonary function was measured by use of head-out whole-body plethysmography as previously described.^{16,17} The technique of head-out whole-body plethysmography required the dog to sit in a whole-body plethysmograph with its head and entire neck exteriorized through a hole in a flexible rubber seal (derived from a dry-suit neck piece), which, when stretched by the dog's lower portion of the neck and shoulders, affixed the seal in place. With the head exteriorized, dogs were fitted with a solid plastic face mask with its own latex seal (positioned 5 to 8 cm behind the external nares). The properties of the plethysmographic chamber (box) have been previously described.^{16,17} Briefly, the interior volume of the box was 330 L, the time constant for pressure decay to 36% peak was 12 seconds, and conditions were adiabatic across all respiratory frequencies without evidence of pressure attenuation across input frequencies ranging 1 to 5 Hz. Box pressure was measured by use of a differential pressure transducer,^b strain gauge amplifier,^c analogue-to-digital card,^d and commercial data acquisition software.^e The box pressure transducer was referenced to atmospheric pressure and calibrated into units of volume change (box volume or V_{box}) by injection of a known volume (60 mL) into the chamber. Flow at the proximal nares (V'_{pn}) was measured by use of a

low-resistance pneumotachograph,^f carrier demodulator amplifier,^g analogue-digital card,^d and commercial software^e as described. Flow was calibrated by injecting a known gas volume through the pneumotachograph and matching the integral of flow with that volume. Head-out whole-body plethysmography therefore permitted the simultaneous measurement of flow-derived variables (ie, spirometry) and V_{box} , which were used together to compute sR_{aw} . These measurements were made during episodes of apparently normal breathing and during progressive hyperpnea that was induced by allowing the dog to rebreathe into connector tubing (dead space, 1.5 L) between the facemask-pneumotachograph assembly and plethysmographic chamber. Specific airway resistance was measured according to the method of Agrawal¹⁸ that was later adapted for conscious dogs by Bedenice et al.¹⁶ Briefly, V'_{pn} was plotted against V_{box} to form the y-axis and x-axis, respectively. The plots formed a polygon with the vertically oriented slopes of interest used to measure the slope (θ) during the transition from inspiration to expiration (−0.4 to +0.4 L/s), allowing computation of inspiratory sR_{aw} , and the slope during the transition from expiration to inspiration (+0.4 to −0.4 L/s), allowing computation of expiratory sR_{aw} (Figure 1). Slopes were measured for 5 representative breaths during normal breathing and 5 breaths during hyperpnea. Measurements were made manually on printouts by use of a standard protractor with accuracy to within 0.5°. Only breaths free from artifacts (such as drift in V_{box} movements or laryngeal artifacts, including swallowing, vocalization, or breath holding) were included. Specific airway resistance was computed by use of the following formula¹⁸:

$$sR_{aw} = 1/\tan\theta \times (P_B - P_{H_2O}) \times Cf \times ([V_{box} - \text{body weight}]/V_{box})$$

where angle θ is the slope in radians of the inspiratory or expiratory segments, P_B is barometric pressure, P_{H_2O} is water vapor pressure at body temperature, and

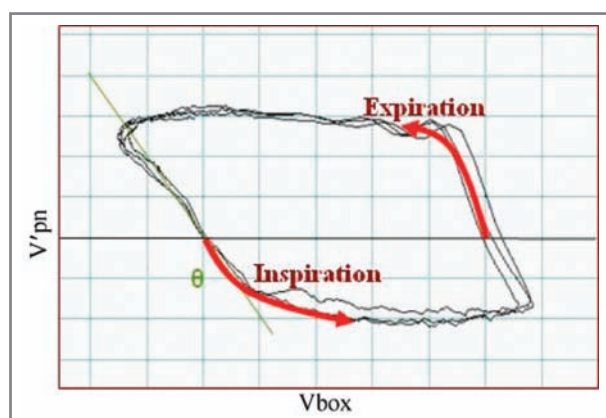


Figure 1—Representative box volume (V_{box}) versus flow (V'_{pn}) plot obtained from a nonobese Retriever via plethysmography. The plot was used to calculate the expiratory angle (θ_e) and the inspiratory angle (θ_i). $\tan \theta$ is the slope of the V_{box} - V'_{pn} plot measured during the transition phase from expiration to inspiration (expiratory slope of θ_e) or inspiration to expiration (inspiratory slope of θ_i).

