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Chronic Cough and OSA: A New Association?

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Chronic cough is defined as cough lasting more than 2 months. Common causes for chronic cough in nonsmokers with normal chest radiographs and pulmonary functions include gastroesophageal reflux disease (GERD), cough-variant asthma (CVA), and upper airway cough syndrome (UACS). Current guidelines recommend diagnosing the etiology of chronic cough based upon the results of therapy for suspected GERD, CVA, and UACS. Despite following current recommendations for diagnosis and treatment, the cause for a significant proportion of chronic cough remains unexplained.

Recent reports indicate the resolution of chronic cough following treatment of concomitantly diagnosed obstructive sleep apnea (OSA). Whether this represents a co-occurrence of two commonly prevalent disorders or a pathophysiologic relationship between OSA and cough remains unknown. This review offers insights into a pathophysiologic link between OSA and the commonly purported etiologies for cough, namely, GERD, UACS, and CVA. In addition, evidence for a relationship between airway inflammation that can trigger or perpetuate cough and OSA is discussed. This review explores mechanisms by which nocturnal continuous positive airway therapy resolves cough by improving underlying airway inflammation secondary to OSA and impacts upon GERD, CVA, and UACS.

Keywords: Chronic cough, obstructive sleep apnea, airway inflammation, gastroesophageal reflux disease, upper airway cough syndrome

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Chronic cough affects 9% to 33% of the adult population.[1,2] A significant proportion of chronic cough occurs in nonsmoking populations with normal chest radiographs and pulmonary function tests, in whom upper airway cough syndrome (UACS), gastroesophageal reflux disease (GERD) and cough-variant asthma (CVA) are empirically treated.[2,3] Despite addressing the etiologies of UACS, GERD, and CVA, a significant proportion of chronic cough patients fail to resolve their cough.[4] The percentage of unexplained cough has varied from 12% to 42%, depending on the clinical series.[5] Recent studies indicate that the treatment of concomitant obstructive sleep apnea may help with cough resolution.[6,7] The current review explores the pathophysiologic bases of the association between cough and sleep apnea, while outlining future areas for inquiry. Two cases are described first to give insight into the spectrum of chronic cough patients who can improve following therapy for OSA.

Case 1

A 61-year-old nonsmoking female was referred with an 18-year history of chronic cough. She presented with a dry cough that was worse at night and during the winter months. She gave a history of occasional GERD, significant sinus congestion, and post-nasal drip with seasonal worsening. In addition, she carried a diagnosis of childhood asthma but had no exercise-induced wheezing, nocturnal awakenings, or specific allergen-related exacerbations. She reported frequent episodes of bronchitis following upper respiratory infections that resulted in use of multiple courses of antibiotics and steroids to relieve dyspnea and nasal and chest congestion. A constant feature of these bronchitic episodes was nocturnal cough that would keep her from sleeping. She was treated by her primary care physician with a second-generation antihistamine, nasal steroid, bronchodilators and inhaled steroids (fluticasone-salmeterol combination), montelukast, and a proton-pump inhibitor. She had multiple normal chest x-rays and pulmonary function tests.

Investigative workup included a negative methacholine challenge test, ENT evaluation including sinus radiography, and UGI endoscopy. Her Rocky Mountain RAST (radioallergosorbent test) panel showed elevated IgE antibodies to Mountain cedar; skin scratch allergy tests showed wheal and erythema reactions to Kentucky bluegrass, Bermuda grass, Mountain cedar, cat hair, and Western Juniper. Sputum eosinophilia is not routinely performed at our institution and therefore was not done. Exhaled nitric oxide measurements were 13 parts per billion (normal < 25ppb).

The patient followed up several times over the next 5 years. Her therapies consistently included an oral antihistamine tablet, a leukotriene-receptor antagonist, and a proton-pump inhibitor, with off and on use of inhaled steroids/bronchodilators. With exacerbations, inhaled steroids, bronchodilators, and antibiotics were added. Each time the cough would improve temporarily. Over time, she started complaining of increasing fatigue and sleep disruptions from her cough. Additionally, she complained of daytime somnolence. An overnight oximetry was abnormal. Five years after her initial presentation, she was diagnosed with severe OSA (apnea-hypopnea index [AHI] 47), and she initiated therapy with nocturnal continuous positive airway (CPAP) therapy at 8 cm water pressure. The patient has followed up for more than a year after initiation of CPAP therapy and notes dra-

matic improvement in her cough. In addition to improvements in sleep quality and reductions in awakenings from nocturnal cough, she has not experienced the frequent episodes of bronchitis as she did prior to CPAP therapy. In addition to using nocturnal CPAP and maintenance proton-pump inhibitors, she uses an antihistamine and a leukotriene receptor antagonist to control her nasal secretions.

