Unexplained Syncope: Diagnostic Evaluation in the Modern Era

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Syncope is defined as a sudden temporary loss of consciousness associated with a loss of postural tone, with spontaneous recovery not requiring electrical or chemical cardioversion. Syncope is a frequent and potentially dangerous disorder, accounting for 1 to 6% of hospital admissions and up to 3% of emergency room visits[1,2]. It has no gender predisposition and can occur at any age. In the Framingham population[3], syncope had occurred in 3% of men and in 3.5% of women, based on biannual examinations, with the highest frequency seen in the elderly. In addition, the annual incidence of syncope in those over 75 years old was 6% and the prevalence of syncope in the elderly was 5.6% compared to a low percentage of 0.7% in the 35 to 44 year old male population. The elderly are most likely to have syncope, to be injured from syncope, to seek medical advice and to be admitted to a hospital.

Although syncope has a large variety of different etiologies, the causes can be classified into four major categories: 1) reflex mediated vasomotor instability syndromes, 2) orthostatic hypotension, 3) neurological diseases and 4) cardiac diseases associated with decreased cardiac output[4]. The etiology of recurrent syncope is often difficult to determine if the diagnosis is not evident from the initial clinical and laboratory investigations. There has been a wide variation in the proportion of patients diagnosed with various causes of syncope, due to patient selection and lack of uniform criteria for the definition of causes of syncope. Studies from the 1980s[5] show that the prevalence of various etiologies reported in unselected patients with syncope are: vasovagal syncope in 18% (range 8% - 37%), severe cardiac arrhythmias in 14% (range 4% - 38%), neurological diseases in 10% (range 3% - 32%), orthostatic hypotension in 8% (range 4% - 10%), situational syncope in 5% (range 1% - 8%) and organic heart disease in 4% (range 1%-8%). A cause of syncope was not diagnosed in 34% (range 13%-41%). In the Framingham Heart study[6], the most frequently identified causes of syncope were vasovagal (21.2%), cardiac (9.5%), orthostatic (9.4%), seizure (4.9%), stroke or transient ischemic attack (4.1%), medication (6.8%) and of unknown origin 36.6%.

According to the task force on syncope of the European Society of Cardiology[7], if the initial diagnostic evaluation (including history, physical examination, measure of blood pressure in the supine and upright position and standard ECG) is negative, syncope is termed as unexplained.

Despite the wider use of ECG ambulatory monitoring, head-up tilt testing and electrophysiological testing, it is estimated that in 20% of syncopal attacks a definite diagnosis is not determined. The major obstacles in diagnosis are the sporadic and unpredictable nature of the underlying pathophysiologic mechanism that leads to syncope and the high spontaneous remission rate.

