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Reveiw Article

Evidence based evaluation of syncope of uncertain origin

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ABSTRACT
Syncope is a common medical condition encountered in clinical practice. The pathophysiology can be complex and at times making a definitive diagnosis can be difficult. It can be associated with high rates of morbidity and mortality. Physicians' approaches to this condition are varied and at times, due to lack of a methodical approach, potential life threatening conditions are missed. Some patients are under investigated while other patients are over investigated. This increases the already high health care costs associated with managing this condition. This article discusses an evidence based methodical approach to diagnosis and treatment of this often complex condition.
KEYWORDS
Syncope, Collapse, Guidelines

Introduction

Syncope is a common condition encountered in acute medical practice. Many patients with syncope are initially labelled as having "collapse query cause". It is defined as transient loss of consciousness (T-LOC) due to transient global cerebral hypoperfusion characterized by rapid onset, short duration, and spontaneous complete recovery[1]. Incidence of syncope is difficult to determine accurately as many cases remain unreported. Some studies quote an overall incidence rate of a first report of syncope to be 6.2 per 100 person-years. Clearly this is age related and the incidence increases dramatically in patients over the age of 70 years[2]. Syncope accounts for 1-6% of hospital admissions and 1% of emergency department (ED) visits per year[3-5]. Hospital episode statistics from NHS hospitals in England reported a total of 119,781 episodes of collapse/syncope for the financial year 2008-09 which is about twice the number of episodes reported in the year 1999-2000. About 80% of patients were admitted and they have an average length of stay of 3 days accounting for over 269,245 bed days during that financial year[6].

Syncope is also associated with significant mortality and morbidity if left untreated. Literature reports a 6-month mortality of 10%, which can go up to 30% if cardiac syncope is untreated[7]. Non-cardiac syncope is associated with a survival rate comparable to people with no syncope[2]. Syncope is also a risk factor for fractures related to falls especially in elderly and can cause significant morbidity in this group[8]. In addition, there are significant health care related costs associated with management of syncope. Cost per diagnosis can vary from over £611 in the UK to €1700 in Italy. Hospitalisation alone accounted for 75% of cost in some studies[9,10]. Diagnosis of this condition can be difficult especially if there is a lack of structured approach. Over the last few years this topic has attracted enormous interest and several studies have been published, aiming at improving the approach to this condition. Standardised syncope pathways improve diagnostic yield and reduced hospital admissions, resource consumption and over all costs[10]. Recently the task force for the diagnosis and management of syncope of the European Society of Cardiology published guidelines for the diagnosis and management of syncope[1]. However, in spite of the available evidence very few hospitals have standardised syncope pathways for the management of this complex condition. Only 18% of EDs have specific guidelines and access to a specialist syncope clinic[11]. This article focuses on evidence based structured evaluation of syncope.

Current practice in the management of syncope

Due to the difficulty in diagnosis and mortality associated with this condition, a cautious approach may be taken by physicians resulting in hospitalisation of majority of patients presenting with syncope.

We recently audited the practice of syncope in our hospital, which is a tertiary centre in the north of Scotland. 58 patients admitted with this condition over a period of a month were included in the audit. It showed an average length of stay (LOS)

of 4.76 days in these patients. Due to a lack of methodical approach and standardised pathway for management of this condition many patients were subjected to several inappropriate inpatient investigations significantly prolonging the LOS and increasing the cost. Only 7 (12%) cardiac events were observed in this group and in retrospect a good methodical approach would have predicted these events. It should be noted that even in the geriatric population, reflex syncope that carries a benign prognosis is more common than cardiac syncope[2].

A systematic approach to the management of syncope (Figures 1 and 2).

