The history of diagnosing carotid sinus hypersensitivity: why are the current criteria too sensitive?

C.T.P. (Paul) Krediet1*, Steve W. Parry2, David L. Jardine3†, David G. Benditt4, Michele Brignole5, and Wouter Wieling6

1Department of Medicine, Academic Medical Center, University of Amsterdam, Meibergdreef 9, NL-1105-AZ Amsterdam, The Netherlands; 2Falls and Syncope Service and Institute for Ageing and Health, Newcastle University, Newcastle upon Tyne NE4 5PL, UK; 3Department of General Medicine, Christchurch Hospital, University of Otago, Christchurch, New Zealand; 4Cardiac Arrhythmia and Syncope Center, University of Minnesota, Minneapolis MN, USA; 5Department of Cardiology, Ospedali del Tigullio, Lavagna, Italy; and 6Syncope Unit, Department of Medicine, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

Received 17 June 2010; accepted after revision 10 August 2010; online publish-ahead-of-print 17 November 2010

The carotid sinus syndrome and carotid sinus hypersensitivity (CSH) are closely related disorders. The first is characterized by syncope triggered by manipulation of the carotid sinus in daily life (e.g. shaving). According to the current European Society of Cardiology guidelines, CSH is diagnosed when carotid sinus massage elicits ≥3 s asystole, a fall in systolic blood pressure of ≥50 mmHg, or both, with symptoms. The question is, however, whether symptoms can be expected when these criteria are met. Although they are widely accepted, we will show that their basis is primarily in arbitrary clinical observations and that in the original publications the link between classification and clinical symptoms was often dubious. The current criteria for CSH are thus too sensitive, explaining the reported high prevalence of CSH in the general older population. The review will conclude with suggesting a stricter set of criteria for CSH that should be evaluated in future studies.

Keywords

Syncope • Bradycardia • Hypotension • Pacemaker therapy • Testing

Introduction

The carotid sinus syndrome (CSS) and carotid sinus hypersensitivity (CSH) are closely related disorders. Carotid sinus syndrome is characterized by syncope triggered by manipulation of the carotid sinus in daily life; classically this is the result of manoeuvres such as shaving or fitting a tie. Bradycardia and/or hypotension can be triggered by carotid sinus massage (CSM) in these patients. Spontaneous carotid sinus syncope is rare (~1% in clinical series of patients with syncope).1 Carotid sinus hypersensitivity consists of bradycardia and/or hypotension triggered by CSM in patients without a typical history.

In the 2009 European Society of Cardiology (ESC) guidelines on the diagnosis and treatment of syncope, CSS and inducible carotid sinus syncope are used as synonyms encompassing the presence of CSH with the reproduction of spontaneous complaints on CSM in a syncope patient.2 Carotid sinus hypersensitivity is diagnosed when CSM elicits ≥3 s asystole (cardio-inhibitory type), a fall in systolic blood pressure of ≥50 mmHg (vasodepressor type), or both (mixed type).2,3 The 2009 ESC guideline states that ‘the diagnosis of CSS requires the reproduction of spontaneous symptoms during 10 s sequential right and left CSM performed supine and erect, under continuous monitoring of heart rate and periodic measurement of blood pressure (…).’ (italics added).2

The question is, however, whether symptoms can be expected to occur when the heart rate and blood pressure criteria for CSH are met. Although these criteria are widely accepted, in this review, we will show that they are based on arbitrary clinical observations from decades ago and have never been systematically evaluated. Furthermore, in the original publications, the link between classification and clinical symptoms was often dubious.

We provide an expert review of the historical backgrounds of current practice of diagnosing CSH, i.e. this is not a systematic review. A literature search was performed using Pubmed (search terms: CSH, carotid sinus syncope, and CSS) and by following up references from older reviews.4,5 Referenced papers were arbitrarily selected based on the relevance to the current review.
History of diagnosing carotid sinus hypersensitivity

Based on this historical review and current insight in the sequel leading to syncope (as recently reviewed), we will argue that the current criteria for CSH are too sensitive, and this may well be the underlying reason for the reported high prevalence of CSH in the general older population. It may also have contributed to the negative results of recent pacemaker trials in patients presenting with falls and a positive response to CSM. The review will conclude with proposing a stricter set of criteria for CSH that should be evaluated in future trials.

