Current investigations used to assess syncope

W Arthur, G C Kaye

Following a thorough history, physical examination, and electrocardiography, the cause of syncope remains undiagnosed in around 50% of patients.¹ Diagnostic investigations are performed to confirm a suspected diagnosis or to explore another potential cause. When exploring the cause of syncope, features of the initial history and examination should direct the investigations wherever possible.

The usefulness of a test can be described in various terms. The sensitivity of a test measures how effective it is in detecting those individuals who are truly diseased (true positives). The specificity of a test measures how effective it is in detecting those individuals who are not diseased (true negatives). The positive predictive value of a test is the probability of actually having a condition given that the test result is positive. The negative predictive value is the probability of not having the disease given that the test is negative. The diagnostic yield of a test is defined by the percentage of patients who receive a diagnosis or have a diagnosis confidently dismissed as a consequence of the test. That is the sum of the number of true positives and, if available, true negatives as a proportion of the total number of tests performed.

Echocardiography

Information gained from the history or physical examination usually indicates whether or not echocardiography would be useful. The diagnostic yield in the absence of historical, physical, or electrocardiographic findings is low.² However, when clinical heart disease is suspected the echocardiogram is very useful for confirming valvar abnormalities, ventricular hypertrophy, and ventricular dysfunction.

Exercise stress testing

Those who experience syncope on exertion in the absence of ventricular outflow tract obstruction should undergo exercise testing. During exercise, increased levels of circulating catecholamines may precipitate ventricular tachycardia in those with ischaemia or catecholamine sensitive ventricular tachycardia. Once again the history alone should direct the clinician towards the correct use of treadmill testing in appropriate cases. Unselective exercise testing delivers a poor diagnostic yield in the investigation of syncope.³

Ambulatory electrocardiographic monitoring

To diagnose an arrhythmia as the cause of syncope requires that the patient has an episode during monitoring. The vast majority of detected arrhythmias are brief and result in no symptoms. Conversely, prolonged ambulatory ECG or Holter monitoring often shows

evidence of arrhythmias in normal asymptomatic individuals.⁴ Complete heart block, sinus pauses of more than two seconds, and ventricular tachycardia are, however, rarely reported in asymptomatic patients. Documentation of significant arrhythmias or syncope during monitoring is rare. A review of several large studies examining the rates of symptomatic correlation using ambulatory monitoring revealed a figure of only 4%.⁴ The patients who benefit most from Holter monitoring are those with multiple or frequent episodes of syncope over a short period of time.

In patients with infrequent symptoms, "loop" ECG recorders are of greater value. The cardiac loop ECG recorder has digital memory as well as a "leading edge" memory loop that continuously stores several minutes of the ECG in digital form. The patient can therefore activate the device during the prodrome of an event or upon arousal. The preceding cardiac rhythm is stored, as well as the subsequent 30 to 60 seconds of rhythm. The patient activated loop recorder has been shown to determine definitively whether an arrhythmia was the cause of symptoms in 25% of cases; this compares favourably with the 10% diagnostic yield of ambulatory Holter monitoring.⁵ Unfortunately many older patients are unable to tolerate the prolonged daily use of these recorders, and up to 20% of patients do not wear or operate the device appropriately.⁵ Loop recorders range in price from between £500 to £1700 (+VAT).

Long term ECG monitoring with an insertable loop recorder (ILR) (Reveal[®]; Medtronic, Minneapolis, USA) extends the monitoring period and reduces patient non-compliance (fig 1). Implantation ensures continuous use and allows capture of the ECG even during physical activity precluded by external devices. An external activation device is used at the time of symptom onset or after syncope. The device continuously records the ECG into its looping memory and can be programmed to store up to three events. Four programmable storage modes are available, allowing up to 42 minutes of diagnostic ECG recording (fig 2).

Figure 1 Reveal[®] insertable loop recorder.

Department of
Cardiology, Castle Hill
Hospital, Castle Road,
Cottingham, East
Yorkshire HU16 5JQ,
UK
W Arthur
G C Kaye

Correspondence to:
Dr Wayne Arthur,
Department of Cardiology,
Peterborough District
Hospital, Thorpe Road,
Peterborough PE3 5DE, UK
wayne@
denecres.freemove.co.uk

Submitted 30 December
1999
Accepted 16 February 2000

Figure 2 The four storage modes of the Reveal® insertable loop recorder.