Fig 1 – Approach to collapse query cause [1,39]

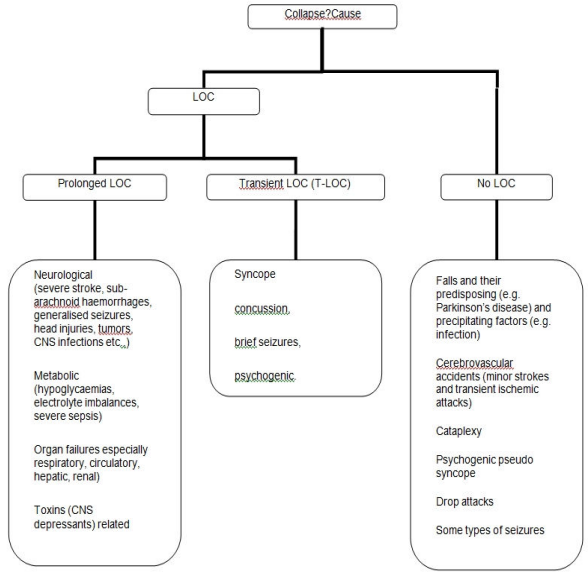
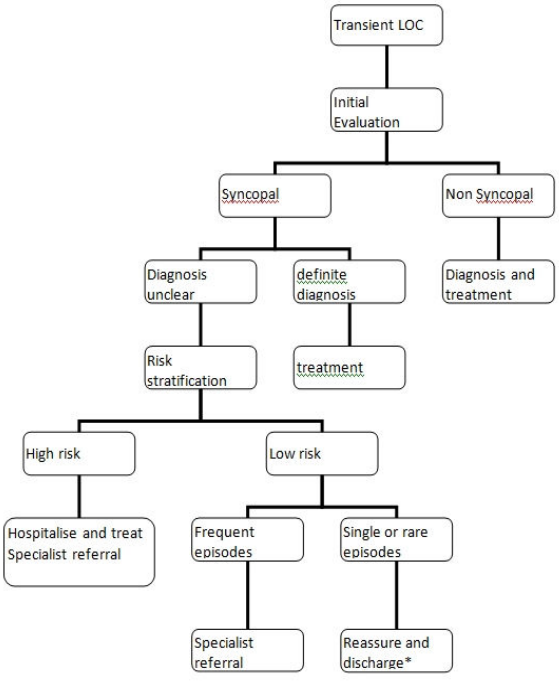


Fig 2 Approach to syncope (adapted from Parry, S.W et al) [40]



*see text for exceptions

The causes of syncope can be broadly divided in to cardiac causes and non-cardiac causes (Table 1). Initial evaluation leads to a diagnosis in less than 50% patients in most instances[4,12-14]. If there is uncertainty about diagnosis then the patient is risk stratified. High-risk patients are hospitalised, evaluated and treated whereas early discharge could be considered in low risk patients.

Aetiology of Syncope[41]

Neurally-mediated (Reflex) Syncope	**Cerebro vascular**
Vasovagal syncope Carotid sinus syncope Situational syncope e.g., Micturition, post prandial, defecation, cough	Vascular steal syndromes
Cardiac	**Orthostatic**
Structural cardio-pulmonary disease Obstructive valvular heart disease/cardiomyopathies Acute aortic dissection atrial myxoma pericardial tamponade pulmonary embolus pulmonary hypertension Cardiac arrhythmias Brady arrhythmias - Sinus node and AV node disease Tachyarrhythmias - Paroxysmal supraventricular and ventricular tachycardia, Inherited syndromes (prolonged QT, Brugada syndrome), Pacemaker or Implantable Cardioverter Defibrillator malfunction	Autonomic failure Primary autonomic failure syndromes e.g. Parkinson's disease, multi system atrophy, pure autonomic failure Secondary autonomic failure syndromes e.g. diabetic neuropathy, amyloid neuropathy Drug and alcohol induced orthostatic syncope Volume depletion

Initial evaluation (Table 2)

History Witness account Physical examination Vitals – heart rate, lying and standing blood pressure, oxygen saturation, blood glucose Standard 12 lead ECG Relevant blood tests (e.g. to rule out metabolic abnormality) Pacemaker check if appropriate

History

Many patients with syncope are initially labelled as having "collapse query cause". Loss of postural tone is termed "collapse". Indeed, the term "collapse query cause" does not give any useful information regarding the underlying condition.