A diagnostic algorithm proposed for the evaluation of patients with syncope is

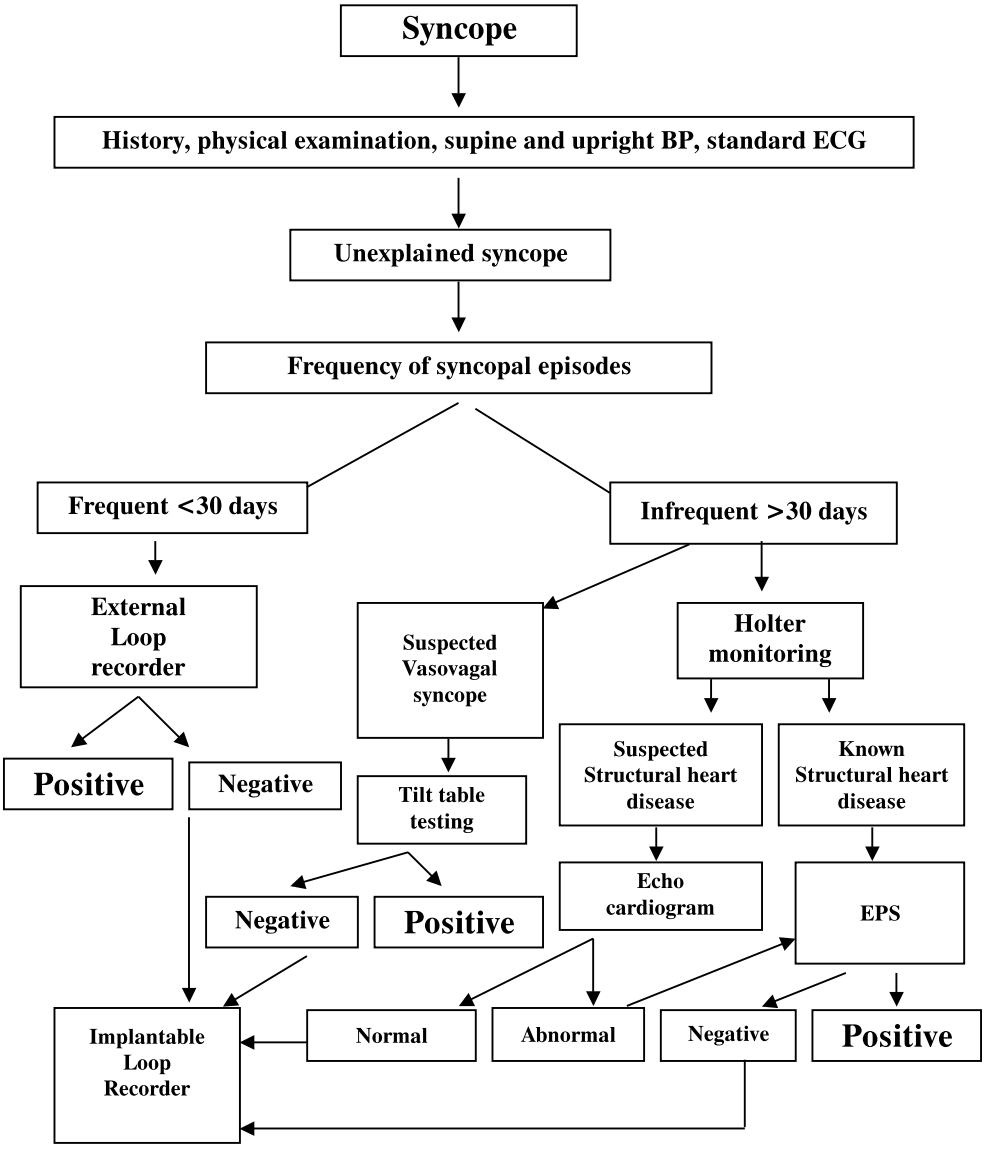

Figure 1. Diagnostic algorithm for the management of unexplained syncope (EPS=electrophysiological study).

presented in figure 1. The initial diagnostic step in patients with syncope is differentiation of individuals with normal cardiovascular status from those with structural heart disease. Attention should be directed to the vital signs, the cardiovascular examination and the neurological examination. The physical examination and the patient's history remain the cornerstones for the initial evaluation of syncope. The history and clinical examination identify a potential cause of syncope in approximately 45% of patients.

A twelve lead surface ECG is recommended in all patients with syncope because abnormalities found on the ECG may guide further evaluation, or if a specific diagnosis is made, the findings can be important in immediate decision making. An abnormal surface ECG is found in 20% to 50% of patients with syncope, but in most patients it is not diagnostic. The diagnostic yield of the surface ECG is low and the cause of syncope is rarely identified (2% to 11% of patients) on the basis of ECG and rhythm strip[5-8].

In patients in whom the etiology of syncope remains unclear or unexplained after physical examination and surface ECG, a series of noninvasive and

invasive diagnostic tests should be performed in order to define the cause of syncope. The ultimate goal of diagnostic testing in syncopal patients is to obtain a correlation between symptoms and detected abnormalities. All testing must be tailored to the patient, based on the findings of the history and clinical examination and with knowledge of the sensitivity and specificity of each test, in order to identify the cause of syncope.

Echocardiography is sometimes also used in order to exclude cardiac structural abnormalities (such as valvular diseases, cardiomyopathies, etc.), as the causative factors for the syncopal episode, although large studies have shown that the diagnostic yield of the method is low in the absence of clinical, physical or ECG findings suggestive of some cardiac abnormality[9,10]. The most common echocardiographic finding in patients with syncope and normal physical examination seems to be mitral valve prolapse[9]. According to the guidelines of the European Society of Cardiology for the management of syncope[7], echocardiography is recommended in patients with syncope when a cardiac disease is suspected (class I recommendation). According to the same source of information this method can only be diagnostic in severe aortic stenosis and atrial myxoma.

Carotid sinus massage is another diagnostic method, which is used in order to reveal carotid sinus hypersensitivity as the causative factor in patients presenting with syncope. It should be avoided in patients with a known history of previous transient ischemic attacks or stroke within the past three 3 months, or in patients with carotid artery bruits heard on carotid artery auscultation[11]. A positive response to the test is characterized by the presence of asystole that lasts more than 3 seconds and/or a fall in systolic blood pressure of 50 mmHg or more. When there is no other competing diagnosis, the positive response could be considered diagnostic of the cause of syncope[10].

