Cardiac Pacing in Neuroendocrine Syncope

Emerging Concepts

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What is Neuroendocrine Syncope?

Neuroendocrine Syncope is a collective phrase to include:

- Vasovagal reflex syncope
- Carotid sinus syndrome
- Situational syncope
- Adenosine related syncope

What is Neuroendocrine Syncope?

- Neuroendocrine Syncope, therefore, comprises both familiar syndromes, some of which have new aspects and also some unfamiliar syndromes.
- There are relationships between them but they are also grouped together as those syndromes where new developments in pacing are taking place.

Three Recent Developments

1. The process of patient selection.
2. Use of a decision algorithm in older patients with reflex syncope.
3. The role of Adenosine and its receptors in causing bradycardias and syncope

Patient Selection

Guidelines attempt to offer help in patient selection.

The most recent ESC Guidelines on Pacing (2013) have recommended a different approach which is to focus on the patient's presentation rather than laboriously trying to place the patient in a diagnostic category.

In the present context, application of this new approach is pertinent to the older patient, suspected of having reflex syncope and very short or no prodrome.

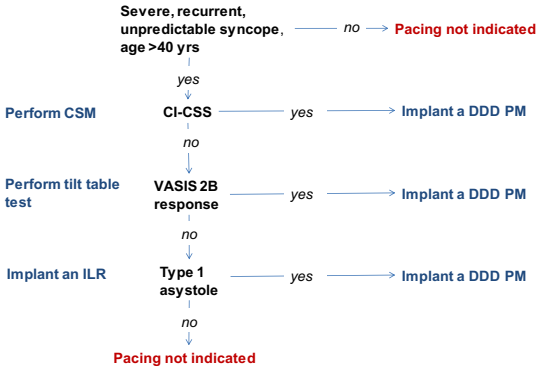
Patient Selection

The recently published SUP-2 study, performed in ten Italian Syncope Units with typical referral patterns, offers both a focus on the older patient's presentation and a decision algorithm to adopt in this clinical situation.

The patient presents syncope which is suspected of being reflex in origin despite a short or no prodrome.

Brignole M et al. SUP-2 Eur Heart J 2015; 36: 1529-1535.

Pacing for neuroendocrine syncope: decision tree



Patient Selection and Follow-up

Given that patients with reflex syncope may be expected to experience some syncope recurrence during follow-up, the decision tree also pays attention to this aspect.

Brignole M et al. SUP-2 Eur Heart J 2015; 36: 1529-1535.
Brignole M et al. SUP-2 Longer FU. Europace 2016; 18:

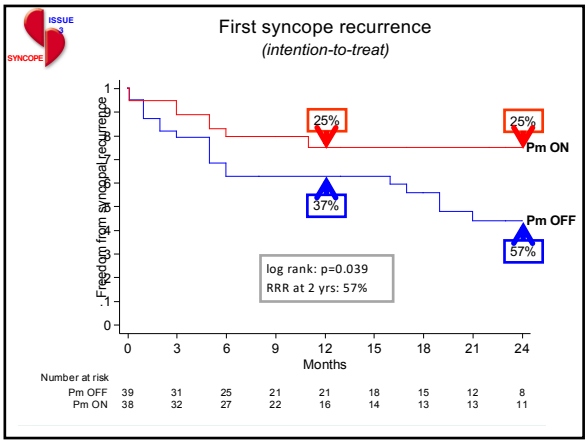
Patient Selection and Follow-up

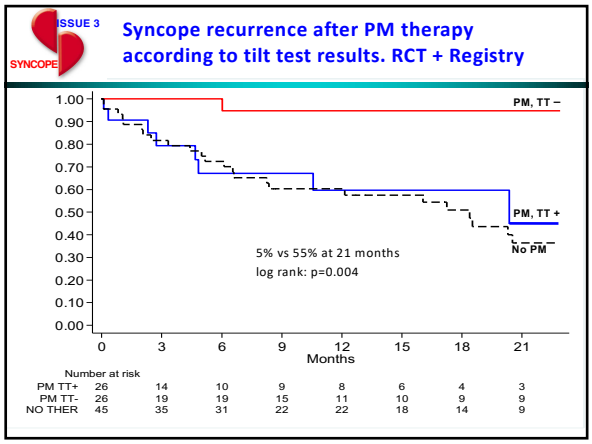
SUP-2 Recurrence of syncope
CSM +: 9% and Tilt +: 3% in 1-year

