PART THREE

Pulmonary Function Testing

CHAPTER 23

Pulmonary Mechanics

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Introduction

Pulmonary function testing is routinely used in human medicine to objectively characterize functional deficits in patients with respiratory disease. In veterinary medicine, although respiratory diseases are a common problem, diagnostic testing is largely limited to localizing disease to and within the respiratory system and to identifying underlying infectious or neoplastic processes. With the exception of blood gas analysis, testing methods to identify specific pathophysiological processes or to define disease severity and progression on a functional basis are not routinely available. Yet this is precisely the information needed to advance our knowledge of some of the more challenging respiratory disease syndromes in small animals (e.g., canine chronic bronchitis,[1] feline bronchopulmonary disease,[2] and chronic interstitial or fibrotic lung disease[3-6]). Just imagine how difficult it would be to manage a patient with diabetes mellitus, renal disease, or hepatic disease without the ability to monitor changes in blood glucose, urea nitrogen, or bile acids, respectively. Analogously, if pulmonary function tests (PFTs) were more widely available, we could objectively evaluate the small animal respiratory patient. In turn, we could better define clinical spectrums of disease and characterize the underlying etiologies and disease mechanisms. Most important, we could monitor natural disease progression (or resolution) and better assess the efficacy of specific treatment protocols.

Part of the difficulty in using PFTs in veterinary clinical medicine is that companion animals are by nature uncooperative and therefore difficult to study using standard spirometric approaches that were developed for adult human beings. Although spirometric testing is noninvasive, rapid, and easy to perform on awake hu-

man subjects, procedures such as maximal expiratory maneuvers require a level of conscious cooperation that is simply not possible in animals.

Nevertheless, a wealth of information exists on the lung mechanical properties of cats and dogs. Nearly 100 articles have been published assessing pulmonary function in the cat, and an equivalent database exists in the dog. In physiology studies, for example, cats have been used extensively to define key reflexes involved in the control of breathing and to determine lung and airway smooth muscle responses to bioactive mediators and pharmaceutical agents.[7,8] In toxicology studies, cats and dogs exposed to inhaled substances (e.g., environmental tobacco smoke, sulfur dioxide,[9] ozone,[10] and diesel exhaust[11]) have undergone pulmonary function testing to establish the toxicity of these agents. As animal models of human lung disease, cats and dogs with experimentally induced pathology (e.g., allergic pneumonitis or bronchitis, [12-15] viral-mediated bronchiolitis,[16-18] or surfactant deficiency[19,20]) have undergone functional assessments to establish the efficacy of new drugs or ventilatory support techniques. With few exceptions, however, it has not been possible to incorporate these experimental testing procedures into veterinary clinical medicine because they include the use of nonrecoverable anesthetics (such as urethane) or unacceptably invasive procedures such as tracheostomy placement or pleural space cannulization.[21]

A few individuals have sought to modify these techniques such that meaningful, albeit somewhat more limited, functional information can be obtained from companion animals. In this chapter we will present some of these approaches, focusing on those that are most applicable for routine clinical use: tidal breathing flow-volume loop assessments; and measures of upper airway resistance, lung resistance, and static or dynamic lung compliance.

Knowledge of basic respiratory physiology is essential in order to understand how PFTs can aid in the diagnosis and management of respiratory disease in small animals. To begin, we will review the basic processes related to movement of air in and out of the respiratory tract under normal conditions. We will then discuss how these processes are disrupted by disease, emphasizing relationships between structural pathological changes and corresponding functional deficits. Brief descriptions of the methods and instrumentation required, advantages and disadvantages of certain procedures, and limitations of data interpretation are included. We will use case examples and, where available, information from clinical studies in cats and dogs to emphasize the utility of these assessments in veterinary medicine. Lastly, we will discuss obstacles that must be overcome as we look towards more routine use of PFTs in the future, in particular the need to standardize testing procedures and to establish appropriate reference ranges. Recent advances in lung function testing in human infants will be explored because pediatric patients, not unlike cats and dogs, are often uncooperative and difficult to study. Therefore some of the same approaches may prove useful for evaluation of the small animal patient.

Respiratory Physiology

The simple act of taking a breath is an amazingly coordinated process. The purpose of breathing is to provide adequate gas exchange for the animal's current metabolic demand, no more and no less. In health, this is accomplished very efficiently. In fact, the average small animal patient takes 10,000 to 30,000 breaths every day without any real effort or thought as to how this is happening. But as disease develops, the respiratory system becomes less efficient and the respiratory muscles must work harder to compensate for this inefficiency. The ability to appreciate or detect respiratory disease in small animals depends on the extent of disease, as well as the activity level of the patient. Incipient disease is often unappreciated by the owner because the animal either minimizes its activity or compensates by subtly altering its breathing pattern and frequency when necessary. As disease progresses, respiratory inefficiency becomes more apparent, especially during periods of increased metabolic demand, and the patient may be presented for exercise intolerance. By the time an animal is presented at rest but with excessively labored respiration, it is clearly in overt respiratory distress. It may be unclear whether the patient has developed acute, fulminant disease, or whether it is experiencing an acute exacerbation of long standing but heretofore occult disease. Many animals effectively hide their illness until critically low levels of lung reserve remain. More routine use of PFTs in veterinary medicine may permit earlier recognition of disease, allowing therapeutic intervention prior to the establishment of chronic, likely irreversible changes.

How does air flow in and out of the lungs of healthy animals with such efficiency? Normally, the elastic and resilient lung is tethered within the thoracic cavity by a thin layer of pleural fluid. The lung's size and shape readily conforms to that of the more rigid chest wall and diaphragm. During resting or tidal breathing, inspiration is initiated as the diaphragm flattens and the chest wall expands outward. In so doing, the lung parenchyma is expanded, and with it the alveolar spaces and small conducting airways become somewhat distended both in length and diameter. Conversely, as the lung collapses during expiration, there is a dynamic narrowing of the small airways. By contrast, the diameter of the nasal passageways, trachea, and larger airways (bronchi) remains relatively unchanged under normal conditions.

The total amount of air moving in and out of the lung during tidal breathing is referred to as the tidal volume (TV or V_T). The breathing frequency (*f;* breaths/minute or bpm) multiplied by the TV (ml/breath) is equal to the minute volume (MV; ml/minute). At rest, dogs and cats normally breathe nasally. Hence during a typical ventilatory cycle, air must first pass through the nares, then through the nasal passageways and nasopharynx, through the laryngeal opening, continuing into the tracheobronchial tree where it traverses a series of ever-narrowing tubes until at last it reaches the alveolar space, the site of gas exchange. The flow of air is, of course, reversed during expiration. In all mammalian

lungs, the O_2-rich inspired air must traverse through the same series of tubes as the CO_2-enriched expired air, and there is continual mixing of new and spent air in the process. Nevertheless, in health, an animal is able to effectively transport sufficient quantities of air to and from the alveolar units to maintain relatively constant O_2 and CO_2 partial pressures within arterial blood. Blood gas analysis allows assessment of the efficiency of gas exchange, considering the lung as one large ventilatory unit. Decreases in arterial O_2 concentrations (hypoxemia) may be detected with or without concurrent increases in CO_2 retention and are associated with hypoventilation, alveolar diffusion impairment, shunts, or ventilation-perfusion mismatch.[22] Such data are complementary to that obtained by pulmonary functional assessments.

By dividing a breath into its component inspiratory and expiratory phases, each phase can be characterized by changes in three parameters: volume, airflow, and pressure. Figure 23-1 is a schematic depicting the changes occurring over a complete ventilatory cycle in a healthy adult cat. For obvious reasons, on average the volume of inspired air must equal that of the expired air. By definition, lung volume increases during inspiration (becomes positive) and decreases during expiration (Figure 23-1, *A*). Airflow describes the volume of air moving in (or out) of the lung over a specific time (ml/sec) (Figure 23-1, *B*). By convention, inspiratory flow rates are often given negative values, although absolute values may also be used. In cats and dogs, the peak inspiratory flow (PIF) typically occurs in mid- to late inspiration, after which the flow rate rapidly returns to zero, thus marking the end of inspiration. Airflow quickly reverses direction (becomes positive) and the maximal or peak expiratory flow (PEF) occurs in early to midexpiration. The flow rate then gradually decreases until the end of the breath.

The pressure changes depicted represent the differential pressures that develop between the atmosphere and the various regions of the thoracic cavity (e.g., the alveolar space or the pleural space) (see Figure 23-1, *C* and *D*). Note that as the chest wall and lungs expand during inspiration, the alveolar pressure drops below zero due in part to frictional resistance generated as the air flows through the air passageways. Note also that the pleural space pressure remains somewhat negative even at the end of expiration (see Figure 23-1, *D*). The solid symbols depict shifts in the actual pressure curve that occur due to the elasticity of the lung parenchyma.

Owing to cyclic generation of these pressure gradients, air from more proximal regions of the respiratory tract moves deeper and deeper into the lung and back out again, over and over. In health, relatively small pressure gradients are required to effectively transport sufficient quantities of air to and from the alveolar spaces. In fact, normally at the end of expiration, a small volume of air remains in the alveoli due to the slightly negative end-expiratory intrapleural pressure mentioned above (see Figure 23-1, *D*), thereby helping to prevent collapse of the tiny alveolar gas exchange units between breaths. In turn, the alveolar septa are held under a certain de-

