Aspiration during swallow in Chronic Obstructive Pulmonary Disease (COPD): prevalence and association with disease outcomes

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A thesis submitted for the degree of Doctor of Philosophy at

Monash University in 2022

Faculty of Medicine, Nursing and Health Sciences

Melbourne, Australia

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ABSTRACT

Introduction: Breathing and swallowing have important defence mechanisms which can be disrupted in diseases such as chronic obstructive pulmonary disease (COPD). This may lead to impaired airway protection during swallow (prandial aspiration) and higher risk of exacerbation events. To date there is considerable evidence favouring an aspiration-exacerbation link, however few studies have recruited large, well-defined populations, explored COPD comorbid diseases, interactions with other pathological processes or examined large liquid volumes representative of everyday drinking. With the potential for a high aspiration-associated COPD burden, detecting aspiration and associated risk factors may be consequential.

Objective: This thesis examines the role of prandial aspiration in COPD. Chapter one outlines a review of the current literature as it relates to aspiration in COPD. Chapter two is a prospective study used to examine the relationship between prandial aspiration and COPD exacerbation. Co-primary outcomes included: 1) incidence of aspiration and 2) adverse respiratory outcomes in the aspiration group as characterised by severe COPD exacerbations. Chapter three provides supplementary material that accompanies the prospective study outlined in Chapter two. Chapter four examines the impact of self-paced and fast-paced cup-drinking on swallow patterns as well as airway protection and swallow efficiency. Chapter five summarises the study findings and highlights the direction for future research.

Methods and Results: Overall, 151 patients (mean±SD age 70.6±5.0 years) with verified and stable COPD across all severities underwent videofluoroscopy to evaluate aspiration during 100-ml self-paced as well as fast-paced cup-drinking. Aspiration was detected in 30 out of 151 patients (20%, 18 males, 12 females) with silent aspiration observed in approximately 70% of cases (22/30 patients with aspiration). Patients with aspiration were slightly older (72.4±4.3 versus 70.2±5.1; $p=0.02$) and showed longer total swallow duration ($p\leq0.05$), longer time per swallow ($p\leq0.002$) and lower swallow frequency ($p\leq0.01$). These findings are likely related to physiological or compensatory modifications induced by breathing-swallow dysfunction. Severe hospitalised exacerbation episodes occurred in more patients with aspiration over a 12-month period (50% of patients versus 18%; OR 4.5, CI 1.9-10.5; $p=0.001$). Patients with aspiration also had more overall exacerbation events (3.03 versus 2.0 per patient; $p=0.022$), more frequent severe exacerbation episodes (0.87 versus 0.39; $p=0.032$), and a shorter exacerbation-free period during follow-up ($p=0.038$). No patient factors predictive of aspiration and exacerbation could be identified in multivariate analyses and notably there were no links with COPD severity, lung hyperinflation, baseline respiratory rate, body mass index, comorbidities, medications, Airway Questionnaire-20, Eating Assessment Tool-10, and oral health risk measurements.

Conclusion: The results of the current studies provide robust evidence that patients with stable COPD and detectable aspiration are at higher risk of severe disease exacerbations. The findings have important clinical implications including suspecting aspiration in exacerbation-prone persons, consideration of swallow retraining as part of COPD rehabilitation and highlighting future research priorities. These priorities include examination of underlying mechanisms, identifying determinants of laryngeal vestibular closure and recognition of silent aspiration. Our studies signify that patients may benefit from these initiatives and help clinicians to reduce exacerbations and thereby reduce morbidity and mortality in COPD.

THESIS INCLUDING PUBLISHED WORKS DECLARATION

I hereby declare that this thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

This thesis includes four original papers published in peer reviewed journals. The core theme of the thesis is an examination of the prevalence of prandial aspiration and its association with disease outcomes in chronic obstructive pulmonary disease. The ideas, development and writing up of all the papers in the thesis were the principal responsibility of myself, the student, working within the Monash Lung and Sleep Unit, Monash Medical Centre, under the supervision of Professor Philip Bardin and Associate Professor Paul King.

The inclusion of co-authors reflects the fact that the work came from active collaborations between researchers and acknowledges input by team members contributing to the overall research programme.

In the case of chapter 1-5 my contribution to the work involved the following:

Thesis Chapter	Publication Title	Status	Nature and % of student contribution	Co-author name(s) Nature and % of Co-author's contribution	Co-author(s), Monash student
1	Swallow and aspiration in chronic obstructive pulmonary disease	Published	80%. Concept, literature review and writing first draft and review	P.G Bardin, input into manuscript 20%	No
2	Aspiration and severe exacerbations in COPD: A prospective study	Published	60%. Concept, recruitment, data collection/reconciliation, data/statistical analysis, and writing first draft and review	N Guiney (recruitment and pulmonary testing), T Nicholson, K.K Lau, P Finlay, K Hamza, C Osadnik, P Leong, M MacDonald, and P.T King, combined input into manuscript 20% P.G Bardin, input into manuscript 20%	No
3	Aspiration and severe exacerbations in COPD: A prospective study Supplementary Material	Published	60%. Concept, recruitment, data collection/reconciliation, data/statistical analysis, and writing first draft and review	N Guiney (recruitment and pulmonary testing), T Nicholson, K.K Lau, P Finlay, K Hamza, C Osadnik, P Leong, M MacDonald, and P.T King, combined input into manuscript 20% P.G Bardin, input into manuscript 20%	No

Thesis Chapter	Publication Title	Status	Nature and % of student contribution	Co-author name(s) Nature and % of Co-author's contribution	Co-author(s), Monash student
4	Swallow patterns associated with aspiration in COPD: A prospective analysis	Published	70%. Concept, data collection/reconciliation, data/statistical analysis, and writing first draft and review	N Guiney, K.K Lau, P Finlay, K Hamza, P Leong, M MacDonald, and P.T King, combined input into manuscript 10% P.G Bardin, input into manuscript 20%	No
5	Breathing-swallow dysfunction in COPD: How silent aspiration may be contributing to exacerbations	Published	80%. Concept and writing first draft and review	P.G Bardin, input into manuscript 20%	No

I have not renumbered sections of submitted or published papers in order to generate a consistent presentation within the thesis.

Student Name: Lydia Cvejic **Date:** 23 March 2022

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the student's and co-authors' contributions to this work. In instances where I am not the responsible author I have consulted with the responsible author to agree on the respective contributions of the authors.

Main Supervisor Name: Philip G. Bardin **Date:** 23 March 2022

ACKNOWLEDGEMENTS

This research was supported by the Australian Government Research Training Program (RTP) Scholarship.

I am grateful to my supervisors Phil and Paul for sparking the fire for research and for their guidance and encouragement.

My special thanks are extended to Nadine, Paul, Tiffany, Ken, Jacqui, Anna, and Kais for their invaluable input and friendship.

Finally, thank you to the research participants that have made learning and sharing of information possible.

"*Never give up, keep going, enjoy every second, learn, make a difference*".

Richard James Gill (1941-2018, Australian music educator and conductor)

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CHAPTER ONE

INTRODUCTION AND LITERATURE REVIEW

Chapter one outlines the current literature and provides a pulmonary perspective on normal mechanisms of swallow and breathing. It also details potential mechanisms of airway invasion (laryngeal penetration and pulmonary aspiration), evidence of penetration-aspiration in COPD and explores therapeutic modalities and research priorities in COPD. This section has been published in the *American Journal of Respiratory and Critical Care Medicine* and is included as a PDF file.

Swallow and Aspiration in Chronic Obstructive Pulmonary Disease

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Swallowing is a complex biomechanical process synchronized with breathing to protect the airway. However, this finely tuned process may not work well in older individuals and in diseases such as chronic obstructive pulmonary disease (COPD). Swallow–breathing dysfunction can have serious detrimental consequences. Individuals with laryngeal penetration are up to 4 times more likely to develop pneumonia and, if pulmonary aspiration occurs, pneumonia is 10 times more likely (1). In COPD, aspiration may occur as a result of dysfunctional upper airway–protective mechanisms, reduced coordination of swallow with breathing, and changes in breathing habits induced by COPD itself (2, 3).

Problems with swallow followed by aspiration have long been recognized in COPD, but, to date, research has been limited. Studies have been characterized by small sample sizes, variations in study methods, diagnostic disparities, and poorly defined patient populations (4–9). The prevalence of aspiration in individuals with stable COPD has been reported to be as high as 25% (4, 5), with a trend toward increased hospitalizations and mortality over 36 months (5). Only one exacerbation study has been conducted reporting aspiration in 17% of patients (10). To date, the overall prevalence of aspiration in patients with COPD remains unknown, and associations with adverse respiratory outcomes have not been prospectively examined.

This Pulmonary Perspective outlines normal mechanisms of swallow and breathing, explores potential mechanisms of penetration–aspiration, examines evidence for penetration–aspiration in COPD and considers therapeutic strategies. Limitations in current knowledge of this field and research priorities are highlighted.

Mechanisms of Swallow, Laryngeal Penetration, and Pulmonary Aspiration

Normal Swallow

During normal swallow, the larynx closes to provide airway protection from aspiration of liquid or solid matter. This involves a series of laryngeal events (valving mechanisms) that include approximation of the vocal folds, laryngeal vestibular closure, and laryngeal excursion by contraction of suprahyoid musculature to facilitate epiglottic-to-arytenoid closure and upper esophageal sphincter opening. There is also horizontal epiglottic movement mediated by the thyroepiglottis muscle to cover the laryngeal aperture and to direct food or liquid laterally (11).

During swallow, an apneic period or respiratory pause precedes laryngeal elevation and laryngeal closure; this normally occurs in the expiratory phase with single smaller ingested volumes (2, 12). The respiratory pause is prolonged during continuous swallowing of larger volumes, leading to potential instability of respiratory–swallow patterns. Swallowing during expiration may assist laryngeal elevation when the diaphragm is relaxed, as opposed to the inspiratory phase, when the diaphragm contracts and the larynx is lowered (12). Expiration after swallow also helps to prevent aspiration by expelling penetrated material as the larynx returns to its resting position (2). Perturbations of this intricately regulated physiology with swallow–breathing dysfunction are likely to trigger detrimental consequences.

Laryngeal Penetration

Laryngeal penetration is defined as entry of material, such as liquid or solid, into the laryngeal vestibule above the level or at the level of the true vocal cords (13) (Figure 1). Penetration can be a normal variant in a healthy population when the penetrated material is ejected from the laryngeal vestibule at the end of swallowing by compression of the supraglottic and subepiglottic space of the vestibule (14, 15). Laryngeal sensory receptors located in the supraglottic mucosa region can detect penetrated material and facilitate laryngeal closure via activation of the internal branch of the superior laryngeal nerve (16). Laryngeal penetration that fails to be expelled from the airway has been reported in approximately 1% of healthy adult cohort studies (14, 15, 17), and is more common with liquid and sequential swallows and in older individuals (17–19). Importantly, penetration may be followed by aspiration of pharyngeal material if the laryngeal vestibule is not effectively cleared.

Pulmonary Aspiration

Aspiration is defined as progression of penetrated material below the level of the true vocal cords (13) (Figure 1). Various types of aspiration can occur, some of which may be more common in COPD.

Prandial aspiration. Prandial aspiration (also known as deglutitive

(Received in original form April 18, 2018; accepted in final form June 20, 2018)

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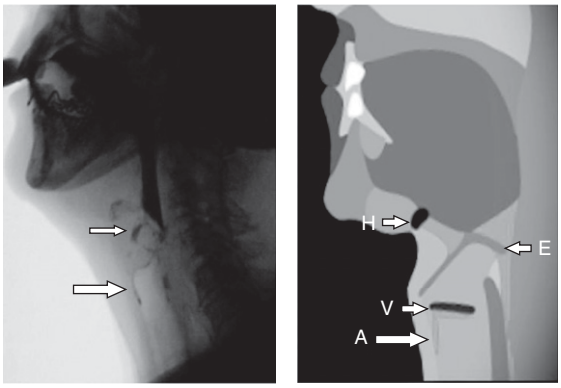
This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org.