Cf is the correction factor for paper size (defined as the arithmetic ratio of values recorded between equal distances [4 cm] on the x- and y-axes). Airway resistance values during inspiration and expiration were obtained by dividing the respective sR_{aw} values by FRC as measured by use of helium dilution. Standard flow-derived variables were recorded including minute volume, TV, total inspiratory time, total expiratory time, PIF, and PEF; their respective ratios (total expiratory time-to-total inspiratory time and PEF:PIF ratios) were calculated. All values (sR_{aw} and flow-derived variables) were recorded during the initial period of normal breathing (30 seconds) and after 1 minute during the development of hyperpnea (defined as minute volume > 200% of initial value). The definition of hyperpnea was arbitrary. The mean value from 5 breaths was used for analysis.

Functional residual capacity and DLCO were measured separately by use of rebreathing techniques.¹⁹ The test gas for these assessments was comprised of 10% helium, 0.3% carbon monoxide, 21% oxygen, and a balance of nitrogen. All tests were performed in duplicate, and the values were averaged unless they exceeded a 10% difference, in which case a third test was performed until 2 test results were similar (ie, < 10% difference). A blood sample was obtained from a dorsal pedal or femoral artery for arterial blood gas analyses,^h and the A-a gradient was calculated by use of the following equation:

$$\text{A-a gradient} = (150 - [\text{Paco}_2/0.8]) - \text{PaO}_2$$

Statistical analysis—Data were normally distributed. Analyses of variance and Student-Newman-Keuls tests were used to compare inspiratory and expiratory sR_{aw} and R_{aw} and flow-derived variables among groups during normal breathing and hyperpnea. A paired *t* test was used to discern differences between data obtained during normal breathing and hyperpnea. Analyses of variance and Student-Newman-Keuls tests were also used to compare arterial blood gas results, DLCO, and FRC among groups. All data analyses were performed with commercial statistical software.ⁱ A value of $P \leq 0.05$ was considered significant.

Results

Thirty-nine dogs were evaluated for possible enrollment in the study. Three dogs did not participate in the study: 1 because of noncompliance, 1 because of audible inspiratory stridor, and 1 because of cardiac disease and pleural effusion. Therefore, the study population was comprised of 36 dogs. Among those dogs, breeds included Labrador Retriever ($n = 28$), Golden Retriever (7), and Chesapeake-Bay Retriever (1). Median age for all dogs was 4 years (range, 1 to 10 years), and median body weight was 33.6 kg (range, 21.0 to 46.8 kg). On the basis of the BCS, 11 dogs were assigned to the nonobese group, 14 were assigned to the moderately obese group, and 11 were assigned to the markedly obese group. No dogs with a BCS > 8 were identified in this study. For the nonobese dogs, median age was 4 years (range, 1 to 9 years); for the moderately obese dogs, median age was 3 years (range, 1 to 10 years); and for the markedly obese dogs, median age was 6 years (range, 2 to 9 years). Age and obesity category were not correlated ($P = 0.429$).

During normal tidal breathing at rest, there was no significant difference in sR_{aw} or R_{aw} values among BCS groups; however, during expiration, the R_{aw} value in the markedly obese dogs was greater than that in other groups, albeit not significantly (Table 1). During hyperpnea, the sR_{aw} value measured during expiration in the markedly obese group was significantly greater than the value in the nonobese group. Similarly, during hyperpnea only, R_{aw} during expiration was significantly increased in markedly obese dogs, compared with values for moderately obese and nonobese dogs.

There was no significant difference in flow-derived values between groups (Table 2). However, as anticipated, there were significant differences in MV, TV, PIF, and PEF during normal breathing and during hyperpnea when data from all dogs were assessed together.

Arterial blood gas results (PaO_2 , Paco_2 , and A-a), FRC, and DLCO, measured only during normal breathing at rest, were not significantly different among groups, although mean FRC in markedly obese dogs was somewhat lower than values in the other 2 groups. The FRC per kilogram value was significantly lower in markedly obese dogs, in contrast to values in moderately obese and nonobese dogs (Table 3).

Table 1—Mean \pm SD values of sR_{aw} and R_{aw} obtained during apparently normal breathing (baseline) and hyperpnea from Retrievers that were classified by BCS as nonobese ($n = 11$), moderately obese (14), or markedly obese (11).

