Effect of Circulating Catecholamines on the Pacing Rate of the Closed Loop Stimulation Pacemaker

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Summary

In developing physiologic pacemaker systems, many approaches have been tried to connect the hemodynamic requirements and the provided pacing rate. In contrast to conventional rate-adaptive systems, Closed Loop Stimulation (CLS) integrates the pacemaker into the natural circulatory regulation system instead of mimicking regulation with the help of artificial sensors. Since the main regulation mechanisms to adjust cardiac output are mediated by catecholamines, the heart rate of chronotropically incompetent patients with implanted CLS pacemakers should be influenced by the level of circulating catecholamines. During a pharmacological stress test using the catecholamine dobutamine, heart rates of patients with CLS pacemakers were examined. The increase in myocardial contractility was measured using an echocardiographic method for dP/dt determination. During dobutamine infusion, all patients showed significantly increasing heart rates. In close correlation, dP/dt -the inotropic parameter- increased under the influence of the catecholamine. The results demonstrate that the CLS pacemaker is a sensitive detector of inotropic mechanisms and translates them into an appropriate chronotropic response. Hence, the CLS system provides the possibility of connecting hemodynamic requirements and heart rate adequately.

Key Words

Closed Loop Stimulation, circulating catecholamines, pharmacological stress, echocardiography, myocardial contraction

Introduction

Since the introduction of the first implantable pacemakers with an option for rate-adaptive cardiac pacing, many different sensor concepts have been evaluated in order to optimize the pacing rate in relation to the hemodynamic requirement in every load situation. Conventional rate-adaptive systems are based on the use of one or more artificial sensors. These sensors measure parameters that are only indirectly correlated to the patient's hemodynamic demands. The ideal method for realizing a physiologic pacemaker system would be the integration of the pacing device into the natural cardio-circulatory system. This concept has been realized in the Closed Loop Stimulation (CLS) system, which converts information from the circulatory center into a heart rate [1][2].

Even under pathophysiologic conditions, the dynamics of the myocardial contractile force still reflect the information from the circulatory center. Because inotropic regulation affects the contraction dynamics of the ventricular myocardium, measuring changes in myocardial contractility can access the hemodynamic state and requirements. Based on that relationship, the CLS pacemaker transfers changes in myocardial contractility into individual pacing rates.

The main mechanism to regulate cardiac output is mediated by myocardial and circulating catecholamines. As a consequence of the CLS pacemaker integration into the circulatory regulation system, it is therefore expected that the heart rate in patients with CLS systems is influenced by changes in the level of circu-

lating catecholamines.
The aim of the presented study was to show that CLS is able to convert inotropic stimulation by circulating catecholamines into a chronotropic response.

Materials and Methods

The CLS pacemaker INOS²CLS (BIOTRONIK) was implanted in 8 male patients (age 63 ± 7 years) with sinus node dysfunction, resulting in an insufficient increase in sinus rate in response to physiologic needs. All patients were symptomatic (dyspnea, fatigue). The diagnosis was confirmed by Holter ECG and exercise stress testing. The sinus rate at maximal load was not higher than 80 bpm.
The pacemaker was programmed in DDD-CLS mode with a maximum closed loop rate (MCLR) of 120 bpm. All tests were performed after successfully documenting the rate-adaptive function following automatic initialization. The appropriate functioning of the rate-adaptive system was confirmed by analyzing the internally stored Holter data.
The INOS²CLS pacemaker detects changes in the myocardial contraction by measuring the unipolar impedance between the tip of the ventricular electrode and the pacemaker case. To enable an analysis of the changes in the impedance curves, the pacemaker's internal Holter system was programmed to a special mode that included recordings of impedance curves and heart rates. Impedance waveforms can be stored every second heartbeat; measurement ensues every 8 ms. The data of the heart rates include also the event type, so sensed and paced events can be distinguished. The rate of rise in left ventricular systolic pressure, dP/dt, was used as the inotropic parameter. It is a marker of global systolic left ventricular function because left atrial pressure changes relatively little during pre-ejection ventricular systole. The rate of change for the mitral regurgitant velocity is primarily determined by the simultaneous change in left ventricular pressure. Hence, in patients with mitral regurgitation, continuous wave Doppler recordings of mitral regurgitant velocity can be used to measure the time interval, dt (in s), during which the mitral regurgitant velocity increases from 1 m/s to 3 m/s. During this interval, the left ventricular to left atrial pressure difference increases from 4 to 36 mmHg. Accordingly, the average rate of pressure change is 32 mmHg/dt, expressed in mmHg/s (see figure 1) [3]. Experimental and clinical studies

