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Clinical Laboratory Testing: What Is the Role of Tilt-Table Testing, Active Standing Test, Carotid Massage, Electrophysiological Testing and ATP Test in the Syncope Evaluation?

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ABSTRACT

The first step in the diagnostic evaluation of patients with suspected syncope begins with an "initial evaluation" consisting of careful history taking, physical examination including orthostatic blood pressure measurement and electrocardiogram. However, even in expert centers the diagnostic yield of this "initial evaluation" is only approximately 50%. In the remaining cases in which a satisfactory diagnosis is either unknown or uncertain after initial assessment, additional clinical testing is needed. This article reviews the role of some of the more commonly used additional diagnostic tests, including: tilt-table testing, the active standing test, carotid sinus massage, electrophysiological testing, and the adenosine triphosphate (ATP) test. The role of angiography, exercise testing and imaging is noted briefly. Other clinical laboratory investigations, such as ambulatory ECG monitoring, are examined in other papers in this issue. In brief, clinical laboratory tests, carefully interpreted, may be useful in the evaluation of the basis of suspected syncope. However, these tests should be selected carefully and performed based on the pre-test probability inferred from the initial examination, and the less invasive tests should be used first.

The first step of the diagnostic evaluation of every patient suspected of presenting with syncope begins with an "initial evaluation" as described in the Guidelines of the European Society of Cardiology[1]; this step consists of careful history taking, physical examination including orthostatic blood pressure measurement and electrocardiogram (ECG). However, even in expert centers the diagnostic yield of this "initial evaluation" is reported to be only approximately 50%.[2] This percentage, while inadequate, remains cost-effective because of the low cost associated with the initial "clinical" examination. However, in the remaining cases in which a satisfactory diagnosis is not made, and for many other patients in whom the suspected cause is 'uncertain' after initial assessment, additional testing is needed.

The aim of this article is to review the role of some of these additional diagnostic tests. The reader is also referred to other contributions in this syncope issue that examine topics such as the strategy for selection of diagnostic tests, and the role of diagnostic ambulatory ECG recordings. Consequently, we focus primarily on tests targeting the various forms of neurally-mediated reflex syncope, and to a lesser extent those causes in which electrophysiological testing is useful.

Tilt table testing

Tilt-table testing (TTT), known for many years by physiologists and used in aerospace medicine, was introduced In 1986 by

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Abbreviations and Acronyms

AECG = ambulatory ECG

ANS = autonomic nervous system

ATP = adenosine triphosphate

AV = atrioventricular

AVB = atrioventricular block

BBB = bundle branch block

CSH = carotid sinus hypersensitivity

CSM = carotid sinus massage

CSS = carotid sinus syndrome

DDD = dual chamber cardiac pacing

OOO = dual chamber pacemaker with outputs turned 'off'

ECG = electrocardiogram

ILR = insertable loop recorder

LVEF = left ventricular ejection fraction

OH = orthostatic hypotension

SNRT = sinus node recovery time

TTT = tilt-table test

VT = ventricular tachycardia

Kenny et al.[3] to evaluate patients with syncope of unknown origin.[3] This test investigates the response of the autonomic nervous system (ANS) to a gravitational stress namely the passive transition from supine to upright position. In this circumstance approximately one liter of blood migrates from the upper part of the body towards the large capacitance vessels of lower limbs and splanchnic areas.

The ANS normally permits successful response to such a major physiological change through an increase in heart rate and vasoconstriction. These adjustments allow maintenance of an adequate blood supply to the upper part of the body and particularly the brain. However, at times in some individuals the ANS response is inappropriate, with the paradoxical triggering of bradycardia (sometimes even cardiac pauses) and vasodilatation; the result is global cerebral hypoperfusion and loss of consciousness. These abnormal cardiovascular responses to stress are the essential features of reflex syncope and particularly vasovagal syncope.

Methodology

The initial TTT protocol proposed by Kenny et al.[3] included a period of supine position for 20 min followed by a period of passive upright position for 45 to 60 min. The test was considered positive when patients experienced syncope or at least near syncope with objective modifications in heart rate (bradycardia) and/or blood pressure (hypotension) measurements. However, this protocol was time-consuming, and shown to have a relatively low diagnostic sensitivity; consequently it was progressively substituted by more sensitive procedures that included pharmacological challenges with isoproterenol or nitrates. Sensitivity and specificity of the different protocols have been previously reported[4] and a few are summarized below.

