Closed Loop Stimulation:  
A Comparison between Inotropic State Index and Muscle Sympathetic Nerve Activity

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Summary
A recently introduced cardiac pacing system featuring Closed Loop Stimulation is based on information derived from the intracardiac impedance signal containing information on the inotropic state of the ventricle. This study compared the inotropic state index (ISI) with muscle sympathetic activity (MSA). Nine patients (66 ± 3 years of age, mean ± SEM) with Inos CLS pacemakers were included. Each patient was studied at rest and during cold pressor test (CPT). Microneurography of the peroneal nerve was performed to measure MSA continuously, which was digitally stored along with the continuous surface ECG and blood pressure (BP). The intracardiac impedance signal was transmitted by the pacemaker and stored simultaneously. The linear correlation between ISI and MSA was calculated for the period of the CPT. During the CPT, mean systolic BP increased from 122 ± 4 to 149 ± 6 mmHg (p < 0.0001), diastolic BP from 74 ± 3 to 86 ± 4 mmHg (p = 0.02), and intrinsic heart rate from 69 ± 7 to 75 ± 7 bpm (p = 0.019). ISI increased by 21 ± 7% (p = 0.018), MSA by 26 ± 6% (p = 0.004). ISI and MSA were positively correlated during the CPT in 8 of 9 patients (R² = 0.86 to 0.99, p < 0.0001). Negative correlation was found in one patient (R² = 0.94). This study demonstrates parallel increases of the ISI and MSA during CPT. ISI and MSA showed a close linear relationship during provoked changes of sympathetic activity. These results provide further evidence that the sympathetic nervous system is responsible for the observed ISI changes.

Key Words
Sympathetic nervous system physiology, heart contractility, Closed Loop Stimulation, intracardiac pacing

Introduction
Under physiologic conditions, cardiac output is regulated by the autonomic nervous system in a closed-loop control system to meet hemodynamic and metabolic requirements. The control system has main inputs from baroreceptors and controls arterial blood pressure by changes of cardiac output and peripheral resistance. Rate-adaptive pacemakers based on different sensors are available for the treatment of chronotropic incompetence. The vast majority of pacemakers offer a rate-modulation function in an open loop approach, i.e., there is no feedback between pacing rate and the control signal [1]. Thus, widely used pacemaker sensors, such as activity detectors [2-7] and minute ventilation sensors [6][8][9], lack a feedback on the sensor signal for pacing rate regulation, which was also true for a range of pacemaker sensors used earlier [6][10-14]. Among present pacemaker sensors, only QT-based rate-adaptive pacing may be regarded as a closed-loop
system [15][16]. This particular realization, however, may lead to a positive feedback of the pacing rate on the sensed signal, making the system potentially unstable. For physiologic rate-responsiveness in patients with chronotropic incompetence, it would be most useful to measure cardiac sympathetic activity and to calculate the pacing rate according to this parameter. As cardiac sympathetic activity cannot be measured directly in vivo, myocardial contractility has proven to represent a satisfying surrogate for sympathetic activity in the heart and allows simulation of normal sinus node function. Contractility has been shown to change even in patients with significant coronary artery disease during exercise [17].

The concept of a new generation of rate-modulating pacemakers is based on the fact that changes of the impedance between the electrode tip and the pacemaker can change due to varying portions of blood and myocardium around the electrode tip. The pacemaker uses a small alternating current between the can and the electrode tip. Blood has a higher conductivity than the myocardium. At the end of the ventricular contraction, the impedance is highest, whereas it is lowest at the end of diastole. These impedance changes represent local contractility and are influenced by the autonomic, mainly sympathetic tone. This concept has been evaluated in several clinical studies using various stress tests [18].

The present study aimed to compare provoked changes of the inotropic state of the heart, determined by intracardiac impedance measurements, with changes of peripheral muscle sympathetic nerve activity.

Material and Methods

Subjects
We studied 9 patients (mean age 66 ± 3 years, weight 74 ± 3 kg, height 172 ± 6 cm, time since pacemaker implantation 7 ± 1.8 months, mean ± SEM) with Inos2 CLS pacemakers (BIOTRONIK, Berlin, Germany). At the time of inclusion, all patients were normotensive (systolic blood pressure 121 ± 5 mmHg and diastolic blood pressure 76 ± 2 mmHg). Patients were examined in the early afternoon after a light lunch. Medication included beta-blockers in 4, other antihypertensives in 5, antiarrhythmics in 1, antiplatelet therapy in 2, and statins in 2 patients and was not changed during the study. The indication for pacemaker implantation was 3rd degree AV block in 5, symptomatic bradycardia in 2, and sick sinus syndrome in 2 patients. The study was approved by the local Institutional Review Board on Human Investigation, and written informed consent was obtained prior to the study.

