

Treatment of Reflex Syncope

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Abstract

This review assesses the role of all types of therapy for reflex syncope including physical counter-measures, diet, behavior, drugs and implantable devices. There are no drugs currently demonstrated to have convincingly beneficial effect by randomized controlled trial. However, provided that the patient experiences warning of an impending attack physical counter-measures are demonstrably effective. Implantable cardiac pacemakers have a role in a carefully selected minority of patients with vasovagal syncope. Pacing, dual chamber of cardio-inhibitory Carotid Sinus Syndrome is the treatment of choice. Modification of lifestyle in terms of fluid, caffeine and salt consumption is necessary in many cases but has little scientific background. Educating and reassuring the patient is an important part of management. The patient must understand that attacks are not as dangerous as they might seem in most cases and learning to anticipate those permits evasive measures.

Keywords: Reflex syncope; Physical counter-measures; Drug-treatment; Vasovagal syncope; Carotid sinus syndrome; Pacemaker-treatment

Introduction

Syncope is the most common form of Transient Loss of Consciousness (TLOC). By definition syncope has rapid onset, complete loss of consciousness and postural tone. It is of brief duration and is associated with speedy and complete recovery. Its cause is cerebral hypoperfusion, itself usually occurring when the blood pressure is very low [1]. TLOC includes other conditions such as epilepsy, which will not be the subject of this communication. The causes of syncope are illustrated in Table 1, where it will be seen that Reflex syncope is the most common and that this may be subdivided into vasovagal syncope, otherwise known as fainting, Carotid Sinus Syndrome and situational syncope. Perhaps surprisingly, Orthostatic hypotension is next most common but it must be emphasized that the greater portion of these patients are those suffering from over-medication for hypertension and thus, iatrogenic disease. Only at third place come Cardiac Rhythm disturbances with obstructive cardiopulmonary lesions least common. The commonness of Reflex syncope justifies the focus of this article.

Carotid Sinus Syndrome is defined as Syncope with positive Carotid Sinus massage yielding not only bradycardia and/or hypotension but also simultaneous reproduction of symptoms, i.e., syncope or pre-syncope. Carotid Sinus massage is performed over the Carotid artery at the level just above the thyroid cartilage for 10 s. It should not be occlusive to the artery. Today, this is best performed on the tilt-table with beat-to-beat blood

Reflex	OH	Arrhythmic	Struct	CP dis
VVS	Iatrogenic	Brady	AS	PHBP
CSS	Primary ANF	Tachy	HCM	Ao Diss
Situational	Secondary ANF		PE	
60%	15%	10%	5%	
Undiagnosed 10%				

The percentage line illustrates current understanding of the incidence of each cause of syncope

Abbreviations: VVS: Vasovagal Syncope; CSS: Carotid Sinus Syndrome; OH: Orthostatic Hypotension; ANF: Autonomic Nervous System Failure; Brady: Bradycardia; Tachy: Tachycardia; Struct: Structural; Dis: Disease; CP: Cardiopulmonary; HCM: Hypertrophic Obstructive Cardiomyopathy; PE: Pulmonary Embolism; PHBP: Pulmonary Hypertension; Ao Diss: Aortic Dissection

Table 1: Causes of Syncope.

pressure monitoring and the ready ability to perform the massage both supine and upright separately on each carotid [1].

Situational syncope is syncope associated with body processes involving a high-degree of autonomic nervous system adjustment. Examples of Situational syncope are the losses of consciousness associated with cough, laugh, sneeze, micturition, defaecation etc. Table 2 offers a classification of Situational syncope [2].

Reflex syncope has a shared pathophysiology wherein lies the challenge that is its therapy. There are two facets of this pathophysiology: cardioinhibition mediated via the vagus nerve and vasodepression probably mediated by sympathetic tone withdrawal dominantly in the splanchnic bed but also widely spread throughout the body. These complex autonomic changes happening almost simultaneously present major therapeutic difficulties. Further, it must be emphasized that attacks are not frequent in any of the clinical syndromes described above posing a problem for drug administration that is necessary every day but will only stand to protect the patient occasionally. In Vasovagal

Resp	Cough Sneeze Laugh Wind instrument playing Weight lifting
GI	Swallow Defaecation Post-prandial
GU	Micturition Orgasm

Abbreviations: Resp: Respiratory; GI: Gastro-Intestinal; GU: Genitourinary

Table 2: Classification of Situational Syncope.