Am J Respir Crit Care Med Vol 198, Iss 9, pp 1122–1129, Nov 1, 2018

Originally Published in Press as DOI: 10.1164/rccm.201804-0704PP on June 25, 2018
Internet address: www.atsjournals.org



Potential contributory causes of aspiration:

Laryngeal/Pharyngeal
- Muscle weakness
- Impaired coordination
- Reduced sensation
- Ineffective clearance

Pulmonary
- Muscle weakness
- High respiratory rate
- Hyperinflation
- Hypoxia
- Acute exacerbation

Other
- Laryngopharyngeal/ Gastroesophageal reflux
- Oropharyngeal colonization
- Pharmaceutical agents/ Cigarette smoking
- Comorbidities
- CNS degeneration
- Altered microbiome

Figure 1. (Left image) Videofluoroscopy image demonstrating laryngeal penetration (narrow arrow) and aspiration below the vocal cords (wide arrow). During penetration, liquid contrast enters the larynx during swallow and can be followed by aspiration into the trachea. (Right image) Illustration showing hyoid bone (H), epiglottis (E), vocal cords (V), and aspiration (A). CNS = central nervous system. Illustration on the right adapted by permission from Reference 58.

aspiration) refers to aspiration of liquid or food during the act of swallowing. It is commonly associated with physiological abnormalities, such as impaired laryngeal closure and an abnormal respiratory-swallow sequence. Prandial aspiration is not a common finding in normal adult populations, with a 0.6% prevalence reported using videofluoroscopy to detect abnormality (17). Prandial aspiration of liquid may be a more frequent event in healthy, older adults, particularly in persons older than 80 years of age. Butler and colleagues (18) used flexible endoscopic evaluation of swallowing (FEES), and reported aspiration of thin liquid in 3% of swallows in 30% of participants (mean age, 80.5 yr). Subjects who aspirated had stable respiratory function for 12 months (20), and aspiration was not associated with abnormal computed tomography chest findings (21).

Predisposing factors associated with prandial aspiration in an aging population and in COPD may include impaired laryngeal vestibule closure and vertical hyoid motion (5, 7, 22). Although changes in swallow biomechanics and trace penetration–aspiration have been identified in healthy aging and in COPD, the clinical significance and functional impact on overall health remain largely unknown.

Retrograde aspiration. Retrograde aspiration (also known as nonprandial or post-prandial aspiration) refers to aspiration of esophageal or stomach contents. The pathophysiology of retrograde aspiration is complex and chiefly appears to be related to reflux. Reflux is characterized by backflow of prolonged or excessive volume of gastric contents into the esophagus or pharynx. Reflux symptoms can become pathological, termed gastroesophageal reflux disease (GERD), and can include acid and nonacid reflux, laryngopharyngeal reflux, or airway reflux. Prevalence of GERD using 24-hour pH monitoring and manometry is up to 74% in COPD and 18.5% in control groups (23). Factors contributing to reflux that are pertinent to COPD include anatomical and physiological changes associated with the aging process, higher prevalence of hiatus hernia, lower esophageal sphincter pressure, increased acid production with reduced clearance, and delayed gastric emptying (24). Reflux may be important, because individuals using proton pump inhibitors had an approximately doubling of the risk of develop community-acquired pneumonia (25). In COPD, an increased risk of exacerbation was associated with symptomatic and asymptomatic GERD and use of acid-suppressive medication (26, 27).

Microaspiration. "Microaspiration" occurs when small amounts of oropharyngeal secretions or gastroesophageal contents are aspirated. Aspiration of saliva during respiration may be present in up to 10% of healthy individuals (28). It occurs frequently in susceptible populations, and has been reported in up to 70% of elderly patients with acute pneumonia (28). Other researchers have also linked poor oral and dental health to aspiration and pneumonia (29). Optimal oral health may therefore help to reduce aspiration of pathogenic bacteria and thereby adverse pulmonary outcomes, but this potential benefit has not been verified.

Silent aspiration. Silent aspiration (also known as asensate aspiration) refers to absence of a cough reflex in response to tracheal stimulation caused by aspirated material. It is linked to increased prevalence of pneumonia and subsequent mortality (1, 16). This type of aspiration is problematic in patients with depressed levels of consciousness, but may also occur if cough sensitivity is reduced in COPD by comorbid conditions, smoking, and with use of medications, such as codeine and other opiate derivatives (30).

Penetration and Aspiration in COPD

Studies Examining the Prevalence of Penetration and Aspiration in COPD

Overall, the clinical and prognostic importance of penetration and aspiration in COPD remains poorly understood. The prevalence of these abnormalities in stable COPD and during exacerbations is not known, and whether the process may be contributing to the excess decline in pulmonary function over time noted in some patients has not been researched. However, in COPD, both penetration and aspiration may be clinically relevant, as the likelihood of developing pneumonia has been reported to be significantly higher if penetration and aspiration is detected (1). Studies that have examined penetration and aspiration in COPD are summarized in Table 1.

Our case–control study using videofluoroscopy found prandial penetration that was not cleared in 12.5% of patients with

Table 1. Studies of Pulmonary Penetration and Aspiration in Chronic Obstructive Pulmonary Disease

Study	Design	Population	Methods	Food/Liquid	Penetration*/ Aspiration	Pathophysiology Aspects	Follow-up Period
Regan *et al.* (50)	Retrospective case–control	30 stable subjects with COPD referred for FEES (20 male, 10 female; mean age = 69.1 ± 16.8 yr) No control group	FEES Spirometry EAT-10	Fluid from cup Spoonful of puree and solid	Penetration not rated Aspiration 40%	Higher EAT-10 scores in aspiration group than in nonaspiration group ($P < 0.001$) EAT-10 predicted aspiration with 92% sensitivity and 78% specificity using a cutoff value >9 No significant difference in COPD severity between aspiration and nonaspiration group No significant difference in COPD severity and EAT-10 scores	Not examined
Cassiani *et al.* (31)	Prospective case–control	16 stable subjects with COPD (15 male, 1 female; mean age = 68 yr; range = 56–77 yr) 15 healthy control subjects (12 male, 3 female; mean age = 65 yr; range = 57–73 yr)	VFSS Spirometry Arterial blood gas analysis (COPD group)	5, 10 ml thick fluid 5, 10 ml paste (pudding) Soft biscuit immersed in liquid barium	0%	Longer oropharyngeal transit duration 5 ml paste ($P = 0.047$) and biscuit ($P = 0.022$) in COPD Longer pharyngeal transit duration 5 ml and 10 ml liquid ($P = 0.002$) and biscuit ($P = 0.015$) in COPD Longer laryngeal vestibular closure duration 5 ml liquid ($P = 0.011$) and 10 ml liquid ($P = 0.038$) in COPD Longer hyoid movement duration 5 ml and 10 ml liquid ($P = 0.001$) in COPD	Not examined
Clayton *et al.* (4)	Prospective case–control	20 stable subjects with COPD (16 male, 4 female; mean age = 71.7 ± 6.8 yr) No control group	FEES Laryngopharyngeal sensory discrimination testing Spirometry Body plethysmography	90 ml thin liquid (water dyed with 0.5 ml blue food coloring) 5 ml puree Biscuit	Penetration not rated Aspiration 5/20 (25%)	Silent aspiration of thin liquid was prevented by neck flexion compensatory maneuver in 2/3 participants	Not examined
de Deus Chaves *et al.* (6)	Prospective case–control	20 stable subjects with COPD (10 male, 10 female; mean age = 59 ± 4.1 yr) 20 healthy control subjects (10 male, 10 female; mean age = 59 ± 4.4 yr)	VFSS Spirometry	3, 5, 10 ml thin liquid 7 ml paste Biscuit dipped in paste	0%	Longer duration of tongue base contact with posterior pharyngeal wall 5 ml liquid ($P = 0.004$) and paste ($P = 0.028$) in COPD Longer pharyngeal transit time 10 ml liquid ($P = 0.001$) and paste ($P = 0.012$) in COPD	Not examined
Macri *et al.* (8)	Prospective case–control	19 stable subjects with COPD (12 male, 7 female; mean age = 66.7 yr; range = 50–85 yr) No control group	FEES Pulse oximetry Spirometry	5, 10 ml, free swallow Liquid Nectar-thick liquid Honey-thick liquid Pudding Solid	0%	—	Not examined

(Continued)

Table 1. (*Continued*)

Study	Design	Population	Methods	Food/Liquid	Penetration*/ Aspiration	Pathophysiology Aspects	Follow-up Period
Robinson *et al.* (10)	Prospective case–control	41 subjects with acute COPD exacerbations with hospital admission (18 male, 23 female; mean age = 71 yr; range = 43–88 yr) 41 control emergency medical admission subjects (non-COPD or neurological; 19 male, 22 female; mean age = 73 yr; range = 39–92 yr)	VFSS (COPD group) Water swallow screening test Clinical swallowing assessment Attrition: 12% in COPD group (two deaths, two noncompliant with VFSS, one lost to follow-up)	Type/amount not specified	Penetration only 10% COPD group Aspiration 17% COPD group	More COPD (56% vs. 29%) tested positive on water swallow screening test ($P < 0.05$) More COPD (44% vs. 5%) tested positive on clinical swallowing assessment ($P < 0.001$)	Not examined
Cvejic *et al.* (5)	Prospective case–control	16 stable subjects with COPD (10 male, 6 female; mean age = 70.7 ± 5.2 yr) 15 healthy age-matched control subjects (8 male, 7 female; mean age = 70.1 ± 7.1 yr)	VFSS Surface EMG Pulse oximetry Spirometry Body plethysmography Intranasal pressure measurement Respiratory inductive plethysmography	5, 10, 20, 100 ml thin liquid	Penetration only in 2/16 (12.5%) COPD group, 0% in control group Aspiration 4/16 (25%) in COPD group vs. 1/15 (6.6%) in control group ($P = 0.07$) with 100 ml liquid Penetration and aspiration 6/16 (37.5%) in COPD group vs. 1/15 in control group (6.6%; $P = 0.04$)	Increased baseline respiratory rate in COPD ($P = 0.01$) Lower baseline oxygen saturation in COPD ($P = 0.05$) Reduced hyoid elevation in COPD ($P = 0.04$) Post-swallow pharyngeal residue in COPD ($P = 0.05$) Inspiration-swallow-expiration pattern during 100 ml liquid 60% in COPD group vs. 20% in control group	36 mo COPD group: hospitalization or death: 4/6 in penetration–aspiration group vs. 1 hospitalization in non–penetration–aspiration group ($P = 0.05$).
Mokhlesi *et al.* (9)	Prospective case–control	20 stable subjects with COPD (19 male, mean age = 69 ± 7.3 yr) 20 subjects in age- and sex-matched historical control group	VFSS Chest X-ray Pulse oximetry Spirometry Body plethysmography	3, 5 ml liquid 1 cup liquid 3 ml paste	Penetration not reported Aspiration 0%	Reduced laryngeal elevation in COPD ($P < 0.001$) Spontaneous protective swallowing maneuvers in COPD ($P < 0.05$)	Not examined
Good-Fratturelli *et al.* (7)	Retrospective study	78 subjects with COPD (male; mean age = 69.5 yr; range = 42–88 yr). COPD group: 85% had dysphagia, 33% neurologic etiology No healthy control group	VFSS	Thin liquid Thick liquid Puree Paste Biscuit Varied sizes (1 tsp self-sized)	Penetration only 5–20% (thin liquid 20%, thick liquid 15%, puree 10%, paste 6%, biscuit 5%) Aspiration (thin liquid 42%, thick liquid 19%)		Not examined

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; EAT = Eating Assessment Tool; EMG = electromyography; FEES = fiberoptic endoscopic evaluation of swallowing; VFSS = videofluoroscopic swallowing study.

*Laryngeal penetration that remained in the airway or equivalent to score of 3–5 on the penetration–aspiration scale (13).

stable COPD. Aspiration was noted in 25% of subjects (5). These findings were similar in a comparable study subsequently conducted by Clayton and coworkers (4) using FEES. Importantly, in both studies, aspiration only occurred when swallowing larger volumes of thin liquid (~100 ml). Silent aspiration (no cough or throat clearing) was observed in up to one-half of events (4, 5). In an earlier study, Good-Fratturelli and colleagues (7) observed a high prevalence of penetration (28%) and aspiration (42%) in a group of patients with dysphagia and suspected aspiration that had been referred for videofluoroscopy. The only study in exacerbated COPD found penetration in 10% and aspiration in 17% of patients (10).

