Moving the Physiological CLS Pacing Concept to the CRT Patient Population

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AUTONOMIC REGULATION

• Activation of the sympathetic nervous system typically increases sinus rate and shortens AV nodal conduction and can predispose to ventricular arrhythmias and sudden cardiac death.

• Parasympathetic activation typically slows the sinus rate, prolongs AV conduction and shortens AERP. It is thought to protect against ventricular arrhythmias (VF during Ischemia can be prevented by an increase in vagal activity) and facilitate atrial fibrillation.

• However, it is a mixed interaction with laterality!
Spinal Cord Stimulation

- Atrial Fibrillation
- CHF; Defeat-HF

Spinal cord stimulation protects against atrial fibrillation induced by tachypacing

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Renal Artery Denervation

- Atrial Fibrillation
- Hypertension
- CHF
- Diabetes
Autonomic Demand Drives Physiologic Cardiac Output

- Heart Rate (HR) x Stroke Volume (SV) = Cardiac Output (CO)
- CO combined with mean arterial blood pressure will affect the neurotransmitters released from the ANS
Most Common Sensors

- Piezo-electric crystal (vibration)
- Accelerometer (forward motion)
- Minute ventilation (respiration)
Sensors and Their Limitations

- **Vibration Sensor (Piezo-Electric Crystal)**
  - Riding in a bumpy vehicle will increase HR
  - Climbing down stairs gives higher HR than up stairs
  - Swimming does not result in HR increase

- **Accelerometer**
  - Running on treadmill does not increase HR
  - Stepping on the accelerator increases HR

- **Minute Ventilation**
  - Intubated patients do not have increase in HR appropriate to illness
  - Does not always respond to mental stress
Closed Loop vs Open Loop

- **Closed**: the physiologic parameter that is monitored is used to effect a change in the pacing rate. Changes in pacing rate in turn induce a physiologic change in the sensor parameter in the opposite direction (i.e., positive and negative feedback).

- **Open**: a change in heart rate does not result in a negative feedback effect on the physiologic or physical parameter monitored.
Example of Open Loop Behavior

- 63 year old female runner with SSS and a dual chamber pacemaker enters a 4K race
- The race starts and her device detects the forward motion (accelerometer)
- Her pacing rate increases in proportion to the sensor activation (forward motion)
- However, the resultant increase in hr has minimal effect on body movement or forward motion (no negative feedback)
Example of Closed Loop Behavior

- 24 year old cyclist with SSS and dual chamber PM with a minute ventilation sensor
- As the race starts, it detects an increase in MV and increases the heart rate accordingly
- Because of the improved cardiac output, his minute ventilation decreases and the device auto-regulates to maintain that balance (feedback to MV regulates the sensor)
Biotronik Closed Loop Stimulation (CLS)

- Measures intracardiac impedance immediately after the QRS
- Impedance increases around the lead tip with systole (and decreases as the blood pool is larger-diaostole)
- This correlates with dP/dt
- A surrogate for inotropy
Inotropy is Highly Accurate Reflection of Cardiac Demand

Impedance reflects inotropy

- Nearly 1 to 1 correlation between right ventricular pressure and impedance readings for paced and sensed beats\(^1\)

- Ventricular impedance correlates well with sinus rhythm as well (\(r^2 = 0.82\))

- Impedance readings during ischemia similar to impedance during exercise, reflecting increased contractility—a physiologic response\(^2\)

Source:

\(^2\)Witte J. et al. ANS-Controlled Rate Adaptive. EJCPE. 1996; Vol. 6: 53-59
Ventricular Impedance (Inotropy) May be Affected by:

- Physical Exertion
- Stress/Mental Exertion
- Ischemia
- Autonomic Imbalances (Vasovagal Syndromes)
- Heart Failure
The only rate sensor that responds to physiologic demands independent of body movement or respiratory rate\(^1\)

CLS reacts to actual circulatory demand by measuring the change in myocardial contractility in the right ventricle, integrating into the natural cardiovascular control loop system

CLS detects changes in heart demand due to medication, lifestyle, disease progression, physical exertion, and acute mental stress

\[ CO = HR \times SV \]

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CLS monitors cardiac contraction dynamics by monitoring a localized intracardiac impedance signal.

This impedance signal provides a direct assessment of myocardial wall motion changes around the vicinity of the tip electrode.
CLS – Impedance Principle

End-Diastole

Smaller Fraction of Myocardium = Low Impedance

End-Systole

Larger Fraction of Myocardium = High Impedance

Intracardiac impedance

Time after Stimulus (s)
CLS – Building a Reference

CLS takes multiple impedance measurements throughout a ventricular contraction. Using these measurements, CLS establishes a reference curve which reflects contraction dynamics during a “rest” state.

- 8 impedance measurements per cardiac event
- Start at 50ms after stimulus; end at 300ms
CLS then compares the *real-time* waveform to the reference. At rest, the differential area is small, translating to very little pacing.
At high exertion, the differential area is greatest; translating into maximum pacing rate
Speed of Onset: Appropriate Beat-to-Beat Exercise Response

CLS therapy emulates the sinus response at the onset and termination of exercise

Proportionality: Rate Equal to Exertion

CLS provides physiologic heart rate based on cardiac demand

Dynamic and Static Activity

Unlike other sensors, CLS provides physiologic heart rates that mimic normal sinus responses to daily-life.

