The DDDR closed loop stimulation for the prevention of vasovagal syncope: results from the INVASY prospective feasibility registry

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Background The contraction dynamics of the ventricular myocardium are affected before and during vasovagal fainting suggesting that the Closed Loop Stimulation (CLS) pacemaker could be useful for the treatment of these patients. CLS is a new concept of heart rate modulation in cardiac pacing. The pacemaker INOS CLS (Biotronik, Germany) derives its information for heart rate optimization from myocardial contraction dynamics, by measuring right ventricular intracardiac impedance. The pacemaker becomes an integral part of the circulatory regulation and, therefore, reacts appropriately to different cardiovascular demands.

Methods In a prospective registry, 34 patients with a history of recurrent vasovagal syncopal events were implanted with INOS DDDR CLS pacemakers. The aim of the study was to evaluate both long term clinical outcome, including the first recurrence of syncope, with DDDR-CLS pacing and acute precipitation of vasovagal fainting with DDDR-CLS mode compared with DDD during head up tilt testing.

Results During a follow up period of 12–50 months, 30 patients experienced no further syncopal events in daily life; 1 patient had no syncope but night palpitations, which were eliminated by pacemaker reprogramming; 2 patients had presyncopal episodes but not syncope; 3 syncopal recurrences occurred in one patient in chronic atrial fibrillation, possibly not an ideal candidate for implantation.

Conclusions Further studies for detailed understanding of the preventive mechanism of DDDR-CLS pacing in vasovagal syncope are warranted. A randomized multicentre prospective new study (INotropy controlled pacing in VAsovagal SYncope: INVASY) is now in progress to confirm the beneficial effect of DDDR-CLS pacing in a larger group of patients with recurrent vasovagal syncope.

Key Words: Closed loop stimulation, pacemaker, vasovagal syncope, head up tilt test.
Closed Loop Stimulation

Figure 1 The INOS² CLS pacemaker, as an integral part of the circulatory regulation, can react appropriately on various kinds of cardiovascular demands. HR: Heart rate. SV: Stroke volume. MABP: Mean arterial blood pressure. CO: Cardiac output, centers=centres.

Methods

Material

In the INOS² CLS pacemaker (Biotronik, Germany) load-dependent changes in myocardial contractility reflect variations in the unipolar intracardiac impedance, measured between the ventricular electrode tip and the pacemaker case. This principle of measurement of intracardiac impedance has been previously described.[1]

During myocardial contraction, the proportions of blood and myocardium vary in the close vicinity (≈1 cm³) of the electrode tip. Since the specific resistance of blood differs significantly from that of the myocardium, the dynamics of the myocardial contraction can be well detected in a time-course impedance curve. Therefore, by monitoring the unipolar intracardiac impedance, changes in myocardial contractility can reliably be measured. Previous studies have shown that the unipolar intracardiac impedance values obtained by INOS² CLS pacemakers were closely correlated with myocardial contractility estimated by dP/dt in right and left ventricles.[12,13]

Due to the automatic initialization feature of INOS² CLS, programming is reduced to a single step. The setting of the lower and the upper rates allows restriction of the pacing rate range according to the underlying cardiac disease and the constitution of the patient.
In the very first days following programme implementation, CLS adjusts itself to each individual patient: a reference curve is created and continuously updated with beat to beat impedance measurements. Starting from the programmed lower pacing rate, the system is designed to change rate dynamics within the full range between the lower and the upper rate.

**Patient's selection**

In 14 Italian centres participating in the INotropy controlled pacing in VASovagal SYncope (INVASY) Italian feasibility study group (see Appendix), 34 patients (26 men; 8 women) of a mean age of 65 ± 10 years (range 33–80 years) were studied: all of them had a severe syncopal history (range 3–20, median of 6 episodes). In all patients an INOS² CLS pacemaker was implanted and programmed in automatic closed loop, contractility dependent, stimulation.