Several studies did not find evidence of aspiration in COPD (6, 8, 9, 31), as noted in Table 1. In all these studies, smaller volumes of liquid were used to assess penetration and aspiration, and compensatory swallowing behaviors (such as prolonged breath hold maneuvers) were noted (6, 9). It seems likely that differences in contrast volume, concentration, and viscosity play a role, and that penetration and aspiration may depend on individual or combinations of these variables. Controlled studies are needed to determine prevalence in larger and well-defined COPD populations using appropriate methodologies.

Possible Mechanisms of Penetration and Aspiration in COPD

Several factors may predispose patients with COPD to penetration and aspiration. One possibility is reduced laryngopharyngeal sensitivity associated with airway inflammation, reflux, medications, such as anticholinergic agents and antihistamines, and cigarette smoking. However, to date, only marginal associations between laryngopharyngeal sensitivity and aspiration have been reported (4, 32).

Another possibility is disrupted breathing and swallowing patterns. Aspiration may occur during swallowing if inspiration occurs at this time, and this can be exacerbated by tachypnea (3) and hypercapnia (33). Hypercapnia can dampen airway-protective reflexes and reduce subglottic pressure during swallowing, resulting in increased pharyngeal residues (33, 34). Swallowing in COPD associated with hyperinflation may contribute to prolonged swallow duration as well as an inspiration post-swallow pattern (34). The importance of this key aspect of COPD pathophysiology is unknown, and the effect of hyperinflation on swallow and penetration and aspiration in COPD requires further study.

Dysfunction of laryngeal–pharyngeal musculature may contribute to penetration–aspiration. Abnormalities of muscle in COPD may be associated with myopathic changes after prolonged use of glucocorticoids, chronic hypoxemia, inflammation, chronic malnutrition, and the effects of cigarette smoking (35). This is pertinent to penetration–aspiration, because laryngeal–pharyngeal muscles involved in swallowing have a high percentage of fast-contracting type II fibers that will be prone to the impact of muscle dysfunction in COPD. Strength training improves respiratory muscle strength and endurance, and has the potential benefit of also improving airway protection in COPD if suitably adapted (36).

The risk of retrograde aspiration associated with reflux may be higher in COPD due to a number of factors. These include altered biomechanics associated with elevated intra-abdominal pressure and chronic hyperinflation, greater respiratory effort, and restricted diaphragmatic excursion impacting lower esophageal sphincter function (23, 24). Medications, such as oral glucocorticosteroids, and anticholinergic agents as well as cigarette smoking can also contribute to impairment of esophageal motility, gastric emptying, lowering of esophageal sphincter pressures, and reduced acid clearance from the esophagus. In addition, chronic cough can further exacerbate reflux (24, 37).

COPD Comorbidities, Penetration, and Aspiration

Coexisting conditions often detected in patients with COPD have also been linked to increased risk of penetration–aspiration and exacerbations of COPD, and may have a pathogenic role in altering swallowing integrity and airway-protective mechanisms in susceptible individuals. These include chronic heart failure, diabetes, chronic kidney disease, white matter brain changes, obstructive sleep apnea, and GERD (23, 29, 38–40). In a study of lung biopsies showing pathology consistent with chronic occult aspiration, the associated comorbidities were GERD (96%), esophageal dysfunction (40%), hiatus hernia (32%), obstructive sleep apnea (32%), and obesity (52%) (41).

Diagnosis and Management of Penetration and Aspiration

Diagnostic modalities to detect penetration and aspiration have improved markedly over the last decade. New innovations in videofluoroscopy and videoendoscopy include enhanced visualization techniques, higher-resolution imaging, digital recording, and computer-based image processing (42). Despite significant improvements, these diagnostic modalities are often not considered and used.

Videofluoroscopy and FEES

Videofluoroscopy is the primary radiographic examination used to assess swallow and airway protection, and is the preferred method for diagnosis of penetration and aspiration. High-resolution imaging at a rate of 30 images per second is a sensitive technique able to capture brief episodes of penetration and aspiration (42). Low-viscosity liquid increases the likelihood of identifying aspiration (43), and this strategy minimizes coating of the pharyngeal–esophageal mucosal surface, reducing false-positive results (42). Thin liquid with approximately 20% weight-to-volume barium generally provides acceptable visualization (42). Videofluoroscopy (and FEES) commonly use Rosenbek's penetration–aspiration scale to score the presence of penetration–aspiration (13). Rosenbek's scale has three categories: score 1–2 (normal); 3–5 (penetration); and 6–8 (aspiration) (*see* also Figure 1).

A flexible endoscopic camera is used during FEES to visualize the pharynx and airway during the act of swallowing. FEES has some advantages, particularly to detect laryngopharyngeal secretions. Concurrent sensitivity testing is also possible using air pulses, and, recently, a "touch" method was developed to assess laryngeal adductor reflex responses (44). FEES may not detect penetration and aspiration during the period of "whiteout" occurring when the tip of the endoscope is covered by contrast medium.

Other Diagnostic Modalities

Nuclear scintigraphy using radioisotope imaging could offer more sensitive detection and quantification of microaspiration (45), especially when used with single-photon emission computed tomography/computed tomography (46). Cough reflex testing introduced as a part of standard clinical swallowing assessments has recently

emerged as an aspiration risk-assessment tool. This may be a useful innovation, as studies have shown that patients with impaired laryngeal cough reflexes (dysussia) were at higher risk of aspiration and pneumonia (1, 47, 48), and absence of a cough response to inhaled irritants indicates laryngeal sensory impairment with the risk of aspiration increased up to eightfold (48). The Eating Assessment Tool-10 (49) identifies abnormal swallowing symptoms, and higher Eating Assessment Tool-10 scores may predict an increased risk of aspiration in COPD (50).

Advancements in high-resolution manometry in conjunction with impedance measurements, 24-hour pH manometry, and barium fluoroscopic examinations provide more detailed analysis of esophageal motility impairment. These investigations, performed in upright and supine positions using dynamic maneuvers, play an important role in diagnosis of abnormal esophageal peristaltic and sphincter function and detection of airway reflux or retrograde aspiration. Studies linking impaired esophageal motility with extra-esophageal symptoms and exacerbations in COPD (23, 26, 51) highlight the importance of accurate identification and targeted prevention approaches.

Management Strategies for Penetration and Aspiration in COPD

Prandial penetration and aspiration are infrequently suspected and diagnosed in COPD (52). Consequently, treatments have been poorly researched, and there are no controlled trials to inform management. Current modalities often include individualized compensatory swallow strategies and preventative education as part of pulmonary rehabilitation programs. Compensatory strategies are based on the physiological swallow abnormality underlying penetration–aspiration, and include use of smaller volumes, double swallows (dry swallows), neck flexion (chin tuck), pausing between mouthfuls, smaller, more frequent meals, cough or hard throat clear to assist clearance of penetrated–aspirated material, dietary and liquid modification, and reflux-preventative measures. Intervention within the pulmonary rehabilitation self-management model of care improves knowledge of dysphagia related to COPD, as well as swallow quality of life (53); however, more research is needed to verify benefits of various therapeutic recommendations. Clinical dysphagia characteristics are also likely to fluctuate, and require ongoing monitoring and review of symptoms and intervention. Consideration should be given to escalation of education about optimal swallow approaches during COPD disease exacerbations.

There is emerging research on respiratory-swallow phase intervention (12) and evaluation of potential cross-beneficial effects of expiratory muscle strength training (36) alongside traditional dysphagia treatment options for patients with COPD. Martin-Harris and colleagues (12) found a significant improvement in optimal expiratory-swallow-expiratory pattern within eight sessions of training in patients with head and neck cancer who also had chronic dysphagia and COPD. Importantly, the recent Global Initiative for Chronic Obstructive Lung Disease guidelines for COPD make only brief mention of penetration–aspiration and preventative approaches (54), and COPD rehabilitation guidelines also fail to emphasize this aspect (55).

Finally, it has been proposed that pharmacological agents, such as angiotensive-converting enzyme inhibitors, have aspiration protection benefits preventing exacerbations in selected individuals with impaired swallow reflexes (56). No controlled trials have been conducted and, overall, more research is needed to strengthen evidence for strategies that enhance swallow preservation and coach patients to optimize swallow and breathing coordination. Conversely, prophylactic low-dose macrolide antibiotics, such as azithromycin, have shown prokinetic, antimicrobial, and antiinflammatory properties, which assist gastrointestinal motility. These attributes may reduce microaspiration associated with reflux and frequency of bacterial exacerbations of COPD (57).

Research Priorities in COPD

Awareness and understanding of penetration, aspiration, and swallowing abnormalities in COPD continue to evolve. There are significant gaps in our current insights that need to be addressed in future research. The key questions are determining the prevalence of penetration–aspiration in COPD, identification of at-risk groups, and ascertaining whether silent aspiration occurs frequently. It is also crucial to establish whether penetration and aspiration contribute to some of the hallmarks of COPD: chronic inflammation, loss of lung function, and exacerbations. The role and predictive value of symptoms such as dysphagia, particularly in COPD, also require investigation. Finally, studies are needed to ascertain whether respiratory muscle strength training and other related strategies might help to reduce penetration–aspiration, perhaps as an integral part of COPD rehabilitation programs.

Conclusions

In COPD, altered upper airway–protective mechanisms and ventilatory adaptations may lead to pulmonary aspiration. Timely identification of individuals with COPD complicated by aspiration is essential. More information is needed about the prevalence of penetration–aspiration, mechanisms involved, and benefits of specific therapies. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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THESIS AIMS

The thesis had two broad aims.

Aim 1:

(a) To determine the prevalence of aspiration in stable COPD,

(b) To identify clinical parameters associated with aspiration, and

(c) To examine the association of aspiration with acute exacerbations of COPD over a 12-month period.

Aim 2:

To examine swallow patterns, airway protection strategies and swallow efficiency in patients with COPD, in the absence and presence of aspiration.

CHAPTER TWO

ASPIRATION AND EXACERBATIONS IN COPD

Chapter two outlines the prospective study on aspiration and severe exacerbations in COPD.

The purpose of this study was to determine pulmonary exacerbation events and its association with prandial liquid aspiration in patients with stable COPD.

This study concluded that prandial aspiration occurs in 20% of patients with stable COPD and that aspiration portends severe COPD exacerbations over 12 months. These findings have been published in *European Respiratory Journal Open Research* and are included as a PDF file.

ORIGINAL ARTICLE
COPD

Aspiration and severe exacerbations in COPD: a prospective study

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ABSTRACT

Rationale: Swallow may be compromised in COPD leading to aspiration and adverse respiratory consequences. However, prevalence and consequences of detectable aspiration in stable COPD are not known.

Objectives: We tested the hypothesis that a significant number of patients with stable COPD will have detectable aspiration during swallow (prandial aspiration) and that they would experience more frequent severe acute exacerbations of COPD (AECOPD) over the subsequent 12 months.

Methods: Patients (n=151) with verified and stable COPD of all severities were recruited at a tertiary care hospital. Videofluoroscopy was conducted to evaluate aspiration using Rosenbek's scale for penetration–aspiration during 100-mL cup drinking. AECOPD was documented as moderate (antibiotics and/or corticosteroid treatment) or severe (emergency department admission or hospitalisation) over the ensuing 12 months.

Measurements and main results: Aspiration was observed in 30 out of 151 patients (19.9%, 18 males, 12 females; mean age 72.4 years). Patients with aspiration had more overall AECOPD events (3.03 *versus* 2 per patient; p=0.022) and severe AECOPD episodes (0.87 *versus* 0.39; p=0.032). Severe AECOPD occurred in more patients with aspiration (50% of patients *versus* 18.2%; OR 4.5, CI 1.9–10.5; p=0.001) and with silent aspiration (36.7% *versus* 18.2%; OR 2.6, CI 1.1–6.2; p=0.045). Aspiration was related to a shorter exacerbation-free period during the 12-month follow-up period (p=0.038).

Conclusions: Prandial aspiration is detectable in a subset of patients with COPD and was predictive of subsequent severe AECOPD. Studies to examine if the association is causal are essential to direct strategies aimed at prevention of aspiration and AECOPD.

@ERSpublications
This study demonstrates that prandial aspiration occurs in ~20% of patients with stable COPD and portends severe COPD exacerbations over the next 12 months https://bit.ly/2Tx5btj

Cite this article as: Cvejic L, Guiney N, Nicholson T, *et al*. Aspiration and severe exacerbations in COPD: a prospective study. *ERJ Open Res* 2021; 7: 00735-2020 [https://doi.org/10.1183/23120541.00735-2020].

