

Therapy of vasovagal syncope: to prevent the vasovagal reflex or to treat the impending reflex?

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Vasovagal syncope (VVS) can be classical (typical) or non-classical (atypical). Classical VVS is diagnosed when precipitating events, such as emotional or orthostatic triggers, are associated with typical autonomic prodromes.¹ If triggers and/or prodromes are not present, VVS is defined as non-classical. The mechanisms of VVS have not been completely elucidated. Our knowledge of the afferent part of the vasovagal reflex (i.e. the step from trigger to autonomic control and central processing) is very limited. In contrast, the efferent part of the reflex is quite certain: hypotension and bradycardia are due to transient inhibition of the sympathetic system and to more or less marked activation of the vagal system, respectively.

Treatments of VVS do not appear to be very effective, although some encouraging results have been published.² Moreover, it is not always easy to understand how the positive results have been obtained, i.e. whether through *prevention of the vasovagal reflex* or through *treatment of the impending reflex*. In this regard, a 'cocktail' of recommendations and treatments is often prescribed which can act in accordance with both strategies. In medicine, prevention and therapy generally represent, at least from a conceptual point of view, two different approaches; however, with regard to the treatment of VVS, there is some confusion in the current literature. In order to investigate this aspect thoroughly, we should analyse the vasovagal reflex.

VVS is often considered a characteristic of humans, since emotional or orthostatic loss of consciousness is not (or extremely rarely) observed in animals. Actually, the vasovagal reflex (hypotension and bradycardia) has been observed in humans and other mammals during hemorrhagic shock. The trigger of the vasovagal reflex appears to be the same during hemorrhagic shock and orthostatic stress (prolonged standing, tilt testing), i.e. thoracic hypovolaemia which activates the afferent pathways. Interestingly, the efferent part of the vasovagal reflex seems to be the same in humans during orthostatic stress and in animals during hemorrhagic shock, i.e. a transient withdrawal of the sympathetic system, as shown by the sudden fall in blood pressure and by

micro-neurographic recordings, and an increase in vagal tone, as shown by the slowing of heart rate.³ This means that the orthostatic vasovagal reflex is predisposed not only in humans but also in other mammals. A typical vasovagal reflex (sudden decrease in both blood pressure and heart rate) has been observed in the cat in an emotional situation, i.e. when preparing to fight in response to an attack by another cat.⁴ A similarity can be seen between the reflex in the cat, which is mediated by emotional distress, and emotional VVS in man, even though the cat does not lose consciousness. Moreover, an 'alarm bradycardia' has been observed in some species of all classes of vertebrates (fishes, amphibians, reptiles, birds, mammals) during tonic immobility, when the animal is suddenly attacked by a predator. The animal is alert, as shown by electroencephalographic recording. A vagal response to fear/threat represents an *atypical response*, since the common response to fear is an increase in heart rate. There are similarities in the physiological mechanisms responsible for bradycardia during emotional VVS in humans and 'alarm bradycardia' in animals.³ All these data show that the vasovagal reflex is not a characteristic of humans. Accordingly, classical VVS should be regarded as a response which originated in the ancient past within some ancestral group(s) of vertebrates.³ If the vasovagal reflex has persisted for millions of years throughout the evolutionary history of vertebrates, we can reasonably assume that it is not dangerous; otherwise, it would have been eliminated by natural selection. On the contrary, it is very likely that this reflex plays a role: since it is sporadically displayed, a possible role as a defence mechanism for the organism appears likely, in particular for the heart. Indeed, during emotional or orthostatic stress, the heart works under stressful and possibly dangerous conditions, mainly because of an increase in myocardial oxygen demand. Inhibition of the sympathetic system, together with the activation of the vagal system, may constitute a beneficial break of the cardiac pump, thereby reducing myocardial oxygen consumption and permitting better diastolic filling and coronary perfusion, even if blood pressure decreases.^{3,5} However, there is an important difference

between humans and other animals; man loses consciousness, whereas animals do not. Recently, van Dijk⁶ offered a possible explanation based on some anatomical and physiological traits that evolved recently in the human lineage, i.e. acquisition of the erect position and the development of a large brain. The former, which is responsible for venous pooling in the lower extremities, facilitates thoracic hypovolaemia, which can activate the vasovagal reflex; the latter, through the increase in cerebral metabolic demand, can more easily induce cerebral hypoperfusion severe enough to elicit the loss of consciousness. In other words, the vasovagal reflex originated hundreds of millions of years ago, whereas loss of consciousness represents a recent complication of this reflex. Loss of consciousness is obviously undesirable because of the psychological consequences, risk of trauma and lifestyle limitations that it implies.