The review will only touch on the subjects of pathophysiology of CSH and its epidemiology as far as relevant to the diagnostic criteria. Therapy for CSH is the subject of an upcoming systematic review published elsewhere.9,10

History

The first blood pressure recording—albeit indirect—of CSH was published in 1866 by J.N. Czermak (1828–73), professor of physiology in Jena (Germany). He used E.-J. Marey’s (1830–1904) wrist sphygmograph, which was the first practical instrument to record the arterial pulse wave, continuously and non-invasively.11 Czermak12 documented that manual pressure on his right carotid artery at the upper margin of the sternocleidomastoid muscle provoked bradycardia and hypotension. Contrary to current concepts, Czermak assumed that direct mechanical stimulation of the adjoining vagus trunk by the bulb-like dilatation of the carotid artery was involved. Czermak was an eminent and highly respected scientist and during more than half a century Czermak’s ‘Vagusdruckversuch’ (vagus pressure test) was the prevailing name for the test to provoke circulatory effects induced by pressure on the carotid arteries, although experimental results which conflicted with this view were published (see for review).13 The issue was definitely settled by Heinrich Hering (1866–1948) professor of normal and pathological physiology at the University of Prague and later in Cologne. In 1905, Hering became interested in Czermak’s vagus pressure test when he provoked profound bradycardia by only a light touch of the rigid carotid artery of elderly women. He followed up his clinical observation with carefully designed studies in experimental animals. He demonstrated that vigorous manipulation of the exposed vagus nerve itself in anesthetized dogs and rabbits did not elicit cardiac slowing, but that very gentle massage of the carotid sinus did. Hering did not publish this work (started in 1905) until 1923 (for review see).14 Czermak’s interpretation was challenged and Hering15 renamed Czermak’s ‘Vagusdruckversuche’ in ‘der Karotisdruckversuch’ (the carotid pressure test). Hering’s work and that of his associate Koch,16 of Heymans and his associates (1929) and of Castro (1929) set the stage for studies on the pathophysiology of CSH in patients with syncope.5,13,17

Interesting clinical observations and case reporting can be found in the literature in the first half of the 19th century. Hering’s contemporary Wenckebach (1864–1940), a Dutch cardiologist who practiced in Vienna, attributed complaints of light-headedness while preaching to pressure of the vicar’s tight collar on a hypersensitive vagus nerve. A light touch of the carotid artery induced asystolic periods of 3 s in this patient. This observation published by Wenckebach in 1914 is probably the first clear clinical description of a spontaneous CSS with documented CSH (Franke18 referring to Wenckebach19). The susceptibility to carotid sinus syncope in older clergymen (who wore high tight collars and fainted while bending the head forward to read from the bible, or lifting the cross) was observed by other clinicians as well and became known the ‘ministers’ disease’ (for review).2 Other classical examples of the CSS from the older literature were syncope in the following situations: sitting in the dentists chair and bending the head back; driving a car and suddenly turning the head to look for traffic; dozing off sitting in a chair as the head fell forward; and when wearing a sling (for review see). In 1930, Roskam20 described fainting due to carotid sinus pressure during soaking and stretching the skin in the carotid area prior to applying the razor. Here Roskam also introduced the terminology ‘hypersensitivity’ (‘hyperreflective’ sic).

From the 1930s on, the CSS (with syncope) was being recognized as a separate entity from isolated CSH (i.e. without symptoms). In the landmark study by Weiss and Baker,21 an implicit distinction was made between subjects with syncope in daily life and those without, although both groups had a positive response to pressure on the carotid sinus region. Nathanson22 in 1946 was the first to explicitly emphasize the distinction between CSH (i.e. a positive CSM test) and CSS (i.e. syncope triggered by one of a set of typical manoeuvres in daily life such as shaving, head turning, fitting of a tie etc.).

