Evaluation and Management of Reflex Vasovagal Syncope—A Review

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Abstract
Syncope is a symptom that is commonly encountered in the practice and may point to a cardiac or neurological diagnosis. The evaluation of syncope rests on a thorough clinical evaluation, aided by electrocardiogram (ECG) findings, followed by risk stratification of the particular case. Once high-risk factors have been ruled out, the patient can be further diagnosed as having a reflex syncope (RS), orthostatic hypotension, or cardiac syncope based on specific clues. If the initial evaluation is not confirmatory various diagnostic tests may be used to guide further management (eg, long-term ECG monitoring, tilt table testing, etc). The management should be based on the overall profile of the patient and not only on any single test. In this review, we discuss the evaluation of a patient with RS and give an overview of treatments available for the patients.

Keywords
Reflex syncope, clinical evaluation, tilt table testing, implantable loop recorder, pacemaker

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Introduction
One of the most challenging symptoms to evaluate, encountered by the medical practitioners, is syncope (pronounced “sing-kuh-pee”). Syncope is a syndrome in which there is a total loss of consciousness due to cerebral hypoperfusion, characterized by a rapid onset, short duration, and spontaneous complete recovery.¹⁻³ Syncope can be caused due to traumatic head injury which is outside the scope of this article. Most of the syncope seen in clinical practice is

Abbreviations

AMI: Acute myocardial infarction
ARVC: Arrhythmogenic Right Ventricular Cardiomyopathy
AV: Atrioventricular
BP: Blood pressure
BrS: Brugada syndrome
CHF: Congestive heart failure
CLS: Closed-loop stimulation
CPM: Counterpressure maneuverers
CSM: Carotid sinus massage
CSS: Carotid sinus stimulation
ED: Emergency department
ELR: External loop recorder
EPS: Electrophysiological study
ILR: Implantable loop recorder
ISSUE: International study on syncope of unexplained etiology
LOC: Loss of consciousness
LQTs: Long QT Syndrome
LVOTO: Left ventricular outflow tract obstruction
NT-TLOC: Non-traumatic transient loss of consciousness
OH: Orthostatic hypotension
POTS: Postural orthostatic tachycardia syndrome
RS: Reflex syncope
SCD: Sudden cardiac death
TLOC: Transient Loss of Consciousness Úfter Sudden cardiac death
TT: Tilt training
TTT: Tilt table testing
UI: Urinary incontinence
VASIS: Vasovagal syncope international study

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The causes of syncope can be broadly classified into reflex syncope (RS) (neurally mediated), syncope due to orthostatic hypotension (OH), and cardiac syncope, as per the European Practice Guidelines (Figure 1). RS is the most common cause of syncope irrespective of age or clinical setting. The epidemiological studies have shown that RS is common in the younger population, whereas cardiovascular causes are common in older individuals. Syncope is considered to be due to cerebral hypoperfusion with a combination of multiple central as well as peripheral mechanisms.

Since the frequency and severity of syncope vary in the patients with RS, there is a myriad of treatment options available ranging from lifestyle management to cardiac ganglion ablation. In this review, we will give a brief overview of the evaluation and treatment of RS.

**Clinical Evaluation and Approach to Symptoms**

The evaluation can be divided into 3 phases: history, examination, and investigations.

*Fig. 1. Classification of Syncope.*

**Abbreviations.** AMI, acute myocardial infarction; LVOTO, left ventricular outflow tract obstruction; OH, orthostatic hypotension.

**History**

The most important component of the evaluation of a suspected case of syncope is history taking. The goal of history taking would be as follows: (a) To establish the etiology of syncope with certainty and differentiate it from epileptic or nonepileptic seizure. (b) Clues to suggest the probable etiology of the syncope like RS.

1. To establish the etiology of syncope with certainty and to differentiate it from epileptic seizure or pseudosyncope (Table 1).