Patients were included if they met the following criteria: (1) history of at least two vasovagal syncopal episodes per year in the last 1–5 years; (2) documentation of one or more positive baseline Head Up Tilt Tests (HUTTs), with cardioinhibitory or mixed (cardio-inhibitory and vasodepressive) response; (3) absence of current administration of drugs known to cause orthostatic hypotension; (4) absence of abnormal response to right and left carotid sinus massage; (5) exclusion of any other causes of cardiac, metabolic and or other cause of syncope.

After implantation, all patients were discharged with a permanent DDDR-CLS mode programmed on.

Clinical follow up was arranged every six months to assess the incidence of syncopal recurrences during daily life and the consequent psychological well-being.

In 12 patients HUTT was performed at one month follow-up; 6 patients repeated HUTT at 6 months of follow-up; moreover, 5 patients (in one hospital) performed 2 HUTTs in a blindly randomized pacing modes: DDD versus DDDR-CLS pacing with 60 bpm programmed lower rate.

**Protocol for head-up tilt test (HUTT) and measurements**

For the HUTT, each patient was positioned in clino-statc position for 10 min; then upright at 70° for a maximum of 45 min on a tilt table provided with a footboard for weight bearing.

The electrocardiogram was continuously monitored: a strip was recorded every minute to check heart rate and atrial and/or ventricular stimulation. Blood pressure was monitored every 1–2 min, using a cuff tube automatic blood pressure instrument (78354A, Hewlett-Packard).

In case of a syncopal event the test was stopped by immediate lowering of the patient.

In 5 patients myocardial contraction changes were recorded via telemetry of intracardiac impedance from the pacemaker connected to an external device (Unilyzer, Biotronik) during HUTT in DDD mode.

**Results**

The pre-implant clinical data, the results of HUTTs performed before, 3–5 weeks and 6 months after pacemaker implant, the patients subjective health conditions at 1–6 months and at 1, 2, 3 and 4 years are shown in Table 1.

Twenty-seven patients had one positive HUTT before the pacemaker implant; 7 patients had two or three positive HUTTs before enrolment.

In five patients (nos 1, 2, 3, 6, 11) HUTT was repeated, after pacemaker implant, both during DDD and DDDR-CLS mode. In one of these patients (no. 1) all HUTTs after pacemaker implant were negative; in additional 2 patients HUTT was positive during DDD pacing (once in 1 patient: no. 3, twice in the other: no. 2) and negative during DDDR-CLS; two patients (nos 6, 11) developed syncopes during all HUTTs tests in both pacing modes, DDD and DDDR-CLS. Same results were observed at 6 months of follow-up (in patients nos 1, 2, 3, 6).

**Figure 2** shows a sample of the measurements detected by the external device (Unilyzer) in a syncopal patient with the pacemaker programmed in DDD 60 bpm. At the beginning of the HUTT, when the patient is raised, the contractility increases and persists on an elevated level for several minutes. Immediately before the syncpe, the contractility increases and, simultaneously to the lowering of the patient to supine position, it returns to initial level again. Consequently, the arterial blood pressure dropped markedly during the syncopal event, since the spontaneous sinus rate also decreased slightly (**Fig. 3**). The same patient showed increased pacing rates up to 90–120 bpm during the tilt test in DDDR-CLS pacing mode. The immediate reaction of the closed loop system to contractility changes may have blocked the hypotensive reflex and the syncpe (**Fig. 4**).

In 7 patients (nos 13, 14, 19, 21, 25, 30, 31) HUTT was performed only during DDDR-CLS pacing at one month of follow-up; 6 of them (nos 13, 14, 19, 21, 25, 31) developed syncpe during the test. In two other patients (nos 9, 24) HUTT was repeated after 6 months of follow up, both positive (one in DDDR-CLS: no. 9; the other one in DDD: no. 24).

During follow-up (range from 12 to 50 months), 30 patients of the study reported no more vasovagal spontaneous syncope (**Table 1**).

Two patients reported presyncopal episodes (patient no. 9 at 6 and 24 months; patient no. 13 at 12 months) but no true syncopal events.

