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REVIEW

Cough syncope

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Summary
Loss of consciousness following cough was first described in 1876 as "laryngeal vertigo" Since then, several hundred cases of what is now most commonly termed cough syncope have been reported, often in association with various medical conditions. Some early authors assumed this entity to be a form of epilepsy, but by the mid-20th century, general consensus reflected that post-tussive syncope was a consequence of markedly elevated intrathoracic pressures induced by coughing. A typical profile of the cough syncope patient emerging from the literature is that of a middle-aged, large-framed or overweight male with obstructive airways disease. Presumably, such an individual would be more likely to generate the extremely high intrathoracic pressures associated with cough-induced fainting. The precise mechanism of cough syncope remains a matter of debate. Theories proposed include various consequences of the marked elevation of intrathoracic pressures induced by coughing: diminished cardiac output causing decreased systemic blood pressure and, consequently, cerebral hypoperfusion; increased cerebrospinal fluid (CSF) pressure causing increased extravascular pressure around cranial vessels, resulting in diminished brain perfusion; or, a cerebral concussion-like effect from a rapid rise in CSF pressure. More recent mechanistic studies suggest a neurally mediated reflex vasodepressor-bradycardia response to cough. Since loss of consciousness is a direct and immediate result of cough, elimination of cough will eliminate the resultant syncopal episodes. Thus, the approach to the patient with cough syncope requires thorough evaluation and treatment of potential underlying causes of cough, as summarized in several recently published cough management guidelines.

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Contents

Introduction

Loss of consciousness following a cough or episode of coughing was first described in 1876 by Charcot [1], who named the condition "laryngeal vertigo" Just twenty years later, a review paper summarized 77 similar cases reported in the literature [2]. The term "laryngeal epilepsy" was also used, reflecting initial opinion that this condition was primarily epileptic in nature [3—5]. However, even some of the earliest authors raised doubt that a neurogenic etiology satisfactorily explained all such cases, and speculated that other mechanisms may be relevant [2,4,6]. In 1949, the term "tussive syncope" was recommended as a more appropriate descriptor [5]. In 1953, Kerr and Derbes [7] described a series of 40 patients with the syndrome of "cough syncope," which has remained the preferred term in the literature since.

By the mid-19th century, a very consistent profile of the typical cough syncope patient had emerged, that being of a middle-aged, overweight male smoker with obstructive lung disease. Discussion and debate regarding the mechanisms of cough syncope has continued to the present, with a number of elegant studies contributing to the understanding of the cardiopulmonary and cerebrovascular effects of cough, and their potential role in cough syncope. The purpose of this review is to summarize the literature on cough syncope to date, with particular attention paid to demographics, associated conditions and proposed mechanisms.

Methods

In July, 2013, we performed a National Library of Medicine (PubMed) search using the terms "cough" and "syncope" restricted to human studies written in English. The 131 publications resulting from that search were reviewed and non-relevant papers were excluded. Non-relevant papers were those that were captured in the search because of the presence of the individual terms "cough" and "syncope," but were not on the subject of cough syncope. Reference lists of articles were reviewed for additional relevant publications not captured by the initial database search. A subsequent search using the terms "tussive" and "syncope" yielded an additional four articles not initially identified, thus resulting in a total of 90 publications comprising the basis for this review [1—90].

Discussion

Demographics

Of the 90 articles comprising our database, 74 reported a total of 430 adult cases of cough syncope. Six of the papers did not provide the gender of the patients described, thus leaving 68 articles reporting 392 patients, of whom 362 (92.3%) were men, and 30 (7.7%) women. Since the majority of these patients were reported between 1876 and 1968, we examined more recently published data. In the past 25 years (1988—2013), 40 articles reported and provided gender data for a total of 83 patients with cough syncope, 76 (91.6%) male and 7 (8.4%) female, an almost identical gender distribution. Although the degree of specific patient information provided in these more recent articles varied greatly, a predominant characteristic was a history or physical examination consistent with obstructive airway disease, consistent with earlier reports.

Six studies reported a total of 33 pediatric cases of cough syncope [16,19,22,38,49,52]. Five of those papers provided gender data for 30 children, 16 (53.3%) male and 14 (46.7%) female. Thus, although the number of children reported is much less than that of adults, the significant gender difference is not observed in this age group. Of the 31 children for whom a diagnosis was provided, 28 (90.3%) were asthmatic, consistent with the common association of obstructive lung disease described in the adult population.

