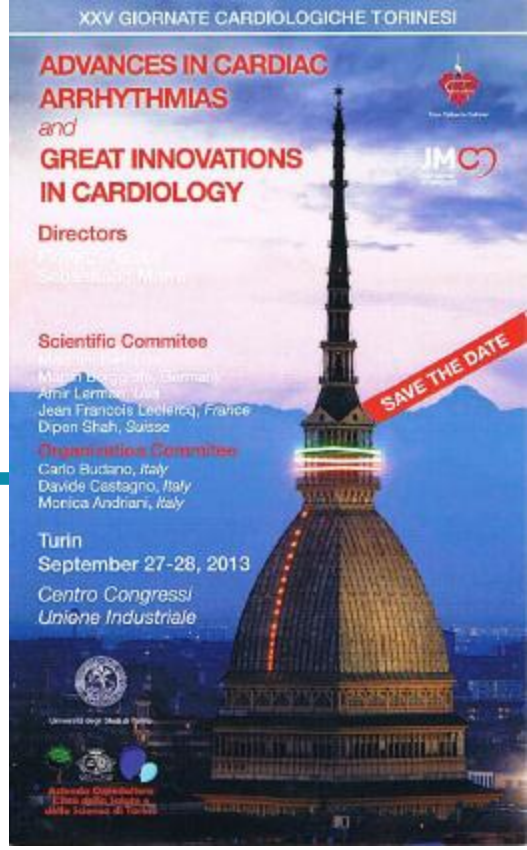



# Rate modulation pacing guided by contractility physiological sensor: which the clinical evidence?

**Eraldo Occhetta**
**SSD Elettrofisiologia e Cardiostimolazione**
**Dipartimento Cardiologico**
**AOU Maggiore della Carità - Novara**

# Physiological rate regulation

## Sensor classification*

| | Tertiary | | |
|---|---|---|---|
| Sensor technology | Accelerometer | | |
| Definition | Detects parameters *resulting* from exercise | | |

*Rickards et al., *Clin Prog Pacing Electrophysiol,* 1983, 1:12.

# Physiological rate regulation

## Sensor classification*

| | Tertiary | Secondary | |
|---|---|---|---|
| **Sensor technology** | Accelerometer | **Minute ventilation, blended sensors** | |
| **Definition** | Detects parameters *resulting* from exercise | **Detects parameters** *resulting* **from metabolic demand** | |

*Rickards et al., *Clin Prog Pacing Electrophysiol,* 1983, 1:12.

# Physiological rate regulation

## Sensor classification*

| | Tertiary | Secondary | Primary |
|---|---|---|---|
| **Sensor technology** | Accelerometer | Minute ventilation, blended sensors | **Closed Loop Stimulation** |
| **Definition** | Detects parameters *resulting* from exercise | Detects parameters *resulting* from metabolic demand | Detects parameters ***influencing*** cardiac function |

*Rickards et al., *Clin Prog Pacing Electrophysiol,* 1983, 1:12.

# Physiological rate regulation

## Closed Loop Stimulation - clinical rational

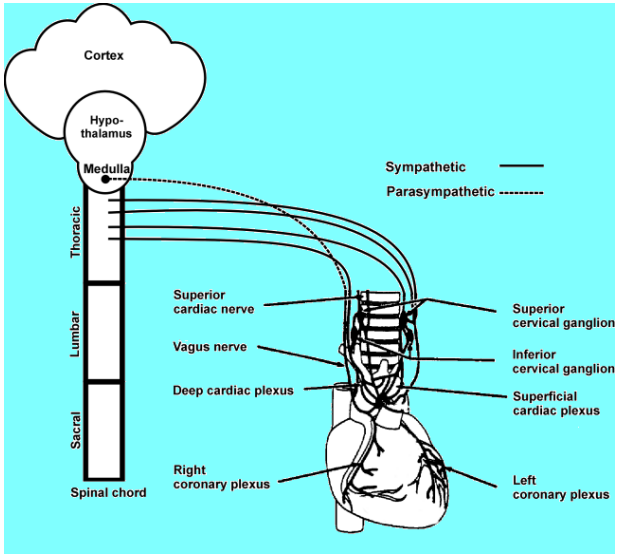
- Accelerometer and minute ventilation algorithms respond only during physical activity, independently of cardiac function.
- Effective response in all other mental situations is needed.
- A modulated response related to the cardiac function is more physiological and clinical appropriate.

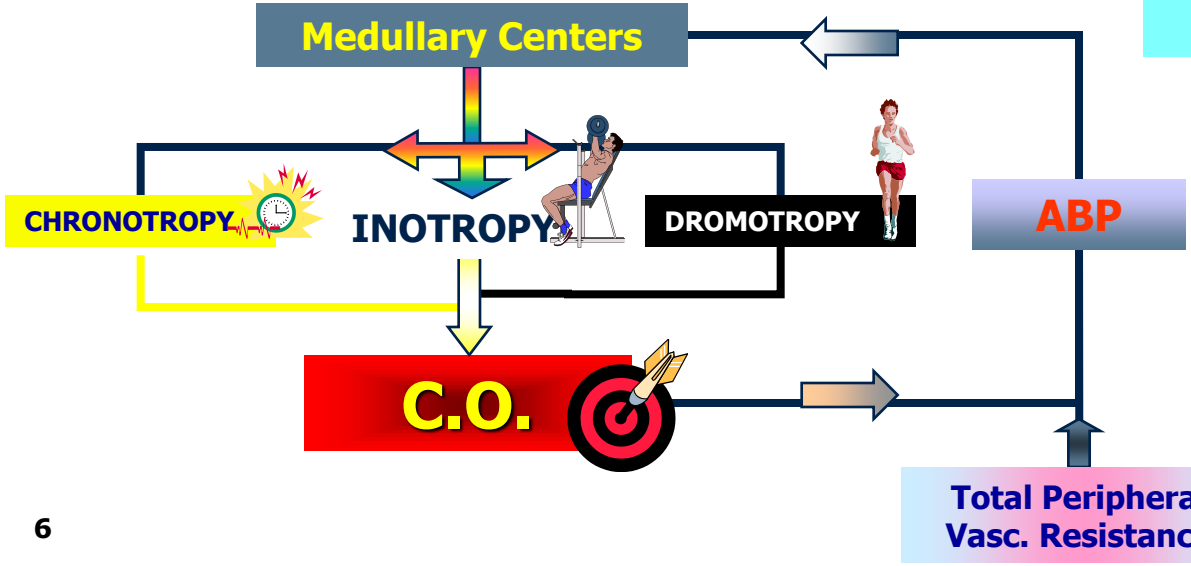
**Therefore, pacing modulation requires a natural mechanism of autonomic and contractility mediated control.**

# The Natural Regulation of the Cardiovascular System

**The main target of the Cardiovascular System is to PRESERVE an optimal perfusion in all tissues of the body.**

**When a controlled variable (e.g. atrial blood pressure, temperature, vasodilatation, etc.) changes its value ALTERING the optimal perfusion, the System reacts modulating the other variables in the attempt to RE-ESTABLISH the conditions of EQUILIBRIUM.**