Measurements
Subjects were studied in the supine position at rest and during cold pressor test (CPT), a test known for its strong stimulatory effects on muscle sympathetic activity (MSA) and arterial blood pressure [19-20]. MSA, one-lead surface electrocardiogram (ECG) and non-invasive blood pressure (Finapres, Ohmeda, Englewood, CO) were continuously recorded using a LabView application, a MIO 16L (National Instruments, TX, USA) A/D conversion board, and a Macintosh Computer (Apple Inc. Cupertino, CA, USA). The signals were sampled at 500 Hz and stored with 12-bit accuracy. Blood pressure was measured every 5 minutes during rest and every minute during the CPT, using an automated sphygmomanometer (Dynamap, Critikon, Tampa, FL, USA). Intracardiac impedance of every heart cycle was recorded by the pacemaker in a time window of 47 to 290 ms after the ventricular stimulus by delivery of 30 µs rectangular current pulses of 600 µA at a frequency of 128 Hz. The impedance samples were transmitted to a coil that had been placed over the pacemaker on the patient’s body surface and digitally stored.

MSA was recorded continuously using microneurography. Electrical activity of muscle vasoconstrictor fibers was measured in the peroneal nerve, posterior to the fibular head by use of tungsten microelectrodes (shaft diameter 200 µm, tapering to an uninsulated tip of 1 to 5 µm) [21-22]. A subcutaneous reference electrode was first inserted 1 to 2 cm away from the recording electrode. The neural signal was amplified, filtered, rectified, and integrated to obtain a mean voltage neurogram of sympathetic activity with the typical blood pressure-triggered bursts.

Protocol
Transmission of the intracardiac impedance from the pacemaker was enabled. When a good MSA signal was found, the pacemaker was programmed to the DDD mode (rate responsiveness switched off) and a basic pacing rate of 40 bpm. The AV delay was set at 80 to 100 ms. This pacemaker setting yielded a relatively constant event type of atrial sensing and ventricular pacing (AsVp). One patient had no spontaneous atrial
rhythm and was symptomatic at the programmed pacing rate of 40 bpm. Therefore, he was paced in the DDD mode at 100 bpm in the atrium and with a delay of 80 ms in the ventricle. The recordings of MSA, ECG, blood pressure, and intracardiac impedance were synchronously started. After resting conditions had been recorded for 20 minutes, the patients were asked to put one hand into ice water (0° C) up to the wrist for 2 min. For later identification of the test period, time markers were set in both simultaneous recordings.

**Signal Processing and Statistical Analysis**

Signal processing was done using Matlab® (The Mathworks Inc., Natick, MA). The ISI was calculated for every cycle as the area difference between the actual impedance curve and the reference curve recorded during the resting period. This time series was then filtered with a 7/8 recursive digital filter. MSA was quantified in a computer-assisted evaluation of the frequency and the amplitude of the sympathetic bursts. The result was a time series with the burst-amplitude where a burst was detected and zero where no burst was found. Then a moving average of 20 s moved on by 5 s was calculated. The result was a time series of mean MSA, averaged over 20 s, sampled at 0.2 Hz with a lag of 20 s.

Both, the ISI and the MSA were resampled at 0.2 Hz in order to obtain equally spaced time series. The cross-correlation of ISI and MSA was computed to obtain the lag between the two signals resulting from different ways to calculate MSA and ISI and the lag of the peripheral reaction to the CPT. In a further step, a low-pass filter with a cut-off frequency of 0.02 Hz was applied to both signals to eliminate short-term changes in the signals. After alignment, the two signals were linearly correlated for the period of the CPT. Linear regression was calculated after normalization of ISI and MSA to pre-test conditions. The regression slopes of patients with and without beta-blockers were compared with the unpaired student t-test. HR-, blood pressure-, and MSA-increases were compared by ANOVA. A P-value of less than 5% was considered statistically significant. Results are given as mean ± SEM.

**Results**

An example of an original recording (surface ECG, non-invasive blood pressure, respiration, MSA, and ISI) is shown in Figure 1. The intrinsic heart rate increased from 69.2 ± 7 to 75.1 ± 7.3 bpm (p = 0.019) during the CPT. The systolic blood pressure increased from 122 ± 4 to 149 ± 6 mmHg (p < 0.0001), and the diastolic blood pressure from 74 ± 3 to 86 ± 4 mmHg (p = 0.02).

Figure 2 shows percent changes during CPT vs. resting conditions. ISI increased by 21 ± 7% (p = 0.018), MSA by 26 ± 6% (p = 0.004), systolic blood pressure by 20 ± 4% (p = 0.0007), and diastolic blood pressure by 11 ± 4% (p = 0.019). A notable stimulation of MSA (> 15% increase compared to baseline) started at 35 ± 4.3 s (range 25 to 65 s) after the beginning of the CPT. The calculated lag between MSA and ISI was 45 ± 4 s of which 20 s were attributable to the way MSA had been calculated. The remaining 25 s corresponded very well to the observed 35 s that it took until activation of MSA was observed and the fast reaction of the ISI after the beginning of the CPT.

Figure 3 shows good to excellent positive correlation between MSA and ISI during the CPT in 8 out of 9 patients ($R^2 = 0.86$ to $0.99$, p < 0.0001). In one patient, the CPT had to be discontinued after 40 s because of discomfort. Only slight changes of ISI and MSA were observed in this patient and they were negatively correlated ($R^2 = 0.94$, p < 0.0001). The percent increases of ISI and MSA during CPT were similar for patients with and without beta-blocker therapy. The mean regression slope was 1.2 ± 0.4 in patients without beta-blockers and tended to be lower in patients with a beta-blocker (0.7 ± 0.2). The patient who did not complete the CPT was excluded from this analysis.

