Optimal Biosensor for the Reestablishment of Chronotropy: Multicenter Study and Long-Term Clinical Results

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Summary

A pacemaker system has been developed that is controlled by the autonomic nervous system (ANS). The system measures the intracardiac impedance via the pacing electrode and evaluates specific characteristics of the impedance signal to derive a measure of the sympathetic tone of the heart. An adaptive rate is derived from this impedance-based ANS measurement, allowing closed-loop control of the heart rate.

To date, single and dual chamber ANS-controlled pacemaker systems (Neos-PEP, Diplos-PEP) have been implanted in 240 patients. Besides the standard follow-up examinations, such as exercise protocols and Holter monitoring, the ideal biosensor characteristics of this system were validated. Appropriate behavior of the sensor signal was validated by assessing the rate history during varying exercise conditions and upon application of inotropically effective drugs.

The system was also successful for rate adaptation of the atrium (AAIR pacing) and for solely humoral coupling to the ANS (cardiac transplant patient).

Introduction

In the presence of chronotropic insufficiency, the dynamic range of cardiac output (CO) is impaired. Nevertheless, CO is still controlled by the ANS through changes in myocardial contractility. The ANS-controlled pacemaker uses this effector-level ANS-signal (the inotropic state) to realize a physiological closed-loop regulation of the pacing rate, thereby restoring the full dynamic range of the CO.

A sensor appropriate for this task should have the following requirements:

- the sensor should be sensitive to changes of the sympathetic tone, which means that it reacts to changing metabolic demands irrespective of the cause for this demand, i.e., for all types of load.
- the adaptive pacing rate, for a given load, should increase to the same level and with the same attack and decay rates as the sinus rate of a chronotropically competent patient.
- the sensor should react specifically to sympathetic tone and be insensitive to other influences such as pre-/after-load or direct frequency effects.
- the rate adaptive response upon application of inotropic effective drugs is expected to mimic the sinus rate response.
- for a transplanted heart, in which only humoral coupling of the contractility to the ANS is present, the sensor should still allow rate adaptation albeit with a delayed response.
- the sensor should be usable in both the ventricle and atrium, in order to allow DDDR, VVIR and AAIR pacing.

These sensor requirements are investigated within the framework of this multicenter study which investigates a sensor principle that determines changes in myocardial contractility through the local motion of the ventricular walls near the stimulating electrode.[1] The mechanical contraction is mapped to the time course of the unipolar intracardiac impedance signal. Since sympathetic influence changes myocardial contraction, the impedance signal inherently contain information about the sympathetic tone.

Methods and Materials

The response to different exercise protocols, daily activity (as assessed by Holter monitoring) and assessment of quality-of-life were investigated during a multicenter study with 178 single chamber pacemakers (Neos-PEP, Biotronik GmbH, Berlin) and 62 dual chamber versions (Diplos-PEP, Biotronik GmbH, Berlin). The average age of the patients was 62±7 years, of whom 64% were male. The mean total follow-up time was 2.6±1.3 years.

In order to compare the sensor signal to the intrinsic sinus rate response, single chamber pacemakers were implanted in chronotropically competent patients with complete AV-block.

The reaction to inotropically effective drug applications was investigated by monitoring the sensor signal during and after bolus injection of glycosides and beta-blockers.

Furthermore the performance of the sensor principle was validated with the measurement electrode positioned in the atrium in 7 patients. The pacemaker was programmed to AAIR mode in six patients with chronotropic insufficiency but intact AV-conduction and in one cardiac transplant patient. In the cardiac transplant patient the pacing rate response time was also investigated.

Results and Discussion

Physiological Rate Response

Figure 1a and 2 show the rate adaptive pacing rate derived from the ANS-pacemaker with the ventricular electrode as impedance sensor. Figure 1a shows rate adaptation during an exercise protocol using bicycle ergometry. A physiological increase in rate is seen during increasing levels of exercise load. Upon cessation of exercise and during the recovery period, the rate response shows a characteristically physiological decay.

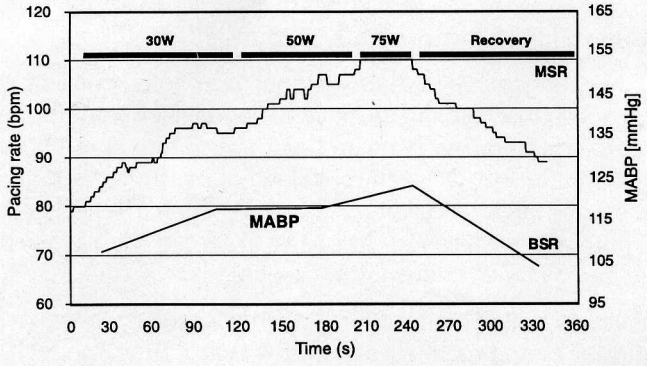

Figure 1a: *Rate-adaptive VVIR pacing: Pacing rate and MABP during bycicle ergometry*