Diagnostic yields of between 60% and 94% have been reported using the ILR.^{6,7} The ILR is of most benefit for establishing a diagnosis when symptoms are recurrent but too infrequent for conventional monitoring techniques. The device is useful for patients who remain undiagnosed despite in depth investigation or for those in whom compliance or lifestyle makes the use of external monitoring systems impracticable. The ILR costs around £1400 (+VAT). There is a small risk of infection at the time of implantation of the ILR, and the device will not detect syncope related to hypotension, although this might be inferred following examination of the heart rate response before and during symptoms. It must be remembered that both the external and internal loop recorders are merely ECG recorders and neither is equipped with diagnostic capabilities to differentiate cardiac arrhythmias.

Electrophysiological testing

Electrodes incorporated into the tips of catheters positioned within the cardiac chambers allow passage and measurement of electric current. Conduction times can be measured between specific cardiac sites, thus determining the predisposition to abnormalities of cardiac conduction. In addition, electrical extrastimuli coupled to normal sinus rhythm or paced rhythms can be used to evaluate the propensity for developing tachyarrhythmias and allow analysis of the mechanism of arrhythmias.

Electrophysiological studies have previously been used to evaluate patients with syncope in whom non-invasive testing has been negative or non-diagnostic. The essential problem with this technique is the need to extrapolate from abnormal test results to a cause for spontaneous syncope. The results of electrophysiological studies are more likely to be “abnormal” or “positive” in those with organic heart disease; the best predictor of a positive study is an ejection fraction of less than 40%.⁸

Various arrhythmias can be evaluated by an electrophysiological study, but the test has differing capabilities for assessing each rhythm disturbance. Generally, electrophysiological studies have a low sensitivity in patients with bradyarrhythmias associated with syncope.

The sensitivity for detecting sinus node dysfunction is low compared with the results from ambulatory monitoring.⁹ Similarly tests for atrioventricular nodal conduction have a low sensitivity and even when detected they are so dependent on autonomic tone that few clinical decisions can be made based on isolated laboratory results.¹⁰ Syncope can be attributed more confidently to abnormalities of His-Purkinje conduction; however, these are rarely found. The combination of pre-excitation and syncope requires an urgent electrophysiological study and radiofrequency ablation of the accessory pathway. Patients with Wolff-Parkinson-White syndrome and syncope are at risk of a rapid ventricular response degenerating to ventricular fibrillation during reentrant tachycardia or atrial fibrillation. Definitive treatment of the accessory pathway should not be delayed even though further evaluation in these patients may occasionally uncover another cause for syncope.

Syncope associated with induced ventricular tachyarrhythmias on electrophysiological testing is accompanied by a high risk of death, similar to that in patients with documented spontaneous ventricular tachyarrhythmias.¹¹ Induction of sustained monomorphic ventricular tachycardia (lasting > 30 seconds) in a patient who has experienced syncope makes this arrhythmia the likely cause of the syncopal episode. Other less specific rhythms such as non-sustained ventricular tachycardia, polymorphic ventricular tachycardia, and ventricular fibrillation can be induced during aggressive electrophysiological studies in normal subjects, so their relevance is more difficult to explain. The type and severity of cardiac disease largely determine the frequency with which ventricular tachycardia can be induced in patients with syncope. Patients with previous myocardial infarction, bundle branch block, and, most importantly, an ejection fraction less than 40% are those most likely to have inducible monomorphic ventricular tachycardia.^{12,13} A negative stimulation response does not exclude a ventricular arrhythmia as the cause of the patient's previous symptoms. Cardiac arrest survivors with poor left ventricular function and negative electrophysiological studies have rates of sudden death of up to 30% at one year.¹⁴ Cardiac arrest survivors with a negative study and good left ventricular function have a sudden death risk of ~5% per year.¹⁴ The underlying functional state of the patient's heart is therefore the most important factor determining the usefulness of the electrophysiological studies and ultimately the prognosis of the patient.

Tilt table testing

There is no gold standard by which to evaluate the presence of neurally mediated reflexes implicated as causes of syncope. Tilt table testing has emerged since 1986 as a safe and effective method of identifying individuals with a susceptibility to neurally mediated syncope.¹⁵ Tilt table testing may be performed alone or with pharmacological provocation using isoprenaline or nitrate preparations. The tilt table

test is best considered for patients with suspected neurally mediated syncope but in whom the cause is not obvious or in patients with syncope of otherwise unknown origin with no evidence of heart disease.