The heterogeneity of carotid sinus provocation techniques

Although already in 1932 Mandelstamm and Lifschütz23 emphasized the need for uniformity in the technique of applying carotid sinus pressure, consistency in the method for testing for CSH remains problematic up to today.9 Morley and Sutton24 wrote the manual massage of the carotid sinus [is rather crude and subjective]. The problems [...] are: [...] duration of the applied stimulus, force of the stimulus, modality of the applied pressure, i.e. phasic massage or static pressure and the implications of carotid artery occlusion [...]. Indeed the literature on the CSM is highly heterogeneous on all these aspects. Also, there is heterogeneity in which physiological parameters were measured and how these measurements were to be done. Especially for earlier authors (up till the 1980s), it was technically not possible to measure heart rate and blood pressure continuously during the massage in a clinical or office setting. This applies especially to the large series on which reference values were based.21,23,25,26 We have to keep this in mind when attempting to apply their results to current practice in which continuous measurements are standard.27,28

Below we provide a summary of the manual technique for applying pressure to the carotid sinus in relation to duration, force, and modality as advocated by different seasoned clinicians and some miscellaneous remarks.

Mandelstamm and Lifschütz (1932)

With the patient lying supine and the head elevated, just overhanging a support and turned slightly to one side, the sinus was located at the angle of the jaw and at the upper border of the thyroid
cartilage. They used the thumb to press and used increasing levels of digital pressure depending on the effect, for a duration of 10–20 s. They pointed out that there was considerable variation in the precise location of the carotid sinus.

From their description, it becomes evident how laborious carotid sinus stimulation was in a time without a method of automated continuous blood pressure and heart rate measurements. They wrote: ‘[…] one of us would continuously measure the systolic and diastolic pressure [with cuff and stethoscope], another would measure the pulse continuously and the third would press the neck’. They showed clearly that carotid sinus reflex hypersensitivity was much more common in older than in younger subjects.23

**Weiss and Baker (1933)**

In the English body of literature, this is one of the most cited papers on the subject and considered a landmark by many.4,18 Among a larger series of hospitalized patients, the authors studied 15 patients, who (except two) complained of spontaneous attacks of dizziness and fainting, and in whom pressure of graded severity on the carotid sinus produced dizziness, fainting, or see-ning ‘convulsive seizures’. Interestingly, they only briefly noted that syncope occurred more quickly when the patient was standing than when supine, consistent with other authors.5,29 They emphasized that heart rate slowing occurred usually instantaneously when starting the massage, while the change in blood pressure was slower. This erroneous observation is likely to have been caused by the interval between blood pressure readings, since in continuous recordings (see Figure 1) an almost instantaneous fall in blood pressure is evident.

**Galdston et al. (1943)**

These authors were the first to make direct intra-arterial continuous blood pressure recordings (a technique that was only just becoming available) during pressure application over the carotid sinus (Figure 2).10 With this technique (and the use of atropine), they were able to show that cardio-inhibition and vasodepression often occurred simultaneously and that pure cardio-inhibitory syncope and pure vasodepressor syncpe were rare. In fact, in this small series (n = 26), they found no patients with pure vasodepressor syncpe.

**Lown and Levine (1961)**

These authors provided an in-depth review of CSM both for diagnostic and therapeutic purposes. Based on their clinical practice, they described how a gentle massage should be applied for no more than five seconds of stimulation; however, when mechanical compression lasting 10–40 s produces these attacks the mechanism is due to occlusion of the underlying carotid artery’. (Note that this reasoning does not consider blood flow via an intact circle of Willis.) In the studies by Morley et al.31,32 in the 1980s, the technique (although not the duration) as described by Lown and Levine was considered to be the standard.24