Five articles reported series of adults presenting with syncope and provided the percentage of those in whom cough was determined to be the etiology [12,34,42,46,74]. In total, 3244 patients evaluated for syncope were described, among whom were 84 cases of cough syncope (2.6%; range 0.9—4.2%). One prospective series of syncope in children reported 3 of 58 (5.2%) cases due to cough syncope [52].

Conditions associated with cough syncope

A variety of disorders of the central nervous system have been associated with the occurrence of cough syncope [14,24,28,30,31,37,48,49,56,61,73,81,82,89]. These are listed in Table 1. Of note, most of the patients reported were described as having evidence of concomitant obstructive pulmonary disease. Table 2 summarizes the

Table 1 Central nervous system (CNS) disorders associated with cough syncope.

CNS disorder	Reference
Cerebral tumors (meningioma, glioblastoma)	[14,82]
Herniation of cerebellar tonsils (Type 1Arnold-Chiari malformation)	[24,30,49,56]
Hydrocephalus	[28]
Carotid and vertebral arterial occlusive disease	[14,37,48]
Basilar invagination	[61]
Autosomal dominant hereditary sensory neuropathy	[73,81]
Medullary infarction	[89]

Table 3 Other disorders/causes associated with cough syncope.

Disorder	Reference
Asthma	[16,19,38,64]
Whooping cough/Pertussis	[32,66]
Cystic fibrosis	[44]
Tracheobronchomalacia	[47,55]
Angiotensin-converting enzyme inhibitor	[50]
Gastroesophageal reflux disease	[53,62,80]
Herpetic tracheobronchitis	[63]
Influenza A infection	[69]
Solitary fibrous tumor of pleura	[77]
Visceral larva migrans with pulmonary involvement	[83]

numerous cardiovascular disorders that have been reported in association with cough syncope [25,29,33,35,40,41,45,59,65,67,71,75,76,85–88,90]. Other disorders or causes associated with cough syncope [16,19,32,38,44,47,50,53,55,62–64,66,69,77,80,83] are shown in Table 3.

We found only one report of death resulting directly from cough, that of a 61-year-old man with history of COPD, cor pulmonale and right ventricular infarction, who developed cardiac arrest during a coughing episode [43]. The patient had a history of multiple previous episodes of cough syncope.

Numerous motor vehicle accidents resulting from cough syncope have been reported [3,13,42,47,50,57,68,69,73]. These reports include the deaths of two drivers [68], in addition to three pedestrians [13,68].

Proposed mechanisms of cough syncope

Although epilepsy continued to be proposed as the underlying mechanism of cough syncope until as late as 1953 [5], several earlier reports doubted this explanation and proposed circulatory changes as the relevant cause of loss of consciousness [2,4,6]. In 1984, DeMaria and colleagues [36] performed electroencephalograms (EEG) in subjects during episodes of cough syncope. They documented lack of epileptiform activity, even though several subjects displayed jerking or rhythmic movements of the limbs in association with syncopal episodes, as had also been described by previous investigators [7,8,12,17,20]. Subjects demonstrated diffuse delta and theta slowing, similar to the pattern seen in other types of syncope, and with cerebral hypoperfusion [36]. Of note, in contrast to other forms of syncope, that following cough may occur in the supine patient [7,10,23].

Table 2 Cardiovascular disorders associated with cough syncope.

Cardiovascular disorder	Reference
Idiopathic hypertrophic subaortic stenosis	[25]
Hypersensitive carotid sinus syndrome	[29]
Atrio-ventricular conduction block	[33,35,40,59]
Impaired heart rate response to cough	[41]
Cor pulmonale	[43]
Sick sinus syndrome/sinus arrest	[45,86]
Constrictive pericarditis	[65,90]
Pulmonary hypertension	[67]
Abnormal reflex vasodepressor-bradycardia response to cough	[71,85]
Premature ventricular complexes	[75]
Internal jugular vein valve insufficiency	[76]
Pericardial effusion	[87]
Jugular venous reflux + increased plasma endothelin-1	[88]

