Heart Cycle Length Modulation by Electrical Neurostimulation in the High Right Human Atrium

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Abstract—Today, high resting heart rates are known to be an independent risk factor for a higher overall mortality, irrespective of underlying coronary diseases. Neurostimulation is a fast growing, wide spread approach to treat various disorders by electrical stimulation of specific nerve cells. We present a technique of intracardiac neurostimulation to the parasympathetic tone in the high right human atrium in the sinoatrial node area. Investigations include recording the decreasing effects of heart rate, the anatomical endocardial visualization of the right atrium, and developing gradient maps with parasympathetic and sympathetic nerve bundles. During an ablation procedure within the sinus rhythm, patients are stimulated with a bipolar electrode catheter which can be detected by an electroanatomical navigation system. Sinus cycle length and corresponding ventricular heart rate are recorded before, during and after stimulation and show a direct correlation with the start and end of stimulation.

Index Terms—Electrical neurostimulation, modulation of heart rate, intracardiac electrograms, heart rate reduction

I. INTRODUCTION

Depending on (among other factors) physical constitution and age, healthy men have a resting heart rate of about 1 – 1.3 Hz, which corresponds to 60 – 80 beats per minute (bpm). Modulation of heart rate is regulated by the autonomous nervous system, which consists of two subcomponents, i.e. the sympathetic and parasympathetic nervous systems. Both these systems act as antagonists: for example, in terms of cardiology, the sympathetic nervous system increases heart rate (positive chronotropic effect) whereas the parasympathetic system decreases heart rate in case of regeneration (negative chronotropic effect).

As an independent risk factor, high resting heart rates can lead to a higher overall mortality even in healthy persons [1]. However, especially individuals with coronary artery diseases, such as heart insufficiency, have an increased mortality rate due to their increased sympathetic tone [2]. For example, Jouven et al. demonstrated that individuals suffering from myocardial infarction have relatively high cardiovascular mortality rates [3].

In most cases, pharmacological approaches to decrease relatively high heart rates are achieved with beta blockers. Beta blockers inhibit the binding of adrenaline to the beta receptors, which are also part of the cells in the heart. The heart beat within sinus rhythm is generated in the sinoatrial node, which is localized in the high right atrium near the vena cava (Fig. 1; left side). The specialized nerve cells forming the sinoatrial node have no constant resting membrane potential. Diastolic depolarization of these pacemaker cells leads to the pulse generating automaticity of the heart. A typical action potential from the sinoatrial node area is shown on the right side of Fig. 1.

As beta blockers cannot exclusively target the sinus node but also decrease blood pressure, this is a major disadvantage. One approach consists of pharmacological blockade of the $i_{f}$-channel, with, for example, Ixivabradine.

The rhythmic activity of the heart is produced according to intrinsic and spontaneous depolarizing ion currents. The hyperpolarizing-activated $i_{f}$-current plays an important role in this process. Because $i_{f}$ is not exclusively expressed in the sinoatrial node, physiological effects on the atria may take place or visual...
disorders caused by the central nervous system may sometimes occur. Besides, as a matter of principle, no medication can ever provide dynamic modulation of the heart rate.

The selective electrical neurostimulation, also called neuromodulation, of the autonomous nervous system is a fast-growing research area which already has widespread application. For instance, stimulation of specific points in the spinal cord is used to relieve pain associated with chronic reflex sympathetic dystrophy syndrome [4]. Deep brain stimulation is under investigation for the treatment of epilepsy [5] and psychiatric disorders [6]. Also, via sacral nerve stimulation lower urinary tract dysfunctions can be improved [7]. The feasibility of chronic parasympathetic stimulation for ventricular rate control during atrial fibrillation has been demonstrated in an animal model and was shown to be safe, effective and well tolerated even on the long term [8].

The current project aims to develop a technique of intracardiac electrical neuromodulation to selectively increase the parasympathetic tone in the sinoatrial node area, with the objective to decrease high resting heart rates. Therefore, during standard procedure of ablation procedures in humans suffering from atrial fibrillation, the sinoatrial node area in the high right atrium was stimulated within the sinus rhythm. We present the design of the study and show the results during intracardiac neurostimulation.

II. METHODOLOGY

To investigate the principle of intracardiac neurostimulation to decrease high resting heart rates, this study included patients undergoing a standard procedure of ablation. Patients are under deep sedation with continuous surveillance of blood pressure, heart rate and oxygen saturation. A multipolar steerable mapping catheter (Thermocool Catheter, Biosense Webster Corp., USA) for radio frequency ablation is guided to the right atrium through the femoral vein. The catheter tip is located with a 3D electroanatomical navigation system (Carto, Biosense Webster Corp., USA). This allows each stimulation point to be recorded. Extrapolation of the space between these stimulation points provides a reconstruction of endocardial maps allowing detailed investigation of the anatomical position of the parasympathetic nerves in relation to the sinoatrial node.

A. Specific Medical Circumstances

In this complicated procedure, it is important to apply appropriate trigger signals, because stimulation during the vulnerable phase can cause atrial fibrillation. Therefore, to exclusively address the parasympathetic nervous system, stimulation is performed in the absolute refractory period of the atrium, whilst the cells cannot be excited. As trigger signal the intracardiac electrogram (IEGM) is detected with an electrode catheter (Fig. 2). The IEGM (blue solid line) represents the excitation of the sinoatrial node area, as the signal correlates with the start of the P-wave which is the first wave during cardiac action (Fig. 2: ECG lead Einthoven I; black dashed line) equal to the atrial excitation. The atrial myocardial effective refractory period (ERP), ensures not to indicate atrial fibrillation and to stimulate nerve cells in musculature, takes more than 150 ms.

