Expert Perspectives

An Update on the Treatment of Vasovagal Syncope

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The results of several recently published trials have changed our approach to the treatment of vasovagal syncope. In this article the most important results are discussed and an evidence-based treatment is proposed.

Initial and additional treatments

In general, the initial "treatment" of all forms of neurally-mediated reflex syncope comprises reassurance as to the benign nature of the syndrome, education regarding avoidance of triggering events and predisposing factors, recognition of premonitory symptoms and manoeuvres to abort the episode, the avoidance of volume depletion and prolonged upright posture. The above measures are sufficient for the vast majority of patients affected by vasovagal syncope.

Additional treatment may be necessary in high risk or high frequency settings which have been defined by the ESC Task force on Syncope[1] when:

- syncope is very frequent, i.e. alters the quality of life
- syncope is recurrent and unpredictable (absence of premonitory symptoms) and exposes patients to a "high risk" of trauma
- syncope occurs during the prosecution of a "high risk" activity (e.g. driving, machine operation, flying, competitive athletics, etc.)

Management of recurrent vasovagal syncope by means of isometric counterpressure manoeuvres

Isometric arm and leg exercises are able to increase blood pressure during the phase of impending vasovagal syncope. The patients trained in their use will be able to enact physical manoeuvres and relieve symptoms in most cases of occurrence of symptoms of impending syncope during their daily life.

Background

During the prodromal phase of vasovagal syncope, blood pressure falls markedly; this fall usually precedes the decrease in heart rate, which may be absent, at least at the beginning of this phase. Hypotension is caused by vasodilatation in the skeletal muscles, due to inhibition of sympathetic vasoconstrictive activity. Acute tilt studies[2,3] have shown that isometric manoeuvres of the arms or of the legs are able to induce an abrupt significant blood pressure increase during the phase of impending vasovagal syncope, which is already evident after 10 s, and allow the patient to avoid or delay losing consciousness in most cases.

This effect seems to be mediated largely by sympathetic nerve discharge and an increase in vascular resistance during the manoeuvres and by mechanical compression of the venous vascular bed in the legs and abdomen. Consequently, symptoms of impending syncope disappear in many patients or remain unchanged in others, and syncope is aborted even when the patient remains in the standing position.

Instruction in counterpressure manoeuvres

Three manoeuvres have been validated.

Arm-tensing consists of the maximum tolerated isometric contraction of the two arms achieved by gripping one hand with the other and simultaneously abducting (pulling apart) the arms.

Handgrip consists of the maximal voluntary contraction of a rubber ball (of approximately 5-6 cm diameter) held in the dominant hand for the maximum time tolerated or until the complete disappearance of symptoms.

Leg crossing consists of leg-crossing combined with maximal tensing of leg, abdominal and buttock muscles.

Patients are instructed to maintain the manoeuvre they choose as long as possible and eventually move on to a second manoeuvre if useful. A session protocol (maximum duration of 1 hour) consists of: explanation of purpose and session-program; explanation of simple physiology and vasovagal reflexes; demonstration and explanation of the 3 manoeuvres; practising of the 3 manoeuvres using beat-to-beat blood pressure recordings and electrocardiographic monitoring as biofeedback signals.

Practical results

Non-pharmacological "physical" treatments are emerging as a new first choice treatment in patients who have vasovagal syncope preceded by prodromal symptoms and age <65 years. This approach seems to be very helpful in real life. In 2 follow-up studies,[2,3] the manoeuvres were self-administered by these patients in >95% of cases and were able to abort syncope in >95% of patients. No patients had injury or other adverse morbidity related to the relapses. The treatment was easy to perform, reliable, safe and well accepted by the patients, who expressed a high degree of satisfaction.

Drug therapy for vasovagal syncope

Evidence for therapy of vasovagal syncope is in general weak. Many drugs have been used in the treatment of vasovagal syncope (beta-blockers, disopyramide, scopolamine, clonidine, theophylline, fluorocortisone, ephedrine, dihydroergotamine, etilefrine, midodrine, serotonin reuptake inhibitors, enalapril). In general, while the results have been satisfactory in uncontrolled trials or short-term controlled trials, the majority of long-term, placebo-controlled, prospective trials have been unable to show a benefit of the active drug over placebo.

Beta-blockers

Beta-adrenergic blocking drugs have failed to be effective in 5 of 6 long-term follow-up controlled studies.[4-9] Atenolol proved to be ineffective in preventing syncopal recurrences in a well-designed, double blind, randomised, controlled trial.[7] As regards this latter, both tilt positive and tilt negative patients with a history of a median of 3 episodes of vasovagal syncope were randomised to receive 50 mg/day of atenolol or placebo. In the intention-to-treat analysis there was a trend towards a better outcome in patients treated with placebo ($p=0.09$), especially in the tilt-negative subgroup. Adverse events occurred more frequently in the active arm patients ($p=0.05$). Thus the evidence fails to support beta-blocker efficacy.

