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CHRIST, T., ET AL.: Recording Atrial Monophasic Action Potentials Using Standard Pacemaker Leads: An Alternative Way to Study Electrophysiological Properties of the Human Atrium In Vivo? AF leads to electrophysiological changes, but it is not known if similar alterations also appear before the onset of the first episode of AF because invasive electrophysiological studies are not justified in otherwise symptom-free patients. To address this question requires a safe method of obtaining atrial electrophysiological parameters at no extra risk or discomfort for the patient. The aim of this study was to test if recording of monophasic action potentials (MAPs) is feasible during pacemaker implantation. The study included 22 patients undergoing pacemaker implantation for symptomatic bradycardia without any history of AF. Using a custommade amplifier and a minor modification of the routine procedure for intraoperatively measured P waves, atrial electrograms could be recorded using a standard active pacemaker lead. MAP-like electrograms were obtained in 15 patients. MAP amplitude was 2.6 ± 0.3 mV, mean action potential duration was 316 ± 12 ms at a spontaneous heart rate of 67.2 ± 3.2 beats/min. MAP duration was decreased when atria were stimulated at shorter cycle lengths (249 ± 12 ms at 150 beats/min, P < 0.05 vs sinus rhythm).

In about two thirds of patients undergoing pacemaker implantation, recording of MAP-like electrograms was feasible with only minor modification of the atrial electrogram recording technique. The method should allow screening patients for electrophysiological alterations even before the onset of AF. (PACE 2004; 27:1632–1637)

electrical remodeling, atrial fibrillation, MAP, pacemaker

Introduction
Electrical remodeling in chronic atrial fibrillation (AF) is defined by a loss of rate dependent regulation of an already shortened action potential duration (APD). The shortening of APD is paralleled by a shortened refractory period that can facilitate the generation of multiple reentrant wavelets and is therefore made in part responsible for the high recurrence rate of AF after cardioversion.1 Electrical remodeling implies primarily electrophysiological changes as the result of spontaneous or induced AF.2,3 However, it is not known if APD is already altered before the onset of the first episode of AF in humans. Recent animal studies demonstrate that heart failure in the goat promotes AF without any changes in the effective refractory period (ERP),4 whereas in dogs ERP even increases.5 (Shinagawa et al., 2002). One reason for the lack of human data is certainly related to the unavailability of monophasic action potential (MAP) recordings from patients in sinus rhythm (SR) who later develop AF.

To overcome this limitation the patients studied required pacemaker implantation to test if atrial MAP recording is feasible using standard active pacemaker leads. This approach has the advantage of no additional invasive burden to the patient. Moreover, pacemaker implantation is predominantly required in an older patient population prone to develop AF in a high percentage. In the present study, the feasibility of the approach was tested.

Patients and Methods
Patient Population
MAP measurements were performed in 22 patients (15 men, 7 women) with a mean age of 71 ± 1.9 years (mean ± SEM, range 51–82 years). All patients underwent routine pacemaker implantation for symptomatic bradycardia. Demographic
Table I.

<table>
<thead>
<tr>
<th>Patients' Characteristics, Brands of Electrode Used, and Indication for Pacemaker Implantation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (range in years) 51–82</td>
</tr>
<tr>
<td>Female/male (n/n) 7/15</td>
</tr>
<tr>
<td>Coronary artery disease (n) 7</td>
</tr>
<tr>
<td>DCM (n) 2</td>
</tr>
<tr>
<td>Diabetes (n) 3</td>
</tr>
<tr>
<td>EF in percent (mean [range]) 49[15–60]</td>
</tr>
<tr>
<td>Indication for pacemaker implantation</td>
</tr>
<tr>
<td>Sinus node syndrome 6</td>
</tr>
<tr>
<td>Sinus arrest 1</td>
</tr>
<tr>
<td>AV block II° 9</td>
</tr>
<tr>
<td>AV block III° 3</td>
</tr>
<tr>
<td>Binodal disease 3</td>
</tr>
<tr>
<td>Electrode type</td>
</tr>
<tr>
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</tr>
<tr>
<td>Biotronik Elox P 4(3)</td>
</tr>
<tr>
<td>Guidant Flextend 4087 4(2)</td>
</tr>
</tbody>
</table>

1Numbers in parenthesis indicate number of patients in which MAPs could be recorded successfully. AV = atrioven- tricular; DCM. dilated cardiomyopathy; EF = ejection fraction.