The goal should be in eliciting the history of sudden or gradual transient loss of consciousness (TLOC) with total recovery after a few seconds/minutes from the patient or bystanders. The following questions will be required to get clues regarding differentiation of syncope from epileptic seizure or nonepileptic seizure:

- a. What was the body habitus?—supine/sitting/standing
- b. What was the activity?—meal, exercise, and so on.
- c. Were there any precipitating factors?—warm crowded place, fear, pain, cough, and so on.
- d. What were the historical details from the eyewitness with regard to the event?—duration, associated body movements, tongue bite, post-event confusion, and so on.
- e. What is the background history?—frequency, h/o sudden cardiac arrest, neurological disease, diabetes mellitus, vasoactive medications, and so on. What was the body habitus?—supine/sitting/standing.

There is a definite value for the video evidence of the event, so the relatives may be asked to record an episode if it occurs in the future again.

2. Is it a reflex-mediated syncope (RS) or syncope due to orthostatic hypotension or cardiac etiology?

Once it is confirmed that the patient has syncope and not any other cause of NT-TLOC, we need to look for the clues to diagnose RS and differentiate it from syncope due to OH and cardiac causes. Table 2 provides a few clues to the diagnosis of the specific type of syncope.

**Examination**

The physical examination should be focused to rule out or confirm the suspected cause of syncope. In particular, evidence of bradycardia, OH, and ejection systolic murmur should be looked out for to rule out organic causes of syncope.

Certain diagnostic clinical tests may aid in the diagnosis of the specific cause of syncope.
**Table 1. Differentiation of Syncope From Epileptic and Psychogenic LOC/syncope.**

| Parameter               | Syncope<sup>2-25</sup> | Epileptic Seizure<sup>21-24,26-34</sup> | Psychogenic LOC (Pseudo-seizure)<sup>27,35-39</sup> |
|-------------------------|-------------------------|------------------------------------------|---------------------------------------------------|
| **Trigger before the attack** | Prolonged standing, noxious stimuli, etc | Flashing lights/startle/sleep deprivation | For seeking attention for something |
| **At the onset of attack** | Change in vision/nausea, vomiting, pallor/ | Ictal cry/rising sensation from abdomen/aura | NA |
| **During the attack**     | Fall                     | Stiff                                     | Any type |
|                          | Movements                | Begin before or after the fall/synchronous/many movements | Pelvic thrusting/repeated waxing and waning in intensity |
| **Duration of LOC**       | Short                    | Few minutes                              | Can be prolonged |
| **UI**                   | Common                   | More common                              | Variable |
| **After the attack**      | Clear-headed             | Very rare                                | Variable |
| **Background history**    | Change in medications/ OI/DM | h/o epilepsy or neurological disease | h/o earlier traumatizing events |

**Table 2. Clues for the Cause of Syncope.**

| RS                        | OH                          | Cardiac                          |
|---------------------------|------------------------------|----------------------------------|
| Long history with age <40 years | After standing              | Abrupt                           |
| No cardiac disease        | Temporal relationship to starting hypotensive medication | Structural heart disease<sup>8</sup> |
| Specific background       | Post exertion               | Diabetes mellitus                 |
| With head rotation or tight collars/shaving/neck tumor | Post-meal/exertion          | Autonomic neuropathy              |
|                          | Prolonged standing or hot-crowded places | Syncope while supine/sleep       |
|                          | Unexpected sight, smell, or pain | During exertion                  |

**Note:** *May be present, not always. Clues in bold are more indicative of the respective diagnoses.

**Abbreviations.** LOC, loss of consciousness; OI, orthostatic intolerance; UI, urinary incontinence.

1. **Active standing test<sup>41,42</sup>**
   This test is used to diagnose different types of orthostatic intolerance.<sup>3</sup> The resting blood pressure (BP) of the patient should be measured in the supine position. Then the patient is made to stand without support and continuous BP monitoring is done. BP should be noted at 1-min and 3-min intervals, if continuous monitoring is not possible. The definition used for the abnormal test is—“abnormal BP fall is defined as a progressive and sustained fall in systolic BP from the baseline value ≥20 mmHg or diastolic BP ≥10 mmHg, or a decrease in systolic BP to <90 mmHg.” The test can classify OH into classical (within 30 s-3 min) and delayed OH (after 3 min).<sup>43</sup> The sensitivity, specificity, and accuracy of the active standing test were found to be 58.8, 63.3, and 60.9, respectively.<sup>44</sup>

