The Implant and the Cardiovascular Feedback Loop

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Summary
The aim of biomedical development activities for therapeutic and diagnostic devices increasingly extends from life-saving tasks to an improvement of the patients’ quality of life, far-reaching device automaticity, and additional functionality supporting the physician during follow-up. For the achievement of these goals, the implant must be equipped with the capability to reliably register and interpret the status of the intrinsic cardiovascular control loop. Suitable sensor signals are required for that purpose, as e.g. contraction dynamics, ventricular evoked response (VER), and monophasic action potential (MAP). The presented paper discusses the role of implanted devices, incorporating such sensor signals, in the cardiovascular feedback loop and the clinical validation of the mentioned signals.

Key Words
Cardiovascular feedback, closed-loop regulation, electrical cellular activity, MAP, VER, mechanical contraction dynamics, rate adaptive pacing

Introduction
For therapeutic and diagnostic devices the aim of biomedical development has changed from merely life-saving and symptom-limiting tasks to more sophisticated achievements, like increasing the quality of life of the patient, providing diagnostic support for the physician, and adding automaticity for the adjustment of the working parameters of the device.

These tasks require a strongly improved ability of the implant to perceive the actual status of important cardiac parameters. Effectively, the implanted device must become an integral part of the cardiovascular control loop.

The aim of this paper is to discuss the implications of the integration of a cardiovascular implant into the body.

Cardiovascular Feedback
The closed-loop regulation is a basic principle in the body that is used, whenever an intrinsic parameter of the organism (e.g. body temperature, blood pressure, blood-glucose level etc.) needs to be kept within certain limits, in spite of environmental disturbances\(^{[1]}\).

The concept of a closed-loop regulation is depicted in figure 1. A sensor detects deviations of the regulated parameter from its current setpoint. The regulation center processes the sensor output and reacts by controlling the effector. The main characteristics of a closed-loop regulation is a negative feedback: if the sensor detects a parameter deviation in one direction, the regulation center causes a change in the opposite direction that compensates for the initial deviation.

One example for such a closed-loop regulation, the blood pressure regulation of the body\(^{[2]}\), is demonstrated in figure 2. The regulated parameter, the mean arterial blood pressure (MABP) is directly influenced by changes in cardiac output (CO) and total peripheral resistance. As changes in MABP occur, the baroreceptors form a negative feedback loop in conjunction with the circulatory centers. This feedback controls
both contraction dynamics and sinus node function via the sympathetic and parasympathetic control of the heart.

![Diagram of cardiovascular control loop](image)

**Figure 2.** Cardiovascular control loop of a chronotropically competent patient.

In case of a disease that affects parts of a closed-loop regulation (e.g. chronotropic incompetence) an optimal therapy is only possible, if the therapeutic device is able to loop into the regulation system. By substituting or supporting the affected part of the control loop, the functionality can be restored in an optimal way.

For that purpose, monitoring and interpretation of information about the control signals that flow in the regulation loop is required. The availability of this information is a valuable tool for the diagnosis of diseases that impede the functionality of a closed-loop regulation.

In the following, the identification of suitable cardiovascular parameters and the realization of the corresponding implantable biosensors is discussed.

**Signals representing Cardiovascular Status**

From the different parameters that are involved in the cardiovascular regulation (figure 2) a suitable signal for detection of the cardiovascular regulation status must be selected.

One possibility is to measure the regulated parameter itself, the MABP, or a signal generated by the baroreceptors. But, besides technical difficulties, this method is not adequate, because the circulation center additionally takes into account a large set of intrinsic parameters (figure 3), that are relevant to the circulatory regulation. This may lead to, e.g., a change of the setpoint for the MABP. In that case, the implant will counteract the intentions of the circulation center. On the other hand, it is impossible to monitor all intrinsic parameters that are important for determination of cardiac demand and to combine them correctly.

