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Aerodigestive disorders in dogs evaluated for cough using respiratory fluoroscopy and videofluoroscopic swallow studies

M.E. Grobman[a], I. Masseau[b], C.R. Reinero[a,*]

[a] University of Missouri, College of Veterinary Medicine, Department of Veterinary Medicine and Surgery, 900 East Campus Drive, Columbia, MO 65211, USA
[b] Université de Montréal, Faculté de Médecine Vétérinaire, Département of Sciences Cliniques, St-Hyacinthe, Québec, Canada

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ABSTRACT

Aerodigestive diseases, hybrid disorders representing a pathologic link between respiratory and alimentary tracts, may manifest with respiratory signs without gastrointestinal signs. These are underdiagnosed in dogs due to poor clinical recognition and diagnostic limitations. We hypothesize that a subset of dogs presenting for cough without gastrointestinal signs would have occult aerodigestive disorders identified using videofluoroscopic swallow study (VFSS). Data were retrospectively obtained from 31 client-owned dogs presenting for cough, with thoracic radiographs, and a VFSS between April 2015 and December 2017. Exclusion criteria were cough of cardiac origin or gastrointestinal signs within 6 months. Swallow study parameters included pharyngeal/esophageal motility, laryngeal obstruction/defects, penetration–aspiration, reflux, excessive aerophagia, megaesophagus (ME), lower-esophageal sphincter achalasia-like syndrome (LES-AS), and sliding hiatal hernia (HH).

The median (interquartile range) duration of cough was 4 (2–8) months. Thoracic radiographs were unremarkable in 11 dogs, with aspiration pneumonia suspected in seven. In 25/31 dogs (81%), VFSS abnormalities were detected and some dogs had more than one defect: pharyngeal ($n = 10$) or esophageal hypomotility ($n = 10$), reflux ($n = 9$), penetration–aspiration ($n = 8$), excessive aerophagia ($n = 6$), laryngeal obstruction ($n = 3$), ME ($n = 3$), HH ($n = 2$), and LES-AS ($n = 1$). A respiratory disorder causing cough was identified in 17 dogs with VFSS abnormalities (laryngeal obstruction/defect and airway disease including chronic or eosinophilic bronchitis, tracheal/mainstem bronchial collapse, bronchiectasis, and bronchomalacia). An alimentary disorder identified on VFSS in absence of a discrete respiratory disorder causing cough was diagnosed in eight dogs. In conclusion, canine aerodigestive disorders can manifest as cough without alimentary signs. VFSS is a useful diagnostic to determine the contribution of esophageal/gastrointestinal pathology in dogs with cough.

Introduction

Aerodigestive disorders in people represent a broad spectrum of diseases that emphasize the complex interrelationship between respiration and swallowing (Coca-Pelaz et al., 2013; De Benedictis and Bush, 2018). Unfortunately, diagnosis is challenging as these conditions frequently present without gastrointestinal signs (Burke et al., 2018). Aerodigestive disease(s) (AeroD) are infrequently investigated in dogs due to a combination of poor clinical recognition and limitations in available diagnostics. Aspiration pneumonia (AP) is the most well recognized example of AeroD in dogs. However, in humans and less commonly dogs, macro-aspiration and chronic micro-aspiration have also been associated with upper and lower airway dysfunction, bronchiolar diseases, interstitial lung disease, and aspiration pneumonitis (Molyneux and Morice, 2011; Smith and Houghton, 2013; Houghton et al., 2016a; Nafe et al., 2018;). Reflux is a common source of chronic microaspiration in people, resulting in acute and chronic pulmonary disease. The prevalence of reflux in chronic cough, asthma and chronic obstructive pulmonary disease is 50% (Celli et al., 2008; Molyneux and Morice, 2011; Praud, 2010; Smith and Houghton, 2013). Comparable studies in dogs with respiratory signs are lacking.

The association between reflux, aspiration, and airway dysfunction has not been thoroughly evaluated in veterinary medicine, though the link has been supported by a number of clinical case reports and experimental canine models.(Loughlin et al., 1996; Poncet et al., 2006; Lux et al., 2012; Nafe et al., 2018) Identifying dogs affected by AeroD could prove important as uncontrolled reflux, a common cause of AeroD in people, leads

* Corresponding author.
E-mail address: Reineroc@missouri.edu (C.R. Reinero).

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to disease progression, exacerbations of clinical signs, increased patient morbidity, and treatment costs (Dal Negro et al., 2007). Dogs with a history of cough which worsens during eating and drinking, or those with concurrent regurgitation/vomiting may prompt consideration of AeroD. However, a subpopulation with occult alimentary disease may prove clinically important by identifying new therapeutic targets and/or by providing a diagnosis in dogs with persistent cough despite unremarkable conventional diagnostics (i.e., idiopathic cough).

Thoracic radiographs are often considered a first line diagnostic test for dogs with respiratory disease. Though widely available, radiography is insensitive compared to alternative imaging modalities for a number of respiratory syndromes (Mantis et al., 1998; Johnson and Wisner, 2007; Wielpütz et al., 2014). This may be especially true for those with AeroD, where cough may be elicited by stimulation of the esophageal-bronchial reflex. This reflex, which involves vagally-mediated bronchoconstriction secondary to acidic stimulation of the distal esophagus, underscores the interplay of acid reflux with respiratory clinical signs. Mechano- and/or chemoreceptor stimulation of the pharynx, larynx, and cervical trachea can also trigger cough which is not well evaluated by standard thoracic radiography (Palombini et al., 1999; Irwin, 2006). As such, in people alternative diagnostics (e.g. VFSS, reflux scintigraphy, impedance manometry) are frequently required (Achilleos, 2016; Turner and Bothamley, 2016).

