JACC: CLINICAL ELECTROPHYSIOLOGY
VOL. 2, NO. 7, 2016

ISSN 2405-500X/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jacep.2016.02.017

Blunted Chronotropic Response to Hypotension in Cough Syncope

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ABSTRACT

OBJECTIVES This study compared hemodynamic and chronotropic responses to cough in cough syncope (CS) patients to those in control subjects.

BACKGROUND Cough syncope is an uncommon form of situational fainting variously attributed to both reflex and mechanical causes. We hypothesized that if baroreflex responses contribute to CS, post-cough hypotension should be associated with cardioinhibition comparable to that observed in other reflex faints.

METHODS The study population consisted of 8 CS patients (group 1), 21 patients with vasovagal syncope (group 2), and 6 patients with nonvertiginous "lightheadedness" (group 3). Testing with patients seated included volitional coughing that achieved a transient blood pressure (BP) of ≥200 mm Hg. Beat-to-beat blood pressure (systolic blood pressure [SBP]) before cough, minimum cough-induced SBP and heart rate (HR) (beats/min) after cough, and HR change during cough-induced hypotension were recorded, along with SBP recovery time from SBP nadir after cough.

RESULTS Compared to controls, cough-induced SBP drop was greater in CS patients (CS patients: −48 ± 13.1 mm Hg vs. −29 ± 11.2 mm Hg for group 2 controls; $p = 0.005$; or −25 ± 10 mm Hg in group 3 controls; $p = 0.02$), and recovery time was longer (CS: 46 ± 19 s vs. 11 ± 3.6 s in group 1 controls; $p = 0.002$; or 12 ± 5 s in group 3 controls; $p = 0.01$). Furthermore, despite greater induced hypotension, post-cough chronotropic response was less in CS patients (+15% above baseline rate) than in either group 2 (+31% above baseline rate; $p < 0.001$) or group 3 (+28%; $p = 0.01$) controls.

CONCLUSIONS In CS patients, post-cough chronotropic response is blunted compared to that in controls despite greater cough-induced hypotension favoring baroreflex cardioinhibition contribution to the pathophysiology of cough syncope. (J Am Coll Cardiol EP 2016;2:818-24) © 2016 by the American College of Cardiology Foundation.

Cough syncope (CS) is a well-known but uncommon form of situational faint, the pathophysiology of which remains incompletely understood (1,2). CS has been variously attributed to both reflex and mechanical causes (3-11). The abrupt increase of systemic arterial pressure associated with forceful cough (**Figure 1**) has been hypothesized to cause loss of consciousness by 1 or more of the following mechanisms: baroreflex-induced bradycardia and vasodilation, or a mechanical cerebral concussive effect, or a transient venous obstruction with reduced cardiac output.

Previously, we observed that volition-induced cough in supine CS patients triggered a period of hypotension and that the duration of hypotension was greater than would be expected by venous obstruction alone (12). We concluded that CS was most likely due to a baroreflex-triggered response as originally proposed by Sharpey-Shafer (3).

In this study, we sought to further assess the concept that baroreflex responses contribute to cough-induced hypotension in CS patients. To this end, we compared the magnitude and duration of cough-induced hypotension with the resulting

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Manuscript received January 19, 2016; revised manuscript received February 16, 2016, accepted February 25, 2016.

chronotropic response during the hypotensive phase after cough in upright, seated patients with clinical CS and in 2 sets of control subjects: 1 group with clinically diagnosed vasovagal syncope and a second group referred for evaluation of nonvertiginous "lightheadedness and dizziness." We hypothesized that if hypotension is principally mediated by reflex vasodilation, then it would be accompanied by a diminished chronotropic response (presumably on a parasympathetic basis) as is observed in other reflex faints (e.g., vasovagal syncope) (1).

ABBREVIATIONS AND ACRONYMS

BMI = body mass index
BP = blood pressure
CS = cough syncope
ECG = electrocardiogram
HR = heart rate
SBP = systolic blood pressure

METHODS

The patient population consisted of individuals referred between January 2012 and December 2015 for evaluation at the Cardiac Arrhythmia and Syncope Center at University of Minnesota (Minneapolis, Minnesota). Three patient groups were defined, as follows: group 1 included patients with a clinical history compatible with CS. These patients presented with a history of multiple syncope and/or near-syncope episodes closely associated with coughing (usually a spasm of coughing). Based on each individual's medical history, only 1 of these patients had experienced syncope unassociated with cough, and in that case the presumed faints had occurred more than 30 years earlier.