The solution for this problem is to choose a sensor parameter, that already contains the information about the cardiac demand. The circulation center includes all relevant intrinsic sensor signals (figure 3, "input path") in its calculation of the cardiac demand and for the generation of the control signals for the required heart performance (figure 3, "output path"). These signals control the sinus rate, the contraction dynamics, and the atrioventricular delay. The contraction dynamics has the advantage to be available even for chronotropic incompetent patients and for patients with atrioventricular block.

Using this approach delegates the complicated, and technologically unresolved, task of combining the different input signals to form the correct rate, to the "natural computer", i.e. the circulation center.

![Diagram of parameters](image)

**Figure 3.** Parameters in the "input path" and "output path" of the circulation center.

**Monitoring of Cardiovascular Feedback- Signals**

For implantable devices, the sensor must fulfill further crucial requirements: it must be biocompatible and long-term stable. Using conventional pacing leads for sensing has the advantage to combine the monitoring abilities with the well-known reliability of these leads. Therefore, in the following, two such sensor signals are presented that fulfill their task by monitoring the electrical activity of myocardial cells (a, b) and one by assessing the mechanical ventricular contraction process (c).

a) **Electrical Activity: Monophasic Action Potential**

The circulation center controls the pumping performance of the heart by adrenergic stimulation of the
myocardium. This causes characteristic changes in the de- and re-polarization behavior of the myocardial cells[3].

The monophasic action potential (MAP) represents a summed signal of action potentials of myocardial cells close to the tip of the electrode. The change in the MAP morphology due to different influences is well known from literature[4].

Due to the low polarizability of fractally coated pacing leads the signal can be measured for stimulated and for intrinsic events in the atrium as well as in the ventricle. The long-term monitoring of this signal is possible for the first time by using fractally coated bipolar electrodes[5].

The MAP morphology is influenced by adrenergic stimulation, medication, arrhythmia, ischemia etc., in a characteristic, well-known, manner[6,7] (e.g. figure 4).

![Graph showing MAP recordings after implantation and 2h before the onset of atrial fibrillation.](image)

**Figure 4.** Atrial MAP recordings after implantation and 2h before the onset of atrial fibrillation (AF): the prediction of AF is possible by analysis of the MAP[8].

b) Electrical Activity: VER

By using a unipolar electrode configuration, the ventricular evoked response (VER) can be measured by fractally coated electrodes without interference of an polarization artifact from the preceding stimulus pulse[8]. The VER is influenced by the same factors as the MAP. Additionally the propagation of the excitation during contraction is reflected by the signal morphology.

Both electrical signals, MAP and VER, allow the determination of the cardiac demand and of the physiological state of the heart. Therefore they offer a wide range of applications, e.g. medication monitoring, transplant rejection monitoring[10], automatic AV-delay optimization, automatic amplitude adjustment, rate adaptation, ischemia recognition, early detection of arrhythmia (figure 4), etc..

c) Mechanical Activity: Contraction dynamics

The adrenergic stimulation of myocardial cells at different parts of the heart affect the pumping efficacy by modulation of the rate (chronotropy), by changing the synchronization of atrium and ventricle (dromotropy) and by adapting the contractility of the myocardium (inotropy). Since the modulation of contractility results in changes in the mechanical contraction process (‘contraction dynamics’) with respect to velocity and amplitude of the wall movement during contraction, a sensor signal, that maps the geometric shape of the myocardium during contraction, is suitable to extract the contraction dynamics.

![Graph showing maximal circumferential fiber shortening velocity.](image)

**Figure 5.** The maximum circumferential fiber shortening velocity, measured by M-mode echocardiography, is closely correlated with the cardiac demand[11].

During increased adrenergic stimulation, caused by e.g. increasing physical load, the contraction velocity increases considerably, as is demonstrated by the behavior of the maximum circumferential fiber shortening velocity shown in figure 5[11].