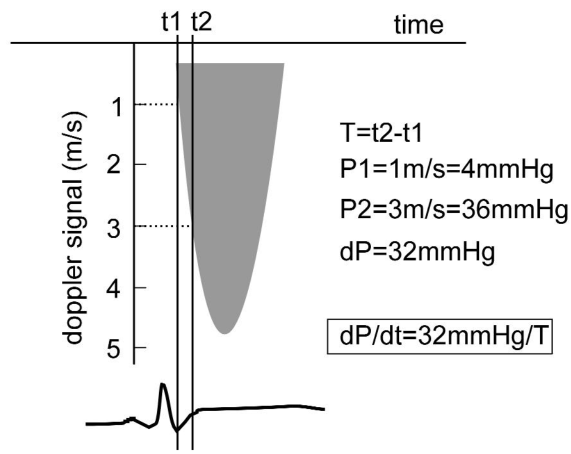
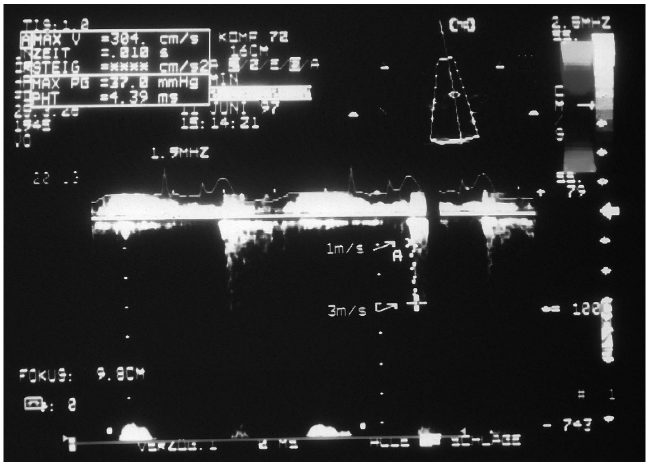


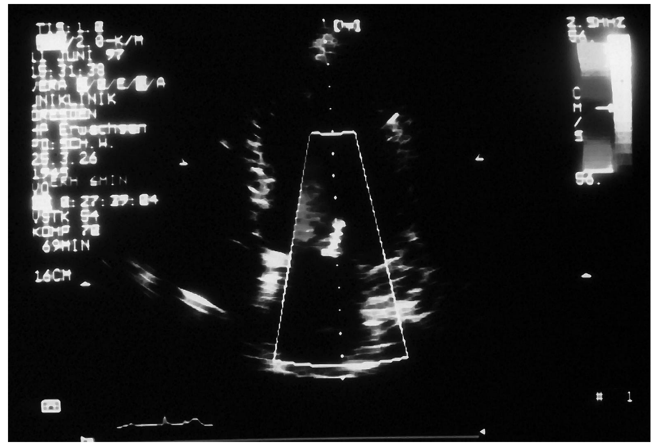
Figure 1. Principle of dP/dt determination using continuous wave Doppler echocardiography.

indicate that Doppler measurements of dP/dt correspond well to invasive measurements using catheter-tip pressure manometry [4]. All measurements were made with an HP Sonos 5500 echocardiography device.
The inotropic stimulation was realized using the standard protocol of pharmacological stress echocardiography [5][6]. Dobutamine, a synthetic derivative of dopamine with strong inotropic properties, was delivered intravenously by infusion pump (starting rate 10 µg/ kg/ min). At 3-min intervals, the infusion rate was increased to 20, 30, and 40 µg/ kg/ min. Heart rate, blood pressure, and 12-channel ECG were recorded each minute. The inotropic signal, dP/dt, was measured and stored at the end of each level. After ending the dobutamine infusion, the patients were monitored for 30 min.

Results

During the pharmacological stress test, no side effects or complications (i.e., nausea, headache, or atrial fibrillation) appeared. Echocardiographic measurements yielded results of sufficient quality for the determination of the maximum pressure change, dP/dt (figures 2 and 3). The inotropic parameter, dP/dt, increased significantly during the pharmacological load levels as the analysis of the echocardiographic examinations shows (figure 4). The morphology of the impedance curves measured by the CLS pacemaker shows clearly





Figures 2 and 3. Continuous wave Doppler signals for dP/dt measurement.

recognizable changes between the different load steps. The correlation between the inotropic parameter, dP/dt, and the impedance waveform is unambiguous (figure 5). The most meaningful result is the response of the heart rate of chronotropically incompetent patients with implanted CLS pacemakers during the pharmacological stress test. All patients showed a significantly increasing heart rate during the infusion. A few minutes after the end of the infusion, all patients reached their original resting heart rate. A typical example of the heart rate behavior during stress is shown in figure 6. Due to the patients' chronotropic incompetence, the heart was paced in the atrium and ventricle during the stress test. In all measurements, a close correlation between heart rate and the echocardiographic examined value of dP/dt was found. The correlation between dobutamine flow and heart rate for all patients is shown in figure 7.

Discussion

As known from previous studies, dobutamine infusion caused a significant increase in inotropy which was reflected in the echocardiographically examined parameter, dP/dt [7][8]. The decrease in the maximum pressure change after an appropriate time of recovery could be measured as well.

