Received: 28 September 2022 | Accepted: 2 March 2023

DOI: 10.1111/jvim.16685

STANDARD ARTICLE

Journal of Veterinary Internal Medicine Open Access

ACVIM American College of Veterinary Internal Medicine

Videofluoroscopic swallow study abnormalities identify aerodigestive disorders in dogs with respiratory disease versus healthy controls

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Funding information
American Kennel Club Canine Health Foundation, Grant/Award Number: 02699

Abstract

Background: Aerodigestive diseases (AeroD) pathologically link respiratory and alimentary tracts. Dogs with respiratory signs lacking dysphagia, vomiting, or regurgitation typically do not undergo diagnostic testing that identifies comorbid alimentary disease. A videofluoroscopic swallow study (VFSS) identifies defects in swallowing, reflux, and aspiration.

Objectives/Hypothesis: We hypothesized that dogs with respiratory and no alimentary disease (RESP) would have significantly more abnormal VFSS metrics versus controls (CON). We hypothesized RESP dogs with pulmonary parenchymal disease would have more reflux and higher penetration-aspiration score (PAS) than those with airway disease.

Animals: Client-owned dogs: RESP (n = 45) and CON (n = 15) groups.

Methods: Prospectively, all dogs underwent VFSS. The RESP dogs had advanced respiratory diagnostic testing. Eight subjective and 3 objective VFSS metrics (pharyngeal constriction ratio [PCR], PAS, and esophageal transit time [ETT]) were assessed. Fisher's exact test compared differences between groups (presence or absence of VFSS abnormalities). The Mann-Whitney rank sum test was used to compare PCR and PAS.

Results: Subjective VFSS abnormalities were present in 34/45 (75%) RESP and 2/15 (13%) CON dogs, with RESP dogs significantly more likely to have VFSS abnormalities ($P = .01$). No difference in PCR was found between groups. Pathologic PAS was more common in RESP than CON dogs ($P = .03$). The RESP dogs with airway disease had higher PAS than CON dogs ($P = .01$) but not RESP dogs with parenchymal disease ($P = .25$).

Conclusions: Most (75%) RESP dogs had VFSS abnormalities, emphasizing that AeroD are common. The VFSS has value in diagnostic evaluation of respiratory disease.

Abbreviations: AeroD, aerodigestive disorders; BAL, bronchoalveolar lavage; CFU, colony forming units; CON, healthy control dogs; CT, computed tomography; ETT, esophageal transit time; GER, gastroesophageal reflux (blinded for review); GI, gastrointestinal; MU-VHC, University of Missouri-Veterinary Health Center; PAS, penetration-aspiration score; PCR, pharyngeal constriction ratio; RESP, dogs with respiratory disease/no alimentary disease; ROI, region of interest; TNCC, total nucleated cell count; TRV, tricuspid regurgitation velocity; VFSS, videofluoroscopic swallow study.

KEYWORDS
aerodigestive disorders, aspiration, gastroesophageal reflux, videofluoroscopic swallow study

1 | INTRODUCTION

Aerodigestive disorders (AeroD) are a complex group of diseases emphasizing the close relationship and shared pathology between the alimentary and respiratory tracts.[1] Impaired airway protection, dysphagia, gastroesophageal reflux, regurgitation, vomiting, or combinations of these can cause or exacerbate respiratory disease. In dogs, aspiration pneumonia is the most commonly recognized AeroD, but a wide spectrum of other disorders is described.[2,3] In humans, AeroD, are linked to chronic sinusitis, laryngeal disorders, chronic cough, inflammatory airway and parenchymal diseases, and other disorders.[4,5] Diagnostic investigations linking respiratory and alimentary tract disorders in dogs are limited by poor clinical recognition and few specific testing modalities.[1,6] Recognition of AeroD is important because they impact a comprehensive therapeutic plan and prognosis. Additionally, idiopathic cough (i.e., cough in the absence of identifiable primary respiratory abnormalities) is thought to arise secondary to digestive disorders, which must be directly addressed for clinical benefit.[7]

The criterion standard for evaluation of functional upper alimentary tract disease and dysphagia in dogs is the videofluoroscopic swallow study (VFSS).[8] A standardized VFSS protocol has been validated in unrestrained dogs allowed to freely consume liquid, slurry, and kibble to investigate dysphagia.[8] The VFSS has been used to identify common swallowing defects in dogs, including abnormal esophageal motility, cricopharyngeal achalasia, and gastroesophageal reflux (GERD),[9-11] and to identify a higher prevalence of esophageal dysmotility in brachycephalic dogs compared to dogs with other head conformations.[12] Additionally, standardized VFSS has been used to refine the diagnosis of cases previously thought to be idiopathic megaesophagus into a known cause (a functional obstruction called lower esophageal sphincter achalasia-like syndrome).[13] Although these studies[8-11] succeeded in characterizing abnormalities observed on VFSS, they failed to investigate potential consequences to the respiratory tract. A recent retrospective study using the standardized VFSS protocol documented swallowing abnormalities in 81% of dogs with cough in absence of reported alimentary tract signs.[6] This finding suggests that a potentially large population of dogs with respiratory signs may have AeroD. If dogs are not evaluated for potential AeroD contributing to respiratory pathology, treatment targeting the alimentary tract to preserve respiratory health may be overlooked.

Prospective evaluation of VFSS in dogs with respiratory clinical signs but without alimentary clinical signs compared to healthy control dogs is warranted. We hypothesized that dogs presented for respiratory disease evaluation but lacking signs of dysphagia, vomiting or regurgitation (RESP group) would have proportionally more abnormal VFSS metrics compared to healthy control dogs (CON) without clinical signs of respiratory and alimentary disease. Our study objectives were to (a) demonstrate that RESP dogs have more occurrences of abnormal VFSS metrics (oral-preparatory phase defects, pharyngeal phase defects, abnormal esophageal contraction and peristalsis, megaesophagus, pathologic gastroesophageal reflux [reflux aboral to the distal third of the esophagus],[6,8] nasopharyngeal reflux, pathologic aerophagia, and hiatal hernia) versus CON, (b) document that objective VFSS metrics in RESP dogs are consistent with swallowing dysfunction (larger pharyngeal constriction ratio [PCR], higher penetration-aspiration score [PAS], and longer esophageal transit time [ETT]) versus CON, and (c) demonstrate that RESP dogs with parenchymal disease have more severe reflux and higher PAS than RESP dogs with airway disease.

