Syncope Evaluation and Management:

Less is Better

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Purpose and Overview:

Syncope, a very common symptom for a variety of medical conditions, is associated with significant morbidity and costs. Although effective diagnosis and treatment can reduce recurrent syncope and improve quality-of-life, one would be hard pressed to find a condition with so much practice pattern variation and low yield tests so often ordered. The purpose of this Internal Medicine Grand Round is to provide an overview on how to best manage patients with syncope, while at the same time explore issues related to cost and low yield testing.

Learning Objectives:

Upon completion of this session, the participant should be able to:

1. Learn how to approach patients who present with syncope.
2. Recognize the value of the history, physical exam and ECG as initial evaluation in syncope.
3. Understand which studies are low yield in syncope.
4. Learn to manage patients with vasovagal syncope.

Introduction

The word syncope is derived from the Greek word *synkope*, which means cessation or pause. It is defined as a transient loss of consciousness and postural tone with spontaneous recovery and no neurologic sequela. Also known as fainting, it is a very common "symptoms" for a wide variety of etiologies, and as such requiring a variety of skills to properly manage patients. The morbidity associated with recurrent syncope can be significant; it is equivalent to other chronic conditions such as severe rheumatoid arthritis and low back pain.(1)

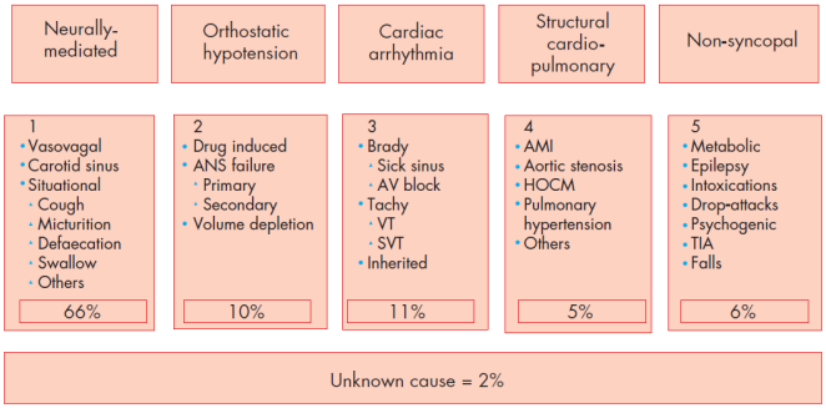
Syncope is also associated with a high health care utilization and expenditure, accounting for 740,000 annual emergency department visits and 460,000 hospital admissions in the United States, at a cost in excess of $2.4 billion per year.[1]

Although effective diagnosis and treatment can reduce recurrent syncope and improve quality-of-life, one would be hard pressed to find a condition with so much practice pattern variation and for which so many unnecessary low yield tests are so often ordered. For that reason, payers and regulators are increasingly scrutinizing health-service use associated with syncope. I hope to explore these issues of cost and low yield testing as we discuss syncope management.

Etiologies, Epidemiology and Prognosis

We can see in figure 1 that etiologies of syncope are very diverse, yet neurally mediated, or vasovagal syncope (VVS), is by far the most common cause, especially in the young.[2] It is also evident that syncope becomes increasingly more common with advancing age (figure 2) since more conditions that can cause syncope occur mainly in the elderly such as sick sinus syndrome, plus for a variety of other reasons including age-related physiologic (reflexes) impairment, polypharmacy, and the presence of co morbidities.

Figure 1. Causes of syncope



Prevalence of the causes of syncope in the EGSYS-2 study. The EGSYS study was aimed at assessing the management of syncope as recently defined by ESC guidelines. By far, the most common cause is neurally- mediated, specifically vasovagal.[2]