Acc: Accelerometer  
MV: Minute Vent.  
MV+: MV blended  
QT: QT interval blended  
CLS: Closed Loop Stimulation  
CG: Control Group

Response to Acute Mental Stress

![Graph showing heart rate over time with annotations for different periods of the experiment: Resting Period Slides (RP), Color Word Test Slides (CWT), Arithmetic Challenge Slides (AC), Intermission, and Magnet Effect (ME).]
Not Limited by Beta Blocker Usage

Quality of Life

- In one study, 75% of patients experienced “significant” or “tremendous” improvement with CLS compared to 22% with an accelerometer¹
- In another study, patients preferred CLS to an accelerometer 2 to 1²
- In a third QoL study patient’s indicated the following³:

![Diagram showing quality of life metrics]

Potentially Unique Therapeutic Benefits

- Reduced atrial tachycardia burden\(^1\) (Burden I and Burden II)
- Reduced episodes and symptoms of Vasovagal Syncope\(^2\) (INVASY)
- Improved ejection fraction\(^3,4\)
- Improved Quality of Life
- CLEAR, CONFIRM (EU), COGNITION (EU)

Source:
\(^3\)William M. Bailey, MD; Denis Hull, RN. Closed Loop Stimulation Improves Ejection Fraction and NYHA Class in Patients with Congestive Heart Failure and/or Ejection Fraction ≤40%. 2005 HRS Abstract.
Rate Adaptive Sensor in CRT Population

Studies suggest that default settings of accelerometer-driven rate adaptation may not reliably work for CRT patients

**Exercise Time vs Average Heart Rate**

Rate-responsive pacing activated

Rate-responsive pacing did not activate

HR distribution at 12 months

PEGASUS CRT trial

of choice in HF patients. Alternatively, an accelerometer may be an acceptable rate sensor, but its sensitivity to activity must be increased in HF patients as these patients are relatively inactive. Finally, it is possible that the optimal programming of atrial support pacing in HF patients is to use an individualized rather than an empirical approach. The results

1. Jorde UP, et. al., Rate responsive pacing using cardiac resynchronization therapy in patients with chronotropic incompetence and chronic heart failure. Europace 2011 13, 1459-143

2. Martin DO, et al. Atrial support pacing in heart failure: results from the multicenter PEGASUS CRT trial. JCE 2012 (23) 1317-1325
Potential CLS Benefits for Heart Failure Patients

- Chronotropic Incompetence (CI) is a common comorbidity in systolic CHF patients¹
- CI is associated with increased mortality and cardiac events²
- Exercise, a class I AHA guideline recommendation for HF patients³, is associated with reduced mortality and HF hospitalization⁴

- Studies show CLS provides appropriate rate response similarly to patients with healthy sinus nodes⁵
  - e.g. slow and brisk walk, going up and down stairs, circular arm movements, picking up object exercise, stationary cycling

- CLS can be very beneficial to elderly and frail HF patients who are mostly participating in low energy activities

Potential CLS Benefits for Heart Failure Patients

- Decreased heart rate variability is a risk factor for HF mortality\(^1\)

- CLS can provide significantly wider heart rate distribution, and closely mimic the physiological HRV\(^2,3\)

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1. Richard, G. et al., Role of Heart Rate Variability in Prognosis for Different Modes of Death in Chronic Heart Failure, PACE 2006; Vol. 29
2. Quaglione R. tet. Al., Autonomic function during closed loop stimulation and fixed rate pacing: Heart rate variability analysis from 24-hour holter recordings PACE 2010; 33: 337-342
Reduction in AF/AT
Clinical research

Impact of Closed-Loop Stimulation, overdrive pacing, DDDR pacing mode on atrial tachyarrhythmia burden in Brady-Tachy Syndrome

A randomized study

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CLS Reduces AT Burden

AT Burden in CLS was statistically significantly lower

- Differences between Overdrive and DDDR AT Burden were not statistically significant
- No correlation between amount of atrial pacing and AT burden
- Mean heart rates were not notably different between Overdrive and CLS
Possible Mechanism by Which CLS Prevents AT

- AT often marked by an increase in adrenergic tone until 10 min pre-onset, followed by abrupt shift toward vagal predominance.

- Abrupt shift before AT onset could induce increased CLS atrial pacing rate in the critical time frame.

- Variation of the neurogenic drive preceding the onset may be reflected in contractility, to which CLS reacts.

Source:
1 Bettoni M, Zimmermann M. Circulation 2002; 105: 2753-59
Potential CLS Benefits for Heart Failure Patients

- Atrial arrhythmia is another common comorbidity for Heart Failure Patients
  
- Burden II study shows CLS significantly reduces the burden of AT episodes\(^1\)
  
- Orthostatic Hypotension (OH) occurs in 30% - 50% of elderly persons with disease and or medication risk factors\(^2\)
  
- CLEAR study shows a 75% reduction in the prevalence of OH with CLS algorithm as compared with accelerometer and no rate response\(^3\)


Summary

- CLS is a self-learning clinical system that receives constant feedback from the heart, allowing it to automatically and optimally adjust over time to changes in exercise tolerance and disease state. This algorithm can provide possibly the most physiologic response for the most levels of exercise.

- CRT may be particularly advantageous in patients with Heart Failure in Need of CRT.