The major problem with tilt table testing is quantifying the test's sensitivity, as there is nothing to compare it against other than a clinical diagnosis. The sensitivity of the test has been calculated at between 20% and 75%.¹⁶ Pharmacological provocation increases the sensitivity of the test at the expense of a reduction in specificity.¹⁶ Despite some concerns over the sensitivity and reproducibility of results, the upright tilt test has provided diagnostic information in a large number of patients who otherwise would have remained undiagnosed. A high proportion of these patients would perhaps proceed to expensive and invasive studies with ultimately little reward. In one series of 745 patients in whom non-invasive investigation had not provided a diagnosis for syncope, the upright tilt test was positive in 62%.¹⁷ Those with the highest tilt test positivity were young (< 25 years old), and had experienced syncope within the preceding 30 days. In those known to have structural heart disease in whom electrophysiological studies have not given a diagnostic clue, tilt table testing may prove cost-effective by avoiding expensive and unrewarding neurological investigations such as computed tomography or electroencephalography which might otherwise be requested.

Interestingly, the frequency of syncope decreases following a positive test regardless of therapeutic intervention.¹⁸ The test may educate the patient to recognise the warning signs of syncope and to make appropriate changes in posture.

Other testing

In the patient with known ischaemia and syncope, coronary angiography is indicated to determine whether revascularisation is required. Cardiac catheterisation may also be indicated in those with structural heart disease to assess the haemodynamic status of the patient.

Unless the patient has focal neurological signs or there is a suggestion of epilepsy from the history, then brain imaging, carotid artery Doppler scanning, and electroencephalography have a very low diagnostic yield in the syncopal patient.¹⁹ Routine biochemistry or haematology tests are rarely cost-effective unless the history offers clues such as the presence of diabetes mellitus or a suggestion of gastrointestinal blood loss. Basic psychiatric evaluation is an important part of the initial clinical assessment. Close attention to this should be paid in younger patients with recurrent syncope who are free of cardiovascular disease.²⁰ Evidence of psychiatric illness may become apparent during the course of investigation, implausible symptoms and signs coupled with consistently normal investigations may be an indication for formal psychiatric evaluation.

Summary points

- When exploring the cause of syncope, features of the initial history and examination should direct the course of investigation.
- The presence of structural heart disease primarily dictates the effectiveness of the investigation of syncope.
- The insertable loop recorder is useful for diagnosing the cause of infrequent episodes of syncope.
- In the absence of neurological symptoms, brain imaging, carotid artery Doppler scanning, and EEG recordings have a very low diagnostic yield.

Conclusions

The history, examination, and initial ECG are the most important steps in the assessment of syncope. From the initial clinical assessment the direction of investigation can be constructed. The older patient with ischaemic heart disease and a low ejection fraction should be directed towards those investigations looking for ventricular arrhythmias. In patients with documented monomorphic ventricular tachycardia an electrophysiological study should be employed early. If structural heart disease is present in the young, ambulatory ECG monitoring is recommended; if non-diagnostic, evaluation with electrophysiological testing should be considered. In the absence of cardiac disease and with no clinical clues, loop ECG recordings or tilt testing may be more appropriate. A large proportion of younger patients (less than 60 years of age) with syncope but without heart disease are likely to have neurally mediated syncope. The insertable loop recorder and tilt testing offer the opportunity to diagnose the cause of syncope correctly in a group of patients who previously would have been labelled as having syncope of unknown origin.