When the patient's history reveals that the syncopal episode is associated with exercise (during or shortly after this), an exercise test should be undertaken. This must be done in order to exclude mainly arrhythmogenic as well as conduction disorders that could lead to a decrease of the cardiac output and to syncope. Furthermore, it should be noted that postexertional syncope is almost always due to autonomic failure[12] or to a neurally-mediated mechanism[13,14]. According to the guidelines of the European Society of Cardiology[7] exercise testing should be considered diagnostic (class I recommendation) in the following cases: 1) when ECG and hemodynamic abnormalities are present and syncope is reproduced during or immediately after exercise, 2) if Möbitz II second or third degree AV block develop during exercise, even without syncope.

Concerning the different diagnostic tests, many centers use ambulatory rhythm monitoring as a first line diagnostic test. Continuous electrocardiographic monitoring until syncope recurs remains the "gold standard" to diagnose or exclude cardiac arrhythmias as the cause for the syncopal episode, but is very often impractical. If arrhythmias are thought to be causative in patients with transient symptoms, the crucial information needed is the recording of an ECG during the precise time when the symptom occurs. With such a recording, one can determine if the symptom is related to an arrhythmia. With an ambulatory ECG recording, the following outcomes are possible:

1) Typical symptoms may occur with the simultaneous documentation of an arrhythmia capable of producing such symptoms. Such a finding is most useful (gold standard) and helps to direct therapy.
2) Symptoms may occur even though an ambulatory recording shows no arrhythmia. In consequence this finding is also useful, because it demonstrates that the symptoms are not associated with the rhythm abnormality.
3) An arrhythmia was recorded, but the patient remained asymptomatic. This finding has equivocal value, because it is unclear if the recorded arrhythmia is relevant to the symptoms.
4) No arrhythmia was recorded and the patient remained asymptomatic. This finding is therefore not useful.

Twenty-four hour ambulatory ECG monitoring is frequently undertaken in patients with syncope, but its diagnostic yield is low (1-2%)[7]. In one large series (433 patients), syncope occurred during monitoring in 1.6% and dizziness occurred in 14.5% of the patients[5]. In studies that evaluated syncope or presyncope with ambulatory monitoring and reported on symptoms, less than 5% of patients had symptomatic correlation with rhythm disorders. Additionally, in 20% of patients, symptoms were not associated with arrhythmias, thus potentially excluding rhythm disturbance as a cause for syncope. In contrast, in 80% of patients no symptoms occurred but arrhythmias were often detected and therefore the causal relationship between these arrhythmias and syncope is uncertain[15-17].

Furthermore, the absence of arrhythmias (without syncope) on monitoring does not exclude the arrhythmogenic etiology of syncope. The central problem and limitation with conventional ambulatory monitoring is that the majority of patients rarely provide a symptom-rhythm correlation, presumably because of the relatively brief period of time sampled, and furthermore, it is not infrequent to record asymptomatic arrhythmias with no specific meaning in this setting, which may confuse rather than reveal the cause of the symptom. Twenty-four hour ambulatory monitoring is often not enough to identify potentially important arrhyhthmias in patients with syncope. Holter monitoring may need to be extended up to 48 or 72 hours, if the first 24 hours are normal[18]. Despite the extension of ambulatory monitoring to 3 consecutive days, the diagnostic yield of this method remains relatively low. Therefore, the only reason to consider short time ambulatory monitoring is when a patient has multiple or frequent episodes of syncope or related symptoms over a short period of time, with a high pretest likelihood of arrhythmias.

Head-up tilt-table testing has been used extensively in order to recognize vasovagal mechanisms in patients with syncopal episodes of unknown origin[19,20]. Two principal methods of tilt table testing have evolved. The two types of testing procedures include upright tilt testing alone (passive testing) and tilt testing with the administration of a chemical agent. The test must be performed in patients with recurrent unexplained syncope in whom cardiac etiology has been excluded or is not likely. Initial testing is recommended by use of a passive protocol for 45 to 60 minutes. In the case of negative passive test and a high likelihood of neurally mediated syncope, additional testing with administration of pharmacological agents (isoproterenol, nitrate, clomipramine, etc.)[21] is indicated. The effectiveness of the test depends on several factors, including patient selection and use of provocative drugs. The specificity of the passive tilt testing is about 90%, whereas the sensitivity of the method ranges between 25-90% (mean value 60-70%). The use of pharmacological agents (provocative test) increases the sensitivity but also decreases the specificity of the method to approximately 75%[22]. The reproducibility of the test over days to weeks is approximately 75% to 80% and the immediate reproducibility over a few hours may be less[23,24]. Finally, the positive diagnostic yields of drug-free and provocative tilt table testing are about 30% to 40% and 65% to 80%, respectively[25].