Group 2 included patients (syncope controls) without carotid sinus hypersensitivity or clinically significant structural cardiac or neurological disease, with reflex syncope of non-cough causes. Group 3 consisted of individuals without syncope or collapse but who were referred for evaluation of nonvertiginous lightheadedness or dizziness and in whom medical history and response to head-up tilt test was nondiagnostic (i.e., did not reproduce spontaneous symptoms).

Written informed consent was obtained after thorough discussion of the study plan with each subject, using an Institutional Review Board-approved consent form. Studies were undertaken after a 3-h fasting state, with intravenous saline (500 ml) administered over a 20-min period prior to initiating testing to attempt to achieve a euvolemic state. All cardioactive medications (primarily antihypertensive drugs in the CS group) had been withheld for approximately 48 h before testing. Prior to study, patients were asked to relax in a sitting position for 10 min in a quiet room with low-level lighting. Baseline heart rate (HR), continuous electrocardiography (ECG), and continuous beat-to-beat blood pressure (BP) (Finometer; Finapres Medical Systems or Nexfin, BMEYE, Amsterdam, the Netherlands) were recorded. In each case, the noninvasive BP recording system was calibrated using a standard sphygmomanometer.

The use of volitional cough as a diagnostic testing procedure has been previously reported (2,12). The cough maneuver was carefully explained to each patient. A practice maneuver was permitted in each case, and another 5 min was allowed prior to the actual test. The cough protocol was undertaken with patients in a seated position to diminish risk of falls.

Subjects were asked to undertake 2 to 3 vigorous coughs in quick succession with the goal of achieving a transient arterial pressure of 200 mm Hg or greater. Duration of the transient pressure >200 mm Hg was approximately 3 to 5 s (**Figures 1 and 2**). Continuous HR and beat-to-beat BP were recorded during coughing and for approximately 5 min after the completion of the coughing intervention. SBP and HR measurements were calculated as the average of 4 consecutive cardiac cycles. A cough test was deemed to have been effective if it induced a transient increase in systolic blood pressure (SBP) to ≥200 mm Hg.

The hemodynamic impact of cough was determined by measuring the change in mean beat-to-beat SBP before and after cough and the associated beat-to-beat HR prior to and immediately after the cough (**Figures 1 and 2**). Recorded hemodynamic responses included mean SBP before cough, mean minimum cough-induced SBP (mm Hg) immediately after the end of cough, mean HR (beats/min) before cough, and mean HR increase during cough-induced hypotensive period.

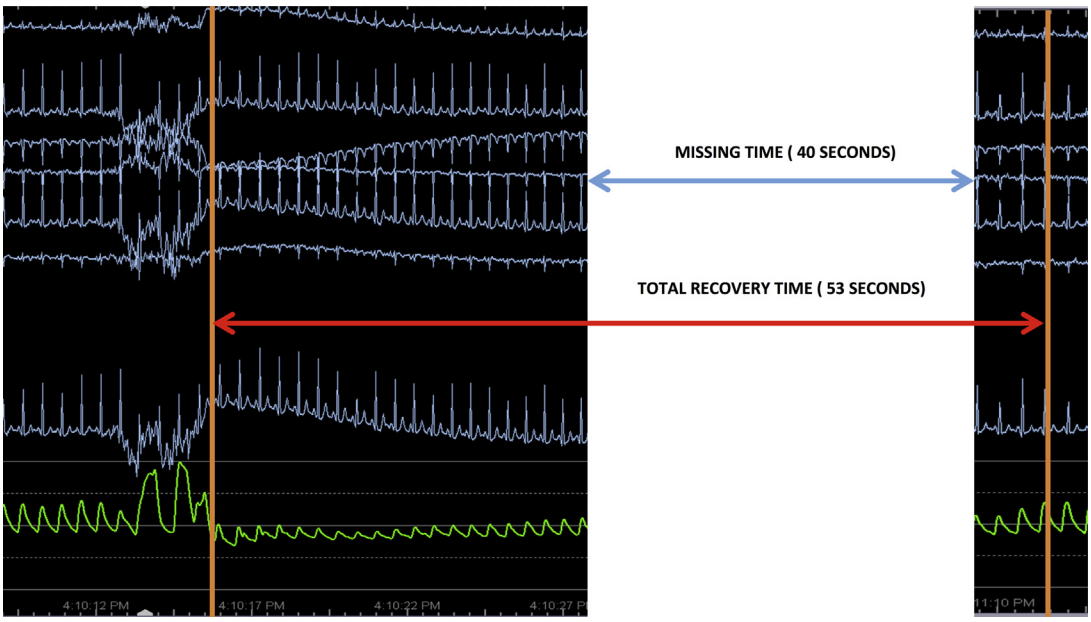
Time to SBP recovery was defined as duration (in seconds) from SBP nadir immediately after cough to the recovery of SBP to its value immediately prior to cough perturbation. All values are mean ± SD. Statistical significance of differences was assessed by Student *t*-test and ANOVA as appropriate. A p value of <0.05 was considered significant.