Videofluoroscopic swallow studies (VFSS) are the criterion standard for evaluating dysphagia in dogs (Harris et al., 2017). Videofluoroscopic swallow studies are sensitive for identifying human patients with aspiration secondary to dysphagia (Martin et al., 1994). Historically, the use of VFSS for dogs with esophageal dysphagia (e.g., megaesophagus (ME)), a risk factor for aspiration, has been limited. This is largely due to the historical VFSS protocol of restraint in lateral recumbancy and force-feeding which carry unacceptable risks of aspiration (Pollard, 2012; Pollard et al., 2017). By allowing free-feeding in unrestrained dogs, the risk of AP is no more than would be expected when feeding at home and allows evaluation of canine patients for which a VFSS would have been previously contraindicated (Harris et al., 2017). Additionally, the upright and free-feeding protocol allows for a more physiologic reflection of (often subclinical) alimentary defects that can contribute to a wide variety of respiratory diseases. It is unknown if VFSS could identify subclinical pathology in dogs without dysphagia or vomiting, but with cough. The objective of this study was to evaluate dogs presenting exclusively for cough using respiratory fluoroscopy (RF) and VFSS to detect occult AeroD. We hypothesized that a subset of dogs presenting exclusively for cough would have documentable evidence of AeroD despite the absence of esophageal or gastrointestinal signs.

Materials and methods

Case selection and criteria

Medical records for dogs presenting to the University of Missouri Veterinary Health Center (MU-VHC) between April 2015–December 2017 with RF and VFSS were retrospectively reviewed. Dogs were included if they had a primary complaint of cough without esophageal or gastrointestinal signs, had thoracic radiographs and complete medical records. When thoracic radiographs were performed with a referring veterinarian and unavailable for review, a radiology report from a boarded radiologist was considered adequate for a final thoracic radiographic diagnosis. Our exclusion criteria were dogs with cough of cardiac origin or esophageal/gastrointestinal signs including clinical evidence of dysphagia (e.g oral/preparatory defect, pharyngeal, or esophageal swallow), regurgitation, and vomiting within the preceding 6 months. A diagnosis of cardiac cough was made where there was evidence of congestive heart failure or substantial left atrial enlargement. Mild generalized cardiomegaly was not considered grounds for exclusion. A terminal retch, after a paroxysm of cough, was not considered evidence of gastrointestinal disease and therefore did not meet our exclusion criteria.

Data extracted from the medical record

Demographic data, bodyweight (BW, kg), body condition score (BCS), head-conformation, presenting complaint including other respiratory clinical signs aside from cough, duration of cough, thoracic radiographic diagnosis, and final clinical diagnosis were acquired from the medical record. The results from neurologic examination, laryngeal function examination, tracheobronchoscopy, bronchoalveolar lavage fluid (BALF) cytology, and culture results were reported when available. Endoscopy was performed using a Fujinon EB 470S. Findings were retrospectively reviewed by a board-certified internal medicine specialist (MG). Cytology samples were evaluated by a board-certified clinical pathologist at the University of Missouri. Culture Samples were processed by the University of Missouri Diagnostic Laboratory (Bacteriology).

Final diagnosis

Canine chronic bronchitis, eosinophilic bronchitis, AP, laryngeal paresis/paralysis, epiglottic retroversion, bronchomalacia (BM), bronchiectasis (BE), and hypoplastic trachea were diagnosed as previously described (King, 2004; Bottero et al., 2013; Meola, 2013; Skerrett et al., 2015; Grobman and Reinero, 2016; Johnson et al., 2016; Tarvin et al., 2016). Specific diagnostic criteria are available in Table 1. Non-respiratory or ‘alimentary’ cough was diagnosed where there was a VFSS abnormality supportive of an AeroD in the absence of an inflammatory or architectural respiratory disorder based on the diagnostics performed.

Table 1
Diagnostic criteria for specific respiratory diagnosis.

Respiratory diagnosis	Diagnostic criteria
Canine chronic bronchitis (CCB)	≥10% non-degenerate neutrophils ± ≥10% eosinophils on bronchoalveolar lavage fluid (BALF) cytology
Eosinophilic bronchitis (EB)	≥10% eosinophils on BALF cytology
Radiographic evidence of aspiration pneumonia (AP)	Interstitial-alveolar pattern in dependent lung regions. A secondary bacterial infection was determined by the presence of intracellular bacteria noted on BALF cytology and/or a positive BALF culture
Laryngeal paralysis (LarPar)	The absence of laryngeal abduction on inspiration after treatment with doxopram
Epiglottic retroversion (ER)	Intermittent retroversion of the epiglottis on inspiration resulting in intermittent obstruction of the rima glottidis
Bronchomalacia (BM)	Static or dynamic collapse of the airways at the level of or distal to the principle bronchi by >50%
Bronchiectasis (BE)	Architectural remodeling resulting in airway dilation with failure of tapering of the lumen with distal progression
Hypoplastic trachea	Fixed narrowing of the trachea with a ratio of trachea to the 3rd rib of <2.0

Respiratory fluoroscopy and videofluoroscopic swallow study

Dogs meeting our inclusion criteria had their RF and VFSS evaluated by two internal medicine specialists (MG, CR) and a board-certified radiologist (IM). Studies were performed at 30 frames/sec using a GE Advantx or GE OEC 9900 Elite Mobile C-Arm system (GE Heathcare) at the MU-VHC. Respiratory fluoroscopy preceded the VFSS. The VFSS was performed as previously described (Harris et al., 2017). Briefly, after a 12-24 h fast dogs were placed in a polycarbonate kennel appropriate for their body size: small/toy (≤16 kg), medium (>16 kg ≤ 30 kg), large (>30 kg to ≤39 kg), and giant breed dogs (>39 kg). A bowl was positioned at the point of the shoulder (i.e. neutral position). Dogs were offered and freely consumed, three standardized food consistencies containing a contrast agent: puree (25% iohexol (350 mg/mL)), liquid (25% iohexol (350 mg/mL)), and kibble (barium 40% w/v). Dogs were unrestrained during data collection. Each study was evaluated for standardized outcome parameters (Table 2). Criteria for evaluation are displayed in Tables 3 and 4.