- 1 Linzer M, Yang EH, Estes NA, *et al*. Diagnosing syncope. Part 2. Unexplained syncope. Clinical efficacy assessment project of the American College of Physicians. *Ann Intern Med* 1997;127:76–86.
- 2 Recchia D, Barzilai B. Echocardiography in the evaluation of patients with syncope. *J Gen Intern Med* 1995;10:649–55.
- 3 Boudoulas H, Schaal SF, Lewis RP, *et al*. Superiority of 24-hour outpatient monitoring over multi-stage exercise testing for the evaluation of syncope. *J Electrocardiol* 1979;12:103–8.
- 4 Kapoor WN. Diagnostic evaluation of syncope. *Am J Med* 1991;90:91–106.
- 5 Linzer M, Pritchett ELC, Pontieue M, *et al*. Incremental diagnostic yield of loop electrocardiographic recorders in unexplained syncope. *Am J Cardiol* 1990;66:214–19.
- 6 Krahn AD, Klein GJ, Norris C, *et al*. The etiology of syncope in patients with negative tilt table and electrophysiological testing. *Circulation* 1995;92:1819–24.
- 7 Krahn AD, Klein GJ, Yee R, *et al*. Use of an extended monitoring strategy in patients with problematic syncope. *Circulation* 1999;99:406–10.
- 8 Denniss AR, Ross DL, Richards DA, *et al*. Electrophysiological studies in patients with unexplained syncope. *Int J Cardiol* 1992;35:211–17.
- 9 Fujimara O, Yee R, Klein GJ, *et al*. The diagnostic sensitivity of electrophysiological testing in patients with syncope caused by transient bradycardia. *N Engl J Med* 1989;321:1703–7.
- 10 DiMarco JP. Value and limitations of electrophysiological testing for syncope. *Cardiol Clin* 1997;15:219–32.
- 11 Olshansky B, Hahn EA, Hartz VL, *et al*. Clinical significance of syncope in the electrophysiologic study versus electrocardiographic monitoring (ESVEM) trial. The ESVEM Investigators. *Am Heart J* 1999;137:878–86.
- 12 Krol RB, Morady F, Flaker GC, *et al*. Electrophysiological testing in patients with unexplained syncope: clinical

- non-invasive predictors of outcome. *J Am Coll Cardiol* 1987; **10**:358–63.
- 13 Olshansky B. Syncope: overview and approach to management. In: Grubb BP, Olshansky B, eds. *Syncope: mechanisms and management*. Armonk, NY: Futura, 1998:15–71.
 - 14 Middlekauff HR, Stevenson WG, Saxon LA. Prognosis after syncope: impact of left ventricular function. *Am Heart J* 1993; **125**:121–7.
 - 15 Kenny RA, Bayliss J, Ingram A, et al. Head up tilt: a useful test for investigating unexplained syncope. *Lancet* 1986; **i**:1352–4.
 - 16 Kosinski DJ, Grubb BP. Neurally mediated syncope with an update on indications and usefulness of head upright tilt table testing and pharmacologic therapy. *Curr Opin Cardiol* 1994; **9**:53–64.
 - 17 Folino AF, Buja G, Martini B, et al. Upright tilt test: correlation between results and patient clinical features. *PACE* 1996; **19**:1582–7.
 - 18 Sheldon R, Rose S, Flanagan P, et al. Effect of beta blockers on the time to first syncope recurrence in patients after a positive isoproterenol tilt table test. *Am J Cardiol* 1996; **78**:536–9.
 - 19 Linzer M, Yang EH, Estes NA, et al. Diagnosing syncope. Part 1. Value of history, physical examination, and electrocardiography. Clinical efficacy assessment project of the American College of Physicians. *Ann Intern Med* 1997; **126**:989–96.
 - 20 Jeong H, Kapoor W. Psychiatric illness and syncope. *Cardiol Clin* 1997; **15**:269–75.

IMAGES IN MEDICINE

Apoplexy in a recurrent pituitary adenoma

A 75 year old woman, with a history of trans-sphenoidal hypophysectomy for a non-secreting pituitary adenoma 15 years ago and currently on glucocorticoid and thyroid hormone replacement, was found unconscious on the floor. On arrival to the hospital she was tachycardic and hypotensive. Stress doses of glucocorticoids were given, resulting in normalisation of her blood pressure. Magnetic resonance imaging of the brain showed a $3 \times 2 \times 2$ cm pituitary macroadenoma with bleeding in the centre (figs 1 and 2). The patient was transferred to the neurosurgical service for further observation.

Pituitary apoplexy is a life threatening condition which requires prompt diagnosis and treatment. Usually it occurs in macroadenomas when the tumour outstrips its blood supply. This case shows that apoplexy can occur and should be suspected even in a patient with a previous history of hypophysectomy.

S BASARIA
A TURCHIN
A KRASNER

Division of Endocrinology and Metabolism,
Johns Hopkins University School of Medicine,
1830 E Monument St, Suite-333, Baltimore, MD 2287,
USA

Figure 1 Magnetic resonance imaging of the brain showed a $3 \times 2 \times 2$ cm pituitary macroadenoma with bleeding in the centre.

Figure 2 The tumour shown in coronal section.