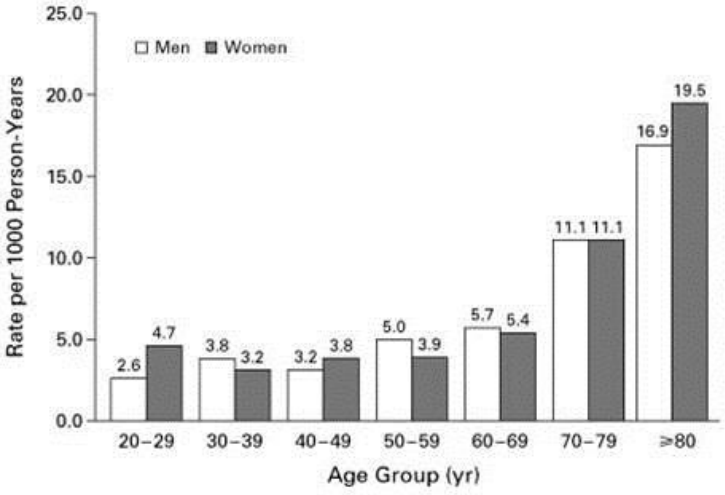
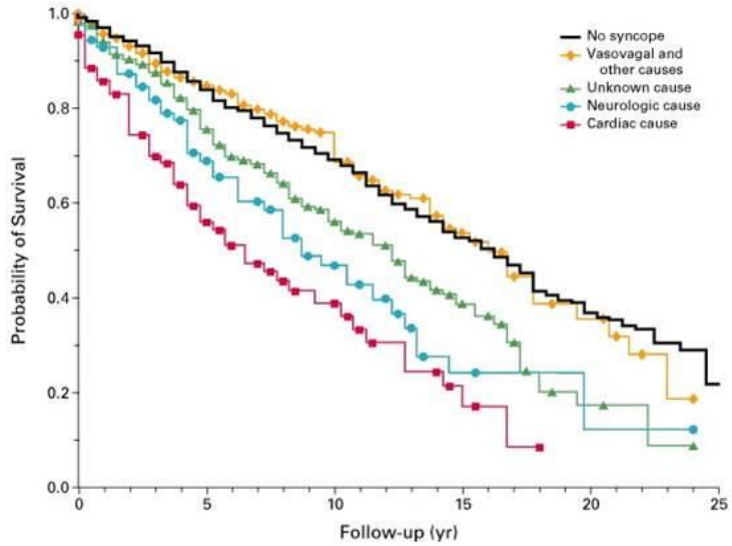


Figure 2.
Incidence Rates of Syncope According to Age and Sex. The incidence rates of syncope per 1000 person-years of follow-up increased with age among both men and women. The increase in the incidence rate was steeper starting at the age of 70 years. Syncope rates were similar among men and women.[3]

Prognosis is determined by etiology of syncope, but according to data from the Framingham Study (figure 3), VVS is generally benign and consistent with a normal life expectancy. Overall outcomes in patients with syncope are determined by underlying etiology, with cardiac syncope having the worse outlook as syncope in this setting is often a reflection of a sicker cardiovascular substrate.[3]

Figure 3



Overall survival of participants Framingham Heart Study from 1971 to 1998 with syncope, according to cause, and participants without Syncope. P<0.001 for the comparison between participants with and those without syncope. The category “vasovagal and other causes” includes vasovagal, orthostatic, medication-induced, and other, infrequent causes of syncope.[3]

Unnecessary Testing in Syncope

It is not very clear why so many low-yield tests are routinely ordered in patients who present with syncope. This is a long standing problem that has been documented across the globe, with great variability in terms of practice patterns, yet in general with great consistency in the fact that many unnecessary tests are often ordered. We can see this problem well described in the table below from a study at Yale involving 2,106 consecutive patients 65 years and older admitted following a syncopal episode, where many low yield test such as neurological studies were frequently ordered, whereas postural blood pressure recordings which had the highest yield, were performed in only about a third of the time and frequently performed inadequately.[4]

Table 2. Diagnostic Tests Obtained in Evaluation of Syncopal Episodes in Older Patients[a]

Test	Obtained	Abnormal Findings[b]	Affected Diagnosis[c]	Helped Determine Etiology[c]	Affected Management[c]
Electrocardiogram	2081 (99)	438 (21)	147 (7)	72 (3)	153 (7)
Telemetry	2001 (95)	314 (16)	212 (11)	95 (5)	245 (12)
Cardiac enzymes test	1991 (95)	108 (5)	31 (2)	9 (0.5)	29 (1)
Head CT	1327 (63)	138 (10)	28 (2)	7 (0.5)	28 (2)
Echocardiogram	821 (39)	516 (63)	35 (4)	13 (2)	36 (4)
Postural BP recording	808 (38)				
Strict criteria[d]		230 (28)	142 (18)	122 (15)	202 (25)
Loose criteria[d]		445 (55)	212 (26)	173 (21)	241 (30)
Carotid US	267 (13)	122 (46)	2 (1)	2 (0.8)	6 (2)
EEG	174 (8)	68 (39)	2 (1)	1 (0.6)	2 (1)
Head MRI	154 (7)	46 (30)	20 (13)	3 (2)	19 (12)
Cardiac stress test	129 (6)	53 (41)	13 (10)	2 (2)	12 (9)