**Franke (1963)**

Franke’s monograph on CSH—although written in German—has a similar landmark standing as the paper by Weiss and Baker.10 For external stimulation of the carotid sinus, he advised to push some 10 but maximal 30 s carefully on the carotid sinus in the supine patient (‘wie bei einem schlüchternen Klingeldruck’, ‘like reluctantly, pushing a door bell’).5,18 When there is asystole for 2–3 s, the massage should be terminated immediately. He advised to repeat the test if it was initially negative, but in a ‘faster and more powerful’ way for another 30 s. He also remarked that longer than 40 s was never needed and that usually 15–20 s was enough to produce a positive result. ‘Faster’ may imply that the massage was indeed a phasic manipulation, but Franke did not explicitly say so. Franke measured blood pressure intermittently using sphygmomanometer cuff and stethoscope and an ECG recorder. He strongly advised against performing CSM in the sitting position to prevent cerebral ischaemia secondary to systemic hypotension.

**Takino et al. (1964)**

These authors are worth mentioning for introducing a device to quantify the pressure exercised on the carotid sinus during external stimulation in an attempt to standardize the CSM technique.33

---

**Figure 1** 78-year-old female patient with hypersensitive carotid sinus from Mandelstamm and Lifschitz. X-axis denotes minutes. Note the intermittent blood pressure (continuous line) and heart rate (intermittent line) registration and that while pulse is loss twice systolic blood pressure is thought to stay ~150 mmHg [reproduced with permission from (23)].
This was a modified ophtalmodynamometer after Baillart, which was basically a Newton meter, put under the massaging fingers. Their device remained buried in the literature, and no later publications appeared on the subject.

**Thomas (1969)**

Thomas wrote an often-cited review on the subject of CSH and described his technique as modified from Franke’s. His patients were also supine during the test. He first gently felt for the carotid sinus and then lightly pressed for 20 s (he did not mention whether this was static or phasic), while simultaneously verifying intact temporal artery pulsation throughout the test. If there was no response, he continued with longitudinal massage for 15 s. If there was still no response, the patients were studied in a sitting position. He remarked that ideally the test should be carried out under ECG control, but this was ‘impractical for routine bedside use’.

**Morley and Sutton, Kenny et al., and Brignole et al. (1980s to present)**

As already stated, in the studies by Morley and Sutton in the 1980s, the technique described by Lown was considered the standard. Kenny did her initial work on syncope with Sutton and used his technique (i.e. during 5 s in a supine patient) in her later studies on CSH. A positive response was defined as a ventricular pause of $\geq 3$ s and/or a fall in systolic blood pressure $\geq 50$ mmHg. These criteria showed a high diagnostic yield in elderly patients with syncope. However, a positive response was also present in 17–20% with no syncope. Subsequently, Brignole and co-workers demonstrated that the specificity of the CSM test was increased by also taking (pre-) syncope symptoms into account. They performed the test both while supine and upright and massaged for 10 s. The reason for 10 s (and not 5) was the idea that this would augment the vasodilator component as suggested in the older literature. The ESC Guidelines Taskforce on Syncope, chaired by Brignole et al., later introduced both Kenny’s and Brignole’s criteria into the 2001 ESC guidelines. After the 2004 ESC Guidelines on Syncope were published, Kenny and co-workers showed that in the general population $> 65$ years, the 95th percentile for CSM response was 7.3 s asystole and a 77 mmHg drop in systolic blood pressure. Using the traditional reference values, CSH was present in 39%.

**Neck chamber**

Attempts to standardize carotid sinus stimulation by the use of a neck collar device increasing stepwise pressure were undertaken during the 1950s, as recently elegantly reviewed by Cooper and Hainsworth. Although the technique was very popular in physiological research studies, it has not been adopted for routine clinical use. Reasons for this probably lay in the technically demanding and time-consuming nature of this device.