Subsequent explanations for cough syncope focused on the various effects of the significant increase in intrathoracic and intraabdominal pressures that can occur with coughing. Early investigators [8,10] documented intrathoracic pressures reaching up to 300 mm Hg during cough episodes, thus supporting the concept that resultant decreased cardiac output (CO) leading to decreased cerebral perfusion led to loss of consciousness. Of note, in his classic studies, Sharpey-Schafer [8,9] demonstrated a distinct pattern of vascular response depending on whether coughing was continuous or intermittent. With continuous coughing, circulatory effects were similar to, but more pronounced than, a Valsalva maneuver, due to a greater rise in intrathoracic pressure. Syncope would typically occur during the period of acute hypotension following cessation of coughing, with peripheral blood flow records demonstrating vasoconstriction. In contrast, in subjects who coughed intermittently (i.e., a coughing episode in which an inspiratory effort followed each cough), peripheral vasodilatation occurred, thought by the author to be due to the stimulation of baroreceptors by large, rapid fluctuations in intrathoracic pressure, followed by arterial hypotension [8]. The occurrence of peripheral vasodilatation and decrease in arterial pressure upon the cessation of intermittent coughing was also demonstrated in healthy volunteers, who similarly showed an opposite, vasoconstrictor effect, after a Valsalva maneuver [9]. More than a half century later, these observations were confirmed using pulse wave analysis, by the demonstration of a marked decrease in total peripheral resistance during episodes of cough syncope, even as CO remained unchanged or even increased [79].

In 1956, McIntosh and colleagues [10] studied 13 subjects with cough syncope and noted that their circulatory response to cough was qualitatively similar to that of normal subjects, but that they were able to cough more forcefully. Furthermore, paroxysms of cough, whether continuous or intermittent, led to a rise in intrathoracic pressure of greater magnitude than the associated rise in arterial pressure. The cerebrospinal fluid (CSF) pressure rose to essentially the same level as did intrathoracic pressure, thus leading the authors to suggest that the increased CSF pressure, by increasing the extravascular pressure around the cranial arteries and veins, causes blood to be "squeezed" out of the cranium, rapidly causing hypoperfusion, with resultant anoxia and syncope. In 1961, Kerr and Eich [21] questioned whether the mechanisms proposed by Sharpey-Schafer [8,9] and McIntosh [10] could explain the vary rapid occurrence of syncope (within 3—5 s) after onset of cough in some subjects (even after a single cough), and before the documentation of a fall in peripheral arterial pressure. They speculated that a cerebral concussion-like effect from the rapid rise in CSF pressure was responsible for the resultant syncope. Pederson and coworkers [15] countered the arguments of McIntosh [10] and Kerr [21] by documenting very rapid circulatory responses to coughing, supporting the position that cough syncope is a direct result of diminution of cerebral blood flow due to significant changes in central circulation.

More recent studies have clearly documented that cough diminishes cerebral blood flow, both in healthy volunteers as well as in subjects with cough syncope. In a study utilizing a Doppler ultrasonic flowmeter catheter, Desser et al. studied 91 coughing episodes in 16 healthy subjects [27]. They demonstrated a significant, cough-induced decline in peak carotid blood velocity that was immediate in onset and uniformly occurring within one second of each tussive effort. Notably, there was an insignificant, low degree of correlation between the level of simultaneously recorded mean right atrial pressure and percent decline in peak carotid blood velocity, suggesting that impaired venous return was not the only factor responsible for the essentially instantaneous reduction in carotid artery blood velocity observed. Mattle and colleagues [54] used transcranial Doppler sonography (TCD) monitoring of middle cerebral artery flow velocities to document a critical reduction of cerebral blood flow in three patients with cough syncope. During coughing, transient cerebral circulatory arrest coinciding with loss of consciousness was observed in two of the subjects. Of note, systemic arterial blood pressure was preserved in one patient during a syncopal episode associated with documented transient cerebral circulatory arrest.

As early as 1953, a baroreflex mechanism was implicated in the etiology of cough syncope [8]. Over a half century later, Benditt and colleagues [71] shed further light on this issue by comparing the effects of a brief, volitional cough effort (requiring the induction of a transient increase in systolic blood pressure to $>$ 220 mm Hg) in subjects with a history of cough syncope and individuals with syncope of other etiologies. The investigators reported a number of significant observations. Subjects with cough syncope demonstrated more profound hypotension for a longer duration than did the subjects with other forms of syncope. The expected positive chronotropic response accompanying cough-induced hypotension tended to be suppressed in cough syncope subjects compared with the other subjects, regardless of whether they exhibited positive or negative results on head-up tilt test. Furthermore, the tendency to slower recovery of blood pressure following hypotension in cough syncope subjects compared with the other syncope subjects suggested an active vasodilation process consistent with a neural reflex mechanism (Fig. 1). Finally, subjects with cough syncope were not more sensitive to the effects of carotid sinus massage than were the other syncope subjects; indeed, none of the cough syncope subjects exhibited an abnormal response to carotid massage. From these experiments, the authors concluded that differences in neurally mediated reflex vasodepressor-bradycardia responses to cough stimuli appear to distinguish subjects with cough syncope from individuals with syncope of other causes. Furthermore, they suggested that the neural reflex trigger sites inducing cough syncope differ from those associated with either carotid sinus syndrome or vasovagal syncope. A subsequently published case study utilizing autonomic and electrophysiological measurements also concluded that cough-induced vasodepressor hypotension was the basis of syncope in the evaluated subject [85].

