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Neurocardiogenic Syncope
Aetiology and Management

Kostas A. Gatzoulis and *Pavlos K. Toutouzas*

University Department of Cardiology, Hippokration General Hospital, Athens, Greece

Contents

Abstract

Neurocardiogenic syncope is the most common cause of syncope presenting in the outpatient setting. It is usually encountered among individuals without an underlying heart disease, but not uncommonly participates in the syncope mechanism of patients with an obstructive or an arrhythmic cardiac cause for syncope as well. The vasovagal event is caused by a transient profound hypotensive reaction most commonly associated with inappropriate bradycardia resulting from activation of a complex autonomic reflex. The pathophysiology of neurocardiogenic syncope has been elucidated by tilt table testing, a noninvasive and well-tolerated method for reproducing the event in susceptible individuals.

Although the majority of people with vasovagal fainting need no specific treatment, treatment is required for those presenting with problematic features such as frequent events accompanied by trauma or accidents, and occasionally by a severe cardioinhibitory pattern response. A number of different drugs have been proposed to favourably act on different aspects of the neurocardiogenic reflex but only a few randomised, placebo-controlled, drug-specific trials are currently available. Alternatively, cardiac pacing has also been introduced for patients who have symptoms that are drug-refractory or for those with a severe cardioinhibitory hypotensive response.

The selection of the appropriate treatment plan should be individualised after consideration of patient history, clinical characteristics and preference, results of the baseline tilting study, and the existing evidence from the few randomised, controlled studies performed so far.

Neurocardiogenic syncope is the most common and most benign cause of transient loss of consciousness in the outpatient clinical setting.[1,2] A number of terms have been used in recent years to describe the common faint or its variants. Thus, neurally-mediated, neurovascular, vasodepressor, vasomotor, vasovagal or malignant vasovagal syncope as well as situational syncope are terms used for a common reflex syncope mechanism characterised by a rather sudden and transient withdrawal

of the sympathetic tone with a concurrent parasympathetic discharge after a preceding period of sympathetic overactivation.[3-6]

Individuals experiencing such a syncope spell are commonly young and otherwise healthy, although similar vasomotor reactions are also known to occur in the elderly and in patients with systemic diseases or an underlying heart disease.[7,8]

As the term implies, neurocardiogenic syncope results from activation of a complex neurocardiovascular reflex initiated by stimulation of a variety of more or less unknown peripheral chemical and/or mechanical receptors transmitting sensory impulses through autonomic afferent fibres to the cardiovascular control centre in the medulla where central modulation through poorly understood mechanisms occurs.[9,10] The result is a sudden response mediated through efferent autonomic fibres to the vessels and the heart leading to the most dramatic hypotensive reaction observed in human beings. It appears that the transient cardiovascular collapse is predominantly due to an intense peripheral loss of the arterial tone, most commonly associated with a bradycardic reaction.[11] However, at times, the cardioinhibitory component may predominate, with well described instances of long asystolic events or complete heart block.[12,13]

It is likely that central modulation as well as the efferent limb of the reflex are common in most vasovagal syncope spells, as clinical observation suggests by the marked similarity of the hypotensive response patterns observed, whether purely cardioinhibitory, vasodilatory or, most commonly, mixed.[14,15] However, it is likely that a rather diverse category of peripheral or even central receptors may be responsible for activating this, at times, 'self-defensive' neurocardiogenic reflex. This explains the multiplicity of terms used to describe the 'common fainting' reaction under different clinical circumstances. Indeed, although the most commonly implicated receptors are the low pressure mechanoreceptors in the left ventricle, vasovagal syncope has been induced in denervated heart transplant recipients during head-up tilt-table testing (TTT).[9,16,17]

Furthermore, we do know that the clinical circumstances surrounding the vasovagal event are diverse. In individuals in whom fainting is common, apart from orthostasis and a preceding period of emotional or physical stress, a sudden increase in the stress burden presented by pain, sight of blood, fright or a distressful thought, are the most common triggers for syncope. A vasovagal presyncope spell is not unusual in the catheterisation laboratory when the patient is facing an 'unfriendly' environment, although he or she is in the horizontal position without volume shifts to the lower body. In situational syncope, it is possible that the activation of different mechanoreceptors distributed among the airways, the intrathoracic cavity, or the gastrointestinal or genitourinary tract, may lead to syncope during a corresponding diagnostic or therapeutic procedure, but may also lead to cough, deglutition, micturition or defecation syncope.[18-23] Activation of the high pressure carotid mechanoreceptors may lead to a different and distinct form of syncope in patients presenting with the carotid sinus syndrome.[24] Thus, it appears that there is an overlap between different forms of reflex syncope reactions with a variety of afferent stimuli activating a rather similar neurocardiogenic response in susceptible individuals.