**Discussion**

This study demonstrates parallel increases of the ISI, as calculated by the pacemaker, and of MSA. ISI and MSA during CPT were well to excellently correlated in the individual patients.

To determine whether the sympathetic nervous system is responsible for the observed changes of the ISI, it is important to discuss if similar changes of these two parameters can be expected during stress tests. Although, at present, there is no method available to directly and continuously measure cardiac sympathetic activity in humans, the available data indicate that the CPT leads to increased chronotropy, inotropy and MSA [20][23], indicating cardiac and peripheral sympathetic activation. The CPT causes an increase of HR from the very start, and the sympathetic nervous system seems to
be responsible for this effect [24]. HR peaks a few seconds after the beginning of the CPT and then, being inhibited by baroreceptors, gradually decreases reaching pre-test values at 3 to 4 min of CPT. On the other hand, MSA and blood pressure gradually increase during the CPT and are well correlated [20]. With impedance cardiography, it has been shown that cardiac output increases early after immersion of the hand into ice water and then remains high. This early increase is thought to be important for the early blood pressure response during the CPT [23]. However, after 30 s, the sympathetic outflow to muscles becomes the dominant cause of the continuous rise in blood pressure [20]. MSA during the CPT occurs at blood pressure levels that are normally associated with total baroreflex-mediated inhibition of MSA, indicating that baroreflex-inhibition is overridden. Although large intra- and inter-individual differences between the answers to the CPT exist [20], this test can be regarded as a powerful activator of the sympathetic nervous system. Thus, both cardiac and peripheral sympathetic activity increase during this maneuver. The onset and course as well as the ability of baroreceptors to inhibit the answer, however, slightly differ, cardiac activation being observed from the beginning of the CPT and peripheral vasoconstriction starting about 30 s later. This slightly different pattern of activation and inhibition made it necessary to align the signals. This allowed to compare ISI with MSA in a period where the inhibitory effect of baroreceptors on MSA was overridden by the strong stimulus, i.e., after activation of MSA is observed. Sympathetic activation is not uniform throughout the body, and regional differences of sympathetic activation during forced mental arithmetics have been described [25]. For example, different formulations of nifedipine can cause similar changes of MSA, but only short acting nifedipine was shown to provoke a reflex increase of the HR [26]. Regional differences of cardiac and peripheral sympathetic activity may also have contributed to the small differences that were observed between the ISI and MSA changes in our patients.

In one patient, the ISI slightly decreased during the CPT despite an increase of MSA, resulting in a negative correlation. This patient had arterial hypertension and a 3-vessel coronary artery disease with severely impaired left ventricular function with an ejection frac-

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**Figure 1.** Original recordings at rest (left) and during cold pressor test (right). Blood pressure (BP) and muscle sympathetic activity (MSA) increase during the cold pressor test. The intracardiac impedance signal changes (bottom). These changes are used to derive the inotropic state index (ISI).
tion of 30%. Stress echocardiography showed lateral, anterior and apical ischemia. The CPT is known to cause paradoxical vasoconstriction in patients with coronary artery disease [27] and arterial hypertension [28]. Vasoconstriction together with the increased workload of the heart due to increased peripheral resistance most probably caused ischemia in this patient, resulting in a reduced ISI. In the DDDR mode, the pacemaker would most probably reduce pacing rate under the given circumstances, thereby limiting oxygen consumption.

Although the number of subjects is too small to make a final statement, beta-blockers do not seem to play a major role. Beta-blockers do not block inotropic changes when given chronically, especially in patients with impaired left ventricular function. Long-term metoprolol increases beta receptor density and the contractile response to catecholamine stimulation [29].

The study has some limitations. In order to have the impedance signal transmitted, it was necessary to switch off the rate-adaptive function of the pacemaker. Changes of the ISI were thus not paralleled by pacing-rate changes. Therefore, we can only speculate on the rate modification behavior of the pacemaker in the CLS mode. Under study conditions, the limitation of pacing-rate changes limited baroreceptor-mediated negative feedback to the sympathetic outflow. In real life, an increase of the pacing-rate would be expected, which would probably be attenuated by baroreceptor-mediated inhibition of sympathetic outflow. In addition, the CPT might not be a typical stimulus of everyday life. But since clear differences are required to demonstrate parallelism of two signals, and the microneurography does not allow even small movements of the body, the choice of possible tests is very limited. Alternative tests would include different forms of mental stress or isometric contractions. However, the sympathetic activation seen with these tests is generally much less pronounced.

In conclusion, the observed changes of ISI and MSA during CPT were very similar, implying a common underlying cause. The results strongly support the hypothesis that the autonomic nervous system is responsible for the changes of the ISI detected by the Inos CLS pacemaker. ISI as well as MSA react promptly on a physical stimulus like the CPT, indicating that the pacing rate derived from the ISI is modulated in a way similar to peripheral sympathetic activity.

References