Simultaneous occurrence of multiple pathophysiological processes, as discussed above, may be required to induce cough syncope, or, different processes, alone or in combination, may be relevant in different patients (Fig. 2). Regardless, a unifying theme among proposed mechanisms of cough syncope appears to be the required generation of very high intrathoracic pressures. This phenomenon likely explains the remarkably consistent profile of the typical cough syncope patient described by numerous authors over more than a century. A large, male subject with obstructive airways disease would be more likely to generate extremely high intrathoracic pressures with coughing than would a woman or a child. When cough syncope has been reported in the pediatric population, the condition was noted to occur almost exclusively in children with asthma [16,19,22,38,49,52].

Approach to the patient with cough syncope

Since loss of consciousness in a patient with cough syncope is a direct and immediate result of cough, elimination of cough will therefore eliminate syncope. Thus, prompt evaluation and treatment of the underlying etiology of cough is essential. In the case of acute ($<$3 weeks duration) and subacute cough (3—8 weeks), the underlying cause is predominantly a viral upper respiratory tract infection. Hence, treatment is limited to symptomatic relief with antitussive therapies, the majority of which are not supported by strong efficacy data and/or are limited by intolerable adverse effects at antitussive doses [91,92]. In contrast, the management of chronic cough depends on the establishment and treatment of the underlying etiology of cough. Guidelines published by multiple societies, including the European Respiratory Society [93] and American College of Chest Physicians [94] provide diagnostic-therapeutic algorithms for evaluation and management of chronic

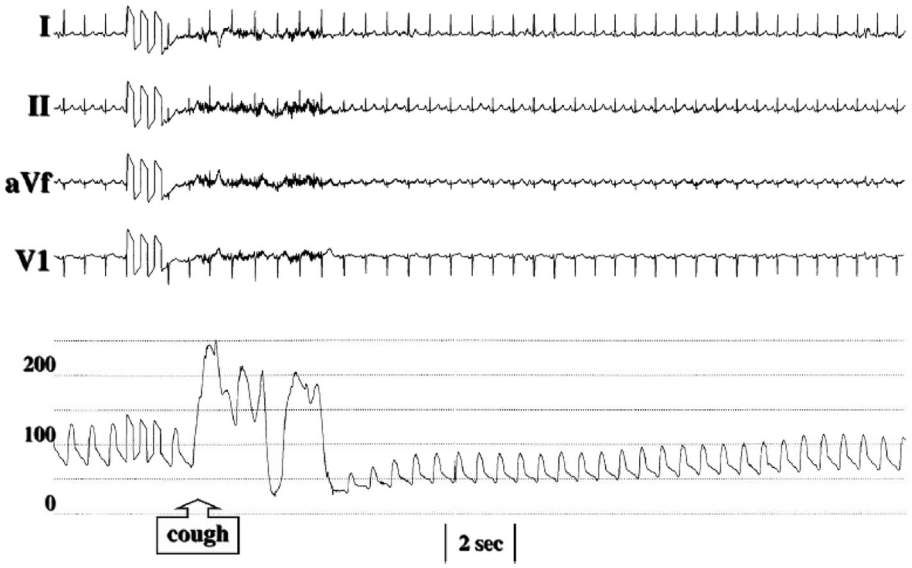

Figure 1 ECG (leads I, II, aVF, and V1) and arterial pressure recordings obtained during a cough test in patient 6. Baseline supine arterial pressure was approximately 120/75 mm Hg. Cough was associated with a fall in systolic arterial pressure of approximately 60 mm Hg. The immediate post-cough value was 60/30 mm Hg. Full recovery to baseline arterial pressure, with the patient remaining in the supine position, required approximately 40 s (from ref. 71, with permission).