A clear history from the patient and the bystander or witness (if available) is the key to the diagnosis. Firstly, determine if the collapse was associated with loss of consciousness (LOC). LOC can be transient (T-LOC) or prolonged. Categorising "collapse"

is important at this stage as the aetiology and approach to each category is different (Figure 1).

Secondly, establish if the collapse was syncopal. The LOC should be transient (e.g. did the patient regain consciousness in the ambulance, before or on arrival to hospital?), of rapid onset and associated with a spontaneous complete recovery. Also the mechanism should be due to transient global hypoperfusion. T-LOC secondary to other mechanisms such as trauma and brief seizures should be excluded. On occasions syncope could be associated with brief jerking movements mimicking seizures[15]. Also note that a transient ischemic attack (TIA), commonly listed as a differential diagnosis of syncope by physicians, is not a cause of syncope as this is not associated with global cerebral hypoperfusion.

The absence of a coherent history because patient had no recollection of events and there was no witness account available can make this distinction difficult. This is also particularly difficult in the elderly with cognitive impairment. Other useful information includes whether the syncope was associated with postural change. Orthostatic hypotension occurs after standing. If present it will be useful to check drug history (new vasodepressive drugs). Features suggestive of Parkinson's disease or amyloidosis may raise the possibility of autonomic neuropathy. A strong family history of sudden cardiac death may be of relevance. Table 3 summarises the features of neurally mediated and cardiac syncope.

Table 3 Features suggesting neurally mediated and cardiac syncope[42]

Neurally mediated	Cardiac
Preceded by prodrome Related to particular activity - e.g., Micturition, postprandial, prolonged standing, unpleasant situations Associated with nausea and vomiting After exertion	Absence of prodrome, no warning Associated with chest pain, breathlessness, palpitation During exertion or supine History of cardiac disease Family history of sudden cardiac death

Physical examination

The next step is a thorough physical examination. This should include an ABC approach if the patient is very ill and particular attention should be given to exclude immediate life threatening conditions such as pulmonary embolism, acute myocardial infarction, life threatening arrhythmias, acute aortic dissection, seizures *etc*… Recording the vital signs is important as it may give a clue to diagnosis (*e.g.*, acute hypoxia may indicate massive pulmonary embolism). Recording postural blood pressure when lying and during active standing for 3 minutes is useful to exclude orthostatic hypotension[1]. Recording a deficit in blood pressure in both arms may be a useful clinical finding especially if acute aortic dissection is suspected. Thorough cardio respiratory examination may reveal an obvious condition such as cardiac failure or aortic stenosis. Patients should also be examined for potential injuries as a result of syncope.

Standard ECG

A 12 lead ECG should be performed in all patients admitted with syncope. The abnormalities in table 4 would suggest a cardiac aetiology. The QT interval should always be measured, as it is a commonly overlooked abnormality.

Blood tests

Blood tests are usually unhelpful in establishing a diagnosis but can detect metabolic abnormalities such as hypoglycaemia, electrolyte abnormalities and other causes to explain LOC especially when witness account is not available. An acute drop in haemoglobin suggests blood loss. One recent study claims the usefulness of brain natriuretic peptide (BNP) for predicting adverse outcomes in syncope but it is not externally validated yet and it is too early to recommend for routine clinical practice[16].

Pacemaker check

It is not uncommon to see a patient with a pacemaker implanted, admitted to hospital with syncope. In these circumstances, it is essential to rule out a device malfunction although this is not a common cause of syncope. A preliminary and easy test will be interrogating the pacemaker if available. This should pick up any problems with the pacemaker in most instances.

With the above information establishing a diagnosis will be possible in a significant proportion of patients. Further investigations and management should be guided by the underlying diagnosis[1]. However in over half of patients the diagnosis may still be uncertain[12,13,17]. The following section explains the management of unexplained syncope.

