

## Vasovagal Syncope and Vasovagal Disease

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Key words:

**Vasovagal, syncope, dysautonomia.**

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**I**solated vasovagal syncope (VVS) is not a disease, but rather the clinical manifestation of an autonomic reflex to which all (or almost all) individuals are predisposed. Why certain subjects appear to be more susceptible than others to the development of paradoxical hypotension and bradycardia, and why the event occurs at one time and not another, remain largely unknown. Isolated VVS should be distinguished from vasovagal disease, in which VVS appears as an expression of a pathological process mainly related to a generalised involvement of the autonomic nervous system. Learning to differentiate these two forms has important therapeutic consequences.

### Isolated (classical) VVS

Classical VVS is mediated by emotional or orthostatic stress and can be diagnosed by history taking.<sup>1</sup> It is diagnosed when precipitating events such as fear, severe pain, emotional distress, instrumentation or prolonged standing are associated with typical prodromal symptoms.<sup>1</sup> Classical VVS generally starts at a young age, yet natural histories are extremely various; some subjects experience only a single episode over the course of their lives while others have frequent episodes. In the vast majority of subjects, classical VVS is not associated with cardiovascular, neurological or other diseases, and therefore classical VVS constitutes an isolated manifestation: "Isolated VVS". Vasovagal syncope is benign and

very common; although it is difficult to estimate, it is likely that up to 50% of all individuals experience a loss of consciousness at some time during their lives. Most of these have only one or a few episodes.<sup>2</sup>

Isolated VVS should be considered a *physiological phenomenon* for two main reasons:

1) *Vasovagal susceptibility is probably present in all healthy humans.* Even if the clinical manifestation, i.e. syncope, occurs in about half of individuals during their lives, a vasovagal susceptibility is probably present in all healthy humans from their youth. This assertion is supported by several data:<sup>2</sup>

- Head-up tilt testing is used to assess individual susceptibility to VVS. Nevertheless, up to 50% of asymptomatic healthy subjects show a positive response to head-up tilt testing when strong stressors are used. Positivity is particularly high in healthy asymptomatic children. Adding this percentage to that of syncopal patients, a vasovagal susceptibility can be evidenced in about 75% of the general population.
- Haemorrhagic shock can trigger a situation similar to VVS. The volume loss caused by haemorrhage results in hypotension and a fall in venous return, which can lead to inappropriate sympathico-inhibition and a subsequent paradoxical response characterised by a further fall in blood pressure, associated with bradycardia. This vasovagal reaction, which is probably secondary to a strong trigger, such as a severe reduction in venous re-

turn, can be observed in subjects with no history of syncope.

- Astronauts are selected on the basis of their great resistance to orthostatic and gravitational changes. Despite this selection, about 20% experience presyncope, and some experience manifest bradycardia syncope during upright posture on the day of landing after a short-duration space flight. This has been attributed to central remodelling, which is a transient dysfunction of central integration of baroreflex afferent input due to the fact that during weightlessness the central nervous system receives no baroreceptor input to counter upright posture.

Thus, an autonomic reflex which is potentially triggered in the vast majority of individuals cannot be regarded as a pathological disorder.

2) *Blood pressure regulation outside the episodes of syncope is normal.* Isolated VVS subjects are generally normotensive and have normal blood pressure regulation outside the episodes of syncope.<sup>2</sup> In general, the behaviour of blood pressure during the first minutes of head-up tilt testing before the beginning of vasovagal reaction is similar in VVS subjects and in control subjects without a history of fainting. Contrary to general belief, subjects with VVS do not have an increased vagal tone during everyday life, suggesting that a generalised state of autonomic involvement is not present in these individuals. Many hormonal factors, such as serotonin, adrenaline, arginine, vasopressin,  $\beta$ -endorphins, adenosine and galanin, have been supposed to have a role in eliciting VVS. However, a causal role of these hormonal factors – and an abnormality of hormonal function – has never been definitely demonstrated.