Case 2

A 60-year-old nonsmoking female presented with a 6-month history of chronic cough following an episode of pneumonia. Three months after her pneumonia, she was diagnosed with severe sleep apnea (AHI 50), but was not using her CPAP. She has a past medical history significant for depression, hypertension, impaired glucose tolerance, GERD, osteoarthritis, and hypothyroidism. She was taking levothyroxine, hydrochlorothiazide-triamterene, fluoxetine, naproxen, trazodone, zolpidem, and omeprazole. Pulmonary function tests and chest x-ray were normal. After starting nocturnal CPAP she had complete resolution of her chronic cough.

DISCUSSION

In the first case, the patient underwent treatment for the most common causes of chronic cough for nearly 20 years. She experienced exacerbations of her cough that improved with antibiotics and oral steroids. However, the cough never resolved completely. Eventually, her daytime somnolence lead to her diagnosis of OSA (her only risk factor for OSA was being postmenopausal). Her cough dramatically improved after the initiation of CPAP. The second patient had a much shorter duration of cough (6 months). She was at higher risk for OSA due to her comorbidities (diabetes, hypertension, thyroid disease, obesity, and depression). She was noncompliant with CPAP therapy and presented with chronic cough. Following re-initiation of nocturnal CPAP, her cough resolved completely.

These two cases depict a clinical scenario increasingly encountered in pulmonary practices, where chronic cough is one of commonest reasons for referral to a subspecialist.[8] The chronic cough guidelines proposed by the American College of Chest Physicians recommend the diagnosis of cough based on the response to directed therapy of the suspected etiology of cough (**Figure 1**).[3] Earlier studies on chronic cough showed that in nonsmokers without underlying parenchymal lung disease, the triad of GERD, UACS (formerly postnasal drip syndrome), and CVA accounted for nearly 90% of causes of chronic cough.[1,9] GERD, UACS, and CVA are highly prevalent clinical conditions in the general population. However, there are few noninvasive tests to reliably diagnose GERD and UACS. Therefore, in the majority of patients suspected to have one or more of these conditions, treatments are based on a clinical history and physical exam. Radiologic and pulmonary function studies help with the diagnosis of chronic rhinosinusitis and asthma, but lack of abnormalities in these studies does not preclude a trial of symptom-based treatment in the majority of patients. An algorithm-driven approach has been shown to improve symptoms in up to 93% of patients presenting with chronic cough.[10-12] Most of the algorithmic approaches are heavily weighted towards the demonstration of recalcitrant GERD or UACS as a potential cause for the cough when resolution of cough has not been achieved with empiric management of one or more of the triad of chronic cough causes.[13] Systematic placebo-controlled studies showing benefit of antireflux therapies[14] and therapies directed at UACS[15] in resolution of cough are lacking. Patients failing to improve their cough with specific therapies for GERD, UACS, and CVA form an increasing proportion of patients at cough referral clinics clumped under the entity of "idiopathic" or unexplained cough (**Table 1**).