2 | MATERIALS AND METHODS

2.1 | Case selection

For this prospective case-control study we studied 60 dogs presented to the University of Missouri-Veterinary Health Center (MU-VHC) between July 1, 2020 and May 1, 2022. Forty-five dogs with clinical signs of cough, audible respiratory disease (e.g., stertor, stridor, wheeze), or respiratory distress, without dysphagia, regurgitation or vomiting in the prior 2 months were enrolled in the RESP group. The RESP dogs underwent unrestrained, free-fed VFSS that included baseline respiratory fluoroscopy views, thoracic computed tomography (CT) with paired inspiratory and expiratory breath holds, tracheobronchoscopy, and bronchoalveolar lavage (BAL) submitted for cytology and bacterial culture. Dogs were excluded if they refused to spontaneously drink or eat the offered liquid, slurry, and kibble during the VFSS. They were excluded to avoid force feeding, which could artificially impact VFSS outcome measures. Additionally, dogs were not allowed to have received prokinetic drugs or sildenafil, which might influence VFSS results. The antitussive hydrocodone administered >6 hours before VFSS and antimicrobials and glucocorticoids were allowed. Fifteen dogs owned by faculty and staff of MU-VHC were enrolled in the CON group based on absence of respiratory and alimentary signs in the preceding 2 months. The CON dogs only had VFSS performed. The CON dogs were excluded if dysphagia or regurgitation was noted visually by observation of the dog in the clear plexiglass kennel during the VFSS. Written informed consent was obtained from owners. The study was performed according to institutional guidelines for animal care and use (IACUC protocol #10121). Demographic data was recorded for both groups from medical records. Heartworm testing results were either acquired from referring veterinarian records (previous 6 months) or performed in hospital using heartworm antigen by point-of-care, SNAP Heartworm RT Test (SNAP; IDEXX Laboratories, Inc., Westbrook, Maine, USA).

2.2 | Videofluoroscopy

Standardized VFSS including baseline survey respiratory fluoroscopy was performed using an unrestrained, free-feeding protocol and plexiglass kennels in RESP and CON dogs as described previously.[8] Dogs were fasted 12 hours before the study. Studies were performed at 30 frames/s using a GE OEC 9900 Elite Mobile C-Arm system (GE Healthcare OEC, Salt Lake City, Utah). A distance calibration marker (19 mm stainless steel ball secured to a plastic coil collar around the neck) was positioned at the midline ventral neck of each dog to facilitate objective quantification of swallowing function. Baseline survey images before feeding were obtained focusing on the oropharynx and upper airways (oropharynx, nasopharynx, larynx, extrathoracic trachea), lower airways (intrathoracic trachea and mainstem bronchi), esophagus, and stomach. Subjective and objective VFSS metrics using liquid and slurry with iohexol (Omnipaque 350, GE Healthcare; diluted to 25% using canned chicken broth or canned pureed food) and barium extruded kibble (40% w/v) were assessed individually based on previously reported recipes and palatability trials.[8] The bowl was positioned approximately 6 inches below wither height, allowing the fluoroscope to remain at a constant height while following swallowed boluses through the upper gastrointestinal (GI) tract.[8] After consuming meals of all 3 consistencies, additional cine loops were obtained while radiology personnel applied abdominal pressure to evaluate for pathologic reflux or sliding hiatal hernia.

Subjective metrics included abnormalities of: (a) oral-preparatory phase (jaw excursion, mastication, collection of the food bolus at the tongue base), (b) pharyngeal phase (pharyngeal constriction, transfer of the bolus from the pharynx through the upper esophageal sphincter), (c) esophageal stage (efficacy of contraction and peristalsis for aboral bolus transport, beginning in the proximal esophagus and initiated by pharyngeal swallows), (d) megaesophagus (esophageal dilatation with poor or absent motility), (e) gastroesophageal reflux (reflux originating in the stomach traversing into the esophagus, with pathologic reflux defined as retrograde movement of ingesta into the proximal or middle third of the esophagus or outside the esophagus [extra-esophageal reflux][6,8]), (f) nasopharyngeal reflux (movement of contrast from the pharynx to nasopharynx during pharyngeal swallow or with esophago-oropharyngeal reflux), (g) excessive aerophagia (swallowing marked volumes of air contributing to more than one-third of the end gastric volume), and (h) hiatal hernia (passive or induced herniation of the stomach into the thoracic cavity through the esophageal hiatus). Analysis of subjective and objective metrics was performed by a single blinded investigator (MG) with experience in interpretation of VFSS who reviewed videos frame-by-frame using Pinnacle Studio 25 video editing software (Corel, Ontario, Canada).

Objective metrics included PCR, PAS, and ETT and when possible, these were assessed for each food consistency. These 3 metrics were selected a priori to capture crucial measures of pharyngeal function (PCR), esophageal function (ETT) and the risk of abnormalities of the upper digestive tract leading to increased risk of respiratory disease (PAS).[9,14-17] Additional objective metrics[8] were not assessed to avoid increased risk of a type I error. Pharyngeal constriction ratio was determined from a representative still frame of the larynx that at rest, was within the fluoroscope field of view for objective quantification purposes with the calibration marker in view.[14] A region of interest (ROI) was digitally drawn using commercially available freeware (NIH ImageJ, National Institute of Health, Bethesda, Maryland) to encompass the supraglottic airspace within the pharynx. The ROI was defined dorsally by the dorsal pharyngeal wall and extended from the hyoid apparatus rostrally to the upper esophageal sphincter caudally. Next, a maximum contraction frame was identified in which the dorsal pharyngeal wall had assumed its most caudoventral position. An ROI was drawn in the corresponding image to outline any residual barium or airspace remaining within the pharynx at this point. Both ROIs were expressed in pixel number. Pharyngeal constriction ratio was calculated as the ratio of pixels in the maximum constriction frame ROI divided by the pixels in the hold frame ROI. The PAS, a metric of airway protection that measures the amount of airway invasion of food or liquid during swallowing, was assigned a score on a scale of 1 to 7, with 1 considered normal, 2-4 considered penetration, and 5-7 considered aspiration as previously described.[18,19] Pathologic PAS was defined as a score ≥3.[19] The ETT was defined as the duration of time from the bolus entering the esophagus after pharyngeal swallow until the tail of the bolus entered the stomach.[8]

2.3 | Respiratory diagnostic testing

For dogs receiving thoracic radiography, 3-view radiographs were obtained, and all were reviewed by a board-certified radiologist. For dogs receiving echocardiography, transthoracic echocardiography was performed using an Artida Aplio (Toshiba Medical Systems Corporation, Otawara, Japan) with standard imaging planes[20] by a board-certified cardiologist or a directly-supervised cardiology resident. When present, tricuspid regurgitation velocity (TRV) was interrogated; supportive clinical signs and a TRV >3.4 m/s were compatible with intermediate to high probability of pulmonary hypertension.[21]

Anesthesia (protocols at the discretion of a board-certified anesthesiologist) was required for advanced imaging. Anesthetic induction took place in the CT scanner room using IV propofol (Diprivan, Fresenius Kabi USA, LLC, Lake Zurich, Illinois) titrated to effect (induction, 6 mg/kg IV once; maintenance, 0.2-0.5 mg/kg/min). A subset of dogs had functional upper airway examination using doxapram hydrochloride (Dopram, Hikma Pharmaceuticals USA, Eatontown, New Jersey) 1 mg/kg IV, to stimulate deep inhalation. Appearance of mucosa, soft palate length, and presence of tonsillar eversion, epiglottic retroversion, laryngeal paresis, and laryngeal paralysis were recorded. Dogs were intubated with a sterile endotracheal tube for CT scans.