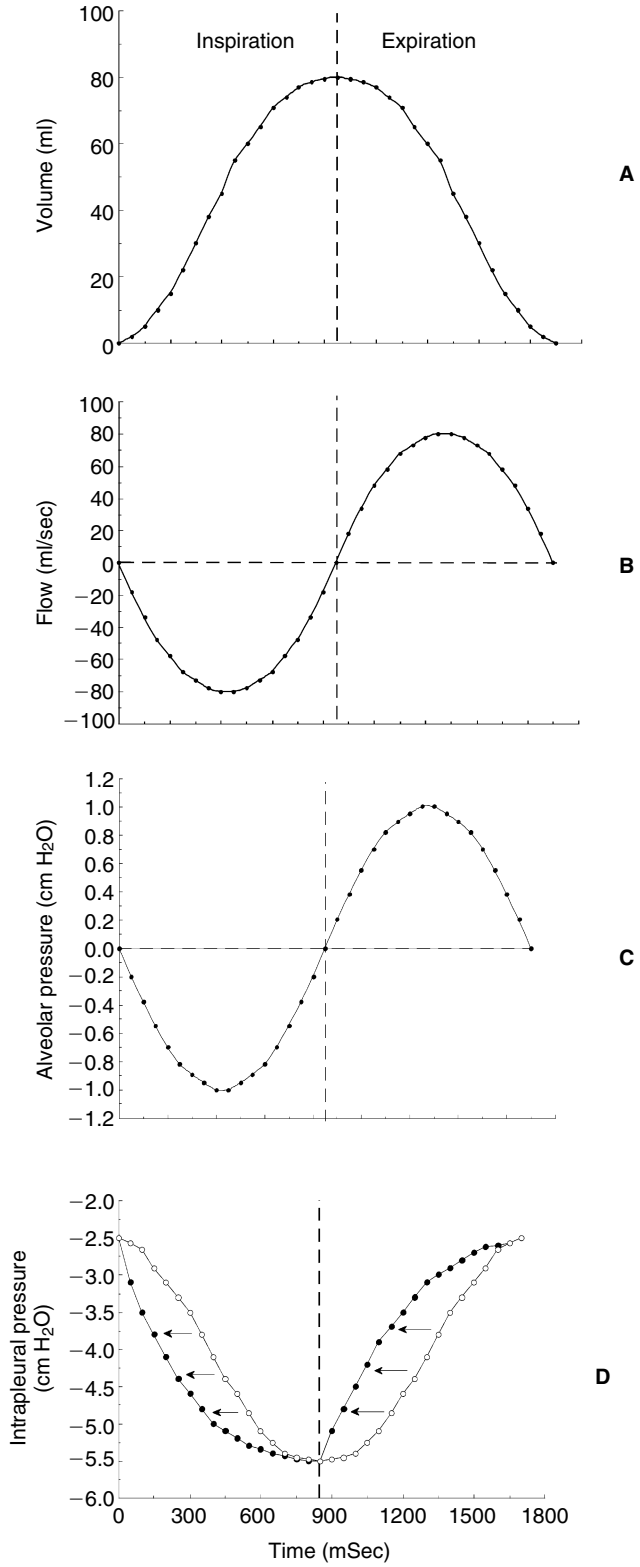

Figure 23-1. *Schematic of a single breathing cycle in a healthy adult cat including changes in* ***(A)*** *lung volume;* ***(B)*** *airflow;* ***(C)*** *alveolar pressure relative to ambient pressure (note that alveolar pressure drops below zero due, in part, to resistance generated as the air flows through the airways); and* ***(D)*** *intrapleural pressure. Solid symbols depict the shift in the pressure curve occurring due to elastic recoil of the lung parenchyma.*

gree of constant tension. Furthermore, because the alveolar septa are connected to the walls of the bronchioles, this tension or interdependency serves to provide radial traction around the small airways, in essence maintaining their patency as well. During tidal breathing, the volume of air remaining within the lung at the end of expiration is referred to as the functional residual capacity (FRC). It represents the balance point between the inward elastic recoil of the lungs and the outward elastic recoil of the chest wall.

Although the analogy is somewhat oversimplified, the inflated lung acts in a manner similar to a stretched rubber band. A certain amount of energy is required initially to stretch the rubber band or to expand the lungs (i.e., the energy needed to overcome the elastic and resistive work of breathing). But in so doing, tension is generated within the elastic components of the lung parenchyma. After inspiration ceases, the lung passively recoils because of this tension and returns to its original or end-expiratory size and shape. In the process, an identical volume of air is passively expired.

In small animals, 60% or more of the inspiratory frictional resistance generated during a tidal breath is due to airflow through the nose, pharynx, and larynx.[23] During exercise, when airflow rates increase dramatically, animals often switch to oral breathing in order to bypass this zone of high resistance. In a like manner, when airflow is impeded by localized disease within the nasopharyngeal region (e.g., by space-occupying masses or brachycephalic airway syndrome) animals often resort to oral breathing even at rest. Measurement of flow and volume changes over a single ventilatory cycle in these animals during nasal breathing would reveal alterations in inspiratory flow rates and airflow patterns. Not surprisingly, this approach (i.e., the use of tidal breathing flow-volume loop analysis) was first used clinically to evaluate upper respiratory disease in dogs.

Tidal Breathing Flow-Volume Loop (TBFVL) Analysis for Upper Respiratory Tract Disease

The primary advantage of TBFVL assessment is that one can quantify changes in airflow, volume, and in the temporal aspects of the ventilatory cycle—all in the conscious, nonsedated patient. Specialized equipment is necessary, however (Figure 23-2, *A*). The patient must be fitted with a sufficiently snug but nonrestrictive face mask to ensure negligible air leakage during the procedure. The mask must conform to the patient's face so that it neither disturbs airflow nor results in excessive dead space. Disproportionate dead space dampens the overall flow signal and allows background noise to become more problematic. The mask is then connected to a pneumotachograph, a device used to measure airflow changes. The pneumotachograph is heated to a constant temperature to avoid wide fluctuations in the inspired versus expired gas temperature. An associated pressure transducer is required to transmit the electrical signal to a preamplifier and receiver unit. The size (sensitivity) of the pneumotachograph and pressure transducer required is dictated by the size of the patient (i.e., the minimum

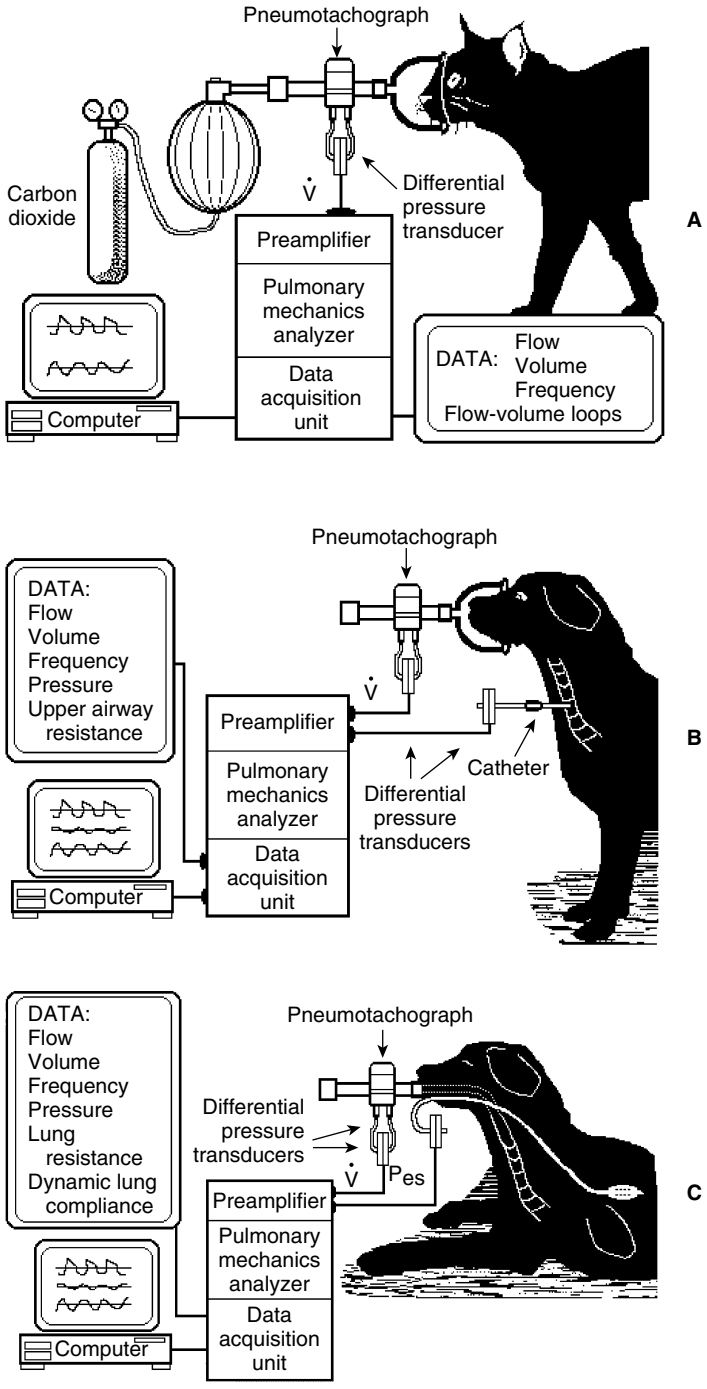

Figure 23-2. *Equipment setup for obtaining respiratory system functional information in small animals, including:* ***(A)*** *TBFVL data acquisition (± breathing increased CO_2 concentrations) for use in unanesthetized patients;* ***(B)*** *upper airway pressure (Puaw) and resistance (Ruaw) measurements in unanesthetized large breed dogs; and* ***(C)*** *lung resistance and compliance measurements in anesthetized small animals.*

flow signal generated). For each patient, the system must be calibrated prior to data acquisition.

Using a pulmonary mechanics analyzer (BUXCO Electronics, Sharon, Conn.) and analytical software program (Respiratory Loop Analysis Software, BUXCO Electronics, Sharon, Conn.), the flow signal can be electronically differentiated into its component volume and time measurements, yielding quantitative breath-by-breath or averaged data on airflow rates, volume, and time parameters. For ease of visual inspection of the data, airflow changes are plotted against volume changes to generate the so-called flow-volume or F-V loop. Although the temporal aspects of the breath are not evident in the F-V loop, this information is collected during data acquisition (i.e., frequency [bpm], time [mSec] associated with inspiration [Ti], and expiration [Te]). Information from the flow, volume, and time assessments can be combined to calculate an extensive list of ancillary parameters: time ratios (e.g., Te/Ti); inspiratory to expiratory flow ratios at the same lung volume (e.g., PIF/PEF, IF50/EF50); flow ratios at different lung volumes (e.g., PEF/EF25); or changes in volume over a defined period (e.g., ml exhaled during the first 0.1 second of a breath).[24,25] In theory, a range of normal values can be established for these parameters, allowing quantification of the abnormalities present in affected patients.

Although potentially promising, the primary disadvantage of this approach is its inherent insensitivity due to lack of maximal respiratory effort. As such its usefulness in detecting incipient or mild disease may be limited. During evaluation, it is important that the animal generates sufficiently deep and consistent breaths. Some animals, in particular cats, become apprehensive when the face mask is applied. They may adopt a shallow, rapid breathing pattern that is not indicative of their true tidal breathing capabilities. Alternatively, they may sniff, lick, vocalize, growl, or even purr during many of the breaths acquired. It is necessary therefore to establish a set of criteria by which only acceptable breaths are selected for inclusion in the final TBFVL analysis.

Analogous to the approach used to assess laryngotracheal disease in human infants,[26] Amis and colleagues originally used TBFVL analysis to evaluate dogs with upper respiratory disease.