2. **Carotid sinus stimulation<sup>45</sup>**
   This test is useful in the diagnosis of carotid sinus syndrome (CSS). Carotid sinus stimulation can be performed with mechanical stimulation (carotid sinus massage [CSM]) or pharmacological stimulation (with nitroprusside and phenylephrine injections). CSM is performed by giving 5-s gentle pressure over the carotid sinus on one side with continuous heart rate and BP monitoring, in supine as well as 60° upright position. Carotid sinus hypersensitivity is considered to be present if CSM elicits asystole ≥3 s (cardio inhibition) and/or a fall in systolic BP >50 mmHg (vasodepression).<sup>6</sup> Reproduction of spontaneous syncope is considered as a relatively specific diagnostic sign for CSS.<sup>46</sup>
Three forms of CSS may be diagnosed based on associated asystole ≥3 s or hypotension (any drop in systolic BP).

a. Vasodepressor: Syncope + Fall in Systolic BP + No Asystole ≥3 s
b. Cardioinhibitory: Syncope + No Fall in Systolic BP + Asystole ≥3 s (sometimes ≥ 6 s)
c. Mixed: Syncope + Fall in Systolic BP (present/absent) + Asystole ≥3 s → Atropine for the elimination of asystole → Symptoms persist

The sensitivity and specificity of CSM to diagnose CSS were found to be 74% and 100%, respectively, in the supine position. The sensitivity increases to 100% if the test is performed in the upright position.

3. Clinical autonomic function tests
   a. Valsalva maneuver
      During the maneuver, the patient is asked to conduct a maximally forced expiration for 15 s against a closed glottis, that is, with a closed nose/mouth, or into a closed system with 40 mmHg resistance. Traditionally, the Valsalva ratio (ratio of maximum heart rate during expiration and minimum heart rate within 30 s after maximum heart rate) has been used to evaluate the autonomic function but it may give erroneous readings in the patients who have inadequate expiratory efforts, square wave BP response, and blunted phase IV overshoot. Therefore, the common findings used are:
      i. Absence of BP overshoot or heart rate increase: r/o autonomic dysfunction
      ii. Pronounced BP fall with a normal chronotropic response: r/o situational syncope
   b. Deep breathing
      The patient is asked to breathe deeply at 6/min under continuous heart rate and BP monitoring. Blunted or abolished heart rate variability during deep breathing (expiratory/inspiratory [E/I] index), that is, <15 bpm in healthy individuals of >50 years of age, is considered abnormal. A parasympathetic dysfunction should be ruled out in these patients.