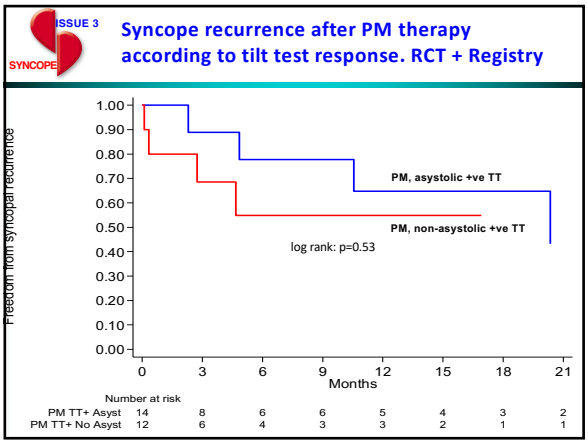
SUP-2 Longer follow-up actuarial recurrence of syncope

	CSM+/Tilt+/ILR Asystole	CSM o/Tilt o/ILR
1-yr:	8%	21%
2-yr:	18%	33%
3-yr:	20%	43%

Brignole M et al. SUP-2 Eur Heart J 2015; 36: 1529-1535.
Brignole M et al. SUP-2 Longer FU. Europace 2016; 18:







Analysis of these results

- In ISSUE 3 (RCT & Registry) syncope recurrence in those paced who had a negative tilt test was 5% in 21 months but in those paced who had a positive tilt test it was 50% which was not significantly different from those who were unpaced (55%).
- SUP-2 (longer follow-up, Europace 2016: 18:) larger numbers.
- In 18 months FU, syncope recurrence was 5% in those who were tilt negative,
- 20% in those paced who were tilt positive but 40% in those who were unpaced (ILR only).

The meaning of a positive tilt test

Reviewing 28 years of research into tilt testing permits reinterpretation of its clinical meaning (Eur Heart J 2014).

Published data from patients with true VVS allow calculation of sensitivity at 65-92%.

In those with no history of syncope specificity is 87-92%.

Thus, there is no real problem with sensitivity and specificity.

The meaning of a positive tilt test

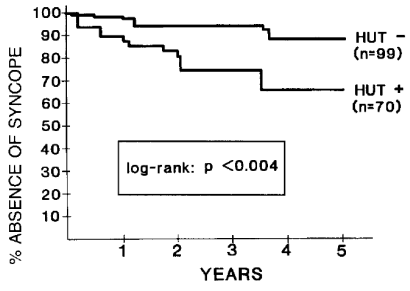
- In populations with syncope of uncertain cause tilt testing fails to deliver.
- TT positive in 51-56% of patients with atypical features of VVS.
- TT positive in 30-36% of those with unexplained syncope.
- TT positive in 45-47% of true cardiac arrhythmic syncope.
- NICE's criticism of tilt is based on these data

The meaning of a positive tilt test

- The new interpretation of tilt positivity is that it is showing a susceptibility to the vasodepressor component of the reflex.
- This susceptibility is present in all humans to a variable extent.
- This susceptibility is most prominent in those with a history of syncope and a positive tilt.
- For example, in arrhythmic syncope the abnormal rhythm and rate trigger the susceptibility to vasodepression.
- There are probably similar mechanisms at play in aortic stenosis, hypertrophic cardiomyopathy, SSS and even probably MI, PHT and Diss Aorta

The meaning of a positive tilt test in CSS patients

Coggioli et al. Am J Cardiol 1995; 76: 720



The meaning of a positive tilt test

The clinical implications of the Sutton and Brignole (Eur Heart J 2014) interpretation of tilt testing positivity are that:

- Tilt testing should be considered as a risk of recurrence stratification tool after therapy.
- Tilt positive patients who are otherwise identical to tilt negative patients will have more recurrences of syncope when paced.

The meaning of a positive tilt test

The further clinical implications of this new interpretation of tilt testing positivity are:

- Pacing can be offered to tilt negative patients with expectation of very little syncope recurrence approximating pacing His-Purkinje disease.
- In those who are tilt positive some reticence to implant is appropriate but SUP-2 results suggest that there will be benefit in syncope reduction.
- If hypotensive medication is reduced or ceased there will be more benefit (STOP-VD trial).

Role of Adenosine in Bradyarrhythmias

Shen WK et al. Adenosine: potential modulator for VVS. J Am Coll Cardiol 1996

Flammang D et al. Can ATP be used to select therapy in severe VVS? Circulation 1997

These two studies raised the question of importance of adenosine but there was controversy about ATP testing.