In trying to understand the reasons behind unnecessary testing in syncope, Kachalia and colleagues conducted a national survey of practice patterns for 2 common clinical vignettes: preoperative evaluation and syncope.[5] A total of 1020 of hospitalists responded and admitted overuse in 82% to 85% of the syncope vignettes, which was rationalized by the physician's desire to reassure patients or themselves rather than lack of awareness that the test was not clinically indicated.[5] Importantly, financial incentives were probably not a factor since few, if any, hospitalists derive financial benefit from unnecessary tests.

In view of these data, it is clear that reasons for so many unnecessary tests in our health care system are complicated and difficult to understand and address. For sure this problem is more complicated than just the commonly cited “fear of litigation”, since over the years I have seen by far more downside from unnecessary testing. Many of the negatives to the patient that I have observed include: 1. more harm due to recurrent syncope based on incorrect diagnosis or waiting for additional tests than from any findings ever uncovered by low yield study, 2. Patients feel they are sicker than they are and it can be hard to make them see otherwise, 3. Loss of trust by patients, and 4. Going down the “incidentaloma” slippery slope.

Potential solutions are a complex issue and a talk by itself, which I will not dive into in great detail, but a variety of options have been suggested such as: enhancing education to physicians on a variety of issues such actual risk of litigation, developing patient satisfaction metrics designed in a manner that avoids creating conflicts for physicians, incorporating evidence base guidelines into every day practice, and hospital protocols with smart order sets to help guide care among others.

General Approach to Syncope

Initial Diagnosis

There is a two-step approach to evaluating patients with syncope. First, when the patient presents to the ER, the most important consideration for the ER physician is to rule out the presence of a catastrophic illness, such as severe bleeding or pulmonary embolism for example. As such, ER based protocols have been designed that look at things such as presence of CHF signs, ECG, hypotension, hematocrit, oxygen saturation. What is most relevant to the general practitioner and the focus of my talk is the next step, which is how to approach the patient once a catastrophic condition has been excluded.

The Fainting Assessment Study (FAST) recruited 503 patients (mean age 53 +/- 19; 56% male) presenting with syncope to an academic medical center in Amsterdam. An initial evaluation consisted of just the history, physical exam and ECG, yet they were able to make a diagnosis in 63% of patients, with 88% (95% CI 84-91%) diagnostic accuracy.[6] Cleary, for this to be possible it is importance to recognize the components of the history necessary in order to make an accurate diagnosis. This requires expertise, but can also be incorporated, as they did in FAST, into a standardized questionnaire created by experts and supported by guidelines. An example of the information in the questionnaire in FAST is in figure 4 below.[6]

Figure 4: Medical questionnaire give to patient in The Fainting Assessment Study (FAST)[6]

TABLE 1
Summary of Guidelines on Management (Diagnosis and Treatment) of Syncope Update 2004 (see Refs. 4 and 6)