One patient (no. 14) reported night palpitations but not syncopal episodes until 12 months of follow up; palpitations were caused by an exaggerated rate responsive pacing (confirmed by Holter monitoring) and were eliminated by pacemaker reprogramming.
Table 1  Clinical features of the patient population

<table>
<thead>
<tr>
<th>Pt</th>
<th>[Age, sex]</th>
<th>Pre-imp. VVS episodes</th>
<th>Pre-imp. HUTT</th>
<th>1 month follow-up</th>
<th>6 months follow-up</th>
<th>12 months follow-up</th>
<th>24 months follow-up</th>
<th>36 months follow-up</th>
<th>48 months follow-up</th>
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<td>HUTT Clinical</td>
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<td>HUTT Clinical</td>
</tr>
<tr>
<td>1</td>
<td>B. P. [78, m] (11/97)</td>
<td>1995: 3 1963: 3 1997: 1</td>
<td>2 pos. DDD: 2 neg. CLS: 1 neg.</td>
<td>Good, No more VVS</td>
<td>DDD: 1 pos. CLS: 1 neg.</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
</tr>
<tr>
<td>2</td>
<td>C.M. [77, f] (03/98)</td>
<td>1997: 2 1998: 3</td>
<td>2 pos. DDD: 2 neg. CLS: 1 neg.</td>
<td>Good, No more VVS</td>
<td>DDD: 1 pos. CLS: 1 neg.</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
</tr>
<tr>
<td>3</td>
<td>G. O. [80, f] (04/98)</td>
<td>2yr in last 3 yr</td>
<td>2 pos. DDD: 1 pos. CLS: 1 neg.</td>
<td>Good, No more VVS</td>
<td>DDD: 1 pos. CLS: 1 neg.</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
</tr>
<tr>
<td>4</td>
<td>S.M.A. [63, f] (07/98)</td>
<td>3yr</td>
<td>1 pos.</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
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<td>Good, No more VVS</td>
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<tr>
<td>5</td>
<td>C.M. [77, m] (10/98)</td>
<td>3yr</td>
<td>1 pos.</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
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<tr>
<td>6</td>
<td>D.G. [63, m] (11/98)</td>
<td>3 in last year</td>
<td>3 pos. DDD: 1 pos. CLS: 1 pos.</td>
<td>Good, No more VVS</td>
<td>DDD: 1 pos. CLS: 1 pos.</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
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<tr>
<td>7</td>
<td>A.M. [68, m] (01/99)</td>
<td>2yr</td>
<td>1 pos.</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
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<tr>
<td>8</td>
<td>P.G. [70, m] (01/99)</td>
<td>1998: 3</td>
<td>1 pos.</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
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<tr>
<td>9</td>
<td>C.D. [33, m] (03/99)</td>
<td>6yr</td>
<td>1 pos.</td>
<td>Good, No more VVS</td>
<td>CLS: 1 pos.</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
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<tr>
<td>10</td>
<td>N.L. [45, m] (03/99)</td>
<td>1998: 2 1999: 1</td>
<td>1 pos.</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
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<tr>
<td>11</td>
<td>P.F. [73, m] (05/99)</td>
<td>2yr in last year</td>
<td>2 pos. DDD: 1 pos. CLS: 1 pos.</td>
<td>Good, No more VVS</td>
<td>DDD: 1 pos. CLS: 1 pos.</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
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<tr>
<td>12</td>
<td>R.E. [78, f] (05/99)*</td>
<td>3yr, atrial fibrillation</td>
<td>1 pos.</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
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<tr>
<td>13</td>
<td>A.G. [75, m] (06/99)</td>
<td>3yr</td>
<td>1 pos. CLS+drug: 1 pos.</td>
<td>Good, No more VVS</td>
<td>1 Episode Pre-syncope</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
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<tr>
<td>14</td>
<td>F.S. [68, m] (06/99)</td>
<td>10 in the last 6 yr</td>
<td>1 pos. CLS+drug: 1 pos.</td>
<td>Night Palpitation</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
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<tr>
<td>15</td>
<td>R.C. [72, m] (06/99)</td>
<td>4yr</td>
<td>1 pos.</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
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<td>Good, No more VVS</td>
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<tr>
<td>16</td>
<td>V.M. [72, f] (06/99)*</td>
<td>2yr</td>