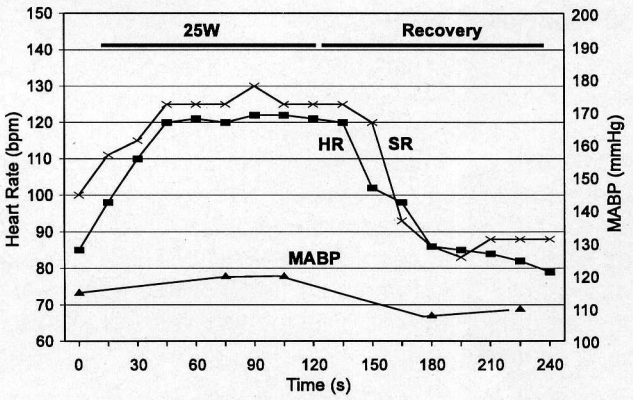

Figure 1b: *Rate-adaptive VVIR pacing: Comparison with intrinsic sinus rate during bicycle ergometry*

Figure 2 shows that the rate response is also appropriate during normal daily activity, as evidenced by using the 24-hour monitoring capability of the pacemaker. These results verify the physiological response of the ANS pacemaker to different types of physical load and emotional stress (for a detailed discussion, see reference [2]).

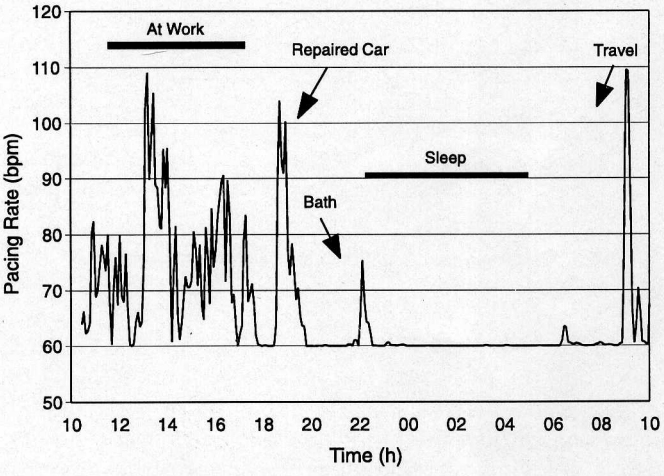

Figure 2: *ANS-controlled pacing: 24h Trend recording of the pacing rate*

Comparison with sinus activity

In a number of patients with intact sinus function, a third degree AV-block and a single chamber pacemaker system, both the calculated pacing rate and the intrinsic sinus rate were recorded (Figure 1b). In these patients, the sinus rate served as an independent indicator of the appropriate heart rate. Both time courses were in excellent agreement during all phases of exercise and recovery period.

ANS-controlled AAIR pacing

In a small subset of patients (3 male, 3 female, mean age 58 years) with sick sinus syndrome, but intact AV conduction, a single-chamber, ANS-controlled pacemaker (Neos-PEP) was implanted with the pacing electrode in the atrium allowing AAIR pacing. During exercise protocols, the rate response and time-course for AAIR pacing was similar to that seen during VVIR or DDDR pacing. Mean arterial blood pressure (MABP) was kept nearly constant during the entire period with a small increase during exercise.

Figure 3 shows the AAIR rate adaptive rate during ambulatory challenges such as walking and climbing up and down stairs, as well as postural changes. The Holter recording capability of the pacemaker again shows an appropriate ANS-controlled pacing rate during these different activities.

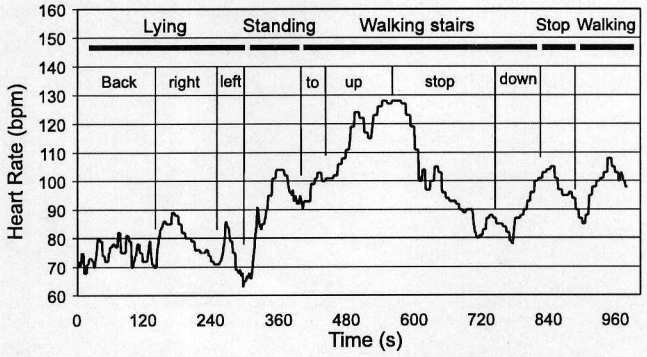

Figure 3: *Rate-adaptive AAIR pacing: Pacing rate during ambulatory challenge*

Thus, the ANS pacemaker can also be used with the atrial electrode as a sensor. The influence of contractility on the sensor signal is usually larger in the ventricle and an influence of preload cannot be excluded in the atrium. Thus, although the ventricular position is preferable, results show that impedance signal dynamics are still adequate for appropriate rate adaptation in the atrium.