Risk stratification in patients with unexplained syncope (Tables 4 and 5)

Table 4 ECG changes in 'high-risk' Syncope[41]

ECG changes favouring bradyarrhythmias

- High degree AV blocks – Mobitz type 2 second degree AV block, complete heart block, trifascicular block (first degree heart block with left bundle branch block (LBBB) or right bundle branch block (RBBB) with axis deviation)
- Bifascicular block (defined as either LBBB or RBBB combined with left anterior fascicular block or left posterior fascicular block) especially if new
- Other intraventricular conduction abnormalities (QRS duration >0.12 s)
- Asymptomatic sinus bradycardia (<50 bpm), sinoatrial block or sinus pause >3 s in the absence of negatively chronotropic medications

ECG changes favouring tachyarrhythmias

- Pre-excited QRS complexes (e.g. WPW syndrome)

- Prolonged QT interval
- Right bundle branch block pattern with ST-elevation in leads V1–V3(Brugada syndrome)
- Negative T waves in right precordial leads, epsilon waves and ventricular late potentials suggestive of arrhythmogenic RVD
- Q waves suggesting myocardial infarction
- Non sustained Ventricular Tachycardias

Table 5 – Clinical features of high-risk syncope[1,18-23]

- History of severe structural heart disease or heart failure, presence of ventricular arrhythmia
- Syncope during exertion or supine
- Absence of prodrome or predisposing or precipitating factors
- Preceded by palpitation or accompanied by chest pain or shortness of breath
- Family history of sudden cardiac death
- Examination suggestive of obstructive valvular heart disease
- Syncope associated with trauma
- Systolic blood pressure less than 90mm Hg
- Hematocrit less than 30% (acute drop in hemoglobin)

When the cause of syncope is uncertain it is essential to risk stratify patients to enable appropriate treatment and further investigation.

Risk stratification tools

There are several scoring systems for risk stratification of syncope. Syncope Evaluation in the Emergency Department Study (SEEDS), Osservatorio Epidemiologico sulla Sincope nel Lazio (OESIL score), Evaluation of Guidelines in SYncope Study (EGSYS score), San Francisco Syncope Rule (SFSR), The Risk stratification Of Syncope in the Emergency department (ROSE) and American College of Emergency Physicians clinical policy are the popular ones and each has its own advantages and disadvantages[1,16,18-23]. Discussing each scoring system is beyond the scope of this article and we shall restrict the discussion to the summary of these risk stratification tools (Table 5). It will be too early to include all the factors mentioned in the ROSE study, as it is not externally validated yet. It could be argued that taking all the risk factors described may increase admission rates but this approach may at least not miss the high-risk patient. This is a developing field and more evidence is likely to be published soon.

High-risk vs. low-risk syncope:

A high-risk syncope patient is the one where a cardiac cause is likely and where the short-term mortality is high due to major cardiovascular events and sudden cardiac death. High-risk syncope is said to be present if **any** of the features in the table 4 or 5 are present.

Management of low-risk syncope

Patients with a single or very infrequent syncope are usually reassured and discharged, as the short-term mortality is low[1,2]. Tilt table test is not usually required where a single or rare episode of neurally mediated syncope is diagnosed clinically. One exceptional circumstance where single rare episodes are investigated further with a tilt table test is when there could be an occupational implication (e.g. aircraft pilot) or if there is a potential risk of physical injury. Patients with recurrent unexplained syncope need to be further investigated (see below).

Management of high-risk syncope / suspected cardiac syncope

High-risk patients usually require hospitalisation and inpatient evaluation. Other high-risk patients who may be considered for admission are vulnerable patients susceptible to serious injuries, for example, elderly patient or a patient with multiple co-morbidities.