This article has supplementary material available from openres.ersjournals.com.

This study is registered at www.anzctr.org.au with identifier number ACTRN12620000513910. All individual de-identified participant data (including data dictionaries) will be shared. Related documents will be available including study protocol and statistical analysis plan. Data are immediately available for a period of 7 years to other researchers with an interest in COPD or related areas.

Received: 12 Oct 2020 | Accepted: 19 Oct 2020

Introduction

COPD may impair airway protection during swallow leading to adverse respiratory outcomes. Factors such as altered laryngopharyngeal musculature and sensitivity, tachypnoea, hyperinflation, hypoxia, gastro-oesophageal reflux, pharmaceutical agents and cigarette smoking may predispose patients with COPD to aspiration [1]. However, it is not clear how often aspiration occurs in stable disease and whether aspiration may predispose to recurrent acute exacerbations of COPD (AECOPD).

Prandial aspiration refers to aspiration that occurs during swallow, as distinct from retrograde aspiration (associated with reflux), microaspiration (involving small amounts of oropharyngeal or gastro-oesophageal contents) or silent aspiration (absence of cough despite material present below the vocal folds) [2]. Aspiration associated with swallow is particularly important due to its associated increased risk of pneumonia [3, 4], yet investigations into the condition in patients with COPD are rare or describe swallowing dysfunction of a different nature [5–10]. Limited data from small studies involving an array of methodologies to detect prandial aspiration suggest the condition may occur in up to 25% of patients with stable COPD [5, 6]. Prevalence of aspiration in COPD and the relationship between aspiration and exacerbations are not known and warrants investigation.

We hypothesised that a significant number of patients with stable COPD will have detectable prandial aspiration related to more frequent severe AECOPD. State-of-the-art videofluoroscopy was used to detect prandial aspiration in patients with stable COPD, and AECOPD events were documented over the subsequent 12 months.

Methods

Study design, patients, baseline and follow-up study measurements

A prospective observational cohort study was conducted, and all patients provided written informed consent. The study protocol was approved by the Human Research Ethics Committee of Monash Health, Melbourne, Australia. STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) reporting guidelines were used, and the study is registered with the Australian New Zealand Clinical Trials Registry (ACTRN12620000513910).

Studies were conducted at Monash Lung and Sleep at Monash Medical Centre, a tertiary care hospital in Melbourne, Australia. Community-dwelling patients were identified from a hospital pulmonary function database (⩾10 pack-year history of smoking, post-bronchodilator forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) ⩽0.7 and FEV_1 <80% predicted [11]) and invited to participate. They had to have a diagnosis of COPD by a general practitioner or respiratory physician, stable lung disease in the preceding 12 weeks and had to be aged 40–80 years. Exclusions are noted in the supplementary material.

The Airways Questionnaire 20 (AQ20), a short version of the St George's Respiratory Questionnaire (SGRQ) [12], was used to evaluate quality of life. The Eating Assessment Tool-10 (EAT-10) [13] identifies abnormal swallowing symptoms (score of ⩾3). The Oral Health Assessment Tool (OHAT) was administered to identify oral health issues [14].

Measurements of spirometry and other outcomes are detailed in the supplementary material.

Videofluoroscopy

Dynamic fluoroscopic imaging used the Philips MultiDiagnost Eleva with Flat Detector unit (Eleva, Philips Healthcare, Amsterdam, Netherlands) to record images at 30 frames·s^{-1}. Total radiation dose for each patient was <0.3 millisieverts. Images were archived in de-identified format. During videofluoroscopy patients were positioned in the seated position. Images were acquired in lateral and oblique positions. Standardised thin oral liquid barium contrast solution (100 mL) at room temperature at 22% weight-to-volume barium concentration [15] was prepared from the X-Opaque-HD barium powder (MCI, Melbourne, Australia) combined with thin fruit juice. Liquid barium was self-administered by each patient during videofluoroscopy. It is possible that rapid drinking predisposes to aspiration, and therefore two methods of ingestion (normal drinking at ease and rapid drinking) were evaluated. Patients were allocated in random fashion to either usual cup drinking, then rapid drinking or the reverse. Instructions were to: "swallow as you normally would" and then, after a 1-min recovery interval, "swallow as quickly as possible". The recovery interval was designed to allow time for clearance of potential pharyngo-oesophageal residue. The penetration–aspiration scale (PAS) was used to quantify the presence of penetration–aspiration as validated by Rosenbek [2]. No or momentary penetration of contrast material was scored as 1–2. Unsafe penetration was defined as scores of 3–5, aspiration was scored as 6–8, with silent aspiration (absence of cough) scored as 8. All fluoroscopy data were stored and then randomly analysed at the completion of the 12-month follow-up period. Two independent certified speech pathologists blinded to the study generated the PAS scores. PAS scoring was judged at conclusion of video

time frame for individual swallow tasks. The highest score for the two swallowing methods was used for analyses. Evaluation of images was done using pause, frame-by-frame, slow motion and reverse options. Intra-observer repeatability (kappa) of observation was >95% based on 15% of randomly selected studies (n=23). If there was discrepancy in penetration–aspiration score between observers, agreement was reached by consensus.

Assessment of AECOPD over 12 months

Episodes of AECOPD in the year prior to study were obtained by patient recall. AECOPD episodes during the 12 months of study were identified using in-person 3-monthly telephone interviews and methodology as detailed by Bischoff and co-workers [16]. All episodes were verified by examination of medical records. Attempts were not made to identify mild AECOPD (worsening of COPD symptoms only) with no healthcare intervention. Moderate AECOPD was defined as a history of worsened COPD symptoms requiring treatment with antibiotics and/or systemic corticosteroids by a general practitioner without emergency department (ED) review or hospital admission. Severe AECOPD was defined as worsening of COPD symptoms that culminated in ED admission with or without hospitalisation for AECOPD [11]. Frequent exacerbators were characterised as patients having ⩾2 exacerbations per year of any severity [17].

Statistical analysis

Primary outcomes were the proportion of patients with detectable aspiration, total number of AECOPD events and patients with at least one episode of severe AECOPD. Secondary outcomes were moderate and combined moderate–severe AECOPD events, and changes from baseline in lung function, exhaled nitric oxide fraction (F_{ENO}), and AQ20 and EAT-10 scores. Sample size was based on an estimated prevalence of aspiration of 25% in COPD [6]. We assumed that the number of patients with aspiration and severe

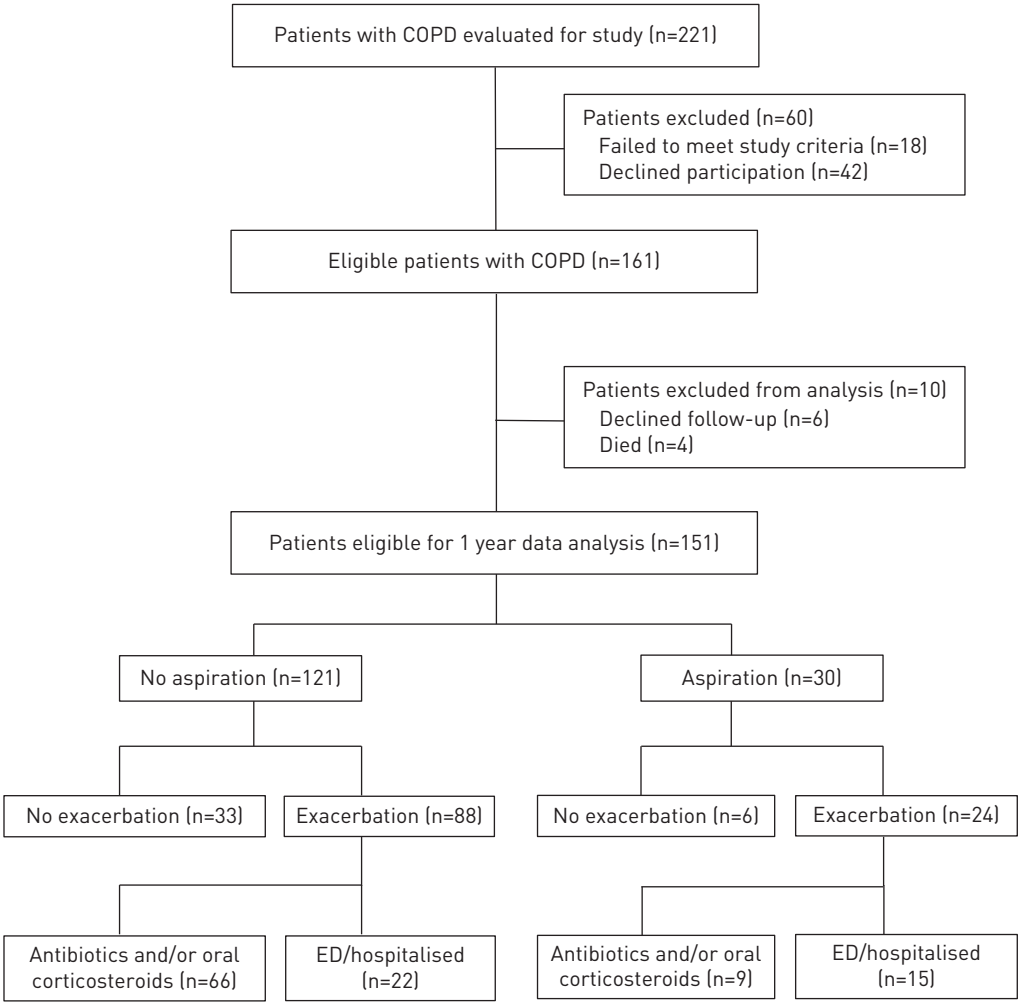

FIGURE 1 Consort diagram of patient participation in the study. ED: emergency department.

AECOPD would be twice those without aspiration. To achieve statistical power of 80% with $p \leqslant 0.05$, the study required 134 patients.

Data were analysed using statistical software package SPSS version 24+. Univariate and multivariate analyses were used to examine whether aspiration could be linked to COPD severity (FEV_1 or FEV_1/FVC ratio), body mass index, baseline respiratory rate, dysphonia, comorbidities, long-term oral corticosteroids, sedatives, OHAT scores and EAT-10 scores. Appropriate regression analyses were conducted to identify variables that may confound the association between aspiration and AECOPD events. Factors evaluated were age, sex, body mass index (BMI), FEV_1, FEV_1/FVC ratio, previous exacerbation history, comorbidities and medications. We calculated 95% confidence intervals. Survival analysis was conducted using the Kaplan–Meier method with log-rank testing. All reported tests were two-tailed and significance was set at $p \leqslant 0.05$.