They first characterized TBFVLs from healthy dogs including breeds with differing nasal anatomy.[24,27] In brief, for each breath a loop is generated as airflow changes are plotted against volume changes. By convention, the loop starts at the 3:00 o'clock position and proceeds in a clockwise direction until closing in on itself (Figure 23-3, *A*). Thus, the lower half of the loop delineates inspiratory changes and the upper half depicts expiration. Amis and colleagues demonstrated that in healthy, large breed, mesaticephalic (Labrador-type) dogs, TBFVLs are quite symmetrical, with the mirror images reflecting along either side of the zero flow axis (see Figure 23-3, *A*). In mesaticephalic dogs the average expiratory time (Te) is slightly longer than the inspiratory time (Ti), resulting in a relatively constant Te/Ti ratio of 1.26 (0.26).[27]

By contrast, Amis and colleagues demonstrated that many dogs with upper respiratory disease have characteristic TBFVL shape changes and decreased Te/Ti ratios. Dogs with relatively fixed or nonmovable obstruction (e.g., pharyngeal or laryngeal masses) have reductions in both inspiratory and expiratory flow rates, with uniform flattening of the F-V hemicurves.[24] Dogs with dynamic upper airway obstruction, however, have predominantly inspiratory flow restrictions.[28] Furthermore, depending on the severity of disease and ventilatory effort at the time of evaluation, dogs with laryngeal paralysis may produce normal TBFVLs, or loops consistent with fixed (inspiratory/expiratory) obstruction or with nonfixed (inspiratory) obstruction.[28] Amis and colleagues confirmed that many of the TBFVL parameters calculated for healthy brachycephalic dogs are dissimilar from those of mesaticephalic dogs, indicating that functional airflow restrictions are often present in dogs of these breeds.[27]

In the case examples that follow, McKiernan and colleagues[25] demonstrated that TBFVL assessments are also sensitive enough to detect airflow changes in cats with upper respiratory disease. These investigators first established a range of normal values for these parameters in healthy cats (Table 23-1).[25] They observed that, similar to healthy dogs, healthy cats exhibit a very symmetrical TBFVL (Figure 23-4, *A*). In fact, the inspiratory and expiratory times in cats are nearly identical, yielding an average Te/Ti ratio of 1.0 (±0.15).

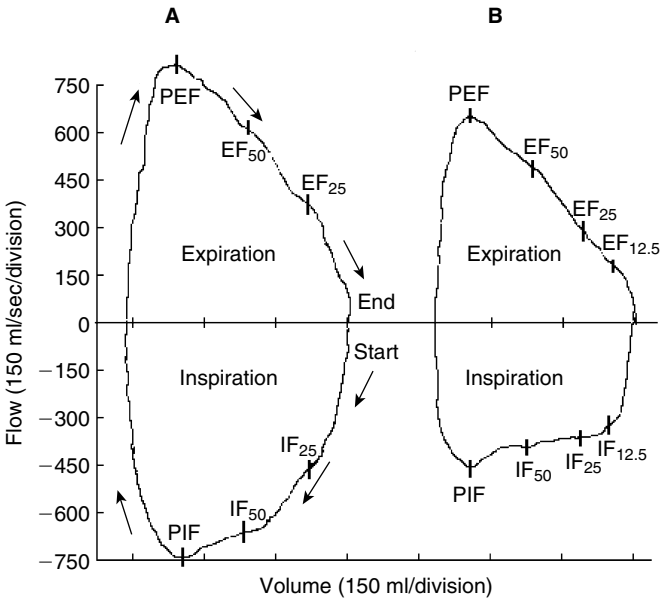

Figure 23-3. *TBFVLs in dogs. Loop **A** is a composite loop representing healthy large breed (mesaticephalic) dogs. The mean values as reported by Amis and colleagues[24] are: TV = 460 ml; PEF = 780 ml/sec; PIF = 740 ml/sec; f = 32 bpm; MV = 14.8 L/min; Te = 1170 mS; Ti = 920 mS; Te/Ti = 1.26; PEF/PIF = 1.07; PIF/IF50 = 1.09; PIF/IF25 = 1.26; IF50/IF25 = 1.16. By comparison, loop **B** was obtained in a Labrador–mixed breed dog after surgery for bilateral laryngeal paralysis. Indices: TV = 425 ml; PEF = 600 ml/sec; PIF = 415 ml/sec; f = 22 bpm; MV = 9.4 L/min; Te = 1420 mS; Ti = 1300 mS; Te/Ti = 1.09; PEF/PIF = 1.43; PIF/IF50 = 1.11; PIF/IF25 = 1.04; IF50/IF25 = 0.93. Interpretation: mild inspiratory airflow restriction is present.*

TABLE 23-1. **TBFVL Changes in a 2-Year-Old Himalayan Cat With Bronchopulmonary Disease**

Parameter (Units)	Day 0	Day 1	Day 8	2 Months	Cat
CLINICAL STATUS	DYSPNEIC	SLIGHT IMPROVEMENT	MUCH IMPROVED	CLINICAL RELAPSE	NORMAL VALUES[25]
Volume					
TV (ml)	50	38	32	28	58 ± 15
MV (ml)	1550	1292	1380	1036	2500
Time					
RR or *f* (bpm)	31	34	43	37	43 ± 7
Ti (mS)	776	744	642	533	717 ± 140
Te (mS)	1160	1028	735	1080	704 ± 134
Te/Ti	1.49	1.38	1.14	2.03	1.0 ± 0.15
Flow					
PIF (ml/sec)	96	80	73	85	111 ± 27
PEF (ml/sec)	92	58	67	81	114 ± 29
PEF/PIF	0.96	0.73	0.91	0.95	1.04 ± 0.18
EF50/IF50	0.51	0.61	0.85	0.35	1.16 ± 0.22
EF25/IF25	0.47	0.56	0.74	0.39	1.06 ± 0.19
EF12.5/IF12.5	0.49	0.65	0.60	0.41	0.94 ± 0.20
PIF/IF50	1.10	1.10	1.2	1.14	1.23 ± 0.15
IF50/IF25	1.24	1.28	1.2	1.27	1.12 ± 0.08
IF25/IF12.5	1.27	1.32	1.16	1.28	1.11 ± 0.06
PEF/EF50	2.04	1.32	1.29	3.1	1.10 ± 0.06
PEF/EF25	2.8	1.81	1.81	3.5	1.35 ± 0.17
PEF/EF12.5	3.4	2.07	2.58	4.26	1.73 ± 0.33

By contrast the non-symmetrical loop (Figure 23-4, *B*) was obtained from a 3-year-old domestic longhair cat presented for making unusual breathing sounds, especially while eating. The cat's breathing pattern was regular but relatively slow (mean $f = 25$ and TV = 77 ml). Visual inspection of the F-V loop revealed severe blunting of maximal expiratory flows and uniform flattening of the expiratory F-V curve. The peak inspiratory flow (PIF) occurred prematurely in inspiration, after which airflow appeared to taper off abnormally. In addition, there was moderate prolongation of the expiratory time relative to inspiratory time (Te/Ti = 1.25). These changes are most consistent with a fixed upper airway obstruction; however, there also appears to be a dynamic component to the obstruction. Oropharyngeal examination of the cat while under anesthesia revealed a nasopharyngeal mass involving the soft palate.

By comparison, the loop in Figure 23-4, *C* was obtained from a 7-year-old domestic shorthair cat. This cat presented for making noisy or unusual sounds when breathing. The cat's breathing pattern was somewhat irregular (mean $f = 37$ and TV = 73 ml). Abnormalities present in the TBFVL included variable flattening and intermittent reversal of inspiratory flow during midinspiration. The Ti was prolonged relative to Te (Te/Ti = 0.73). No expiratory abnormalities were detected. Results were consistent with a dynamic upper airway obstruction. Oral examination of the cat under anesthesia revealed a large, right-sided, somewhat pedunculated tonsillar mass. Presumably, depending on the angulation of the head while the loops were acquired, the mass was intermittently drawn into the laryngeal opening during inspiration, resulting in profound inspiratory flow restriction. However, when the mass was displaced by reversal of airflow during exhalation, there was no evidence of expiratory airflow obstruction.

By providing a means of quantifying airflow obstruction, several investigators have used TBFVL analysis in dogs to assess the efficacy of different surgical approaches used in correcting laryngeal paralysis or collapse.[29-31] As an illustration, the loop in Figure 23-3, *A* is a composite loop representing healthy mesaticephalic, large breed dogs. By comparison, the loop in 23-3, *B* was obtained from a 14-year-old mixed breed dog 1 week after undergoing a left-sided laryngeal tie-back for bilateral laryngeal paralysis. Of note, the dog also had a generalized decrease in muscle mass and mild rear limb conscious proprioceptive deficits. At rest, its breathing pattern was slow and regular ($f = 22$ bpm, TV = 425 ml, MV = 9400 ml). The inspiratory time was only mildly prolonged compared with expiration (Te/Ti = 1.09; normal 1.26 ± 0.26). The overall loop shape was nearly symmetrical, although mild blunting of the inspiratory flow rates (compared with expiratory flow rates) was still evident (e.g., PEF/PIF = 1.43; normal 1.07 ± 0.13). These measurements were much improved compared with those obtained preoperatively.

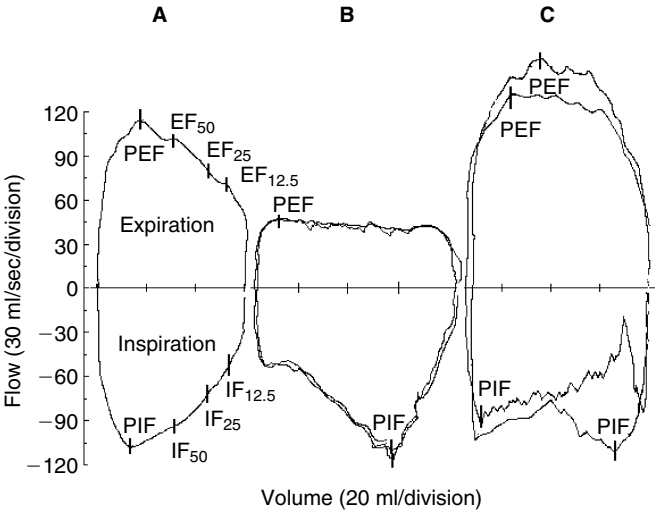

Figure 23-4. *Comparison of TBFVLs from healthy cats and cats with upper respiratory disease. Loop **A** is a composite loop representative of healthy adult cats. Values for select indices obtained in healthy cats are presented in Table 23-1. By comparison, loop **B** was obtained in a 3-year-old DLH cat presented for noisy breathing. Indices: TV = 77 ml; MV = 1925 ml; f = 25 bpm; Ti = 1080 mS; Te = 1350 mS; Te/Ti = 1.25; PIF = 121 ml/sec; PEF = 55 ml/sec; PEF/PIF = 0.45; PIF/IF50 = 1.23; IF50/IF25 = 0.87; IF25/IF12.5 = 1.39. Loop **C** was obtained in a 7-year-old DSH cat presented for making unusual sounds when breathing. Indices: TV = 73 ml; MV = 2700 ml; f = 37 bpm; Ti = 960 mS; Te = 698 mS; Te/Ti = 0.73; PIF = 114 ml/sec; PEF = 158 ml/sec; PEF/PIF = 1.40; PIF/IF50 = 1.71; IF50/IF25 = 0.92; IF25/IF12.5 = 1.05. (See text for loop interpretation.)*