Condition	Group	sR_{aw} (cm H ₂ O/s)		R_{aw} (cm H ₂ O/L/s)	
		Inspiratory	Expiratory	Inspiratory	Expiratory
Normal breathing (baseline)	Nonobese	6.11 \pm 2.5	8.16 \pm 2.1	4.45 \pm 2.6	6.03 \pm 3.0
	Moderately obese	6.8 \pm 2.6	9.02 \pm 4.3	5.34 \pm 2.2	6.93 \pm 3.4
	Markedly obese	5.41 \pm 3.0	11.36 \pm 5.8	4.81 \pm 3.1	9.81 \pm 5.6
	<i>P</i> value	0.438	0.186	0.692	0.075
Hyperpnea	Nonobese	7.2 \pm 2.3	8.3 \pm 1.0 ^a	5.4 \pm 3.4	6.1 \pm 2.2 ^a
	Moderately obese	8.3 \pm 2.1	11.1 \pm 4.6 ^{a,b}	6.5 \pm 2.0	8.7 \pm 3.6 ^a
	Markedly obese	7.5 \pm 4.8	15.3 \pm 7.4 ^b	6.7 \pm 4.7	13.2 \pm 6.6 ^b
	<i>P</i> value	0.665	0.009	0.661	0.002

^{a,b}During hyperpnea, values of a variable with different superscript letters are significantly ($P < 0.05$) different.

Table 2—Mean \pm SD values of flow-derived variables obtained during normal breathing (baseline) from Retrievers that were classified by BCS as nonobese (n = 11), moderately obese (14), or markedly obese (11) and from the entire study population (n = 36 dogs) during apparently normal breathing and during hyperpnea.

Condition	Group	MV (L)	TV (L)	PIF (L/s)	PEF (L/s)	Frequency (breaths/min)
Normal breathing (baseline)	Nonobese	19.0 \pm 7.9	0.46 \pm 0.14	0.98 \pm 0.31	1.03 \pm 0.30	43.2 \pm 14.8
	Moderately obese	23.2 \pm 9.1	0.46 \pm 0.17	1.12 \pm 0.27	1.26 \pm 0.35	54.5 \pm 21.4
	Markedly obese	20.7 \pm 5.7	0.45 \pm 0.20	1.07 \pm 0.32	1.07 \pm 0.32	52.9 \pm 16.5
	P value	0.418	0.991	0.494	0.193	0.296
Normal breathing	All dogs	21.2 \pm 7.8	0.46 \pm 0.16	1.06 \pm 0.30	1.13 \pm 0.33	49.2 \pm 17.8
Hyperpnea	All dogs	44.1 \pm 16.5	0.95 \pm 0.25	2.23 \pm 0.64	2.59 \pm 0.86	50.6 \pm 18.3
	P value	< 0.001	< 0.001	< 0.001	< 0.001	0.764

Table 3—Mean \pm SD values of P_{aO_2} , P_{aCO_2} , A-a, DLCO, and FRC obtained during normal breathing (baseline) from Retrievers that were classified by BCS as nonobese (n = 11), moderately obese (14), or markedly obese (11).

Variable	Group			P value
	Nonobese	Moderately obese	Markedly obese	
P_{aO_2} (mm Hg)	90.9 \pm 7.8	94.2 \pm 7.7	90.8 \pm 8.2	0.548
P_{aCO_2} (mm Hg)	29.9 \pm 3.1	28.5 \pm 3.0	28.8 \pm 3.6	0.543
A-a	21.8 \pm 6.4	20.2 \pm 6.5	23.2 \pm 5.3	0.473
DLCO (mL/min/mm Hg)	32.4 \pm 8.2	34.6 \pm 14.8	26.8 \pm 13.8	0.316
FRC (L)	1.5 \pm 0.35	1.3 \pm 0.21	1.2 \pm 0.25	0.068
FRC/kg (mL)	47.5 \pm 8.2 ^a	40.0 \pm 3.3 ^a	31.4 \pm 6.7 ^b	< 0.001

^{a,b}Values of a variable with different superscript letters are significantly ($P < 0.05$) different.

Discussion

To our knowledge, results of the present study are the first indication of respiratory dysfunction in association with naturally occurring obesity in dogs. Our hypothesis, that obesity in Retriever breeds causes mechanical dysfunction of the airways, thereby increasing resistance during both inspiration and expiration in the absence of hypoxemia, was partially supported by these data. In markedly obese dogs, there was a 2-fold increase in expiratory resistance (sR_{aw} or R_{aw}) during hyperpnea, compared with findings during normal breathing at rest. During normal breathing at rest, effects on pulmonary mechanisms or gas exchange (including DLCO) were not detected in those markedly obese dogs, suggesting that airway dysfunction is an isolated problem. Similar findings of impaired pulmonary function in obese humans have been reported.^{10-12,20} In a study¹⁰ of 46 healthy subjects, respiratory system resistance (determined via the forced oscillation technique) and R_{aw} (determined via body plethysmography) increased significantly with the degree of obesity, and these effects were independent of differences in thoracic-wall resistance. Following weight loss in obese persons with asthma, there was a significant reduction in R_{aw} ¹¹ and significant increases in vital capacity, expiratory reserve volume, and forced expiratory volume in 1 second.²⁰ Airflow limitation and air trapping have been identified in obese humans.²¹ Our data are compatible with those findings because airflow limitation (ie, increased expiratory R_{aw}) was evident in markedly obese dogs during hyperpnea, when alveolar pressure gradients are the greatest. The interaction between lung volume (ie, FRC) and R_{aw} is worth