OSA as a Cause of Chronic Cough

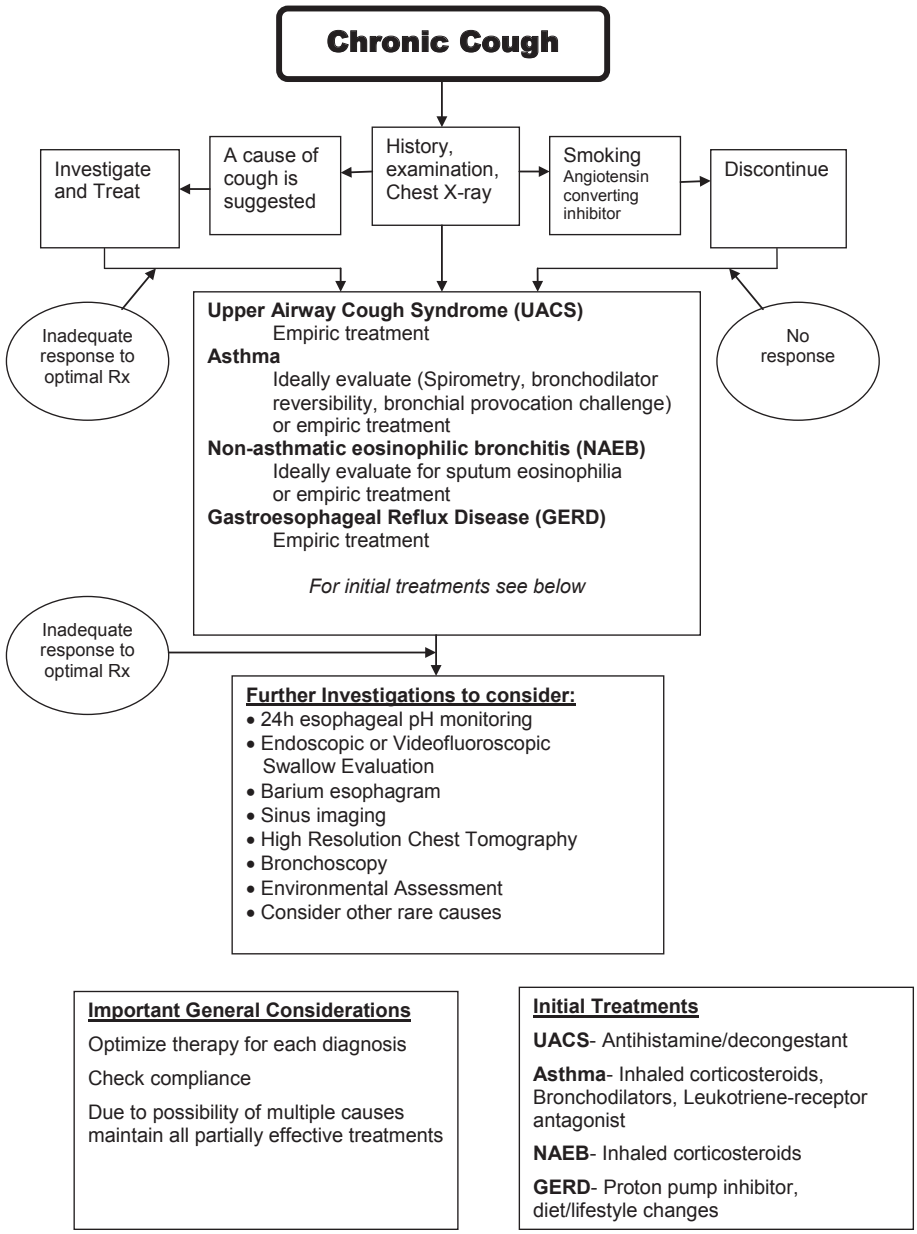
OSA is postulated to perpetuate chronic cough based upon reports of improvement of cough following application of nocturnal CPAP for concomitant sleep apnea.[6,7] Usually therapies for OSA are rendered in conjunction with other therapies for UACS, GERD or CVA; therefore the impact of treatment of OSA in relation to cough resolution has not been determined in isolation.[7] A retrospective study on 75 patients with chronic cough in community-based pulmonary practice found that 44% of patients had OSA.[7] Improvement of cough was seen in 93% of patients optimized on CPAP therapy with treatment of OSA.[7] Current guidelines are yet to incorporate evaluation of OSA as a part of evaluation for chronic cough.[16] In order to better understand the association between OSA and chronic cough, a number of aspects have to be considered.

1. Chronic cough and OSA are common disorders

The prevalence of OSA increases with age and body mass index. OSA prevalence based on values of AHI ≥ 5 increases with age, from 8% in 20- to 44-year-olds to 20% in 45- to 64-year-olds, and to 30% in 65- to 100-year-old men.[17] Even though the prevalence of cough is quite high in the general population, unexplained cough is higher in middle-aged females, with the mean age of chronic cough in studies being 46-60 years.[5] This overlaps with the age group in which the prevalence of OSA as assessed by clinical and laboratory criteria (AHI ≥ 10) starts peaking.[17] Even though the prevalence of sleep apnea is lower in adult females, there is a significant increase in OSA prevalence in postmenopausal females, with a higher prevalence of REM-related sleep disordered breathing in women under the age of 55 years.[18,19] In addition, sleep apnea tends to be underdiagnosed in women because of atypical manifestations of sleep disordered breathing.[20]