Further investigations (Table 6)

Non invasive	Invasive
Echocardiography ECG monitoring Telemetry Holter monitoring External loop recorder* Carotid sinus massage Cognitive testing (in elderly) Ambulatory blood pressure monitoring Tilt table test* Exercise stress test	Implantable loop recorder* Coronary angiography* Electrophysiology*

* Specialist Investigation

Echocardiography

Echocardiography is a relatively inexpensive and non-invasive investigation. It should be performed if there is a clinical suspicion of a significant structural abnormality of heart such as ventricular dysfunction, outflow tract obstruction, obstructive cardiac tumours or thrombus, pericardial effusion *etc*… The yield of this test is low in the absence of clinical suspicion of structural heart disease. However in the presence of a positive cardiac history or an abnormal ECG, one study detected LV dysfunction in 27% of patients and half of these patients had syncope secondary to an arrhythmia. In patients with suspected obstructive valvular disease 40% had significant aortic stenosis as a cause of syncope[24].

ECG monitoring

These tests have utility in identifying arrhythmogenic syncope. If a patient has syncope correlating with a significant rhythm abnormality during the monitoring period with the device, then the cause of syncope is due to the underlying rhythm abnormality. On the other hand, if no rhythm abnormality is recorded during a syncopal attack, then an underlying rhythm problem as a cause of syncope is excluded. Therefore, these tests are meaningful only if there is a symptom-rhythm correlation, which is the working principle of

these devices. In the absence of syncope, during the monitoring period, these tests may pick up other abnormalities that may be relevant. For example, rapid prolonged supra-ventricular tachycardias, ventricular tachycardias, periods of high degree AV blocks (mobitz type 2 or complete heart block) or significant sinus pauses >3seconds (except during sleep, negatively chronotropic therapy and trained athletes), which will require further investigation or treatment.

Telemetry

Telemetry can be used in inpatients. Although the diagnostic yield of this investigation is only 16%, given the high short-term mortality, this test is indicated in the high-risk group [1]. Usually patients are monitored for 24 to 48 hours although there is no agreed standard period for monitoring[25].

Holter monitoring

This involves connecting the patient through cutaneous patch electrodes. It records the ECG activity conventionally over 24-48 hours or at times up to 7 days.

It is particularly useful only in patients who have frequent regular symptoms (≥1 per week). For this reason, the yield of this test can be as low as 1-2% in unselected population[1]. Long inpatient waiting lists in some hospitals can significantly prolong the length of stay and cost. Selecting patients carefully for this test based on risk stratification will reduce costs and waiting lists.

Carotid sinus massage

This simple bedside test is indicated in patients over the age of 40 years with syncope of unexplained origin after initial evaluation. A ventricular pause lasting >3 s and/or a fall in systolic BP of >50mmHg defines carotid sinus hypersensitivity (CSH) syndrome. It is contraindicated in patients with recent cerebrovascular accidents (past 3 months) or with carotid bruit except when a Doppler study has excluded significant stenosis[1].

Cognition test

If an elderly patient had forgotten about the events, in the absence of an obvious cause, it may be useful to test cognition. If cognitive impairment is present, common problems associated with cognitive dysfunction should be considered e.g. falls, orthostatic hypotension.

Other investigations

In spite of the above tests if a cause is not determined, early specialist input is recommended for further investigation and treatment. The following non-invasive and invasive investigations may be appropriate in these circumstances.

An external loop recorder

This is a non-invasive form of electrocardiographic monitoring. The principle is same as that of Holter monitoring. External loop recorders have a loop memory that continuously records and deletes ECG. When activated by the patient, typically after a symptom has occurred, 5 – 15 min of pre-activation ECG is stored and can be retrieved for analysis. Studies have shown that they have increased diagnostic yield compared to Holter[1]. They should be considered in patients who have symptoms on a monthly basis.