2. Long-term ECG monitoring
   a. Holter (24 h or 3 days)—will be useful for daily syncopal events, with normal/unclear presenting ECG.
   b. External loop recorder (3-30 days)—for a less frequent event and implantable loop recorder (ILR) (up to 3 years)—for infrequent events only in the patients with high suspicion of arrhythmic cause. A major limitation with Holter monitoring is frequent noncompliance with keeping a log of symptoms and event markers (from the patient’s side), which may cause errors in the interpretation of Holter findings as symptom-event correlation becomes difficult. The significant pause detected on long-term monitoring is traditionally considered to be ≥3 s, which has been included as an indication for permanent pacing in the American and European guidelines. This is based on observational evidence with low specificity, which has been challenged by recent studies. Most of these studies concluded that the follow-up was not sufficient enough to decide on the benefit of permanent pacing. ECG recordings on ILR were analyzed on follow-up in the first international study on syncope of uncertain etiology (ISSUE) study which has divided the findings into—Type 1 (asystole ≥3 s) [IA: sinus arrest, IB: sinus bradycardia with AV block, IC: AV block]; Type 2 (bradycardia) [2A: decreased HR >30%, 2B: HR <40 bpm for >10 s]; Type 3 (no/slight rhythm variation) [3A: none/≤10% HR variation, 3B increase 10-30% and HR <120 or decrease 10-30% and HR >40 bpm]; Type 4 (tachycardia, ie, increase in HR >30% or >120 bpm) [4A: progressive sinus tachycardia, 4B: atrial fibrillation, 4C: supraventricular tachycardia (non-sinus), 4D: ventricular tachycardia]. A series of studies was carried out to define the need and clinical significance of ILR in patients with suspected RS. These studies have defined cardioinhibitory responses based on the international study on syncope of uncertain etiology (ISSUE) classification as type 1 (asystole) or 2 (bradycardia).
   c. Mobile phone-based monitoring
      The use of mobile phones and different apps focusing on cardiovascular disease (eg, atrial fibrillation) has increased tremendously over the last few years. Mobile phone-based plethysmography and handheld ECG recorders with external sensors have been used for monitoring cardiac rhythm. The study comparing various applications (apps) used for this purpose showed that there is wide variability in quality, functionality, and adherence to self-management behaviors in these apps. Further studies are warranted in order to use these mobile phone
applications for large-scale screening of heart rhythm abnormalities. Artificial intelligence and its subfields (ie, machine learning and deep learning) have found their utility in the monitoring of heart rhythm, diagnosis of certain conditions, and correlation of ECG findings with imaging (eg, left ventricular ejection fraction).63-65

3. Tilt table testing

Tilt table testing (TTT) has been considered complementary to clinical examination since its inception in 1986.66 The test typically carried out after 2 to 4 h fasting that involves ≥20 min supine phase (post-venous cannulation) followed by ≥20 min of tilt (60-80°) (passive phase) with or without the use of a provocative agent (nitroglycerine, isoproterenol, or clomipramine) for 5 to 20 min (active phase) if the first phase of the test is negative.67-70 TTT is considered to be positive only if there is syncope during the testing.3 The response can be mixed (type 1), cardioinhibition without asystole (type 2A), or cardioinhibition with asystole (type 2B), and vasodepressor (type 3) as per the new Vasovagal Syncope International Study (VASIS) classification.71 Cardioinhibitory response means that HR falls to less than 40 bpm for more than 10 s but asystole >3 s doesn’t occur (BP falls before HR fall) (Type 2A) or asystole occurs for >3 s (BP falls with or before HR fall) (Type 2B). The positivity rate of TTT depends upon the indication for the test and provocative agent used—highest for vasovagal or emotional syncope with clomipramine (>90%), around 50% for atypical syncope (without classical features of vasovagal syncope72) with nitroglycerine, and lowest ≤30% for unexplained syncope.73-75 The sensitivity and specificity of TTT with the use of isoproterenol or sublingual nitrate have been reported to be similar (sensitivity: 61-69%; specificity: 92-94%).68,69

Recently, there have been contrasting publications regarding the usefulness of TTT. One of these has advocated the abolishment of the test in view of no additional diagnostic benefit, high false positivity rates, use of active standing test instead of TTT in the patients with OH or postural orthostatic tachycardia syndrome, and no mortality benefit.76 The other has highlighted the benefits of TTT as an ancillary test in the evaluation of suspected syncope and reiterated that it should be used as a part of the diagnostic workup, not as a standalone to draw any conclusions.77 We propose that TTT may play a role in cases where the history is not diagnostic, provided the more serious causes like cardiac syncope are ruled out.