At the present time, the most commonly used protocols are:

1) An initial period of 70° head-up tilt for 20 to 40 min (I.e., passive upright TTT), followed if non-diagnostic by intravenous injection of incremental low-doses (usually 3 mg/min) of isoproterenol titrated to raise baseline heart rate by 20%–25%[5] and,
2) a similar period of passive tilt followed if non-diagnostic by 300–400 mg of sublingual nitroglycerine.[6] Omission of the passive phase and beginning the test immediately with nitroglycerine have recently been proposed and may be effective to improve compliance in older patients.[7]

In both TTT protocols patients should be fasted for approximately 4 h, and the test should be performed in a quiet room with resuscitation equipment similar to that required for stress tests. In the isoproterenol protocol a pre-tilt phase of 20 min is required after venous cannulation, whereas with sublingual nitroglycerine the pre-tilt phase can be shortened to 5 min. Both protocols have similar rates of positive responses (61%–69%), with a high specificity (92%–94%).

The positive (diagnostic) TTT endpoint has remained unchanged since the initial introduction of the test,[3] and is induction of syncope or near-syncope associated with hypotension and/or bradycardia. Depending on the predominance of vasodilation (vasodepressor reflex) or bradycardia (cardioinhibitory reflex), responses have been classified as cardioinhibitory, vasodepressor, or mixed.[8] However it should be stressed that the type of response observed during TTT is not strongly predictive of the type of response observed during spontaneous syncope.[9,10]

Studies that have compared parameters observed during a positive TTT with those recorded by implantable loop recorder (ILR) during a spontaneous syncope in the same patients have concluded that a cardioinhibitory TTT response predicts with a relatively high probability a similar bradycardic outcome during spontaneous syncope. However, occurrence of a vasodepressor or mixed response does not exclude the presence of an asystole/bradycardic response during spontaneous syncope.[9,10] Finally a negative response to TTT does not eliminate vasovagal syncope as a cause of faints in particular patients.

Complications

Passive TTT is very safe and occurrence of death during the test has never been reported. Some very prolonged asystoles have been recorded (20–30 s is not rare), but normal rhythm resumed promptly when the patient returns to supine position. Some rare life-threatening ventricular arrhythmias have been described but only with isoproterenol provocation and in the presence of ischemic heart disease[11] or sick sinus syndrome.[12] Although unusual, these adverse events lead to avoiding administration of isoproterenol as a provocative measure in patients with ischemic heart disease, uncontrolled hypertension, left ventricular outflow tract obstruction, significant aortic stenosis or known ventricular arrhythmias.

Only minor side effects such as headache have been reported with the use of nitroglycerine. Atrial fibrillation is

uncommon, but has been observed during or immediately after a positive TTT; however, it is usually self-limited after a short duration.[13]

Indications

In the 1990's TTT was extensively used in many laboratories even when the vasovagal origin of syncope was quite obvious from the history. Now, TTT is less often performed and reserved for patients in whom the diagnosis of vasovagal syncope is suspected but cannot be definitely confirmed by medical history alone, including witness accounts.

In a sense, the initial success of TTT leads to its being less necessary. The early use of TTT in many patients with syncope has improved the knowledge of vasovagal syncope among clinicians, and thereby permitted the diagnosis to be made more readily only from history. As a result, TTT is no longer needed in patients in whom vasovagal syncope is highly probable after history taking.[14] However in some patients, even with a definite diagnosis of reflex syncope, TTT could be useful to demonstrate to the patient and/or to his/her family that the diagnosis is established; the positivity of the test in this situation plays a major role for reassurance and offers the patient the opportunity to learn of and respond to premonitory warning symptoms. It has been shown that the recurrence rate of spontaneous reflex syncope is significantly lower after a positive TTT.[15] In part patient adaptation may be at fault. In any case, due to this relatively low reproducibility, TTT is not of value for assessing effectiveness of treatment.[16]