Although in most patients with neurocardiogenic syncope a well defined clinical trigger is present followed by preliminary warning symptomatology related to an overactivated sympathetic state, not uncommonly we do encounter patients with vasovagal syncope where such triggers and preceding symptoms are lacking. It is under these circumstances that the differential diagnosis becomes extremely important in order to rule out other life-threatening causes of syncope. Even in such patients, a limited non-invasive cardiological evaluation including a 12-lead electrocardiogram, a 24-hour Holter recording, echocardiography and TTT will usually establish the diagnosis.[25-27] Further exploration of a probable arrhythmic cause of syncope is occasionally required in the electrophysiology laboratory or through long term recordings via implantable devices, whereas the com-

monly applied extensive neurological evaluation is most often nonproductive.[28,29]

Neurally-mediated reflexes play a significant pathophysiological role in the syncope mechanism, even in patients with an underlying cardiovascular disease such as idiopathic hypertrophic cardiomyopathy, aortic valvular stenosis, pulmonary embolism or coronary artery disease, conditions characterised by acute loading or ischaemia of the left or the right ventricle. It has also been demonstrated in patients with syncopy that neurocardiogenic syncope is commonly induced with head-up TTT in those who also have sick sinus syndrome as well as occasionally in those with induced tachycardias during the electrophysiology study.[30-32] Thus, even among patients with syncopy who have an obstructive or an arrhythmic cardiac cause for syncope, namely patients with a poor long term prognosis, the vasovagal component may contribute decisively to the mechanism causing transient cerebral hypoperfusion.

1. Role of Head-Up Tilt-Table Testing

TTT has been extensively used worldwide over the last decade for the evaluation and management of the patient presenting with syncope of unknown aetiology in the absence of organic heart disease.[6,14,15,25,26,33] Indeed, it is an excellent tool for establishing the diagnosis of neurocardiogenic syncope with a good safety record. Its application makes unnecessary further unrevealing and expensive testing in those patients where the syncope remains unexplained after a limited initial work up in the outpatient setting.[29] Furthermore, it can potentially be a guide for therapy either through the selection of medications preventing the induction of neurocardiogenic syncope on repeat testing or by identification of the occasional patient with predominantly cardioinhibitory vasovagal syncope that may benefit from cardiac pacing.[34-38]

The role of TTT as a prognostic tool among patients with unexplained syncope is under investigation. Although it has been suggested that of the patients with unexplained syncope, those with a negative baseline TTT have a lower recurrence rate, this observation has recently been questioned.[34,39,40] The reliability of the test to induce the clinical event rather than a nonspecific laboratory reaction is supported by the marked similarity of the premonitory symptomatology followed by the same sequence of hypotension and bradycardia response, which is preceded by similar hormonal changes during both the induced and the spontaneous syncope spell.

As a research tool, TTT has markedly improved our understanding of the biochemical events involved in the mechanism of neurocardiogenic syncope. Thus, during tilting and the induced overactivated sympathetic state, adrenaline (epineprine) levels are elevated in association with modest elevation in cortisol, adrenocorticotrophic hormone and prolactin levels.[6,41-43] During the syncope attack, a marked elevation of vasopressin and β-endorphin levels has also been documented.[44,45] Heart rate variability studies during tilting suggest potentiation of both parasympathetic and sympathetic nervous system activity before the induced syncope event, when probably an intense vagal response is the result of 'accentuated antagonism'.[46,47] In the genesis of the profound hypotensive response during syncope, vasodilatory substances such as nitric oxide and prostaglandins may participate.[48,49]

As a clinical tool, TTT has a number of limitations related to its sensitivity, specificity and reproducibility of inducing a vasovagal response in susceptible individuals. Indeed, the methodology of TTT has not been standardised and remains a matter of debate.[50-52] Various protocols have used different angles and duration of tilting, with or without a number of provocative drugs employed to improve the sensitivity of the test, most commonly at some considerable expense of its specificity.[6,14,15,26,33] Furthermore, in a significant proportion of patients who commonly faint, the TTT remains negative.[39,40] Thus, it is advisable for each electrophysiological laboratory to establish one or two tilting protocols after defining their sensitivity and specificity before screening larger patient populations.