**Location of the carotid sinus**

There is one crucial aspect of the technique of CSM that received surprisingly little attention in all the above-mentioned literature: the variation of the location of the carotid sinus. The early authors tended to focus on a detailed description where the sinus is to be found: at the upper border of the thyroid cartilage, medial to the sternocleidomastoid muscle. Any subtle reference to anatomical variation (such as by) was not followed up by systematic research into the matter. Later authors mention that they localize the carotid sinus by identifying the point of maximum carotid pulsation. Two recent cadaver studies in elderly subjects, and an ultrasonography study in young subjects showed there is a considerable variation in the carotid artery anatomy (Figure 3). The level of the human carotid sinus may vary in cranial-caudal position by up to two cervical vertebrae. In some subjects, there was no bifurcation of the internal and external carotid artery at all. And within subjects, the level of the right and left sinus often differed. Another study showed that the transmission of externally applied pressure to the carotid sinus (by means of a pressure collar) may differ considerably depending on the anatomical location of the sinus.

The uncertainty of the exact location of the carotid sinus may explain the reported increase in blood pressure during carotid massage in some of the older studies (as pointed out by Weiss and Baker). The rise in blood pressure was likely caused by lowering internal sinus pressure by applying the external pressure...
three main types of haemodynamic responses were described: Lifschitz
doned the idea of a mixed response as posed by Mandelstamm and
there was always a dominant mechanism. They thereby aban-
the idea that there was always a dominant mechanism, they thereby aban-
heart reflexes' triggered by carotid sinus stimulation were often
Mandelstamm and Lifschitz had observed that the 'vessel-and
up-stream (i.e. caudally) to the sinus thus inducing baroreflex-

Classification
The classification of cardiovascular responses resulting from
pressure on the carotid sinus goes back to the 1933 paper of
Weiss and Baker. Their tests included both intravenous and
intramuscular application of atropine and epinephrine/ephedrine.
It must be said that both in their experimental set up and their
data interpretation they followed Mandelstamm and Lifschitz.
Mandelstamm and Lifschitz had observed that the 'vessel-and
heart reflexes' triggered by carotid sinus stimulation were often
simultaneous. But Weiss and Baker made a clear distinction
between several categories of carotid hypersensitivity implying
that there was always a dominant mechanism. They thereby aban-
doned the idea of a mixed response as posed by Mandelstamm and
Lifschitz.

Based on the idea that there was always a dominant mechanism,
three main types of haemodynamic responses were described:

(i) marked asystole or sudden slowing of the pulse, with or
without (sic) fall in the arterial pressure. This type of reaction
could be prevented by the use of atropine.

(ii) marked fall in the blood pressure without essential cardiac
slowing (<10 bpm). This type did not respond to the appli-
cation of atropine, but did to epinephrine.

(iii) marked pallor of the face followed by intense flush but
without essential slowing of the heart rate and without fall
in the arterial pressure. Neither epinephrine nor atropine
had any effect on these attacks. Weiss and Baker attributed
the fainting and convulsions in the latter group to reflex con-
striction, followed by dilatation of the cerebral vessels. In later
studies, this ‘cerebral’ type was abandoned. The symptoms
were then thought to result from mechanical interference
of carotid blood flow in patients with coexistent obstruction
of the other cerebral arteries.

The precise terminology of cardio-inhibitory and vasodepressor
responses was not used in the original publication by Weiss and
Baker although the categories were clearly set out. They rec-
commended performing pharmacological blockade interventions
to determine the dominant mechanism. In their 1936 paper,
they introduced the terms ‘cardio-inhibitory’ and ‘vasodepressor’
responses. Franke used a similar terminology in his monograph
(in German) published in 1963. He then reintroduced—30 years
after Mandelstamm and Lifschitz—a mixed-response group (‘kom-
binierter vagal-kardial-vasodepressorischer Typ’). The classification
has been around ever since.

This classification of the response to CSM into cardio-inhibitory
(asystolic), vasodepressor (isolated fall in systolic blood pressure
without bradycardia), and mixed subtypes gained wide acceptance
and is used in current international guidelines. The mixed
response is diagnosed when there is a combined asystole of
>3 s and a decline in systolic blood pressure of >50 mmHg on
rhythm resumption from the baseline values.