Statistical analysis

Descriptive statistics were performed where appropriate. A Wilcoxon rank-sum test or a one-way ANOVA on ranks was performed to detect significant differences in RF and VFSS parameters for demographic data (age, sex, and breed), BW (kg), BCS and head-conformation. *P* values < 0.05 was considered significant. Post-hoc analysis (Dunn's method for multiple comparisons) was performed where appropriate.

Results

Animals

One hundred and thirty VFSS were performed between April 2015 and December 2017 with 31 dogs meeting criteria for further evaluation. Demographic and clinical data are presented in Table 5.

Diagnostic evaluation

Multiple ancillary respiratory diagnostics were performed. With each test, some dogs had more than one abnormality identified. All dogs had thoracic radiographs per our inclusion criteria. Radiographic findings were diverse including unremarkable radiographs in 11/31 dogs. Abnormalities were noted in 12/15, 13/13, 11/13, and 11/13 dogs on laryngeal function examination, tracheobronchoscopy, BALF cytology, and BALF culture respectively. Results are presented in Table 5.

VFSS abnormalities were detected for 25/31 (81%) dogs, including 9/11 (82%) dogs with unremarkable radiographs. Six of 11 (55%) dogs with a bronchial pattern on radiographs and 6/9 (67%) dogs with sterile neutrophilic and/or eosinophilic inflammation on BALF had VFSS abnormalities. All dogs with BE ($n = 5$) and BM ($n = 5$) had VFSS abnormalities. Five of seven (71%) dogs with radiographic evidence of AP had abnormalities detectable on VFSS, including all of those with a history of recurrent AP.

Oral-preparatory phase defects were found in 6/25 dogs. Penetration was observed in five dogs and aspiration in three dogs; there was both penetration and aspiration in two of those dogs (Fig. 1). Penetration of the larynx was exclusively by kibble. All aspiration events occurred with puree and/or liquid. Both were commonly in conjunction with pharyngeal dysfunction (pharyngeal hypomotility, $n = 4$; pharyngeal spasticity, $n = 1$). Pathologic reflux was noted in 36% of dogs with abnormal VFSS.

Epiglottic retroversion was identified in two dogs by RF; only one of these dogs was also identified by functional oral/laryngeal function examination. A laryngeal polyp was identified in one dog via RF and was associated with aspiration and pathologic GER. In 6/7 dogs (85.7%) with LarPar, an abnormal VFSS was present. Abnormalities included pharyngeal hypomotility ($n = 3/7$), GER ($n = 3/7$), penetration + aspiration ($n = 2/7$), and esophageal hypomotility ($n = 1/7$). No significant differences were found for any VFSS based on demographic data (age, sex, or breed), BW (kg), BCS, or head-conformation ($P > 0.05$ for all). A summary of all VFSS findings are presented in Table 6.

Final clinical diagnoses

Diagnosis of more than one disease was frequently made in dogs with either respiratory cough or non-respiratory alimentary cough (Table 6). Respiratory cough without VFSS evidence of alimentary disease was found in 4/31 (13%) dogs. Respiratory cough with concurrent VFSS abnormalities was found in 17/31 (55%) dogs. Alimentary cough was identified in 8/31 (26%) dogs. Neither a respiratory nor alimentary source of cough could be identified in two dogs.

Table 2
Standardized VFSS scoring rubric for aerodigestive disorders in the dog.[a]

VFSS metric	Feature		
Oral preparatory phase	Normal	Abnormal	
Pharyngeal phase	Normal motility	Hypomotile	Spastic
Esophageal phase	Normal motility	Hypomotile	Spastic
Megaesophagus	Present	Absent	
Reflux			
Gastroesophageal reflux (GER)	Present	Absent	Consistency
Esophago-oropharyngeal reflux (EOR)	Present	Absent	Consistency
Nasopharyngeal reflux (NPR)	Present	Absent	Consistency
Distance of refluxate (GER)	Distal 3rd of the esophagus		
	Middle 3rd of the esophagus		
	Proximal 3rd of the esophagus		
Lower esophageal sphincter achalasia-like syndrome	Present	Absent	
Hiatal hernia	Present	Absent	
Laryngeal obstruction/defect	Present	Absent	
Penetration[a]	Present-score: 2, 3, 4	Absent	
Aspiration[a]	Present-score: 5, 6, 7	Absent	
Aspiration/penetration consistency	Liquid	Puree	Kibble
Marked aerophagia	Present	Absent	

[a] Penetration–aspiration scoring system displayed in Table 3. Reflux extending past the middle 3rd of the esophagus was considered pathologic.