RESULTS

CLINICAL FEATURES. The study population consisted of 28 patients referred for diagnostic evaluation and treatment of suspected reflex syncope and an additional 6 individuals referred for evaluation of nonvertiginous lightheadedness or "dizziness" but without reported transient loss of consciousness and with nondiagnostic response to head-up tilt (i.e., study did not reproduce spontaneous symptoms).

The CS group included 8 individuals, 7 of whom were men (group 1). The syncope control group (group 2) included 21 individuals with a medical history of transient loss of consciousness and an

FIGURE 1 Recording of Response to Cough in a Cough Syncope Patient



The 6 traces at the **top** in **blue** are ECG recordings. **Green** trace was obtained by Finapres recording. Maximum pressure generated by cough was 200 mm Hg. Baseline SBP was 140 mm Hg. Minimum SBP recorded was 96 mm Hg. Hypotension persisted for approximately 53 s. ECG = electrocardiography; SBP = systolic blood pressure.

ultimate diagnosis of vasovagal syncope based on medical history and/or reproduction of symptoms during head-up tilt table testing. The subjects being evaluated for lightheadedness and dizziness were designated group 3 and consisted of 6 individuals, of whom 4 were male.

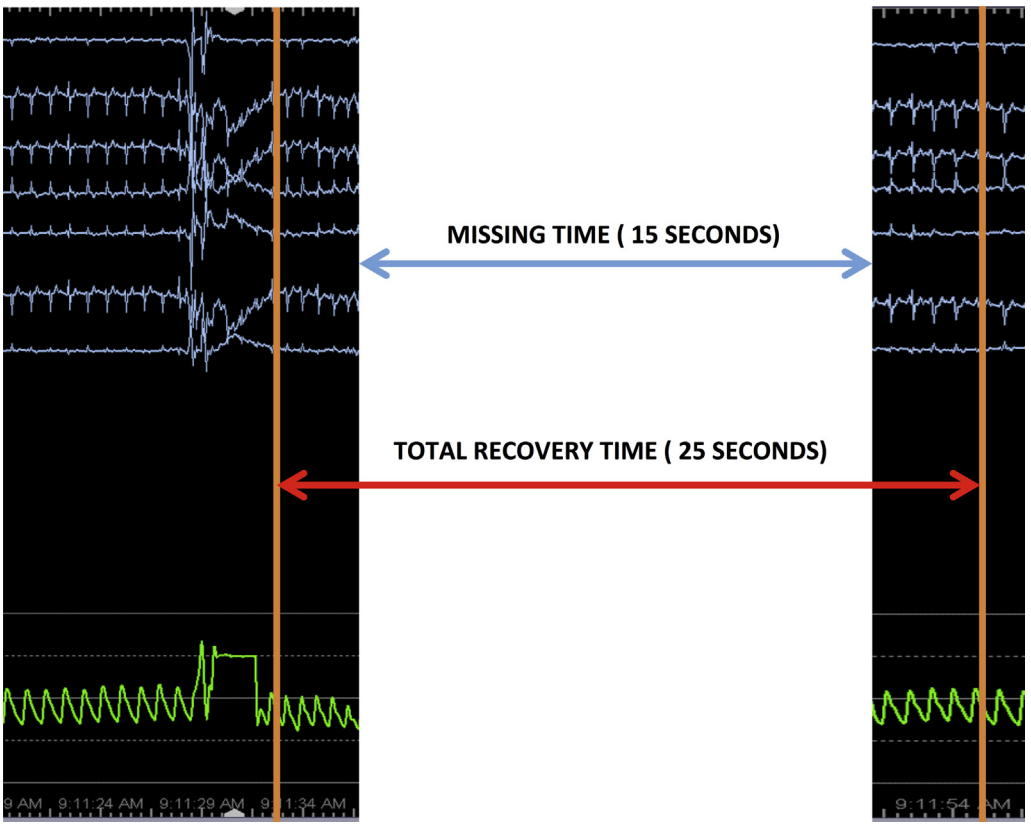
Clinical features and comorbidities in the 3 patient groups are summarized in Table 1. Compared to group 2, group 1 CS patients were older (60 ± 15 years of age vs. 38 ± 17 years of age, respectively; $p = 0.013$) and had a greater propensity to be smokers (Table 1). Furthermore, CS patients tended to have a higher frequency of hypertension, hyperlipidemia, coronary artery disease, diabetes, and obstructive airway disease (Table 1), but given the small numbers of CS patients, these apparent differences were not statistically significant. Group 3 individuals did not differ from CS patients with regard to age, smoking habit, body mass index (BMI), or associated comorbidities (Table 1).