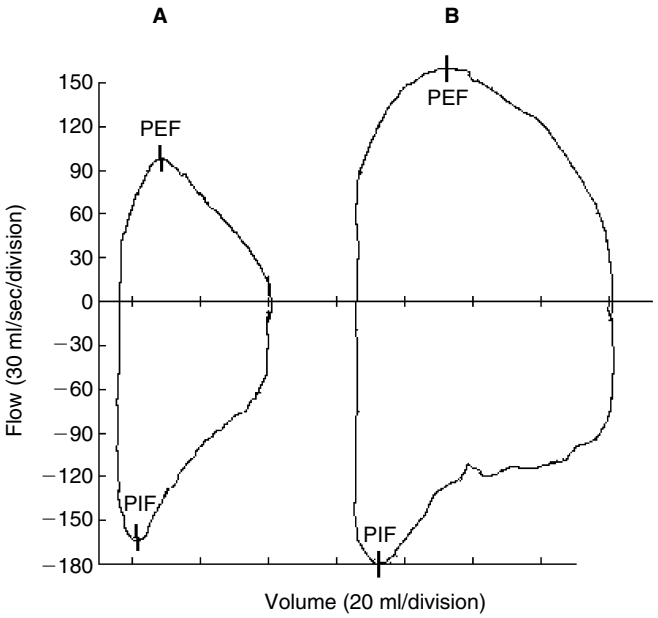

Figure 23-5. *These TBFVLs were obtained in a 14-year-old Persian cat before **(A)** and after **(B)** receiving chemotherapy for a thymoma. (See text for loop interpretation.)*

Tidal Breathing Flow-Volume Loop Analysis for Lower Respiratory Tract Disease

Although the changes are not as visually apparent, TBFVL analysis can also be used to critically evaluate intrathoracic or intrapulmonary disease in dogs and cats. To illustrate, the F-V loops depicted in Figure 23-5 were obtained from a 14-year-old Persian cat. Functionally this cat had restrictive lung disease because it was not able to fully inflate the lungs due to the presence of a large intrathoracic, extrapulmonary mass. The mass had been previously debulked and was diagnosed histologically as a thymoma. After a time the cat represented with signs of respiratory insufficiency. On physical examination the cat was mildly tachypneic and the cranial thorax was noncompressible. As part of the reevaluation, the loop in 23-5, *A* was obtained. Consistent with restrictive lung disease, TBFVL measurements revealed a relatively small TV (45 ml; normal 58 ± 15 ml) with a normal rate (f = 46 bpm; normal 43 ± 7) and thus a moderately reduced MV (2070 ml/min; normal around 2500 ml/min). The shape of the inspiratory half of the loop appeared somewhat concave and the PIF was elevated (166 ml/sec; normal 111 ± 27 ml/sec). Although the overall expiratory loop shape and expiratory flow rates were within normal limits (PEF = 104 ml/sec; normal 114 ± 29 ml/sec), the Te/Ti ratio was notably increased (1.61; normal 1.0 ± 0.15) consistent with the presence of expiratory airflow limitation. Six weeks later, after receiving COAP chemotherapy, the cat was clinically improved and the loop in Figure 23-5, *B* was obtained. TBFVL analysis revealed that with a respiratory rate in the upper normal range (f = 50 bpm), and considerable improvement in the TV (71 ml), the MV assessment was notably increased (3550 ml/min). Furthermore, the Te/Ti ratio had normalized (Te/Ti = 0.90). In spite of the fact that the loop shape abnormalities persisted, the flow rates, in particular the maximal expiratory flow rates, were much improved (PEF = 186 ml/sec). It is possible that some of the inspiratory curve shape changes were related to the altered nasal anatomy of the Persian breed.

TBFVL analysis can also be used to detect airflow changes in animals with lower respiratory disorders. For example, in dogs with excessive collapsibility of the large conducting airways, the TBFVL abnormalities observed depends on the region(s) of primary collapse. If the extrathoracic portion of the trachea has inadequate cartilaginous support, it will tend to collapse during inspiration when the pressure within the airway drops below that of the atmosphere. The chondromalacic airways below the thoracic inlet tend to remain open during inspiration because the intraluminal pressure remains greater than that of the pleural space. Consequently, TBFVLs from these patients reveal relative inspiratory flow limitations and prolongation of Ti relative to Te.[32] Conversely, during expiration these same intrathoracic airways tend to collapse because the intrathoracic pressure becomes less negative and may actually exceed that

of the airway opening pressure. This is especially problematic during forced expiration or coughing when the intrathoracic pressure becomes markedly increased. Therefore, in dogs with primary intrathoracic tracheal and principal bronchi collapse, expiratory TBFVL abnormalities predominate. And finally, if both the extra- and intrathoracic tracheal regions are involved, or if tracheal collapse occurs in combination with chronic bronchitis, mixed inspiratory/expiratory F-V loop abnormalities are often present.[32,33]

In an earlier report, Amis and colleagues[24] used TBFVL analyses to characterize the airflow restriction occurring in a group of dogs with clinical evidence of chronic bronchitis or tracheal/bronchial collapse. Interestingly, the F-V loops in many of the affected dogs demonstrated concavity or late expiratory phase flattening, consistent with expiratory airflow limitations.[24] Subsequently, Padrid and colleagues[1] used bronchoscopy to identify a group of dogs primarily affected with chronic bronchitis, and demonstrated that in addition to having end-tidal airflow abnormalities, these dogs had decreased Pao_2, and abnormal radioaerosol ventilation scans. Repeated administration of the bronchodilator albuterol was not associated with improvement in the Pao_2 or ventilatory scan assessments. However, in 5 of 7 dogs that had posttreatment TBFVL analysis, bronchodilator therapy was associated with increases in end-tidal airflow that corresponded with the clinical improvement observed in individual animals.[1,32] Although these results are encouraging, the authors caution that larger studies, performed under more stringent conditions, are necessary. Nevertheless, this study demonstrates the utility of PFTs in objectively assessing the efficacy of specific drug therapies.

McKiernan and colleagues[25] used TBFVL analysis to evaluate whether chronically bronchitic cats had evidence of end-tidal airflow restriction. They demonstrated that, compared with healthy adult cats, a group of clinically affected cats had significant (1) increases in the Te/Ti ratios; (2) reductions in expiratory flow rates compared to inspiratory flow rates at the same lung volume; (3) decreases in area-under-the-total and peak-expiratory flow-curve assessments; and (4) decreases in expiratory volume as calculated during the first 0.1 or 0.5 seconds of the tidal breath.[25] These changes are consistent with the presence of bronchial or bronchiolar airflow obstruction.

Because of its ease of use and noninvasiveness, TBFVL analysis can be used repeatedly in the same patient to objectively assess clinical deterioration or response to therapy. By way of example, the loops depicted in Figure 23-6 were obtained from a young adult Himalayan cat presented for chronic but intermittent coughing. During initial presentation (Day 0), the cat was moderately dyspneic and the loop in Figure 23-6, *A* was obtained. Oral glucocorticoid therapy was initiated and the loop in Figure 23-6, *B* was obtained the next day (Day 1). Seven days later, after daily glucocorticoid administration, the cat was clinically improved and the loop in Figure 23-6, *C* was obtained (Day 8). Over the next month, the cat continued to improve and was subsequently tapered off of all glucocorticoid medication.

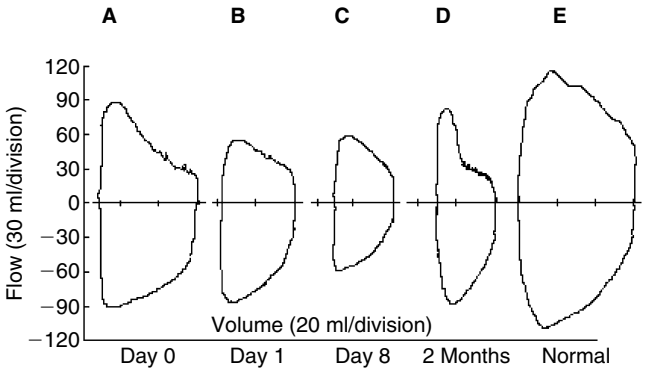

Figure 23-6. *This series of TBFVLs were obtained in a 2-year-old Himalayan cat presented for chronic coughing and intermittent dyspnea (loop **A**). The cat was started on oral glucocorticoid therapy, and follow-up evaluations included loop **B** 1 day later and loop **C** 1 week later. Two months later the cat relapsed clinically and loop **D** was obtained. For comparison, loop **E** is a composite loop representing healthy cats. (See Table 23-1 for changes in the corresponding TBFVL parameters.)*

Shortly thereafter, however, the cat relapsed and the loop in Figure 23-6, *D* was obtained (2 months). For ease of comparison, a composite loop (Figure 23-6, *E*) representing healthy cats has been included (see Table 23-1 for comparison of the calculated TBFVL indices).

In this patient, the signs of lower airway obstruction are most evident during expiration, and most of the abnormalities relate to the expiratory phase. As this cat decompensated clinically, the airway obstruction became more severe as evidenced by decrements in the mid- to end-tidal expiratory flow rates, especially in comparison to the peak expiratory flow rates (i.e., the PEF/EF25 and PEF/EF12.5 ratios were markedly elevated). As a result, the cat seemingly modified its breathing pattern to allow relatively more time for expiration (i.e., the Te/Ti ratio increased markedly). Even when the cat appeared to be improved clinically (Figure 23-6, *C*), the end-tidal airflow and Te/Ti ratios remained abnormal (see Table 23-1). When this cat represented after discontinuation of the glucocorticoid medication, the end-tidal airflow restriction was even greater than during initial presentation. In retrospect, glucocorticoid therapy should probably have been continued until the TBFVL parameters normalized, with more gradual tapering of the dose thereafter.

Enhanced Flow-Volume Loop Analysis

Due to the lack of maximal respiratory effort during TBFVL evaluation, there is a wide range of normal for many of the calculated indices. In an attempt to increase the sensitivity and reproducibility of F-V loop assessments, a variety of approaches have been used to artificially stimulate more maximal ventilatory efforts. The first approach was simply to induce partial rebreathing of the animal's own exhaled CO_2 by increasing the dead

space of the tube connected to the pneumotachograph. Although the acute increases in reinspired CO_2 concentrations resulted in increased MV measurements, the results were somewhat variable.

To better define the CO_2 concentration being inhaled, Ambu bags were prefilled with defined gas mixtures containing increasing CO_2 concentrations. Each Ambu bag was then sequentially attached to the nonpatient side of the pneumotachograph (see Figure 23-2, *A*). This approach was evaluated in healthy cats using 2.5%, 5.0%, 7.5%, 10%, or 12.5% CO_2 with 21% O_2 and the balance N_2.[34] The gas mixtures containing the higher CO_2 concentrations tended to smell like stale air that had escaped from an old inner tube. Most, but not all cats tolerated breathing CO_2 concentrations of 6% to 10%, and occasionally 12.5%, without aversion to placement of the face mask. In healthy cats, the CO_2 increases were linearly associated with commensurate increases in minute ventilation, as well as in many of the standard TBFVL parameters, and TV increased two- to threefold. Notably, breathing frequency was not affected. In healthy cats, CO_2 concentrations of 10% were necessary to achieve statistically significant increases in most end points relative to values obtained on room air.[34] However, breathing of CO_2 concentrations $\geq$10% appeared to induce changes in the overall shape of the F-V loop, possibly due to irritancy or odor, the significance of which is as yet undetermined. On a cautionary note, because hypoxia potentiates the ventilatory response to CO_2, more valid measurements may be obtained if, in addition to increasing the percentage of CO_2, one also increases the O_2 content somewhat to help ensure that hypoxic lung or vascular reflex responses are not inadvertently elicited in the test subject.