There are fundamental problems with this classification [i.e.
cardio-inhibitory (asystolic), vasodepressor (isolated fall in systolic
blood pressure without bradycardia), and mixed subtypes]. All authors who contributed significantly to the body of literature on
the clinical characteristics of the CSH up till the 1980s used cuff
and stethoscope to measure blood pressure. This measure-
ment technique needed (depending on the heart rate) usually at
least 10 s between different blood pressure measurements. This
explains how the concept of asystole without a fall in blood pressure
was introduced (Figure 1). However, it is evident that if the heart
does not pump, blood pressure will fall rapidly (Figure 2) and this
rapid fall is what is observed during continuous arterial pressure
measurements. In addition, several studies have shown that in the
cardio-inhibitory type of CSH, some degree of vasodepression can
be found in nearly all patients. In reality, all patients with CSH
lie on a spectrum of cardio-inhibition and vasodepression.

Reference values
As described above, the cut-off values used to identify patients
with CSH during laboratory testing (a systolic pause ≥3 s or a
fall in systolic blood pressure ≥50 mmHg) have been used for
decades. How these cut-off levels were derived is, however, not
widely known.

Source of 3 s pause criterion
Naturally, under physiological circumstances, asystole of 3 s (and
the corresponding heart rate of <20 bpm) is a rarity (although

Figure 3 Frequency distribution of right and left carotid sinus bifurcation location. Location of right and left carotid sinus bifurcation was measured from the gonion of the mandible (n = 95) and determined by Doppler ultrasound. Location of the right bifurcation was 3.2 cm (median 3.0 cm, range 0–6.5 cm) and the left bifurcation was 3.6 cm (median 3.5 cm, range 0–7.5 cm) below the angle of the mandible [reproduced with permission from (41)].
not unheard of). But this per se does not necessarily define a clinical disorder. In his oft-quoted review, Thomas attributed these reference values for CSH to the work of Franke. Franke himself clearly mentioned the pioneering work of Sigler as the starting point. Sigler performed CSM in a large number of his patients. In 1948, he published on the subjective manifestations of the hyperactive carotid sinus reflex in 1193 patients (750 males) aged 15–75 years with greater or less degree of cardiovascular disease, mainly atherosclerotic but predominantly without a history of syncope. Patients were arbitrarily divided in four groups according to the degree of cardio-inhibition. Grade 4 (marked slowing) was defined as a cardio-inhibition for at least 3 s. [This degree of cardio-inhibition was present in 245 of 1170 patients (25%).] His source for this cut-off value may be the 1933 paper by Weiss and Baker that included two patients (of total of 13 syncope patients) who were considered to have a pathological response to CSM having asystole durations of 3 s. This is likely to be the source of 3 s as the cut-off value to define a positive test.

**Source of the 50 mmHg criterion**

The vasodepressor type of CSH has traditionally received less attention than the cardio-inhibitory type. This may have an epidemiological background, but it is the technical limitations of detecting the vasodepressor component that was probably the more important determinant. Mandelstamm and Lifschitz used categories of blood pressure fall during carotid massage: 10–30, 30–60, and >60 mmHg and showed that young subjects (soldiers) never had a blood pressure response in the third category. Based on Sigler’s reports (who also refers to Mandelstamm and Lifschitz), Franke introduced 50 mmHg as a cut-off value for the fall in systolic blood pressure to define a positive response.

The availability of continuous methods for beat-to-beat blood pressure monitoring has improved insight into the blood pressure responses in CSH. Especially, the advent of non-invasive systems such as finger volume-clamp-plethysmography since the 1990s (i.e. Finapres technology BMI, Amsterdam, The Netherlands) had a major impact on the diagnostic work-up on syncope patients since it enabled routine measurement during CSM. Using this technology, Kerr et al. showed that in the general population >65 years, the 95th percentile for CSM response was drop of 77 mmHg in systolic blood pressure. The reproducibility of the vasodepressor response to CSM is unknown.

