Rate-Adaptive Pacing Based on Contraction Dynamics: A View from Basic Electrophysiology

T. CHRIST, U. RAVENS
Department of Pharmacology and Toxicology, Medical Faculty, University of Technology, Dresden, Germany

Summary

Ten years ago, rate-adaptive pacing systems that utilized unipolar intracardiac impedance as a sensing parameter were introduced for the treatment of chronotropic incompetence. This pathologic state is defined as diminished sinus node responsiveness to catecholamines accompanied by preserved inotropic responses of the working myocardium. Since unipolar intracardiac impedance correlates well with the inotropic state of the heart, this parameter should sense exercise-induced positive inotropic effects of circulating catecholamines released during physical activity, and hence may serve as a sensor principle for rate-adaptive pacing. In this brief review, the history of the Inos^2 DDDR pacemaker is outlined from the initial concept to its current, highly developed stage with complex and automatic algorithms for analysis of impedance signals and delivery of rate-adapted pacing stimuli. We discuss how our understanding of the heart's contraction dynamics and its regulation has promoted further development of this closed-loop pacemaker system.

Key Words

Closed Loop Stimulation, contractility, contraction time, force-frequency relation

Introduction

Common pacemakers available during the 1980s provided fixed-rate stimulation that effectively prevented syncope but were inadequate for treating chronotropic incompetence. In this disease, the myocardium responds to catecholamines with a normal positive inotropic effect, while the sinus node fails to respond with an increase in heart rate. Hence, there was a clinical need for a rate-adaptive pacemaker that incorporated a sensor for detecting acute hemodynamic needs during physical activity.

In 1990, Schaldach proposed using unipolar ventricular impedance (VIMP) as a sensor signal for rate-adaptive pacing [1], and in 1992 the Neos pacemaker was introduced. In principle, intracardiac impedance is measured by applying biphasic rectangular sub-threshold pulses between the tip of a right ventricular lead and the pacemaker case during a certain time period following a paced ventricular event [2]. As these sub-threshold pulses propagate towards the relatively large pacemaker case, about 90% of the voltage drop will occur within the close vicinity of the lead tip; hence the impedance detection will remain fairly independent of thoracic movement artifacts. Credit goes to Schaldach for suggesting unipolar VIMP as an indicator of ventricular contractility, which could be used for adapting the paced heart rate. Although use of the first derivative of right ventricular pressure (dP/dt_{max}) as an index of contractility was also promoted in pacemaker technology during that time [3], pressure sensors posed numerous technical problems with long-term stability [4]. Thus, measurement of the unipolar VIMP appears to be a more attractive indicator of contractility because no additional sensor is needed.

Since the VIMP signal was regarded as a cardiac parameter under strong control of the autonomic nervous system (ANS) [5], the new rate-adaptive pacemaker

was envisioned as an integral part of the ANS. This new paradigm completely changed the concept of closed-loop pacing. Such pacing systems had originally been defined by their negative feedback loop that allowed the sensed physiologic variable to return towards its baseline value after an appropriately modulated pacing rate [6]. However, the closed-loop system containing impedance-measuring devices indirectly reassociated heart rate and the ANS by sensing the catecholamine-induced changes in contractility and feeding into the regulatory loop and assigned paced heart rate. This affected contractility instead of the respective changes in heart rate. In other words, the defective chronotropic response to catecholamines that had led to disruption of the feed-back loop was replaced by the still functioning positive inotropic response. Thus, the feedback loop was reconnected rather than a new one being established.

In this concept, an inappropriately large increase in pacing rate was believed to be prevented by counter-regulation of the ANS. At least theoretically, the impedance-based, rate-adaptive pacing system should produce the appropriate pacing rate in every situation without the need for programming parameters such as basic rate or upper rate limits, maximum sensor rate, or sensor slope.

A remarkable step in this direction was achieved by successfully implementing the Inos² pacemaker's automatic initialization. Despite its proven feasibility and long-term stability [7], some important questions in relation to this topic remain unresolved. In the following sections, we will discuss some of the current problems.