Electrophysiological testing is generally accepted as the final arbitrator when noninvasive testing is negative or inconclusive. This arises from the assumption that electrophysiological testing is characterized by high sensitivity and specificity in terms of determination of the cause of syncope. Despite this, several issues need to be considered while using this invasive and provocative test in the evaluation of syncope: 1) induced arrhythmias presumed to be diagnostic should be associated with or capable of producing the symptom or severe hypotension; 2) the clinical significance of some of the electrophysiological abnormalities may be difficult to determine, because of problems related to the clinically relevance of several electrophysiological findings; 3) the variations in the proportion of positive or negative findings according to the patient population and to the presence or not of organic heart disease. Abnormal test results are reported in 7% - 50% of patients selected for study[26-28]. This wide range of results reflects patient selection. Electrophysiological study is more likely to be positive in patients with known structural heart disease, low ejection fraction or abnormalities on the surface ECG or on Holter monitoring. Induction of sustained monomorphic ventricular tachycardia is the most common abnormality observed in this group of patients selected for testing. Predictors of a negative electrophysiological study include the absence of heart disease, normal ventricular function, normal surface ECG, negative ambulatory monitoring and finally, prolonged episodes of syncope that last more than 5 minutes. In patients with structural heart disease and/or abnormal surface ECG, the diagnostic yield of the method is approximately 50% and in patients without heart disease the diagnostic yield is approximately 10%[29-31]. As a consequence, electrophysiological testing may be useful for patients suffering from syncope, under the following circumstances: 1) if other tests are negative, 2) if syncope frequently recurs, 3) if there are prolonged episodes of nonsustained ventricular tachycardia on monitoring, 4) if there are late potentials in the signal averaged electrocardiogram.

Despite the fact that an abnormal finding in the electrophysiological study or a positive response to the head up tilt testing has a diagnostic value, it must be considered that these diagnostic tests are provocative tests that can show abnormalities likely to be the cause of syncope, but they do not give definite information about the etiologic correlation between those findings and syncope. In addition, a substantial

proportion of patients have more than one abnormal finding on these tests and the clinical significance of these findings must be judged.

Following the partial inability of the previous tests to identify the underlying etiology of syncope, it is obvious that the reference standard for establishing a diagnosis in patients with recurrent and unexplained syncope is the recording of physiological parameters during a clinical episode. Devices that are worn continuously and have memory capacity can record and save data that occurred before and after the symptom that is under investigation. This type of device is called a continuous-loop event recorder.

Recent advances in external and implantable loop recorder technology have enhanced the ability to detect or rule out intermittent arrhythmias in patients with recurrent syncope. The external loop recorder is a quite useful device for the management of syncope and the assessment of its potential arrhythmic causes. This device is connected to the chest wall of the patient with surface electrodes. The newer devices are technologically superior and smaller than the older ones, with a larger battery capacity, so that they can be attached to the patient for weeks or months at a time. When the device is activated by the patient (who pushes a button on the recorder), the system stores the ECG recordings obtained during the previous minutes and some minutes after activation[32]. This time interval recorded before the button is pushed is often programmable and depends on the type of monitor; it is acceptably long compared to the length of syncopal episodes. In one study of 57 patients with multiple recurrences of syncope (median of 10 episodes), an external loop recorder was used. With a follow-up period of 4 weeks, 32 patients experienced syncope. In 14 patients the loop recorder showed normal sinus rhythm, therefore an arrhythmia as the cause of syncope was excluded, while in 7 patients some type of arrhythmia was recorded. The arrhythmias recorded were ventricular tachycardia in one, supraventricular tachycardia in one, atrioventricular block in two and bradyarrhythmias in the remaining three patients that were considered to be a neurally mediated rhythm disturbance. In the remaining patients, the recording during syncope was not feasible, mainly due to technical problems with the electrode contact to the skin or because the patients had the device disconnected or not in use during the syncopal episode[33]. The use of an external loop recorder may increase the diagnostic yield but long-term compliance with this device can be problematic due to skin irritation and waning patient motivation in the absence of a recurrence. This device appears to have its greatest role in highly motivated patients with frequent syncope where spontaneous symptoms are likely to recur within two to four weeks. Therefore, a loop recorder which is worn continuously, may be particularly useful if symptoms are quite brief or if symptoms include only very brief incapacitation such that the patient can still activate the recorder immediately after the episode and record the stored ECG. However, even a loop recorder with a long memory may not be useful if loss of consciousness includes prolonged disorientation on awakening that would prohibit the patient from activating the device.

