Influence of Provoked Regional Ischemia and Inotropically Effective Drugs on the Rate-Adaptive Response provided by ANS-controlled Pacing Systems

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Summary

Unipolar intracardiac impedance measurement provides an ideal biosensor for the re-establishment of physiological closed-loop rate adaptive pacing. The underlying principle of this sensor technology, i.e., the monitoring of myocardial contractility, was validated directly by changing the contractile state of the ventricular myocardium. A reduction in the contractile state was achieved by provoking a local ischemia using percutaneous transluminal coronary angioplasty, whilst an increase in contractile state was induced by application of an inotropic agonist (digoxin) and antagonist (beta-blocker) effective drugs.

In both investigations, an ANS-pacing system was used to monitor changes in the sensor signal. Blood pressure and ECG were also monitored. The result showed that there was a direct correlation between changes in contractility and the sensor signal, and proves the validity of the unipolar impedance sensor principle as used for closed-loop rate adaptation in the ANS pacing system.

Introduction

In order to achieve the goal of physiological closed-loop rate adaptive pacing, the ANS-pacemaker systems use a unique sensor principle. The sensor technology monitors variations of the impedance signal during the cardiac cycle and derives a control parameter which describes the contraction dynamics within the proximity of the electrode tip. This control parameter correlates well with contractility and therefore with sympathetic tone.

The applicability, physiological rate adaptation, and therapeutical benefit of the ANS pacemaker has been demonstrated in a multicenter clinical study with 240 patients. The results of this study are published in several papers.[1-3] The present study attempts to show explicitly, the influence of changing sympathetic tone on the measured sensor signal.

Methods

Provocation of regional ischemia

Depending upon the location of the stenotic coronary artery, provoking a localized ischemia will have a negative effect on myocardial contractility in the immediate vicinity of the occluded vessel, but a paradoxical positive inotropic effect in areas unaffected by the induced ischemia. This scenario can be used to test the influence of regional myocardial ischemia on the impedance sensor signal during ischemic episodes induced by percutaneous transluminal coronary angioplasty (PTCA).

In 7 patients (2 female, 5 male, mean age 53±4 years), the intracardiac impedance waveform was measured after the stimulation pulse between the unipolar stimulation electrode at the apex of the right ventricle and a counter electrode (guide wire) positioned in the vena cava inferior. Pacing was performed with an external pacemaker (Diplos-PEP, Biotronik GmbH, Berlin).

Occlusion of the left anterior descending artery (LAD) or right circumflex artery (RCX), which predominantly serve the left heart myocardium, was expected to effect a paradoxical sympathetic increase in contractile performance in the area of the pacing electrode. Conversely, occlusion of the right coronary artery (RCA) leads to a decrease in myocardial contractility in the vicinity of the pacing electrode, because of a oxygen deficit in the right ventricular apical region. The expected effects are shown in Figure 1.

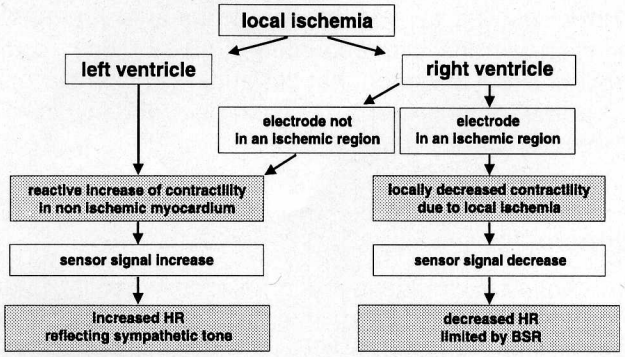

Figure 1: Effect of provoked ischemia on the sensor signal and rate adaptive rate

Application of inotropically active drugs

The concept of this portion of the study is to change the inotropic state of the myocardium by bolus injection of inotropically active drugs. In 5 patients, (4 female, 1 male patient, mean age 46.4±7 years), intracardiac impedance, ECG and blood pressure were recorded pre, peri- and post intravenous injection of 0.4mg digoxin and 10mg metoprolol. The evaluated sensor signal was post-processed to calculate the rate adaptive rate upon drug application. The expected effect on the sensor signal and the adaptive rate is shown in Figure 2.

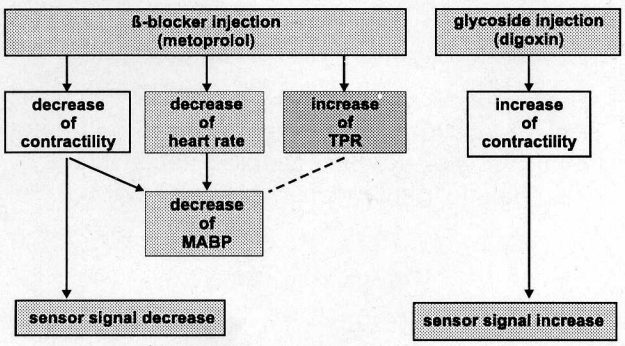

Figure 2: Effect of inotropically effective drugs on the impedance sensor signal and adaptive rate

Results and Discussion

Effect of provoked regional ischemia

A two-minute occlusion of the RCX provoked a local ischemia in the left ventricular myocardium (Figure 3) and was accompanied by angina pectoris and significant ST-deviation in ECG. During occlusion the sinus rate (black line) increased, an increase which is mediated by a reactive increase of sympathetic activity. The gray line represents the adaptive pacing rate calculated from the ANS-related sensor signal. The increase of this signal is an expression of the increased contractility, an effect of enhanced sympathetic activity.