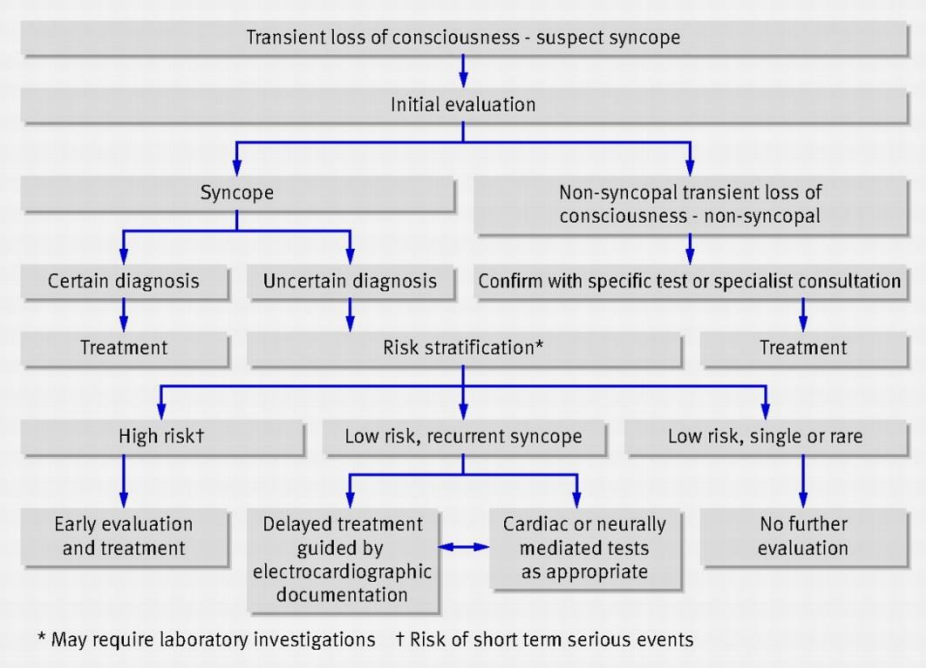
	The Results of the Initial Evaluation are Diagnostic (Certain) of the Cause of Syncope in the Following Situations:	Suspected Diagnosis (Highly Likely)
Neurally mediated syncope		Absence cardiac disease; long history syncope; after unpleasant sight, sound, smell, or pain; prolonged standing or crowded, hot places; nausea/vomiting associated with syncope; during/in the absorptive state after meal; with head rotation, pressure on carotid sinus; after exertion after unpleasant sight, sound, smell, or pain; prolonged standing or crowded, hot places; nausea/vomiting associated with syncope; during/in the absorptive state after meal; with head rotation, pressure on carotid sinus; after exertion
Vasovagal syncope	Precipitating events such as fear, severe pain, emotional distress, instrumentation, or prolonged standing are associated with typical prodromal symptoms	
Situational syncope	Syncope during or immediately after urination, defecation, cough, or swallowing	
Orthostatic syncope	Documentation of orthostatic hypotension associated with syncope or presyncope. A decrease in systolic blood pressure of 20 mmHg or a decrease of systolic blood pressure to <90 mmHg is defined as orthostatic hypotension regardless of whether or not symptoms occur	After standing up; temporal relationship with start of medication leading to hypotension or changes of dosage; prolonged standing especially in crowded, hot places; presence of autonomic neuropathy or Parkinsonism; after exertion
Cardiac syncope		Presence of severe structural heart disease; during exertion, or supine; preceded by palpitation or accompanied by chest pain; family history of sudden death
Cardiac ischemia	Symptoms are present with ECG evidence of acute ischemia with or without myocardial infarction, independently of its mechanism	
Arrhythmia	Sinus bradycardia <40 beats/minute or repetitive sinoatrial blocks or sinus pauses >3 seconds in the absence of negatively chronotropic medications; Mobitz II 2nd or 3rd degree atrioventricular block; alternating left and right bundle branch block; rapid paroxysmal supraventricular tachycardia or ventricular tachycardia; pacemaker malfunction with cardiac pauses	
Cerebrovascular syncope		With arm exercise; differences in blood pressure or pulse in the two arms

There are other aspects of the history that are also critical, for example knowing medications commonly associated with syncope such as Flomax. Also, classic aspects of the history pointing at vasovagal syncope are worth knowing such presence of an autonomic prodrome, clustering of episodes, and a profound and prolonged post syncope fatigue reported by about ¾ of patients.

Further testing

Figure 5 provides an outline of the evaluation of the patient with syncope.[7] As already mentioned, the most important diagnostic intervention is a detailed history and examination, including lying and standing blood pressure, plus a 12 lead ECG. The history has the important dual role of helping with diagnosis as well as with risk stratification for high risk conditions. In the majority of cases the initial assessment will lead to a definitive or provisional diagnosis, which will inform the need for further treatment or evaluation. A clear diagnosis of vasovagal syncope or orthostatic hypotension can be made without further testing if the history is suggestive and cardiac examination and electrocardiography are normal. Patients with cardiac syncope and those with non-cardiac syncope in whom diagnostic and management difficulties exist should be referred to specialist services.