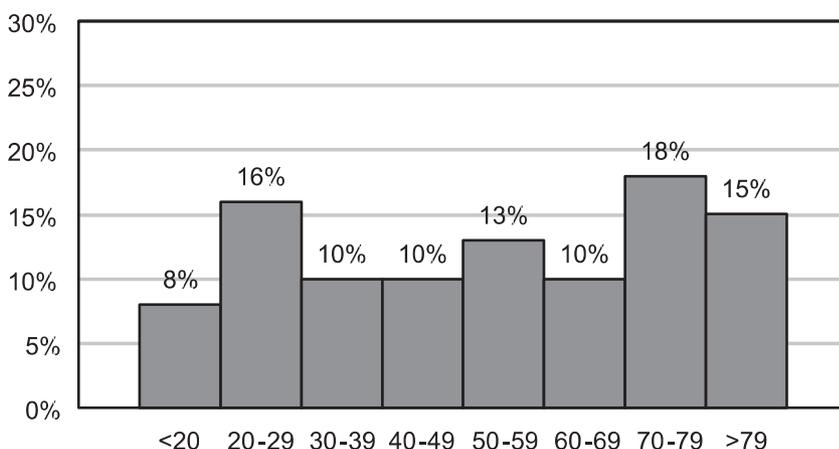
To summarise, isolated VVS seems to be not a disease, but rather the clinical manifestation of an au-

tonomic reflex present in all (or almost all) individuals. The reasons why VVS is more likely to occur in specific subjects or at specific times are still unclear.

### Vasovagal disease

The classification of the causes of syncope used by the Task Force on Syncope of the European Society of Cardiology includes some forms of non-classical VVS which are diagnosed on the basis of minor clinical criteria, exclusion of other causes of syncope (absence of heart disease), and a positive response to head-up tilt testing.<sup>1</sup> Examples of non-classical VVS include episodes without (or with minimal) triggering events or prodromal symptoms.

1) *Vasovagal symptoms begin in advanced age in diseased patients.* It is known that the clinical manifestations of VVS change significantly in older subjects and that medical history has a limited value in establishing the cause of syncope in older people.<sup>3</sup> In the EGSYS 2 study<sup>4</sup> the age of onset of VVS in 190 subjects admitted urgently to hospital was  $52 \pm 23$  years.<sup>2</sup> This study involved a population-based sample of consecutive patients referred to the emergency department, a sample which was biased only by access criteria. Their age distribution showed that the age of onset was distributed throughout life, peaking at the age of 20 and after the age of 70 years (Figure 1). In subjects in whom VVS starts in old age, loss of consciousness cannot be regarded as an isolated manifestation, as it is frequently associated not only with cardiovascular or neurological diseases, but also with other dysautonomic disturbances, such as carotid sinus hypersensitivity, post-prandial hypotension, progressive orthostatic hypotension and symptoms of au-



**Figure 1.** Age at onset of vasovagal syncope in 190 patients in the EGSYS 2 study.<sup>4</sup> The age of onset is distributed throughout life, peaking at the age of 20 and after the age of 70 years.

tonomic dysfunction (abnormal sweating, abnormal thermoregulation, etc.).<sup>5,6</sup> Even though VVS starting in old age shares the same pathophysiological mechanism of hypotension –bradycardia with isolated VVS both during head-up tilt testing and during documented spontaneous syncope– these findings should be regarded as an expression of a pathological process mainly related to a generalised involvement of the autonomic nervous system or, more generally, to aging processes. Vasovagal disease starting in old age progressively worsens over time and major injuries are frequent,<sup>7</sup> mainly when prodromes are lacking. In this regard, a specific therapy is often needed.

2) *Blood pressure regulation outside the episodes of syncope is frequently abnormal.* Apart from the frequent association with hypertension, a progressive orthostatic hypotension is commonly seen in these patients because of age-related impairment in baroreflex-mediated vasoconstriction and chronotropic responses of the heart, as well as deterioration of the diastolic filling of the heart.<sup>8</sup> The cerebral hypoperfusion caused by hypotension leads to an inability to tolerate the standing position and causes significant impairment of the quality of life, mainly because of dizziness, presyncope, weakness and palpitations.

In summary, VVS starting in old age appears to be an expression of a disease.

The clinical features of isolated VVS and of vasovagal disease are summarised in Table 1. Although this subdivision engenders the risk of over-simplification, since several intermediate forms are present, it may nevertheless be useful for practical purposes.