Thoracic CT was accomplished with assistance from a mechanical ventilator (Engstrom Carestation ventilator, GE Healthcare, Chicago, Illinois) in the volume-controlled ventilation setting with the following standardized parameters: 40% fraction inspired oxygen, tidal volume of 10 mL/kg, respiratory rate of 10 breaths per minute, inspiratory: expiratory ratio of 1:3.5, and positive end expiratory pressure (PEEP) of 5 cm H_2O. Ventilator settings were adjusted to meet patient needs.

The CT images were acquired using inspiratory and expiratory breath holds with the expiratory breath hold having PEEP = 0 cm H_2O. Additional inspiratory and expiratory breath hold series were performed after IV administration of contrast (Omnipaque, GE Healthcare Inc., Marlborough, Massachusetts). After acquisition of CT images, patients were transferred to a gas anesthetic machine and maintained on 100% oxygen while moved to the endoscopy suite for tracheobronchoscopy and BAL. The CT studies were interpreted by board-certified radiologists.

Dogs were positioned in sternal recumbency and before bronchoscopy a sterile endotracheal tube was replaced with a sterile red rubber catheter to provide oxygen. A sterilized flexible fiberoptic bronchoscope (Models EB-450t or FB-120p Fujinion, Tokyo, Japan) was passed through the larynx into the tracheobronchial tree. The tracheobronchial tree was evaluated in a standard fashion and the site for BAL was chosen based on findings from thoracic CT, bronchoscopy, or both. Collection of BAL fluid was performed by instilling 1-3, 20 mL aliquots of sterile saline through the channel of the bronchoscope when wedged in an airway. Samples were pooled, placed on ice, and delivered to the MU-VHC clinical pathology laboratory and diagnostic microbiology laboratory for culture and bacterial sensitivity, respectively.

Total nucleated cell count (TNCC) was determined using an automated cell counter (Advia 120; Siemens, Deerfield, Illinois). A 100 to 500 cell count differential was performed by a board-certified clinical pathologist using Wright-stained cytospin material. Reference ranges for normal BAL cytology were as follows: TNCC <500 cell/μL, >78% macrophages, <7% lymphocytes, <5% neutrophils, <6% eosinophils, <1% mast cells and <1% epithelial cells.[22] Samples submitted for culture were plated on MacConkey and blood agar for aerobic, and on

TABLE 1 Additional definitions for respiratory diagnoses and pathologic lesions.[a]

Diagnosis	Definition
Epiglottic retroversion	Caudal displacement of the epiglottis into the rima glottidis during inspiration causing upper airway obstruction. Documented by respiratory fluoroscopy and the criterion standard test of functional upper airway examination during robust inspiratory effort
Laryngeal paresis	Symmetric or asymmetric submaximal abduction of the arytenoids during inspiration. Documented by functional laryngeal examination during robust inspiratory effort[b]
Uncharacterized parenchymal disease	Evidence of increased opacity or attenuation of the pulmonary parenchyma on thoracic radiography or computed tomography (CT), without or with inflammatory airway cytology lacking obvious infectious organisms or neoplastic cells, and with negative bacterial culture of airway lavage. There is no histologic confirmation of a specific etiology including aspiration pneumonia, bacterial or other infectious pneumonia, interstitial lung disease, or neoplasia.
Developmental lung disease	Histologic evidence of airway dysplasia often with diminished terminal bronchioles and associated alveolar dilatation
Pyothorax	Septic purulent exudate within the pleural space identified via cytologic examination with positive aerobic or anaerobic bacterial culture
Idiopathic cough	Chronic cough with absence of abnormalities on thoracic radiography, respiratory fluoroscopy, functional upper airway examination, thoracic CT, tracheobronchoscopy and bronchoalveolar lavage and culture. Suspected to be caused by extra-esophageal reflux
Cystic lung disease	Thoracic radiography or computed tomographic evidence of air-filled lucencies bordered by a thin wall
Pulmonary nodule(s)	Solitary or multiple round opacities of varying size (from micronodules to masses) observed on thoracic radiography or CT that reflect infection, noninfectious inflammation, fibrosis, or neoplasia

[a]These definitions are intended to supplement those provided in Gamracy, J. et al, 2022, table S1.[23]
[b]Stimulation of deep inspiration during functional upper airway examination is performed by administration of doxopram.

TABLE 2 Proposed anatomic category of respiratory disease in dogs presenting without alimentary signs.

Category	Definition
Airway disease	Laryngeal, tracheal, or bronchial pathology
Parenchymal disease	Pathology focused on the interstitium and alveoli
Both airway & parenchymal disease	Subjective assessment that magnitude of airway and parenchymal pathology are substantial and equally responsible for clinical signs
Airway predominant disease but with both airway and parenchymal pathology	Subjective assessment that the magnitude of airway pathology was responsible for clinical signs, with subtle evidence of parenchymal pathology
Parenchyma predominant disease but with both airway and parenchymal pathology	Subjective assessment that the magnitude of parenchymal pathology was responsible for clinical signs, with subtle evidence of airway pathology
No evidence of airway or parenchymal pathology	No evidence of respiratory disease; may need to consider clinical signs are attributable to a primary digestive disorder (ie, idiopathic cough)