Figure 5: Diagnostic algorithm for evaluation of patients with syncope.[7]



Tilt table testing in general is often ordered to diagnose vasovagal syncope (or autonomic syndromes) but it is seldom necessary these days in view of studies already mentioned supporting the diagnostic ability of the basic initial evaluation. Tilt testing is therefore not

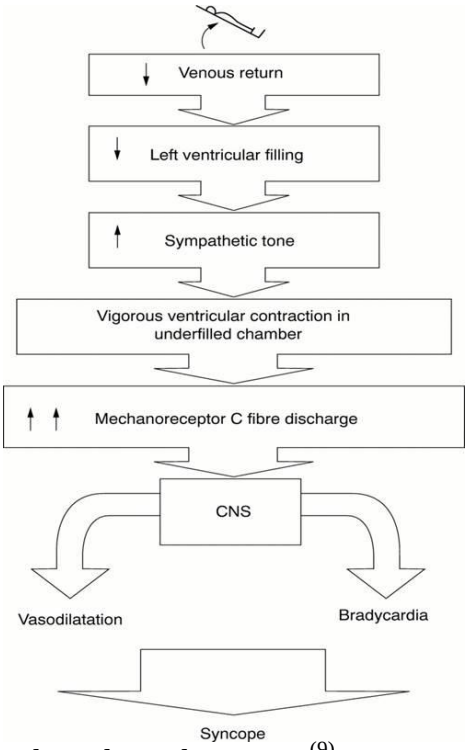
indicated after a single episode and/or when the history is very compelling. Some advantages of tilt might be that the patient learns VVS warning symptoms and may help guide therapy.

In those patients in whom the etiology of syncope remains in doubt, most recent data supports the use of Implantable loop recorders (ILR). The ILR is a small device that is highly programmable and can last up to 3 years. IRL can be programmed to auto record arrhythmias but can also be activated by the patient with a magnet for better symptom correlation. Several studies have shown that device provides a higher yield that traditional testing, with a probability of diagnosis of 40-60%, with fewer hospital days and improved quality of life reported in one study.[8] Other technologies are available which allow for prolonged cardiac monitoring, such as the Zio Patch, which is an option but limited to patients with frequent symptoms since monitoring is limited to a few weeks. The main consideration is that syncope is a rare event, and can be a long time between episodes, as such an IRL is an ideal tool since it can remain in place for a months to years and do not rely necessarily on potentially erroneous human operation.

High Risk Conditions

I am not going to cover all potential high risk conditions in detail since that is beyond the scope of this lecture, but in general, the initial evaluation should point at the possibility of structural or electrical heart disease, in which case additional testing and therapies would be indicated. As such, the ECG is very useful beyond its diagnostic yield since it can give clues about underlying pathology. For example, ECG may reveal the presence of Q waves due to a prior infarction, or LVH suggesting hypertrophic cardiomyopathy. Alternatively, a normal ECG is often reassuring since it is suggestive of benign syncope. On the exam, it is important to look signs of CHF, a murmur, etc. Other important considerations are family history of sudden death, brady or tachy arrhythmias, the presence of significant conduction system disease, possible genetic arrhythmia syndromes, syncope with no warning symptoms (Stokes-Adams attack), syncope during exercise, drugs legal or illegal that can cause syncope, etc.
Once a high risk condition is identified, therapy is individualized. For example, syncope in the setting of advance cardiomyopathy has been shown to predict a poor outlook and ICD may be indicated, WPW mandates EP study, the presence of conduction system disease may mandate a pacemaker, etc.

Vasovagal Syncope



VVS is by far the most common cause of fainting; as such we will cover it in more detail. Clinically, these episodes may present as an isolated event with an identifiable trigger, or manifest as a cluster of recurrent episodes warranting intervention. The mechanism of vasovagal syncope is incompletely understood, but it is believed to be a paradoxical response to stress. On standing, 300 to 800 ml of blood shift from the body's core to the lower extremities, which lowers venous return and cardiac output. Normally this leads to reduced stimulation of baroreceptors in the carotid sinus and aortic arch and mechanoreceptors (vagal C fibres) in the wall of the left ventricle, which leads to increased sympathetic tone and maintenance of the blood pressure. It is thought that the mechanoreceptors in the left ventricle are not only innervated by stretch but also by vigorous and forceful systolic contraction. In patients with neurocardiogenic syncope, excessive left ventricular contraction occurs in response to reduced venous return, leading to an inappropriate decrease in sympathetic tone and an increase in parasympathetic (vagal) tone. The result is hypotension, bradycardia and syncope.[(9)]