2. Drug Treatment

The vast majority of vasovagal syncope episodes are sporadic and easily recognisable by the preceding symptoms and signs in the appropriate clinical environment. Thus, the occasional occurrence of transient loss of consciousness in the individual facing a painful experience, whether somatic or psychological, especially when it is accompanied by warning symptoms in the absence of physical, electrocardiographic and echocardiographic findings of an underlying heart disease, needs no further assessment or specific therapy.[53] However, there is a rather small subset of individuals presenting with truly worrisome features. The neurocardiogenic syncope may be recurrent, not be preceded by warning symptoms or signs, occasionally be accompanied by physical trauma such as cranial injury or accident, or in extremely rare cases be so dramatic that it may even require resuscitative efforts.[33,54] Occasionally, a severe cardioinhibitory response during tilting in the form of a long asystolic pause is elicited. This type of severe vasovagal syncope has been termed 'malignant', even though the long term prognosis of patients remains good.[12,40]

The management of such severely affected patients is challenging and specific measurements should be undertaken. Even among these seriously affected patients, important questions about their management have not yet been answered. How long should they be treated for? What is the true efficacy of various drugs prescribed? How well are these drugs tolerated in otherwise healthy individuals? What is the compliance rate among patients prescribed these drugs? Should we carefully follow up these patients to exclude other important causes of syncope not being recognised in the first place?

Retrospective observations among individuals who have recurrent untreated frequent syncope suggest that the likelihood of recurrence is higher among those presenting with numerous syncope spells over a relatively short period of time.[55] Thus, we could hypothesise that certain individuals with vasovagal fainting present with some form of exacerbation caused by a persistent autonomic nervous system instability. It is also noteworthy that when such patients with recurrent common fainting received thorough medical attention, including a detailed noninvasive examination and tilting studies, they improved clinically with a marked drop in the syncope burden occurring during follow-up without specific medical treatment.[55] It could be argued that a psychological 'white coat' placebo effect may play an important role in the natural history of these patients.

Apart from the general, mostly educational measures, including reassurance about the non–life-threatening nature of the episodes, recognition of the oncoming spell and avoidance of triggering events, a number of medications have been utilised to prevent recurrent vasovagal events in patients with severe neurocardiogenic syncope attacks.[56] The medications used include agents aiming to modify different aspects of the neurocardiogenic reflex such as β-blockers, disopyramide, theophylline, selective serotonin reuptake inhibitors (SSRIs), scopolamine, various peripheral vasoconstrictors, or salt- and fluid-retaining agents such as fludrocortisone.[6,33-37,57-64] The selection of the initial medication to be used will depend upon the clinical characteristics of the patient, such as the concurrent presence of relative bradycardia, relative hypotension or hypertension, and psychological profile.

The drug effectiveness can be 'acutely' tested with a repeat TTT before longer term therapy is prescribed.[34,37] In a large retrospective study, the usefulness of serial drug tilting studies was suggested by a lower long term recurrence rate among patients with vasovagal syncopy in whom drug therapy prevented the reinduction of syncope on repeat TTT as opposed to those in whom drug therapy either was not given or was prescribed empirically without serial tilting studies.[34]

However, the usefulness of this approach has been questioned by others.[37] Furthermore, it should be emphasised that the usefulness of serial drug tilting studies has not been demonstrated in prospective, randomised trials so far.

In patients with recurrent syncopy, a second or even a third agent is commonly prescribed. A number of early non-controlled, small trials have consistently demonstrated a beneficial effect of such drug therapy based on both repeat TTT as well as long term clinical follow-up data. The most commonly used β-blockers included metoprolol, atenolol and pindolol, while SSRIs recently used included fluoxetine, paroxetine and sertraline.[6,34,36,57,58,65] Peripheral vasoconstrictors studied were etilefrine, ephedrine, dihydroergotamine mesylate, methylphenidate and midodrine, the latter agent showing a better tolerance rate.[35,66,67] However, it should be emphasised that only a few placebo-controlled trials have been performed so far (table I).[59,62,68-70] It is remarkable that in 2 of the 5 trials, no drug benefit was demonstrated.[62,69] In the other 3 drug trials, using atenolol, paroxetine and midodrine, a consistent drug benefit was shown but with a rather limited follow up period of 1 month in two of them.[59,70] The long term drug tolerance rate, with the exception of one disopyramide study, was acceptable, with the adverse effect profile not being significantly different from the placebo effect. It is clear that well designed, drug-specific, larger, randomised, placebo-controlled studies are necessary in order to define the most effective drug treatment plan for those selected patients with severe and/or recurrent neurocardiogenic syncope.