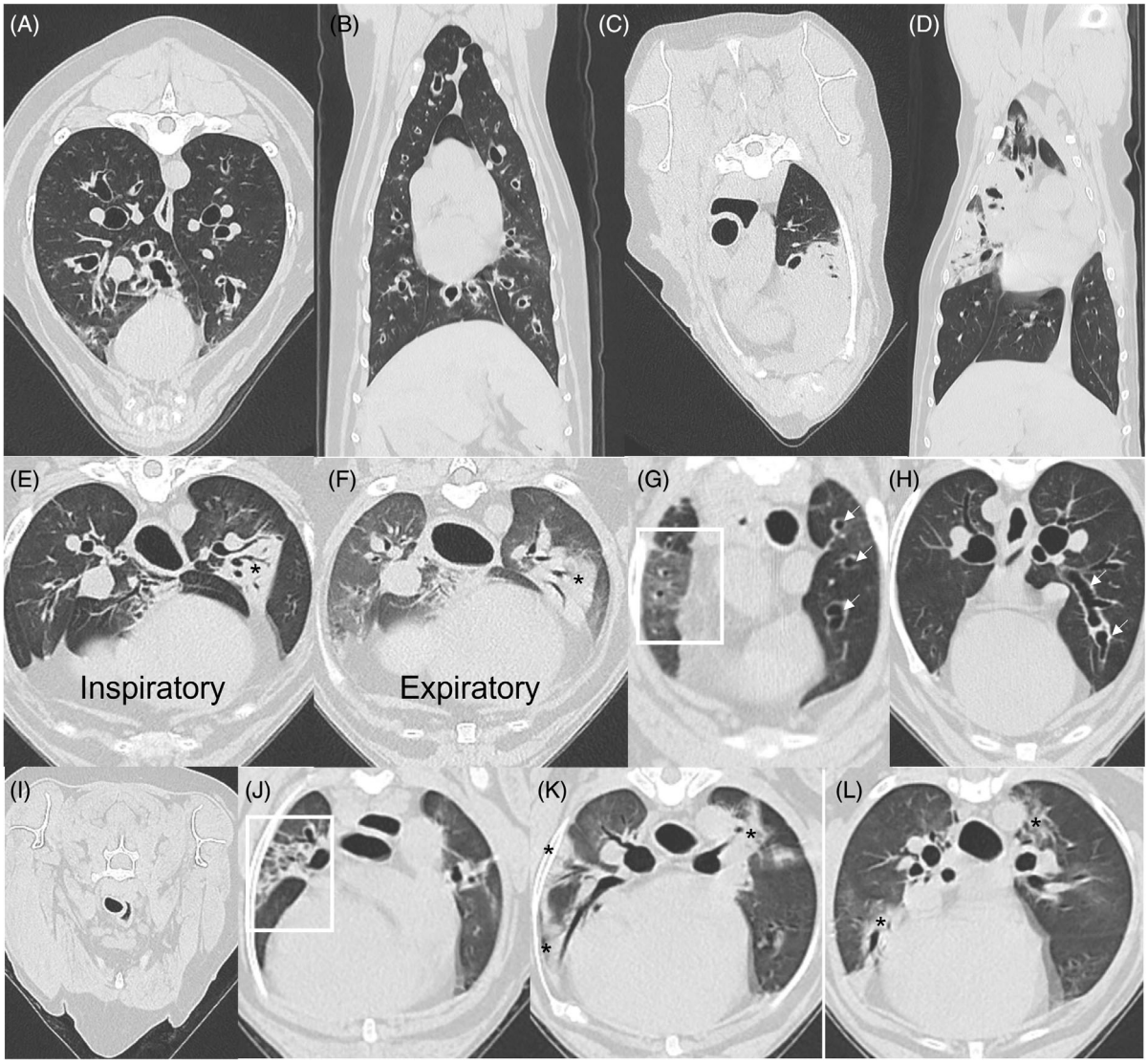

FIGURE 1 Use of thoracic computed tomography to aid in classification of final diagnosis in dogs with respiratory disease based on airway, parenchymal or mixed airway and parenchymal involvement. (A, B) Transverse and dorsal sections from a 6-year-old MC Siberian Husky with airway disease. Note the marked peribronchovascular thickening creating an appearance of peribronchial cuffing in cross-section. Bronchiectasis was noted by dilatation and lack of tapering of airways traversing to the periphery. The final diagnoses were eosinophilic bronchitis and bronchiectasis. (C, D) Transverse and dorsal sections from a 10-year-old FS Labrador retriever with parenchymal disease. Note the extensive regions of consolidation. Histology and response to immunosuppression confirmed an immune-mediated lung disease. (E, F) Paired ventilator-assisted inspiratory: expiratory breath hold transverse sections from an 11-year-old MC French bulldog with both airway and parenchymal disease substantially contributing to clinical signs. On the inspiratory series, increased peribronchovascular thickening and focal consolidation (*) are noted. On the expiratory series, the caliber of the segmental and subsegmental airways are smaller than on the inspiratory series with a corresponding loss of lung volume and presence of more global ground glass opacity because of downstream effects of bronchomalacia. The previously noted region of consolidation (*) remains present. The final diagnoses included brachycephalic obstructive airway syndrome, bronchomalacia, aspiration pneumonia, and suspect pulmonary fibrosis (corresponding lesions not shown). (G, H) Transverse images from a 13-year-old FS French bulldog with predominating airway lesions and mild, focal evidence of parenchymal disease. In (G), ground glass opacification in the mid-zone of the lung (within the white box), with Hounsfield units ranging from −425 to −550. The white arrows on the right side of the figure show bronchiectatic airways. Further evidence of cylindrical bronchiectasis is seen in (H) with a lack of tapering as shown by the white arrows. Using data from the clinical picture and other advanced diagnostics, the final diagnoses were chronic bronchitis, bronchiectasis, mainstem bronchial collapse, hiatal hernia, and uncharacterized parenchymal disease. (I-L) Transverse images from a 14-year-old FS Pomeranian with predominating parenchymal disease and a lesser contribution of airway disease. In (I) taken from the expiratory series, grade II tracheal collapse is demonstrated by a 50% reduction in luminal diameter with a flattened shape. In (J), the box outlines a region of architectural distortion characterized by traction bronchiectasis/bronchiolectasis superimposed on a background of reticulation and ground glass opacity, compatible with pulmonary fibrosis. In (K) and (L), there are multifocal regions of ground glass opacity and consolidation (*). Final diagnoses were grade II tracheal collapse, grade I mainstem bronchial collapse, grade I bronchomalacia, extra-esophageal reflux, suspect pulmonary fibrosis, and uncharacterized parenchymal disease.

chocolate agar for capnophilic cultures. Dogs that had received antimicrobials before airway lavage had BAL inoculated into a growth medium with antimicrobial removal devices. Organisms were identified and reported semi-quantitatively using colony-forming units (cfu)/mL.

2.4 | Final respiratory diagnoses

A comprehensive evaluation of the medical record, including signalment, prior referral veterinary records, history, physical examination, respiratory diagnostic testing, (including review of all CT images and, when available, video clips of tracheobronchoscopic examination), and reports of lung histology (2 antemortem, 1 postmortem) was performed by 1 author with expertise in respiratory disease (CR) to assign final diagnoses. Final diagnoses determined for each RESP dog were based on previously published 25 definitions (Table S1[23]) and definitions for additional diagnoses in Table 1. A classification scheme for anatomic site of pathology in RESP dogs based on airway and parenchymal involvement is shown in Table 2 with examples of thoracic CTs representing each category shown in Figure 1. For statistical comparisons, RESP dogs with airway disease and airway predominant disease were grouped together in the airway disease group, and dogs with parenchymal disease and parenchymal predominant disease were grouped together in the parenchymal disease group.