4. 24-h ambulatory BP monitoring

24-h ambulatory BP monitoring is recommended for the diagnosis and management of hypertension, as per the recent guidelines.77 This can help in the diagnosis of OH based on nocturnal “non-dipping” (decrease in BP of less than 10% during night-time) or “reverse-dipping” (increase in BP at night) patterns.78

5. Echocardiogram—resting and exercise

Echocardiography is useful to rule out underlying structural heart disease which can present with syncope viz. left ventricular outflow tract obstruction (ie, aortic stenosis or hypertrophic cardiomyopathy), obstructive masses, pericardial tamponade, aortic dissection.79-84 In the cases where resting echocardiography is normal but there is high clinical suspicion, a stress echocardiogram may help in the confirmation of the level of obstruction in the patients with hypertrophic cardiomyopathy.85,86

6. Electrophysiological Study

The group of patients in which there is suspicion of cardiac syncope based on ECG changes (eg, sinus pauses, bifascicular blocks, etc) or history of acute myocardial infarction/low ejection fraction, electrophysiological study may aid in deciding the further course of action (eg, need for a pacemaker in a patient with bifascicular block and pharmacological challenge [≥80% positive predictive value] or need for implantable cardioverter-defibrillator in patients with low ejection fraction [yield of 42% in whom VT was inducible], etc).3,87-89

Evaluation Algorithm

For any patient presenting with syncope, the most important part of the evaluation is the history of the event. Physical examination and ECG may help in confirmation of the diagnosis and to rule out causes for severe syncope in the emergency setting. The risk factors that may guide the decision regarding admission are given in Table 3. Figure 2 gives the proposed evaluation algorithm for these patients.

| Table 3. High-Risk Factors Which Warrant Admission. |
|-----------------------------------------------|
| High-risk factors in history | History of structural heart disease |
| Old history of myocardial infarction |
| Syncope related | Syncope during exercise |
| Syncope associated with head/body injury |
| Examination related | Slow or fast heart rate |
| Low blood pressure |
| Ejection systolic murmur |
| ECG | Ischemic changes on ECG |
| Prolonged QTc, Brugada pattern |
| Bradyarrhythmias or tachyarrhythmias |
| Bundle branch blocks |
2. Reduction of hypotensive drug therapy
The patients with hypotensive susceptibility (HS) may be helped with the reduction of hypotensive therapy targeting a systolic BP of 140 mmHg to reduce symptoms.3

3. Physical counterpressure maneuvers
Isometric muscle exercises and counterpressure maneuvers viz. leg crossing, hand gripping, and hand tensing may help reduce syncopal episodes.94,95 They need to be taught and should be employed when the patient recognizes the prodrome.5 These maneuvers may help prevent and/or abort an episode of RS or orthostatic fainting. Leg crossing is done with maximum tensing of the leg, abdominal, and buttock muscles for the maximum tolerated time or until the disappearance of symptoms. Hand gripping means squeezing a rubber ball or similar soft object in the dominant hand for the maximum tolerated time or until the disappearance of symptoms. Arm tensing consists of maximum tolerated isometric contraction of the 2 arms achieved by gripping 1 hand with the other and at the same time abducting for the maximum tolerated time or until the disappearance of symptoms.6

4. Tilt training (orthostatic training) and yoga therapy
In patients with RS which is triggered by orthostatic stress, the prescription of a prolonged period of enforced upright posture is called tilt training.96 The training is generally started in a hospital setting with 10- to 50-min sessions based on the prodromal symptoms and then home training is advised.97 The hospital training generally is similar to the protocol used for diagnostic TTT. After discharge, the patient is advised to continue the training with feet 15-cm away from the wall with upper back resting on the wall for increasing time starting from 15 min based on the symptoms.98 There is conflicting evidence regarding the use of tilt training, with a few studies showing benefit96,99,101, while the others reporting no benefit.102,103 Zeng et al104 studied 125 consecutive patients with positive TTT; they found that there was no recurrence of syncpe in 72.6% of patients undergoing orthostatic training (OT), as against 36.1% in patients without any treatment, at 1-year follow-up and as against a placebo-controlled trial demonstrated a positive trend in terms of the benefit of home OT (20% vs 50%, P = 0.2) but it did not reach statistical significance level.104 The contrasting results of the studies may be due to the non-uniformity of methods and variable compliance of the patients with tilt training.