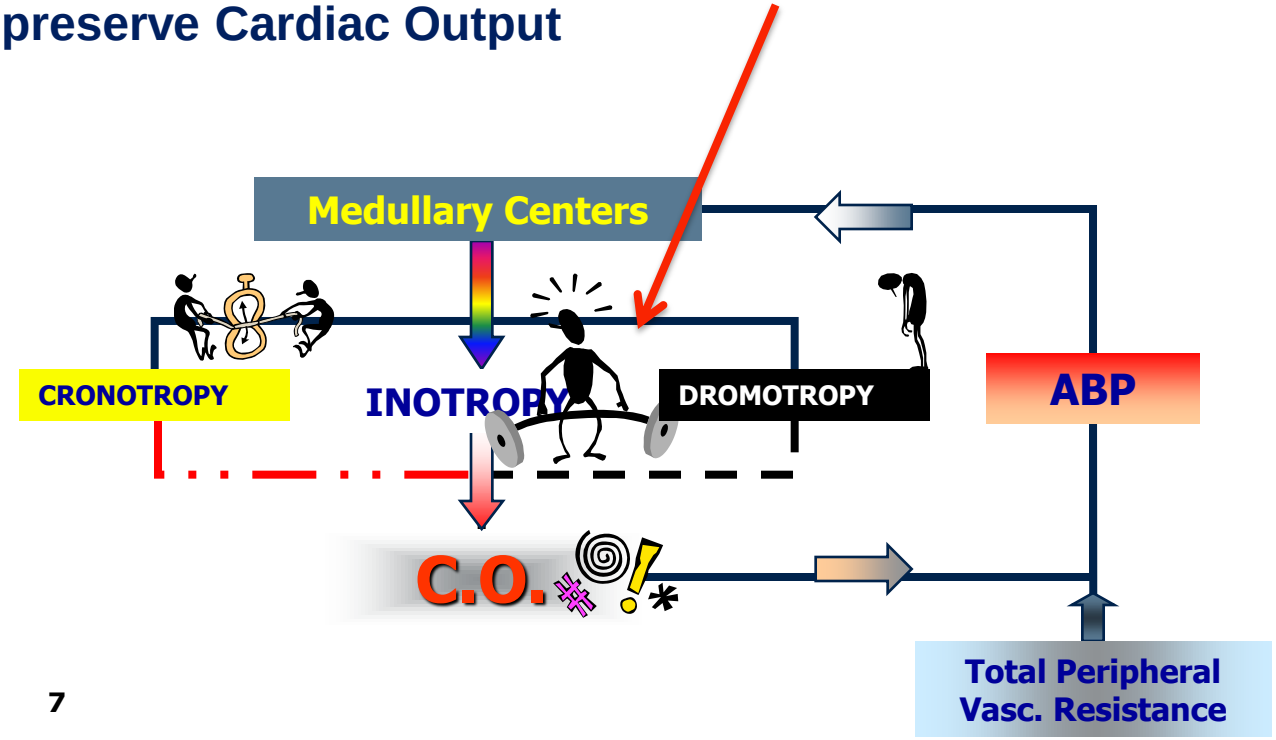




**Natural CLOSED LOOP Control *with* NEGATIVE FEEDBACK**

# Impaired Cardiac Dynamics in Presence of Rhythm Pathology

**When CHRONOTROPIC and/or DROMOTROPY functions are depressed**

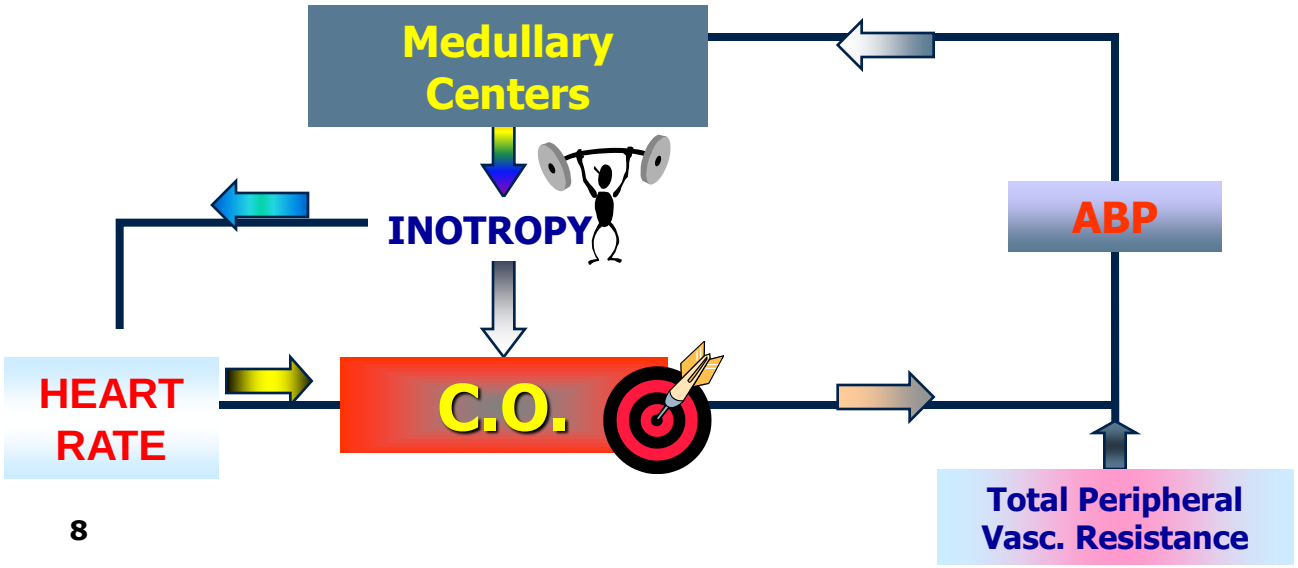
**The Cardiovascular System attempts to restore the hemodynamic equilibrium increasing the INOTROPIC response (Myocardial Contractility) to preserve Cardiac Output**



# Control of Impaired Cardiac Dynamics with CONTRACTILITY related Pacing

**The CONTRACTILITY RELATED PACING modulates the Heart Rate in accordance with real and contingent physiopathological needs, since it is driven by INOTROPY (Contractility) variations.**

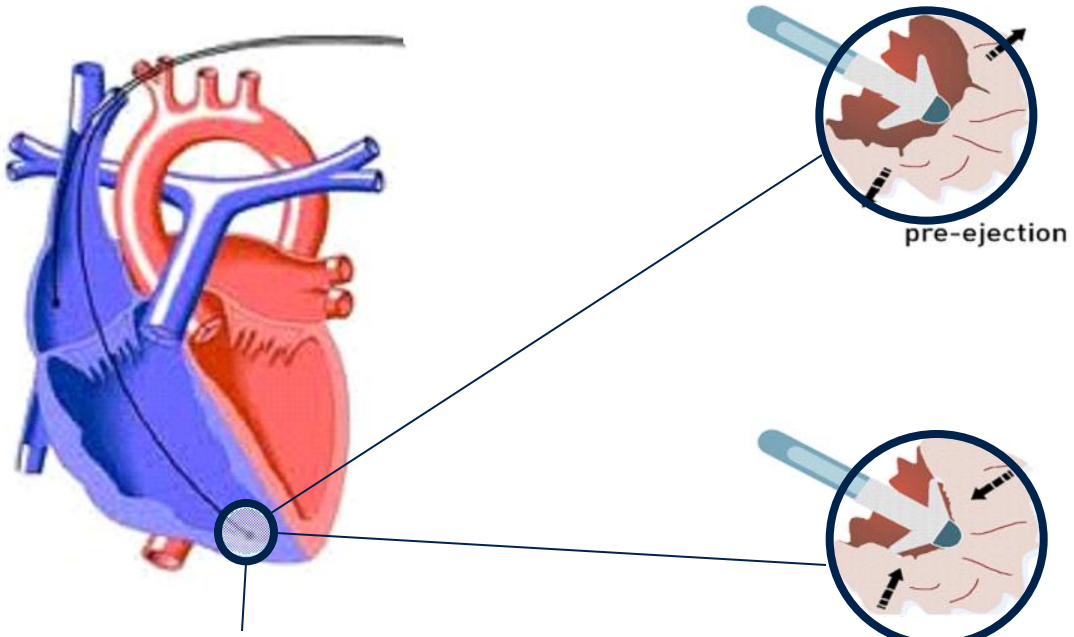
**By this way, the device is integrated in the closed loop of the natural control system and allows to the Autonomic Nervous System to maintain the total control on Cardiac Output.**




**Restored CLOSED LOOP Control *with* NEGATIVE FEEDBACK**

# Closed Loop Stimulation - measuring impedance

- Impedance has a direct correlation with myocardial wall motion (inotropy).
- Changes in myocardial wall motion directly correlate to changes in autonomic tone.
- Increased inotropy compensates for the decreased heart rate.