<td>1 pos.</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
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<tr>
<td>Pt [Age, sex] (Imp. date)</td>
<td>Pre-imp. VVS episodes</td>
<td>Pre-Imp. HUTT</td>
<td>1 month follow-up</td>
<td>6 months follow-up</td>
<td>12 months follow-up</td>
<td>24 months follow-up</td>
<td>36 months follow-up</td>
<td>48 months follow-up</td>
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<td>HUTT</td>
<td>Clinical outcome</td>
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<tr>
<td>18 M.A. [77, m] (07/99)</td>
<td>4/yr</td>
<td>1 pos.</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
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<tr>
<td>19 C.E. [53, m] (08/99)</td>
<td>2/yr</td>
<td>1 pos. CLS 1 pos.</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
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<tr>
<td>20 L.B. [78, m] (09/99)</td>
<td>2/yr</td>
<td>1 pos.</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
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<tr>
<td>21 D.G. [73, m] (10/99)</td>
<td>20 in the last 3 yr</td>
<td>1 pos. CLS+drug: 1 Pos.</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
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<tr>
<td>22 B.F. [50, m] (10/99)*</td>
<td>1999: 3 5 in last 2 yr</td>
<td>1 pos.</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
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<tr>
<td>23 L.M. [57, m] (11/99)</td>
<td>2/yr</td>
<td>1 pos.</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
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<tr>
<td>24 F.G. [51, m] (11/99)</td>
<td>1/yr</td>
<td>1 pos. CLS 1 pos</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
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<tr>
<td>25 S.G. [53, m] (12/99)</td>
<td>1999: 8</td>
<td>2 pos. CLS: 1 neg.</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
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<tr>
<td>26 L.R. [70, m] (12/99)*</td>
<td>1/yr</td>
<td>1 pos.</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
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<tr>
<td>27 C.N. [70, m] (12/99)*</td>
<td>2 last yr</td>
<td>1 pos.</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
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<tr>
<td>28 B.D. [67, f] (02/00)</td>
<td>&gt;3 last yr</td>
<td>2 pos.</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
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<tr>
<td>29 B.G. [69, m] (03/00)</td>
<td>&gt;3 last yr</td>
<td>1 pos.</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
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<tr>
<td>30 C.Z. [58, f] (05/00)</td>
<td>1/yr last 3 year</td>
<td>1 pos. CLS: 1 neg.</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
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<tr>
<td>31 G.P. [73, m] (06/00)</td>
<td>&gt;3 last yr</td>
<td>1 pos. CLS: 1 pos.</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
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<tr>
<td>32 PR [62, m] (06/00)</td>
<td>&gt;2 last yr</td>
<td>1 pos.</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
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<tr>
<td>33 M.R. [60, f] (07/00)*</td>
<td>&gt;10 last yr</td>
<td>1 pos.</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
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<tr>
<td>34 A.C. [61, m] (10/00)*</td>
<td>&gt;10 1993, VVI PM; 6 last yr</td>
<td>1 pos.</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
<td>Good, No more VVS</td>
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Notes: Implant date: month/year; VVS: Vasovagal Syncope; HUTT: Head Up Tilt Test; *previous PM implanted; pos: positive.
As shown in Table 1, 7 patients had already been implanted with a conventional pacemaker (DDD in six and VVI in one). Frequent recurrences of vasovagal fainting, persuaded the physician to upgrade the implanted system in DDDR-CLS. In six of the patients of the registry, this measure allowed the total prevention of vasovagal syncope recurrences, confirming the superiority of the DDDR-CLS pacing mode compared with