Brignole M et al. Adenosine-induced AVB in patients with unexplained syncope. The diagnostic value of ATP test. Circulation 1997

Brignole M et al. Lack of correlation between the responses to tilt and ATP testing and mechanism of spontaneous neurally-mediated syncope (ISSUE 2). Eur Heart J 2006

Role of Adenosine in Bradyarrhythmias

- A1 receptors are located on SA and AV nodes – A1R

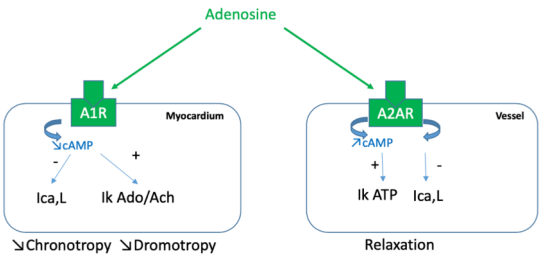
If plasma Adenosine is chronically low and suddenly rises A1R are highly stimulated causing AV or SA block

- VVS patients have high Adenosine levels implying that A1R are little affected by sudden Adenosine release
- A2aR are located in the vasculature and when stimulated by Adenosine relax leading to vasodilatation
- In VVS patients A2aR are overexpressed and release of Adenosine can cause vasodilatation in synchrony with sympathetic withdrawal resulting in the vasodepressor component of VVS

Role of Adenosine and its Receptors in Neuroendocrine Syncope

	APL (μM)	A2AR expression (arbitrary units)
Control subjects	0.5 (0.3-0.8)[1,*]	0.85 (0.75 -1.1)[1,*]
Vasovagal syncope	1.2 (0.3-3.3)[1,*]	1.2 (0.8-1.5)[1,*]
Idiopathic paroxysmal AV block	0.33 (0.2-0.56)[2,**]	Not studied
Syncope with normal heart and no prodromes	0.18 (0.12-0.36)[3,§]	0.5 (0.3-0.6)[3,§]
Carotid sinus syncope	0.16 (0 .10-0.31)[3,§]	0.5 (0.4-0.5)[3,§]
Situational syncope	0.60 (0.43-0.70)[3,§]	0.9 (0.9-1.0)[3,§]

Actions of Adenosine



Adenosine in bradyarrhythmias

Focus on intrinsic Adenosine revealed hitherto unappreciated form of paroxysmal AVB as a distinct syndrome presenting:

- syncope without prodrome,
- clinically normal heart,
- tilt negative
- low plasma adenosine (high in VVS),
- paroxysmal AV block,
- older than typical VVS patients (60-yr)
- good response to pacing. tilt negative and ATP positive.

Brignole M et al. Syncope due to idiopathic paroxysmal AV block: long-term follow-up of a distinct form of AV block. J Am Coll Cardiol 2011.

Deharo JC et al. Syncope without prodrome in patients with normal heart and normal ECG: a distinct entity. J Am Coll Cardiol 2012

Adenosine in bradyarrhythmias

Further studies from Brignole, Deharo, Guieu inform us both carotid sinus syndrome and adenosine-mediated syncope have:

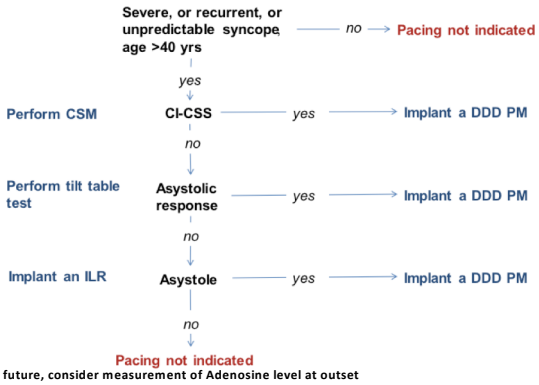
- low plasma adenosine (in contrast to VVS high)
- compatible with activation of low affinity A2a adenosine receptors and deactivation of high affinity A1 adenosine receptors.
- Low affinity A2a receptors are vessel located and mediate vasodilatation. Thus, syncope, at least in part, may be related to the vasodilatory effect of A2a receptor activation, acting in synergy with sympathetic withdrawal.

Guieu R et al. Adenosine and clinical forms of neurally-mediated syncope. J Am Coll Cardiol 2013

Recurrence of syncope in different forms of neuroendocrine syncope

Clinical form	Expected syncope recurrence rate at 2 years with cardiac pacing
- CI-CSS and negative tilt test - Asystolic ILR and negative tilt test - Low adenosine AV block	High efficacy (≤5% recurrence rate)
- Asystolic (VASIS 2B [11]) positive tilt test	Moderate efficacy (5% to 20% recurrence rate)
- CI-CSS and M or VD positive tilt test - Asystolic ILR and M or VD positive tilt test	Low efficacy (>20% recurrence rate)
- M or VD positive tilt test - Non-asystolic ILR	Probably ineffective (pacing not indicated)

Pacing for neuroendocrine syncope: decision tree



In future, consider measurement of Adenosine level at outset

Adenosine in bradyarrhythmias

Conclusions

- There is a role for Adenosine in some or all of the neuroendocrine syncopes
- Careful assessment of patients for application of pacing, usually dual chamber, will successfully address a wider spectrum of bradycardias than presently undertaken
- Further developments are expected