Regulation of Lower and Upper Sinus Rate

During physical exercise, adequate oxygen delivery to all organs is maintained by multiple factors, including alveolar gas exchange, respiratory muscle mechanics, shifts in pulmonary vascular resistance and systemic regional blood flow, oxygen transport capacity, and by an appropriate increase in cardiac output (CO), which is the product of heart rate (HR) and stroke volume (SV). During low-intensity exercise, increases in both SV and HR contribute to enhanced CO, whereas increases in SV tend to level off above HRs of about 110 – 120 beats/min. With increasing levels of exercise, there is a linear relationship between increased HR and maximum ventilatory oxygen uptake. Near peak exercise, the major adaptive mechanism is provided by enhanced oxygen extraction as further increments in HR tend to level off [6]. Therefore, the first problem in dealing with rate adaptation during exercise consists of setting the lower and upper limits for paced atrial rate.

Kirchheim et al. found in their extensive review on baroreflex sensitivity, that increases in HR reduce the baroreflex slope [8]. Thus, under conditions of high sympathetic activity, the baroreflex mechanism is of lesser importance, illustrating again that sinus rate tends to level off during extreme exercise.

Regulation of lower HR at the cellular level was addressed by a recent patch-clamp study by Mangoni et al. [9]. In enzymatically isolated spontaneously beating sino-atrial myocytes, L-type calcium current is one of the pacemaker currents. Performing the experiments with isolated cells exclude any influence of the ANS. The authors found a depolarization-induced facilitation of L-type calcium current, which developed during prolongation of the diastolic interval; it is expected to oppose excessive rhythm slowing. Therefore, lower sinus rate seems to be predicted by distinct electrophysiologic properties of sino-atrial cells. A comparable mechanism could prevent excessive rhythm acceleration, but this hypothesis remains to be proven. On the other hand the input/output relationship of sino-atrial cells in cholinergic modulation of rate was found to be non-linear in contrast to previous expectations [10]. The authors confirmed that acetycholine-induced changes in cycle length occurred mainly by a change in the diastolic depolarization rate. Within a physiologic range, this rate depends linearly on the acetylcholine concentration. Surprisingly the dependency of cycle length on the diastolic depolarization rate was found to be strongly curvilinear, with a maximum steepness at the lower diastolic depolarization rate. These findings illustrate the concept that in sinus node cells transduction between neural input and cycle lengths are at least partially predicted by intrinsic electrophysiologic properties of the sinus node cells [11]. Therefore, the idea of an automatic pacemaker that would independently find an adequate HR without any settings for basic and maximal rate is out of touch with reality when compared with the physiologict situation.

Provided that the range of operating frequencies must be pre-set, the next question is this: How will the pacemaker system select a frequency within this range?

This brings us back to the problem of which physiologic parameter is actually reflected by the unipolar VIMP signal?

The True Nature of the Impedance Signal

The first pacemakers using unipolar VIMP measurements analysed the impedance curve in order to obtain a surrogate for the duration of the pre-ejection period [1]. Due to difficulties in determining the end of the pre-ejection period using impedance measurements, the signal was later analyzed with respect to the maximum slope of the curve. This signal was believed to represent the inotropic state of the heart muscle as reflected by the initially introduced term "ventricular inotropic parameter" (VIP) [2]. However, further refinement was necessary in order to obtain the later-called "VIMP" signal, indicating a change in concept [12]. Nevertheless, the early notion of the impedance signal being an accurate indicator of the sympathetic tone was in part supported by the recent results of Osswald et al. They showed a close relationship between the first derivative of right ventricular pressure (dP/dt_{max}) and the impedance signal under the condition of dobutamine infusion [12]. However, this finding does not necessarily imply that VIMP does in fact sense inotropy.
Unipolar intracardiac impedance is recorded during the systolic phases of both isometric contraction and ejection, and curve analysis is based on time-dependent changes during this part of the cardiac cycle. Nevertheless, several explanations of the nature of the impedance signal have been published [13], and applications of different algorithms analyzing the impedance curves (see below, Figure 1) can change the nature of the resulting signal. We propose that the impedance signal is mainly based on the contraction-time because at least two phenomena observed in the clinical application of the Inos² pacemaker can be explained by such an assumption, i.e., the lack of a positive feedback during dobutamine infusion, and an inappropriate increase in paced heart rate under resting conditions.