The adaptation to changing loads is mediated by the

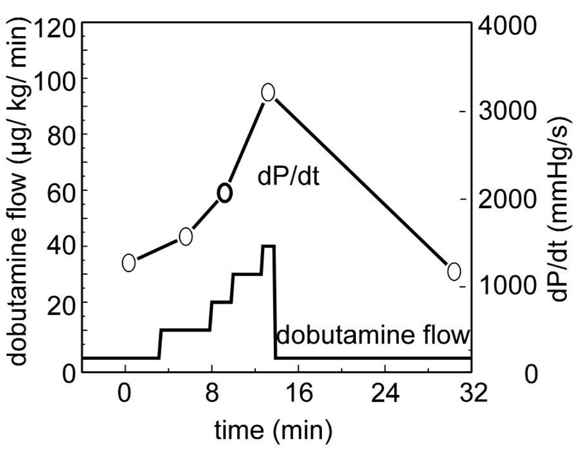


Figure 4. Results of dP/dt measurements showing a significant increase during dobutamine infusion.

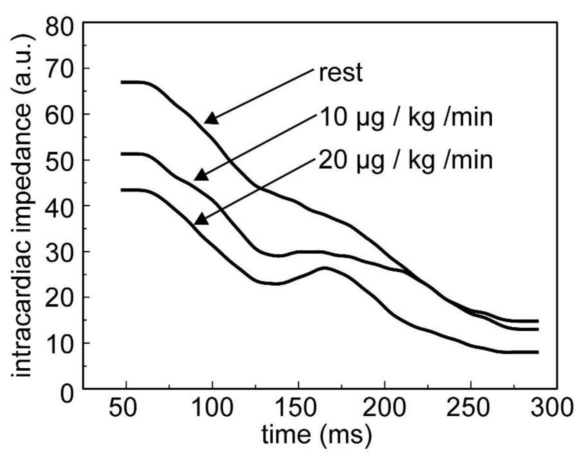


Figure 5. The unipolar intracardiac impedance reflects the changes in myocardial contractility during dobutamine flow.

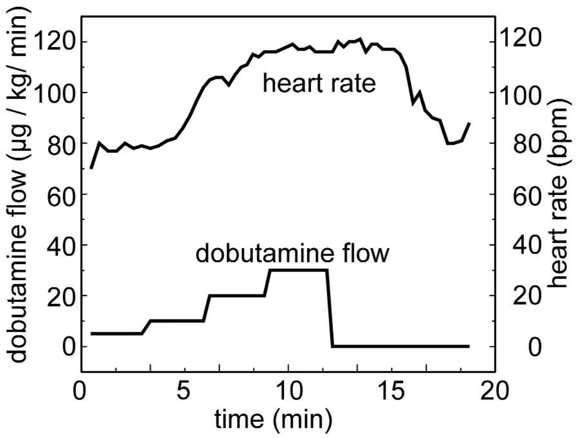


Figure 6. Behavior of the heart rate in a chronotropic incompetent patient with CLS pacemaker during pharmacological stress.

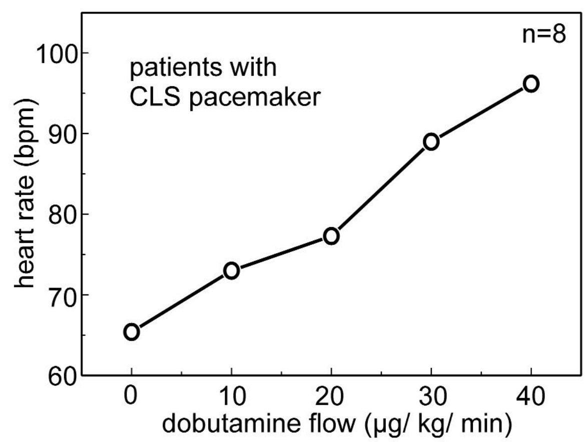


Figure 7. Correlation between dobutamine flow and heart rate in patients with CLS pacemakers.

dynamics of the catecholamine release, which are in turn controlled by the medullary circulation center. Chronotropically incompetent patients are not able to increase their heart rate in response to catecholamine release. However, in a typical case of sick sinus syndrome, the inotropic reaction of the heart is usually still functioning. Hence one of the basic prerequisites for a realization of a closed loop pacemaker is its ability to extract information from the circulatory system by measuring a parameter that strictly correlates to inotropic regulation. The analysis of the morphology of the impedance curves measured with the CLS pacemaker shows a clear correlation with the inotropic parameter, dP/dt. Thus, the unipolar impedance measurement is a suitable method to detect the actual inotropic tonus of the myocardium. In this way it becomes possible to obtain a reliable indicator for the status of the circulatory regulation system.

Application of this method of measuring and analyzing the inotropic regulation for rate adaptation led to a significant increase in the pacing heart rate during dobutamine infusion. These results confirm the hypothesis of a chronotropic reaction to increased catecholamine levels with the CLS pacemaker.

The possibility of a synchronization between inotropic and chronotropic regulation is a promising basis for optimizing rate-adaptive stimulation. While this study was based on a simplified model of the circulatory regulation system and did not evaluate the clinical benefit, the results indicate that the CLS system is a suitable device for the therapy of patients with chronotropic incompetence.

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