LABORATORY FINDINGS. All patients underwent active standing test (10 min), Valsalva maneuver (to 40 mm Hg), cough testing, and head-up tilt table testing (passive tilt for 20 min in duration, followed by sublingual nitroglycerin provocation if required) as part of their overall evaluation. The active standing test and Valsalva responses were deemed to be physiological in all cases. Head-up tilt test results (passive and provoked) were negative in all CS patients and group 3 controls. However, the solitary female CS patient (age 62 years) became progressively hypotensive 4 to 5 min after nitroglycerine administration, and the test was terminated; she indicated that the symptoms during the test were not typical of her spontaneous episodes. Among group 2 patients, a diagnosis of vasovagal syncope was based primarily on medical history, but head-up tilt was undertaken to further support the diagnosis and/or provide an opportunity for the patient to recognize premonitory warning symptoms. Head-up tilt reproduced spontaneous symptoms in 14 group-2 controls (6 with passive tilt and 8 after nitroglycerine).

Prior to cough, baseline heart rates were similar in all 3 groups (81 ± 14 beats/min in group 1 CS patients versus 84 ± 11 beats/min in group 2 and 78 ± 9 beats/min in group 3). Mean pre-cough SBP values were similar in the 3 groups (CS patients: 132 ± 14 mm Hg; group 2: 143 ± 17 mm Hg; group 3: 135 ± 10 mm Hg).

Compared to either control group, CS patients exhibited a lower SBP nadir after cough and a more

FIGURE 2 Recording of Response to Cough in a Control Patient



Traces in **blue** are ECG recordings. **Green** trace was obtained by Finapres recording. Baseline SBP was 125 mm Hg. The minimum SBP recorded was 96 mm Hg. SBP recovery to approximate baseline value was complete after approximately 25 s. Abbreviations as in Figure 1.

prolonged SBP recovery time (Table 2). The mean SBP drop from baseline after cough in CS patients was almost twice that observed in the control groups (-36% compared to -20% and -23% in group 2 and group 3 controls was respectively) (Table 2). Nonetheless, the SBP recovery time was approximately 4-fold longer in CS patients than in the control groups (Table 2).