Contraction Dynamics Depend on Both Frequency and Catecholamines

One possible explanation for VIMP-based, rate-adaptive pacing is the assumption that the sensor signal primarily reflects the inotropic state of the heart. Since any increase in HR by itself increases contractility [14], an inotropically driven system could lead to positive feedback with an inappropriate response speed. Nevertheless, positive feedback in patients implanted with the $Inos^{2+}$ pacemaker was not observed during daily activity [15]. Even direct employment of the accepted inotropic index dP/dt_{max} (as the sensor signal

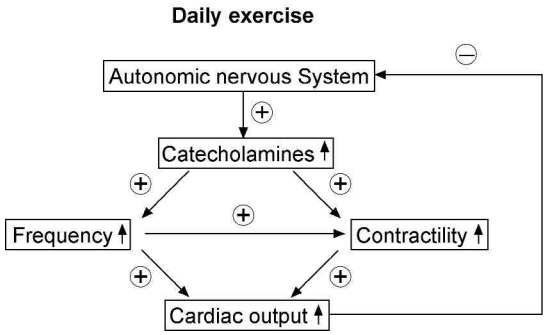

Figure 1. Simplified scheme of regulation of chronotropy and inotropy with respect to catecholamines under physiologic conditions. Locally and systemically-released catecholamines decrease cycle length of sinus node cells (positive chronotropy) and enhance contractility in the working myocardium (positive inotropy). Both effects increase cardiac output that influences via a negative feedback autonomic nervous system leading to inhibition of further release of catecholamines.

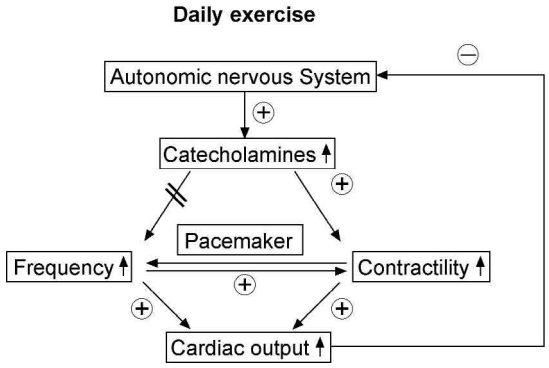

Figure 2. Presumed principle of closed-loop pacing using the Inos software. The device measures a contractility-based index used as surrogate parameter for the activity of the autonomic nervous system, assigning values of the contractility parameter to actual pacing rates. Positive feedback via positive force frequency relation would lead to an inappropriate increase in cardiac output by inhibiting catecholamine release avoiding any inappropriate increase in pacing rate.

in an earlier pacemaker system) was quite unexpectedly devoid of any positive feedback [4]. It may be speculated that under daily activity the endogenous force-frequency relationship is counter-regulated by the ANS, thus offsetting possible positive feedback. An inappropriate increase in pacing rate was believed to be prevented by counter-regulation of the ANS-; an increase in pacing rate enhances the inotropic state, which in turn is sensed by the ANS and counter-regulated by reduced sympathetic drive.

Under the experimental conditions of infusing dobutamine, we could not detect any sign of positive feedback when comparing HR response in patients without sinus node disease. This confirmed a more linear correlation between pacing rate and catecholamine dose as reported in an earlier study published in this journal [16]. This finding needs further attention since application of high doses of catecholamines preclude any relevant counter-regulation via the ANS. Therefore, at least under this condition, positive feedback should have occurred.