Table 3
Standardized criteria for evaluation for respiratory fluoroscopy and videofluoroscopic swallow studies.[a]

Criteria for evaluation	Definition
Respiratory fluoroscopy	
Upper airway: airways proximal to the thoracic inlet	Upper airway structures including the naso-, oro-, and laryngopharynx as well as the cervical trachea were evaluated for static or dynamic collapse during quiet breathing.
Laryngeal obstruction/defect (LO/D)	Movement of the epiglottis with respect to swallow and respiration was evaluated. The larynx was also evaluated for appropriate rostral movement during pharyngeal swallow. Laryngeal defects were considered to contribute to aerodigestive disease (AeroD) when there was concurrent evidence of penetration, aspiration, esophago-oropharyngeal reflux (EOR), or defect in pharyngeal swallow.
Lower airway: airways distal to the thoracic inlet	The intrathoracic trachea and main-stem bronchi (MSB) were evaluated for static or dynamic collapse/compression during quiet breathing.
Diaphragm and thoracic cage	Movement of the diaphragm and ribs were evaluated for appropriate movement during quiet breathing. Diaphragm: Flattening on inspiration Ribs: Rostral movement on inspiration
VFSS	
Oral preparatory (O-P) phase	Dogs were assessed for appropriate jaw excursion, mastication, and collection of the food bolus in the valleculae (between the base of the tongue and the epiglottis).
Pharyngeal phase	Dogs were assessed for appropriate pharyngeal constriction and conduction of a bolus from the pharynx through the upper esophageal sphincter (UES) into the proximal esophagus. Greater than one swallow attempt per bolus or pharyngeal bolus discohesion (incomplete bolus clearance) for the majority of swallows was considered abnormal. Residual contrast in the pharynx during respiration was considered abnormal regardless of the number of swallow attempts or the presence of aspiration into the trachea.
Esophageal contraction and peristalsis	These were defined as waves initiated by pharyngeal swallow, beginning in the proximal esophagus and capable of conducting the food bolus aborally towards the lower esophageal sphincter (LES).
Megaesophagus (ME)	Subjective assessment of esophageal dilation
Gastroesophageal reflux (GER)	Orad movement of contrast from the stomach into the esophagus. The maximal orad movement of contrast during GER was recorded: proximal 3rd of the esophagus, middle 3rd of the esophagus, distal 3rd of the esophagus. Reflux extending past the middle 3rd of the esophagus was considered abnormal (Harris et al., 2017).
Esophago-oropharyngeal reflux (EOR)	Orad movement of contrast from the esophagus into the oropharynx.
Nasopharyngeal reflux (NPR)	Movement of contrast from the pharynx to the nasopharynx during pharyngeal swallow or with EOR.
Lower esophageal sphincter achalasia-like syndrome (LES-AS)	Dogs were assessed for a failure of the LES to relax in response to a pharyngeal swallow (Grobman, 2017).
Hiatal hernia (HH)	Dogs were assessed for herniation of the stomach into the thoracic cavity through the esophageal hiatus either passively or in response to abdominal pressure. During abdominal compression, a licensed veterinarian wearing appropriate personal protective equipment applied abdominal pressure to a standing dog in order to induce a sliding hiatal hernia.
Penetration–aspiration (A–P)	Penetration: material enters the airway but remains above the vocal folds
A–P scale (Table 4)	Aspiration: material enters the airway and extends past the vocal folds
Aerophagia	This was defined as the swallowing of substantial volumes of air. Aerophagia was considered 'marked' if gas comprised >1/3 of the bolus volume and/or resulted in gastric distention (air accounting for >1/3 of the end gastric volume).

[a] Penetration–aspiration scale is available in Table 4.

Table 4
Penetration–aspiration scale (Holman et al., 2013) describing entrance of liquid or food into the larynx and trachea (Fig. 1).

Classification	Score	Description
Normal	1	Material does not enter the airway
Penetration	2	Material is in the supraepiglottic space, remains above the vocal folds but leaves the airway before epiglottis returns to rest position
	3	Material is in the supraepiglottic space, remains above the vocal folds after epiglottis has returned to rest position
	4	Material is in the supraepiglottic space, large amount remains in above the vocal folds after epiglottis returns to rest position
Aspiration	5	Material passes bellow the vocal folds, and is actively ejected
	6	Material passes bellow the vocal folds and is not ejected despite effort
	7	Material passes below the vocal folds, no effort is made to eject

Discussion

In dogs presenting for cough without clinical evidence of alimentary disease, VFSS documented abnormalities in 81% of cases highlighting the common link between the respiratory and alimentary tracts (i.e., AeroD). Identifying dogs with disorders of the pharynx, esophagus and stomach as a primary source of or contributor to their respiratory signs may enhance our understanding of the pathogenesis of chronic respiratory disease in dogs, opening the door for evaluation of novel, targeted therapies.

Aerodigestive disorders span a broad range of diseases reflecting defects in respiratory-swallow coordination. These represent a diagnostic challenge because many patients present without gastrointestinal signs. Importantly, GER occurs commonly in healthy, asymptomatic humans and physiologic reflux been documented in up to 41% of asymptomatic dogs using VFSS (Harris et al., 2017). Pathologic and physiologic reflux differ in volume, timing and location within the esophagus. In people, pathologic reflux often remains occult until patients develop deleterious sequelae: esophagitis, laryngeal dysfunction, regurgitation and a wide spectrum of respiratory diseases. The association between reflux, aspiration, and airway dysfunction has not been thoroughly evaluated in dogs, despite several supportive clinical case reports, experimental canine models, and a review of aspiration-related respiratory disorders (Loughlin et al., 1996; Poncet et al., 2006; Lux et al., 2012; Tarvin et al., 2016; Nafe et al., 2018). Detection of reflux and aspiration is possible by several imaging modalities, including VFSS. However dynamic, functional, and extra-esophageal abnormalities are best evaluated by VFSS.