TABLE 1 Baseline Characteristics

	Group 1 (n = 8)	Group 2 (n = 21)	p Value vs. Group 1	Group 3 (n = 6)	p Value vs. Group 1
Age, yrs	60 ± 15	38 ± 17	0.013	48 ± 8	NS
Males	7 (88%)	10 (47.6%)	NS	4 (67%)	NS
Hypertension	7 (88%)	6 (28.6%)	NS	2 (25%)	NS
Hyperlipidemia	5 (63%)	6 (28.6%)	NS	2 (25%)	NS
CAD/MI	3 (38%)	2 (9.5%)	NS	1 (12.5%)	NS
COPD/Asthma	3 (38%)	2 (9.5%)	NS	0 (0%)	NS
BMI, kg/m^2	30 ± 4	25.5 ± 5	0.034	26 ± 5	NS
Smoking	7 (88%)	4 (19%)	0.05	4 (50%)	NS

Values are mean ± SD or n (%).

BMI = body mass index; CAD/MI = coronary artery disease/myocardial infarction; COPD = chronic obstructive pulmonary disease; NS = not statistically significant.

Cough-induced hypotension was more prolonged and more severe in CS patients than in control subjects (Figures 1 and 2). Compared with baseline mean SBP, the drop on cough-induced SBP averaged 48 mm Hg (39.3%) in CS patients and 29 mm Hg (19.6%) in group 2 and 25 mm Hg in group 3 (Table 2).

Despite lower cough-induced SBP, the cardiac chronotropic response to induced hypotension was less in CS patients (+9.5 ± 5.2 beats/min) than that recorded in group 2 (+26.2 ± 12.4 beats/min; p = 0.001) or group 3 (+22 ± 13 beats/min; p = 0.01) (Table 2).

SYMPTOM OBSERVATIONS. None of the CS patients developed frank syncope during the cough studies reported here. However, 4 of 7 CS patients complained of lightheadedness during and after

TABLE 2 Results

	Group 1 (n = 8)	Group 2 (n = 21)	p Value vs. Group 1	Group 3 (n = 6)	p Value vs. Group 1
ΔSBP, mm Hg	−48 ± 13.1	−29 ± 11.2	0.005	−25 ± 10	0.02
ΔHR, beats/min	+9.5 ± 5.2	+26.2 ± 12.4	0.0001	+22 ± 13	0.01
% drop in SBP	−36 ± 9.5	−20 ± 7.6	0.0014	−23 ± 5	0.02
% increase in HR	+15 ± 6.6	+31 ± 15.5	0.001	+28 ± 12	0.01
SBP recover time, s	46 ± 19	11 ± 3.6	0.002	12 ± 5	0.01

Values are mean ± SD.
ΔHR = change in heart rate; ΔSBP = change in systolic blood pressure; SBP recovery time = time to recovery of SBP to baseline pre-cough value.

cough that was similar to but less severe than their spontaneous symptoms. The fact that studies were conducted with patients in a seated position may have moderated the severity of symptoms. None of the control subjects reported cough-induced symptoms.

POTENTIAL SEX BIAS. Inasmuch as all but 1 of the CS patients were male, a subanalysis was undertaken comparing clinical features and cough-induced hemodynamic changes in the 7 male group-1 CS patients and the male syncope control patients (group 2B, n = 10) (Table 3). Findings once again indicated that cough-induced hypotension was more marked and persisted for a longer time period, in group 1 patients than in male syncope controls (Table 4). Additionally, cough-induced cardioinhibition remained.

DISCUSSION

This study provides 3 main findings with respect to the pathophysiology of cough syncope in selected individuals referred for evaluation to a Syncope center. First, the magnitude of hypotension induced by volitional cough with subjects in an upright seated posture was significantly greater than in similarly situated control subjects. Second, despite being subjected to a greater cough-induced hypotensive stress, the chronotropic response to hypotension in CS patients was significantly less than was observed in non-cough syncope control subjects. Finally, the duration of hypotension was substantially longer in CS patients than in control subjects.

TABLE 3 Baseline Characteristics in Male Subjects

	Group 1 Males (n = 7)*	Group 2B Males (n = 10)	p Value
Age, yrs	59.5 ± 15	43.3 ± 17	0.076
Hypertension	6 (85.7%)	4 (40%)	NS
Hyperlipidemia	5 (71.4%)	3 (30%)	NS
CAD/MI	3 (42.9%)	1 (10%)	NS
COPD/Asthma	3 (42.9%)	1 (10%)	NS
BMI, kg/m^2	30.1 ± 4	27.4 ± 6	0.260
Smoking	7 (100%)	2 (20%)	0.05
Alcohol	7 (100%)	4 (40%)	NS

Values are mean ± SD or n (%). Group 1 consisted of all male CS patients, and group 2B was male control subjects. *Group 1 CS male patients excluding the solitary female patient.
Abbreviations as in Table 1.