Results

Patients and aspiration

Overall, 221 patients were screened for inclusion in the study (figure 1) and 60 were excluded (42 declined participation; 18 did not meet entry criteria). The remaining 161 patients entered the study of whom 10

TABLE 1 Baseline characteristics of 151 patients enrolled in studies of aspiration in COPD

	Aspiration not detected	Aspiration[#] detected
Subjects n	121	30
Age years (range)	70.2±5.1 (60.1–80.6)	72.4±4.3[¶] (65.7–78.8)
Male/female	74/47	18/12
Body mass index kg·m^{-2}	29.4±5.8	27.7±6.4
FEV_1 % predicted	49.2±15.3	45.3±15.3
FEV_1/FVC ratio %	53.1±13.9	51.0±11.1
TLC % predicted	129.2±22.0	129.0±20.5
RV/TLC %	58.4±8.8	60.5±8.2
F_{ENO} ppb	24.5±23.8	22.4±22.1
S_{pO_2} %	95.3±1.8	94.7±2.8
Respiratory rate breaths·min^{-1}	17.9±4.0	18.7±4.7
Comorbidities		
Cardiovascular disease	99 (82)	28 (93)
Chronic kidney disease	7 (6)	1 (3)
Gastro-oesophageal reflux disease	72 (60)	17 (57)
Obstructive sleep apnoea	20 (17)	3 (10)
Diabetes	18 (15)	7 (23)
Anxiety–depression	27 (22)	8 (27)
Medication		
ICS/LABA only	15 (12)	2 (7)
ICS/LABA/LAMA	94 (78)	27 (90)
Systemic corticosteroids (long term)	36 (30)	12 (40)
Antibiotics (long term)	28 (23)	7 (23)
Oxygen therapy	21 (17)	7 (23)
Influenza vaccination	41 (34)	11 (37)
Pneumococcal vaccination	11 (9)	4 (13)
Antihypertensives	96 (79)	26 (87)
Antianxiety/antidepressant	47 (39)	13 (43)
Angiotensin-converting enzyme inhibitors	26 (22)	7 (23)
Reflux medications	79 (65)	17 (57)
AQ20 score	9.6±4.2	10.9±3.9
AQ20 score >8	79 (65)	23 (77)
EAT-10 score	2.3±3.9	2.9±4.6
OHAT score	2.2±2.1	3.1±2.7
Resting saliva pH	6.5±0.5	6.4±0.7

Data are presented as mean±SD or n (%), unless otherwise indicated. FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; TLC: total lung capacity; RV: residual volume; F_{ENO}: exhaled nitric oxide fraction; S_{pO_2}: oxygen saturation measured by pulse oximetry; ICS: inhaled corticosteroids; LABA: long-acting beta agonists; LAMA: long-acting muscarinic antagonist; AQ20: Airways Questionnaire-20; EAT-10: Eating Assessment Tool; OHAT: Oral Health Assessment Tool. [#]: aspiration score of 6–8 on the penetration–aspiration scale [2]; [¶]: $p \leqslant 0.02$.

patients (2 with aspiration) failed to complete 12 months of follow-up (6 declined follow-up, 4 died: 2 pneumonia, 1 post-operative complications, 1 bowel obstruction). Characteristics of these 10 patients are included in supplementary table S1. Baseline patient demographic data for 151 patients (mean age 70.6±5.0 years; mean±SD) who completed studies over 12 months are shown in table 1 and figure 1. Aspiration (PAS scores 6–8) was detected in 30/151 patients (19.9%). Silent aspiration (PAS score 8) was found in 22/151 patients (14.6%) and in the majority of those patients in whom aspiration was detected (22/30 patients, 73.3%). Penetration plus aspiration (PAS scores 3–8) was detected in 48/151 patients (31.8%) and penetration only (PAS scores 3–5) in 18 patients (11.9%).

Patients with aspiration were slightly older (72.4±4.3 *versus* 70.2±5.1, p=0.02, table 1). Univariate and multivariate analyses found no evidence linking aspiration to COPD severity (FEV_1 or FEV_1/FVC ratio), body mass index, AQ20 scores, baseline respiratory rate, dysphonia, comorbidities, long-term oral corticosteroids, sedatives, OHAT scores and EAT-10 scores. Interestingly, penetration plus aspiration (PAS scores >2) were detected more frequently in diabetes mellitus despite the limited number of patients with a history of the condition (n=25; 14/25 with penetration and aspiration; p=0.01).

Aspiration occurred in 19/30 patients during normal drinking and in 15/30 patients during rapid drinking, and aspiration was observed in 4/30 patients with both methods. Overall PAS scores were 2.39±2.12 for normal drinking and 2.45±1.93 for rapid drinking (p=0.81).

Aspiration and AECOPD

In the year prior to study, 55 patients (out of 151; 36.4%) had at least one AECOPD event of any severity. There were prior events in 13/30 patients (43.3%) with aspiration and 42/121 in the group with no aspiration (34.7%; p=0.402). The number of patients with at least one severe AECOPD episode in the prior year was 11/30 (36.7%) in the aspiration group and 24/121 (19.8%) in the no aspiration group (p=0.057).

All patients could be contacted by phone (occasionally after repeated attempts) after 3, 6, 9 and 12 months to administer the AECOPD questionnaire and all reported AECOPD events were verified by examination of medical records. Overall, 334 AECOPD moderate and severe episodes were recorded in the study group over 12 months of follow-up. There were 91 events recorded in patients with aspiration (n=30) and 243 events in the no aspiration group (n=121; 3.03 events per patient in the aspiration group *versus* 2.0 per patient; p=0.022). Patients with aspiration had a total of 26 severe AECOPD events noted in 30 patients *versus* 48 severe events in 121 patients with no aspiration (0.87 events per patient *versus* 0.39; p=0.032; figure 2a, left panel).

Individually 112 patients experienced at least one episode of AECOPD of any severity over the 12 months of follow-up, 24/30 patients with aspiration (80%) and 88/121 (72.7%) if aspiration was absent (p=0.491). However, more patients with aspiration had severe AECOPD (15/30; 50%) *versus* individuals with no aspiration (22/121 (18.2%); OR 4.5, CI 1.9–10.5; p=0.001; figure 2a, right panel). Similarly, severe

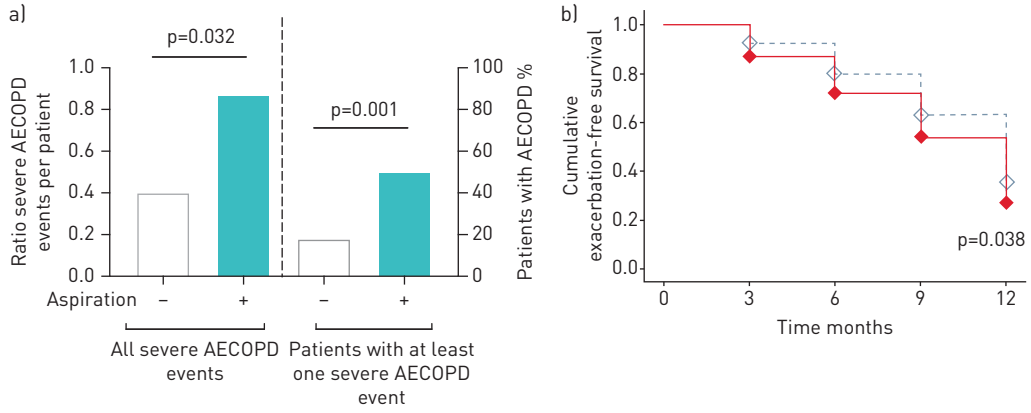

FIGURE 2 a) Aspiration was associated with severe episodes of acute exacerbations of COPD (AECOPD). Left panel: severe AECOPD events were more frequent in patients with aspiration (ratio 0.87; n=30) than if no aspiration (ratio 0.39; n=121). Right panel: number (%) of patients with at least one severe episode was greater in patients with aspiration (50%) than if no aspiration (18%). (-): aspiration not detected; (+): aspiration detected. b) Kaplan–Meier analysis of patients with no aspiration (open diamonds) and aspiration (closed diamonds) who were exacerbation-free over 12 months of follow-up. Difference between groups analysed using log-rank testing.

AECOPD was more frequent in patients with silent aspiration (36.7% *versus* 18.2%; OR 2.6, CI 1.1–6.2; p=0.045). Aspiration was related to a shorter exacerbation-free period in the 12-month follow-up period (p=0.038; figure 2b).

Appropriate regression analyses were conducted to identify variables that may confound the association between aspiration and AECOPD events. Factors evaluated were age, sex, AQ20 score, BMI, FEV_1, FEV_1/FVC ratio, previous exacerbation history, comorbidities and medications. None of these variables altered the association of aspiration with AECOPD. Subgroup analyses of severity and prior history of AECOPD are shown in figure 3 and supplementary table S2.

Pulmonary function and F_{ENO} measurements

After 6 months all indices were unchanged between patients with and without aspiration (data not shown). Hyperinflation has been proposed as a factor favouring aspiration [18, 19], but both total lung capacity (TLC) and residual volume (RV)/TLC were not predictive. F_{ENO} levels ⩾25 ppb were detected in 31/151 patients (20.5%) and ⩾50 ppb in 7/151 (4.6%), and there was no association with aspiration.

EAT-10 scores and other patient characteristics

EAT-10 scores ⩾3 at baseline were noted in 8/30 from the aspiration group (26.7%) *versus* 37/121 (30.6%) if aspiration was absent. EAT-10 scores >9 have been proposed as a marker of aspiration [8] but were not predictive (data not shown). Other baseline characteristics including oral health risk measurements and presence of dysphonia (23/151; 15.2%) were not associated with aspiration.

Discussion

We hypothesised that prandial aspiration occurs in COPD contributing to severe episodes of AECOPD. Our findings establish that aspiration, measured *via* "gold standard" videofluoroscopy, is found in ~20% of patients and that individuals with evidence of aspiration have an increased propensity to severe AECOPD. Further research is needed to establish whether this association is causative, to define pertinent mechanisms and to investigate practical strategies to diagnose, manage and prevent aspiration in COPD.

Eating and swallowing are important aspects of everyday living. During normal swallow, the larynx serves as a valving mechanism to provide protection from aspiration of liquid or solid material [20]. Laryngeal penetration occurs when there is entry of material into the laryngeal vestibule at or above the true vocal folds that can be cleared by supraglottic and subepiglottic compression [21, 22], expiration [23] or cough. Aspiration is defined as progression of penetrated material below the true vocal folds. Studies in healthy individuals have indicated that prandial aspiration is rare across all age groups [24–26]. However, in COPD penetration and aspiration with swallow may take place more frequently and could be of prognostic significance due to its association with pneumonia [3, 4].

Uncertainty surrounds the prevalence of prandial aspiration in stable COPD. Our previous [6] and other small studies [5] have suggested that aspiration is detectable in ~25% of stable COPD, and two retrospective studies noted aspiration in up to 40% [7, 8]. However, several other investigations failed to detect any evidence of aspiration in this patient group [19, 27–29]. These differences are likely to reflect methodological variations including poorly characterised, small patient study groups, confounding by comorbidities (such as neurological and swallow impairment) and use of small volume or solid contrast materials and high liquid viscosity that may preclude detection of aspiration.

The current study recruited a larger cohort of patients with COPD compared to previous smaller studies [5, 6, 8, 10, 19, 27–29]. Patients had stable, verified disease at baseline, conditions that may predispose to

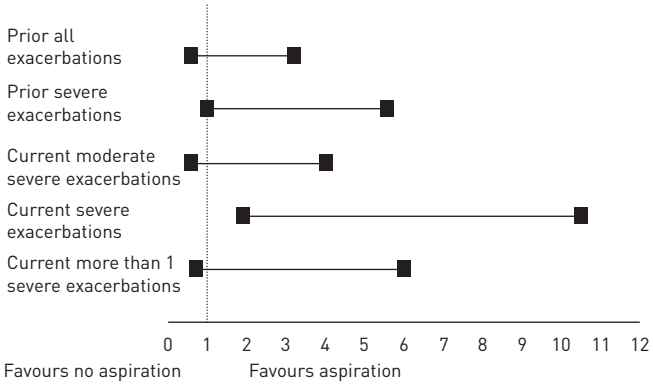

FIGURE 3 Subgroup analyses of history and types of acute exacerbations of COPD (AECOPD) associated with aspiration or no aspiration. Prior: 12 months prior to study; Current: 12 months of current study.

prandial aspiration were excluded and the volume of contrast material was optimised for accurate imaging by means of videofluoroscopy. In this context our findings confirm that aspiration can be detected in up to one fifth of patients with stable COPD, confirming previous small studies [5, 6]. However, since testing was only performed on one occasion, it is possible that the recorded prevalence of 20% is an underestimation, and it will also be important to assess in further studies whether aspiration is persistently detectable.

Up to 30% of AECOPD events have no discernible cause, and other mechanisms such as aspiration may play a role [30–32]. Our previous case–control study hinted at adverse outcomes and more frequent severe AECOPD events in patients who had detectable prandial aspiration [6]. The current study therefore examined whether aspiration is associated with more frequent ED or hospital admission for AECOPD over a 12-month period. The study findings provide affirmative data with increases in overall as well as individual severe AECOPD episodes in patients with aspiration. Importantly, there was a four-fold increase in odds ratio linking aspiration with severe episodes of AECOPD in individual patients indicating that this association was not the result of a few "super-exacerbators". These observations provide evidence that aspiration itself, or as a marker for other predisposing factors such as older age and sarcopenia, is associated with a key adverse outcome in COPD. For that reason, aspiration merits consideration in diagnostic and management approaches aiming to prevent severe AECOPD, perhaps more so in patients who have a history of frequent severe events. Future research examining aspiration and differentiating the causes of AECOPD in detail will help to ascertain the extent to which the association is causal and to explain how aspiration contributes to AECOPD.

Aspiration may cause incremental lung damage and could contribute to the excess decline in lung function noted in COPD [17, 33]. We assessed whether a greater decline in function was measurable 6 months after detection of aspiration (review after 12 months was not feasible due to logistic constraints). No differences in any parameters were noted, a not unexpected result given relatively small patient numbers, individual variations in lung function decline and the short period of study. F_{ENO}, as one measure of airway inflammation, was also evaluated at baseline and after 6 months with no detectable differences.