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syncope 6 attacks per year represents a very high frequency of attack [3]. Many medicines are untenable on the basis of side-effects when they are needed to act perhaps only once or twice per year.

Other considerations for pharmaceutical agents are that warning of an impending attack, if present, is quite brief and often less than two minutes making any kind of 'as required' medication ineffective. Lastly, many of those who suffer vasovagal syncope are young females and even drugs with some effect have not been subjected to teratogenic studies and again are untenable for this reason without effective contraception.

Pharmaceutical Agents

There is probably no drug that acts on the cardiovascular system that has not been tried to prevent vasovagal syncope. The medical literature, not just the cardiology literature, abounds with anecdotal reports of many drugs having positive effects in the control of syncope but when subjected to Randomized Controlled Trials (RCTs) all of these drugs are disappointing and some are proven to be ineffective. In the 1980s and 1990s beta-blockers received favorable reports but as soon as trials were done they demonstrably lacked effect. This aspect has been thoroughly reviewed in the recent past [1,4]. When the actions of beta-blockers are considered against the pathophysiology of syncope it is to be expected that they would be ineffective. The possible mode of action could be by blocking the sinus tachycardia that seems to trigger attacks in some vasovagal patients. This sinus tachycardia has been shown to be caused by a rise in catecholamines prior to an attack [5]. Beta-blockers could be administered in a tolerable dose to prevent this tachycardia. Unfortunately, there has been no trial to date that has selected specifically these patients. A second possible action is to modulate the triggering of the reflex from receptors in the left ventricle and the right atrium, however, little is known about these actions in Man.

It is generally held by syncope specialists that Midodrine may be a useful drug. This agent is mildly both an alpha and a beta agonist with its greatest effect on venous tone. Therein lies its attraction in antagonizing the withdrawal of sympathetic tone in the splanchnic bed. There are trials demonstrating some efficacy but in practice only some patients gain benefit and the frequency of medication, three to four times per day because of its short half-life, its limited availability being unlicensed in most western countries and its lack of information on its teratogenicity all militate against its widespread use. Midodrine will be the subject of a large RCT based in Canada, which is greatly needed (Sheldon R personal communication POST Prevention of Syncope 4) [6-9].

Fludrocortisone has been proposed in the treatment of reflex syncope on the basis of expansion of blood volume. Again studies have been unconvincing and the POST 3 has been completed in some 300 vasovagal patients but remains unpublished (Sheldon R personal communication POST 3 marginal benefit in favour of fludrocortisone was demonstrated).

One relatively new drug worthy of consideration is Ivabradine. This drug reduces the rate of diastolic depolarization in the sinoatrial node on the basis of its I(f) current inhibition. Its attraction is its very specific action only overlapping with some retinal cells causing a disturbance of colour vision. This side-effect does not appear to be common and is not dangerous to vision. Those same patients who have not been considered for a beta-blocker trial might be even more suitable for an Ivabradine trial as the side-effects of beta-blockers are much more prominent than those of Ivabradine. Ivabradine is expected to antagonize the sinus tachycardia that seems to trigger an attack in a subgroup of vasovagal patients. No trial has yet been performed but an encouraging pilot study has been recently

published [10]. Unfortunately, this drug also has insufficient teratogenic data. However, it can be taken once or twice per day.

In summary, drugs face a huge number of problems and so far it must be stated that none is effective.

Alternative Approaches

In medicine, when there are very numerous different treatments advocated for a certain indication it is safe to assume that nothing is effective. This is very true in the field of vasovagal syncope. However, we need to use our pathophysiological knowledge to apply management in the most effective way possible. For this it is really necessary to know the patient and establish rapport with the patient. A five minute consultation is never going to achieve this. Many questions must be asked about the patient's social background, medical history and family history. Patients present themselves to their physicians, when they are in trouble. So a recent rise in frequency of attacks is likely. The background for this may be stress. There may be a family history of syncope with resolution within a few years suggesting a good prognosis for this patient. In so doing a rapport is established as a side benefit. The physician must be explicatory especially emphasizing the benign nature of attacks despite their appearing quite the contrary to the patient and family. An understanding of the pathophysiology by the patient is an important early step in their treatment. This will also help in educating the patient to recognize early symptoms and thence be able to take evasive action such as squatting, lying down or possibly if recognized early enough leaving the room.