Figure 2  During the HUTT in DDD mode, intracardiac impedance waveforms were collected by an external device (Unilyzer, BIOTRONIK) through pacemaker telemetry transmission. Figure shows the measurements in a syncopal patient: at the beginning of the tilt when the patient is raised, the contractility increases and persists on an elevated level for several minutes. Shortly before the syncope occurs, the contractility increases and, simultaneously with the lowering of the patient to supine position, it returns to the initial level.

Figure 3  As shown in the figure, the arterial blood pressure fell markedly during the syncopal event and the spontaneous sinus rate also decreased slightly. BP=blood pressure, syst=systolic, diast=diastolic.
traditional DDD pacing. Only one patient (no. 12) complained of syncopal recurrences (at 6, 12 and 24 months of follow up); the patient was a 78-year-old woman in chronic atrial fibrillation; the role of cardiac pacing in patients with vasovagal syncope and chronic atrial fibrillation is still unclear and perhaps the pacemaker implant was not appropriate.

**Discussion**

The results of our study show that DDDR-CLS pacing is safe and seem to confirm that it is also effective in preventing vasovagal syncope in patients with recurrent episodes.

The inappropriate reduction of heart rate and systemic hypotension caused by arteriolar vasodilatation is called ‘vasovagal’ (or ‘neurocardiogenic’ or ‘neurally mediated’) syncope[14]. This phenomenon is associated with an abnormal cardiovascular reflex, but the underlying pathophysiological mechanisms are largely unknown[15]. Bradycardia is thought to result from sudden increase of efferent vagal activity and hypotension from sudden decrease or cessation of the previously increased sympathetic outflow.

Two different types of vasovagal syncope, central and peripheral types, have been described[16].

In the central type the medullary cerebral centres are directly affected by efferent hypothalamic signals triggered by emotional stress, pain, fear, etc., which, increasing vagal activity, cause hypotension, bradycardia and lypotimia.

On the other hand, the peripheral type of vasovagal reaction is consequent upon a sudden reduction of central blood volume: the central hypovolaemia may be due to impaired venoconstriction and by ineffective tone of splenic and other resistance vessels[17,18]. That induces a compensatory increase in the sympathetic discharge, an increase in the heart rate and in the inotropic state of the myocardium[19,20]. The more vigorous contraction of an insufficiently filled ventricle stimulates ventricular mechanoreceptors[21]. The afferent signals of these receptors, transmitted through the vagus nerve, reach the circulatory centres and trigger an increase in efferent vagal activity and a withdrawal of efferent sympathetic discharge[22].

Thus, in the peripheral vasovagal syncope, the triggering signals originate from myocardium and result in severe hypotension and bradycardia[23]. This neurocardiac reflex, with its afferent and efferent limbs, is called the Bezold–Jarisch reflex[24]; this is reproduced by HUTT[25,26].

If the baseline HUTT is negative, the sensitivity of the test can be improved with drugs (isoprenaline infusion or sublingual nitroglycerin) to enhance the contractility response and provoke the Bezold–Jarisch reflex[27,28].

A vasodepressive response is characterized by a systolic blood pressure fall, while at the time of syncope the heart rate does not fall more than 10% from its peak. In the mixed response, blood pressure falls before the heart rate; the ventricular rate does not fall to less than 40 bpm, or falls to less than 40 bpm for less than 10 s, with or without asystole (<3 s). If the bradycardia and/or asystole are more important the HUTT response is classified as ‘cardioinhibitory’[29].

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**Figure 4** Trend of arterial blood pressure and heart rate during negative HUTT in DDD-CLS pacing. In the same patient an increased pacing rate up to 90–120 bpm inhibited the hypotensive reflex and the syncope.

Figure 4: Trend of arterial blood pressure and heart rate during negative HUTT in DDD-CLS pacing. In the same patient an increased pacing rate up to 90–120 bpm inhibited the hypotensive reflex and the syncope.
The present therapeutic options in vasodepressive vasovagal syncope include general counselling, tilt training, drugs that improve volaemia by peripheral vasoconstriction, drugs that decrease the contractile myocardial response resulting in blunting the Bezold–Jarisch reflex.

On the contrary, in case of vasovagal ‘mixed’ responses, characterized by hypotension and severe bradycardia, drugs and/or DDI pacing are indicated\cite{30}. Dedicated algorithms, associated with pacing for a better prevention of the vasovagal mixed peripheral syncope, have been developed as:

- DDI with rate hysteresis\cite{31};
- DDD with automatic mode commutation;
- DDI with rate drop response algorithm\cite{32,33}.