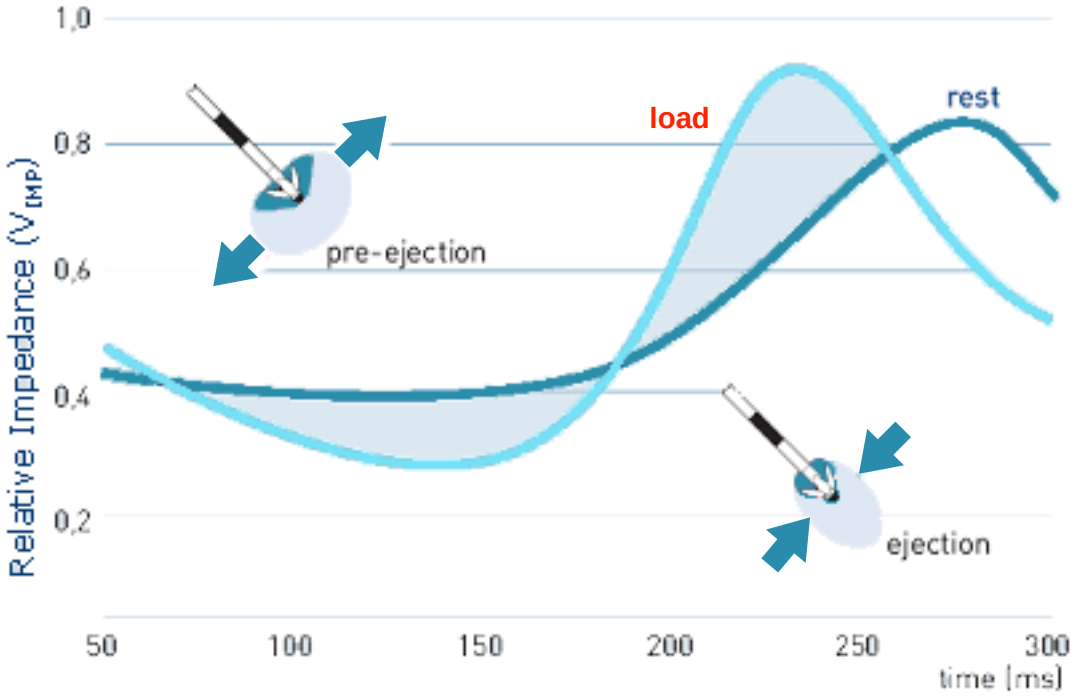



**Smaller fraction of myocardium = low impedance**

**Larger fraction of myocardium = high impedance**

# Closed Loop Stimulation - reference versus load curve

- **With each heartbeat, CLS determines the impedance curve ($V_{IMP}$) during ventricular contraction (load curve) and compares it to its reference curve at rest (rest curve).**

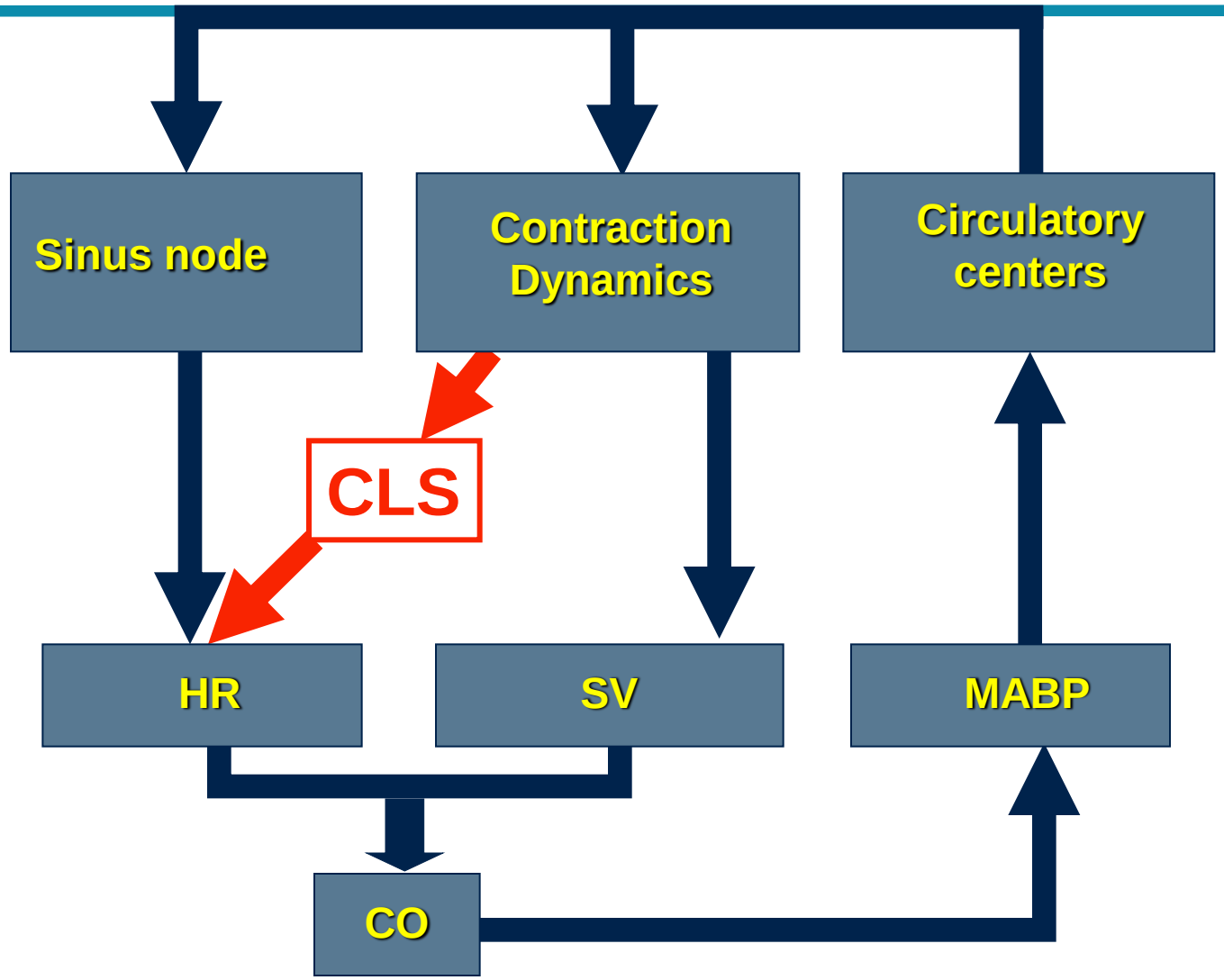



**No particular lead needed**

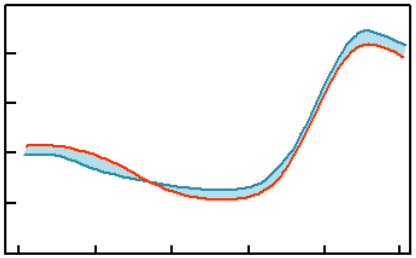
# Clinical applications of CLOSED LOOP STIMULATION - CLS

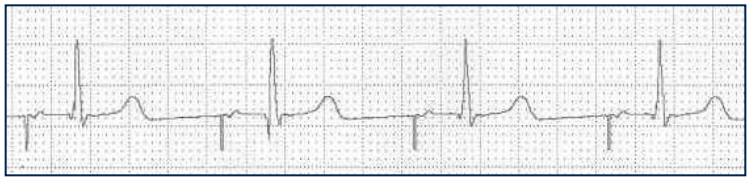
1) Rate responsive pacing regulation
2) Ventricular function related pacing rate control
3) Hemodynamic cardiac function monitoring
4) Vaso Vagal syncope prevention