The physician must ascertain the patient's habits notably concerning the drinking of caffeine in any form tea, coffee; Colas and Red Bull must all be assessed. More than 2-3 drinks per day of this nature need to be eliminated as caffeine is a diuretic and we know that a reduced central blood volume is a trigger for vasovagal syncope. Secondly, media and heart society campaigns have been very successful in reducing salt consumption by the population but for vasovagal syncope patients this is inappropriate as they require an increase in salt often by quite substantial amounts. The American Heart Association is now recommending 2.5 g/day of salt but a vasovagal patient requires at least 6 g/day and some as much as 10 g/day. Fortunately, perhaps causatively, most of these patients have low blood pressure. In case of a hypertensive patient, these salt recommendations do not apply but for them changes in medication can often be helpful. Discontinuation of Thiazide diuretics, because of their adverse effect on blood volume, is most important and there should be an inclination toward beta-blockers as we now know that they are neutral in syncope.

We must also investigate the patient's fluid consumption [1]. Many drink too little water. For a young active patient 3 liters/day is necessary and on days of vigorous exercise this should be greater and 4 liters may not be enough. The lack of fluid consumption is often prominent in older people for they lose their natural thirst and may subconsciously reduce their drinking in the latter part of the day to try to avoid nights of frequent urine passage. To encourage an older patient to drink more than 1.5 liters/day takes time and patience but may prove helpful. It must also be borne in mind that alcohol is dehydrating and substitution of alcohol for water is counterproductive for the vasovagal patient.

There is no known adverse effect of smoking on vasovagal syncope. This discussion reveals how inadequate the five minute consultation is when none of this will emerge. Scientific proof of much of these life-style measures is awaited in most cases.

Counter-Pressure Manoeuvres

Counter-pressure manoeuvres are the essence of simplicity. These manoeuvres can be employed by most vasovagal sufferers, providing they have warning of an impending attack. They are based on the known fact that isometric exercise raises the blood pressure much more than dynamic exercise. Patients are advised to perform various activities, which consist of linking the fingers of the two hands and pulling apart but not releasing them, crossing the legs and forcing them together and clenching buttock muscles. Any of these is valuable to a patient with imminent vasovagal syncope. All of them are more powerful together. Patients may be best taught the manoeuvres on the tilt table where one manoeuvre can be expected to reverse the falling of blood pressure into a rise of about 20 mmHg. Two or three manoeuvres together may even achieve as much as 50 mmHg rise in blood pressure. Two trials have been performed that have demonstrated the value of these manoeuvres [11,12]. Clearly, manoeuvres are more strongly performed by young people and thus a better effect in this age group is to be expected. For old people, crossing the legs and pressing them together may destabilize them prompting falling over. This would be counter-productive so it is better not advised. However, the buttock muscle bulk is the largest remaining muscle mass in older people so they should be encouraged to perform this clenching manoeuvre. These methods should now be the mainstay of management of patients with warning of impending attacks beyond trying to understand them, establish a rapport and giving advice about fluid, salt and caffeine.

Tilt or Standing Training

This is an approach to attempt to improve the patient's tolerance for the upright posture [13]. Initially in Leuven where the technique was introduced patients were admitted to hospital and tilted daily until they stopped having syncope. Later the therapy was followed by out-patient standing training. The patient was asked to stand for up to 30 minutes, once or twice per day, leaning against a wall in a relaxed posture without any disturbance. The patient had to do this for as long as tolerated. The effect was to prolong the benefit of the hospital treatment. Recurrence was likely if training was discontinued. Results were good in Leuven but they have been difficult to reproduce elsewhere. There is some evidence of retraining of the autonomic nervous control to provide better tolerance of the upright posture [13]. Most countries have insufficient hospital beds to permit admission of vasovagal patients for many days. The lack of this part of the therapy may prejudice results achieved. The most recent ESC Guidelines on syncope reviewed the evidence and did not strongly recommend tilt training, Class 2b [1].