Some recent experimental findings using the new work-loop technique in cardiac trabeculae provide possible explanations. Until a few years ago, the effects of inotropic interventions on the mechanical performance of isolated muscle were generally assessed using either isometric or isotonic techniques. However, neither technique accurately reflects the dynamics in vivo. When a sinusoidal length trajectory was applied to isolated muscles to approximate simulated physiologic length changes, a positive force-frequency relation and a shift to the right (to higher frequencies) by stimulation of the β_1-adrenoceptor with isoprenaline was confirmed [17]. As reported earlier [18] increased stimulation frequency reduces the duration of contraction, but this frequency-induced shortening is overruled by the greater decrease in contraction time in the presence of isoprenaline. The mechanism for the frequency-depen-

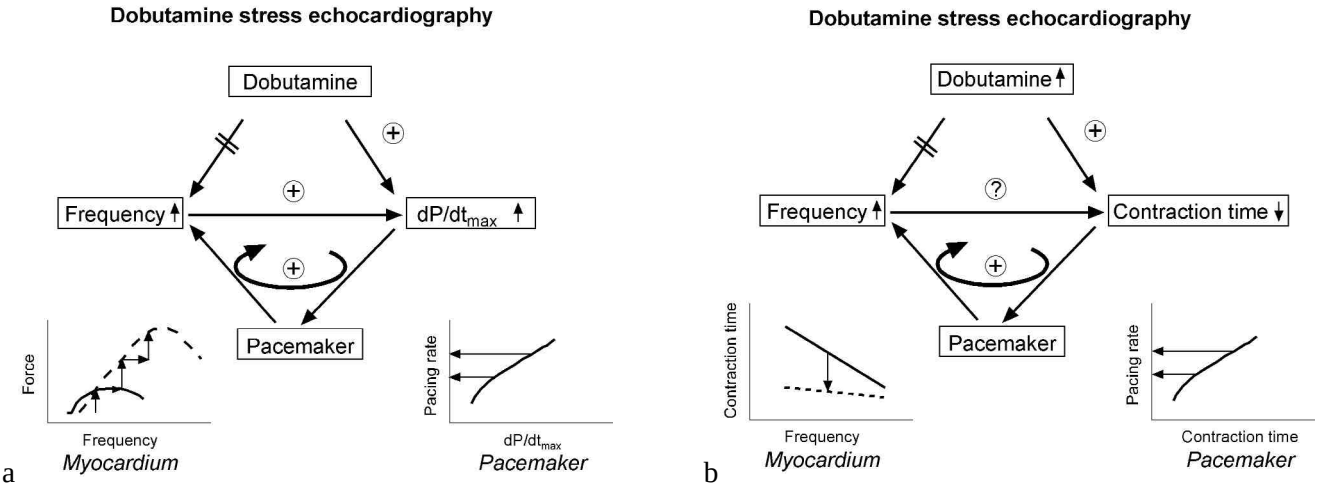

Figure 3. Illustration of two different concepts in understanding the principle of rate-adaptive pacing using the Inos software. As reported earlier, dobutamine was infused in this situation [16]. Infusion of high doses of catecholamines rules out any significant negative feed-back via the autonomic nervous system. Therefore this regulatory loop is no longer indicated in the following 2 figures.

Panel a) shows the concept of the signal as an index of contractility. The signal is reflected as a surrogate parameter of contractility and assigns an actual pacing rate (right inlet). In the left inlet the effect of catecholamines on the relation of force frequency are given (solid line: control, dashed line: after exposure to catecholamines). The force frequency curve is shifted to the right and the maximal force is increased. The arrows indicate the effects of increasing force by the catecholamines (vertical) respectively, by increase in frequency (horizontal). Any increase in force would lead to a further increase in pacing rate and subsequently increase force, and so on.

Panel b) shows the concept of the signal primarily reflecting contraction time. Any value for contraction time is assigned an actual pacing rate (right inlet). In the left inlet the effect of catecholamines on the contraction time-frequency relationship is shown (solid line: control, dashed line: after exposure to catecholamines). Catecholamines decrease contraction time to a minimal value leading to a flat slope of the curve. The effect of catecholamines at one frequency is indicated by the arrow. The difference in contraction time is highest for low frequencies (i.e., at the beginning of an exercise) but small at high frequencies (possible level off). Note that under controlled conditions a steep curve facilitates positive feedback.

dent acceleration of twitch duration remains unclear. Layland et al. suggested that Ca^{2+} uptake by the sarcoplasmic reticulum was stimulated since frequency-dependence was abolished if the uptake rate was already maximally stimulated due to prior phoshorylation of phospholamban in response to β-adrenoceptor stimulation [17]. These experiments were done using rats, and the results remain to be demonstrated in human tissue. If the assumption holds true, this finding could have remarkable implications using a contraction time-based system for rate-adaptive pacing. The profound effect of β-adrenoceptor stimulation on twitch duration could explain the system's sensitivity toward catecholamines, whereas the steep slope between frequency and twitch duration under control condition without any adrenergic stimulation should favor a positive feedback with an inappropriate rate response during rest. This question could be addressed by registering impedance signals at different stimulation frequencies under varying catecholamine levels.