The relationship between OSA and BMI is relatively a linear one, especially until the age of 60.[20] Even a 10% increase in weight in subjects with mild or no OSA increases the risk of developing significant OSA (AHI ≥ 15) by 6-fold.[21] In contrast, despite the high prevalence of cough reported in general population that has been attributed to airway diseases, GERD, smoking, and air pollution,[1,22] only 2 studies have reported BMI values in their subjects.[7,23] One retrospective study showing linkage between chronic cough and OSA had a mean BMI of 32 in its 75 chronic cough subjects, with a female-to-male ratio of 1.5.[7] The study by Smith et al. looking at cough-reflux associations found a mean BMI of 27.3 in 71 subjects, with a female-to-male ratio of 77%.[23] Future studies on chronic cough should report the BMI values of their subjects, especially given the associations of obesity with asthma and GERD, 2 conditions that are implicated often in the etiology of chronic cough.[22]

Figure 1—ACCP outline for approach to chronic cough in adults (Reprinted with permission)[84]



2. Pathophysiologic bases of chronic cough is unclear

The simplistic view that prolonged treatment of the etiologies of UACS and GERD in patients without CVA or EB can potentially improve chronic cough is based upon non-randomized, non-placebo controlled clinical studies. The pathological substrate for chronic cough in these subjects remains elusive. It is not possible to localize the source of cough to upper vs. lower airways with current modalities. One small study examining the histopathology of the airways in patients with chronic cough showed submucosal infiltration with mast cells and other changes of airway remodeling.[24] Airway inflammation in chronic cough subjects has also been surmised from abnormalities on exhaled breath condensate[25] and increased airway wall thickness on chest CT scans.[26] Despite the demonstration of airway inflammation by various modalities, there has been considerable debate about the contribution to airway inflammation from the traumatic act of coughing.[27]

A number of studies have shown that chronic cough often starts with a cold-like or a flu-like illness, with a tendency of the cough to persist after an acute productive phase (**Figure 2**).[28] In this model of chronic cough, a number of factors, especially airway hyperreactivity, GERD, and continuing postnasal drip can continue to perpetuate the cough.[28] Even though a mechanism of protracted airway inflammation perpetuated by multiple etiologies may explain the persistence of the cough, no other abnormalities apart from the finding of eosinophilic airway in-

Table 1—Studies on idiopathic cough

Study	Number of patients (% female)	Mean age (years)	Duration of cough	Description of study
O'Connell, 1993[85]	16 (81%)	51 (range 31-70)	72 mths (12-240)	Showed enhanced cough sensitivity in patients with unexplained cough.
McGarvey, 1998[11]	8 (75%)	47.4 (range 31-60)	19 mths (6-36)	Evaluated the efficacy of a comprehensive diagnostic protocol to diagnosis and management of cough in 43 patients.
Jatakanon, 1999[86]	10 (50%)	60 ± 4 SE	5yrs ± 1.5 SE	Assessed sputum neutrophilia, IL-8 and TNF-α levels in patients with GERD-cough, UACS-cough and idiopathic cough.
McGarvey, 1999[87] & Forsythe, 2000[88]	6 (83%)	46.5 ± 5.0	73.3 mths ± 3.3	Both studies looked at bronchoalveolar lavage fluid from patients with different etiologies of cough, with the 2000 study showing mast cell histamine release to neuropeptides.
Lee, 2001[89]	25 (60%)	39.8 ± 12.0	2-6 months	Assessed airway inflammation using bronchial biopsies and showed eosinophilic bronchitis in 21/25 and lymphocytic bronchitis in the rest.
Birring, 2003[90]	19 (79%)	54 ± 2 SE	7 yrs ± 3 SE	Showed BAL lymphocytosis and increased frequency of autoimmune antibodies in patients with idiopathic cough as compared to 11 patients with explained cough.
Birring, 2004[91]	22 (77%)	58.8 ± 3.3 SD	12 mths (range 7-360)	Showed increased occurrence of organ-specific autoimmune disease and autoantibodies in patients with idiopathic cough as compared to 65 community controls.
Chaudhuri, 2004[92]	10 (60%)	57.7 ± 8.7 SD	13.9 yrs ± 18.6	Assessed effect of inhaled fluticasone in a double-blinded placebo-controlled crossover study on cough severity and sputum inflammatory mediators.
Haque, 2005[93]	31 (76%)	57 yrs (range 32-81)	72 mths (8-324)	Described characteristics of a large cohort of patients with chronic idiopathic cough, with nearly 48% reporting an upper respiratory tract infection initiating cough.
Irwin, 2006[27]	11 (27.3%)	51.6 (range 40-69)	9.2 yrs (range 0.67-20)	Compared endobronchial biopsies between unexplained cough patients and 13 patients with specific cause of cough.
DeCalmer, 2007[94]	82 (67%)	54.9 ± 11.2 SD	5 yrs (0.5-30)	Looked at yield of diagnostic bronchoscopy in patients with sole presentation of persistent unexplained cough
Ryan, 2010[95]	17 (53%)	61 (Range 34-83)	60 mths (147 interquartile range)	Showed benefit of speech pathology evaluation and treatment in patients with chronic refractory cough.
Murry, 2010[96]	16 (% females not given)	29-69	> 3 mths	Demonstrated improvement in laryngeal sensory response and paradoxical vocal cord movement after respiratory retraining.
Bucca, 2011[97]	61 (74%)	40.9 (37.4-44.4)	Not given	Demonstrated finding of reflex laryngoconstriction in a higher percentage of cough patients (66% in unexplained cough)