2.5 | Statistical analysis

Statistical analyses were performed using SigmaPlot data analysis software (version 12.0, Systat Software Inc. Chicago, Illinois). Descriptive statistics were performed where appropriate. All data were found to be non-normally distributed using a Sharpio-Wilk test. Data were evaluated non-parametrically with results presented as median and interquartile ranges (IQR). A Mann-Whitney rank sum test was used to determine differences between RESP and CON groups in terms of presence or absence of evaluated metrics. A Fischer's exact test was used to compare presence or absence of evaluated metrics between subgroups of RESP dogs (those with predominating airway disease or parenchymal disease) and CON. Significance was set at $P < .05$.

3 | RESULTS

3.1 | Animals

Cases (n = 147) were identified for inclusion over 2 years. A flowchart of inclusion and exclusion criteria is shown in Figure 2. Forty-five dogs met enrollment criteria for the RESP group. Respiratory signs included cough (36), excessive panting (7), collapse (7), exercise intolerance (5), sneezing (1), and nasal discharge (1). When owners were questioned specifically, 3 dogs were noted to cough while eating or drinking. The median (IQR) for duration of clinical signs was 5 months (2-12 months).

Fifteen dogs met inclusion criteria for enrollment in the CON group. Demographic data and temperature, pulse, respiration and body weight for RESP and CON dogs are shown in Table 3. Comorbid diseases included atopic dermatitis (n = 2) and American College of Veterinary Medicine (ACVIM) Stage B2 degenerative mitral valve disease (1). Follow-up on all healthy CON dogs 1 year after VFSS indicated that 4 dogs had developed respiratory signs, 3 had developed a cough and 1 dog experienced a single episode of aspiration pneumonia.

When comparing age, body weight, body condition score, temperature, pulse and respiration, the only significant difference between RESP and CON dogs was that RESP dogs were significantly older ($P = .04$).

3.2 | Fluoroscopy

Baseline (pre-feeding) respiratory fluoroscopic images disclosed respiratory abnormalities in 19 RESP dogs. These included narrowed mainstem bronchial diameters spontaneously or with cough (n = 14), dynamic pharyngeal collapse or narrowing (5), cervical lung herniation (5), elongated soft palate (5), tracheal collapse (5), caudal movement of the epiglottis on inspiration (2 persistent, 1 intermittent), and a tracheal opacity (1). For CON dogs, respiratory fluoroscopy identified mainstem bronchial collapse in 1 dog. The RESP dogs were significantly more likely to have baseline abnormalities on respiratory fluoroscopy than CON dogs ($P = .02$).

Diagnostic quality VFSS were obtained in all RESP and CON dogs. Abnormal subjective metrics on VFSS were noted in 34/45 (75%) RESP dogs. Examples of selected subjective VFSS abnormalities are shown in Figure 3. Oral preparatory defects were noted in 9 dogs and pharyngeal phase defects in 7 dogs. Esophageal weakness was present in 10 dogs; no dogs had megaesophagus. Sixteen RESP dogs had pathologic reflux. Physiologic reflux (considered a

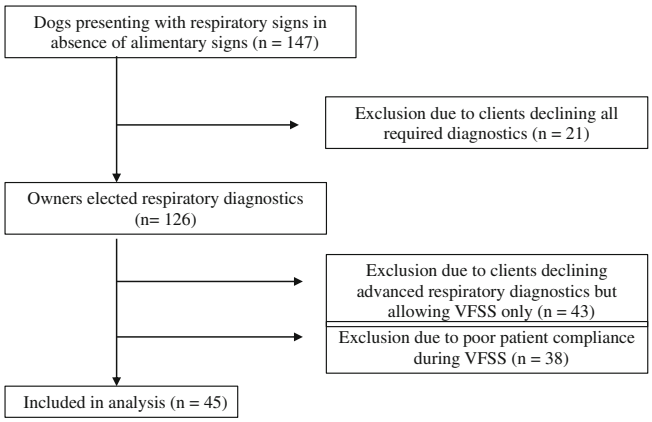

FIGURE 2 Flow chart showing inclusion and exclusion of dogs with respiratory clinical signs in absence of alimentary signs.

TABLE 3 Demographic data, temperature, pulse and respiration rates, and body weight for RESP and CON dogs.

Variable	RESP	CON
Age (years)		
Median	9	4
Interquartile range	4.3-11	3-8
Range	0.9-14	0.9-14
Sex (n)		
Male castrated	24	8
Male intact	6	1
Female spayed	15	6
Female intact	0	0
Head conformation (n)		
Mesaticephalic	34	14
Brachycephalic	7	0
Dolichocephalic	4	1
Breed (n)		
Labrador retriever	8	1
Australian shepherd	5	0
Mixed breed	5	10
Golden retriever	3	0
Yorkshire terrier	3	0
Pug	2	0
French Bulldog	2	0
Miniature Poodle	2	2
Catahoula leopard dog	0	1
Siberian Husky	1	0
Dachshund	1	0
Border collie	1	0
Beagle	1	0
Havanese	1	0
Pomeranian	1	0
German Shepherd dog	1	0
Shih Tzu	1	0
Norwegian elkhound	1	0
Miniature pinscher	1	0
Chihuahua	1	0
Shetland sheepdog	1	0
Tibetan terrier	1	0
West Highland white terrier	1	0
American Staffordshire terrier	0	1
Heart rate (beats per minute)		
Median	120	120
Interquartile range	100-127	105-122
Range	80-200	88-128
Temperature (°Celsius)		
Median	38.8	37.8
Interquartile range	38.3-39.1	38.4-39
Range	36.5-40.2	36.5-39.6

TABLE 3 (Continued)

Variable	RESP	CON
Respiratory rate (breaths per minute)		
Median	32	24
Interquartile range	24-42	22-28
Range	12-76	16-36
Weight (kg)		
Median	20.8	19
Interquartile range	9.0-31.3	10.75-24.9
Range	2.6-50.8	4.6-32.4