Table 5
Signalment and diagnostic data from 31 dogs presenting for cough in the absence of gastrointestinal signs.

Signalment data
Age: range (median, interquartile range, IQR):
6 months–13 years (6 years, 3–13 years)
Sex
Castrated males: *n* = 13
Intact males: *n* = 9
Spayed females: *n* = 8
Intact females: *n* = 1
Breed
Mixed breed dogs: *n* = 3
Golden retrievers: *n* = 3
Labrador retrievers: *n* = 3
French bulldogs: *n* = 2
English bulldogs: *n* = 2
Yorkshire terriers: *n* = 2
German shepherd dogs: *n* = 2
Staffordshire terrier: *n* = 1
Miniature poodle: *n* = 1
Pembroke Welsh corgi: *n* = 1
Standard poodle: *n* = 1
Doberman pinscher: *n* = 1
Jack Russel terrier: *n* = 1
Springer spaniel: *n* = 1
Brittany spaniel: *n* = 1
Wheaten terrier: *n* = 1
Miniature schnauzer: *n* = 1
Maltese: *n* = 1
West Highland white terrier: *n* = 1
Boxer: *n* = 1
Coonhound: *n* = 1
Head-conformation
Brachycephalic: *n* = 6
Mesaticephalic: *n* = 19
Dolicocephalic: *n* = 6
Bodyweight (kg): range (median [IQR]): 1.4 kg–55.8 kg
(23.4 kg [12.6 kg–31.3 kg])
Body condition score (9 point): median (IQR): 5 [5–5]
Presenting complaint
Cough: *n* = 31
Dysphonia: *n* = 3
Sneezing/nasal discharge: *n* = 2
Exercise intolerance: *n* = 2
Reverse sneezing: *n* = 2
Signs worse while eating and drinking: *n* = 6
Paroxysms of cough with terminal retch: *n* = 2
Recurrent aspiration pneumonia: *n* = 3
Excessive panting: *n* = 3
Increased respiratory effort: *n* = 2
Duration of clinical signs prior to presentation: range (median (IQR)):
2–43 months (4 months (2–8 months))
Neurologic abnormalities[a]: *n* = 4
Diffuse neuromuscular disease: *n* = 2
Facial nerve paralysis: *n* = 1
Peripheral vestibular disease: *n* = 1
Diagnostic evaluation
Thoracic radiographs (*n* = 31)
Unremarkable: *n* = 11
Diffuse bronchial pattern: *n* = 11
Radiographic evidence of aspiration pneumonia: *n* = 7
Other
ME: *n* = 3
Tracheal and main-stem bronchial collapse: *n* = 1
Hypoplastic trachea: *n* = 1
Bronchiectasis: *n* = 1
Diffuse pulmonary osteomas: *n* = 1
Cardiomegaly: *n* = 1
Laryngeal function examination (n = 15: under propofol;
respiration stimulated with doxapram)
Erythema: *n* = 12
Laryngeal paralysis: *n* = 7
Unremarkable: *n* = 3
Laryngeal edema/swelling: *n* = 1
Epiglottic retroversion: *n* = 1
Laryngeal polyp: *n* = 1
Tracheobronchoscopy (*n* = 13)
Diffuse erythema: *n* = 7
Bronchiectasis: *n* = 5
Bronchomalacia: *n* = 5
Tenacious mucous: *n* = 4
Increased tracheal vascularity: *n* = 1
Tracheal stripe[b]: *n* = 1
BALF cytology (*n* = 13)
Neutrophilic: *n* = 6
Non-septic: *n* = 4
Septic: *n* = 2
Eosinophilic: *n* = 2
Mixed inflammation: *n* = 3
Unremarkable: *n* = 2
BALF culture (*n* = 13)
Negative: *n* = 11
Positive: *n* = 2
n = 1: beta hemolytic *Streptococcus spp*, *Klebsiella oxytoca*, *E. coli*, and *Salmonella typhimuirium*
n = 1: *Pseudomonas aeruginosa*

[a] Advanced diagnostics including MRI and electromyography (EMG) were not performed in dogs with neurologic disease.
[b] Tracheal stripe: proximal erythema of the trachea that dissipates toward the carina (Fig. 2).

In our study, VFSS abnormalities were detected in 81% (25/31) of dogs presenting with cough with no owner-reported alimentary tract signs. This demonstrates that, like people, AeroD presents in the absence of dysphagia, regurgitation or vomiting (Ramsey et al., 2005; Fass and Dickman 2006; Decalmer et al., 2012b; Houghton et al., 2016b). This study emphasizes a previously under-recognized and common canine population with alimentary tract disease causing or contributing to cough. No significant differences were noted for any VFSS metric based on demographic data (sex, age, breed), BW (kg), BCS, or head-conformation. The lack of age-related differences mirrors a study in healthy dogs which found no differences in objective VFSS metrics with age (Harris et al., 2017). Bodyweight and BCS in this study were likewise not associated with statistically significant changes in VFSS metrics. The dogs in this study had ideal or nearly ideal BCS which may, in part, account for our observations. Both findings are counter to the human literature which found increased risk of aerodigestive disease in elderly and obese people (Matsuse et al., 1996; Teramoto et al., 1999; Kendall and Leonard, 2001; Barak et al., 2002; Shaker et al., 2003; Kikawada et al., 2005; McClean et al., 2008). In our study, no statistically significant differences were detected with head conformation for any VFSS metric. This is in opposition to the veterinary literature, which has reported brachycephalic breeds at increased risk of aspiration pneumonia (Ovbey et al., 2014). The differences found in this study may reflect type 2 error though a lack of sensitivity for detecting microscopic reflux and aspiration events (i.e. microaspiration) may also be considered. These differences are clinically relevant as dogs are considered models of human aerodigestive disease (McMahon et al., 2002; Chopra et al., 2016). As such, larger studies evaluating specific at-risk populations using techniques capable of detecting microaspiration are still needed.