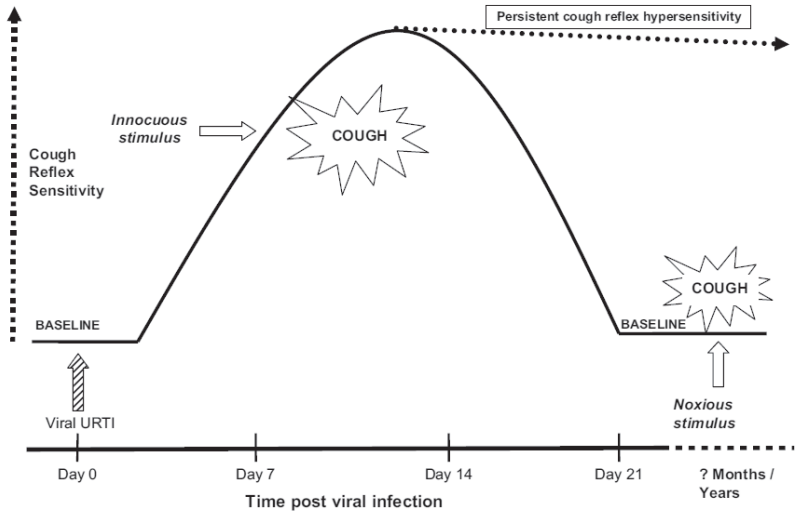
IL-8, Interleukin-8; TNF-α, Tumor necrosis factor- α; BAL, Bronchoalveolar lavage.

flammation[29] have been shown to cause cough. This opens the scope for a wide variety of etiologies that can result in airway inflammation, ranging from air pollution to OSA to perpetuate cough in susceptible subjects.[22]

3. OSA can be associated with all major etiologies of chronic cough, upper respiratory infections that initiate chronic cough, and abnormal upper airway pathology

There are several likely mechanisms by which obstructive

Figure 2—Worsened cough reflex sensitivity following a viral infection that returns normal in the majority; in subset of patients however the cough hypersensitivity persists (Reprinted with permission)[28]



sleep apnea can lead to cough. OSA worsens the postulated triggers of GERD, UACS, and asthma. In addition, OSA is associated with a higher frequency of upper respiratory tract infections that may initiate cough.

OSA and GERD: OSA and GERD are inextricably related with the plausible increase in reflux during the increasing negative intrathoracic pressures encountered during an apneic episode.[30] Studies have shown increased reflux events in patients with OSA, characterized by increased nocturnal time spent with an esophageal pH < 4.0 and delayed esophageal clearing.[31] However, a temporal relationship between reflux and apneic events has not been clearly established,[31,32] and obstructive apneic events have not been shown to decrease lower esophageal or upper esophageal tone.[32,33] A relationship between OSA and non-acid esophageal reflux has not been shown. In addition, the effect of lax lower esophageal sphincter tone,[32] hiatal hernias,[34] and reflux esophagitis[35] in furthering acid reflux in patients with OSA is also unclear. Despite the lack of clear cut mechanistic associations, CPAP therapy improves GERD with CPAP therapy by abolishing apneic spells and reflexly increasing lower esophageal sphincter tone.[31,36,37] With regard to chronic cough, a link between chronic cough and OSA occurring through GERD was postulated a decade ago.[38] Even though an improvement in GERD (and possibly non-acid esophageal reflux) can be anticipated in chronic cough patients with concomitant OSA, further studies examining acoustic cough monitoring and combined pH-impedance measurements during apneic episodes are needed.