# Contractility guided rate responsive

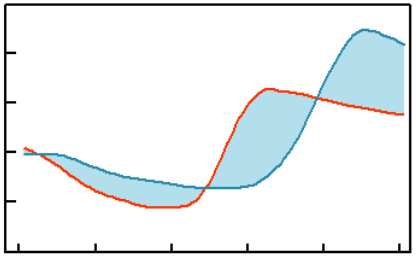


# Pacing regulation in response to changes in contraction dynamic

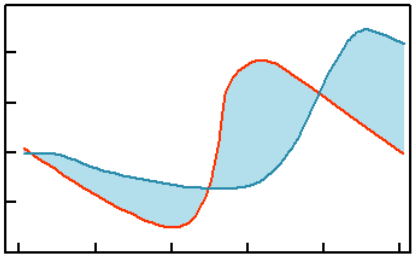




**Low rate regulation**



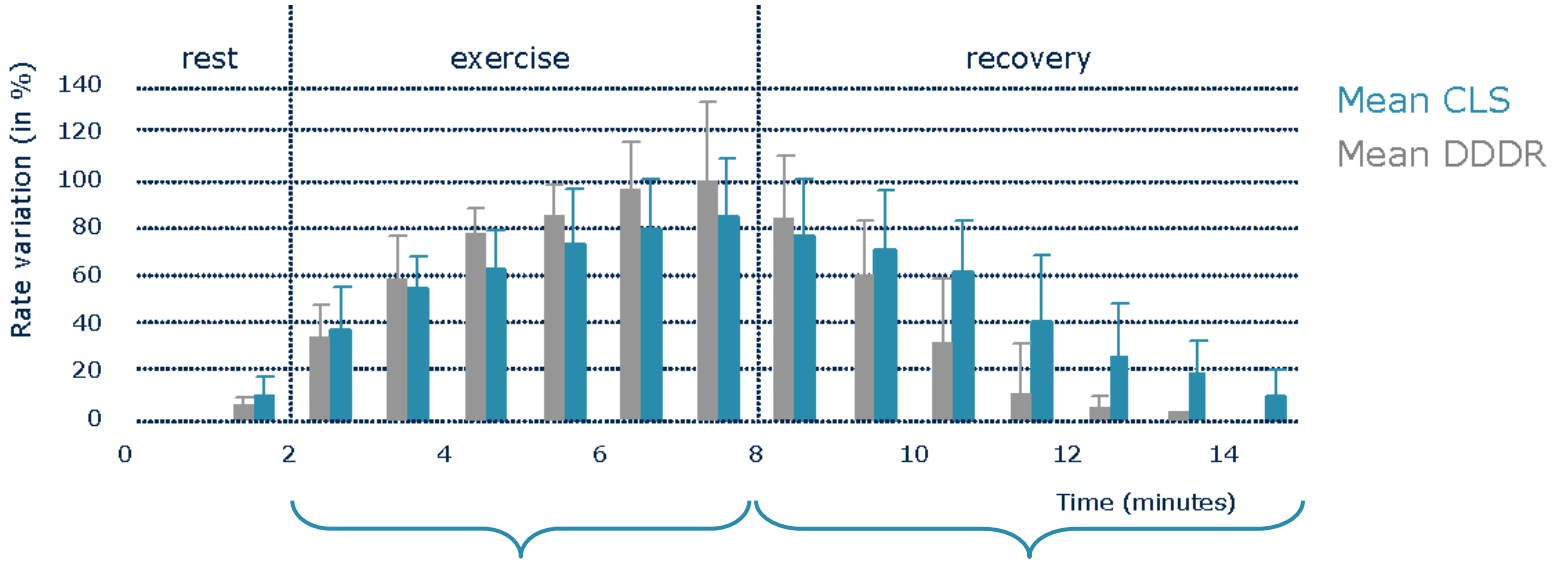
**Medium rate regulation**



**High rate regulation**

# Closed Loop Stimulation - clinical examples*

- **Adequate heart rate adaptation during physical activity, even with differing levels (e.g., treadmill, cycling)**




**Accelerometer is more aggressive at the start of exercise**

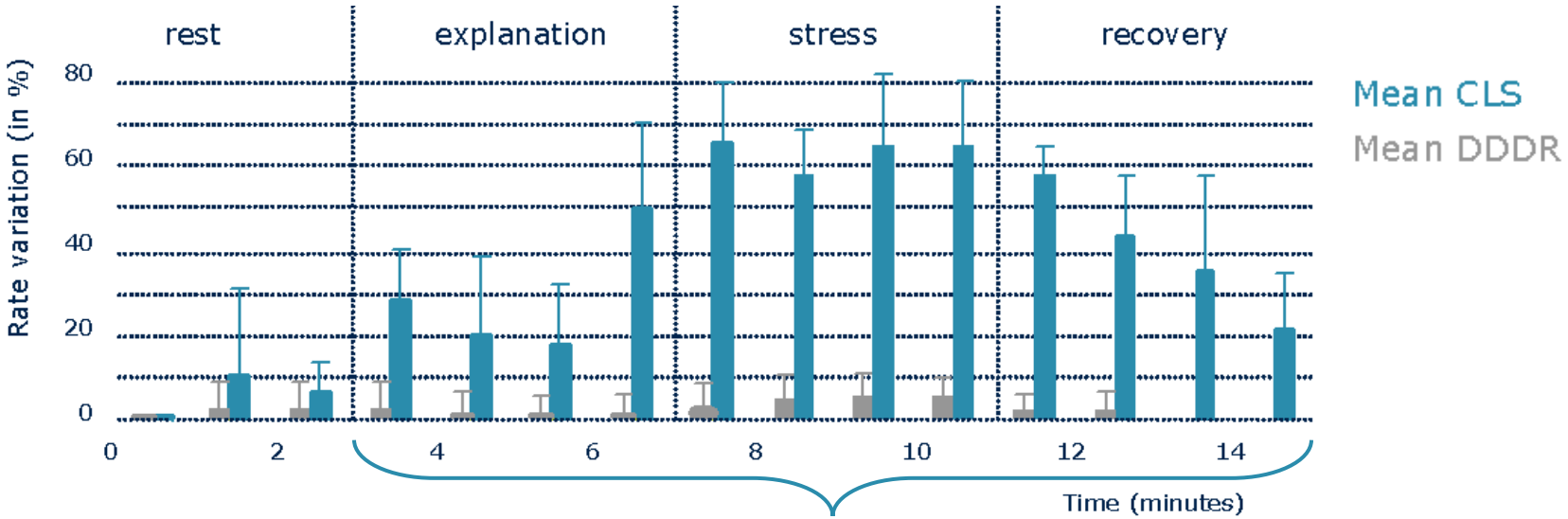
**CLS is more appropriate to metabolic demand during the recovery phase**



*Zecchi et al.; CLS vs. DDDR pacing: Benefits of hemodynamic pacing, *Prog Biomedical Res,* 2000, 5:292–296.

# Closed Loop Stimulation - clinical examples*

- **Restoration of ANS control enables patients to respond to daily activities that involve mental stress.**




**CLS clearly demonstrates superior rate adaptation compared with accelerometer**



*Zecchi et al.; CLS vs. DDDR pacing: Benefits of hemodynamic pacing, *Prog Biomedical Res,* 2000, 5:292–296.

# Latest publication 2010 - present

## CLS - Rate Response physiological response

- *Clinical observations with Closed Loop Stimulation pacemakers in a large patient cohort: the CYLOS routine documentation registry (RECORD),* **M. Lindovskà et al., EUROPACE, 2012**

- *Closed Loop Stimulation is Effective in Improving Heart Rate and Blood Pressure Response to Mental Stress: Report of a Single-Chamber Pacemaker Study in Patients with Chronotropic Incompetent Atrial Fibrillation,* **R. Proietti et at, PACE, 2012**

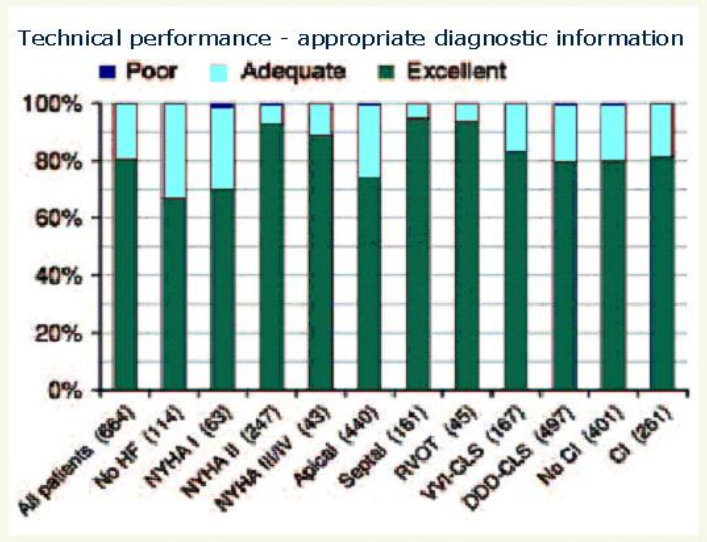
- *Effect of rate-adaptive pacing on performance and physiological parameters during activities of daily living in the elderly: results from the CLEAR (Cylos Responds with Physiological Rate Changes during Daily Activities) study,* **Freddy M. Abi-Samra et Al., Europace, 2013**