A Tilt table test

This is indicated in cases of recurrent unexplained syncope after relevant cardiac causes of syncope are excluded and a negative Carotid sinus massage performed in the absence of contraindications. It is also indicated when it is of clinical value to demonstrate patients susceptibility to reflex syncope and thereby to initiate treatment. Other less common indications are recurrent unexplained falls, differentiate jerking movements secondary to syncope and epilepsy, diagnose psychogenic pseudo syncope and differentiate orthostatic and reflex syncope. Indication of this test in the context of a single unexplained syncope is discussed above.

Ambulatory blood pressure monitoring

This may be useful in patients with unexplained syncope particularly in old age to check if there is an element of autonomic failure and if a single set of orthostatic blood pressure recording is not helpful. In one study, it has been shown that 25% of the elderly patients admitted with falls or syncope had postprandial hypotension especially after breakfast[26]. It may be more readily available than a tilt table test in some centres.

Exercise stress test

This may be useful in a rare entity called exercise induced syncope. Outflow tract obstruction should be excluded by echocardiography before subjecting a patient to this test especially in the presence of relevant signs. However there is no evidence for supporting this test in investigating syncope in general population.

Implantable loop recorders

These are implanted subcutaneously. It needs to be activated either by the patient or a bystander after a syncopal attack. It is indicated in high-risk patients where a comprehensive evaluation did not establish an underlying diagnosis. In the absence of high risk factors, it is also indicated in patients with recurrent unexplained syncope especially if infrequent. Conventionally it is used as a last resort in patients with recurrent unexplained syncope as the initial costs are high. It has been shown in one study to be more cost effective

than the conventional strategy and was more likely to provide a diagnosis in patients with recurrent unexplained syncope[27]. However patients with poor LV function and those at high risk of life-threatening arrhythmias were excluded from this study.

Coronary angiography or CT coronary angiography

This may be helpful in suspected myocardial ischemia or ischemia related arrhythmias. Electrophysiological study may be considered in certain circumstances by cardiologists. When a standardised pathway is used, diagnosis is ascertained in 21% patients on initial evaluation and further 61% patients with early investigations. Only in 18% patients the diagnosis was still uncertain[12]. Other studies have shown similar results[28]. Although these results are from a dedicated syncope unit following a standardised pathway, these could be extrapolated to any unit following these standardised pathways. Further management is dictated by the underlying diagnosis with early specialist input for appropriate treatment.

Treatments

Single or rare episodes of reflex syncope do not require treatment. However, recurrent troublesome reflex syncope may warrant treatment. Treatment modalities are primarily non-pharmacological such as tilt training, physical counter pressure manoeuvres (leg crossing, hand gripping) and ensuring adequate hydration[29]. If refractory to non-pharmacologic measures midodrine (alpha agonist) may be considered in patients with frequent hypotensive symptoms[30,31]. Fludrocortisone may be used in elderly but there is no trial evidence to support this. Betablockers have been presumed to lessen symptoms but are shown to be ineffective in several studies [32]. They may potentially exacerbate bradycardia in carotid sinus syncope and are not recommended in treatment of reflex syncope. Treatment with cardiac pacing in reflex syncope is controversial and may be considered in patients with predominant cardio inhibitory response on carotid sinus massage (in CSH syndrome) or on tilt test (in reflex syncope). It should be noted that cardiac pacing has no effect on the often-dominant vasodepressor component of reflex syncope.

In patients with orthostatic hypotension, non-pharmacologic measures like increased salt and water intake, head up tilt sleeping, physical counter pressure manoeuvres, abdominal binders and compression stockings may help reducing symptoms. Midodrine is an efficient alternative in these circumstances and fludrocortisone also can be used.[33,34] Syncope secondary to cardiac arrhythmias needs treatment if a causal relationship is established. Potential reversible causes such as electrolyte abnormalities and drug induced causes should be excluded. Cardiac pacing is a modality of treatment in significant bradyarrhythmias secondary to sinus node or advanced AV nodal disease such as mobitz type 2 block, complete heart block or tri-fascicular block. Catheter ablation and anti-arrhythmic drug therapy are the main modalities of treatment for tachyarrhythmias. Implantable cardioverter defibrillator may be indicated in patients susceptible to malignant ventricular tachyarrhythmias. Treatment of syncope secondary to structural cardio pulmonary abnormality will need surgical intervention if possible.