Supportive clinical and/or neurologic signs may further increase our index of suspicion for AeroD. In our study, all dogs with historical recurrent AP had VFSS abnormalities. Such historical information may increase the index of suspicion for AeroD in dogs. Additionally, 6/31 (19%) of dogs had a history of worsening clinical signs during eating and drinking. As such, specific lines of questioning emphasizing the relationship between the respiratory and alimentary tracts may be helpful in identifying dogs with AeroD. Concurrent nasal disease (sneezing, nasal discharge and reverse sneezing) were also encountered, paralleling human studies where extra-esophageal reflux (EER) results in nasopharyngeal as signs as well as cough (Madanick, 2014;

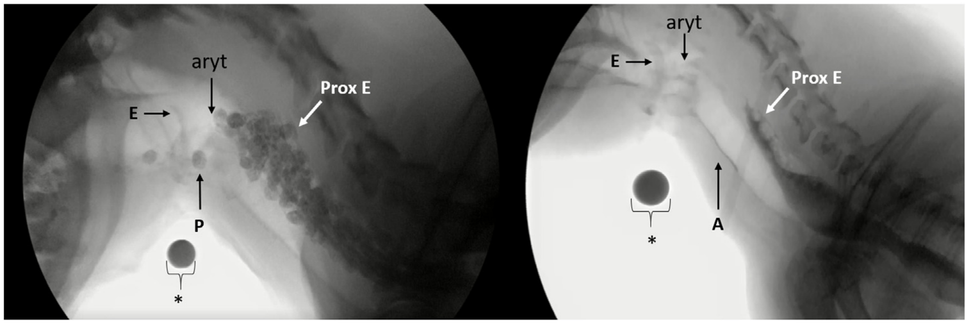

Fig. 1. Videofluoroscopic swallow study example of penetration (P) and aspiration (A). The head is oriented to the left and the tail to the right. A 1 cm size marker is denoted by *. A food bolus is present in the proximal esophagus (Prox E). In the left image, a piece of barium-extruded kibble is found between the epiglottis (E) and the arytenoids (aryt) but does not extend past the larynx. In the right image, a line of aspirated contrast (A) is present in the ventral trachea after drinking liquid containing iohexol. A scoring system for penetration–aspiration is displayed in Table 3.

Yuksel and Vaezi, 2012; Sidhwa et al., 2016). Four dogs had neurologic deficits on physical examination. Though this was identified in a relatively small number of dogs, this study and others support a relationship between neurologic dysfunction, dysphagia, and respiratory disease (Stanley et al., 2010; Tarvin et al., 2016). As such, studies evaluating dogs with neurologic dysfunction for occult AeroD may be warranted.

Approximately 26% of dogs in this study were diagnosed with alimentary or 'idiopathic cough' based on their diagnostic evaluation. Respiratory cough with VFSS abnormalities was found in 17/31 (55%) of dogs, reflecting the complex relationship between respiratory and alimentary disease; it is likely that each contributes to disease progression (Decalmer et al., 2012a). For example, reflux contributes to laryngeal dysfunction, a known risk factor for aspiration (Lux et al., 2012; Wilson and Monnet, 2016). Likewise, cough induces reflux in humans likely contributing to a self-perpetuating cycle in some patients (Smith et al., 2010). Therefore, treatment in dogs with mixed respiratory and alimentary disease is likely to be multimodal reflecting the contribution of alimentary tract disease in such cases. Given the percentage of dogs with alimentary or mixed alimentary and respiratory disease, AeroD should be investigated in dogs with chronic cough and not solely in those with evidence of AP. Identifying dogs with AeroD is important as failing to treat occult GI disease may, as in people, allow for progression of disease and contribute to patient morbidity and mortality (Palombini et al., 1999; Sontag, 2005; Molyneux and Morice, 2011; Coca-Pelaz et al., 2013; Sidhwa et al., 2016; Ozdemir et al., 2017).

Thoracic radiographs are considered a first line diagnostic in humans and dogs with chronic cough (Achilleos, 2016; Turner and Bothamley, 2016). However, thoracic radiographs fail to identify the source of disease especially when it is dynamic (intermittent or changes are dependent on phase of respiration), extra-thoracic in origin, subacute to acute where radiographic lesions lag behind clinical signs, or with certain small or subtle lesions (Woodcock et al., 2010; Achilleos, 2016; Turner and Bothamley, 2016). In this study, 35% of dogs had unremarkable radiographs despite nearly 82% having detectable abnormalities on VFSS. This speaks to a lack of sensitivity for detecting the source of AeroD by radiographs alone and underscores the utility of VFSS as an adjunctive tool in dogs with cough, particularly in the face of unremarkable thoracic radiographs.

