PACEMAKER IN NEURALLY MEDIATED SYNCOPE

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The efficacy of cardiac pacing for prevention of syncopal recurrence in patients with neurally mediated syncope

<table>
<thead>
<tr>
<th>In favour of pacing (open-label)</th>
<th>Failed to prove superiority of cardiac pacing over placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multicenter, randomized</td>
<td>Randomized, double-blind</td>
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<table>
<thead>
<tr>
<th>SYDIT (Circulation 2001)</th>
<th>VPS II Trial (JAMA 2003)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-year estimated syncope</td>
<td>6-months syncope recurrence rate was 31%</td>
</tr>
<tr>
<td>recurrence rate was 7.2%</td>
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</tbody>
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<thead>
<tr>
<th>VASIS (JAMA 2003)</th>
<th>SYNPACE Trial (Eur Heart J 2004)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-year estimated syncope rate</td>
<td>1-year syncope recurrence rate was 29%</td>
</tr>
<tr>
<td>was 6%</td>
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</tbody>
</table>
Context and Background:

ISSUE 2
International Study on Syncope of Uncertain Etiology 2

It showed the capacity of ILR to guide the specific therapy in the context of NMS, and confirmed that there is not a correlation between the results of TTT and the mechanism documented by ILR at the time of the syncope.

ISSUE 3
International Study on Syncope of Uncertain Etiology 3


Pacing is effective in reducing recurrence of syncope in patients ≥40 years with severe asystolic NMS (ILR). There was 32% absolute risk reduction and 57% relative risk reduction.

Circulation
May 7, 2012
ISSUE 3

International Study on Syncope of Uncertain Etiology 3
# Context and Background

Guidelines for the diagnosis and management of syncope (version 2009)

The Task Force for the Diagnosis and Management of Syncope of the European Society of Cardiology (ESC)

## Recommendations

<table>
<thead>
<tr>
<th>Classa</th>
<th>Levelb</th>
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<tbody>
<tr>
<td>Explanation of the diagnosis, provision of reassurance, and explanation of risk of recurrence are indicated in all patients</td>
<td>I C</td>
</tr>
<tr>
<td>Isometric PCMs are indicated in patients with prodrome</td>
<td>I B</td>
</tr>
<tr>
<td>Cardiac pacing should be considered in patients with dominant cardioinhibitory CSS</td>
<td>IIa B</td>
</tr>
<tr>
<td>Cardiac pacing should be considered in patients with frequent recurrent reflex syncope, age &gt;40 years, and documented spontaneous cardioinhibitory response during monitoring</td>
<td>IIa B</td>
</tr>
<tr>
<td>Midodrine may be indicated in patients with VVS refractory to lifestyle measures</td>
<td>IIb B</td>
</tr>
<tr>
<td>Tilt training may be useful for education of patients but long-term benefit depends on compliance</td>
<td>IIb B</td>
</tr>
<tr>
<td>Cardiac pacing may be indicated in patients with tilt-induced cardioinhibitory response with recurrent frequent unpredictable syncope and age &gt;40 after alternative therapy has failed</td>
<td>IIb C</td>
</tr>
<tr>
<td>Cardiac pacing is not indicated in the absence of a documented cardioinhibitory reflex</td>
<td>III C</td>
</tr>
<tr>
<td>β-Adrenergic blocking drugs are not indicated</td>
<td>III A</td>
</tr>
</tbody>
</table>
Standardized algorithm for cardiac pacing in older patients affected by severe unpredictable reflex syncope: 3-year insights from the Syncope Unit Project 2 (SUP 2) study

Michele Brignole¹*, Francesco Arabia², Fabrizio Ammirati³, Marco Tomaino⁴, Fabio Quartieri⁵, Martina Rafanelli⁶, Attilio Del Rosso⁷, Maria Rita Vecchi⁸, Vitantonio Russo⁹, and Germano Gaggioli¹⁰, on behalf of the Syncope Unit Project 2 (SUP 2) investigators†

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**Syncope Unit Project 2 (SUP 2)**

**Context and Background:**

Met inclusion criteria

- Underwent CSM: 253
- Underwent tilt table test: 185

- Received a PM: 66
  - #2 dropped out
  - #17 dropped out

- Received an ILR: 134
  - Type 1 asystole: 25
    - 10 Lost to FU
    - 82 Ongoing
    - 4 Tachyarrhythmia
    - 13 No rhythm variations

- Received a PM: 34
  - VASIS 2B response

- Received a PM: 32

- Received a PM: 65
The recurrence rate was similar in the 65 CSM+ (11%), 32 TT+ (7%) and 23 ILR+ (7%) patients.