OSA and UACS: OSA can be associated with increases in nasal inflammation that is improved with humidification of nasal CPAP.[39-41] Nasal inflammation in OSA patients occurs directly from the OSA itself[39] and from the effects of CPAP therapy.[41] Whether there is any relation between nasal inflammation occurring in OSA patients and propensity to cough is unknown. Apart from these studies, the bulk of the literature pertaining to nasal and sinus disease in OSA relates to the effects of increased nasal resistance causing sleep disturbances, particularly in children.

OSA and Asthma: Current asthma guidelines recommend testing for OSA in overweight or obese patients with poorly controlled asthma.[42] Recent studies indicate that the association of OSA with uncontrolled asthma may be independent of obesity.[43] A number of different pathways can bring about heightened airway inflammation and hyperresponsiveness in patients with OSA.[44] These include local and systemic mechanisms that can cause heightened airway inflammation and potentiate asthmatic responses in patient with OSA.[44]

OSA and Triggering Respiratory Infections: OSA patients experience frequent respiratory infections, especially common colds.[45] These upper respiratory infections initiate cough in a third of patients with chronic cough.[7,28]

OSA and Upper Airway Pathology: Abnormalities in the soft palate, uvula, and upper airway musculature are invariable in patients with OSA secondary to trauma stemming from recurring obstructive events.[46-48] The implications of upper airway abnormalities in triggering cough receptors are unknown.

4. OSA can be associated with airway inflammation

OSA and obesity have been shown to increase airway inflammation.[49] While it is not clear whether the airway inflammation seen in OSA patients can initiate or perpetuate chronic cough in susceptible patients, the association of airway inflammation with OSA points to the possibility of airway inflammation being the substrate for chronic cough. It is therefore imperative to understand the mechanisms of airway inflammation in OSA patients that may be responsible for cough. **Table 2** enumerates the studies and methodologies used to demonstrate airway inflammation in patients with OSA.[40,50-55] Since obesity per se can lead to airway inflammation,[56] there exists controversy about the contributions of OSA vs. obesity in the causation of increased airway inflammation in obese sleep apnea patients.[50,51,53] Similarly, bronchial hyperreactivity has been reported in OSA,[57] with the additional development or worsening of bronchial hyperresponsiveness with CPAP.[57,58] Bronchial wall thickness is increased in

Table 2—Studies on obstructive sleep apnea and airway inflammation

Study	No. of subjects	Source of specimen or methodology used	Findings
Olopade, 1997[40]	20 OSA pts and 8 controls	Exhaled nasal and oral pentane & NO	Increased pentane and NO values post-sleep in OSA pts as compared to controls.
Carpagnano, 2002[98]	18 OSA pts, 10 obese pts, 15 controls	EBC	↑ IL-6, 8-isoprostane levels in OSA pts with correlation of these two markers with AHI and neck circumference.
Carpagnano, 2003[55]	18 OSA pts, 12 obese matched controls	EBC and plasma	↑ 8-isoprostane levels in EBC and plasma of OSA pts as compared to obese controls with reduction after CPAP therapy. Correlation of 8-isoprostane levels with AHI and neck circumference.
Devouassax, 2007[58]	57 OSA pts, 13 controls	eNO, sputum and BH	↑ PMNs, IL-8 in OSA pts. IL-8 correlated with AHI. No change in inflammatory cell pattern with CPAP and occurrence of significant BH after CPAP.
Carpagnano, 2008[53]	30 Obese OSA pts, 20 non-obese OSA pts, 10 Obese non-OSA controls	EBC, eNO and sputum	↑ eNO and neutrophils in sputum, ↓pH in EBC of OSA pts and obese pts.
Alonso-Fernandez, 2009[99]	31 males with OSA and 15 controls	Plasma	↑ 8-isoprostane levels and lower total nitrate/nitrite levels in OSA pts that normalized with CPAP.
Kimoff, 2010[100]	25 OSA pts and 10 controls	UPPP specimens	↑ IL-1α, IL-6, interferon γ, RANTES, TGFβ, L-selectin, protein carbonyls in OSA pts as compared to controls.
Sariman, 2010[80]	16 OSA pts and 10 controls	Plasma biomarkers, BH and airway thickness by CT scans	↑ fibrinogen, pro-BNP, D-dimer, hsCRP, α1AT, hsCRP, bronchial wall thickness in OSA as compared to controls. Correlation of bronchial wall thickness with AHI.
Carpagnano, 2010[73]	12 Obese OSA pts, 10 non-obese OSA pts, 10 obese non-OSA pts, 10 healthy controls	Plasma, sputum and EBC	↑ IL-8, ICAM-1, neutrophils in plasma and EBC of obese and OSA patients as compared to controls. No difference between obese non-OSA and non-obese OSA pts.
Depalo, 2010[74]	18 obese OSA pts, 15 obese non-OSA, 10 healthy controls	eNO and sputum	↑ eNO, sputum PMNs, ↑ iNOS expression in PMNs and macrophages in OSA pts and obese pts. Correlation between eNO, iNOS expression and AHI.