Because neurostimulation will shorten the myocardial ERP, the duration of stimulation bursts must be significantly below the ERP minus an average latency interval of 20 – 40 ms to the local atrial myocardial excitation. Accordingly, stimulation burst periods should last for 40 – 80 ms. Therefore, the frequency of the neurostimulation bursts is optimally higher than in cases of continuous stimulation. Low frequency stimulation would not emit effective energy to the nerve cells. For this reason, the stimulation burst frequency was chosen to be 200 Hz.

To evaluate the effect on local neurostimulation, the sinus cycle length is measured before, during and after the stimulation period. According to these recordings in correlation with the strength of the negative chronotropic effect, gradient maps of the functional formation of nerve fibers in the sinoatrial node area have been established.

B. Neurostimulation Setup for a Study Case

Fig. 3 shows the setup for the study on human intracardiac neuromodulation. In human studies, only technical equipment that has been approved for clinical trials is used. Therefore, the IEGM trigger signal,
detected with the electrode catheter, is passed through the ablation generator and the electrophysiological recording system, to a sense/trigger stimulator (UHS 3000, Biotronik, Germany) with a sense sensitivity of 1 mV. For the high frequency stimulation bursts another stimulation system (HF stimulator) is needed (Bloom DTU 215B, Electrophysiology Stimulator, Fischer Medical Technologies LLC, USA), providing symmetric biphasic rectangular stimulation bursts. With a delay of 25 ms, IEGM synchronized high frequency pulses of 200 Hz with a duration of 50 ms at a maximum of 2 V are generated. Passing an isolation unit (Remote Stimulus Isolation Unit, Fischer Medical Technologies LLC, USA) driven with 9 V batteries for maximum patient safety and isolation, and a catheter input module synchronizing and connecting signals, the stimulation bursts are transferred back to the electrode catheter. The bursts have been emitted bipolar between the first two electrodes at the catheter tip. For 3D visualization map of the region of interest (ROI) the signals are connected to the navigation system. Measuring the cycle length and heart rate indicates whether the reaction of the parasympathetic tone has been achieved.

III. RESULTS

Fig. 4 shows a recording of a short episode of intracardiac neurostimulation. It can be seen that directly after the first IEGM excitation (blue solid line) the ECG Einthoven lead I (black dashed line) shows the normal cardiac cycle. The stimulation period started at 6.7 s (green dotted bar). Therefore, immediately after the second IEGM excitation, the stimulation is clearly seen to start.

A representative plot of a complete neurostimulation episode is shown in Fig. 5. At the top, the ECG Einthoven lead I as gold standard is shown in correlation with the middle display with the IEGM taken from the sinoatrial node area. Heart rate in bpm is recorded in the lower picture. The vertical green dotted bar at 6.7 s indicates the start of the stimulation episode and the active period of stimulation bursts is shown in the middle picture. The second vertical bar at 51 s denotes the end of stimulation. In the lower picture, a 20 % decrease in heart rate can be seen. Although the given heart rate was relatively low before stimulation (60 – 65 bpm), the stimulation effect can be clearly seen. After the end of stimulation the heart rate increases immediately within 10 s.

The resulting gradient map of this patient is shown in Fig. 6. The right-hand side presents a 3D visualization of the patient’s right atrium in frontal plane view can be seen and the left-hand side shows the right atrium in posterior view. The shape of the atrium depends on the number of sampling points which have been made at the beginning of the standard procedure. Interpolation of the sampling points result in the presented views. Also the
venae cavae and the pulmonary artery can be seen. Round markers indicate the points of stimulation. A color map is correlated with the decrease or increase in heart cycle length.

Heart cycle length is measured by detection of RR intervals in the ECG Einthoven lead I, averaged every 10 R-peaks. The cycle length at the very start of the stimulation period was recorded with 970 ms, equivalent to 61.9 bpm. Heart cycle length measurement over the last 10 stimulation bursts shows an increase to 10950 ms, equivalent to 54.8 bpm. In this case the strongest increase in heart cycle length was +134 ms and the correlated area is marked in the red-orange area (ROI 1) on the left display. This is the sinoatrial node area, where we expected to observe the most significant decrease in heart rate. The surrounding area shows a minor increase in cycle length (green). In the upper part of that picture, an area (ROI 2) occurs where a slight decrease in heart cycle length or an increase in heart rate can be detected according to a bundle of sympathetic nerves.

IV. CONCLUSION

Based on these results, it can be seen that the principle of heart rate reduction, respectively the increase in heart cycle length, through electrical neurostimulation of the parasympathetic tone in the sinoatrial node area is an appropriate approach. Not only was a decrease in heart rate shown, but even a slight increase in heart rate could be detected. After termination of the stimulation, the negative chronotropic effect ends immediately.

With respect to pharmacological approaches, the direct control (within a few seconds) of heart rate is a major advantage of this approach. Nevertheless, transferability has to be demonstrated in future studies, as well as identification of the best stimulation parameters, such as burst stimulation frequency, stimulation patterns (e.g. monophasic or biphasic), for maximum outcome at low energy consumption. Integrated into modified pacemakers, the neurostimulation modality is easily accessed for patients and might be a major step in the therapy of patients with chronic heart failure.

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REFERENCES


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