cough. Multiple prospective studies have shown that in the vast majority of adult nonsmokers without evidence of active disease on chest radiograph, chronic cough will be due to one or more of the following etiologies: upper airway cough syndrome (formerly, postnasal drip syndrome); eosinophilic airway inflammation (asthma, non-asthmatic eosinophilic bronchitis); and, gastroesophageal reflux disease [93,94]. However, the chronic cough of some patients will prove refractory despite thorough and appropriate evaluation and treatment. These patients may have underlying hypersensitivity of the cough reflex, a condition recently termed the Cough Hypersensitivity Syndrome [95—97]. In such difficult cases of refractory cough, it may still be possible to eliminate or at least lessen the frequency of resultant syncopal episodes by reducing the magnitude and severity of individual cough events, as well as the duration of cough paroxysms. Doing so will minimize the intrathoracic pressures attained with a coughing

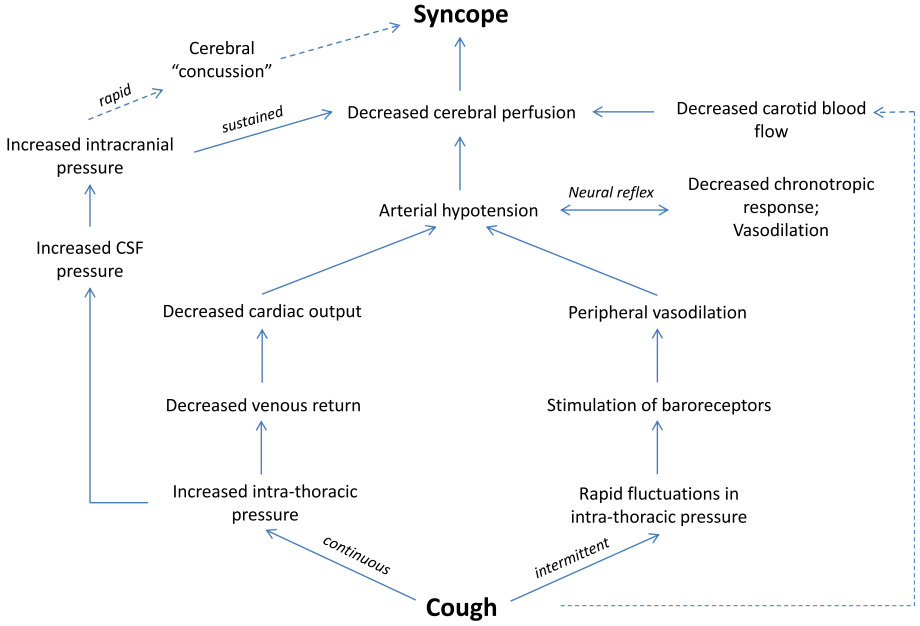

Figure 2 Proposed mechanisms of cough syncope. Simultaneous occurrence of multiple pathophysiological processes may be required to induce cough syncope. Alternatively, different processes, alone or in combination, may be relevant in different patients. The amount and quality of published data supporting these various proposed mechanisms is highly variable (see discussion in text).

episode, thus ameliorating its cardiothoracic and cerebrovascular effects.

Patients in whom cough syncope is associated with identifiable conditions such as those listed in Tables 1—3 provide the opportunity to specifically address the underlying cause(s) of syncope. Surgical and non-surgical procedures, as well as medical management of treatable conditions, may eliminate syncopal episodes resulting from cough. Therapeutic success has been achieved with appropriate treatment of neurological abnormalities [24,49,61,82], idiopathic hypertrophic subaortic stenosis [25], hypersensitive carotid sinus [29], atrio-ventricular conduction block [33,35,40,45,59,86], tracheobronchomalacia [47], carotid artery obstruction [37,48], post-tussive hypotension [39,85], constrictive pericarditis [65], premature ventricular complexes [75], and pleural tumor [77].

Future directions

Future clinical research in the field of cough syncope is certainly needed, but investigators will continue to face the challenge of a relative dearth of patients in their quest to generate robust data sets. Thus, multicenter collaborations among referral centers will likely be required. As cough syncope appears to be the final common pathway of several pathophysiologic processes, prospective trials could investigate, for example, whether different pathophysiological processes prevail in individual patients, or, whether cough syncope is the result of simultaneous contributory events. A further fascinating question is whether all individuals are vulnerable to cough syncope under certain threshold conditions of elevated intrathoracic pressures, or whether the occurrence of syncope under similar conditions is limited to individuals somehow predisposed. Recent technological advances in the measurement of cardiac function, intrathoracic pressures, and cardiac rhythm could help elucidate these questions, and studies incorporating these new diagnostic modalities are eagerly awaited.

Conflict of interest

There are no conflicts of interest.

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