The contraction dynamics is assessed by unipolar intracardiac impedance measurement, using any standard ventricular pacing lead[12]. This monitoring method is validated clinically to reliably provide a measure for the ventricular contraction dynamics[13].
Furthermore this signal is a direct measure of the myocardial status, that is suitable for the detection of any excessive stress for the myocardium. This information can be used to preserve the inotropic reserves of the myocardium, e.g. by implementing a rate-adaptive algorithm based on this principle in a pacemaker.

**Clinical Validation: Rate Adaptive Pacing**

A rate adaptive pacemaker system, using the approach discussed above, provides several distinct benefits for the patient.

**Benefits for the patient**

For chronotropic incompetent patients even small exercise levels, or mental load, may lead to a strongly increased stress for the myocardium, since the increasing circulatory demand has to be provided mainly by an increase of the myocardial contractility due to the insufficient heart rate increase (see figure 6). For still higher load the required cardiac demand (dashed line) cannot be provided any more, i.e. the maximum load for the patient is strongly reduced by chronotropic incompetence.

![Figure 6. Cardiac output, heart rate, contraction dynamics and mean arterial blood pressure (MABP) during a three-step bicycle ergometry is plotted schematically. The dashed curves indicate the behavior for a chronotopically competent patient, the solid curve corresponds to a chronotopically incompetent patient.](image)

A closed-loop rate-adaptation, as is achieved by using rate adaptation based on myocardial contraction dynamics, eliminates both shortcomings: Since the pacing rate is coupled to the contraction dynamics[13], any excessive increase of contractility is rendered superfluous by an appropriate parallel increase of the heart rate (figure 7). This principle works for all types of demands, e.g. for mental stress.

![Figure 7. Ergometry of chronotopically incompetent patient with implanted rate-adaptive pacemaker, that couples the pacing rate to the contraction dynamics.](image)

Because the full dynamic range of the heart rate is restored, the maximum load level of the patient is also recovered, providing an increased quality of life. Furthermore, due to the closed-loop control with negative feedback, the rate adaptation works correctly, independent on the cause for the increased cardiac demand. Each deviation from the correct pacing rate caused by, e.g. load change or posture change, is corrected automatically by the negative feedback. From this principle it is concluded, that the sensor fulfills the requirements of an optimal sensor for rate-adaptation, as compiled by Lau[15].

**Clinical validation**

This rate adaptive concept has been validated clinically for 429 patients (176 single chamber, 253 dual chamber, 36% female, age 62 ± 15 years) and has been implemented in a rate-adaptive pacemaker system (Inos®DR, Biotronik). For chronotropic incompetent patients during DDDR-pacing ambulatory exercises, bicycle ergometry and mental stress tests were performed according to standardized protocols. The pacemaker system responds to all types of physical and psychological load in an adequate manner maintaining the necessary perfusion of the organs with blood and without overstressing the reserves of the heart (figure 8, see Res et al.[14]).

As this pacemaker becomes part of the natural regulatory system, the optimal response timing and attack- and decay-rates are continuously controlled by the circulatory center via the contraction dynamics. Therefore, no timing parameters need to be programmed. Only the rate limits (basic and maximum sensor rate) have to be adjusted by the physician.
Conclusion

The next generation of diagnostic and therapeutic cardiovascular devices will make use of a sensor signal that provides feedback from the body about the actual cardiac state in order to realize a high degree of automaticity of the implant. Especially for rate adaptive cardiac pacing, the availability of feedback about the effect of the pacing therapy is crucial for the aim of improving the quality of live and restoring the physical capabilities of the patient.

Suitable sensor signals based on different approaches are available and clinically validated.

The electrical signals MAP and VER of the myocardium can be measured by fractally coated biocompatible electrodes and provide access to the de- and repolarization characteristics of myocardial cells. The monitoring of mechanical contraction dynamics works with any standard pacing lead. All these signals are suitable for determination of the cardiac status.

The monitoring of contraction dynamics, already is implemented and successfully clinically validated with a pacemaker providing closed-loop rate adaptation.

References