mentioning. Because R_{aw} is inversely proportional to lung volume ($R_{aw} = sR_{aw}/FRC$), the fact that FRC appeared to decrease as the degree of obesity increased in the study dogs (although these changes were not significant) may have contributed to increased R_{aw} . However, the change in R_{aw} exceeded the expected effect of a lower FRC, which suggests that the change in airway resistance may have been multifactorial. An alternative explanation for the effects of obesity that are volumetric by nature might be the reduced ability (or willingness) to perform routine deep inspirations, which are known to dilate the airways.²² Further studies that characterize the tidal breathing pattern longitudinally in obese versus nonobese dogs would therefore be of interest.

In contrast, on the basis of our study findings, the hypothesis regarding resistance of airways during inspiration was partially refuted. Reasons for the lack of increase in inspiratory R_{aw} could include the possibility that obesity may not affect the upper airways, the lack of severely obese individuals in the study population, or a lack of sensitivity of the methods used.

In addition to effects of obesity on airway function in humans, there are reports^{10,13,20} of decreased lung volumes (values of FRC, vital capacity, expiratory reserve volume, and total lung capacity) in obese humans. Similarly, lung volumes in asthmatic and nonasthmatic individuals are known to increase following weight loss.^{11,20} In the study of this report, markedly obese dogs appeared to have lower FRC values, compared with moderately obese and nonobese dogs; although these differences were not significant, they may have been if severely obese dogs had been recruited. Functional residual capacity should be re-evaluated in obese dogs following weight loss to de-

termine whether their lung volumes also increase, as occurs in humans.

Obesity may lead to dynamic changes in airway diameter or airway compliance, which at high flow rates would be expected to cause turbulence. In contrast to theories concerning the effects of obesity on R_{aw} through alterations in lung volume or breathing pattern, there are other suggested causes of increased R_{aw} values in obese humans that are based on recognition of obesity as a proinflammatory condition. Circulating concentrations of several inflammation-associated cytokines (eg, tumor necrosis factor- α ; transforming growth factor- β ; and interleukin- β , -6, -8, and -10) and acute phase proteins (eg, C-reactive protein and haptoglobin) are increased in obese mice as well as in people.²³ It is possible that increased levels of inflammation (caused by various factors) could contribute to airway inflammation and, subsequently, increased R_{aw} . In 1 study,²⁴ obese mice had greater airway hyperresponsiveness to ozone or methacholine, compared with nonobese mice; after those exposures, the obese mice had greater increases in concentrations of inflammatory markers in bronchoalveolar lavage fluid than those detected in samples from nonobese mice. On the basis of epidemiologic and research data, there is strong support for a relationship between obesity and asthma in humans—the development of obesity precedes the development of asthma.²⁴ As in humans, circulating concentrations of particular adipokines are increased in obese dogs, compared with nonobese dogs. For example, plasma leptin concentrations have been positively correlated with body-fat content in dogs.^{25,26} More recently, circulating concentration of adiponectin (an important regulatory cytokine) has been negatively correlated with obesity in dogs.²⁷ Future work in this area may increase our understanding of the influences of obesity and inflammation on airway dysfunction. Evaluation of cytokines (eg, leptin, adiponectin, tumor necrosis factor- α , and interleukins) and acute phase reactants (eg, C-reactive protein and haptoglobin) in obese and nonobese dogs may provide evidence to support the suggestion that obesity is also an inflammatory condition. These cytokines and acute phase reactants may serve as markers of disease.

Plethysmography appeared to more precisely detect the airway effects of obesity than assessments of simple flow-derived variables in the present study, which is supported by results of a previous research investigation¹⁶ that examined external resistive loads in dogs and dogs with naturally occurring laryngeal paralysis. Further application of plethysmography to monitor clinical cases (ie, dogs with chronic bronchitis, pulmonary neoplasia, or bacterial pneumonia) should be interpreted in light of the patient's obesity and BCS. Repeated measures of sR_{aw} , R_{aw} , and lung volume (FRC/kg) within an individual may be affected considerably by changes in body weight. The effects of obesity on airway function during exercise and determination of potential improvement of R_{aw} with weight reduction should be further studied, and the selected study populations should include breeds other than Retrievers and more severely obese dogs than those used in the study reported here.

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