Measurements of Atrial MAPs

Pacemaker leads were introduced via the subclavian vein and positioned in the right atrial appendage and the right ventricle. Only active leads were used in the atrium (Table I). After obtaining acceptable and stable measurements (pacing threshold <1.5v/0.5ms, sensing >1.5 mV, impedance <2,000 Ω) electrograms were recorded for 20 seconds. For this purpose a custom-made amplifier (Hoermann Medizintechnik, Chemnitz, Germany) was used. The full frequency range of the amplifier was split into two subbands, a lower band (0.1 Hz – 1 KHz) and a higher band (300 Hz – 2.5 kHz). The signals were digitized with a sample rate of 5 kHz and an amplitude resolution of 16 bit. The data were stored on the hard disk of a personal computer (AD unit: Lotech, City, OH, USA). The high frequency subband of the two-stage difference amplifier increases time resolution of the local depolarization. The signal filtering, resampling, and superposition of the two subbands was performed offline using the Signal Processing Toolbox of Matlab software (Natick, MA, USA). The computed composite signal has the bandwidth of the low frequency amplifier channel (0.1–1,000 Hz).

Once an acceptable tipposition of the electrode was found, the size and direction of the intratrial loop of the pacemaker lead was varied to get maximum electrogram amplitudes. To reduce the signal to noise ratio, the proximal ring electrode of the pacemaker lead and a surface electrode on the left leg were electrically connected and used as the indifferent electrode. Initial recordings of spontaneous electrograms were followed by recordings during pacing at different cycle lengths (i.e., just above spontaneous rate and at cycle lengths of 600, 500, and 400 ms). Pacing and electrogram recordings were performed using the same lead.

Data Analysis

For data analysis the Bioview software (Biotronik, GmbH & Co., Berlin, Germany) was used. Five consecutive MAPs under identical conditions were averaged for analysis of MAP data. Spontaneous MAP-like electrograms were analyzed by measuring peak amplitude and MAP duration (MAPD). In spontaneous or paced electrograms, MAPD was estimated as the time between onset of upstroke, respectively stimulus artefact and the point when MAP voltage had dropped again to the value registered 50 ms before the MAP.

Statistical Analysis

Results are presented as mean values ± SEM or median values (25–75% percentile rang), respectively. For comparison of normally distributed variables, the paired t-test (modified by Welch for nonequal variance) was used. Nonnormally distributed data were analyzed using the notched box plots by Turkey according to modification from McGill and Chambers. The variables within the group were examined by the Wilcoxsns signed rank test. A value of P < 0.05 was considered statistically significant.

Results

Patients’ Characteristic

The indications for pacemaker implantation in 22 patients of this pilot study were different, with 12 patients suffering from ventricular bradycardia due to second-and third-degree atrioventricular (AV) block (Table I). Left ventricular ejection fraction was clearly reduced in some, but normal in most patients. Patients received standard cardiac medication (12 angiotensin-converting enzyme [ACE] inhibitors, 7 β-blockers, 3 digitalis). Serum potassium concentrations were almost normal (4.2 ± 0.1 mmol/L).
Feasibility of Recording

All three commercially available pacemaker leads allowed recordings of electrograms in the described setup. Recording of MAP-like intracardiac atrial electrograms was successful in 15 of 22 patients. Mean MAP amplitude (baseline to peak) was 2.6 ± 0.3 mV. All MAP-like electrograms displayed a monotone repolarization pattern as typically found in atrial tissue. Far-field potentials from ventricular myocardium were clearly distinguishable by their rapid depolarization. Typical examples of MAP recording at spontaneous sinus rhythm are shown in Figure 1. At the mean sinus frequency of 67.2 ± 3.2 beats/min the values for MAPD ranged between 233 and 426 ms (mean 316 ± 12 ms, n = 15). This value was not different from the mean MAPD value of 321 ± 12 ms obtained when the atria were paced slightly above the spontaneous heart rate. Typical MAP recordings and the respective MAPD values at different cycle lengths are given in Figure 2.

Though ventricular bradycardia was the indication for pacemaker implantation, 12 of the 22 patients studied had rather high spontaneous atrial rates so that the frequency response curves for MAP could not be followed over a broad range of cycle lengths. Figure 3 depicts individual MAPD values for cycle lengths of 400, 500, and 600 ms. With exception of one case, MAPD increased with longer cycle lengths. The median value of 245 (219–277) ms at 400 ms was significantly shorter than 280 (265–305) ms at 600 ms cycle length (P = 0.005).