3. Pacing Therapy

In most patients, neurocardiogenic syncope results from a mixed type of hypotensive response due to vasodilatation associated with a relative bradycardia. A predominant cardioinhibitory response pattern in the form of long asystolic pauses or even complete heart block has been repeatedly documented both in the clinical setting and, more commonly, in the electrophysiological laboratory.[12,13] In the mixed type of vasovagal response, the hypotension usually precedes the bradycardic component followed by a more profound blood pressure drop when the bradycardia enters the picture a few seconds later. Atropine administered intravenously frequently aborts the loss of consciousness by preventing the bradycardic component of the reflex, even though this does not usually completely restore the hypotensive component of the attack.[71]

It is on the basis of such observations that cardiac pacing was proposed to prevent the vasovagal syncope attack by treating the bradycardic component of the event.[72,73] Indeed, cardiac pacing is highly effective in neurally-mediated reflex syncope situations where the cardioinhibitory component of the response predominates, such as in patients with carotid sinus syndrome.[74] By appropriate dual chamber cardiac pacing during carotid sinus massage, the syncope spell is aborted with a minimal and clinically unapparent fall in arterial blood

Table I. Randomised, placebo-controlled drug trials in patients with neurocardiogenic syncope

Reference	Pts (n)	Active drug (dosage)	Follow up (mo)	Negative short term TTT results (drug *vs* placebo)[a]	Long term effectiveness (active drug *vs* placebo)[b]	Reported adverse effects (drug *vs* placebo)
Morillo et al.[62]	22	Disopyramide (200mg bid)	30	73% *vs* 82% (NS)	73% *vs* 70% (NS)	8/11 (drug discontinuation)
Mahanonda et al.[59]	42	Atenolol (50-100mg)	1	62% *vs* 5% ($p < 0.0004$)	71% *vs* 29% ($p < 0.02$)	None
Ward et al.[70]	16	Midodrine (5mg tid)	1	62.5% *vs* 12.5% ($p < 0.01$)	68.7% *vs* (?)	'Minor'
Di Girolamo et al.[68]	68	Paroxetine (20mg qid)	25 ± 8	61.8% *vs* 38.2% ($p < 0.001$)	62.4% *vs* 47.1% ($p < 0.0001$)	'Severe' (1 pt)
Raviele et al.[69]	126	Etilefrine (25mg tid)	12	52% *vs* 45% (NS)	76% *vs* 76% (NS)	17/63 *vs* 13/63 (NS)

a Prevention of reinducing syncope on repeat tilt-table testing.

b Prevention of syncope recurrence during long term treatment.

bid = twice daily; **mo** = months; **n** = number; **NS** = not significant; **pts** = patient; **qid** = four times daily; **tid** = three times daily; **TTT** = tilt table testing.

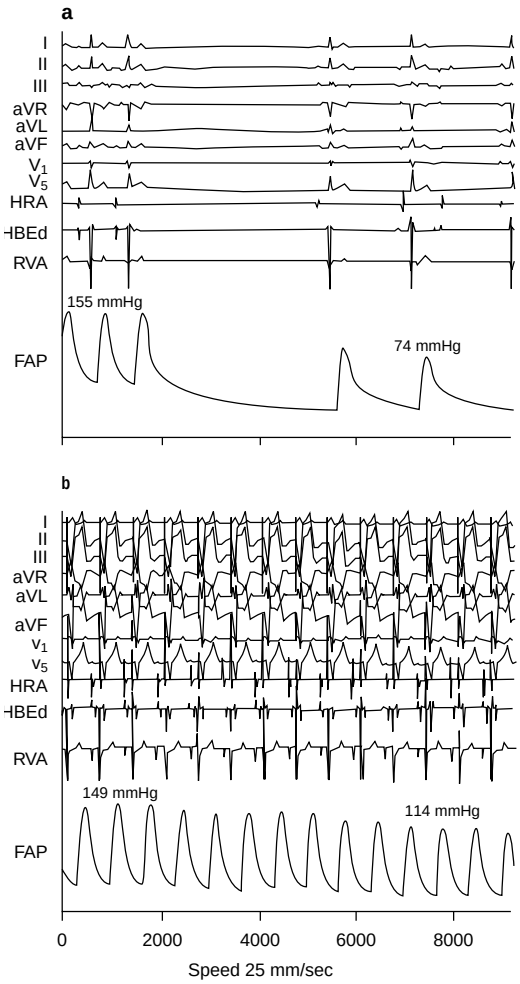

Fig. 1. 67-year-old patient with recurrent syncope in the absence of organic heart disease. (**a**) During left carotid sinus massage, presyncope is reproduced in the horizontal position as a result of a 4-second pause followed by bradycardia and relative hypotension. (**b**) When repeating the left carotid sinus massage during dual chamber (DDD) pacing at 90 beats/min, the presyncope symptoms are prevented by aborting the bradycardic component of the reflex although there is still an insignificant fall in the systolic blood pressure. From top to bottom, surface leads I, II, III, aVR, aVL, aVF, V_1 and V_5 followed by intracavitary electrograms from the high right atrium (HRA), the distal His bundle site (HBEd) and the right ventricular apex (RVA) with concurrent recording of the right femoral arterial pressure (FAP).