As another alternative approach, transient increases in lung volume by stimulation of the medullary respiratory center using doxapram hydrochloride were also evaluated.[35] In healthy cats, increasing doses of doxapram resulted in proportionate increases in many TBFVL indices and area-under-the-curve assessments. Unlike CO_2 stimulation, however, doxapram usage did not appear to affect overall loop shape. Unfortunately, the higher doxapram doses were associated with unacceptable side effects such as excessive salivation, vocalization, nervousness, vomiting, and diarrhea.[35]

Exercise-FVL testing is used in humans to identify subclinical respiratory deficiencies.[36,37] Similarly, horses are exercised on slanted treadmills to increase O_2 consumption and CO_2 production, resulting in MV increases proportionate to the level of exercise. Lumsden and colleagues[38] reported that in horses with upper airway obstruction, the F-V loop shape was more consistent and the coefficients of variation for many of the indices were smaller for breaths acquired during exercise, compared with tidal breathing conditions. Comparable methods are unlikely to be of use in cats, but such an approach has potential for dogs, in particular large breed or working dogs.

Admittedly none of these techniques simulates a true maximal expiratory effort; however, based on one author's experience relative to tidal breathing, breathing

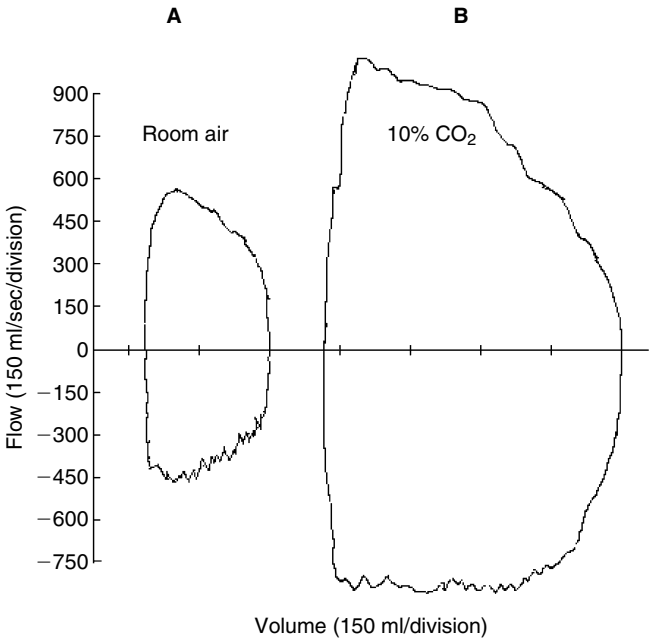

Figure 23-7. *These F-V loops were obtained in a 4-year-old bull terrier 6 weeks after corrective surgery for bilateral laryngeal paralysis. In loop* ***A*** *the subject was breathing room air; in loop* ***B*** *it was breathing 10% CO_2. Note that TV increased (280 to 624 ml), while f decreased (40 to 22 bpm), yielding an increase in MV (11.2 to 20.6 L/min). Peak expiratory flow (PEF) increased (566 to 1050 ml/sec) as did PIF (458 to 836 ml/sec), whereas the Te/Ti ratio was relatively constant.*

10% CO_2 approximates half the increases in volume and flow achieved during a maximal expiratory maneuver. Using these or related modifications, it may be possible to effectively increase the sensitivity and reproducibility of the F-V loop assessment but still retain its overall ease and safety. Thus establishment of more narrowly defined reference values for healthy subjects may allow detection of significant differences in mildly affected patients. For example, it appeared that 10% CO_2 levels were necessary to elicit significantly enhanced F-V loop measurements in healthy cats.[34] Diseased patients, however, may require much lower levels to achieve the same enhanced or maximal response.

An example of how breathing 10% CO_2 can unmask flow limitations minimally evident during tidal breathing is shown in Figure 23-7. The F-V loops were acquired from a bull terrier with bilateral laryngeal paralysis that had undergone corrective surgery 6 weeks earlier. The loop shown in Figure 23-7, *A* was obtained while breathing room air. Although the overall shape is relatively symmetrical, there is evidence of mild blunting of inspiratory flow relative to expiratory flow (i.e., the PEF/PIF ratio was slightly increased at 1.26; normal 1.07 $\pm$ 0.13). In response to breathing 10% CO_2, the lung volume increased 2.2-fold, the PEF rate increased 1.9-fold, and the mid- to end-inspiratory airflow attenuation was more pronounced (Figure 23-7, *B*).

Another example of how 10% CO_2 can accentuate the patient's ventilatory efforts is shown in Figure 23-8. The

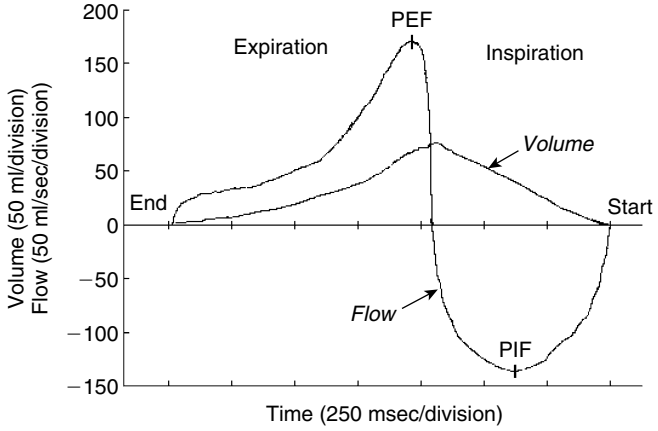

Figure 23-8. *Volume versus time and flow versus time graphs were obtained in a 7-year-old Siamese cat with chronic bronchopulmonary disease while breathing 10% CO_2. Indices: TV = 69 ml; MV = 2340 ml/min; f = 34 bpm; Ti = 720 mS; Te = 972 mS; Te/Ti = 1.35; PIF = 128 ml/sec; PEF = 163 ml/sec; PEF/PIF = 1.28. (See text for interpretation.)*

data were obtained from a 7-year-old Siamese cat with longstanding bronchopulmonary disease. Clinically stable at the time of evaluation, the cat tolerated breathing 10% CO_2. Rather than plotting the typical F-V loop, in Figure 23-8 the changes in lung volume and airflow have been plotted against time. Despite breathing 10% CO_2, the lung volume measurement is only minimally increased over that obtained on room air. This suggests that further increases in lung volume were not possible, likely owing to chronic airway remodeling. In addition, one can readily appreciate the concavity or scooping out of the terminal portion of the expiratory flow-time and expiratory volume-time curves and the disproportionate length of time dedicated to the terminal phase of expiration. As a consequence, this cat seemed to adopt a breathing strategy that allowed more time for the terminal phase of expiration to be more complete. In so doing, on the subsequent breath a proportionately larger volume of inspired air would be able to pass back into the affected alveoli. This case demonstrates that in animals with small airway obstruction, the volume versus time and flow versus time graphs may be more illustrative of end-tidal airflow limitations.

Upper and Lower Airway Resistance and Lung Compliance Assessments

Incorporation of pressure measurements, along with flow and volume assessments, allows for a more in-depth evaluation of breathing mechanics. During examination of the respiratory patient, we attempt to ascertain whether the patient's work of breathing is appropriate—an important but highly subjective clinical assessment. It can be quantified by measuring pressure changes required to generate a breath of known volume or airflow rate, which is the basis of respiratory mechanical assessment, often referred to as function testing. By incorporating pressure changes into ventilatory information, we can calculate direct measures that relate to airflow and tissue mechanics associated with breathing, namely resistance and compliance. These measurements provide clues as to whether the animal has obstructive or restrictive disease.

During inspiration, the alveolar pressure normally becomes slightly negative (see Figure 23-1, *C*), driven by the intrapleural pressure (Ppl) that becomes slightly *more* negative (see Figure 23-1, *D*) relative to ambient pressure. As pressure along the airway drops below atmospheric pressure, air flows inward toward the more negative pressure in the alveolar region. The greater the differential pressure generated, the greater the resultant lung volume. In health, relatively small pressure changes are required to generate a normal tidal breath. The magnitude of the pressure change (P) required is integrally related to several factors, including the tidal volume, the flow rates generated, the ease with which the lung is expanded (lung compliance), and the ease with which air flows through the air passageways (resistance of the upper and lower airways).[39] This is demonstrated mathematically as[23,40]:

$$\Delta P = \frac{\Delta TV}{Compliance} + (\Delta Airflow \times Resistance)$$

Knowing that the diameter of the airways changes with changes in lung volume and with the dynamics of airflow itself, at first glance it may seem impossible to accurately assess all of these parameters simultaneously. On further examination of this equation, however, it becomes apparent that the driving pressure needed to elicit the coincident change in lung volume is closely linked to compliance, whereas that related to airflow is integrally linked to resistance. By imposing certain assumptions on the physiological conditions we use to estimate resistance or compliance, we can define the mechanical behavior of the respiratory system in relatively simple terms. Put another way, if we select two points in the ventilatory cycle where there is no airflow, the corresponding pressure change will primarily be influenced by the elastic properties of the lung. If we select two points where the inspiratory and expiratory volumes are equivalent, the differential pressure will principally reflect resistive effects.

More specifically, resistance can be estimated at a specific point during the inspiratory and expiratory portion of the breath (e.g., at 50% of TV), or it can be computed as a mean of the inspiratory and expiratory phases of the ventilatory cycle. In human experimental physiology laboratories, various methods have been used to make these estimations, many of which require considerable sophistication both in both hardware and software, or involve voluntary participation of the patient (e.g., controlled panting) not readily amenable to veterinary medicine. These methods have been described in practice and in theory elsewhere.[40,41] Fortunately, two methods provide reasonable estimates of resistance and compliance using data collected during tidal breathing. One method, the Mead and Whittenberger[42] approach described nearly 50 years ago, is the more complex but

more accurate of the two. With this approach, one first computes compliance from both the inspiratory or expiratory limbs of the breath cycle at a point where there is no airflow. Then, at a given percent of the tidal volume of the next breath, the respective compliant pressure is incorporated into the equation, in essence eliminating the influence of the elastic lung properties from the pressure changes and allowing one to compute resistance. Although straightforward, the algorithms and calculations involved are best left to computer processing. Alternatively, an easier but somewhat less accurate approach uses the isovolume method, sometimes referred to as the poor man's respiratory mechanics.[43] This method uses the same tidal measures of volume, airflow, and pressure, but it computes resistance as an average occurring across inspiration and expiration. The flow and pressure measurements are attained at mid-tidal volumes, ideally at points where airflow is near maximal. With this approach, the volume term on either side of the ventilatory cycle is equivalent. Hence the change in volume is negligible, and the influence of compliance on total pressure is theoretically constant. Thus compliance drops out of the equation and resistance is computed as the quotient of the difference between the pressures and airflows at these two midvolume points. These calculations can be performed by hand by dropping lines across the corresponding points of the volume, flow, and pressure traces (similar to those depicted in Figure 23-1, *A, B,* and *D*). Fortunately, pulmonary mechanics software programs exist that make these calculations automatically. In the studies below, the isovolume method was primarily used for estimating resistance and compliance.