Discussion

This study demonstrates that atrial MAP-like electrograms can be recorded during routine pacemaker implantation using commercially available active pacemaker leads, and that recording of MAP-like electrograms does not require specially designed electrophysiological catheters. To the contrary, only slight modifications of the pacemaker implantation procedure are sufficient to record MAP-like electrograms of reasonable signal to noise ratio to allow further analysis via ordinary pacemaker electrodes. Mean MAP amplitudes were 2.6 mV and were smaller than reported for MAPs obtained with the classical recording technique.7,8

The electrograms recorded could be interpreted as “injury” potentials since the oldest MAP recording in 1882 were performed by cutting the myocardium with the resulting MAPs being called “monophasic injury currents.”9 Fixing active pacemaker leads by their sharp screw resembles in somewhat controlled injury of the myocardium, thereby allowing similar potentials as monophasic injury currents to be recorded. However, since modern definition of MAPs encompasses the close bipolar recording mode the authors have called the potentials reported here MAP-like electrograms.

The attempt to use pacemaker leads or catheters for MAP recordings is not new. Advanced pacemaker lead technology has been used to record MAP in the ventricle10 and ablation catheters have been used for MAP recording even in the atrium.11

Unlike transmembrane action potential (AP) amplitude which is measured between resting potential and peak of the upstroke, MAP amplitude is defined as the difference in millivolts from baseline to the crest of the MAP plateau. Defining the plateau crest is hampered by the more triangular shape of action potentials in human atrial muscle.12 Therefore, the intersection between a tangent to phase 3 repolarization and the baseline diastolic potential may be used alternatively to determine MAPD. Moreover in the present study, stimulation artifacts can affect the shape of MAP-like electrograms during the early repolarization phase (Fig. 2). Here we have estimated the end of MAP-like electrograms by the point when voltage returned to the value registered 50 ms before the onset. Despite this simplification, the values of MAPD of the present study compare well with those previously reported7,8,13–16, and display the typical rate dependency of MAPD, with shorter MAPs at short than at long cycle lengths.

All three brands of active pacemaker leads used in this study permit registration of MAP-like electrograms suggesting that differences in lead
Figure 2. Frequency dependence of atrial monophasic action potential duration. Monophasic action potentials (MAPs) were recorded at the same location but with different pacing intervals: slightly shorter interval than during spontaneous atrial beating (i.e., 1,000 ms [upper panel], 600 ms [middle panel], and 400 ms [lower panel]. Please note that the last MAP in the upper panel was not stimulated (arrow). Calibration as indicated.

Figure 3. (A) Monophasic action potential duration at the pacing intervals of 400 ms and 600 ms. The lines connect the values at the two pacing intervals for each patient. (B) The median values at the pacing intervals of 400 ms, 500 ms, and 600 ms, 25% and 75% percentiles and range are given as bars and whiskers plot.
Far-field signals from the ventricle are known to interfere with atrial sensing. Due to slow AV conduction late far-field signals could superimpose on the late repolarization phase of atrial MAP-like electrograms. The present study group included some patients with AV block II (Mobitz) and III when at rest. Others developed AV block II (Wenckebach) during fast atrial pacing. Far-field signals were clearly distinguishable by their sharp deflections (Fig. 4) and rarely interfered with estimation of atrial MAPD.

Because of the authors long-standing interest in electrical remodeling due to chronic atrial fibrillation, they are interested in recording atrial MAPs even before the first episode of AF since it is at present unclear if electrical properties are affected before AF in humans.

It could be argued that the described method is not reliable to detect differences in MAPD between patients since APD can vary not only between individual patients but also between different recording sites within one patient and, therefore, steady-state values of APD may not be easily interpreted. However, one hallmark of electrical remodeling in AF is loss of frequency dependent changes in APD that can be detected in vivo with the newly suggested method.

With the described technique for measuring MAPs, new epidemiological aspects of AF can be studied. MAPD and its frequency dependence provide invasive electrophysiological data at the time of pacemaker implantation. These parameters can be associated with prospective periods of AF during long-term follow-up because the pacemaker lead will faithfully detect AF even if
the quality of the MAP recording has deteriorated due to reactive fibrosis in the vicinity of the chronically implanted lead tip.\textsuperscript{21} Larger follow-up studies should answer the question of whether patients who develop AF have shorter MAPD and/or reduced rate dependency of MAPD while in SR.

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References