Continuous ECG recording, though, would appear to be a promising diagnostic method for correlating the symptom with the cardiac rhythm. As a result of technological development, and in order to improve the diagnostic yield of the external loop recorder, an implantable loop recorder has been developed and is now available as a diagnostic tool in the evaluation of patients with recurrent and unexplained syncope. This is a pacemaker-sized device, small and light, which can be implanted in the subpectoral or submammary region. The most preferable region to implant the device is the left pectoral region near the first rib, close to the sternum and away from the lower half of the pectoral area. The device provides storage of both patient-activated and automatically detected (autoactivated) events and has an expected battery life of approximately 14 months. The duration of the stored ECG for each episode is longer than that of the external loop recorder, increasing the possibility of recording cardiac rhythm abnormalities during prolonged episodes of palpitations or syncope. The fact that this device is implanted subcutaneously eliminates the possibility of contact problems or artifacts.

In a recent study, 85 patients with diagnosed syncope, or near syncope, underwent insertion of an implantable loop recorder[34]. During a 10.5±4 month follow-up period, syncope recurred in 58 patients (68%). An arrhythmia was recorded in 42% of patients who recorded a rhythm during recurrent symptoms, with bradycardia present in 18 and tachycardia in 3 patients. Five of the 18 bradycardic patients and 2 additional sinus rhythm patients received a clinical diagnosis of neurally mediated syncope. The authors reported that the diagnostic yield of the

implantable loop recorder is approximately 65%. Results from other studies are similar, reporting that a normal heart rhythm during syncope was recorded in approximately 50% of all patients with syncope. In the other 50%, bradycardia and asystole were recorded more often than tachycardia. In addition, a high diagnostic yield of the method was reported, along with a low non-compliance rate[35-37]. In another very important study called ISSUE[38], an implantable loop recorder was applied in 52 patients with bundle branch block and negative findings from the typical diagnostic procedures. During a follow-up period of 3 to 15 months, syncope recurred in 22 patients (42%) and in 19 of them the event was documented after a median of 48 days. One or more prolonged asystolic pauses, mainly attributable to AV block, proved to be the most frequent finding in 17 patients, while in the other 2 patients normal sinus rhythm or sinus tachycardia were found. Moreover, 2 patients had presyncope due to AV block with asystole and 3 patients developed nonsyncopal persistent 3rd degree AV block.

Therefore, the implantable loop recorder seems to be a useful diagnostic tool in patients with recurrent syncope of unknown etiology. The device is easy to implant and is of most benefit for establishing a diagnosis when syncope is recurrent but too infrequent for conventional monitoring techniques. The limitations of the system are the necessity for surgical implantation and the inability to monitor blood pressure. The diagnostic problems related to the inability of the device to evaluate the arterial blood pressure can be partially resolved by analyzing the heart rate behaviour before, during and after the occurrence of symptoms. Another point is the cost of the device, which is a problem in many countries because public and private insurance companies are unwilling to pay for diagnostic implantable devices[39].

In summary, syncope remains a difficult diagnostic problem because of the intermittent, sporadic and unpredictable nature of the symptoms. The physician must obtain a symptom-rhythm correlation in light of the concern that syncope reflects a malignant but treatable cardiac arrhythmia. In patients with syncope, a history and physical examination and resting ECG are indicated. Testing after the initial assessment is of low yield (Table 1) unless directed by clinical suspicion arising from the assessment. The noninvasive diagnostic tests are associated with a very low diagnostic yield in the syncopal patient. On the other hand, the provocative diagnostic tests, such as head-up tilt testing or electrophysiological study, do not always have high prognostic value and are hampered by the need for considerable clinical interpretation of results and unknown sensitivity and specificity in the absence of a gold standard. Ideally, the clinician would like to obtain a correlation between symptoms and multiple physiologic parameters including heart rate, arterial blood pressure and nervous system functional status. Loop recorder technology represents a step toward obtaining this gold diagnostic standard.

Table 1. Diagnostic yield of different tests in patients with unexplained syncope. (EPS=electrophysiological study).

Diagnostic test	Diagnostic yield
Surface ECG	2-11%
Holter monitoring	1-2%
Exercise testing	< 1%
Passive tilt table testing	30-40%
Provocative tilt table testing	65-80%
EPS in pts with known structural heart disease	50%
EPS in pts without structural heart disease	10%
Implantable loop recorder	65%

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