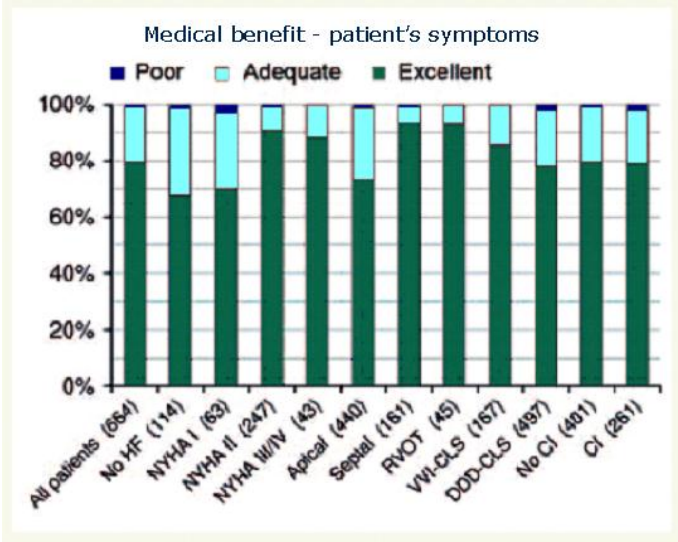
# CLS - Physiological Response

## Lindovskà, RECORD Study (Europace 2012)

- Aim: 706 patients were enrolled in the clinical investigation 'Record registry. Physicians' satisfaction with medical benefits and technical performance of CLS in each patient was measured.
- **Results: "clinical performance of CLS was very satisfactory in the large cohort studied". RECORD investigators' satisfaction with CLS performance did not depend on the chronotropic status of the patient.**

**Physicians judgments on technical perfomance and medical benefits of CLS**



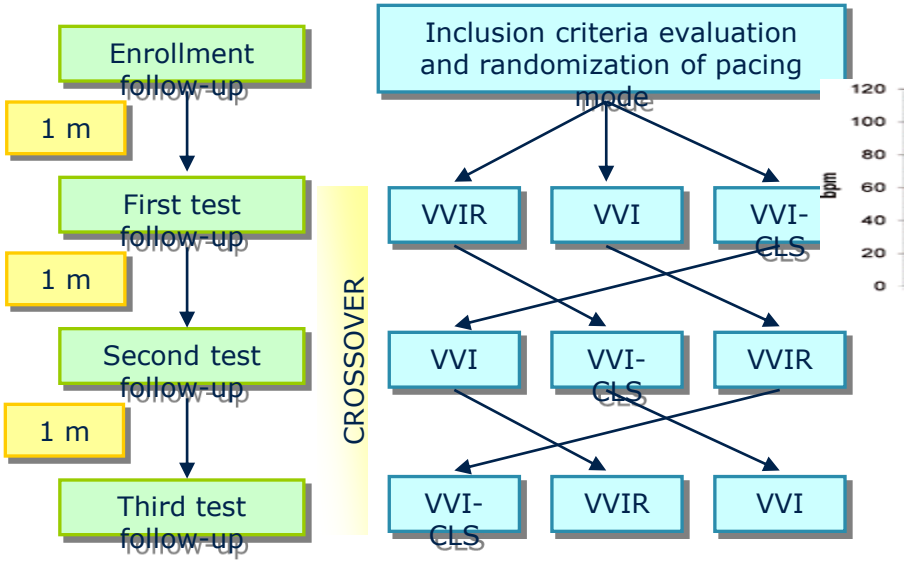

Patients subgroups were formed according to the NYHA functional classification, right ventricular lead position, pacing mode, and chronotropic incompetence.

# CLS - Physiological Response

## Proietti (PACE 2012)

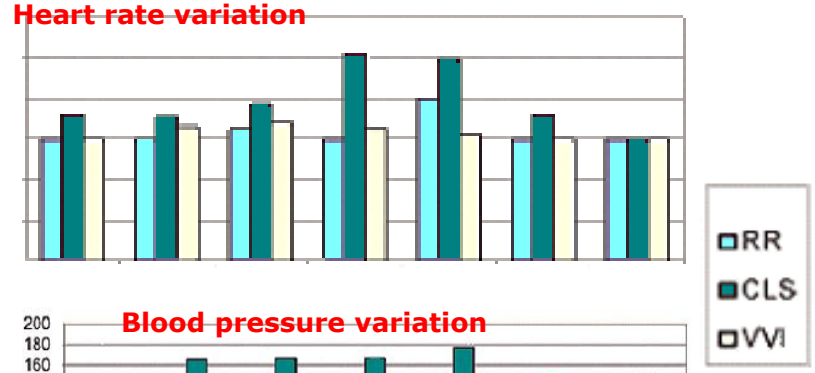
- Aim: CLS and accelerometer sensor were compared intraindividually during a mental stress test (MST) in 36 patients with single chamber pacemaker implants (AF with chronotropic incompetence).
- **Results: "CLS algorithm in a single-chamber device is more effective than accelerometer in detecting an hemodynamic demand due to emotional stress and supplying a proper HR increase and a better pressure profile during mental stress".**

**Study flowchart**

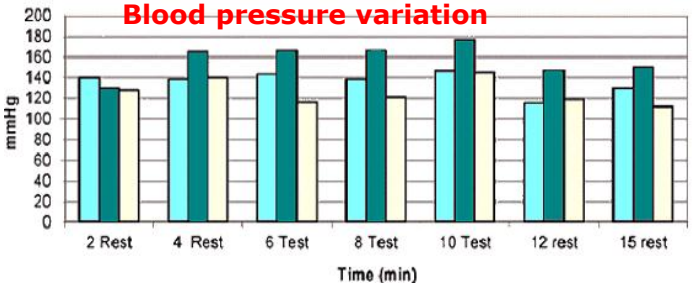



**Patient example: Higher variation in HR and Blood pressure during mental stress**

**Heart rate variation**



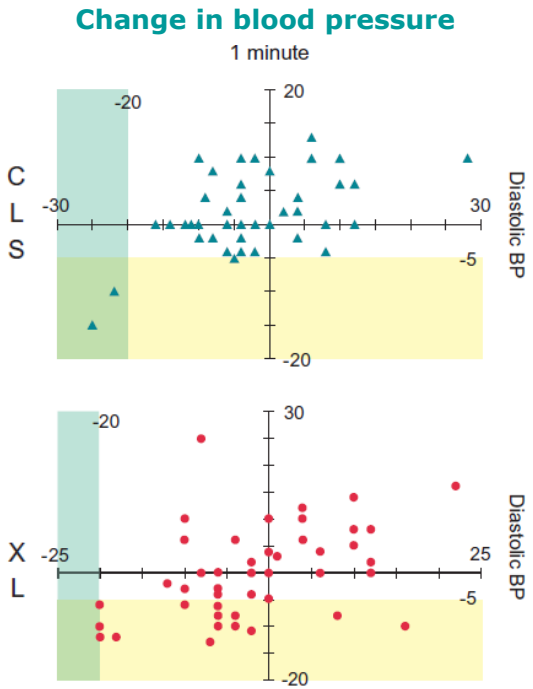

**Blood pressure variation**



# CLS - Physiological Response

## Abi-Samra, CLEAR study (Europace 2013)

- Aims: compare the performance and physiological response of the CLS sensor to accelerometer during typical daily activity in 74 elderly patients
- Results: **"CLS provides a more physiological response during the performance of activities of daily livingin patients with ≥80% pacing".**
  - "Use of CLS resulted in over a 75% reduction in the prevalence of orthostatic hypotension (OH) after standing 1 min as compared with XL and DDD."




Scattergram of change in blood pressure from baseline for each subject included in the stand-and-go test.

The linear correlation coefficient is close to 0 only for CLS in 1 minute (the dispersion is similar to a cyrcle), so there is no linear correlation between systolic and diastolic pressure.

**Table 3** Prevalence of OH during stand-and-go test

| | OH, *n* (%) | Unadjusted results OR (95% CI) CLS vs. | *P* value CLS vs. | Adjusted for order effect OR (95% CI) CLS vs. | *P* value CLS vs. |
|---|---|---|---|---|---|
| Immediately after standing ($n = 46$) | | | | | |
| CLS | 6 (13.0) | | | | |
| XL | 12 (26.1) | 0.43 (0.14, 1.25) | 0.188 | 0.40 (0.12, 1.31) | 0.126 |
| DDD | 10 (21.7) | 0.54 (0.18, 1.63) | 0.410 | 0.48 (0.14, 1.62) | 0.228 |
| After standing 1 min ($n = 46$) | | | | | |
| CLS | 3 (6.5) | | | | |
| XL | 14 (30.4) | 0.16 (0.04, 0.60) | 0.006 | 0.10 (0.02, 0.53) | 0.008 |
| DDD | 13 (28.3) | 0.18 (0.05, 0.67) | 0.012 | 0.10 (0.02, 0.53) | 0.008 |

OH, orthostatic hypotension; OR, odds ratio; CI, confidence interval; CLS, closed-loop stimulation.