About half of older patients with severe recurrent syncopes without prodromes have an asystolic reflex for which cardiac pacing is effective in preventing syncopal recurrences. The recurrence rate is low irrespective of the index diagnostic test.
The benefit of pacemaker therapy in patients with presumed neurally-mediated Syncope and documented asystole is greater when tilt test is negative.

An analysis from the Third International Study on Syncope of Uncertain Etiology (ISSUE-3)


52 Patients (26 TT+, 26 TT-) with asystolic ILR were treated with a PM.

- recurrence of syncope in
  8 (31%) in patients with TT+
  1 (4%) in patients with TT-
Context and Background:

Table 3: Estimated recurrence rate of syncope, analysed by means of Kaplan–Meier survival curves, in paced patients according to TT findings

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>TT– (n = 20)</th>
<th>TT+ VASIS 2B (n = 38)</th>
<th>TT+ M or VD forms (n = 23)</th>
<th>TT not performed</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-Year recurrence rate (95% CI)</td>
<td>5 (0–10)</td>
<td>3 (0–9)</td>
<td>10 (0–24)</td>
<td>11 (3–19)</td>
</tr>
<tr>
<td>2-Year recurrence rate (95% CI)</td>
<td>5 (0–10)</td>
<td>17 (3–31)</td>
<td>27 (7–47)</td>
<td>20 (8–32)</td>
</tr>
<tr>
<td>3-Year recurrence rate (95% CI)</td>
<td>5 (0–10)</td>
<td>23 (5–41)</td>
<td>27 (7–47)</td>
<td>20 (8–32)</td>
</tr>
</tbody>
</table>

Recurrence of syncope

Log rank for trend: $P = 0.01$
1. Asystolic Tilt Test and PM

2. Dual Chamber pacemaker with RDR-algorithm vs other possible algorithms
Benefit of dual-chamber pacing with Closed Loop Stimulation (CLS) in tilt-induced cardio-inhibitory reflex syncope. A randomized double-blind parallel trial
# Steering Committee

<table>
<thead>
<tr>
<th>PI</th>
<th>Site</th>
<th>City</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr. Michele Brignole (study coordinator)</td>
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<tr>
<td>Dr. Marco Tomaino (study coordinator)</td>
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<td>CHUS - Centre hospitalier universitaire de Sherbrooke</td>
<td>Sherbrooke</td>
<td>CA</td>
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</table>
Patients affected by clinical diagnosis of reflex (neural-mediated) syncope who meet all the following criteria:

age ≥ 40 years

significant limitation of social and working life due to unpredictable or frequent syncope recurrences: ≥2 within the last year.

type 2B cardio-inhibitory response (VASIS classification) during TT performed according to the 'Italian protocol'.

alternative therapies have failed or are not feasible

exclusion of other possible competitive causes of syncope
Study population - Exclusion Criteria (1 of 2)

- Any other indication to IPG, implantable defibrillator (ICD), cardiac resynchronization therapy (CRT), according to current guidelines
- Any cardiac dysfunctions possibly leading to loss of consciousness:
  - overt heart failure;
  - ejection fraction (LVEF) <40% (Echo-assessed within 3-month prior to study participation);
  - myocardial infarction;
  - diagnosis of hypertrophic or dilated cardiomyopathy;
  - clinically significant valvular disease;
  - sinus bradycardia <50 bpm or sinoatrial block;
  - Mobitz I second-degree atrioventricular block;
  - Mobitz II second and third degree atrioventricular block;
  - ...(continues)
Study population - Exclusion Criteria (2 of 2)

- ... 
- bundle-branch block; 
- rapid paroxysmal supraventricular tachycardia or ventricular tachycardia; 
- preexcited QRS complexes; 
- prolonged QT interval; 
- Brugada syndrome; 
- arrhythmogenic right ventricular cardiomyopathy)

- Symptomatic orthostatic hypotension diagnosed by standing BP measurement;
- Symptomatic cardioinhibitory carotid sinus hyper-sensitivity.
- Nonsyncopal loss of consciousness (eg, epilepsy, psychiatric, metabolic, drop-attack, cerebral transient ischemic attack, intoxication, cataplexy).
Trial Design - Flow-chart

Enrollment before implant

IPG implant hospitalization

1:1

OTP

Optional
In-hospital visit
30 ± 14 days
after discharge
for TT exam

Optional
in-hospital visit
30 ± 14 days
after discharge
for TT exam

Collecting questionnaires
every 3 months

In-hospital visits
@ 12±1 months
after discharge

In-hospital visits
@ 24±1 months
after discharge

Monitoring of primary endpoint event occurrence

In-hospital visits
Patient Questionnaires

In-hospital visits

Closeout

Scheduled follow-up

Unscheduled follow-up
Study procedures – Patient questionnaires

- Questionnaires (x25)
- Pre-addressed, pre-stamped envelopes (x8)
- Filling and mailing Instructions