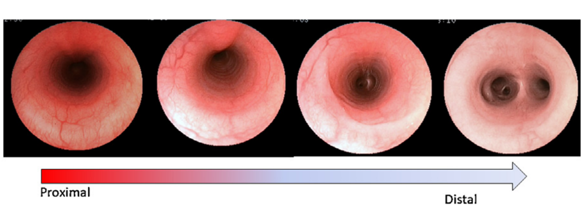

Fig. 2. The tracheal stripe is an endoscopic finding characterized by proximal erythema that dissipates distally toward the carina. Changes were noted prior to intubation. Oxygen was administered via red rubber catheter alongside the bronchoscope.

A bronchial pattern on radiographs, which was found in 11 dogs, is considered non-specific evidence of lower airway disease (Mantis et al., 1998). In isolation, this finding provides little information to aid in clinical decision making without additional diagnostics including BALF cytology/culture. In our study 7/11 dogs with a bronchial pattern were later diagnosed with inflammatory airway disease based on BALF cytology. Six of those seven dogs had abnormalities detectable on VFSS. Investigating a link between chronic inflammatory disease and repetitive microaspiration is warranted. Cultures of BALF were sterile in 11/13 dogs. This is consistent with the human literature where chronic cough secondary to reflux and aspiration is rarely associated with an infectious inoculum (Son et al., 2017). We consider this finding important given the need for more judicious use of antibiotics in dogs. Though markedly under diagnosed by thoracic radiographs, BE and BM were each detected in five dogs in this study. Microaspiration has been implicated in the pathogenesis of sterile airway inflammation in people (Tibbling, 1993), and is a known contributor to the development of BE and BM (Bibi et al., 2001; Boogaard et al., 2005; Dorgan et al., 2015). Four of five cases of BE and BM were associated with VFSS abnormalities including laryngeal penetration, reflux, and pharyngeal/esophageal dysmotility suggesting that, like people, AeroD may contribute to airway inflammation and architectural remodeling. Aspiration pneumonia is the most widely recognized AeroD in dogs. Radiographic evidence of AP was present in 23% of dogs in our study including two dogs with a concurrent diffuse bronchial pattern. The majority (71%) of these dogs had abnormalities on VFSS suggesting that dogs with chronic clinical signs (>2 months) and radiographic evidence of AP may warrant a more thorough investigation than radiographs alone. As such, a thorough diagnostic evaluation of respiratory disease in veterinary medicine should be multimodal with clinical consideration for AeroD.

Laryngeal function was abnormal in 12 dogs despite only three dogs presenting with dysphonia. Laryngeal erythema was found in 80% of dogs that underwent a laryngeal function examination including all dogs with evidence of pathologic reflux. While laryngeal erythema has been previously discussed as a non-specific finding of chronic cough (Johnson, 2016), based on the findings of this study, a contribution from EOR would be strongly suspected. Laryngeal paralysis, a known risk factor for AP, is not considered a consequence of chronic cough but has been associated with reflux diseases as well as other dysphagic disorders (Tarvin et al., 2016; Wilson and Monnet, 2016). These findings were supported by our study where 6/7 dogs with laryngeal dysfunction has concurrent swallow study abnormalities, including PH, penetration, and aspiration. Common innervations to pharynx, larynx, and proximal esophagus through the recurrent larnygeal nerve may explain this spectrum of dysfunction, and may suggest an increased risk of aspiration in these dogs beyond laryngeal dysfunction alone (Stanley et al., 2010).

Table 6
Videofluoroscopic swallow study (VFSS) and respiratory abnormalities for all dogs.

Dog	Respiratory diagnosis	VFSS findings	Localization	OP	P-cont	LO/D	A	P	NPR	ME	E-P	LES-AS	Ref	HH	Aero
1	None	None	None	N	Norm	N	N	N	N	N	Norm	N	N	N	N
2	None	None	None	N	Norm	N	N	N	N	N	Norm	N	N	N	N
3	CCB	None	Airway	N	Norm	N	N	N	N	N	Norm	N	N	N	N
4	BE BM	None	Airway	N	Norm	N	N	N	N	N	Norm	N	N	N	N
5	EB	None	Airway	N	Norm	N	N	N	N	N	Norm	N	N	N	N
6	AP,bact LarPar	None	PP Lar	N	Norm	N	N	N	N	N	Norm	N	N	N	N
7	None	EH	Alimentary	N	Norm	N	N	N	N	N	Norm	N	N	N	N
8	None	EH ME LES-AS	Alimentary	N	Norm	N	N	N	N	Y	EH	Y	N	N	N
9	None	OP PH P NPR	Alimentary	Y	PH	N	N	Y	Y	N	Norm	N	N	N	N
10	None	OP PS P EH	Alimentary	Y	PS	N	N	Y	N	N	EH	N	N	N	N
11	None	OP Ref	Alimentary	Y	Norm	N	N	N	N	N	Norm	N	Y	N	N
12	None	PH	Alimentary	N	PH	N	N	N	N	N	Norm	N	N	N	N
13	None	PH EH	Alimentary	N	PH	N	N	N	N	N	EH	N	N	N	N
14	None	Ref	Alimentary	N	Norm	N	N	N	N	N	Norm	N	Y	N	N
15	Airway collapse (Trachea/MSB)	Aero	Airway	N	Norm	N	N	N	N	N	Norm	N	N	N	Y
16	CCB BM	EH P PH	Airway	N	PH	N	N	Y	N	N	EH	N	N	N	N
17	CCB	PH	Airway	N	PH	N	N	N	N	N	Norm	N	N	N	N
18	CCB LarPar	HH Ref	Airway Lar	N	Norm	N	N	N	N	N	Norm	N	Y	Y	N
19	CCB LarPar BM	OP P Ref PH	Airway Lar	Y	PH	N	Y	Y	N	N	Norm	N	Y	N	N
20	EB ER	PH LO/D	Airway Lar	N	PH	Y	N	N	N	N	Norm	N	N	N	N
21	LarPar BE BM	Ref EH	Airway Lar	N	Norm	N	N	N	N	N	EH	N	Y	N	N
22	CCB LarPar BE BM	Aero	Airway Lar	N	Norm	N	N	N	N	N	Norm	N	N	N	Y
23	LarPar	A P PH OP	Lar	Y	PH	N	Y	Y	N	N	Norm	N	N	N	N
24	Lar. polyp	Ref A LO/D	Lar	N	Norm	Y	Y[a]	N	N	N	Norm	N	Y	N	N
25	AP,rad	Aero ME EH	PP	N	Norm	N	N	N	N	Y	EH	N	N	N	Y
26	AP,rad	Aero Ref EH	PP	N	Norm	N	N	N	N	N	EH	N	Y	N	Y
27	AP, bact BE BM	Aero Ref PH HH	PP	N	PH	N	N	N	N	N	Norm	N	Y	Y	Y
28	AP, rad ER	OP LO/D	PP	Y	Norm	Y	N	N	N	N	Norm	N	N	N	N