No one knows for sure why this reflex happens. 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.[(10)] A vagal response to fear/threat represents *an atypical response*, since the common response to fear is an increase in heart rate. Humans have evolved into having larger brain (20% of cardiac output) and upright posture, which can make them more prone to fainting. Some authors have suggested that, although seemingly a disadvantageous evolutionary adaptation, the faint causes the body to take on a gravitationally neutral position, and thereby provides a better chance of restoring brain blood supply and preserving long-term brain function.(10) In any case, we just don't know the reason, but appears to be a reflex that has persisted for millions of years throughout the evolutionary history of vertebrates, so at least we can reasonably assume that it is not dangerous.

Therapy

Therapies for VVS are primarily aimed at *prevention of the vasovagal reflex* or at *aborting the impending reflex*. As such, non-pharmacological lifestyle changes and ''countermeasures'' are usually the first line treatment.
It is important to understand that most patients with VVS syncope do well with preventive and abortive measures, and therefore additional treatment options should considered only considered for those with recurrent and refractory symptoms.
When VVS is documented, three different responses can be observed; a cardioinhibitory response where a dramatic drop in heart rate and even asystole is observed, a vasodepressor response in which a more prominent drop in blood pressure

relative to the drop in heart rate is observed, and last, which is seen more commonly, a mixed response. As such, therapies can be also aimed individually according to the patient's specific response. For example, even though drug therapies have been disappointing in general, Midodrine, a vasoactive drug, have shown some degree of efficacy in patients with a vasodepressor type response.

Therapy: Countermeasures

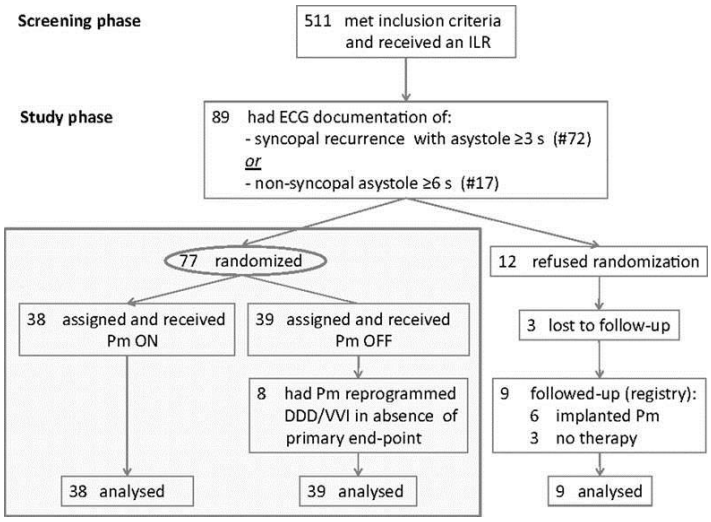
In view of the lack of evidence-based treatment options for patients with recurrent VVS, additional research has led into the use of physical counterpressure maneuvers (PCM). One study evaluated leg crossing with muscle tensing as physical counter-maneuver. The technique was performed in 20 of 21 subjects during tilt table. Systolic blood pressure rose from 65+/-13 to 106+/-16 mm Hg (mean+/-SD, P<0.001), and diastolic blood pressure rose from 43+/-9 to 65+/-10 mm Hg (P<0.001). During the maneuver, prodromal symptoms disappeared in all patients, and none lost consciousness.[11] Isometric arm counter-pressure manoeuvres have also shown to be effective, especially in younger patients.

However, the results of the aforementioned studies were based on a limited number of patients in laboratory conditions. With that in mind, The Physical Counterpressure Manoeuvres Trial (PC-Trial), a multicenter, prospective, randomized clinical trial that included 223 patients, looked at the effectiveness of PCM in preventing recurrent episodes of vasovagal syncope in real life conditions.[12] During a mean follow-up period of 14 months, 50.9% of the patients with conventional treatment and 31.6% of the patients trained in PCM experienced a syncopal recurrence (p = 0.005). Actuarial recurrence-free survival was better in the treatment group, resulting in a relative risk reduction of 39% (95% confidence interval, 11% to 53%). An important limitations was that arm tensing was the maneuver of first choice in 36.0% of patients, and the maneuver that I favor which is leg crossing was only selected first by 23.6% of patients.[12] Yet, we can concluded that PCM are effective at aborting impending syncope, but not universally so, and is especially limited in patients with no prodrome and the elderly. Practicing the maneuvers regularly at home is essential.