NO, nitric oxide; eNO, exhaled nitric oxide; EBC, exhaled breath condensate; BH, bronchial hyperreactivity; UPPP, uvulopalatopharyngoplasty; CT, computerized tomography; IL-6, Interleukin-6; AHI, apnea-hypopnea index; IL-1α, Interleukin-1α, IL-6, Interleukin-6; TGFβ, Transforming growth factor-β; hsCRP, highly sensitive C-reactive protein; α1AT, α1 anti-trypsin; IL-8, Interleukin-8; ICAM-1, Intercellular adhesion molecule-1; iNOS, inducible NO synthase.

patients with OSA and shows a positive correlation with AHI, the most widely used measure of OSA severity.[57]

A number of mechanisms have been postulated to increase airway inflammation in sleep apnea patients:

a. **Recurrent trauma secondary to obstructive apnea.**[49,50,54] Even though this kind of mechanical trauma is well understood in the case of upper airways,[54] models explaining the mechanisms of lower respiratory tract inflammation from recurrent upper airway obstruction are lacking.

b. **Ischemia-reperfusion injury to lower airways occurring from obstructive episodes.**[49-55] This remains the most widely ascribed mechanism for airway inflammation secondary to OSA. The correlation of degree of hypoxemia (most profound in REM sleep of OSA patients) and degree of lipid peroxidation measured in exhaled breath condensates lends weight to this hypothesis.[55]

c. **Coaggregation of obesity in OSA patients.**[49,51,53,57] Obesity can be independently associated with airway inflammation and ongoing research to explain the occurrence of a higher prevalence of asthma in obese patients has focused on leptin-mediated systemic inflammation.[59] Adipose tissue acts as an endocrine organ serving as a reservoir for cytokines (adipokines) that can lead to low-grade systemic inflammation that may account for the increased inflammation observed in the respiratory tract.[59]

d. **Spillover from systemic inflammation secondary to OSA.**[60] Apart from local inflammation brought about the above-mentioned mechanisms, systemic inflammation occurring in OSA patients is manifested in the form of increased levels of C-reactive protein, TNF-α, IL-6, elevated oxidant tone,[61,62] and increased sympathetic tone.[63]

5. Positive pressure therapy may improve cough via multiple mechanisms

A case series and a large retrospective study till date have shown a benefit with CPAP on chronic cough.[6,7] Improvements in these reports occurred in patients that had been tried on multiple other therapies for cough.[6,7] Interestingly, the clinical profile of patients improving with CPAP and those who did not require CPAP therapy does not appear different.[64] CPAP has also been shown to

be helpful in treating chronic nocturnal cough that is present in the supine position.[65] This study had a small sample size and did not clearly address if these patients underwent a polysomnogram.[65]

A number of potential mechanisms can explain the improvement of cough with CPAP therapy