These considerations suggest that the enemy to fight is not the vasovagal reflex per se, but the complication of this reflex, i.e. the loss of consciousness. In subjects with classical VVS, some measures, such as assuming the supine position and carrying out physical counter-pressure manoeuvres, can prevent loss of consciousness when the vasovagal reflex is already activated. This is possible because the prodromal symptoms last long enough to allow the subject to implement these manoeuvres. However, in many subjects, VVS starts in old age, is generally non-classical (without triggers or autonomic prodromes) and is frequently associated with other autonomic disturbances, mainly carotid sinus hypersensitivity. Whereas classical VVS appears to be a selected evolutionary trait, the VVS that starts in old age seems to be related to the emergence of a pathological process of the autonomic nervous system that is not yet well defined in nosology.⁷ In these subjects, because of the absence of prodromal symptoms, the above-mentioned measures to prevent loss of consciousness when the vasovagal reflex is activated cannot be effective. At present, the only possible treatment to counteract the impending reflex is pacemaker implantation in selected patients. Therefore, in most patients with non-classical VVS, we should act on the afferent part of vasovagal reflex, i.e. we should try to prevent this reflex. Some recommendations and treatments are commonly proposed which should act upon this mechanism; however, they have not been thoroughly investigated and the level of evidence of their efficacy is generally C¹ (Table 1). Avoidance of prolonged standing and of hot crowded environments, volume expanders and tilt training should prevent the orthostatic vasovagal reflex. Moderate exercise training has proved to be effective in some small non-controlled trials; this may act upon the same mechanism by increasing blood volume and muscle tone.⁸ Other treatments may act on the afferent part of the vasovagal reflex (or on central processing); indeed, in some small studies, psychological therapy has been seen to reduce syncopal recurrences in subjects with anxiety and/or depression.⁹ Paroxetine, which reduced syncopal recurrences in a small randomized trial,¹⁰ probably also acts on the afferent pathways and/or central processing.

With regard to the therapeutic approach to VVS, i.e. prevention of the vasovagal reflex or treatment of the impending reflex, midodrine appears to be a promising treatment. This drug is a potent peripherally acting pure $\alpha-1$ agonist and has proved effective in

Table 1 Recommendations and treatments of vasovagal syncope

Prevention of the vasovagal reflex	Treatment of the impending vasovagal reflex
Avoidance of prolonged standing	Assumption of supine position
Avoidance of hot crowded environments	Physical counter-pressure manoeuvres
Hydration, salt intake	Pacemaker implantation
Moderate exercise training	Midodrine?
Tilt training	Withdrawal of vasodilator agents?
Psychological therapy	
Paroxetine	
Midodrine?	
Withdrawal of vasodilator agents?	

the prevention of VVS recurrences in small studies.¹¹ It exerts its effects on $\alpha-1$ adrenergic receptors of the arteriolar and venular musculature, producing vasoconstriction and venoconstriction, respectively. Midodrine may therefore play a therapeutic role by promoting venoconstriction, which reduces venous pooling, thereby preventing the vasovagal reflex, or by promoting vasoconstriction, which could counteract the fall in blood pressure when the reflex is already activated. The mechanism of action of this drug is not yet clear, although the first hypothesis appears more likely. The same considerations can be made with regard to the withdrawal of vasodilator drugs, which facilitate the occurrence of VVS.¹²

In conclusion, non-classical VVS is difficult to treat for two main reasons: (i) as prodromal symptoms are often absent or very short, there is no time to counteract the impending vasovagal reflex, and (ii) as the triggers are not identifiable, we cannot give adequate recommendations and treatments to prevent the reflex. Ongoing studies are trying to improve our knowledge on the triggers and the afferent pathways of the vasovagal reflex and new pathophysiological knowledge could suggest new treatments. In my opinion, in order to optimise future developments, it is important, in the fight against loss of consciousness, to make a distinction between the concept of preventing the vasovagal reflex and that of treating the impending reflex, an aspect which is somewhat confused in the current literature.