Application of TTT may be useful for certain special circumstances. For instance, patients with jerking movements during loss of consciousness are often considered to have experienced an epileptic spell and are treated with antiepileptic drugs.[17] Nevertheless, some of them continue to have recurrence of symptoms in spite of seemingly adequate treatment. In such cases, a high percentage has, in fact, vasovagal syncope diagnosed by TTT.[17] Similarly, in some patients the psychiatric origin of loss of consciousness (i.e., pseudo-syncope) may be unmasked by reproduction of the symptoms during TTT but without objective changes.[18] Finally TTT may be useful in older patients to discriminate between reflex syncope and accidental falls.[19]

Active standing test

Orthostatic hypotension (OH) differs from vasovagal syncope as it is an inadequate sympathetic nervous system response leading to deficiency of vasoconstriction and an abnormal decrease in systolic blood pressure upon standing. The origin may be primarily neurologic disease in some patients, but is often triggered by or aggravated by iatrogenic factors such as drug therapy (e.g., diuretics, vasodilators, beta-adrenergic blockers) for concomitant conditions (e.g., hypertension). Another important orthostatic intolerance syndrome, Postural Orthostatic Tachycardia Syndrome (POTS) is not typically associated with syncope as a principal symptom, and is not discussed here.

Methodology

The delay in reflex blood pressure response between the change from recumbent to upright position and the appearance of symptoms (syncope is only one of these symptoms) leads to different OH syndromes.[1] Briefly immediate OH is defined as a rapid decrease in systolic blood pressure within 3 min after standing while delayed OH occurs in older persons and is characterized by a slow and very progressive decrease of systolic blood pressure after assuming erect position.

"Classical OH" investigated during the "initial evaluation" of the syncope patient requires repeated measurements of blood pressure for 3–5 min after standing. A sphygmomanometer may be appropriate in this case. Other types of OH also require repeated measurements but for longer periods and in these situations automatic arm-cuff devices are more appropriate. When frequent values are needed continuous beat-to-beat non-invasive measurements (e.g., Finapres®) can be used as is preferred during TTT. Orthostatic hypotension is diagnosed when systolic blood pressure decreases by≥20 mmHg (30 mmHg in hypertensive patients).[20]

Indications

Screening for OH is part of the "initial evaluation" and therefore should be done in every patient with syncope at least at the first visit, and particularly in older patients or in patients who have been prescribed anti-hypertensive or anti-depressive drugs. More delayed OH should be suspected in older patients essentially in the presence of other manifestations of ANS dysfunction or in the presence of diseases known to induce such dysfunctions (e.g., diabetes, Parkinson's disease, primary autonomic failure, etc.)[21]

Carotid sinus massage

Massage at the site where the common carotid artery bifurcates produces a slowing in heart rate and a decrease in blood pressure. In some individuals, generally older males, this physiological reflex is over expressed and results in an exaggerated response. Carotid sinus hypersensitivity (CSH) is characterized by occurrence of a ventricular pause lasting≥3 s and/or a fall in systolic BP of≥50 mmHg during carotid sinus massage (CSM). Although considered too sensitive by some authors[22] these criteria are currently generally accepted in clinical practice.[1] When associated with spontaneous syncope, CSH becomes carotid sinus syndrome (CSS).

Methodology

Carotid sinus massage is performed for a duration of 7 to 10 s sequentially at the right and left glomus in the supine patient. However, if CSM with the patient supine is non-diagnostic, it is repeated with the patient in a head-up posture (e.g., on a tilt-table) to allow a better evaluation of the vasodepressor component of the syndrome. In either case, CSM should be undertaken using continuous monitoring of heart rate and

optimally with beat-to-beat blood pressure measurement (e.g., Finapres ®). If the latter equipment is not available, then periodic (approximately each minute) measurements of blood pressure should be recorded.[23]

CSS is diagnosed if CSH associated with a history of spontaneous syncope or near-syncope is detected during CSM. Isolated CSH is a common finding in older individuals particularly males,[24,25] but CSS is uncommon and very exceptional in subjects under 40 years of age.[23]

Complications related to CSM are most often neurological, but very rare; 21 instances among 7319 patients.[23,26,27] However, the neurologic risk contraindicates CSM in patients with previous transient ischemic attack or stroke within the past 3 months, or with carotid bruits, unless carotid Doppler studies have excluded significant stenosis.[26]

Indications

Indications of CSM are broad and in fact it could be reasonably included in the clinical examination of patients with syncope aged ≥40 years in whom a precise diagnosis was not established after the "initial evaluation" alone. However, one must be careful to assess both the cardioinhibitory and vasodepressor components.