Cardiac Transplant Patient

Due to surgical denervation a transplanted heart is compromised in its ability to adapt to different circulatory demands. The missing nervous coupling of the donor heart to the ANS causes a smaller dynamic range and a delay in the chronotropic and inotropic response, leading to longer time constants. The aims of this study are: a) to verify the delayed inotropic response through intracardiac impedance measurements in the donor atrium, and b) to evaluate the rate adaptation achieved with an atrial electrode in the transplanted heart.

A dual-chamber ANS-pacemaker (Diplos-PEP, Biotronik GmbH, Berlin) was implanted in an cardiac transplant-patient as atrio-atrial pacemaker. The impedance measurements were performed in the atrium of the donor heart. An *atrial inotropic parameter* (AIP) was derived from the impedance sensor signal measured during bicycle ergometry (25W/50W), and an adaptive pacing rate was calculated (Figure 4). The sensor-derived pacemaker rate increases during the first few minutes and "saturates" after about 6 minutes. This reflects the expected delay of inotropic response for cardiac transplant-patients.

A few months after heart transplantation the recipient atrium showed permanent flutter that could not be terminated. Therefore, after calibration, the pacemaker was programmed to AAIR-pacing. Exercise protocols and 24-hour Holter monitoring of the heart rate showed that the rate adaptation works well even in this extreme application. Further investigations will be performed to validate the long-term behavior of the time constants for inotropic response in the transplanted heart.

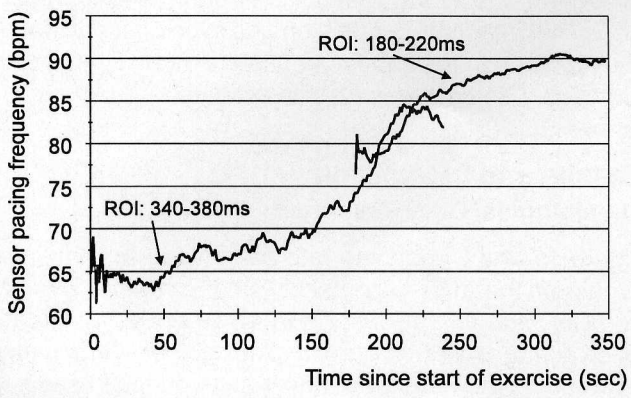

Figure 4: *Cardiac transplant patient, showing time course of sensor signal after start of exercise (AA'T-mode).*

Response to Inotropically Effective Drugs

The changes in impedance signal morphology provoked by application of either positive or negative inotropic drugs were compared to the signal variations measured upon calibration with different physical loads. For a negative inotropic effect, intravenous bolus injection of a ß-blocker (metoprolol) was used. A positive inotropic effect was obtained by intravenous injection of digoxin.

After injection of metoprolol, the impedance sensor signal changed in a way that would cause the ANS-pacemaker system to calculate a lower pacing rate, corresponding to the reduction of contractility. The effectiveness of the medication was confirmed by a significant reduction in MABP.

Digoxin injection caused a change in the sensor signal similar to that found during exercise, corresponding to an increase in myocardial contractility. The concomitant increased in calculated pacing rate was as expected.

In summary, the changes in morphology of the unipolar intracardiac impedance reflect changing contractile state of the heart as provoked by inotropically effective drugs.

Improvement in Quality of Life

Several studies have shown that rate-adaptive ventricular pacing offers symptomatic improvement and a better quality of life in patients who received such rate adaptive pacing systems.[3,4]

In the study population implanted with ANS-controlled pacemakers, patients reported a higher quality of life, a more active life-style, and a greater confidence regarding their cardiac condition and their pacemaker. This is not altogether surprising, since rate adaptation, particularly during exertion, provides protection against myocardial overstress. Most patients also reported the disappearance of palpitations, which were present with their previous pacemaker (usually fixed-rate pacemakers). They also noted a more appropriate increase in heart rate with respect to the level of physical activity and psychological stress associated with daily life activities.

Conclusion

The characteristic properties of an ANS-controlled closed-loop pacing system concept with respect to ideal biosensor behavior were demonstrated. This sensor principle can be used with the ventricular and the atrial electrode. As shown by exercise protocols and 24-hour Holter monitoring, the adaptive pacing rate responds to hemodynamic requirements in a physiological way and is independent of the nature or origin of the demand. The attack- and decay-rates related to changing stress are not determined by adjustable parameters, but are integral part of the sensor response. Lastly, it should be noted that after an appropriate individualized sensor calibration, the long-term follow-up experience available thus far demonstrates the excellent chronic stability of the sensor signal.

In conclusion, the unipolar intracardiac impedance possesses all the requirements of an ideal biosensor for the re-establishment of chronotropy. Importantly, it requires no special sensor device and thus has the additional advantage in that it allows the ANS-controlled pacing system to be used with any existing electrode in the atrium or the ventricle,[5] thereby offering a practical, simple and extremely effective closed-loop pacing system.

References

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