Conflict of interest: none declared.

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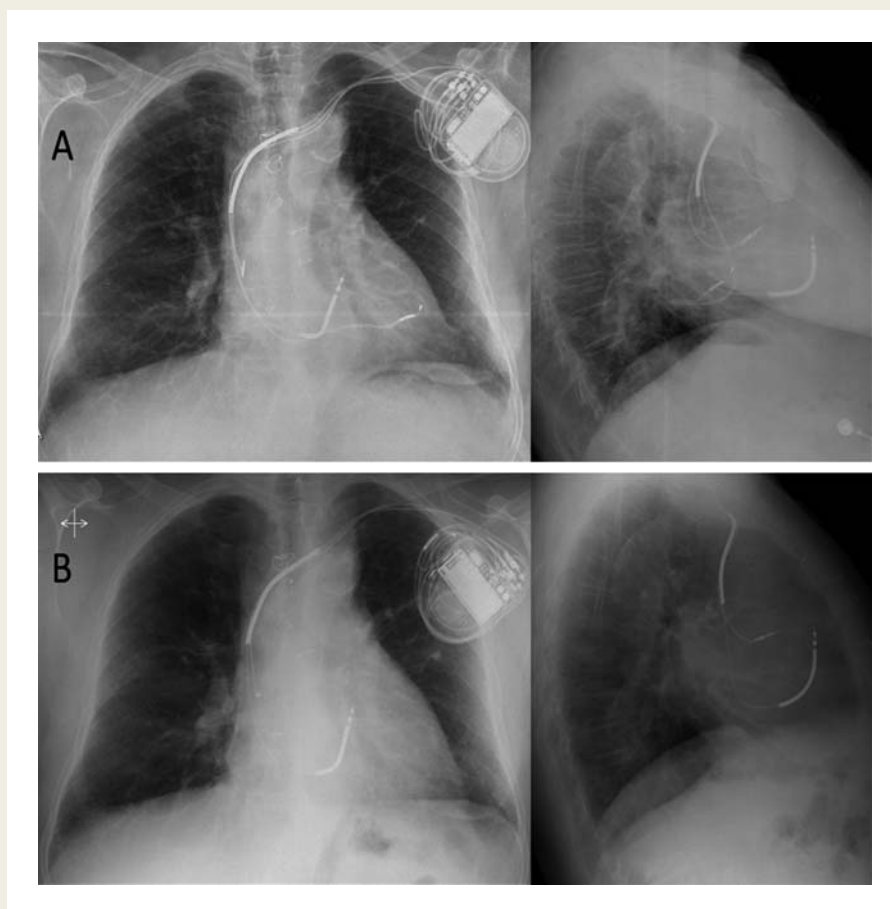
An unusual case of cardiac resynchronization therapy non-responder: the reel syndrome

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A 62-year-old man with ischaemic cardiomyopathy complained of an increase of basal dyspnoea. A CRT-D (Medtronic InSync III Marquis, Minneapolis, MN, USA) was implanted 7 months ago. The leads were inserted without complication through the left subclavian vein and secured with a non-absorbable ligature to the fascia. The generator was not sutured to the pectoral fascia. The patient had been better since the device was implanted, but in the last 3 months had worsened. A radiograph of the chest demonstrated a displacement of the left ventricular lead (Medtronic Attain 4194, 88 cm, Minneapolis, MN, USA), with winding of the lead around the pacemaker box, which presented an horary rotation (Panel A: pos CRT-D implantation; Panel B: left lead dislocation). When he was interrogated he referred a spontaneous twist of the box 3 months ago. Spontaneous displacement of the pacemaker lead due to the rotation of the generator on its transverse axis is known as the 'reel syndrome'. An insufficient fixation of the leads/generator may contribute to it. In this case, the rotation of the generator (not secured to the fascia) resulted in reeling in of the pacemaker lead. The box and a new lead were fixed securely and carefully without complications.



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