### Practical implications

Patients who seek medical advice after experiencing an isolated (classical) VVS require reassurance and education regarding the nature of the disease and the avoidance of triggering events. In general, education and reassurance are sufficient for most patients and no specific therapy is generally warranted in most subjects. Non-pharmacological “physical” treatments are emerging as a new front line treatment of vasovagal syncope. In highly motivated patients with recurrent vasovagal symptoms, the prescription of progressively prolonged periods of enforced upright posture (so-called “tilt-training”) may reduce syncope recurrence. However, this treatment is hampered by the low compliance of the patients in continuing the training programme for a long period.<sup>9</sup> Some recent clinical trials<sup>10-12</sup> have shown that isometric counterpressure manoeuvres of the legs (leg crossing), or of the arms (hand grip and arm tensing), are able to induce a significant blood pressure increase during the phase of impending vasovagal syncope, which allows the patient to avoid or delay losing consciousness in most cases.

On the other hand, in patients affected by vasovagal disease, modification or discontinuation of hypotensive drug treatment for concomitant conditions and avoidance of triggering situations are often the first line measures for the prevention of syncope recurrences. Treatment is not necessary for patients who have sustained a single syncope and are not having syncope in a high risk setting. Additional treatment may be necessary in high risk or high frequency settings when syn-

**Table 1.** A comparison of the clinical features of isolated vasovagal syncope and vasovagal disease.

Isolated vasovagal syncope	Vasovagal disease
<p>Differences:</p> <ul style="list-style-type: none"> <li>• Onset at a young age</li> <li>• Otherwise healthy people</li> <li>• Typical vasovagal prodromes/triggers (“classical” form)</li> <li>• Affects about 50% of all individuals</li> <li>• 70% of population predisposed</li> <li>• Strong stressor</li> <li>• No genetic basis</li> <li>• No evidence of autonomic involvement or hormonal disorders</li> <li>• Low risk of trauma</li> <li>• Frequent spontaneous disappearance in advanced age</li> </ul>	<ul style="list-style-type: none"> <li>• Onset in old age</li> <li>• Patients with cardiovascular or neurological disease</li> <li>• Presentation without prodromes/atypical triggers (“non-classical” form)</li> <li>• Often diagnosed only after a positive head-up tilt test</li> <li>• Overlap with carotid sinus syndrome</li> <li>• Overlap with situational syncope</li> <li>• Overlap with orthostatic hypotension or other dysautonomic symptoms</li> <li>• High risk of trauma</li> <li>• Sometimes progressively worsening over time</li> </ul>
<p>Similarities:</p> <ul style="list-style-type: none"> <li>• Similar hypotension-bradycardia mechanism</li> <li>• Similar rate of positive responses during tilt testing</li> <li>• Similar rate of cardioinhibitory and vasodepressor forms during spontaneous syncope</li> </ul>	

cope is very frequent, i.e. alters the quality of life, or syncope is recurrent and unpredictable (absence of premonitory symptoms) and exposes patients to a “high risk” of trauma. In these latter situations, a careful investigation of the relative importance of the cardioinhibitory and vasodepressor components of the reflex is mandatory before embarking on specific treatment. Lower limb compression bandaging is effective in avoiding orthostatic systolic blood fall and reducing symptoms in elderly patients affected by progressive orthostatic hypotension. Home treatment based on self administered elastic leg stockings seems feasible, safe, and is well accepted by most patients.<sup>8</sup> Cardiac pacing appears to be beneficial in VVS patients who also have carotid sinus hypersensitivity and, although only one relatively small randomised controlled trial has been undertaken, pacing is acknowledged to be the treatment of choice when bradycardia has been documented.<sup>1</sup> The role of cardiac pacing for vasovagal disease in the absence of carotid sinus hypersensitivity is not yet established. It seems that pacing therapy might be effective in certain, but not in all patients. This is not surprising if we consider that pacing is probably efficacious for asystolic reflex but has no role in combating hypotension, which is frequently the dominant reflex in neurally-mediated syncope. A recent study using the implantable loop recorder as reference standard<sup>7</sup> showed that only about half of the patients had an asystolic pause recorded at the time of spontaneous syncope. A new strategy of treatment with cardiac pacing delayed until proper documentation of the mechanism of syncope is established –limited to those patients who had asystole at the time of syncope– proved to be very effective. It reduced syncopal recurrence rate by 90% to an absolute value of 5% at one year.<sup>7</sup>

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