# Latest publication 2010 - present

**CLS and hemodynamic response**

Usefulness of Hemodynamic sensors for physiologic cardiac pacing in heart failure patients. **E. Occhetta et al, Cardiology Research and Practice, 2011**

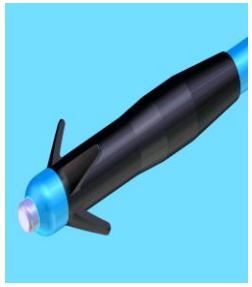
**CLS and Heart Failure**

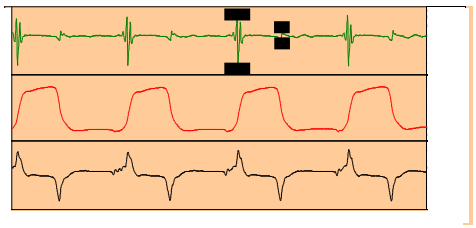
Biventricular pacing improves cardiac function and prevents further left atrial remodeling in patients with symptomatic atrial fibrillation after atrioventricular node ablation. **M.V. Orlov et al, American Heart Journal, 2010**

# CLS and Hemodynamic Response

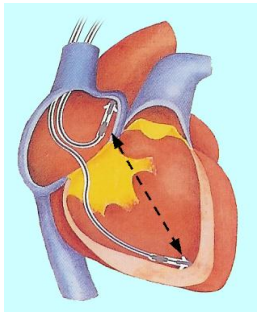
## Occhetta (Cardiology Research and Practice, 2011)

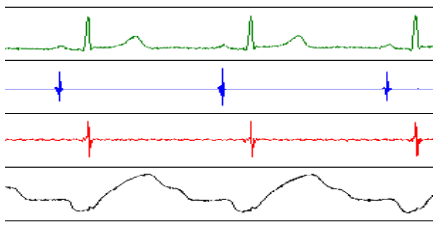
- Aim: evaluation of different hemodynamic sensors in terms of advantages and benefits they can offer.



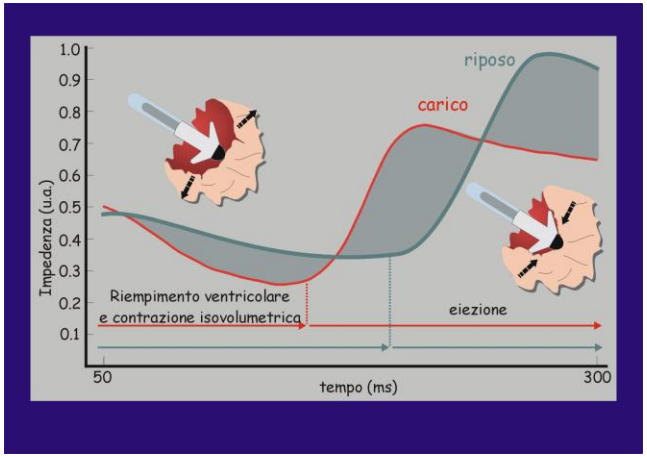


**Peak Endocardial Acceleration**
**Sorin Group**





**Trans Valvular Impedance**
**Medico**




**Closed Loop Stimulation**
**Biotronik**

# Hemodynamic Response

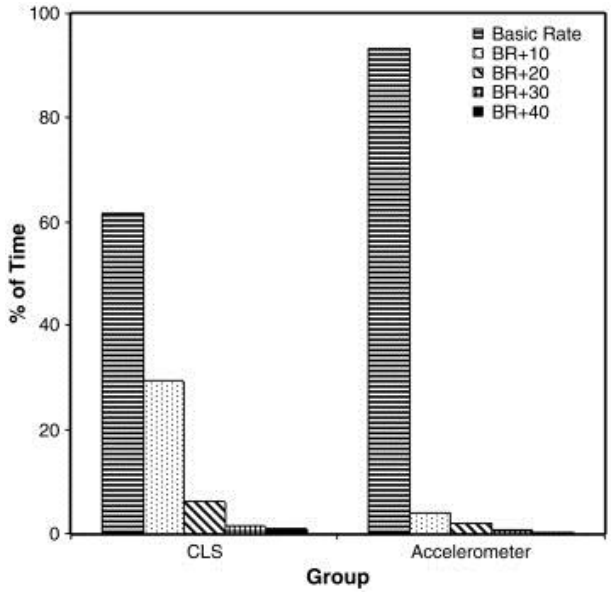
## Occhetta (Cardiology Research and Practice, 2011)

- **Results:**
  - **"The fourth generation of CLS devices, operating on both sensed and paced ventricular beats, have overcome the major limitation of the previous systems which required permanent ventricular pacing".**
  - **"Specially in heart failure patients CLS could assure an optimal upper rate limit control, reducing deleterious inappropriate rate response induced by motion sensors"**
  - **"Hemodynamic sensors might play a role in the long-term monitoring of heart failure, helping the physician in the individual care of each patient".**

# CLS and Heart Failure

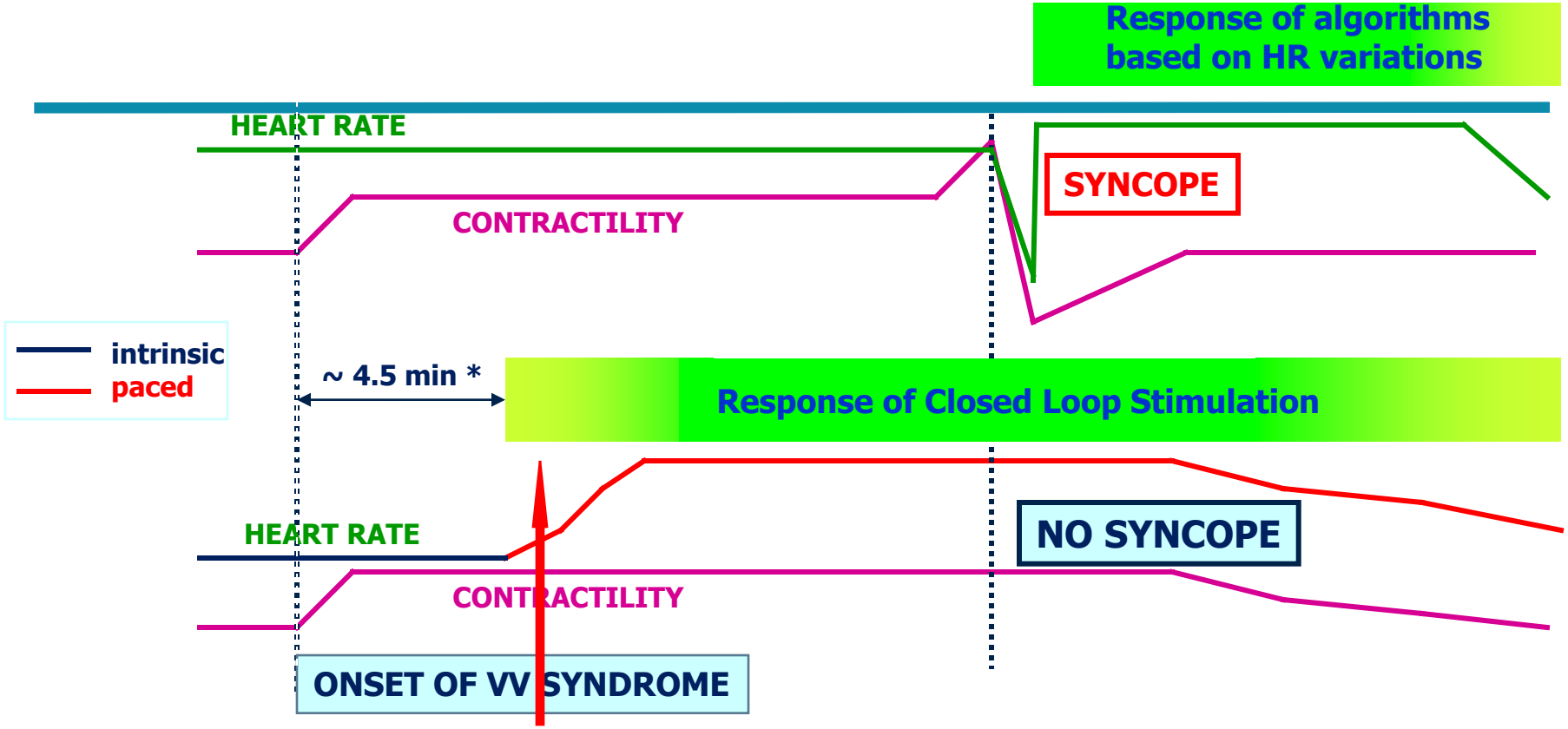
## Orlov (American Heart Journal 2010)

- Aim: 108 patients with refractory AF underwent AV node ablation and were randomized (2:2:1) to BiV pacing with CLS, BiV pacing with accelerometer, or right ventricular (RV) pacing.
- Results: "RV pacing results in significant increase in left atrial volume, LV mass, and worsening of LV contractility compared to patients receiving BiV pacing post-AV node ablation for refractory AF".
- **"Closed Loop Stimulation was not associated with structural changes; and heart rate distribution was significantly wider with CLS"** (decrease of sympathetic tone)




The data demonstrate that there was a significantly wider heart rate distribution in patients with CLS, as compared to patients with accelerometer-based rate adaption.