Pacemaker Treatment

Pacemakers are well established in the treatment of bradycardia. However, rectifying a slow heart rate or pacing asystole is only half the battle in reflex syncope because these devices presently do nothing to combat vasodepression. This statement implies that pacing must be applied very carefully in reflex syncope and its benefit is always limited by vasodepression. In cardioinhibitory Carotid Sinus Syndrome, a disease of older people, pacing results are quite good and this indication is now Class 1, level of evidence B in the latest European Society of Cardiology Guidelines for pacing [14]. Long-term follow-up shows that there is a recurrence of syncope, which is presumed to occur due to the vasodepressor component of the attack. It is of the order of 20% in 5 years [15].

Pacemaker treatment is not only invasive at the time of delivery of the device but the system remains implanted for the life of the battery

in those where there are no complications. For a young person this represents a serious burden and an expectation in a twenty year-old of perhaps more than 10 pulse-generator changes in a lifetime and more than likely at least one change of transvenous leads and generator site. Further, having an implanted device may be prejudicial in employment. This sort of trauma should be avoided at all costs and not recommended unless there is no alternative and with the understanding that recurrence of attacks is still likely in the longer term.

The attraction for cardiologists is the bradycardia component of vasovagal syncope especially when this is observed to be asystole for an extended period (e.g. >20s) either on a tilt test or from an Implanted ECG Loop Recorder (ILR). ILR studies have shown that this is not uncommon [16]. Prolonged asystole in this context seems to be relatively benign and probably should not provoke the reaction it does in cardiologists.

Pacing in vasovagal syncope has received much study beginning in the 1990s. The first trials were comparisons of implanted dual chamber pacemakers versus no therapy, maintenance of previous therapy or beta-blockers, now known to be ineffective [17-19]. The results were strongly in favor of pacing more in Europe than USA probably due to selection of older patients in Europe. The next wave of trials implanted a pacemaker in all the patients and essentially disabled function of the device in those randomized to no therapy [20,21]. The results of these trials were very different with no significant benefit being shown. Some criticisms of the methods in both trials could be made especially in terms of patient selection where those with intense cardio-inhibition were not rigorously chosen for inclusion. The great benefit received by a few patients who had been paced for vasovagal syncope led a group to study further. The ISSUE 2 Registry aimed to select patients by implanting an ILR so that the heart rhythm in spontaneous attacks was clearly documented [22]. Being a Registry no treatment plan was imposed on the caring physicians. One hundred and three patients had a rhythm diagnosis made by the ILR and most of these were intense bradycardia or asystole. Remarkably, the caring physicians divided almost equally between using the ILR information to deliver specific treatment (e.g., pacing in asystole/bradycardia) and not using the rhythm information. At follow-up those receiving pacemakers for bradycardia/asystole did much better than those who did not. This result prompted the ISSUE 3 trial published last year [23]. This RCT identified patients by means of an ILR and implanted a pacing system in all the patients with bradycardia/asystole randomizing half to pacemaker ON and the other half to pacemaker OFF. The patients selected for pacing did significantly better than those without pacing ($p < 0.039$) demonstrating that careful selection of older patients (mean age 63 years) with bradycardia/asystole in spontaneous events can offer benefit. However, recurrence of syncope in two years of follow-up was 25% i.e., worse than can be expected in Carotid sinus Syndrome. As blood pressure was not available from the implanted device in these trial patients it can only be speculated that the vasodepressor component was the cause of these recurrences.

This trial in older patients cannot be construed to be relevant to younger people for whom no such information is available. Further work is necessary to understand the nature of recurrences and the possible role of pacing in highly selected younger patients. Thus, today pacing younger patients (<40 years) cannot be recommended, as there is no supporting evidence base.

Catheter Ablation

There have been reports of success in control or elimination of

vasovagal attacks by catheter ablation using radiofrequency energy endocardially to ablate ganglionic plexi in close anatomical relation to the left and right atria on the surface of the heart [24,25]. This is a difficult technique even for an experienced operator and must be considered to offer risk to the patient despite the reports not indicating complications. This procedure must be considered experimental at this stage.

Conclusions

Treatment of reflex syncope leaves much to be desired. Drugs are insufficiently effective. Life-style changes help but are rarely a complete solution. Counter-pressure manoeuvres are very helpful in those who have warning of an impending attack. Pacemakers have very limited applicability and only any proof of efficacy in older patients with asystolic spontaneous vasovagal attacks or with Carotid Sinus Syndrome.

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