**Test characteristics**

In the absence of a gold-standard reference test, the test characteristics of CSM can only be derived from intervention studies. These are only available for cardio-inhibitory responses. Based on the positive effect of pacemaker therapy on syncope recurrence rate, in prospective open-label studies in patients with a cardio-inhibitory response (i.e. a relative risk reduction up to 85%, for review see Romme et al.), a good positive predictive value is assumed. On the other hand, the work by Kerr et al. who found a prevalence of 24% in the asymptomatic older population, the specificity is probably poor. Sensitivity is limited by the reproducibility of the cardio-inhibitory response, which may vary considerably (41–100% depending on subject selection, see for review). For the vasodepressor and mixed response, the test characteristics are unknown.

The low specificity of the current criteria for CSH may hamper selection for therapeutic interventions in trials and lead to wrong diagnoses in clinical practice. These over-sensitive criteria may also be the main reason for a recent, otherwise well-designed, double-blinded, randomized controlled trial to show no effect of cardiac pacemaker therapy in patients with carotid hypersensitivity and a history of falls.

**Figure 4** Relation between age and the prevalence of carotid sinus hypersensitivity [reproduced with permission from (5)]. The continuous line depicts the total number of subjects studied.
Complications

In the older literature, there are a number of case reports on severe complications, such as cerebrovascular events and ventricular tachy-arrhythmias.58–61 Based on these reports, the presence of carotid bruits (indicating severe carotid atherosclerotic disease), recent myocardial infarction, or any previous ventricular tachy-arrhythmia is considered a contra-indication for CSM. Prospective studies that used these contra-indications showed that CSM holds a minimal risk of (transient) cerebrovascular events, i.e. $\sim1:500–1000$.62,63 In these studies, no ventricular arrhythmias were reported.

Signs and symptoms

The signs and symptoms of syncope were recently reviewed and it is beyond the scope of this paper to discuss the details again.6 However, when trying to identify a cut-off point for asystole during CSM that is clinically relevant, it is critical to understand that the clinical sequelae depend on the duration of arterial hypotension, as an indicator of failing cardiac output, and causing cerebral hypoperfusion.

When the heart stops beating, mean arterial pressure starts to decline rapidly and reaches a level below 60 mmHg in 3–5 s (unpublished clinical observations). Because there is a lag-time of 3–6 s in the effect of sympathetic vasoconstrictor nerve activity, sympathetic withdrawal probably does not affect this blood pressure fall significantly. On resumption of ventricular contraction, blood pressure will increase progressively with each beat, but during the first few beats blood pressure may still be critically low. The typical overshoot in blood pressure that is present after an Adams-Stokes attack (e.g. non-reflex-mediated third degree block) is typically absent after resumption of ventricular action in carotid sinus syncope.64 This is likely to be caused by a low systemic resistance due to the already mentioned effector-lag-time of sympathetic activity.67

If cerebral blood flow is sustainably below 30–40 mL/100 mg brain tissue/min, cerebral functions are compromised.52 In an average 1500 mg brain, this is a flow of $\sim600 \text{ mL/min}$; normal perfusion (i.e. while supine) would be 1000 mL/min. So, cerebral function is compromised at a flow decrease of $\sim40\%$ (i.e. from 1000–600 mL/min). This is in full agreement with the observation that near-syncope occurs at an decrease of flow velocity in the cerebral medial artery—a relative measure for cerebral perfusion of 36%.64

In clinical practice, systemic blood pressure serves as a reliable surrogate for cerebral blood flow, which is seldom routinely measured. The systemic pressure at heart level, at which adequate cerebral perfusion fails is $\sim40–60 \text{ mmHg}$ while standing and 30–40 mmHg while supine, relating to the difference in the hydrostatic pressure column.68 This is why loss of consciousness after cardiac stand-still occurs more rapidly when the individual is standing (after $4–8\, \text{s}$) than when supine (after $\sim12\, \text{s}$).69 The time span from the start of critical cerebral hypoperfusion to loss of consciousness is known as ‘cerebral ischemic anoxia reserve time’.70 There are only a limited number of studies on this reserve time and they are all in healthy military personnel. However, they show that the cerebral anoxia reserve time may vary considerably (5–8 s).70 When the duration of cerebral hypoperfusion is shorter than the cerebral ischaemic anoxia reserve time (e.g. $<7\, \text{s}$), the event may go unnoticed. It may be accompanied by only non-specific cerebral complaints (e.g. ‘light-headedness’). Note that cerebral auto regulation fails to balance the fast occurring fall in blood pressure because of its lag time of $\sim5\, \text{s}$.71