The use of yoga for the treatment of RS has been recently studied in a randomized study by Shenthal et al.105 The yoga module described in the trial consisted of warmup, asanas (yoga postures), pranayama (breathing exercises), dhyana (meditation), and deep relaxation technique with each session of 60 min at least 5 times/week for 12 months. At 12 months follow-up, there was a significant reduction in syncpe recurrence in the yoga therapy group as against conventional

Figure 2. Evaluation and Management Algorithm for Reflex Syncope.

Note: *May not be possible on out-patient basis.
Can be done after admission for confirmation.

Treatment

Overall management depends upon the predictability and frequency of the symptoms. Patients may be classified into 2 groups:

1. Group I: Unpredictable or high-symptom-frequency of syncope → will need specific therapy.
2. Group II: Predictable or low-symptom-frequency of syncope → education/reassurance may be enough.

The treatment should start with the education of the patient and relatives regarding the cause of syncope and then further treatment may be required in cases where there are high-risk ECG features, recurrence of symptoms, or nonresponse to conservative management.

The various treatment modalities used are:

1. Education and lifestyle modification

This forms the cornerstone of the treatment of RS, but its long-term effects have not been evaluated with randomized studies.3 The main components are:

a. Reassurance about the benign nature of the disease
b. Education regarding triggers/precipitants
c. Early recognition of prodrome (if any)
d. Increased oral fluids (2-3 L/day)
e. Salt supplementation96): 10 gm/day or 6-10 gm/day91,92
conservative therapy (without yoga) (3.8 ± 3.2 episodes vs 1.1 ± 0.8, \( P < 0.001 \)).

5. Pharmacological therapy (Figure 4)

a. Fludrocortisone \(^{106} \)

These work by the mechanism: increasing renal sodium reabsorption → expansion of plasma volume → reducing orthostatic component of the syncope.

b. Alpha agonists—these act by peripheral vasoconstriction (increasing peripheral resistance).

c. Beta-blockers have been tried in the past for the treatment of RS, presumed to be acting by decreasing the ventricular mechanoreceptor activation by their negative inotropic effect. There was no benefit in the treatment of RS in the randomized trials. \(^{107,108} \)

Moreover, if the patient has underlying borderline or low heart rate, these may worsen the condition. The latest ESC guidelines have given class III indication for the use of beta-blockers in the treatment of RS. \(^{3} \)

There is recruitment going on for the trial COMFORTS (comparison of outcomes with Midrodrine and Fludrocortisone for objective recurrence in treating syncope) [NCT04595942] which will give us a better picture regarding the benefit of pharmacological therapy in RS. \(^{109} \)

6. Pacing (with or without counteracting HS)

A pacemaker may be indicated in a specific subset of the patients with RS. A small subset of patients has a predominant cardioinhibitory response (VASIS type 2 or ISSUE type 1 or 2) on TTT or long-term ECG monitoring (eg, ILR) with or without HS, which is common in the elderly population. \(^{5,57,71} \)

These patients may be treated with the conservative line of management, along with medications, at the initial presentation but may require additional treatment if:\(^{112} \)

a. Recurrent symptoms are not responding to medications
b. Very short prodrome
c. Syncope during high-risk activities, for example, driving, machine operations, flying, etc.