1. **CPAP and the cough reflex:** Widdicombe's groundbreaking studies on elucidation of afferent vagal activity following lung inflation and deflation identified a variety of stretch receptors.[66] Among these, the tracheal/bronchial rapidly acting receptors and intermediate receptors mediate the cough triggered by mechanical and chemical stimuli.[66] In addition to these stretch receptors, the activation of unmyelinated C-fibers that account for the majority of afferent nerves innervating the lungs leads to cough.[67] While a number of these "cough" receptors are likely to be affected by the increase in pulmonary functional residual capacity induced by positive pressure therapy, it is not clear how stabilization of the mechanical stresses induced during sleep disordered breathing affects peripheral cough sensitivity.
2. **Impact of CPAP on the purported etiologies of cough**
   a. GERD: Despite the lack of clear relation between GERD and OSA as discussed above, CPAP therapy has been shown to improve reflux as measured symptomatically[36,68] and as measured using esophageal pH-impedance measurements.[30,31,35-37,69] These benefits may be more pronounced in patients with a patulous lower esophageal sphincter, hiatal hernia, and abnormal esophageal motility.[34] The main mechanism of increased reflux in OSA patients is via an increase in transient lower esophageal relaxations rather than the increased gradient between the negative esophageal pressure and the positive gastric pressure.[32,35] Postulated mechanisms for improvements in CPAP-related reductions in GERD include increases in tone of the lower esophageal sphincter, thereby reducing the gradient for reflux.[32,35,69] In addition, patients on CPAP have less frequent and lesser durations of transient lower esophageal sphincter relaxations.[32,35-37] The effect on GERD by CPAP has been postulated to be the main mechanism by which CPAP can improve chronic cough.[38]
   b. Asthma: No studies exist on the effect of CPAP on cough-variant asthma. While large scale prospective studies on asthma improvement following OSA treatment are lacking, current studies indicate an improvement in asthma control following CPAP therapy.[70,71] There is, however, a concern about CPAP use causing bronchial hyperactivity.[58,72]
   c. UACS: CPAP use has been shown to cause increased nasal inflammation that can improve with heated humidification.[41]
3. **Effect of CPAP on airway inflammation:** Measurements of exhaled breath condensates in OSA patients show improvement following CPAP therapy.[55,73,74] In addition, multiple studies show improvement in systemic inflammation following CPAP therapy in OSA patients.[75-77] How this improvement in systemic and airway inflammation can improve chronic cough remains to be proven.

In addition to the above, while the mechanisms perpetuating chronic cough remain elusive, factors that lead to resolution of cough remain largely unexplored. It is expected that patients resolve cough following acute respiratory infections with the inflamed airway "healing" with time following resolution or removal of the acute insult. However patients with OSA may not be able to "heal" this acute insult due to sleep deprivation related immune dysfunction[78] and/or perpetuation of ongoing mechanical and inflammatory insults to the respiratory tract during apneic-hypopneic episodes. The impact of restorative sleep in improving disease-related injury and inflammation may be most significant in the respiratory tract, where the effects of recurrent mechanical trauma coupled with inflammatory effects of arousals has the potential to cause continuation of airway inflammation.

While most series have concentrated upon the approach and management to a single protracted episode of cough, 18% of patients' cough reoccurs within 3 months of follow-up.[79] While this recurrence of cough has been attributed to ongoing reflux, UACS, or CVA,[79] untreated OSA as a cause of cough recurrence has not been investigated.

FUTURE DIRECTIONS

The association between chronic cough and sleep apnea is based upon a few reports.[6,7,80,81] Cough is a frequent complaint in patients with OSA,[82] and OSA prevalence appears to be high in patients with chronic cough.[7] Despite this limited evidence, the need for OSA evaluation and therapy has been incorporated in one set of chronic cough guidelines[16] and for management of cough in pediatric patients.[81] The finding of improvement in cough with CPAP therapy raises a number of questions about potential pathologic substrates for chronic cough and the impact of untreated OSA in the causation or perpetuation of cough. Following areas of research may lead further insight into mechanistic relationship between OSA and cough

1. Mechanisms of lower airway inflammation in OSA patients.
2. Temporal relationships between acid and nonacid reflux, apnea and cough.
3. Effect of CPAP on cough reflex.
4. Prospective evaluation of chronic cough patients for OSA and impact of CPAP therapy in improving capsaicin sensitivity and chronic cough.

CONCLUSIONS

The field of chronic cough is entering into an exciting phase with identification of airway receptors that mediate cough reflex in a wide variety of conditions[82] and the ability to monitor cough and link it to potential etiologies.[83] OSA can impact multiple aspects of upper and lower airway structure and function that can potentially lead to lowered cough sensitivity and/or perpetuation of cough. Understanding mechanisms by which OSA can lead to inflammation at various parts of the airway and how positive airway pressure influences the cough reflex and OSA-related inflammation is crucial to elucidate the relationship between OSA and chronic cough.

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