Upper Airway Resistance (Ruaw) Assessments

How are ventilatory pressure measurements obtained in small animals? To evaluate upper respiratory airflow disturbances, an over-the-needle catheter may be transcutaneously placed into the lumen of the trachea to assess changes in intratracheal pressure (see Figure 23-2, *B*). This can be accomplished using local anesthesia, similar to the technique used for transtracheal aspiration. The catheter is placed perpendicular to the long axis of the trachea in order to minimize airflow bias at the catheter tip. A pressure transducer connected to the catheter detects pressure changes occurring across the upper airways (Ruaw [i.e., the difference between atmospheric and intratracheal pressure]). Analogous to the TBFVL procedure, a face mask technique can be used to noninvasively obtain measures of volume and airflow. When two transducers are used to measure different aspects of the same functional event, the transducer outputs should be phase-matched to a defined frequency (typically 5 to 10 times the highest *f* encountered) to ensure that any difference in timing is due to the patient and not to the measuring system.[44] Any system-related phasing errors will result in incorrect computations. A pulmonary mechanics analyzer and software analysis program are used to calculate the overall resistance to airflow, or in this instance, upper airway resistance (Ruaw). Ruaw is a composite of the resistance to airflow through the nares, nasal passages, nasopharynx, larynx, and proximal (upstream) portion of the trachea.

Using this technique, Rozanski and colleagues[45] established normal reference values for Ruaw in mesaticephalic dogs. This minimally invasive approach was well tolerated in untrained, large breed dogs, and the Ruaw values obtained in individual dogs were quite reproducible.[45] Ruaw was calculated using the isovolume method (at 70% of TV) as:

$$R_{uaw} = \frac{\Delta P_{uaw}}{\Delta Flow}$$

The units for Ruaw are $cmH_2O/L/sec$. Hence Ruaw reflects the overall pressure change required to generate a given change in airflow through the upper airways.

A change in the diameter of a single air passageway significantly influences the resistance measurement. Assuming that the length is held constant, if the airway's diameter is progressively reduced, greater and greater pressure changes will be necessary to achieve the same airflow over an equivalent time. Consequently, decrements in airway caliber require generation of greater differential pressure gradients in order to achieve comparable airflow. This, however, is not a linear relationship. In fact, resistance to airflow through the airway is inversely proportional to the radius of the airway taken to the 4th power.[46] Accordingly, if the radius is cut in half, resistance increases sixteenfold. In the respiratory system as a whole, all patent air passageways influence the resistance measurement; however, the upper airways account for $\geq$60% of the inspiratory frictional resistance occurring during tidal breathing.[23]

Rozanski and colleagues[45] further compared Ruaw values from healthy mesaticephalic dogs with that of healthy dolichocephalic dogs. Despite their elongated nasal profile, collies did not have elevated Ruaw measurements; if anything, there was a trend toward lower absolute Ruaw values in this breed.[45] Conversely, despite their shortened nasal profile, brachycephalic dogs often have increased upper airway resistance due to relatively stenotic nares, elongated soft palates, or hypoplastic tracheas.[47] These examples illustrate the disproportionate influence of decrements in airway caliber (particularly of the upper airways and lower central airways) on the resistance measurement.

Again using the method described in Figure 23-2, *B,* Alsup and colleagues[31] used Ruaw measurements in dogs to validate that the TBFVL improvements noted after corrective surgery for laryngeal paralysis were in fact associated with decreased resistance to airflow through the larynx. Similarly, Greenfield and colleagues[48] used Ruaw measurements in combination with TBFVL analysis to validate an experimental model of canine laryngeal paralysis. Not only did bilateral recurrent laryngeal neurectomy result in analogous clinical signs, the inspiratory airflow impairment was comparable with that of dogs with naturally occurring disease.[48]

Lung Resistance and Compliance Assessments

If assessment of pulmonary function is the priority, the influence of the upper respiratory tract must be excluded, and instead measures of transpulmonary pressure must be obtained. In small animals, alveolar pressure can only be measured indirectly using body plethysmography. Intrapleural pressure (Ppl) can be measured by surgical placement of a cannula into the pleural space. Fortunately, however, pressure changes within the pleural space closely parallel those of the midthoracic esophagus. Thus the least invasive method of obtaining estimates of Ppl is to place a balloon-tipped catheter into the esophagus (just caudal to the heart to avoid movement artifact related to cardiac contractions) and record changes in esophageal pressure (Pes). Although horses commonly tolerate this procedure without general anesthesia, few untrained dogs and presumably no cats would be so tolerant. The esophageal catheter is connected to a pressure transducer (see Figure 23-2, *C*). Volume and airflow measurements could be obtained using a face mask; however, because we are primarily interested in assessing pulmonary disease, and because anesthesia is required for placement of the esophageal catheter, as a rule the animal is intubated and the endotracheal tube is connected directly to the pneumotachograph and associated pressure transducer (see Figure 23-2, *C*).

The main disadvantage of this approach is that it requires a brief period of general anesthesia for placement of the esophageal balloon/endotracheal tube and for data acquisition. Furthermore, because all recoverable anesthetic agents are associated with some degree of respiratory depression, the measurements obtained are likely to be somewhat biased, depending on the agent(s) and the depth of anesthesia. It may be possible to overcome some of the respiratory depression by incorporating methods to partially augment respiratory efforts (e.g., low doses of doxapram or moderate increases in CO_2 during data acquisition). In addition, the endotracheal tube is associated with a certain degree of resistance to airflow. For consistency, when comparing similarly sized healthy and diseased patients, care must be taken to ensure that the endotracheal tubes used are of equivalent length and inner diameter. Alternatively, the airflow resistance of the endotracheal tube may be subtracted from the overall resistance value obtained for the patient. In so doing, however, a portion of the resistance related to the laryngeal/upper tracheal region will also be subtracted.

Analogous to Ruaw, lung resistance (R_L) is calculated by dividing the change in transpulmonary pressure (estimated by Pes) by the change in airflow, again using isovolume conditions. Although all patent airways influence R_L, the large conducting, central airways predominantly influence this measurement.[49] Airway resistance varies inversely with lung volume because the expanding lung parenchyma exerts traction on the walls of the airways. Therefore, lung resistance calculations should always be related to lung volume. The small peripheral airways (defined in humans as 2 mm) normally contribute little to the overall resistance because the airflow per airway is very small and there are so many arranged in parallel, in effect making the combined cross-sectional area of the small airways very large. As such, the R_L measurement is relatively insensitive to small airway changes. It is generally inferred that an increase in R_L is indicative of central airway obstruction with or without concurrent peripheral airway obstruction.

Airway resistance is often increased in humans with chronic inflammatory airway disease (e.g., chronic bronchitis or asthma) due to reductions in airway caliber.[50] Resistance is also influenced by changes in tissues surrounding the airways (e.g., emphysema).[51] During peripheral airway obstruction, lung volume (FRC) is often increased due to air trapping. As the small airways become overly distended, R_L decreases. Unless adjustments are made for the increase in lung volume, the sensitivity of R_L in detecting small airway obstruction is further reduced. In small animals, FRC can be quantified using an open circuit nitrogen washout technique, similar to the method used in human infants.[52] Thus measures of R_L can be used to establish the presence and degree of airway obstruction but cannot discriminate between the conditions that contribute to airway obstruction.

The other commonly used pulmonary mechanical parameter, lung compliance, is used mainly to assess changes in overall lung elasticity or stiffness. As changes in volume, airflow, and pressure are recorded during tidal breathing, if the change in volume is measured at periods when there is no airflow (i.e., at the beginning and end of inspiration), the coincident pressure change related to the resistance term (Δ flow $\times$ resistance) is negated, leaving compliance to be calculated simply as:

$$C = \frac{\Delta TV}{\Delta Ppl}$$

Hence compliance represents the change in lung volume corresponding to a given change in pressure. Compliance determined in this manner is referred to as dynamic lung compliance (C_{dyn}; ml/cm H_2O). Static (or quasistatic) lung compliance is another means of assessing lung distensibility. It can be measured using a number of variations on a theme[40,53,54]; but in each, volume and pressure changes are measured as the lung is incrementally inflated (typically to total lung capacity) and then incrementally deflated. At each step, airflow transiently ceases, thus allowing for computation of compliance with minimal resistive effects. Thoracic static compliance can be likewise estimated; however, with this approach, changes in elasticity may relate not only to lung parenchymal changes but also to changes in the chest wall, and thus pleural space.[51]

A major determinant of dynamic lung compliance is the relaxation state of the smaller airways (i.e., those larger than terminal bronchioles). C_{dyn} is reduced if sufficient numbers of the small airways are constricted or become obstructed.[56] Lung compliance, in particular static compliance,[53] may also be reduced if the lung parenchyma becomes stiffer due to infiltrative processes

(e.g., interstitial edema) or fibrotic processes (e.g., cryptogenic fibrosing alveolitis).[57] Conversely, in emphysema and possibly in chronic airway remodeling, as the elastic support structures of the lung parenchyma become weakened or destroyed, Cdyn is abnormally increased.[51] In this situation, R_L also increases due to generalized loss of the radial traction that normally serves to maintain small airway patency.[51]

Few clinical reports in companion animals have used lung mechanical assessments. Conceptually, however, R_L and compliance measurements should prove useful in understanding whether the respiratory disease is obstructive or restrictive and in establishing the extent of the functional impairment. Lung resistance is likely to increase in animals with tracheobronchial collapse or inflammatory airway disease.[1,2,32] Compliance is likely to decrease in patients with diffuse small airway disease. Reductions in compliance are also likely in parenchymal infiltrative diseases (e.g., pulmonary edema related to congestive heart failure,[58] idiopathic pulmonary fibrosis in dogs,[3-5] peribronchiolar fibrosis,[59] and fibrosing alveolitis[6] in cats). Chronic airway wall remodeling—loosely defined as the destructive airway changes occurring as a sequela to persistent airway injury and inflammation[60,61]—may be associated with increased C_{dyn} measurements, because the normal elasticity of the lung is slowly reduced. Bronchiectasis has been reported in dogs[32] and cats,[62] most commonly in association with chronic inflammation. However, the functional abnormalities attributable to bronchiectasis are difficult to distinguish from changes related to the coexisting lung conditions. And finally, although uncommon in small animals, generalized loss/destruction of intraalveolar connections (e.g., emphysema, COPD,[63] chronic pulmonary overinflation states, and bullous emphysema) are likely to be associated with increases in C_{dyn} and small increases in R_L.