Electrophysiological testing

During the 1980's electrophysiological studies (EPS) were widely performed in patients with syncope.[28] However, it soon became apparent that their value for determining the cause of syncope was low and dependent on pre-test probability.

In a retrospective analysis of 8 studies including 625 patients with syncope, EPS showed positive results in a limited number of patients and almost exclusively in those with overt structural heart disease: 41% in patients with heart disease versus 5% in those without.[29] Furthermore development of non-invasive assessment such as long-term ECG monitoring has dramatically reduced the need for EPS for evaluation of patients with syncope. Recent registries show that patients with unexplained syncope evaluated by cardiologists undergo EPS in fewer than 2% of cases, and even fewer if they are evaluated by experts.[30–32] Nevertheless, EPS, if correctly performed, remains useful in specific situations.

Methodology

When preformed, EPS due to its invasive nature needs to be as complete as possible to avoid repeated examinations (e.g., a patient with a left bundle branch block could have a paroxysmal atrioventricular block (AVB) but also a ventricular tachycardia). However the EPS strategy should be guided by the pre-test analysis (suspected bradycardia or tachycardia). However, in the absence of clear pre-test possibility, sinus node and AV functions should be evaluated in addition to attempts to induce tachycardia using standard protocols for such testing.

Another major problem is that an "abnormal" finding during EPS is not necessarily definitive as the cause of syncope; for example a prolonged HV interval at 65 ms does not mean that the spontaneous syncope has been the consequence of a paroxysmal AVB.

Indications

EPS is indicated only when the cause of syncope remains doubtful after the initial evaluation and there is a high probability that this syncope is related to paroxysmal bradycardia or tachycardia (e.g., history suggesting palpitations, presence of structural heart disease).

Suspected intermittent bradycardia

In the case of suspected sinus node disease, EPS is not the most effective test to confirm the diagnosis. Ambulatory ECG (AECG) monitoring (often extending over many days or even weeks) is much more effective and used in most published series.[33] An insertable loop recorder (ILR) may be essential to provide sufficient recording duration to capture a spontaneous event. Furthermore. the value of a prolonged sinus node recovery time (SNRT) remains questionable. An abnormal SNRT after abrupt cessation of rapid atrial pacing is typically defined as a value>1.6 s or 525 ms for corrected SNRT.[34] However these values seem "too limited" and a corrected SNRT >800 ms has been reported to be more sensitive in patients with syncope.[33]

Patients with syncope and bundle branch block (BBB) on standard ECG are at higher risk of developing paroxysmal AVB. In this situation, AECG monitoring, with the notable exception of ILRs and mobile cardiac telemetry (MCOT in the USA), is not generally diagnostic. EPS with evaluation of intra and infra-Hisian conduction time is a recommended option.[1] An HV interval≥70 ms in patients with syncope and BBB is considered abnormal and highly suggestive of AVB when ≥100 ms.[35]

Development of intra- or infra-His block during incremental atrial pacing or pharmacological challenge by class I antiarrhythmic drugs is highly predictive of impending AVB, but has a relatively low sensitivity. In this population specificity of HV duration assessed in patients with ILR was also reported to be low and approximately 30% of the patients with a normal EPS developed intermittent or permanent AV block during follow-up.[36] Finally EPS is indicated in patients with syncope and BBB but conclusive only when exhibiting evident abnormal intra or infra Hisian conduction.

Suspected paroxysmal tachycardia

Tachycardia may be suspected when syncope is preceded by a brief period of sudden-onset palpitations. However, absence of this symptom does not exclude tachycardia as the putative cause of syncope.

The tachycardia is assumed to be supraventricular in patients with previous documented narrow QRS tachycardia or in young otherwise healthy, normal heart individuals. Conversely, a ventricular tachycardia (VT) is more likely to be suspected in older patients or those patients with overt heart disease. In these situations EPS could be useful particularly if

an ablation procedure is planned when tachycardia is induced during EPS.