# CLS pacing and Vaso Vagal physiopatology




**CLS detects onset of VV spell through variations of contractility and reacts with a rate increase after ~ 4.5 min from tilt up. This timely intervention early suppresses the bradycardic effect and counterbalances the associated hypotension.**



* Griesbach L and Coll. Prog Biomed Res 2002; 7: 242-247

# CLS pacing in VVS prevention: RATIONALE

At the **onset** of a VV spell **Sympathetic Tone** and **Contractility** increase.

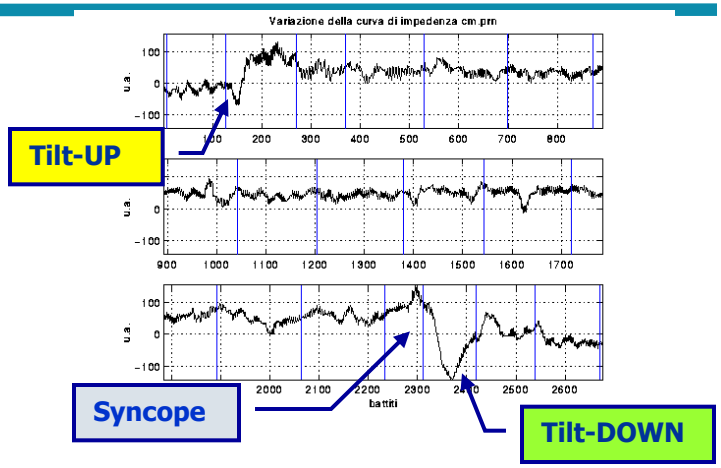
**CLS Pacing will early react with a dominant pacing rate**

**Preventing** the Sympathetic Tone ↓
and **contrasting** the Vagal Tone ↑

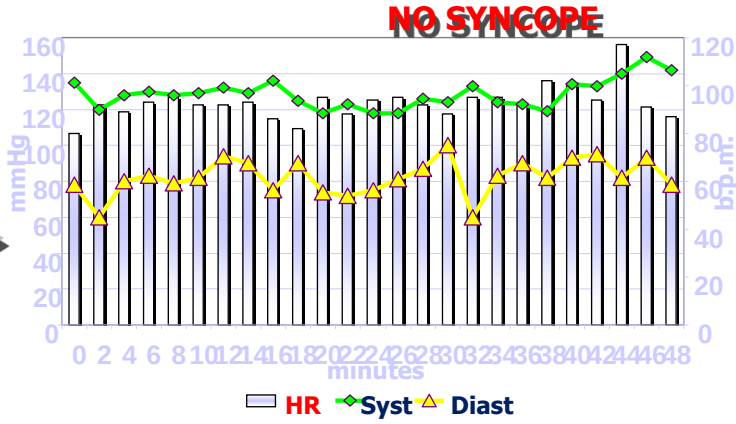
**Hypotension and Bradycardia** are prevented