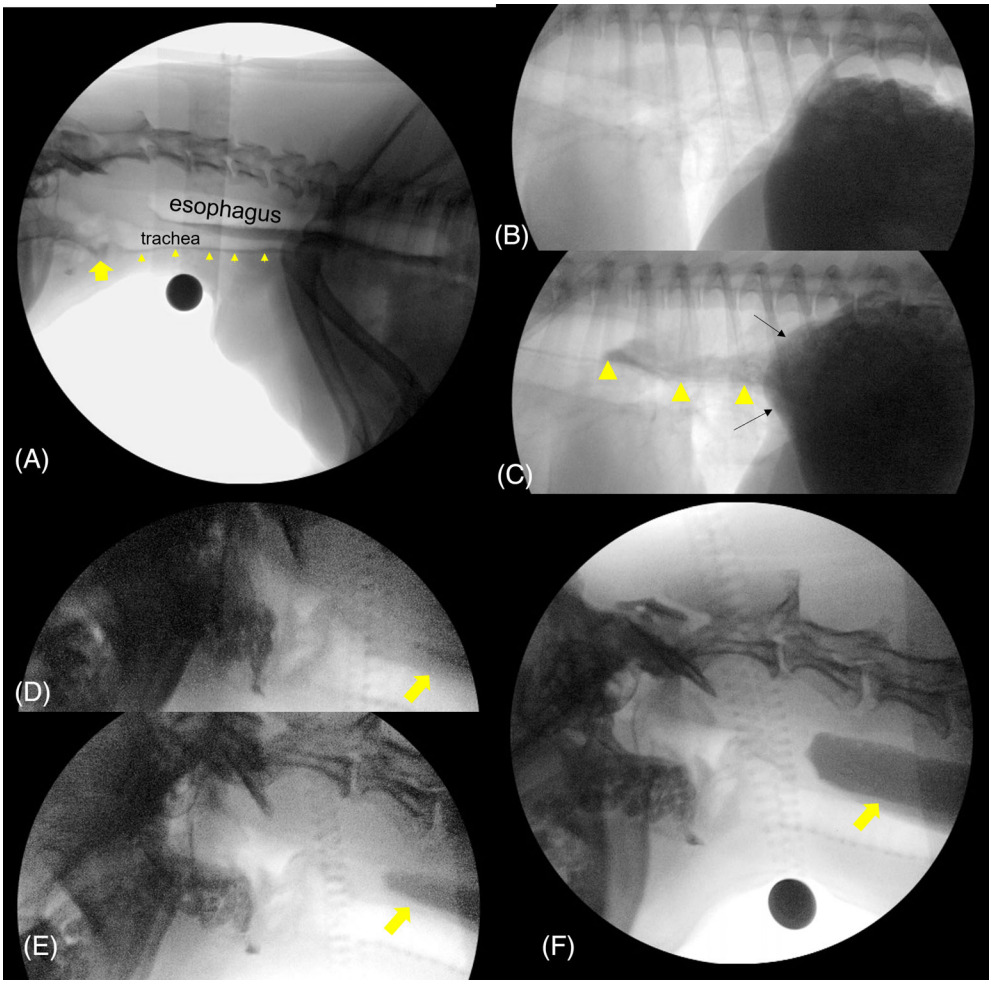

FIGURE 3 Examples of subjective abnormalities detected on videofluoroscopic swallow study (VFSS) in RESP dogs. (A) VFSS images from a 13-year-old female spayed Tibetan Terrier presenting for chronic cough demonstrating penetration (large yellow arrow) and aspiration (yellow arrow heads) in the proximal trachea during swallowing of liquid. (B, C) VFSS images of a sliding hiatal hernia and pathologic reflux from a 3-year-old Australian Shepherd presenting for cough. In (B), the distal esophagus and proximal stomach is imaged after consumption of all consistencies and filling of the stomach. In (C), cranial herniation of the cardia of the stomach into the thoracic cavity (small black arrows) with subsequent pathologic reflux marginating to the middle third of the esophagus (yellow arrowheads). (D-F) Serial VFSS images from an 11-year-old male castrated Golden Retriever presenting for cough and recurrent pneumonia. Sequential images display retrograde movement of increasing volumes of reflux (yellow arrows) of previously ingested liquid/slurry during consumption of kibble.

variant of normal) was noted in 11/45 RESP dogs. Pathologic aerophagia was identified in 21 dogs. Four dogs had hiatal hernia. Comparatively, only 2 CON dogs had abnormalities on VFSS: 1 with pathologic reflux, esophageal weakness, and hiatal hernia and the other with pathologic reflux only. Follow-up at 1 year in these 2 CON dogs determined that both had developed respiratory

clinical signs. Physiologic reflux was noted in 6/15 CON dogs. Overall, RESP dogs were significantly more likely to have abnormal subjective VFSS metrics than CON dogs ($P = .01$).

Complete data sets were not available for all dogs for all food consistencies for analysis of objective metrics. Pharyngeal constriction ratio could be measured in 27 RESP dogs and 10 CON dogs with median (IQR) PCR being 0.0961 (0.0057-0.0259) and 0.0098 (0.0044-0.0129), respectively. No significant difference was found in PCR measurements between groups. Twelve RESP dogs had pathologic PAS (score ≥ 3). The median (IQR) for non-pathologic PAS in RESP dogs was 1 (1, 2) and for pathologic PAS, 7 (3-7). No CON dog had penetration or aspiration noted. When comparing RESP and CON dogs, the former were significantly more likely to have pathologic PAS ($P = .03$). In RESP dogs, ETT could be measured for puree (n = 15), liquid (9), and kibble (18) with the median (IQR) being 4.6 (4.0-5.4) s, 3.1 (2.2-3.7) s, and 4.9 (3.8-5.5) s, respectively. In the CON group, ETT were only measurable for 3 dogs with puree and 2 dogs each with kibble and liquid. Statistical comparisons between RESP and CON groups were not performed because of small sample size for this metric.

3.3 | Respiratory diagnostic testing

Thirteen dogs had thoracic radiographs performed. Radiographic pulmonary patterns included bronchial (n = 10), interstitial (3), and alveolar (1) or were unremarkable (2). Three of 22 dogs had echocardiography results showing intermediate to high probability of pulmonary hypertension. Heartworm testing was positive in 2/45 dogs.

Sixteen dogs had functional upper airway examination performed (Table 4). Findings on thoracic CT included both airway and parenchymal changes, with most dogs having >1 type of pattern. Airway changes included peribronchial cuffing (19), bronchiectasis (17), bronchomalacia (16), tracheal collapse (9), and mainstem bronchial collapse (3). Major pulmonary patterns included increased attenuation (28), linear pattern (22), decreased attenuation (9), and a nodular/mixed pattern (1). Examples of these patterns are shown in Figure S1.