Induction of VT is highly predictive of spontaneous VT in patients with ischemic heart disease and moderately altered left ventricular ejection fraction (LVEF)[37] whereas induction of ventricular fibrillation is generally considered to be a non-specific finding.[38] Absence of induction of VT in patients with heart disease identifies a subset of patients with syncope and good outcomes.[39] It should be emphasized that in patients with low LVEF (<35%) EPS is not as essential as these patients are already candidates for implantation of a defibrillator (ICD).[40] However, confirming a basis for syncope is still worthwhile. Further, VT induction may help define appropriate ICD programming.

In patients with channelopathies and syncope, EPS is generally considered unproductive. In these circumstances patients with syncope are considered at higher risk of sudden death. While treatment recommendations may vary, ICD therapy is often recommended in high-risk scenarios. Many attempts have been made to show that EPS could more accurately stratify these patients but, as of now, there is no consensus, even in patients with Brugada syndrome.[41]

It should be stressed that in patients with syncope and suspicion of Brugada or Long QT syndrome injection of antiarrhythmic drugs may unmask a typical ECG morphology and thereby confirm the diagnosis (although establishing that the syncope was due to Torsades de Pointes VT is another matter).

ATP test

In 1997 Flammang et al. proposed the ATP test as a useful tool to identify the cause of syncope of unknown origin.[42] They reported that in a high proportion of such patients, injection of ATP induced AVB for a longer period of time than in control patients. In spite of these results this test never gained wide acceptance and was challenged by some studies that concluded that the results of ATP test was not closely matched by the findings obtained by ILR during spontaneous syncope.[9] Recently, however, two studies have re-energized consideration for this test as a possible "discoverer" of AVB.[43,44]

Methodology

The test is performed under continuous ECG monitoring and requires intravenous injection of a 20 mg bolus of ATP (adenosine has been tried in countries without access to ATP, but appears to be an inferior option) dissolved in 10 ml of saline solution. Patients should be advised of the likelihood of face flushing and sensation of warmth. The contraindications are asthma or severe respiratory disease.

The outcome of the ATP-test has been determined in 2 ways: (i) a >10 s ATP-induced cardiac pause (CP) whether due to suppressed SN automaticity or AVN conduction block, considering conducted QRS complexes only; and, (ii) the longest RR interval >6 s irrespective of the origin of the bordering QRS complexes. The former appears to be the more useful and predictive measure.[42]

Indications

Induction of AVB in patients with syncope of unknown origin but not in controls suggests that a paroxysmal AVB could be the cause of the spontaneous syncope particularly in older females.[45] However the relative poor correlation between ATP-induced AVB and ECG recordings during spontaneous syncope led to consider that a positive ATP test is not useful to recommend pacemaker implantation.[1] Nevertheless a multicenter trial demonstrated recently that patients with positive ATP test and randomized to DDD pacing had significantly fewer syncope recurrences than those randomized to OOO pacing.[44]

Finally it seems that the ATP test could be helpful in patients, particularly older women, with unexplained syncope, a "normal" ECG and without overt heart disease. In this subgroup of patients induction of a prolonged but self-terminating AVB during injection of ATP is a strong argument that AVB is the cause of spontaneous syncope and that a pacemaker is therefore appropriate.

Additional tests

Many other tests such as coronary angiography, signal-averaged electrocardiography, and cardiac imaging could be proposed in patients with syncope. However, they are only recommended in specific situations after careful history taking suggesting that they could be helpful. For example, exercise stress test may be useful to reproduce the circumstances in patients in whom syncope was associated with physical exertion. Such testing might uncover ischemic heart disease, chronotropic incompetence or autonomic failure in such a case.

Conclusion

Although the "initial evaluation" remains the cornerstone in the diagnostic strategy of patients with syncope, additional carefully selected tests may be mandatory in a large proportion of patients. However all of these examinations have one major limitation: they are temporally removed from the syncope itself, and as such their results are always questionable as they rarely reproduce the patient's symptoms precisely, or the patient is simply uncertain if their symptoms have been replicated. Furthermore even in the event that syncope is reproduced, another cause may have been at fault during spontaneous syncope especially in older patients. In spite of these limitations, selected tests, carefully interpreted by experienced practitioners, are useful and should be completed but with two prerequisites: they should be performed based on the pre-test probability inferred from the initial examination, and the less invasive tests should be used first.

Statement of Conflict of Interest

All authors declare that there are no conflicts of interest.

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