**Syncope is PREVENTED**

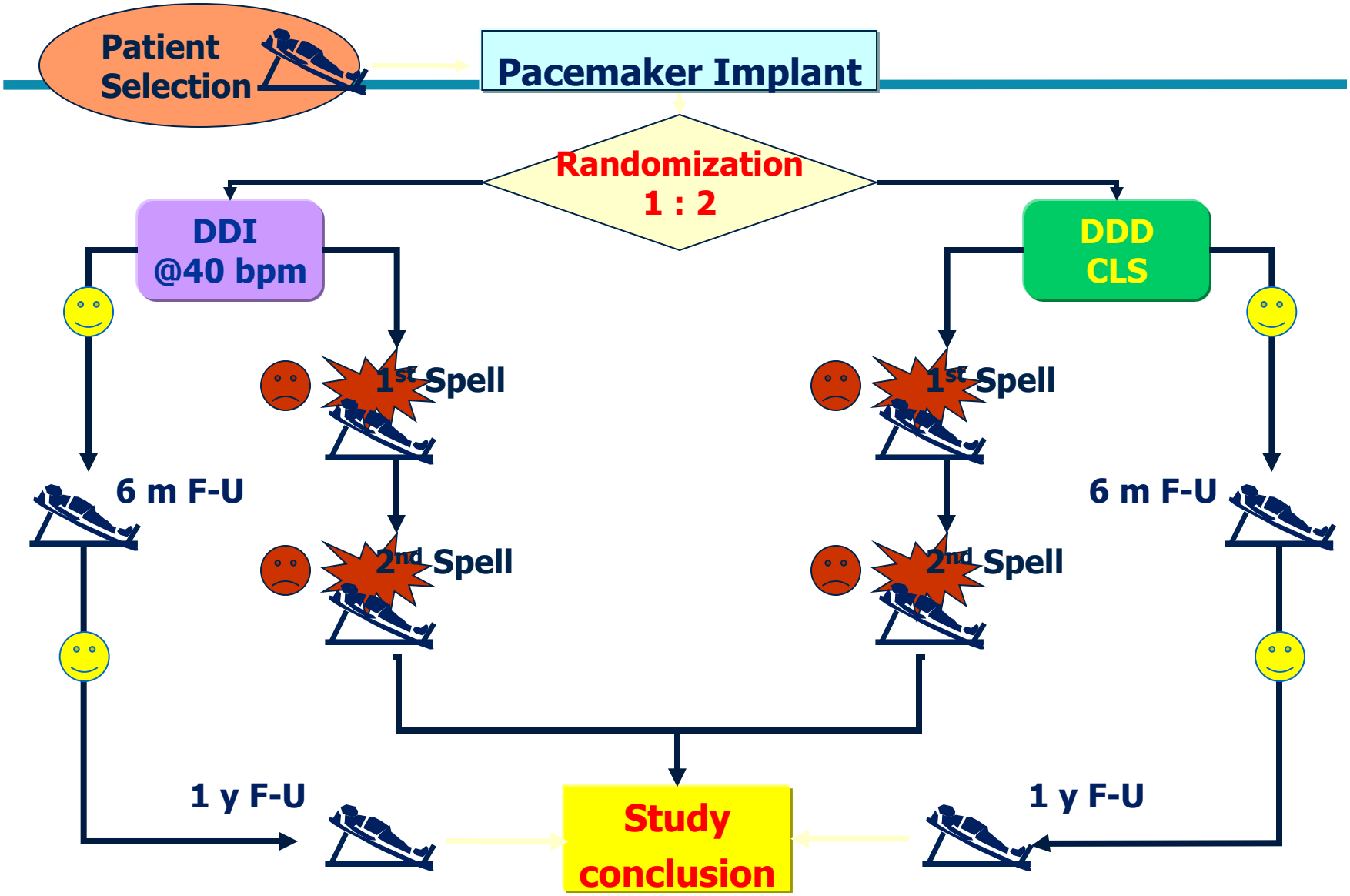
**Contractility index [DDD pacing]**



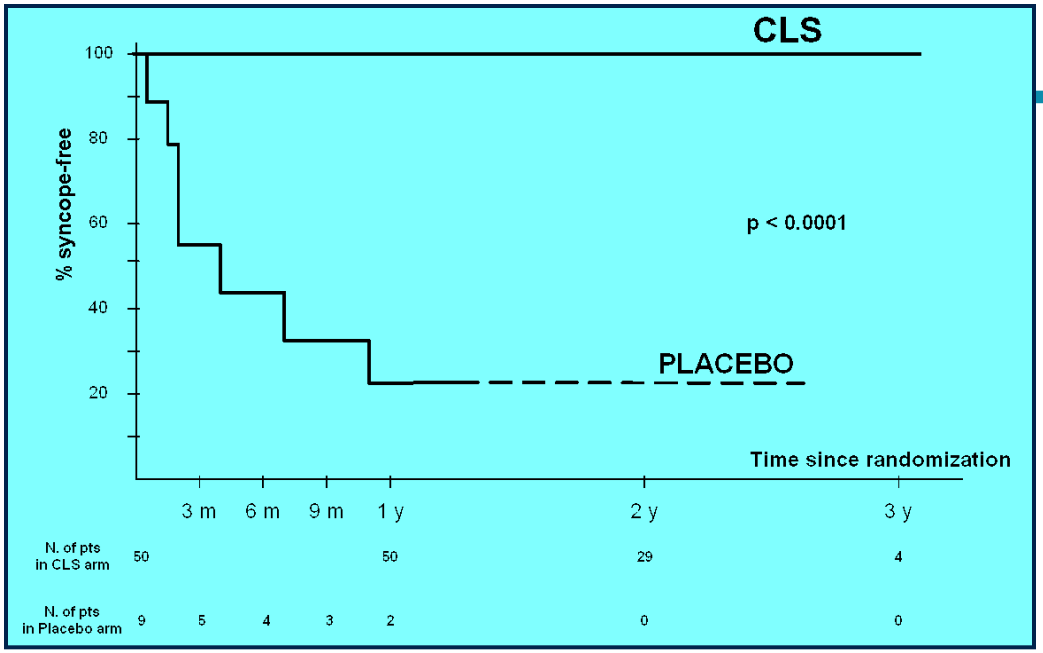

**HR and BP [HUTT in DDD-CLS]**



# INVASY Study (Occhetta et al. Europace 2004; 6:538-547)



# INVASY Study (Occhetta et al. Europace 2004; 6:538-547)




**Kaplan-Meier event-free curve for both arms**

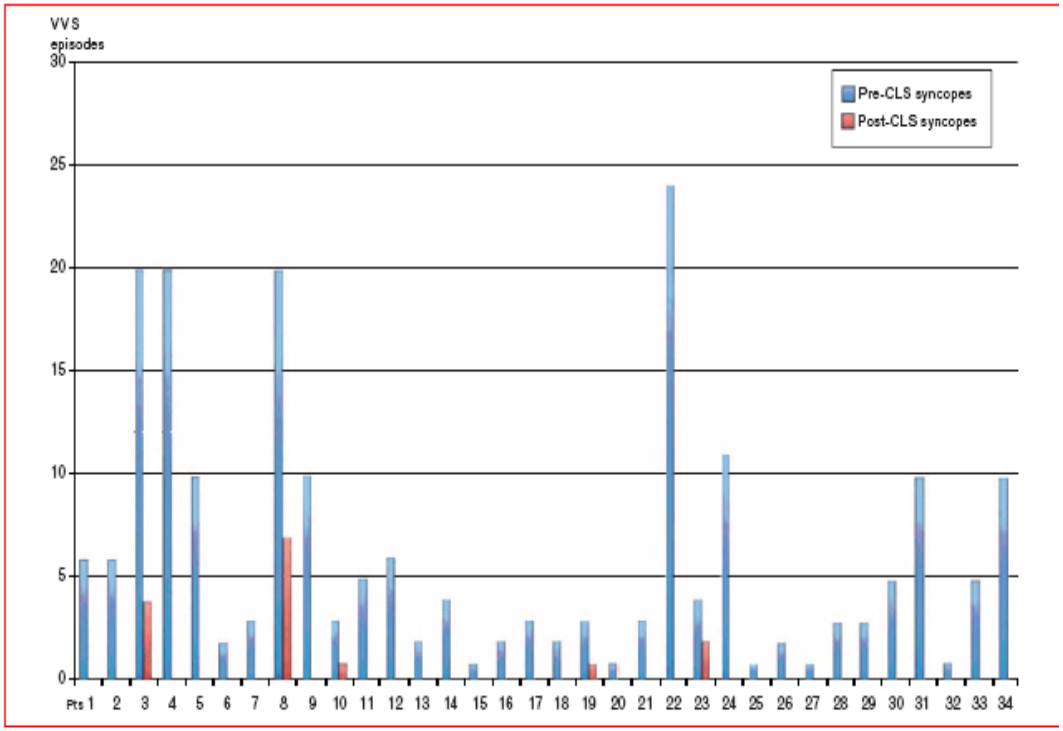
| | CLS arm | PLACEBO arm |
|---|---|---|
| Patients, n | **41** | 9 |
| Pts with VVS recurrence, n (%) | **0 (0)** | 7 (78) |
| Total VVS episodes, n | **0** | 11 |
| Mean VVS spells per pt, n | **0** | 1.2±0.8 |
| Median time to 1st recurrence, months (range) | **-** | 4 (0.5-11) |
| Rate of VVS spells per year | **0** | 1.52 |

FIC Federazione Italiana di Cardiologia
Italian Federation of Cardiology

# Long-term follow-up of DDDR closed-loop cardiac pacing for the prevention of recurrent vasovagal syncope

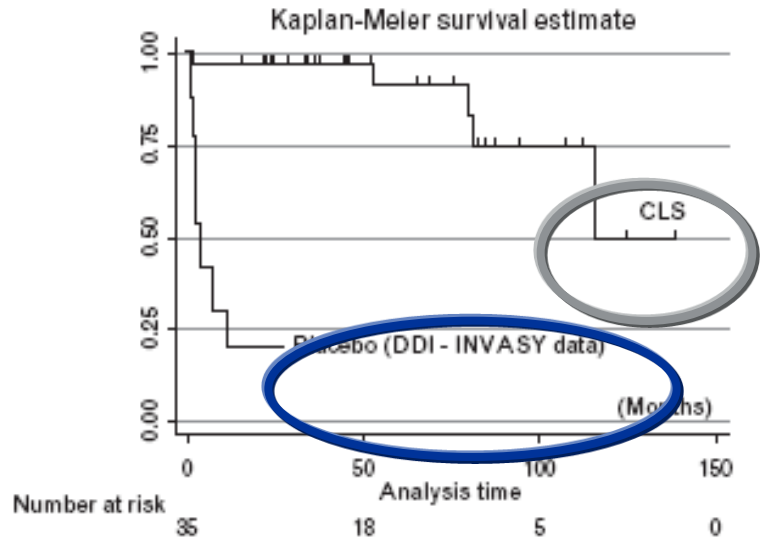
Miriam Bortnik, Eraldo Occhetta, Gabriele Dell'Era, Gioel G. Secco, Anna Degiovanni, Laura Plebani and Paolo Marino

**J Cardiovasc Med 2012; 13:242-245**




Number of preclosed-loop stimulation (pre-CLS) and post-CLS pacing for each patient are shown. It is noteworthy that only five patients were symptomatic for vasovagal syncope (WS) after CLS implant, and that a benefit was observed in all the patients (the number of post-CLS syncop was never greater than the one before CLS pacing). One patient is not represented because of the too high number of syncopal spells befor pacemaker implant.

**Fig. 3**




Kaplan–Meier analysis, freedom from vasovagal syncope is showed. Closed-loop stimulation (CLS) pacing shows a great benefit over conventional pacing ('placebo' data from the INVASY study), providing a very long syncope-free time span.

# CLS pacing in VVS prevention

**2007 ESC Task Force "Guidelines for Cardiac Pacing and Cardiac Resynchronization Therapy"**
**… the "recurrent severe vasovagal syncope with prolonged asystole during ECG recording and/or tilt test, after failure of other therapeutic options and being informed of the conflicting results of trials"**

**…. It has been shown in small series that pacemakers with haemodynamic sensors (intracardiac impedance and peak endocardial acceleration) have the capability to diagnose the vasovagal episode earlier than at the moment of rate drop……**

**European Heart Journal 2007, 28:2256-2295**
**Europace 2007; 9:959-998**

# Clinical applications of CLOSED LOOP STIMULATION - CLS

## CONCLUSIONS

**Clinical benefits in:**

1) Rate responsive pacing regulation
   - optimal rate increase related to exercise or mental stress
   - pacing rate automatic control related to left ventricular function

2) Hemodynamic cardiac function monitoring

3) Vaso Vagal syncope prevention

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