Bronchoscopic findings are summarized in Table 4. Total nucleated cell count median (IQR) of BAL was 210/μL (140-380/μL). Nineteen dogs (19/45, 42%) had neutrophilic inflammation (3 septic), 9 dogs had eosinophilic inflammation (9/45, 20%), 6 had mixed inflammation (6/45 13%), 5 dogs had normal cytology (5/45, 11%), 4 had macrophagic inflammation (4/45, 8%), 1 dog had mastocytic inflammation (1/45, 2%) and 1 had lymphocytic inflammation (1/45, 2%). Twenty-five dogs had BAL culture performed. Although 16 cultures had isolates of ≥1 organisms, only 2 dogs had growth considered clinically relevant with >100,00 cfu/mL with septic neutrophilic inflammation on cytology. In all other dogs with positive cultures, organisms were not considered pathogenic based on only being recovered on enrichment broth and absence of septic inflammation on BAL cytology.[24]

TABLE 4 Laryngeal examination and bronchoscopic findings in RESP dogs.

	n
Laryngeal examination findings	
Erythema	7
Laryngeal paresis	5
Laryngeal paralysis	4
Epiglottic retroversion	2
Bronchoscopic findings	
Erythema	40
Bronchomalacia	16
Bronchiectasis	13
Tracheal collapse	9
Mainstem bronchial collapse	3

3.4 | Final diagnoses

Final respiratory disease diagnoses are shown in Table 5. Thirty-seven dogs had >1 final diagnosis (range, 2-7 diagnoses). Nineteen dogs were considered to have an airway or airway predominant disorder

TABLE 5 Final respiratory disease diagnoses.

Diagnosis	Number of dogs (n)
Bronchiectasis	17
Bronchomalacia	16
Chronic bronchitis	14
Uncharacterized parenchymal disease	11
Tracheal collapse	10
Bronchiolar disease	9
Pulmonary fibrosis (suspected)	8
Eosinophilic bronchitis	6
Laryngeal paresis	5
Laryngeal paralysis	4
Eosinophilic bronchopneumopathy	4
Aspiration pneumonia	4
Mainstem bronchial collapse	3
Epiglottic retroversion	3
Eosinophilic pneumonia	1
Pyothorax	1
Pulmonary nodule	1
Pulmonary bulla (cystic lung disease)	1
Brachycephalic obstructive airway syndrome	1
Interstitial lung disease	1
Pulmonary vascular disease	1
Developmental lung disease	1

Note: Intermediate or high probability of pulmonary hypertension, considered a sequalae to variety of cardiac, vascular, and respiratory disorders and not a disease per se,[21] was noted in 3 dogs.

and 13 dogs a parenchymal or parenchymal predominant disorder. Eleven dogs had equal distribution between airway and parenchymal disorders and 3 dogs had no airway or parenchymal lesions and were diagnosed with idiopathic cough. All dogs with idiopathic cough had VFSS abnormalities including extra-esophageal reflux (n = 2) and hiatal hernia (1).

Presence of pathologic reflux was not significantly different ($P = .28$) among CON dogs (2/15), RESP dogs with airway disease (7/19) and RESP dogs with parenchymal disease (3/13), nor was any difference found in presence of pathologic reflux between RESP dogs with airway disease or parenchymal disease ($P = .47$). Presence of pathologic PAS was significantly different ($P = .02$) among CON dogs (0/15), RESP dogs with airway disease (7/19) and RESP dogs with parenchymal disease (2/13). Post-hoc analysis showed RESP dogs with airway disease were more likely to have pathologic PAS than CON dogs ($P = .01$). No significant difference was found in presence of pathologic PAS between RESP dogs with airway disease and RESP dogs with parenchymal disease ($P = .25$).

4 | DISCUSSION

In dogs presented for evaluation of respiratory clinical signs without owner-reported dysphagia, regurgitation, or vomiting, 75% had subjective abnormalities of metrics on VFSS, emphasizing the critical interplay between the shared respiratory and upper digestive tracts. A prior retrospective study documented a high rate (81%) of VFSS abnormalities in dogs presented solely for cough, and our current study supports similar findings in dogs with more diverse respiratory clinical signs and in a prospective manner, with healthy control dogs and using uniform and standardized advanced diagnostic testing.[6] Pathologic reflux did not differ between RESP (15/45, 33%) and CON (2/15, 13%) dogs, but interestingly, both CON dogs with pathologic reflux developed overt respiratory clinical signs within a year. Further study is warranted to determine if pathologic reflux noted on VFSS is an early predictor for development of clinical respiratory disease. Although significantly more subjective VFSS abnormalities were found in RESP versus CON dogs ($P = .01$), the only objective VFSS metric that significantly differed between RESP and CON dogs was pathologic PAS ($P = .03$). When comparing pathologic PAS among RESP dogs with airway disease, RESP dogs with parenchymal disease, and CON dogs, there was a significant difference attributable to RESP dogs with airway disease having higher pathologic PAS than CON dogs. Thus, higher PAS in dogs with airway disease suggests a contribution of penetration-aspiration to the pathogenesis of disease in these patients. Collectively our results emphasize the need to identify, understand, and address silent alimentary tract disease as a contributor to a large spectrum of respiratory disorders.

Although RESP dogs were significantly older than CON dogs, a prior study documented lack of age-related changes on VFSS in healthy dogs.[8] Brachycephalic breeds are predisposed to aspiration-related respiratory disease such as aspiration pneumonia and also have a high prevalence of multiple digestive tract abnormalities.[25,26] Our study could not statistically compare difference in head conformation between groups because our CON group lacked brachycephalic dogs, perhaps because the majority of brachycephalic dogs have at least some evidence of respiratory or digestive clinical signs and thus would have failed our inclusion criteria.

A thorough diagnostic evaluation indicated that most dogs (37/45, 82%) had multiple respiratory disorders and the VFSS was key to provide evidence of overlap between pathology of the digestive and respiratory tracts. Airway diseases included functional, structural, and inflammatory etiologies. Functional laryngeal examination showed laryngeal erythema (n = 7), laryngeal paresis (n = 5) and laryngeal paralysis (n = 4). In humans, repetitive, silent aspiration is a cause of laryngeal paresis or paralysis.[27] Although a prior study found that a subset of dogs presented for cough had abnormalities on laryngeal examination suggestive of abnormal airway defenses that the authors speculated could lead to micro- or macro-aspiration, it was not proposed that the laryngeal abnormalities themselves resulted from repetitive micro- or macro-aspiration.[28] Bi-directional pathology is likely. Inflammatory airway diseases were commonly identified in our current study, emphasizing a link between the 2 systems.

Thirteen RESP dogs had evidence of a parenchymal predominant disorder, perhaps suggesting swallowing abnormalities, including aspiration of gastric acid and digestive enzymes, can incite inflammation and potentially lead to parenchymal pathology. Studies in humans have shown higher prevalence of GER, anatomic abnormalities predisposing to GER, and dysphagia in patients with idiopathic pulmonary fibrosis and interstitial pneumonia when compared to those without pulmonary disease.[29-31] It is possible that GER in dogs similarly can contribute to parenchymal pathology such as pulmonary fibrosis or other uncharacterized parenchymal diseases.[32]

In support of our hypothesis, RESP dogs had more subjective VFSS abnormalities than CON dogs, with prevalent abnormalities including reflux (16/45, 36%) and esophageal weakness (10/45, 22%). In people, a higher prevalence of GER compared to the general population has been observed with chronic obstructive pulmonary disease and asthma.[33,34] Similarly, dysphagia or esophageal weakness or both are highly prevalent in people with chronic respiratory diseases such as chronic obstructive pulmonary disease or sleep apnea.[35] Given the high number of RESP dogs with these findings noted on VFSS, it is possible that these abnormalities may be contributing to respiratory disease.