Driving and Syncope

Doctors are poor at addressing and documenting this issue[35]. Table 7 gives some useful information from the DVLA website (http://www.dft.gov.uk/dvla/medical/ataglance)[36]. This information is country specific and subject to change.

Table 7 – Driving and Syncope in the UK[36]

Type of Syncope	Group 1 entitlement (car, motorcycle etc.,)	Group 2 entitlement (Large goods vehicle, passenger carrying vehicle)
Simple faint	No restrictions	No restrictions
Unexplained syncope with low risk of recurrence*	Allowed to drive 1 month after the event	Allowed to drive 3 months after the event
Unexplained syncope with high risk of recurrence** and cause identified and treated	Allowed to drive 1 month after the event	Allowed to drive 3 months after the event
Unexplained syncope with high risk of recurrence** and cause not identified	Licence is refused or revoked for 6 months	Licence is refused or revoked for 12 months

*Absent clinical evidence of structural heart disease and normal ECG

** Abnormal ECG, clinical evidence of structural heart disease, syncope causing injury, recurrent syncope

Syncope units

Syncope units aim to evaluate syncope (and related conditions) in dedicated units consisting of generalists and specialists with an interest in syncope. A sufficient number of patients are required to justify such a unit. They are well equipped with facilities for recording ECG, blood pressures, tilt table, autonomic function testing, ambulatory blood pressure monitoring, and invasive and non-invasive electrocardiographic monitoring. It has been shown to be cost effective and reduces health care delivery costs by reducing admission rates, readmission rates and event rates. Examples include the Newcastle model, Manchester model and the Italian model.[12,18,37,38]

Conclusions

The incidence of syncope is increasing in the UK with an aging

population. There is significant cost incurred in the delivery of health care for this condition. The approach to syncope varies widely amongst practising physicians due to lack of a methodical approach. A thorough initial evaluation yields a diagnosis in less than half of the patients. When the cause of syncope remains unexplained after initial evaluation, the patients should be risk stratified. While a patient with a single episode of low risk syncope can be reassured and discharged, those with high-risk features should be hospitalised for further management. Outpatient evaluation could be offered for low risk patients if recurrent. Early specialist input should be sought in high-risk syncope and recurrent unexplained syncope. This standardised approach or pathway will reduce cost by reducing hospitalisation, inappropriate investigations and length of stay.

Key Facts

- Collapse associated with transient loss of consciousness is called syncope if it is due to transient global cerebral hypoperfusion and characterized by rapid onset, short duration, and spontaneous complete recovery
- Standardised syncope pathways improve diagnostic yield and reduce hospital admissions, resource consumption and over all costs
- A thorough initial evaluation yields a diagnosis in less than half of patients. If the cause of syncope is undetermined after initial evaluation, patients should be risk stratified.
- Early discharge should be considered in low risk patients while high-risk patients need urgent evaluation.
- Early specialist referral is recommended in patients with high risk syncope and recurrent unexplained syncope

Future Interests

Syncope had been known for several decades and still remains a complex condition, as the exact mechanisms are poorly understood especially in non-cardiac syncope. Mechanism of syncope in the elderly patients may be different from those of young patients and studies should focus in understanding the mechanics. Further research is needed in risk stratifying syncope. It may enable us to develop more robust care pathways for management of syncope. The role of BNP in investigating and risk stratifying syncope need to be further clarified. In spite of sophisticated tests the cause of syncope in a proportion of patients remain uncertain. Studies should focus on the long-term outcome and management of syncope in this group. The role of implantable loop recorder in the investigation of syncope should be better defined and more studies should focus on when it should be offered in the pathway of management of syncope. Studies are also required to develop effective pharmacotherapies for this condition.

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