By way of specific clinical examples, relatively simple parameters (e.g., TV, MV, and peak inspiratory pressure) are useful objective data in determining whether an animal needs continued mechanical ventilatory support (e.g., after a thoracotomy procedure, with neuromuscular blockade,[64] or for critical patients with primary parenchymal disease[65] or thoracic trauma[66]). Note however, that because ventilated critical patients are under positive pressure ventilation, the Pes measurement is a less reliable indicator of Ppl changes.[67] Thus for human patients receiving mechanical ventilatory support, changes in static compliance are considered a better estimate of whether the pulmonary parenchyma is becoming less distensible. Decrements in total thoracic compliance may be useful, not only in detecting lung parenchymal changes such as edema or pneumonia but also in identifying disorders of the thoracic wall such as pneumothorax or pleural effusion.[55] Because all of these conditions are not uncommon complications in chronically ventilated patients, King and colleagues[55] assessed whether a similar approach could be used to evaluate ventilated small animal patients. These investigators demonstrated that static thoracic compliance could be measured safely and easily in anesthetized, intubated dogs.[55] In addition, when thoracic static compliance was normalized to body weight, values obtained in dogs with respiratory disease were considerably lower than those obtained in healthy dogs.[55] King and colleagues have continued to use similar assessments in animals requiring positive pressure ventilation[65] (e.g., acute respiratory distress syndrome,[68] thoracic trauma with pulmonary contusions,[66] and hypoventilatory states related to spinal cord disorders[69]). Overall, the ability to objectively assess changes in compliance has proven indispensable both for diagnostic and prognostic purposes, as well as for ventilator management in these small animal patients.

As another example, Stobie and colleagues[70] used R_L and C_{dyn} measures in dogs to evaluate the effectiveness of analgesic protocols after a thoracotomy procedure. Results indicated that both anesthesia and thoracotomy were associated with significant changes in lung function, and, moreover, that interpleural administration of the analgesic bupivacaine allowed for an earlier return to normal based on several of the functional assessments evaluated.

Furthermore, Dye and colleagues[2] used R_L and C_{dyn} measures to evaluate airway obstruction in cats with naturally occurring bronchopulmonary disease. Cats were first grouped according to relative disease severity based on scored clinical assessments, then anesthetized using a short-acting barbiturate, and measures of R_L and C_{dyn} were obtained. Data indicated that significant airway obstruction was present in many of the affected cats. Specifically, compared with healthy cats with a mean R_L value of 28.9 cm H_2O/L/sec, the mildly, moderately, and severely affected cats had R_L values of 38.3, 44.8, and 105.2 cm H_2O/L/sec, respectively. Similarly, healthy cats had a mean C_{dyn} value of 19.8 ml/cm H_2O, whereas affected cats had values of 14.7, 17.7, and 13.0 ml/cm H_2O, respectively.[2] Thus despite the fact that most of the cats were not in obvious respiratory distress at the time of evaluation, many cats, in particular those with moderate and severe disease, had considerably abnormal PFT results. The R_L elevations were consistent with obstruction of either the larger airways or with severe, diffuse small airway disease. Cats with decreased C_{dyn} measurements were presumed to have either obstruction of the smaller airways or parenchymal fibrotic/infiltrative disease. Some of the cats had abnormal R_L and C_{dyn} measurements consistent with obstruction/constriction of both the large and small airways. A few cats with particularly longstanding disease had moderate increases in R_L in combination with C_{dyn} increases, possibly due to chronic airway remodeling.

Also in this study, Dye and colleages[2] administered a test dose of the β_2-agonist terbutaline to assess acute reversibility of the airway obstruction. A few affected cats demonstrated nearly complete reversal, suggesting that the majority of the airway obstruction was caused by excessive smooth muscle constriction. Other cats had only partial reversal, at least acutely (similar to the cat depicted in Figure 23-9, *A*). Not surprisingly, this cat had particularly longstanding disease. The partial response suggests that other factors in addition to smooth muscle constriction were present (e.g., retention of mucous secretions, intraluminal and submucosal inflammation, or

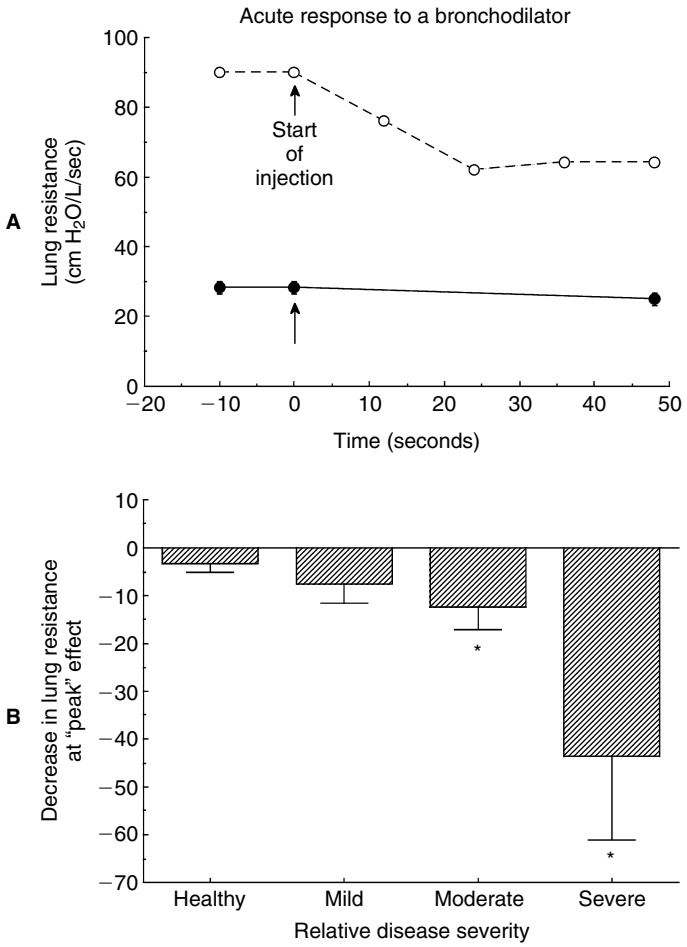

Figure 23-9. A, *Acute response to a test dose of the bronchodilator terbutaline in a cat with chronic bronchopulmonary disease* (open circle) *and a healthy cat* (solid circle). ***B,*** *Group responses to a test dose of terbutaline in healthy cats and cats with mild, moderate, and severe bronchopulmonary disease. Asterisk* (*) *indicates a significantly greater response than was observed in the healthy cats (p 0.05).*

airway remodeling). Some cats showed negligible improvement following bronchodilator administration. The overall R_L group responses to terbutaline administration are depicted in Figure 23-9, *B.* Compared with healthy control cats, as a group, the moderately and severely affected cats had greater absolute R_L decreases, which was not unexpected remembering that R_L changes inversely with the radius taken to the 4th power. As such, even minor improvements in airflow can be associated with substantial decrements in airflow resistance.

Interestingly, after administration of terbutaline the healthy cats had R_L decrements of approximately 10% and C_{dyn} increases of over 30%. This finding is consistent with the general observation that cats normally have a considerable degree of cholinergic small airway smooth muscle tone.[71] By contrast, resting bronchomotor tone in dogs appears to be minimal.[32] Airway tone is a result of a balance between cholinergic[72] (i.e., acetylcholine-, methacholine-responding receptors), adrenergic (i.e., epinephrine-, β-agonist-responding receptors), and noncholinergic nonadrenergic (NANC) or C-fiber–mediated reflex responses (i.e, tachykinin-, neurokinin-responding receptors).[73] Reflex regulation of airway smooth muscle tone is an area of considerable investigation. A variety of species have been evaluated, no two of which appear to be under identical neurological control. Generally speaking, however, cats appear to be quite similar to humans (and to primates, rabbits, guinea pigs, ferrets, horses, sheep, cattle, and swine), in that the NANC neurons contribute significantly to relaxation of the airway smooth muscle.[7,74-76] In dogs (and rats), virtually all the relaxant innervation to the airway is adrenergically mediated.[76,77]

The cat has been used extensively as a model to investigate the in vivo effects of a variety of bioactive mediators. Some of the bronchoconstrictive mediators evaluated include substance P,[78,79] cold air,[80] cyclooxygenase products and leukotrienes,[8] platelet activating factor (PAF),[81] serotonin (5-HT),[82] oxygen radical species,[83] thromboxanes,[84] and endothelins.[85] Bronchodilatory mediators have included vasoactive intestinal protein (VIP)[86]; PGE_1, 6-keto-PGE_1, and PGI_2[87,88]; and histamine.[78,89] Whether any of these mediators relate to the pathological processes underlying naturally occurring bronchopulmonary disease in cats remains to be determined.

More recent studies suggest that nitric oxide (NO) is involved in the acute NANC-induced airway relaxation in cats[90] and further that NO is an important factor modulating the degree of airway responsiveness (AR) of cats in vivo.[91] This finding is consistent with an earlier report that ozone-induced airway epithelial damage in cats was associated with increased AR to the cholinergic mediator acetylcholine. The authors hypothesized that ozone exposure resulted in decreased production of epithelium-dependent relaxant factor(s).[10] Knowing now that airway epithelial cells are an important source of NO in the lung, one of the relaxant factors alluded to in the previous study was likely to be NO.

In humans, AR is defined as the ease with which airways narrow in response to a nonspecific (nonallergic or nonsensitizing) stimulus.[92] Increased AR is a hallmark feature of asthma[61] and further, the degree of AR may correlate with disease severity and therapy requirements.[93] In the study by Dye and colleagues,[2] a subset of affected cats with relatively normal baseline R_L and C_{dyn} values underwent bronchoprovocation testing to see if they had increased AR analogous to that of human asthmatics during asymptomatic periods. Six (of seven) affected cats had increased AR compared with a group of healthy cats, based on the effective concentration of aerosolized methacholine required to double the baseline R_L measurement ($EC_{200}R_L$).[2] These results suggest (but do not prove) that these cats were predisposed to developing bronchoconstriction and that this may have contributed to their intermittent respiratory signs. On a related note, increased AR has been reported in cats with experimental allergen-induced lung inflammation.[13-15] The AR increases were inhibited by treatment with the potent immunosuppressive drug cyclosporine.[15] Moreover, Miura and colleagues[13] demonstrated that during allergen reexposure, the NANC inhibitory response was diminished in

cats, leading to increases in lung resistance. The investigators suggested that protease release during the allergic inflammatory response played a role in dysfunction of airway smooth muscle.