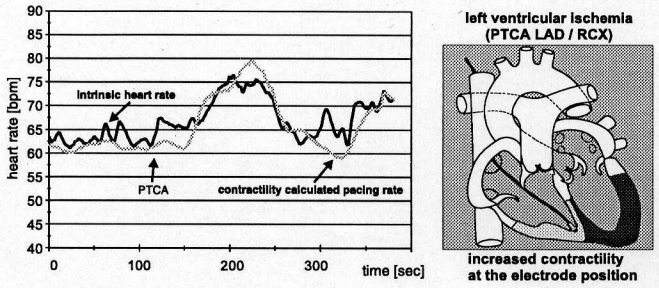

Figure 3: Effect of left ventricular ischemia on the sensor-calculated rate and intrinsic heart rate

The effect of a 3-minute occlusion of the RCA leads to a decrease in contractility in the right apical myocardium caused by ischemia in this region (Figure 4). The intrinsic sinus rate remained unchanged. A decreased contractility in the region of the electrode tip, reflected by the sensor signal, theoretically leads to a dramatic reduction of the sensor calculated rate, however, this potential decrease (thick black line) is limited by the programmed base sensor rate (BSR).

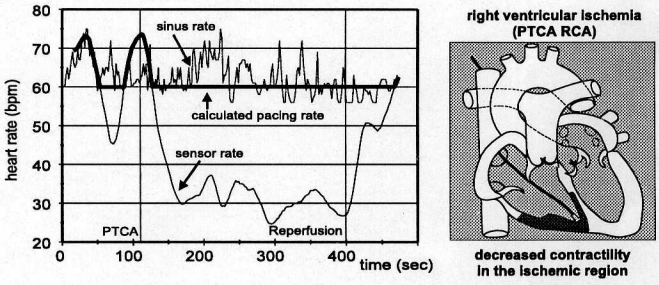

Figure 4: Effect of right ventricular ischemia on sensor-calculated rate, paced rate and intrinsic sinus rate

In the more frequent case of ischemia in the left ventricle, the behavior of the ANS-pacemaker system is comparable to the reaction of the intrinsic heart rate regulation. This is expected because the ANS-pacemaker re-establishes a closed- loop regulation of the heart rate. In the case of ischemia in the region of the pacing electrode the pacing rate is reduced, but a minimum pacing rate is maintained by programming a lower limit (BSR).

Effect of inotropically active drugs

In the 5 patients undergoing pharmacological intervention, the sensor heart rate reacts appropriately to the injection of glycosides and beta-blockers.

Upon glycoside injection, the sensor calculated pacing rate increases to reach a plateau after about 30 minutes (Figure 5).

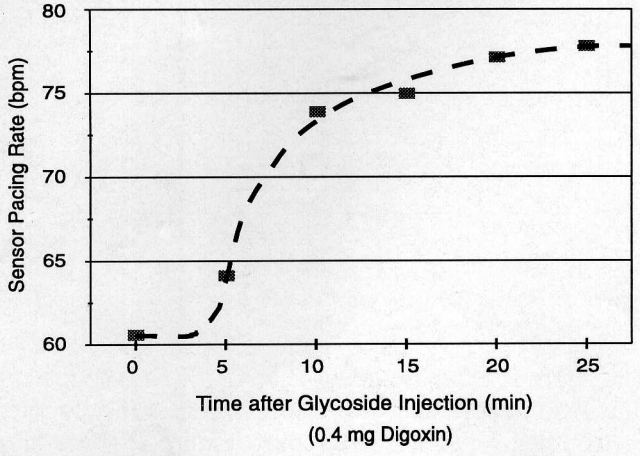

Figure 5: *Effect of glycoside injection on the sensor-calculated pacing rate*

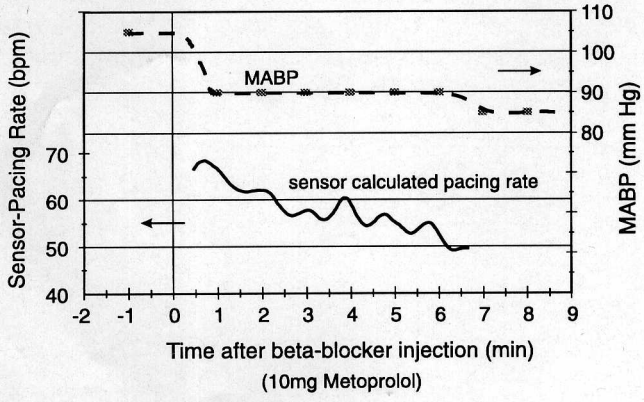

Figure 6: *Effect of a beta-blocker bolus injection on the blood pressure and the sensor-calculated pacing rate*

Conversely, the sensor calculated rate after metoprolol injection decreases appropriately (Figure 6). Both results provide direct evidence that the underlying sensor principle appropriately measures changes of the myocardial contractile state.

Conclusions

A provoked decrease in myocardial contractility, either by inducing ischemia or injection of a beta-blocker, consistently caused a decease of sensor signal. In contrast, an increase in myocardial contractility always led to an increase of sensor signal.

The results of this study validate the ability of the unique sensor principle incorporated within the ANS-controlled pacing system. By monitoring changes in the sympathetic tone of the heart, the sensor re-establishes closed-loop ANS controlled adaptation of the heart rate.

References

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