This patho-physiological reasoning (i.e. relating the occurrence of symptoms to the duration of asystole) fits with the results of a study on the occurrence rate of spontaneous asystolic episodes during long-term follow-up in 23 patients with asystolic responses during laboratory-induced vasovagal reactions.56 During a total of 357 patient months of monitoring, asystolic episodes occurred in 17 patients. Only 12 of 1765 asystolic episodes of 3–6 s (0.7%) but 20 of 47 episodes of $\geq6\, \text{s}$ (43%) resulted in pre-syncopal or syncopal symptoms. In an ISSUE-2 substudy,72 the average pause at time of syncope (recovery) was of 9 s (range 8–18).

Revising the diagnostic criteria for carotid sinus hypersensitivity

Although small, this risk for cerebrovascular events necessitates a sound clinical indication for the CSM as dictated by the ESC Guidelines.2

Technique

As there are no controlled studies on the subject, the clinician should hold on to evolved ‘best practice’. Before starting the test, the absence of contra-indications (i.e. complications from previous massage, presence of carotid bruits, myocardial infarction or cerebrovascular accident in the previous 3 months, and any ventricular arrhythmia in the past) should be verified. To rule out a highly sensitive carotid sinus that would certainly lead to prolonged asystole while upright, massage of 5–10 s to each carotid sinus consecutively is executed while supine. Carotid sinus massage is first applied to the right carotid sinus, as CSH is more prevalent on the right than on the left side.18 Carotid sinus massage is performed by phasic rubbing with the thumb or index and middle finger over the carotid sinus with a frequency of $\sim1.5\, \text{Hz}$. If the test is negative, CSM is repeated while the patient is seated or head up tilted at an angle of 60–70°. On the occurrence of symptoms, CSM is terminated and the patient is returned to the supine position immediately. Diagnostic CSM should always be performed under continuous ECG and blood pressure (i.e. beat-to-beat) monitoring.

Criteria

The currently accepted cut-off values for CSH have important limitations (see Table 1). Based on the patho-physiological reasoning discussed above, we suggest the following criteria should be evaluated in future studies. These criteria include that CSM is positive if it triggers an asystole of $\geq6\, \text{s}$ or a fall in mean arterial pressure below 60 mmHg lasting for $\geq6\, \text{s}$. These values are based on current best evidence (Table 1), but may be challenged during prospective evaluations to come. The patient should also report similarity to the spontaneous clinical symptoms. This
'method of symptoms' appears to have a good specificity and is able to predict efficacy of cardiac pacing, indicating high specificity. However, the predictive values of this new set of criteria for CSH should be systematically evaluated in future studies.

### Conclusion

The current quantitative criteria for CSH are based on multiple, mainly small older studies that are hampered by the technical limitations of their time. In particular, inability to record simultaneous continuous ECG and blood pressure recordings prevented careful assessment of the frequency and magnitude of CSM effects in patients and large numbers of control subjects. Additionally, the studies that we have relied on exhibit considerable heterogeneity in terms of the method of carotid sinus manipulation. As a result, we believe that the current diagnostic criteria for CSH are excessively sensitive and thereby encompass many false-positive test results. We recommend that new diagnostic criteria for CSM—for which we have made a suggestion based on current best evidence—be tested prospectively before being introduced in the ESC guidelines.

### Conflict of interest

none declared.

### Funding

This work was supported by funds from the Amsterdam Pathophysiology of the Circulation Foundation to C.T.P.K. and D.L.J.

### References