In summary, reflex regulation of airway smooth muscle tone, and thus airway patency, is mediated by multiple, carefully regulated pathways, both inhibitory and excitatory. Although the nature of the regulatory processes varies between species, airway inflammation appears to be a universal disruptor of the balance between constrictor and dilatory input. The ability to define lung function (R_L and C_{dyn}) in small animals is essential not only to document the presence of airway obstruction but also to determine its reversibility. Similarly, lung function assessments can indicate whether the airways are more responsive than normal, thus predisposing the animal to developing obstruction after exposure to irritating or infectious agents.[17,94]

Future Direction and Cautionary Notes

A general limitation of the use of PFTs to assess individual small animal patients is the lack of more specific reference values for comparison. To date, no validated protocols for clinical use are available, and they are unlikely in the foreseeable future. Even in the experimental setting, different investigators use slightly different testing systems, making it difficult to compare results across a number of studies.[40] Until standard protocols are available, investigators should describe the methods and instrumentation used in substantial detail.

Hence one of the goals that must be achieved before PFTs can be used routinely in small animals is the establishment of standard testing protocols. Then, using standard methodologies, longitudinal studies are needed to evaluate sufficient numbers of healthy and affected subjects to define reference values and to generate predictive equations for a variety of clinical syndromes. Reference ranges are likely to need considerable refinement to account for differences in an individual animal's size; age; sex; and, most likely, breed. This reflects the tremendous variability existing especially among dogs, in terms of body size and thoracic shape (from Chihuahuas to Great Danes), and nasal anatomy (from exercise-efficient sight hounds to mouth-breathing bulldogs). Although cats are relatively similar in body size and thoracic shape, differences in nasal anatomy exist (e.g., dolichocephalic Siamese cats, brachycephalic Persians).

Despite these similarities, Dye and colleagues[2] observed that even in healthy cats, C_{dyn} measurements were more variable (coefficient of variance, CV = 37%) than R_L measurements (CV = 22%). Attempts were made to normalize C_{dyn} to some index of the animal's size. There was no clear correlation between C_{dyn} and the animal's body weight, but a significant correlation existed between C_{dyn} and thoracic girth measurements. Clark and colleagues[95] observed that in healthy dogs (ranging in weight from 11.8 to 26.4 kg), C_{dyn} correlated more closely with trunk length than with either body weight or chest circumference. In humans, a number of lung function indices correlate more closely with an individual's height than with weight.[96] Clearly, further work is necessary.

Another major obstacle that must be overcome is the selection of appropriate sedative or anesthetic protocols for PFTs requiring an endotracheal tube, esophageal balloon, or paralysis to achieve total ventilatory control. The anesthetic protocol must allow for safe recovery of the respiratory patient, but it must not unduly influence the underlying pathologic processes. An inhalant anesthetic would seem ideal, however agents such as halothane and isoflurane are considered potent bronchodilators and also appear to induce reflex inhibition of breathing during face mask induction.[97] Likewise, intravenous use of propofol has been shown to have bronchodilatory effects in humans.[98] Use of these or similar agents, or the use of premedicants with anticholinergic activity, is likely to transiently mask the functional deficits we are trying to document. On the other hand, virtually all sedative and anesthetic agents tend to relax the upper airway dilating muscles, further compounding airflow resistance in brachycephalic animals and making any procedure involving sedation or anesthesia in these subjects extremely risky.[42]

Two older agents, α-chloralose and chloral hydrate, have potential for use during PFTs in companion animals. The hypnotic agent α-chloralose preserves vagal and central baroreceptor reflexes, making it a commonly used agent for experimental physiological studies in dogs.[99-101] Lemen and colleages have used it for recovery PFTs in laboratory beagles for over a decade,[17,18,100] reporting that even in puppies, it is safe when administered intravenously up to 8 to 12 times/dog/year, at a cumulative dose of 1.18 gm/kg.[100] Controversy remains whether it is a true anesthetic or simply an immobilizing agent with sedative-hypnotic properties[99]; however, for nonpainful PFT procedures its use seems appropriate. The drug is sparingly soluble,[102] and customized mixing may be necessary, raising possible problems with shelf life and sterility.

Chloral hydrate, a related agent, is another very old sedative hypnotic drug. Despite concerns about its safety, it is currently used extensively in human pediatric patients as an oral agent for non–operating room procedures because it provides an adequate level of sedation without compromising protective reflexes, airway patency, or cardiopulmonary stability.[103,104] Its use in laboratory animals is less common, in part because intraperitoneal administration is not recommended for survival procedures, and oral administration, at least in dogs, is associated with gastric irritation.[101] A recent experimental study in cats used oral chloral hydrate to determine its effect on esophageal smooth muscle tone, in comparison with oral midazolam or an intramuscular cocktail of meperidine, promethazine, and chlorpromazine.[105] Although all sedated cats had some degree of decreased esophageal tone, of the two oral agents, chloral hydrate had the least effect. More definitive studies are needed to determine whether these older agents or

whether other newer compounds (possibly in combination), can be used safely in companion dogs and cats and yet effectively preserve pulmonary reflexes and smooth muscle tone. Until standard anesthetic protocols are in place, if sedative/anesthetic agents are used during function testing, one should include a detailed summary of all agents used, including dosages, route(s) of administration, and level of effect. Importantly, these factors influence breathing frequency, lung volume, and bronchomotor tone, and thus may alter PFT assessments.

Although standard end-expiratory lung volume data and tidal F-V curves have provided objective assessment of airway function in pediatric patients, more recent assessments have focused on the latter portion of the expiratory curve in an effort to distinguish maturation changes from those related to airway obstructive disease.[106] For example, in infants with acute bronchiolitis, the ratio of time to reach peak tidal expiratory flow to total expiratory time (tPTEF/Te) allowed demonstration of acute responses to nebulized epinephrine.[107] Still, difficulties arise in interpreting TBFVL data due to dependency on simple differences in measurement conditions[108] and to high inter-subject variability.[109] As such, a variety of approaches have been used in infants in an attempt to simulate the maximal expiratory effort used for FEV_1 (forced expiratory volume in 1 second) measurements. In adults, FEV_1 is one of the most commonly used and reproducible lung function tests used to assess small airway function.[110] A forced deflation technique, used in pediatric patients with an endotracheal tube in place, can simulate maximal expiratory airflow. Typically the infant is given several manual inflations to establish a consistent volume history. Once total lung capacity is reached on the final inflation, the endotracheal tube is exposed to a constant negative pressure until either expiratory flow ceases or for a maximum of 3 seconds (FEV_3).[111] Alternatively, a sedated infant may be fitted with an inflatable jacket designed to apply sudden, but uniform pressure over the thorax and abdomen at the peak of inspiration.[111]

Another approach to assess airway resistance is the use of forced oscillation over a range of frequencies.[36] When used noninvasively for infants (by applying pressure at the mouth), the variable contribution of the upper airways limits the usefulness of the technique for clinical assessment of lung disease.[36] In addition, using a signal processing technique, inductive plethysmography has been used in infants to establish phase relationships between abdominal and thoracic displacement.[112] Despite considerable effort to standardize these approaches for use in very young patients, much work remains.[111]

Similar to the strategies used for function testing in infants, methods to obtain functional assessments less invasively in companion animals have included use of an unrestrained barometric, whole-body plethysmograph[113] or a minimal restraint dual-chamber plethysmograph. Although one cannot discriminate between upper and lower respiratory effects as definitively with this technique, data indicate that this approach is sufficiently sensitive to detect airflow decrements in cats undergoing bronchoprovocation testing[113] or, alternatively, to detect airflow improvement in asthmatic cats following aerosol administration of a bronchodilator.[114]

Finally, a few miscellaneous precautions are worth mentioning. If an endotracheal tube is used during testing, care must be taken to ensure that the tube is not acting as a critical orifice, creating artifactual flow limitation within the tracheal lumen. If strategies to enhance the ventilatory efforts of the patient are used, one must ensure that the pneumotachograph and pressure transducers are still in range to acquire the augmented signals, and that the system remains appropriately phase-matched. If maneuvers that tend to cause transient hypocapnia are used repeatedly (e.g., rapid lung deflation), changes in CO_2 retention may result in secondary effects on lung vascular and bronchomotor tone. In a similar fashion, alterations in lung volume history as is used during bronchoprovocation testing may recruit additional airspaces, yielding results that underestimate the functional deficits of the steady state diseased condition. And lastly, owing to the potentially labile nature of airway tone and patency, continuous ECG and pulse oximetry monitoring of all animals during and immediately after testing is considered prudent, as is providing general patient support (e.g., supplemental oxygen, anticholinergic or bronchodilating medication) until the animal is stable and fully recovered from the procedure.

As standard protocols are defined and as more complete reference values are available, we hope that PFTs will become more widely used in veterinary clinical medicine. Possibly by combining PFT assessments with other commonly available tests (e.g., blood gas analyses, thoracic radiography, bronchoscopy, and bronchoalveolar cytological/cultural examination), or with newer tests (e.g., pulse oximetry and end-tidal NO or CO_2 concentrations), we can better delineate the clinical spectrums of naturally occurring respiratory disease syndromes. For example, Wiester and colleagues demonstrated that in humans undergoing bronchoprovocation testing, acute decrements in SaO_2 measurements were highly correlated with decreases in lung functional endpoints (FEV_1 and SR_{AW}).[115] Similar innovative approaches may provide noninvasive means for determining AR in companion animals.

With this combined database, we aim to better characterize the etiologies and mechanisms of disease and, most important, to establish the efficacy of specific treatment protocols. Our overall goal is simply to provide a high quality of care for today's pet-owning public. To this end, cooperation between veterinary practitioners; small animal internists and surgeons; and specialists in respiratory physiology, anesthesiology, and critical care medicine will be essential.

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CHAPTER 24

Lung Mechanics Using Plethysmography and Spirometry

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Background Physiology and Definition

The goal of pulmonary function testing (PFT) is to provide an objective evaluation of the efficiency of the respiratory system to move air (ventilate) and exchange gases. Historically, in veterinary medicine, assessment of these two main features of the respiratory system has been subjective, largely based on clinical examination. Recently, arterial blood gas analysis, end-tidal CO_2 analysis, and pulse oximetry have become popular as measures of gas exchange and ventilation, but they do not provide a measure of lung mechanics (i.e., the amount of work required by the animal to maintain those blood gases or saturation). Hence the weakness in veterinary pulmonology is in the area of ventilation and lung mechanics, which constitute half of the picture.

The first lung function tests were described over 150 years ago by Hutchinson, who described a method of measuring vital capacity.[1] Since that time, measurement of lung volume has become routine in both the physiology laboratory and the physician's office. PFT is routinely used in human medicine to provide an objective assessment of pulmonary function and a method for judging response to therapy. In veterinary medicine, PFT is most widely used to assess horses presenting with cough or exercise intolerance.[2] In small animal practice, PFT has been largely used in university settings.[3-6] PFT that has been described in small animal practice includes spirometry and tidal breathing flow-volume loop analysis, plethysmography, and measurement of compliance and resistance.[3-6] This chapter discusses the advantages and limitations of spirometry and plethysmography. Both techniques are currently available and have value for case management, particularly in critical care settings.