It would be useful to identify clinical or other parameters predictive of aspiration but in this respect our findings were disappointing. Although patients with aspiration had a higher age than those without aspiration, this finding is of doubtful clinical significance given a difference in mean age of only ~2 years (table 1). Notably, aspiration was not linked to lower FEV_1 measurements or higher lung volumes (TLC) nor was there an association with respiratory rate at rest.

How and why aspiration occurs in COPD is not understood. Our data indicate that reduced laryngopharyngeal sensitivity may be important since the majority of patients had silent aspiration (Rosenbek PAS score 8 noted in >70% of individuals with aspiration) implying a degree of airway sensory impairment in this group. Absence of an effective cough reflex may thus reflect a reduced ability to sense aspirated material and to generate appropriate cough and other protective responses to clear the airway. We therefore posit that a dysfunctional "middle airway", perhaps due to reduced timing of laryngeal vestibular closure and sensory mechanisms in COPD [5, 34], may underlie defective protection against aspiration. Finally, an interesting finding was more frequent penetration–aspiration in patients with a history of diabetes mellitus, a condition linked with sarcopenia [35], laryngeal sensory disruption [36], diabetic neuropathy and abnormal oral bacterial loads [37].

The current investigations have several caveats. First, it was a single tertiary centre study with a limited number of patients. Next, an age-matched healthy control group was not studied. Original design of the study had included this group, but the investigators were unable to obtain ethics approval due to local restrictions on radiation exposure for research purposes in healthy individuals. Moreover, there is ample evidence that aspiration is rare in healthy persons [24–26], and comparison of patients with COPD, with and without aspiration, has yielded helpful information. Third, AECOPD events were not assessed during the event itself but documented 3-monthly by patient self-report using a healthcare-based questionnaire combined with medical record confirmation that has been shown to have acceptable accuracy in this context [16]. Fourth, low-dose systemic glucocorticoids (10 $mg \cdot day^{-1}$ or less) were used in ~30% of patients. Although not recommended by current Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, similar high levels of oral glucocorticoid use have been reported in other countries [38, 39]. This medication may impact muscle function leading to AECOPD, even though no association with aspiration or AECOPD was detected. Finally, other quantitative assessments such as intranasal pressure measurement for quantification of respiratory phase during swallow [6, 18], hand grip strength to assess associations with sarcopenia and a standardised instrument for frailty or age-related susceptibility may have provided additional useful information.

In conclusion, prandial aspiration can be detected in a subgroup of patients with COPD. The presence of aspiration is associated with severe AECOPD requiring ED or hospital admission. It is unclear why aspiration occurs and how this may predispose to severe episodes of acute deterioration. Future research should aim to verify causative links, improve understanding of mechanistic aspects, examine early and accurate diagnosis and design appropriate studies testing effective approaches to prevent aspiration. Finally, the findings reinforce the importance of swallow-breathing strategies [40] in COPD educational and rehabilitation programmes.

Author contributions: Conception and design: L. Cvejic, P. Finlay, P.T. King and P.G. Bardin; data acquisition: L. Cvejic, N. Guiney and T. Nicholson; data analysis: L. Cvejic, K.K. Lau, K. Hamza and P.G. Bardin; drafted and critically revised the manuscript: L. Cvejic, C. Osadnik, P. Leong, M. MacDonald, P.T. King and P.G. Bardin; final approval for publication: all authors

Conflict of interest: L Cvejic has nothing to disclose. N. Guiney has nothing to disclose. T. Nicholson has nothing to disclose. K.K. Lau has nothing to disclose. P. Finlay has nothing to disclose. K. Hamza has nothing to disclose. C. Osadnik reports they were the recipient of a Lung Foundation Australia COPD Research Fellowship (2016–2018; AUD$160 000) and is the recipient of a Rebecca L. Cooper Medical Research Foundation Project Grant (2020–2021; AUD$100 000). P. Leong is supported by the National Health and Medical Research Council Postgraduate Scholarship and the Royal Australasian College of Physicians, outside of this work. Views expressed do not necessarily reflect those of the funding bodies. M. MacDonald has nothing to disclose. P.T. King has nothing to disclose. P.G. Bardin has nothing to disclose.

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CHAPTER THREE

ASPIRATION AND EXACERBATIONS IN COPD: SUPPLEMENTARY MATERIAL

Chapter three details the supplementary material that accompanies this thesis, specifically the prospective study on aspiration and severe exacerbations in COPD outlined in Chapter two. The aim of this chapter is to examine other disease and patient variables that may impact the association between aspiration and acute exacerbation of COPD (AECOPD). A section of the supplementary material has been published online in *European Respiratory Journal Open Research.*[1] Additional information is provided below. In conclusion, while there was a trend towards a link with a more severe previous exacerbation history, no other variables examined in this study altered the association between aspiration and AECOPD.

Aim

To examine other disease and patient variables that may impact the association between aspiration and acute exacerbation of COPD (AECOPD).

Methods

Study design, patients, and baseline and follow-up study measurements

Studies were conducted at Monash Lung and Sleep at Monash Medical Centre, a tertiary care hospital in Melbourne, Australia. Community-dwelling patients were identified from a hospital pulmonary function database (≥10 pack-year history of smoking, post-bronchodilator $FEV_1/FVC \leq 0.7$ and $FEV_1 < 80\%$ predicted)[2] and invited to participate. They had to have a diagnosis of COPD by a general practitioner or respiratory physician, stable lung disease (no exacerbations) in the preceding 12 weeks and had to be aged 40-80 years. Participation was restricted to those with no known neurological disease, no significant head or neck surgery impacting swallow, no abnormal cranial nerve function on examination, no history of head or neck cancer and no current smokers. Clinical examination conducted at the point of initial assessment did not involve oral trial of food or liquid. Medication use and relevant health history information including comorbidities associated with COPD were obtained from patient history, hospital medical records and medical practitioners.

Measurements of spirometry, gas transfer, lung volumes by body plethysmography and exhaled nitric oxide (FE_{NO}) (MGC Diagnostics Medisoft® and Aerocrine NIOX NO monitoring systems) were obtained as per American Thoracic Society and European Respiratory Society guidelines.[3-10] Lung function testing was performed and post-bronchodilator data were used to verify COPD. Where possible short-acting bronchodilators were withheld for at least 4 hours and long-acting bronchodilators for up to 12 hours prior to assessments. Measurements were made at baseline and repeated after 6 months.

Transcutaneous oximetry (Nellcor™ PM10N, Covidien) was used to measure peripheral capillary oxygen saturation (S_pO_2). The pulse oximeter had an accuracy specification of ±2% which includes motion and low saturation measurement accuracy. The oximetry probe was fitted to the patent's non-dominant finger to minimise artefact associated with motion during cup-drinking. Readings were performed at rest and up to 5 minutes after completion of individual swallowing tasks. Respiratory rate was recorded at rest and one minute after drinking.

The Airways Questionnaire 20 (AQ20), a short version of the St George's Respiratory Questionnaire (SGRQ),[11] was used to evaluate quality of life. It is a validated measure of disease severity and healthcare utilization in COPD[12, 13] with scores ≥8 predictive of exacerbations.[14] The Eating Assessment Tool-10 (EAT-10)[15] identifies abnormal swallowing symptoms (score of ≥3) and higher scores (>9) may be predictive of increased risk of aspiration in COPD populations.[16] Patients completed the AQ20 and EAT-10 at baseline, 6 months and 12 months.

Baseline assessments of voice function employing auditory perceptual evaluation and a numerical rating scale for impairment adapted from the standardised Australian Therapy Outcome Measures[17] (0 = no voice problem/disruption; 1 = mild disruption to voice production or occasional episodes of dysphonia; 2 = moderate with frequent episodes of dysphonia; and 3 = severe voice disruption) were performed.

The Oral Health Assessment Tool (OHAT), a valid screening instrument was administered at baseline to identify oral health issues in eight categories: lips, tongue, gums and tissues, saliva, natural teeth, dentures, oral cleanliness and dental pain.[18] Resting pH of unstimulated saliva was also measured as per manufacturer's instructions (GC Australasia Dental) using pH reference ≥6.4.[19] Oral hygiene practices were not investigated.

Videofluoroscopy swallowing protocol and measurements detailed in Chapter two were conducted on all patients on the day of initial assessment. Briefly, aspiration presence was coded as dichotomous rating yes or no using the worst Penetration-Aspiration Scale (PAS)[20] score on ultra-thin liquid barium solution for two swallowing tasks (self-paced cup-drinking and fast-paced cup-drinking).

Results

Association between aspiration and AQ20, EAT-10 and AECOPD outcomes

Detailed demographic data of 151 patients who completed studies over 12 months is summarised in Chapter two, Table 1. Baseline characteristics of 10 patients who failed to complete 12 months of follow-up are shown in Table S1. All patients were on unmodified solids and fluids; were independent with self-feeding and oral care; and were independent with mobility for at least short distances.

Regression analyses were conducted to identify variables that may confound the association between aspiration and AECOPD events. None of these variables described in Chapter two altered the association of aspiration and AECOPD. One of these factors included previous exacerbation history. Subgroup analyses of history and types of acute exacerbations of COPD in 151 patients who completed 12 months of follow-up are shown in Table S2.

Pharmacological treatment for severe AECOPD included systemic corticosteroids and empirical antibiotic therapy in 13/15 patients from the aspiration group (87%) versus 21/22 (95%) without aspiration. No patient received speech pathology intervention during hospital admission.

Changes in the AQ20 and EAT-10 scores over the 12-month period and the relationship with exacerbations were also examined. These are provided in Tables S3 and S4. There was no association between AQ20 or EAT-10 scores with or without aspiration in the severe AECOPD group (Table S3) or the non-severe aspiration group (Table S4).

Association between aspiration and dysphonia, oxygen therapy and oral health risk characteristics

No association was identified between presence of dysphonia and aspiration. Dysphonia was identified in 6/30 (20%) patients from the aspiration group versus 17/121 (14%) if aspiration was absent. All 23 patients had mild dysphonia characterised by rough or breathy quality which may be suggestive of irregular vocal fold vibration patterns or incomplete vocal fold adduction. 9 patients with dysphonia had a history of reflux symptoms, 4 reported voice changes associated with inhaled corticosteroid medication, 4 were on oxygen therapy, 2 complained of dry throat symptoms, and 2 had laryngoscopy investigations which revealed no significant abnormality. No patient demonstrated hydrophonic voice quality, which may indicate secretion aggregation within the glottic space, and no patient reported odynophagia in response to EAT-10 question six ‘swallowing is painful’.

Concurrent oxygen therapy was used in 28/151 (18.5%) patients but did not influence the assessment or prevalence of aspiration. Xerostomia which can promote oral dysbiosis was a common complaint (106/151; 70.2%) but was not more frequent in the aspiration group. There was also no association between OHAT scores based on presence or absence of aspiration in patients with severe AECOPD (2.8±2.3 versus 2.6±2.5; p=0.798) and non-severe AECOPD (3.3±3.2 versus 2.2±2.0; p=0.061).

Conclusion

While there was a trend towards a link with a more severe previous exacerbation history (p=0.057), no other variables examined in this study altered the association between aspiration and AECOPD. Larger, prospective longitudinal studies are needed to explore associations of aspiration with exacerbations, particularly in patients with repeated hospital admissions, in those people with higher frailty and dyspnoea indices and if pertinent COPD comorbidities are present. Improved identification and characterisation of exacerbation subtypes specific to patients with aspiration risk would add value to risk stratification and ultimately clinical decision-making. A better grasp of these disease interactions has potential to complement existing COPD treatment options and offer more targeted and preventive management approaches.

