CASE REPORT
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Edward P. Sharpey-Schafer was right: evidence for systemic vasodilatation as a mechanism of hypotension in cough syncope
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Cough syncope typically occurs in middle aged and senior, muscularly built males with a history of chronic obstructive lung disease. Originally, cough syncope was thought to be a form of epilepsy and only in the 1940s it was recognized to be of syncopal nature. The circulatory pathophysiology is, however, still not fully understood. We present data on two cough syncope patients in whom we documented the beat-to-beat changes in cardiac output and total peripheral resistance during cough syncope using pulse wave analysis. Our results give support to Edward P. Sharpey-Schafer’s hypothesis that a decrease of total peripheral resistance plays a pivotal role in the pathophysiology of cough syncope. Systematic studies are needed to confirm this mechanism in larger series of patients.

Keywords Situational syncope; Cardiac output; Total peripheral resistance; Sneezing; Modelflow; Smoking; COPD

Introduction
Cough syncope typically occurs in middle aged and senior, muscularly built males with a history of chronic obstructive lung disease.1,2 The syndrome was first described by J.-M. Charcot (1825–1893) in 1879.3 Originally, cough syncope was thought to be a form of epilepsy,4 and only in 1940s, it was recognized to be of syncopal nature.4,5 Typically, syncope occurs immediately after coughing, but rarely it has also been reported interrupting a cough.2,6 Cough syncope usually occurs while sitting or standing, but may also occur supine.7 Consciousness rapidly recovers (i.e. within seconds), typically with few vasomotor or other sequelae.7 The diagnosis of cough syncope may be confirmed by having the patient cough while sitting up-right, and continuously measuring blood pressure and heart rate. This may also provide an opportunity to show the patient that avoiding violent coughing may prevent syncope.2

Three main mechanisms have been postulated to be involved in cough syncope. First, the increased intra-thoracic pressure during a cough is transmitted to the cerebrospinal fluid,7 causing an acute pressure increase in the skull, compromising cerebral perfusion.6,7 In addition, the combination of increased venous pressure in the skull (by the increased intra-thoracic pressure8) and the lowered arterial pressure results in perfusion stand-still or even back-flow in the brain.6 Secondly, ‘cough concussion’ has been suggested as a potential mechanism which holds that during coughing the combination of acute increases of arterial, venous, and cerebrospinal fluid pressures in the skull, directly compromise cerebral functions.9 The importance of ‘cough concussion’ is unclear.

Thirdly, muscularly built persons with obstructive lung disease are capable of building up the high intra-thoracic pressures that trigger cough syncope (300–450 mmHg compared with < 100 mmHg in healthy young subjects6,10,11). These abrupt very high intra-thoracic pressures diminish venous return and cardiac filling and thereby cardiac output (CO).2 On the arterial side, the abruptly increased intra-thoracic pressure is transferred to the systemic circulation, causing arterial baroreflex-mediated vasodilatation.2,8 In 1950s, E.P. Sharpey-Schafer (1908–1963)12 documented a decreased fore-arm vascular resistance after coughing in a series of 27 cough syncope patients by venous occlusion plethysmography.8 (He also demonstrated that this decrease occurs only during a bout of coughing—i.e. a repetitive increase of intra-thoracic pressure—in contrast to what happens during a Valsalva’s manoeuvre when there is a baroreflex-mediated increase in resistance during a prolonged and steady increased intra-thoracic pressure.) Whether these local changes would have a systemic significance remained to be elucidated.

We present data on two cough syncope patients in whom we documented the beat-to-beat changes in CO and total peripheral resistance during cough syncope using pulse wave analysis. Our results give support to Sharpey-Schafer’s hypothesis that a decrease in total peripheral resistance plays a pivotal role in the pathophysiology of cough syncope.
Patient A was an obese 59-year-old male with a history of smoking who had experienced eight episodes of transient loss of consciousness (TLOC) following coughing for 3 years. Physical examination revealed obesity [body mass index (BMI), 30 kg/m$^2$], a symmetrically low standing, hypokinetic diaphragm, and generally decreased respiratory sounds. There was no orthostatic hypotension, and there were also no clinical symptoms or signs of cardiovascular disease. An ECG did not reveal any abnormalities related to TLOC. During cardiovascular reflex assessment with continuous non-invasive blood pressure monitoring (BP, by Finapres, Finapres Medical Systems, Amsterdam, The Netherlands), coughing was followed by a decrease of systemic blood pressure and pre-syncopal complaints (Figure 1, left panel).

Patient B was a 58-year-old male with TLOC following bouts of coughing and sneezing. Apart from obesity (BMI, 28 kg/m$^2$), physical examination was unremarkable. An ECG was normal. During cardiovascular reflex assessment, a bout of spontaneous sneezing induced pre-syncopal complaints, associated with a decreased systemic blood pressure (Figure 1, right panel).

We performed a pulse wave analysis by Modelflow of the continuous blood pressure records in patients A and B. Modelflow is a model-based algorithm that computes the aortic flow waveform from the arterial blood pressure pulsation by simulating a non-linear, self-adaptive, three-element Windkessel model of the aortic input impedance.\textsuperscript{13} Modelflow computes stroke volume (SV) by calculating the time-integral of the flow pulse in systole. Subsequently, cardiac output is calculated as SV/HR. This approach provides reliable indexes (i.e. tracks the relative changes) of CO and total peripheral resistance (TPR) on a beat-to-beat basis.\textsuperscript{13,14}

The results of the pulse wave analysis are also shown in the figure. From these results it seems that after coughing CO is unchanged (or even increased), whereas total peripheral resistance is markedly decreased.

**Conclusion**

On the basis of these findings in two patients, we conclude that cough syncope could indeed (in part) be facilitated by a baroreflex-mediated fall in total peripheral resistance. Unfortunately, the clinical setting in which our results were obtained did not allow a baroreflex modulating intervention to investigate further this mechanism. However, our data do demonstrate that the findings of Dr Sharpey-Shafer on fore-arm vasodilatation triggered by a bout of coughing have indeed systemic consequences in cough syncope patients. Systematic studies are needed to confirm this mechanism in larger series of patients and to further test the baroreflex involvement.

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**Figure 1** Cardiovascular reflex assessment. BP, blood pressure; HR, heart rate; CO, cardiac output (arbitrary units); TPR, total peripheral resistance (arbitrary units). Left panel: patient A; right panel: patient B.
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