Idiopathic cough is a syndrome recognized in people where cause of cough is undetermined despite thorough diagnostic evaluation. Although no cause can be found, several possibilities exist including undetected GER or organ-specific autoimmune disease.[7,36] Three RESP dogs had unremarkable advanced respiratory diagnostic testing, and all had abnormalities on VFSS and were diagnosed with idiopathic cough. In these 3 dogs, the presence of multiple VFSS abnormalities without respiratory pathology could support a diagnosis of idiopathic cough as in human medicine, and idiopathic cough in dogs could be related in part to digestive disorders.[36]

Our study determined that RESP dogs were significantly more likely to have pathologic PAS than CON dogs, with overt macroaspiration

being a clear risk factor for injury to the respiratory tract. Multiple protective mechanisms of the upper airways must be overcome for penetration and aspiration to occur. A pathologic PAS is common in dogs undergoing VFSS regardless of initial clinical signs (GI, respiratory, or both) with 39% of dogs in a recent study having a PAS >3.[18] Identifying patients with penetration and aspiration is important not only in elucidating a link between upper digestive and respiratory disorders, but also may help in future studies to investigate responses to treatment targeting the underlying alimentary abnormalities. Because of intermittent poor patient compliance and inability to capture desired frames (e.g., calibration marker for PCR, a complete clip from pharyngeal swallow to gastric filling for ETT), we were unable to obtain PCR and ETT measurements on all dogs, thus limiting statistical comparisons. Studies in both human and veterinary medicine have shown that higher PCRs are associated with dysphagia.[9,14,37,38] Additionally, in humans, prolonged ETT has been associated with increased risk of aspiration and reflux.[39] Future studies in dogs with respiratory disease, including healthy control dogs in which these metrics can be consistently measured, are needed to determine if they are indicative of AeroD, even in absence of other alimentary abnormalities.

Reflux and aspiration have been documented in humans with airway and parenchymal diseases including chronic obstructive pulmonary disease and pulmonary fibrosis.[4,5] Investigating differences in pathologic reflux and pathologic PAS between RESP dogs with airway versus parenchymal disease and CON dogs, the only significant finding was that RESP dogs with airway disease were more likely to have pathologic PAS compared to CON dogs. We were unable to confirm our hypothesis that dogs with parenchymal versus airway disease would have more severe reflux and higher PAS. This hypothesis was based on the presumption that aspirated reflux contacts the airways first and, assuming a smaller volume and adequate mucociliary function, it should be cleared before damaging the parenchyma.[27] Additionally, in dogs with repetitive micro- or macroaspiration, airway defenses may be overwhelmed leading to parenchymal damage. Although neither pathologic reflux nor pathologic PAS differed between dogs with airway and parenchymal disease, this finding could have been a consequence of small sample size, capturing small durations of time on VFSS clips, and missing penetration or aspiration events or because no association may exist with higher PAS based on airway versus parenchymal location.

Limitations of our study include short cine loops of data capture and sporadic presence of some VFSS abnormalities. Additionally, VFSS cannot identify micro-aspiration, which may be a key contributor to respiratory pathology when repetitive. Thus, our study, despite finding a high frequency of VFSS abnormalities, may have underestimated the true incidence of aerodigestive pathology. Another limitation was the inability to obtain PCR and ETT in all dogs because of poor patient compliance (e.g., movement within the kennel, refusal to eat an adequate amount of a particular food or liquid) or inability to identify required landmarks or calibration markers within the captured frame because small shifts in body position precluded certain statistical comparisons. Although a prior study found no effect of age on VFSS metrics in healthy dogs,[8] sample size of different age groups was small. In our study, dogs were significantly older in RESP versus CON groups, yet despite the former having a nearly 10-fold increase in median PCR than the latter, no significant difference in PCR was found between groups. This finding could indicate our current study was underpowered to detect a difference in metrics of pharyngeal function with advanced age. Finally, although our goal was to include a diverse population of dogs with various respiratory disorders, in doing so the number of dogs with each disease was limited. Future studies should investigate a uniform respiratory disease population (e.g., bronchiectasis, pulmonary fibrosis) to characterize VFSS abnormalities more specifically with a single disorder.

In conclusion, in dogs presented for evaluation of a spectrum of respiratory disorders with advanced diagnostic imaging including VFSS, a pathologic link between the alimentary and respiratory tracts (i.e., AeroD) was observed. Importantly, maintaining a high index of suspicion for AeroD is important because dogs with respiratory disease frequently may have silent alimentary disease as seen in people.[27] Most (75%) RESP dogs had subjective VFSS abnormalities, and RESP dogs with airway disease had significantly higher PAS than CON dogs. At present, VFSS is an underutilized tool in respiratory disease evaluation. Identification of AeroD is the first step in improving medical management of respiratory disease by developing a comprehensive treatment plan targeting both respiratory and alimentary tract pathology. Abnormalities on VFSS can allow the clinician to tailor specific treatment to patients with AeroD, including optimizing food consistency to decrease risk of aspiration, or in identifying structural abnormalities and recommending surgical intervention for disorders such as hiatal hernias or lower esophageal sphincter achalasia-like syndrome.[6] Our study shows that VFSS is a valuable tool for identifying AeroD in dogs and should be considered part of a thorough diagnostic evaluation of dogs with respiratory disease, even in the absence of alimentary signs.

ACKNOWLEDGMENT

Funding provided by the American Kennel Club (AKC) Canine Health Foundation (Grant 02699). Preliminary results were presented as an on demand abstract at the 2022 American College of Veterinary Internal Medicine (ACVIM) Forum, Austin, Texas.

CONFLICT OF INTEREST DECLARATION

United States Patent No. 9107385 for the free-feeding kennels is held by Lever Scientific LLC (owner Teresa Lever), but no financial incentives from this group were provided for the study. The remaining authors have no financial or personal relationships that could inappropriately influence of bias the content of the paper.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobial. Although some dogs were treated with antimicrobials, the selection of antimicrobials was at the discretion of the attending clinician and was not a part of the study.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Approved by the University of Missouri IACUC protocol #10121.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Howard J, Grobman M, Lever T, Reinero CR. Videofluoroscopic swallow study abnormalities identify aerodigestive disorders in dogs with respiratory disease versus healthy controls. *J Vet Intern Med*. 2023;37(3):1166-1178. doi:10.1111/jvim.16685