Table S1. Baseline characteristics of 10 patients who did not complete 12-month follow-up

Subjects n	10
Age (years, range)	71.0±11.5 (41.2-78.8)
Gender (M/F)	5/5
Body Mass Index (kg/m^2)	28.6±6.4
FEV_1 (% predicted)	48.3±17.4
FEV_1/FVC ratio (%)	50.4±16.3
TLC (% predicted)	134.6±24.3
RV/TLC (%)	61.4±8.5
FE_{NO} (ppb)	31.2±20.7
S_pO_2 (%)	93.5±6.6
Respiratory rate (breaths/min)	20.4±2.5

Comorbidities (n)	
Cardiovascular disease	9
Chronic kidney disease	0
Gastro-oesophageal reflux disease	4
Obstructive sleep apnoea	1
Diabetes	0
Anxiety-depression	3
Medication (n)	
ICS/LABA only	4
ICS/LABA/LAMA	5
Systemic corticosteroids (long term)	2
Antibiotics (long term)	0
Oxygen therapy	3
Influenza vaccination	3

Pneumococcal vaccination	2
Antihypertensives	8
Antianxiety/Antidepressant	4
Angiotensin-converting enzyme inhibitors	1
Reflux medications	4
AQ20 score	10.1±5.6
AQ20 score >8 (n)	6
EAT-10 score	4.1±6.2
OHAT score	2.0±2.4
Resting saliva pH	6.4±0.5

Data shown as mean ± SD unless otherwise indicated; LABA, long-acting beta agonists; LAMA, long-acting muscarinic antagonist; ICS, inhaled corticosteroids; AQ20, Airways Questionnaire-20;[11] EAT-10, Eating Assessment Tool;[15] OHAT, Oral Health Assessment Tool.[18]

Table S2. Subgroup analyses of history and types of AECOPD associated with aspiration or no aspiration in 151 patients

	Aspiration not detected	Aspiration† detected	Odds Ratio (95% CI)	P Value
Subjects n	121	30		
All exacerbations previous year ≥1	42 (34.7)	13 (43.3)	1.44 (0.64-3.24)	0.402
Hospital/ED exacerbations (severe) previous year ≥1	24 (19.8)	11 (36.7)	2.34 (0.98-5.57)	0.057
All moderate/severe exacerbations current study	88 (72.7)	24 (80)	1.5 (0.56-4.00)	0.491
Hospital/ED exacerbations current study	22 (18.2)	15 (50)	4.5 (1.92-10.55)	0.001
Hospital/ED exacerbations ≥2 current study	13 (10.7)	6 (20)	2.08 (0.72-6.02)	0.216

Data are presented as n (%). †Aspiration score of 6-8 on the penetration-aspiration scale;[20] ED, Emergency Department; AECOPD, acute exacerbation of COPD.

Table S3. Comparison of AQ20 and EAT-10 scores over 12-months in patients with severe AECOPD based on presence/absence of aspiration

	Aspiration not detected	Aspiration† detected	Mean difference (95% CI)	P Value
Subjects n	22	15		
AQ20 scores				
Baseline	11.3±3.5	12.7±3.4	1.46 (-0.90-3.82)	0.217
6 months	11.7±3.3	12.3±3.4	0.61 (-1.65-2.86)	0.589
12 months	12.2±2.5	11.1±4.6	1.12 (-1.28-3.51)	0.351
EAT-10 scores				
Baseline	3.3±5.6	4.0±6.0	0.73 (-3.19-4.64)	0.709
6 months	2.2±5.3	2.5±4.2	0.31 (-3.03-3.64)	0.853
12 months	2.6±5.6	2.8±4.6	0.21 (-3.32-3.74)	0.905

Data are presented as mean±SD. †Aspiration score of 6-8 on the penetration-aspiration scale;[20] AQ20, Airways Questionnaire-20;[11] EAT-10, Eating Assessment Tool;[15] AECOPD, acute exacerbation of COPD.

Table S4. Comparison of AQ20 and EAT-10 scores over 12-months in patients with non-severe AECOPD based on presence/absence of aspiration

	Aspiration not detected	Aspiration† detected	Mean difference (95% CI)	P Value
Subjects n	99	15		
AQ20 scores				
Baseline	9.2±4.2	9.1±3.6	0.09 (-2.20-2.38)	0.939
6 months	9.6±4.4	9.1±2.3	0.51 (-1.81-2.84)	0.663
12 months	8.9±4.6	7.7±4.0	1.22 (-1.28-3.73)	0.336
EAT-10 scores				
Baseline	2.1±3.4	1.8±2.5	0.25 (-1.54-2.04)	0.782
6 months	1.7±3.6	1.4±2.2	0.35 (-1.54-2.24)	0.717
12 months	1.9±3.0	1.0±1.5	0.89 (-0.68-2.45)	0.263

Data are presented as mean±SD. †Aspiration score of 6-8 on the penetration-aspiration scale;[20] AQ20, Airways Questionnaire-20;[11] EAT-10, Eating Assessment Tool;[15] AECOPD, acute exacerbation of COPD.

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CHAPTER FOUR

SWALLOW PATTERNS ASSOCIATED WITH ASPIRATION IN COPD

Chapter four details the swallow patterns evaluated by videofluoroscopy during a 100-ml drinking challenge in patients with COPD.

The primary aim of this investigation was to determine the impact of self-paced and fast-paced cup-drinking on swallow patterns as well as airway protection and swallow efficiency.

This study concluded that swallow patterns were altered and slower swallow was linked to aspiration using both self-paced and fast-paced methods of ingestion. In a clinical context videofluoroscopy, with both self-paced and fast-paced drinking methods, is likely to provide the most sensitive detection of aspiration in COPD. These findings have been published in *European Respiratory Journal Open Research* and are included as a PDF file. Perspectives on future clinical and research considerations have been added as detailed below.

Swallow patterns associated with aspiration in COPD: a prospective analysis

Received: 11 March 2021
Accepted: 5 May 2021

To the Editor:

Aspiration during swallow may have devastating consequences in COPD. It is known that COPD can impair swallow efficiency and safety [1–3] and a better understanding of how patients with COPD swallow is essential to inform preventative strategies. To date, no studies have examined swallow of large liquid volumes representative of everyday fast-paced drinking in an ample number of patients with COPD. In this letter we detail swallow patterns evaluated by videofluoroscopy in patients with COPD, with and without evidence of aspiration.

Normal sequential swallow involves the hypopharynx [4] and evidence indicates that breathing during sequential liquid cup swallows can increase the risk of aspiration [5]. Shorter breaths with active cessation of respiration may be one important airway protection feature during swallow that is compromised in COPD when patients may be unable to breath-hold for long. Conversely, shorter swallow duration during drinking of larger volumes of liquid may interfere with bolus movement through the oesophagus and contribute to increased risk of retrograde flow and post-swallow aspiration. In that context our previous studies in COPD suggested that patients may use adaptive airway protective strategies to prevent aspiration [6].

Detecting aspiration in COPD is best achieved using videofluoroscopy [3]. Swallow testing using ∼100 mL water is common practice in clinical settings, but sequential drinking has not been considered standard practice in videofluoroscopic examinations. However, recent studies have indicated that poorer swallow performance during 100 mL water testing could indicate potential swallowing difficulty [7] and revealed that sequential thin liquid drinking has the highest probability to detect impaired airway protection [8]. We used this improved methodology in recent studies [6].

Our observational study of swallow in COPD [6] provided data to evaluate swallow patterns linked to aspiration in COPD. The study protocol was approved by the Human Research Ethics Committee of Monash Health, Melbourne, Australia. Patient characteristics and methods were as published [6]. Briefly, patients swallowed 100 mL of ultra-thin liquid barium solution during videofluoroscopy using two methods (self-paced cup-drinking allowing single discrete swallows and fast-paced cup-drinking with sequential swallows). Penetration–aspiration scale (PAS) [9] and pharyngo-oesophageal measurements were made by two speech pathologists and a radiologist. Number of swallows was the number of total liquid swallows used to consume 100 mL volume. Total swallow duration was time from swallow onset until the last liquid contrast passed through the upper oesophageal sphincter (adapted from [7]) using media player frame-by-frame analysis. Swallow speed ($mL \cdot s^{-1}$) was calculated as volume (100 mL) divided by total swallow duration and was evaluated for fast-paced drinking. Swallow frequency was calculated as number of swallows divided by total swallowing duration. Swallow patterns were defined as sequential (closure of laryngeal vestibule for duration of swallows), discrete (laryngeal vestibule opened in between swallows) or mixed [5]. Pharyngeal retention was defined as presence of residual liquid volume greater than coating of contrast material within the pharynx and oesophageal retention was defined as inefficiency in bolus flow through the oesophagus [10]. Statistical analysis was undertaken using IBM SPSS Statistics software version 24+ (IBM Corp., Armonk, NY, USA). Appropriate univariate and multivariate regression analyses were conducted to identify variables that may confound associations between swallow patterns and aspiration. Factors evaluated were age, sex, body mass index, forced expiratory volume in 1 s (FEV_1), FEV_1/forced vital capacity ratio, previous exacerbation history,

Shareable abstract (@ERSpublications)
Few studies have examined swallow of large liquid volumes representative of everyday drinking in COPD. Swallow by cup-drinking was evaluated in COPD using videofluoroscopy. Slower swallow was linked to aspiration indicating altered swallow habits in COPD. https://bit.ly/3wpdnO3

Cite this article as: Cvejic L, Guiney N, Lau KK, *et al*. Swallow patterns associated with aspiration in COPD: a prospective analysis. *ERJ Open Res* 2021; 7: 00170-2021 [DOI: 10.1183/23120541.00170-2021].

comorbidities and medications. Number of patients with sequential, mixed and discrete swallow were evaluated using Chi-squared and Fisher's exact test analyses. Significance was set at $p \leqslant 0.05$.

Overall, 151 patients (mean±SD age 70.6±5.0 years) with verified and stable COPD across all severities underwent videofluoroscopy. Patients had no history of neurological or neuromuscular disorder, head and neck surgery or cancer impacting swallow. Other patient demographic data have been reported [6]. Patients with aspiration were marginally older compared with patients without aspiration (72.4±4.3 *versus* 70.2±5.1, p=0.02) [6], but no other significant differences were noted between the groups.

All patients were able to consume the 100 mL volume using the two methods of drinking with aspiration (PAS scores 6–8) identified in 30 out of 151 patients (19.9%). Patients with aspiration took longer to swallow compared with patients without aspiration (self-paced drinking: time per swallow 2.92±1.68 s for aspiration *versus* 2.17±0.99 s without aspiration; p=0.002 and fast-paced drinking: 1.90±0.73 s for aspiration *versus* 1.51±0.41 s without aspiration; p<0.001; table 1). Total swallow duration was also longer for both swallow methods with self-paced drinking: 19.80±10.97 s *versus* 15.97±9.11 s (p=0.050) and fast-paced drinking: 11.07±7.81 *versus* 8.83±4.17 (p=0.033; table 1). Finally, patients with aspiration had a lower swallow frequency for both self-paced drinking (0.44±0.19 *versus* 0.53±0.17; p=0.011) and fast-paced drinking (0.59±0.18 *versus* 0.70±0.16; p=0.001; table 1).

Swallow speed <10 $mL \cdot s^{-1}$ has been proposed as a marker for reduced swallow capacity for 100 mL volumes using fast-paced drinking [7], but was not predictive of aspiration (<10 $mL \cdot s^{-1}$ in 11 out of 30 patients with aspiration compared to 26 out of 121 patients without aspiration; OR 2.12 (95% CI 0.9–5); p=0.09). Pattern of swallow (sequential or discrete) was different between self-paced and fast-paced drinking; however, there was no association with aspiration. For example, as expected single discrete swallows occurred less often during fast-paced drinking (15 out of 151 patients, 9.9%) compared to self-paced drinking (47 out of 151 patients, 31.1%; p<0.001), but there was no difference in other swallow metrics (not shown).

Rates of pharyngeal retention (13.2%), oesophageal retention (20.5%), and more frequent thoracic location observed in up to half of patients were similar to findings in studies of asymptomatic older adults [11]. Oesophageal clearance was not linked to the mode of drinking (p=0.79), there was no significant obstruction that impacted bolus flow and cricopharyngeal indentation was not associated with aspiration (p=0.078). Our findings are consistent with previous comparable studies in healthy older individuals [12].

Surprisingly, our findings indicate that aspiration is not linked to fast-paced swallowing suggesting that patients may have the ability to respond to aspiration by amending individual swallow modes. One key adaptation may be a slower swallow time, but disappointingly this factor alone cannot be used to identify individuals who aspirate. In a clinical context videofluoroscopy, with both self-paced and fast-paced swallow, is likely to provide the most sensitive detection of aspiration in COPD.