pressure resulting from the associated vasomotor component of the reflex (fig. 1). However, whenever the vasomotor component of the vasovagal syncope reflex predominates, such pacing treatment may be ineffective or, at best, partially effective, giving the patient the opportunity to lie down before losing consciousness.[57]

Early non-controlled trials suggested a beneficial effect of cardiac pacing in patients with recurrent vasovagal syncope and either a mixed or mostly a predominant cardioinhibitory pattern response during TTT.[57,72,75] In these non-randomised trials, the mode of cardiac pacing was important. Thus, the dual chamber (DDI) pacing mode with a rate hysteresis feature was more effective for ameliorating the recurrent syncope episodes than the single ventricular chamber (VVI) mode.[75] Although the prevention of presyncope or syncope spells was not always possible with pacing therapy, both the frequency and the severity of recurrent attacks was significantly improved as judged by repeat TTT and the long term clinical follow up.

An even better clinical result has been obtained with the incorporation of a rate drop response feature in newer dual chamber pacemakers.[76,77] When the pacemaker recognises a sudden and significant drop in heart rate occurring over a short period of time, it responds with dual chamber pacing at a programmable high rate for few minutes to treat the presumed bradycardic component of the imminent vasovagal event. This pacing system was tested in the only prospective, randomised pacing in vasovagal syncope study available so far.[78] It is interesting that this pacing therapy proved effective in preventing recurrent syncope episodes in patients with a very heavy vasovagal syncope burden, patients in whom the baseline TTT induced mostly a mixed rather than a severe cardioinhibitory hypotensive pattern response. Although the syncope recurrence was significantly reduced during follow up, that of presyncope was not significantly affected. The study suggests that although pacing during the vasovagal event does not prevent the vasodilatation-related premonitory symptoms of the attack, it does protect the patient from true loss of consciousness by treating the associated bradycardic component.

Before this study became available, patients with mostly cardioinhibitory neurocardiogenic

syncope were considered a class II indication for pacing by the American and the British Heart Societies.[74,79] However, there are still some considerations regarding pacing therapy in patients with recurrent vasovagal syncope. Most of these patients are relatively young and otherwise healthy, and frequently reluctant to accept a foreign-body dependency for the rest of their life. Indeed, the issue of implanting a pacemaker for a relatively benign medical condition, such as vasovagal syncope, is not that simple when the need for replacement and the risk for device-related complications in the long run are taken into account. Consideration should be given to the patient with so-called malignant vasovagal syncope presenting with the worrisome features described in section 2. Thus, the current potential candidates are only those who are extremely symptomatic and have symptoms refractory to other conservative or drug treatment measurements, or those selected patients with rather few but severe cardioinhibitory vasovagal events.

4. Conclusions

Neurocardiogenic syncope is the most common cause of syncope, usually presenting as a sporadic event in otherwise healthy individuals. The transient loss of consciousness is due to a severe hypotensive response resulting from activation of a complex neurocardiogenic reflex incorporating various receptors and the autonomic nervous system controlling the peripheral vascular tone and the impulse-generating and conducting system of the heart. Specific therapy needs to be instituted for those selected patients with recurrent or severe cardioinhibitory vasovagal syncope attacks. A number of different drugs have been successfully used to prevent recurrent vasovagal syncope, mostly in small, uncontrolled trials. Cardiac pacing has also been proposed as an alternative form of therapy for those patients with severe neurocardiogenic syncope when drugs are ineffective or whenever the cardioinhibitory component of the reflex leads to dramatic symptoms. Before selecting the optimal mode of treatment for the patient seriously affected by vasovagal syncopy, the history, the results of the baseline TTT, the clinical profile, and the lack of large volume, randomised, drug-specific or pacing in vasovagal syncope trials so far all need to be taken into account.

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Correspondence and offprints: Dr *KA Gatzoulis*, Fragogianni 34, GR-156 69 Papagos-Athens, Greece.