The benefit of pacing in this particular subset is based on the rationale—pacing may be able to modulate RS episodes if acted sufficiently early at a rate higher than lower pacing rate and with atrioventricular (AV) sequential pacing. \(^{113} \)

Early studies have used cardioinhibitory response on TTT to decide on the need for pacing. \(^{114,115} \)

Few of the nonblinded studies were positive but the metaanalysis by Sud et al\(^{116} \) including both blinded and nonblinded studies found that there was no benefit of pacing based solely on TTT response and the benefit shown in nonblinded studies was an “expectation effect.” The most convincing evidence regarding this was provided by the ISSUE-3 study, in which all the patients had undergone ILR implantation and found that pacing in the patients with syncope with \( \geq 3 \) s or without syncope with \( \geq 6 \) s pause reduced recurrent syncope over 2 years follow-up. \(^{59} \)

Since the earliest evidence of the usefulness of pacing in RS, it tried to use various specific algorithms which may help the patients with recurrent syncope like rate-drop response (RDR) algorithm and closed-loop-stimulation (CLS) pacing. \(^{117-120} \)

RDR algorithm detects a sudden decrease in heart rate and increases the rate of pacing so that the syncopal event can be avoided. The detection portion of the algorithm has a programmable “heart rate change-time duration” window which is helpful in the detection of imminent RS (based on decreasing heart rate) and triggers AV sequential pacing at a programmable rate. \(^{117} \)

In the ISSUE-3 study, all the patients receiving pacemakers had an RDR algorithm and it showed 57% relative risk reduction in syncope recurrence. \(^{59} \)

The main issue with the RDR algorithm is that it takes time to respond in an episode of RS. \(^{121} \)

CLS is the proprietary algorithm of Biotronik (Berlin, Germany), which detects right ventricular (RV) impedance as an indirect measure of RV contractility and uses it to counteract RS events. \(^{122} \)

RV lead constantly measures impedance, which is dependent on the amount of myocardium interfering with the lead tip. In diastole, there is maximum blood in RV so impedance is low. In contrast, in systole, when there is minimum blood pool in RV, the amount of myocardium interfering with lead tip is highest and so is the impedance. This high impedance triggers pacing at the CLS intervention rate (programmable). This beat-to-beat monitoring of RV impedance can detect inotropic changes early in an RS event.

### Table 4. Pharmacological Agents Useful in the Management of RS.

| Group          | Drug       | Dose           | Indication                      | Outcome in RS                                                                 |
|----------------|------------|----------------|---------------------------------|-------------------------------------------------------------------------------|
| Mineralocorticoid | Fludrocortisone | 0.05-0.2 mg OD | Recurrent syncope with low-normal BP without comorbidities like HTN | Marginal nonsignificant benefit; more benefit if a dose of 0.2 mg OD was given (randomized study) \(^{106} \) |
| Alpha agonist | Etilfrine   | 25 mg          | Recurrent vasovagal syncope     | No benefit on 1 year follow-up in terms of syncope recurrence and time to first syncope \(^{10} \) |
| Midodrine      | 2.5-10 mg TDS |                | Recurrent vasovagal syncope and/or orthostatic symptoms | There are mixed data regarding benefits. Overall, low evidence of benefit based on small nonrandomized studies \(^{111} \) |

**Abbreviations.** HTN, hypertension; OD, once a day; TDS, thrice a day.
The response time is relatively fast for the CLS algorithm. An elegant study has recently been done to evaluate the benefit of the CLS algorithm in 127 patients aged 40 years and older with at least 2 episodes of unpredictable severe syncope in last year and a systolic pause of ≥3 s induced by TTT. The syncope recurrence, at 11.2 months of median follow-up, was reduced by 77% with the use of the CLS algorithm (16% vs 53%, \( P = .00005 \)) as compared to the control population (with ODO pacing mode). The patients who have mixed or hypotensive responses on TTT (type 1/3) are suspected of having HS. These patients may require the measures to counteract HS like discontinuation/reduction in hypotensive drugs, optimal salt/fluid intake, use of medications (eg, fludrocortisone/midodrine), and so on.

We propose an algorithm based on the European Society of Cardiology (ESC) guidelines to decide on pacing in patients with RS (Figure 3).