Contraction Dynamics Depends on the Disease State

Early in the development of impedance-based, rate-adaptive pacemakers it was noticed that the shape of the impedance curves could differ remarkably (interindividually and intraindividually) depending on the implantation site. Theoretical field calculations based on a finite element model could predict lead positions far from the apex of the right ventricle with impedance shifts in the opposite direction from what was expected to occur. In fact, in a small percentage of patients, this behavior was observed [13], leading to a new analysis algorithm based on the differential area between the curve under scrutiny and a reference curve obtained during rest. Since this system is independent of the direction of shift, a body motion detector is required to indicate the resting condition. Presently, it is unclear whether unexpected shifts from the impedance signal observed in patients are the consequence of a disadvantageous lead position or of intrinsic properties in the patient. In this context, recently published data on contraction dynamics in humans are of special interest. Duncan et al. investigated the influence of dobutamine infusion on contraction time and peak aortic acceleration in healthy persons and patients with coronary artery disease [19]. While in both groups dobutamine led to a strong inotropic reaction, differences in activation patterns of the left ventricle occurred. In controls the "Z-ratio," the rate-adjusted time index of left ventricular activation fell correlating with a shortening of the QRS, whereas in patients the opposite was observed. These results were obtained when diseased left ventricles were studied, whereas the impedance signal is recorded in the right ventricle, which does not necessarily have to be severely affected. Once more, Duncan's results illustrate the subtle regulation of time-based contraction parameters and inotropy in response to catecholamines that seem to be much more complicated under pathologic conditions. An algorithm using only the difference of the area of the impedance signal irrespective of the direction of the shift could be an appropriate approach to overcome this problem. However in any case, analysing the shift of the impedance signal in patients with different right ventricular function seems to be an attractive attempt to get more information about the nature of the impedance signal. We consider this topic as relevant, since the patient's condition can change with time due to acute [20] or chronic impairment of the right ventricle.

Conclusion

Impedance-based, rate-adaptive pacing systems were initially developed in order to use the sensor signal as the surrogate parameter for pre-ejection time, which is well-defined in physiology and experimental cardiology. This concept is still fascinating from a biological as well as a technical point of view. We would get a signal reflecting the acute inotropic state of the ventricle by initially measuring the simple parameter for lead impedance. Difficulties in analyzing the signal as well as the developments for maximal practicability in application have led to a remarkable evolution of the system. As a consequence of these efforts, the current principle used to analyze impedance curves appears more inexplicable compared to the introduction of the first generation of such pacemakers. Refinement of the impedance curve analysis has raised some questions about the true nature of the measured signal as well as the calculated parameter, which is presently called the VIMP parameter. In reviewing recent findings in experimental electrophysiology dealing with the regulation of sinus rate and contraction dynamics modulated via the ANS, it becomes quite clear that, even under physiological conditions, regulation is more complex than initially expected.

Despite these new and partially unexpected findings and the difficulties in developing a solid analytical algorithm, a large amount of data presently provide evidence for the suitability and long-term stability of closed-loop pacing using ventricular impedance; such findings underscore the justifiable technological effort that is being made in this field [7]. The growing knowledge of contraction dynamics regulation under physiologic and pathologic conditions in response to catecholamines could reignite interest in the impedance signal in a more general view. We would suggest that the expected increase in knowledge should lead to a better understanding of the basics of this rate-adaptive pacing principle and stimulate new directions for research in this field.

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Contact
Dr. med. Torsten Christ
Institut für Pharmakologie und Toxikologie
Fetscherstrasse 74
D-01309 Dresden, Germany
Telephone: +49 35 145 86279
Fax: +49 35 145 86315
E-mail: Christ@rcs.urz.tu-dresden.de