In vasovagal syncope beta-blockers, owing to their negative inotropic effect, have been supposed to lessen the degree of mechanoreceptor activation associated with an abrupt fall in venous return and to block the effects of elevated circulating adrenaline, but this theory has not been supported by facts. A rationale for the use of beta-blockers is lacking in the other forms of neurally-mediated syncope and they may be detrimental in dysautonomic syndromes. Beta-blockers may enhance bradycardia in carotid sinus syndrome and in all other cardioinhibitory forms of neurally-mediated syncope.

Alpha-agonists

Since failure to achieve proper vasoconstriction of the peripheral vessels is common to all forms of neurally-mediated syncope, several vasoconstrictive substances have been employed, but only etilefrine and midodrine have been evaluated by means of a randomised, controlled trial. Etilefrine proved to be

ineffective in preventing syncopal recurrences in one arm of the large, multicentre, double blind Vasovagal Syncope International Study (VASIS).[10] The 126 patients had had a median of 4 syncopal episodes during the previous 2 years and had a positive response to tilt test. During the follow-up the patients were treated with etilefrine or placebo 25 mg twice a day; syncope recurred in 24% of patients and in 24% of controls and the time to first syncopal recurrence was also similar (106 days etilefrine versus 112 days placebo). Thus, the evidence fails to support etilefrine's efficacy.

Midodrine - at a dose of 5-15 mg t.i.d. - seemed to be effective in reducing symptoms (syncope and presyncope) and improving quality of life (evaluated by standardised questionnaires) during the short term in 2 small, open label, controlled trials[11,12] involving patients affected by very frequent "hypotensive" symptoms (>1 syncope/month). The spontaneous symptoms were reproduced during a tilting test, which showed a dominant vasodepressor response. Although defined as "neurocardiogenic", the clinical features of the patients of these studies seem different from those of the typical vasovagal syncope and of the VASIS-like patients and probably overlap with some forms of orthostatic hypotension. Vasoconstrictor drugs are potentially more effective in orthostatic hypotension caused by autonomic dysfunction than in the neurally-mediated syncopes. Midodrine was thoroughly investigated for orthostatic hypotension and was shown to be an effective treatment in some randomised, controlled trials.[13,14] Thus, available data are insufficient to prove an efficacy of midodrine for typical vasovagal syncope. Orthostatic hypotension and vasovagal syncope are two different syndromes: while midodrine is an effective treatment for orthostatic hypotension, the data to support its use in vasovagal syncope are far less compelling.

Miscellaneous drugs

Paroxetine (serotonin reuptake inhibitor) has been shown to be effective in one placebo-controlled, open-label trial[15] which included a small number of highly symptomatic patients in one institution, but failed to show a significant effect on baroreflex control of sympathetic nerve activity in a double-blind, randomised, 6-month follow up study performed in healthy subjects.[16] Until the study is confirmed by others, use of this drug cannot be recommended.

Transdermal scopolamine was ineffective for the prevention of neurally-mediated syncope in a randomised, placebo-controlled evaluation performed in 60 patients:[17] during follow up syncope recurred in 79% of patients with scopolamine and in 75% of patients with placebo.

Clonidine was not superior to metoprolol in one study.[18]

Finally, no follow up randomised controlled trials exist for disopyramide, enalapril, theophylline, fluorocortisone, ephedrine, and dihydroergotamine.

Conclusion

The evidence fails to support the efficacy of beta-blocking drugs. To date there are not sufficient data to support the use of any other pharmacological therapy for vasovagal syncope.

Pacemaker for vasovagal syncope: good for few

The decision to implant a pacemaker needs to be kept in the clinical context of a benign condition which frequently affects young patients. Thus, cardiac pacing should be relegated to the choice of last resort in a very select small proportion of patients affected by severe vasovagal syncope. How to select these patients still remains partially uncertain. According to the ESC Guidelines,[1] cardiac pacing may be reserved for those patients with cardioinhibitory vasovagal syncope with a frequency >5 attacks per year or severe physical injury or accident and age >40.

Pacing for vasovagal syncope has been the subject of five major, multicentre, randomised, controlled trials:[19-23] three gave positive and two gave negative results. Putting together the results of the 5 trials, 318 patients were evaluated; syncope recurred in 21% (33/156) of the paced patients and in 44% (72/162) of the non-paced patients ($p<0.0001$). However, all the studies had weaknesses and further follow up studies addressing many of these limitations (particularly the pre-implant selection criteria of the patients who might benefit from pacemaker therapy) need to be completed before pacing can considered an established therapy.

It seems that pacing therapy might be effective in some, 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 va-

sovagal syncope. How to stratify the patients is still uncertain. A recent study using the Implantable Loop Recorder as reference standard[24] showed that only about half of the patients had an asystolic pause recorded at the time of spontaneous syncope, which might eventually benefit from a pacemaker. In the other patients a pacemaker is unlikely to be effective. The role of the Implantable Loop Recorder for selecting patients who may benefit from cardiac pacing is currently under evaluation.

A widely used method for selecting patients as candidates for cardiac pacing is the finding of a cardioinhibitory form during tilt testing. Nevertheless, recent data showed that the mechanism of tilt-induced syncope was frequently different from that of the spontaneous syncope recorded with the Implantable Loop Recorder.[24] These data show that the use of tilt testing for assessing the effectiveness of different treatments has important limitations and its use is now disregarded in the ESC Guidelines.[1]

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