### 7. Management of situational syncope

Common precipitants associated with syncope are micturition, gastrointestinal stimulation (swallowing and defecation), cough, sneeze, laughing, and so on. The easiest way to avoid these episodes is to educate the patient regarding the events and if possible avoid the specific situations which may induce symptoms, but it may not be possible always. In all these patients, the addition of salt and water in the diet, an inclination of the head end of the bed by 10 degrees, and avoiding a sudden change of posture may avoid precipitation of the symptoms. For micturition syncope, patients are advised to do an intermittent voiding and avoid sudden bladder emptying of the bladder. For gastrointestinal-related syncope and cough/sneeze-related syncope, the underlying cause of difficulty in swallowing/defecation has to be determined for the definitive management of the patient.

### 8. New emerging therapies: still need more robust trials to evaluate their effectiveness.

a. **Low-adenosine syncope**

Some patients affected with recurrent syncope have a very short duration prodrome (<5 s) with a structurally normal heart and normal ECG. This particular population has been found to have low plasma adenosine levels and is susceptible to even a small increase in adenosine, which may act on the A1 receptor located in the AV node and sinus node, which may lead to heart block. The most common mode of presentation is paroxysmal AV block, some patients may present with symptomatic bradycardia. In the recent case series of 16 patients, it was found that use of theophylline (adenosine receptor blocker) in this specific type of syncope helps in the reduction of syncope (2.6 syncope/year vs 0.4 syncope/year; \( P = .005 \))

b. **Low-norepinephrine syncope**

RS is associated with the sudden withdrawal of sympathetic activity and release of epinephrine from the adrenal medulla as a “fight” response. Similarly, in the nerve endings of the cardiac sympathetic nervous system (SNS), there is an increase in norepinephrine levels. This is associated with increased serum levels of metabolic by-products of norepinephrine (ie, dihydroxy phenyl glycol or DHPG). With the use of norepinephrine reuptake transporter inhibitors (ie, reboxetine, sibutramine), there is a decreased peripheral (adrenal medulla) adrenaline secretion, increased local norepinephrine concentration (in cardiac SNS), and decreased DHPG levels (indicating decreased degradation of norepinephrine). This correction of the catecholamine milieu has been found to be beneficial in improving orthostatic tolerance in the patients presenting with recurrent syncope with a positive TTT (TTT duration 35 ± 1 min vs 29 ± 2 min, \( P = .001 \)). These medications are found to increase BP and HR in all the subjects due to locally increased norepinephrine concentration, hence it has been advised to be given to the patients with low baseline levels of norepinephrine.

c. **Cardioneuroablation (CNA)**

RS may be very rapid in some patients which may not provide enough time for the use of any other management modalities like counterpressure maneuvers or pacing to abort.

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**Figure 3. Algorithm to Decide on Pacing in Reflex Syncope.**

**Abbreviations.** CLS, closed loop stimulation; CPM, counterpressure maneuvers; CSS, carotid sinus stimulation; ILR, implantable loop recorder; PPI-DDD, dual-chambered pacemaker; TT, tilt training; TTT, tilt table testing.
a particular episode.136 Catheter ablation to attenuate vagal activity on sinus and AV node has evolved as one of the treatment modalities in a subgroup of patients not responsive to other treatments.136-138 This technique of treatment of bradyarrhythmia is termed CNA. In this technique, ganglionated plexi (GPs) are targeted systematically—left-sided plexi first, aorto-superior vena cava (Ao-SVC) GP (for tackling atrial vagal innervations), posteromedial left GP (in case of AV block as the presenting feature), and an additional right-sided ablation if left-sided ablation was not sufficient.138 This has recently been compared with conventional management without the use of CNA in the propensity-matched patient subset (recurrent syncope with VASIS-type management without the use of CNA in the propensity-based model tested in four independent datasets. PLoS One. 2013;8(9):e75255.

Concluding Remarks

Syncope needs meticulous evaluation on the part of the physician. The diagnosis of RS centers around the history and examination of the episode. The other diagnostic modalities can help in the confirmation of the diagnosis and in deciding the treatment of the condition. The management of RS may be conservative if the episodes are infrequent or may require additional management in case of recurrence.

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