Our clinical investigation suggests an additional sophisticated method in dual chamber pacing, namely DDD Closed Loop Stimulation (CLS), for the prevention of vasovagal syncope.

This concept of cardiac pacing integrates the pacemaker into the physiological cardiovascular control loop. The effectiveness of CLS in preventing vasovagal syncope may result from this integration. Our measurements, in accordance with previous investigations\cite{34,35}, have demonstrated, that increased myocardial contractility precedes the vasovagal syncope. A pacing system able to convert this input information into pacing rates high enough to counteract the pathological Bezold–Jarisch reflex, is likely to alleviate central hypotension and prevent vigorous contractions against underfilled ventricles\cite{31}.

The rationale for closed loop stimulation correlated with the myocardial contractility to prevent vasovagal syncope, may be that high rate ventricular stimulation, correlated with the increased contractility in the first stage of head up tilt test, could prevent the failure of sympathetic tone and counterbalance the increase in vagal tone avoiding arterial hypotension, bradycardia and consequently the syncope.

The INOS2 CLS pacemaker was used to prevent vasovagal malignant syncope also in previous studies\cite{36-38} with good results. Other pacing systems modulated by the sympathetic system have also been already used to prevent vasovagal malignant syncope\cite{39,40}.

In our study, we confirmed that DDDR Closed Loop Stimulation guided by the contractility status seems to be a promising therapeutic approach to prevent vasovagal mixed syncope.

In nearly all patients in our study no syncope recurrence occurred during daily life after pacemaker DDDR-CLS implant, and patients subjective health condition was good.

Our study confirms also the important role of the HUTT to individualize patients suffering from vasovagal syncope; moreover our data, as those of a recent study\cite{31}, suggest that the use of HUTT for assessing the effectiveness of pacing therapy has some limitations.

The discrepancy observed in our study between the negative HUTT results (six patients among the seven that repeated the tilt test during DDDR-CLS pacing fainted) and the very encouraging clinical outcome could be explained if we consider that tilt test prolongs and carries to extremes a clinical situation which, in daily life, the patient tries to avoid.

Although the current results of Closed Loop Stimulation in vasovagal syncope seem very promising, several issues still remain to be clarified.

The most obvious aspect in this context is that the effectiveness of cardiac pacing concepts in preventing vasovagal fainting is directly related to the degree of bradycardia, which develops during the syncope. Secondly, the response of the CLS-pacemaker depends on the grade of sympathetic changes affecting the heart during the syncopal event. If central hypovolaemia occurs without or only with little change in ventricular contractility\cite{36,37}, the pacemaker will not respond properly. A reduction in contractility response can also arise from the use of beta-blockers, which are used as an elective drug therapy in such patients. It could be useful to intensify investigations using contractility monitoring during head up tilt test to screen these unresponsive patients.

The last aspect to be discussed in this context focuses on the possible placebo effect. This is a non-randomized study with no control-group; so we cannot exclude that the positive clinical results observed are partly due to the pacemaker implantation. In the population of the registry the placebo effect seems unlikely, as six patients had already been treated with a DDD conventional pacemaker and still complained of syncopal recurrences.

Beside our preliminary encouraging results, further larger studies are mandatory to understand the preventive mechanism in detail and to confirm the beneficial effect of Closed Loop Stimulation in vasovagal syncope in a larger group of patients.

For this purpose, the INVASY (INotropy controlled pacing in VAsovagal SYncope) clinical trial has been designed\cite{40} and is at present running\cite{41}. Main aim of the study is to investigate whether DDD-CLS pacing is able to prevent syncopal recurrences. In this prospective controlled, multicentre study, patients with recurrent vasovagal syncope and significant bradycardia during HUTT are centrally randomized either to DDD-CLS pacing or to back-up DDI. The results of this study could clarify the role of cardiac pacing, and in particular of DDDR-CLS, in preventing vasovagal syncope.

**Appendix**

**INVASY Italian prospective feasibility Registry:**

- D. Igidibashian. Ospedale Civile, Legnago (Verona).
References