Therapy: Pacemakers in VVS

The efficacy of pacemaker therapy for prevention of recurrent events in patients VVS has been under question since prior randomized studies failed to show a statistically significant superiority of cardiac pacing over placebo in unselected patients with positive tilt testing. The main criticism has been that those prior studies included all comers with VVS and as we already discussed, a large number of these patients have a significant vasodepressor component, in which a pacemaker would not be of benefit. With that in mind, the ISSUE-3 trial was double-blind, randomized placebo-controlled multicenter study that examined the effect of dual chamber

pacing in 77 patients ≥40 years old who had experienced ≥3 syncopal episodes in the previous 2 years and who demonstrated asystole. Initially, 511 patients received an implantable loop recorder; 89 of these had documentation of syncope with ≥3 s asystole or ≥6 s asystole without syncope within 12 ± 10 months and met criteria for randomization. Ultimately 77 patients received pacemakers and were randomly assigned to dual-chamber pacing with rate drop response or to no pacing.[13] The study showed a 32% absolute and 57% relative reduction in syncope recurrence, bearing in mind that patients were ≥40 years old with long asystolic pause (mean, 11 seconds) documented by use of ILR.[13] The overall strategy of using an ILR, with the consequent relatively certainty regarding mechanism, likely contributed to the positive findings.



The fact that pacing is effective in this population does not mean that it is always necessary. It must be emphasized that the decision to implant a pacemaker needs to be undertaken in the clinical context of a benign condition, which frequently affects young patients. Thus, cardiac pacing should be a last choice in highly selected patients affected by severe VVS with asystole who have failed to respond to initial intervention. In this regard, the ISSUE studies focused on VVS subjects with a history of recurrent syncope beginning in middle or older age, and frequent injuries probably due to lack of prodrome. Also, the great majority of patients with VVS would not qualify since in ISSUE 3 inclusion criteria was met by only 9% of all patients referred for evaluation.[13]

Preventive Measures

Often patients are advised on lifestyle changes and as such are provided with a variety of instructions. We are going to discuss some of these, keeping in mind that many of these instructions have not been securitized in well-designed trials. Also VVS often fades away anyway and as such any intervention would appear to be effective in observational studies.

Certainly, some interventions would make sense, such avoiding potential triggers, and avoiding prolonged standing and hot crowded environments. Water ingestion (16 ounces) have shown to enhance tolerance to upright posture, as such has been suggested as a preventive measure prior to exposure to potential triggers, such as blood donation.[14] Exercise training have shown to also improve orthostatic tolerance , and is beneficial for everything else, so why not? Raising head of the bed few inches (10-30 degrees) increases plasma volume, but compliance is a concern. Liberalizing salt in diet is also advised since salt loading have shown to improve orthostatic tolerance as well, but there is no prospective data to support this recommendation and many patients are already on high salt diets.

One prospective observational study examined the effects of non-pharmacological treatment in patients with > or =3 episodes of VVS in the 2 years prior to the start of the study. Patient were openly assigned to lifestyle changes plus countermeasures; a beneficial effect on both syncopal

recurrence and QoL was reported, but nearly half of these patients still experience episodes of syncope.[15] A such, these interventions appear to be effective but not universally so and it is hard to differentiate precisely which one of the numerous instructions given was most responsible for the observed benefit if any.

So recommendations can be tailored to the patient but must keep in mind that there are no good randomized studies, recurrences are likely, and VVS often fades away anyway.

Conclusions

Syncope is a worldwide clinical dilemma associated with high morbidity, health service utilization, and costs. By far, the most common etiology is vasovagal, for which simple interventions are most effective and additional therapies are reserved for patients with debilitating and refractory symptoms. Current practice patterns are characterized by high variation, and frequent use of low yield diagnostic tests. Improved diagnostic algorithms and practice protocols are urgently needed to reduce morbidity, low-value health service use, and system expenditure. The core of the syncope work up remains a detailed history and physical examination.

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