The current study has some caveats. The sample size is relatively small, which may cause bias in results and conclusions. We did not have an aged-matched healthy control group due to restrictions on radiation

TABLE 1 Swallow characteristics for fast-paced drinking in 151 patients with COPD based on presence/absence of aspiration

	Aspiration not detected	Aspiration[#] detected	Mean difference (95% CI)
Subjects n	121	30	
Timed swallow metrics			
Total swallow duration (s)	8.83±4.17	11.07±7.81	2.24 (0.19–4.29)
Number of swallows to complete task	5.92±2.28	5.60±2.06	0.32 (-0.58–1.22)
Time per swallow (s per swallow)	1.51±0.41	1.90±0.73 **	0.39 (0.19–0.59)
Swallow frequency (swallows per s)	0.70±0.16	0.59±0.18 **	0.11 (0.04–0.18)
Swallow pattern			
Sequential	74 (61)	16 (53)	
Mixed	36 (30)	10 (33)	
Discrete	11 (9)	4 (13)	

Data are presented as mean± SD or n (%), unless otherwise stated. [#]: aspiration score of 6–8 on the penetration–aspiration scale [9]. *: p≤0.05; ***: p≤0.001.

exposure and swallow of solids was not examined. Other measurements such as high-resolution manometry with impedance may have provided detailed information on oesophageal function.

In summary, swallow patterns are altered in patients with COPD who aspirate. Individual swallows take longer in patients who aspirate, both with self-paced and fast-paced drinking. Whether this pattern is the cause or result of aspiration is unclear, but it is feasible that it is a reflex physiological response to preceding aspiration and that respiratory–swallow-modulated task adaptation is used in an attempt to prevent aspiration. Current treatment practices that aim to prevent aspiration emphasise a similar strategy [3] and our findings provide support for strategies to prevent aspiration such as swallow at a slower pace and pauses between swallows to optimise respiratory–swallow coordination. This approach may also permit patients to use clearing swallows. Given the potentially calamitous impacts of aspiration, prospective studies are needed to examine how this occurs and to ascertain whether altering swallow patterns through retraining can prevent aspiration in COPD.

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Data availability: Data will be shared on request.

Conflict of interest: L. Cvejic has nothing to disclose. N. Guiney has nothing to disclose. K.K. Lau has nothing to disclose. P. Finlay has nothing to disclose. K. Hamza has nothing to disclose. P. Leong is supported by the National Health and Medical Research Council Postgraduate Scholarship and the Royal Australasian College of Physicians, outside of this work. Views expressed do not necessarily reflect those of the funding bodies. M. MacDonald has nothing to disclose. P.T. King has nothing to disclose. P.G. Bardin has nothing to disclose.

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Future clinical and research considerations

Swallow biomechanics related to aspiration during cup drinking or consecutive swallows may include a series of events such as disruption or variability in respiratory phase patterning, respiratory pause duration, laryngeal vestibular closure interval, and hyolaryngeal displacement. This study attempted to capture swallow characteristics during two cup-drinking tasks. However, in the clinical environment the fast-paced drinking task may be too challenging for certain individuals. Where possible, clinical and instrumental swallowing assessments should replicate the individual's habitual drinking and attempt to capture impairment during the drinking task that is characteristic for that person. Videofluoroscopy was also conducted during stable disease with results likely to reflect different swallow patterns and less severe swallow impairment compared to episodes of AECOPD.

The clinical decision on when and how often to perform instrumental examinations such as videofluoroscopy should be based on individual circumstances with priority warranted in patients with a high index of aspiration suspicion and high COPD flare rates. Accurate diagnosis of aspiration is essential however instrumental examination also details the physiological swallow function and the effects of targeted therapeutic intervention specific to the individual which may change with disease instability, progression and swallow adaptation. Factors such as variability in swallow performance depending on volume and consistency tested, number of oral trials performed, and drinking method used will also need to be considered.

While controlled single sip (bolus hold) was not assessed during videofluoroscopy in this study, it is an important task that could easily be administered as a preliminary step prior to executing consecutive swallows. The bolus hold approach could be useful as a clinical diagnostic and treatment consideration and has been shown to improve respiratory-swallow coordination in people with Parkinson's disease (Curtis et al 2021). Prospective studies are needed to examine the effects of bolus hold method, respiratory pause duration, airway protective manoeuvres, and compensatory or adaptive behaviours on swallow function in the COPD population. Future research considerations include exploring more detailed swallow physiology parameters, laryngeal vestibular closure adaptation, and the effects of respiratory-swallow retraining and biofeedback on swallow safety.

CHAPTER FIVE

CONCLUSION

Chapter five provides conclusions based on the outcomes of the research that has been conducted to date. It summarises the research findings and provides an interpretation, with integration with previous research findings, of our recently published prospective studies on breathing-swallow dysfunction and how aspiration may be linked to adverse respiratory outcomes in COPD. This section explores key areas: 1) The tipping point for aspiration; 2) The association of aspiration with COPD exacerbations; and 3) The approaches that may be required to identify and mitigate prandial aspiration risk. This *Commentary* has been published in *Respirology* and is included as a PDF file.

Received: 28 July 2021 | Accepted: 14 September 2021

DOI: 10.1111/resp.14157

COMMENTARY

Official Journal of the Asian Pacific Society of Respirology
Respirology APSR WILEY

Breathing–swallow dysfunction in COPD: How silent aspiration may be contributing to exacerbations

In health, coordination of breathing with swallow is critical to ensure effective ingestion of nutrients and to avert aspiration. In disease conditions such as chronic obstructive pulmonary disease (COPD), safe swallow is of particular importance as aspiration has been linked to serious adverse respiratory outcomes.[1] There is now considerable evidence of breathing–swallow dysfunction leading to aspiration with increased rates of acute exacerbations of COPD (AECOPD) in a substantial subgroup of patients with COPD. These findings warrant reflection and merit careful consideration by clinicians involved in the care of this patient group.

The potential risk of AECOPD caused by prandial aspiration has received scant attention. A recent large prospective study has established that patients with verified aspiration, detected during stable disease, have increased propensity to develop AECOPD.[2] The study employed two methods of ingestion (self-paced and fast-paced cup drinking) using a 100-ml volume of ultra-thin liquid and videofluoroscopy in 151 patients with verified and stable COPD of all severities.[2] Findings indicated that severe AECOPD episodes were more frequent over a 12-month period if aspiration was detected (50% vs. no aspiration 18%; OR = 4.5; $p = 0.001$). Severe AECOPD was also more common in patients with silent aspiration (in whom cough was entirely absent during the event) and patients with aspiration experienced a shorter time to a first AECOPD event (Figure 1). No factors predictive of aspiration and AECOPD could be identified in multivariate analyses and notably there were no links with COPD severity, lung hyperinflation, BMI, baseline oral health risk measurements, baseline presence of dysphonia, comorbidities, long-term oral corticosteroids, sedatives, Eating Assessment Tool-10[3] and Airway Questionnaire 20.[4] Aspiration as a causative factor in AECOPD episodes thus appears to be life-threatening in a subgroup of patients and should be considered as an important modifiable factor to be taken into consideration for inclusion in future exacerbation risk prediction models.[5]

A key question is whether the way patients with COPD swallow is altered leading to aspiration and worsening of pre-existing disease. Drinking at a faster rate can be challenging in COPD and may require respiratory–swallow reconfiguration to ensure airway protection. This possibility was also examined, and the investigators detected a longer total swallow duration, longer time per swallow and lower swallow frequency in patients with aspiration.[6] This was noted during both self-paced and fast-paced drinking. It is uncertain if this swallow pattern is the cause or effect of aspiration; however, it is likely related to physiological or compensatory modification induced by breathing–swallow dysfunction. Surprisingly, there was no difference in aspiration comparing self-paced and fast-paced drinking suggesting that patients may respond (perhaps not deliberately) to aspiration by adjusting swallow behaviour. These findings provide conditional support for aspiration risk minimization strategies such as pausing between swallows or use of single sips over consecutive swallows.[7] These strategies could improve integration of breathing with swallow efficiency, minimize interruption to laryngeal closure and expiratory phase of swallows,[8] whilst enabling opportunity for secondary swallows to clear any post-swallow residue.

What approaches are needed to identify and mitigate aspiration risk, particularly in COPD? A high index of suspicion is warranted in patients with this common condition, especially in people with frequent episodes of AECOPD. Accurate diagnosis of aspiration is essential and the importance of using methodologies that aid detection of aspiration, particularly silent and episodic aspiration events, cannot be overstated. Creative use of modern informative and diagnostically accurate radiographic or endoscopic instrumentation is vital and recent observations support the advantages of a diagnostic process employing sequential, ultra-thin, liquid drinking to detect impaired airway protection and aspiration.[6,7] Repetition of swallowing tasks and testing on more than one occasion can provide enhanced ability for the clinician to detect aspiration and to estimate ongoing risk. Patients with COPD tend to be older and use of standardized questionnaires and other instruments to detect and measure frailty and sarcopenia is essential to quantify related comorbidities. Finally, quantitative combined measurements of swallow and respiratory activity, particularly during and following repeated swallowing, may provide additional information and inform management.

Important questions remain. Repeated episodes of aspiration may have serious consequences,[9] but it is not clear if interventions need to be implemented in selected patients such as people with low AECOPD rates, those with frailty and those in whom other pertinent comorbidities are present. Alternatively, adopting a 'wait-and-see' approach can be considered to determine clinical significance of breathing–swallow dysfunction over time and the need for intervention based on an individual's evolving health and COPD profile. Current evidence supporting therapeutic intervention specific to the COPD population is limited and requires confirmation.

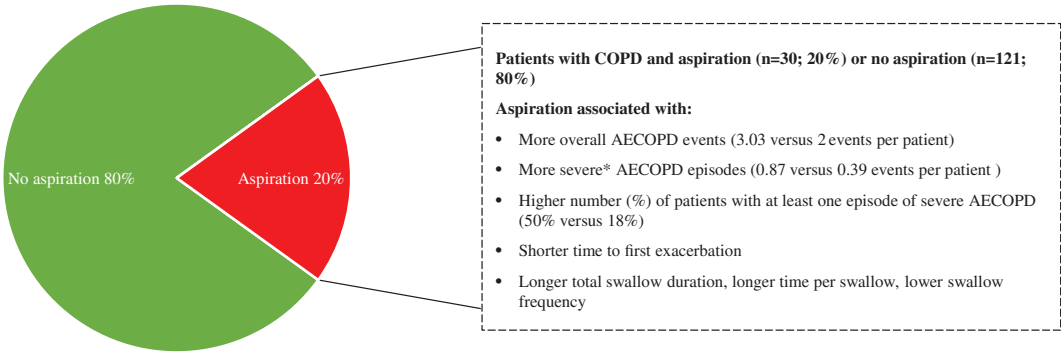

FIGURE 1 Aspiration detected during stable COPD is strongly associated with episodes of AECOPD. Patients with aspiration also had different swallow characteristics. *Severe episodes defined as patients requiring hospital admission. AECOPD, acute exacerbations of COPD; COPD, chronic obstructive pulmonary disease

What are the current options and priorities? In other conditions, respiratory–swallow retraining has shown promise by improving optimal expiratory–swallow–expiratory patterns and laryngeal vestibular closure with reduced penetration–aspiration scores.[8] Clinical studies by speech pathologists and other craft groups are now needed to examine the underlying mechanisms with a focus on determinants of laryngeal vestibular closure, silent aspiration and to assess if enhancement of cough sensitivity can benefit at-risk patients. Importantly, design and testing of an aspiration–risk algorithm and/or COPD aspiration–intervention–support tool are attractive options that could be combined with reviews of patient knowledge and insight about COPD and their risk profile for aspiration.

In conclusion, recent evidence strongly implicates aspiration as a cause of AECOPD in a subgroup of patients with COPD. Aspiration is also associated with AECOPD requiring hospital admission signifying the serious aftermath of aspiration in people with already compromised lung function. In COPD, several factors may predispose to aspiration, and these aspects will require further investigation to make it possible to suspect, detect and manage this hazardous clinical scenario. More research is needed to verify causation, attempt earlier diagnosis and design appropriate clinical trials to test effective management. Finally, research is needed to assess the benefits of breathing–swallow training approaches[8] used in other conditions and to examine whether these strategies are applicable to COPD.

KEYWORDS
aspiration, COPD, COPD exacerbation

CONFLICT OF INTEREST
None declared.

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How to cite this article: Cvejic L, Bardin PG. Breathing–swallow dysfunction in COPD: How silent aspiration may be contributing to exacerbations. Respirology. 2021;1–2. https://doi.org/10.1111/resp.14157

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