PATHOPHYSIOLOGICAL BASIS OF COUGH SYNCOPE. Cough syncope is an infrequent form of situational faint. In this regard, Mereu et al. (2) identified only 29 cases of cough syncope among more than 5,100 patients referred for diagnostic evaluation of syncope and collapse with tilt-table testing. Consequently, studies examining the clinical features and pathophysiology of cough syncope necessarily consist of small numbers of affected individuals, as is the case in our report.

The first description of cough syncope dates from the late 19th century (13). Initially, cough syncope was considered a form of epilepsy. However, although that concept is no longer accepted, uncertainty remains regarding the basis for the syndrome, and several pathophysiological mechanisms have been proposed. First, it has been suggested that increased intrathoracic pressure during a cough is transmitted to the cerebrospinal fluid, causing an acute increase in intracranial pressure. Inasmuch as cerebral perfusion is determined largely by the difference between intracranial pressure and arterial pressure (assuming venous systemic pressure is not changing substantially), cerebral perfusion could be compromised during cough. However, this mechanism would not be expected to explain the prolonged nature of induced hypotension with single coughs or very brief coughing spells that occur in CS-susceptible individuals. “Cough concussion” is a second mechanism proposed for transient cerebral dysfunction with cough. In this case, the disturbance is not true syncope but a traumatic (concussive) cause in which the combination of acute increases of arterial, venous, and cerebrospinal fluid pressure directly compromise cerebral function. In this case, prompt recovery would seem unlikely, and the development of concomitant systemic hypotension is difficult to explain. A third hypothesis is based on the development of transient cough-induced high intrathoracic pressures. Although of brief duration, transient high intrathoracic pressure may diminish venous return to the heart and consequently cardiac output. This mechanism may explain the relatively short-lived hypotension observed in our control subjects. However, a prolonged period of hypotension, far exceeding the duration of the cough, cannot be

TABLE 4 Results in Male Subjects

	Group 1 Males (n = 7)	Group 2B Males (n = 10)	p Value
ΔSBP, mm Hg	50.8 ± 13.1	30.4 ± 11.9	0.011
ΔHR, beats/min	8.1 ± 6.1	26.5 ± 12.4	0.001
% drop in SBP	39.3 ± 9.5	21 ± 7.6	0.002
% increase in HR	10.6 ± 6.6	33.3 ± 15.5	0.0009
SBP recovery time, s	49.2 ± 18.9	11.2 ± 3.6	0.002

Values are mean ± SD.
Abbreviations are as shown in Table 2.

explained by transient diminution of venous return alone.

The potential role of neural reflex contribution (i.e., vasodepression and cardioinhibition) to cough syncope was proposed approximately 65 years ago. Sharpey-Schafer (3,4), using venous occlusion plethysmography, demonstrated decreased forearm vascular resistance after coughing in a series of 27 CS patients. This decrease was shown to occur only during a bout of coughing, in contrast to baroreflex-mediated increase in resistance during prolonged and steady increase in intra-thoracic pressure with Valsalva maneuver. Recently, Krediet and Wieling (14) offered additional support for the reflex pathophysiology concept. In their report of findings in 2 CS patients, the authors documented beat-to-beat changes in cardiac output and total peripheral vascular resistance during cough syncope using pulse wave analysis. Their finding that a decrease in total peripheral resistance plays a pivotal role in the pathophysiology of cough syncope is consistent with Sharpey-Schafer's hypothesis (3,4).