Table 6 (*Continued*)

Dog	Respiratory diagnosis	VFSS findings	Localization	OP	P-cont	LO/D	A	P	NPR	ME	E-P	LES-AS	Ref	HH	Aero
29	AP, rad HT	EH	PP Airway	N	Norm	N	N	N	N	N	EH	N	N	N	N
30	AP, sterile BE	Ref ME EH MG	PP Airway	N	Norm	N	N	N	N	Y	EH	N	Y	N	N
31	AP,rad LarPar	Aero PH	PP Lar	N	PH	N	N	N	N	N	Norm	N	N	N	Y

Dogs 1–2: no diagnosis was made despite standard respiratory workup and VFSS.
Dogs 3–6: a respiratory diagnosis was made with no concurrent alimentary abnormalities detected on VFSS.
Dogs 7–14: dogs were determined to have non-respiratory (alimentary cough) based on VFSS abnormalities and the absence of a concurrent respiratory diagnosis.
Dogs 15–31: dogs had a respiratory source of cough in addition to VFSS abnormalities.
Respiratory diagnoses: AP, rad, radiographic diagnosis of aspiration pneumonia (AP); AP, bact, radiographic evidence of AP with confirmed secondary bacterial infection; AP, sterile, radiographic evidence of AP without a secondary bacterial infection; LarPar, laryngeal paralysis; EB, eosinophilic bronchitis; CCB, canine chronic bronchitis; MSB, mainstem bronchi; BE, bronchiectasis; BM, bronchomalacia; ER, epiglottic retroversion
VFSS criteria: OP, oropharyngeal defect; P-cont, pharyngeal contraction; LO/D, laryngeal obstruction/defect; A, aspiration; P, penetration; NPR, nasopharyngeal reflux; ME, megaesophagus; E-P, esophageal peristalsis; LES-AS, lower esophageal sphincter achalasia-like syndrome; Ref, reflux; HH, hiatal hernia; Aero, aerophagia; Norm, normal.
VFSS Diagnoses: Y, yes; N, no; PH, pharyngeal hypomotility; PS, pharyngeal spasticity; EH, esophageal hypomotility.
Disease localization: Lar, laryngeal; PP, pulmonary parenchymal.
[a] Aspiration with both puree and liquid.

Penetration or aspiration was witnessed in six dogs (eight total incidences). Two dogs with documented aspiration exhibited no attempts to clear the aspirated material from the trachea (Penetration–aspiration score of 7). In both cases aspirated material extended past the thoracic inlet within the trachea suggesting diminished airway protective mechanisms. While evidence of aspiration during VFSS helps confirm the link between an abnormal swallowing and respiration, absence of witnessing aspiration during the limited period video clips are obtained does not rule it out. Dogs with penetration of kibble without aspiration on VFSS were considered at high risk for future macro-aspiration events (Friedman and Frazier, 2000) and possibly microaspiration. Micro-aspiration is not detectable via VFSS.

Fluoroscopy has advantages over thoracic radiography in that VFSS capture data over a longer period and dynamic processes are captured. However, intermittent abnormalities may be missed using this modality. Thus, an important limitation of this study is the duration of data collection. Additionally, VFSS for detection of dogs with occult AeroD is not widely available requiring referral; not all referral centers use unrestrained free-feeding protocols. Earlier studies have noted that increased motion artifact was noted in dogs undergoing upright VFSS (Pollard et al., 2017). This was not observed during this study and is not considered an important limitation. The retrospective nature of this study is another limitation wherein not all dogs received the same diagnostic evaluation. Future prospective studies are warranted objectively evaluated the findings of this study.

Conclusions

Aerodigestive diseases occur in dogs in the absence of esophageal and gastrointestinal signs and in the face of normal thoracic radiographs. Identifying this under-recognized population opens doors for treatment targeting alimentary tract disease in dogs with what may have previously been considered ‘idiopathic cough.’ This study highlights the need for multimodal evaluation incorporating free-feeding VFSS in dogs presenting with cough, regardless of presence of alimentary tract signs and particularly for those with unremarkable thoracic radiographs.

Conflict of interest statement

United States Patent No. 9,107,385 for the free-feeding kennels is held by the Curators of the University of Missouri, listing as inventors: Teresa Lever, Joan Coates, Mitchell Allen, and Laila Al-Khashti. None of the authors has any other financial or personal relationships that could inappropriately influence or bias the content of the paper.

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