NEURAL REFLEX CHRONOTROPIC INHIBITION. The vascular mechanoreflex (or baroreflex) system in humans is complex and has multiple interactions that remain incompletely understood (15). In general terms, baroreflexes residing in both the arterial and the venous systems provide negative feedback to buffer pressure fluctuations over both relatively long time periods as well as in response to abrupt transient changes (15,16). In regard to the acute hypertensive arterial pressure transients that occur with cough, baroreceptor fibers in arterial vessel walls, principally in the carotid sinus region and aortic arch, are expected to initiate within several seconds a compensatory blood pressure-lowering response (16). Furthermore, in the setting of diminished venous return due to temporarily increased intrathoracic pressure with cough (and perhaps other clinical scenarios such as "trumpet blowers syncope"), the magnitude of the reflex response is accentuated (15). Potentially, this accentuation may be greater in patients susceptible to CS, with the net effect potentially being a symptomatic compensatory decrease in blood pressure. Additionally, in this setting, and despite a tendency to hypotension, the expected positive chronotropic response may be absent or blunted.

In this study, CS patients exhibited a blunted chronotropic response after transient cough-induced hypertension despite a transient post-cough hypotensive period. This observation is compatible with a baroreflex-induced neural reflex triggered by transient hypertension and persisting into the period of post-cough hypotension (Figure 1). Thus, arterial baroreceptor-triggered cardioinhibition may contribute to hemodynamic manifestations in cough syncope.

STUDY LIMITATIONS. This study was designed to offer insight into the pathophysiology of cough-induced syncope by examining associated heart rate and hemodynamic changes induced by volitional cough in patients seated upright with clinical CS. However, findings reported here are subject to important limitations, and inferences derived from our observations must be taken with caution. First, cough syncope is an infrequent condition; thus, the study population is inherently small. Consequently, nonsignificant results could be due to lack of power, while other comparisons among subgroups may be at greater risk of Type 1 error. Additionally, the CS patients included in this report were a "selected" group in that their symptoms were severe enough to warrant referral for evaluation. Second, due to uncertainty regarding the reproducibility of cough responses and the requirement to complete the diagnostic testing in each individual, pharmacologic interventions (e.g., atropine, phenylephrine) designed to better isolate the basis of post-cough cardioinhibition were not undertaken. Third, attempts to record stroke volume and cardiac output proved to be difficult due in part to body movement accompanying forceful cough. Consequently, this potentially useful information could not be provided. Fourth, the investigators were not blinded to the clinical diagnosis of CS. Fifth, despite forceful cough and its associated hemodynamic consequences, syncope was not reproduced in the laboratory. However, most CS patients noted a sensation that they indicated was similar to, albeit less severe than, their spontaneous events. Finally, the CS patient population were older and tended to manifest a greater number of co-morbidities than did the syncope control group (group 2). Although, most of the co-morbidity differences did not achieve statistical significance, they could have introduced

unaccounted for biases. For example, a greater frequency of atherosclerotic disease and hyperlipidemia has been associated with increased baroreceptor sensitivity in carotid sinus syndrome, and could have a similar impact in CS patients.

CONCLUSIONS

Cough syncope (CS) is a situational faint, which is both uncommon and of incompletely understood pathophysiology. Our study demonstrates that individuals who, based on clinical presentation, are apparently susceptible to cough-induced syncope, manifest a blunted post-cough HR response (i.e., a less than expected positive chronotropic response in the setting of hypotension) and a marked delay in blood pressure recovery compared to non-CS control subjects. This observation strongly favors a neural reflex basis for CS as originally proposed by Sharpey-Shafer (3,4) more than 60 years ago. However, why certain individuals appear to be susceptible, and even in these cases manifest spontaneous CS only infrequently, remains unclear and in need of further study.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Cough syncope is an uncommon but clinically distinctive condition in which transient loss of consciousness tends to be abrupt and without warning, leading to substantial risk of accident and injury. The suspicion of cough-induced syncope should lead to a thorough search for causes of recurrent coughing (e.g., smoking, air pollution, obstructive airway disease). Ameliorating cough triggers is an essential component of the treatment strategy.

TRANSLATIONAL OUTLOOK: Our findings tend to favor an important reflex contribution to the pathophysiology of CS. Potentially, agents that diminish excessive baroreflex response to transient arterial pressure transients may merit study for prevention of recurrent cough-induced faints.

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KEY WORDS chronotropic response, cough, hypotension, syncope