Developing a New Electrode System for Detection of the Repolarization Processes of the Heart

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Summary

The aim of our studies was to create an electrode system suitable for long-term recording of monophasic action potential (MAP) and ventricular evoked response (VER) under different experimental and clinical conditions. We compared the MAP signals recorded with silver-silver chloride (Ag-AgCl) and fractal iridium (Ir) coated electrodes. We studied the effects of rate and treatment with different drugs on the MAP and VER, and we investigated the patho-mechanism of ventricular arrhythmias induced by low dose intracoronary endothelin-1 infusion using MAP recordings in experimental in vivo studies. We were the first to perform continuous MAP recordings during a clinical electrophysiologic study with fractal coated electrodes. The studies demonstrated that both MAPs or VERs recorded with Ag-AgCl and Ir-coated electrodes reflected the expected changes of the transmembrane action potential under all investigated experimental and clinical interventions. However, only the Ir-coated electrodes can be used as chronically implantable leads. Using implantable MAP leads in combination with an implant with high-resolution telemetry of the intracardiac signals, monitoring and controlling of drug therapy with a higher time resolution becomes available.

Key Words

Fractal coated lead, monophasic action potential (MAP), ventricular evoked response (VER)

Introduction

In-vivo experimental and clinical examinations and therapies of the heart, such as arrhythmia analysis and treatment, require specific electrodes to provide suitable signals referring to the electrophysiologic events in small myocardial areas.

Monophasic action potential (MAP) and ventricular evoked response (VER) are extracellular waveforms recorded in vivo from the endo- or epicardium that reproduce the time course of the transmembrane action potential (TAP). These techniques are suitable for studying the myocardial repolarization in vivo and may make the basic electrophysiology available for clinical use [1]. The unipolar VER recorded between the tip and an indifferent electrode outside the heart characterizes not only the action potentials of almost the whole ventricular muscle but also the excitation course in the ventricle [2]. The bipolar MAP is recorded with tip and ring electrodes close to each other [3]; it represents the summed signal of the TAP of a small volume of cells surrounding the tip [1].

The main limitation in recording these signals with the standard "Franz" catheter [3] is that the used silver-silver chloride (Ag-AgCl) electrodes are not stable in the long term and thus not usable for implantable leads. The proven long-term stability of fractal coating with iridium (Ir) provides long-term stable leads [4,5] and allows the recording of intracardiac signals with low impedance, without rate-dependent damping, and with low polarization for measurements even directly after a stimulus, without any disturbing artifact [4].

The aim of our studies was to create an electrode system that is suitable for long-term recording of MAP and VER signals under different experimental and clinical conditions.

Materials and Methods

Experimental Protocols

MAP recordings: Simultaneous recordings of the MAP with Ag-AgCl and Ir-coated electrodes were studied in 20 mongrel dogs (18 ± 11 kg). Radiofrequency ablation of the AV node was carried out in 10 dogs. The Ag-AgCl catheter (EP Techn, USA) was placed directly next to the Ir-coated catheter (MAPCath, Biotronik, Germany). The stimulation was performed using the separate stimulation electrodes of the Ag-AgCl catheter. The right ventricular apical endocardial MAP signals were recorded during intrinsic rate and stimulation with 200 to 800 ms cycle lengths, and after administering i.v. boli of isoproterenol (2 μg/kg) and verapamil (0.2 mg/kg).

MAP and VER recordings: Effects of rate changes and antiarrhythmic drugs on the MAP and the VER were studied in 10 mongrel dogs (18 ± 3 kg, 2 – 5 years). Right ventricular epi- and endocardial MAP and VER leads were studied. Following high-frequency (HF) AV-node ablation, the effects of i.v. boli of 2 μg/kg isoproterenol and 0.5 mg/kg sotalol were investigated during VVI pacing at 80 – 180 beats/min. VER signals were recorded in a unipolar configuration, and MAP signals were recorded in a bipolar configuration of the fractal coated pacing leads (Synox 60 BP or TIR 60, Biotronik). Unipolar pacing for VER recording was carried out using an external pacemaker (EP 20, Biotronik) and the above mentioned leads. For reference recordings, MAP measurements were performed using an Ag-AgCl catheter (EP Technologies, USA).

Induced arrhythmias: Experimental study of the patho-mechanism of endothelin-1 (ET-1), an endogenous peptide with strong arrhythmogenic properties [6], was carried out to induce arrhythmias in 14 mongrel dogs (15 – 31 kg). Following HF AV-node ablation (AbControl, Biotronik), bipolar right ventricular pacing (70 beats/min) was performed. The ventricular refractory period and the inducibility of ventricular arrhythmias were determined by programmed electrical stimulation (300 ms basic stimulation with one and two extrastimuli). Femoral artery was canulated for invasive blood pressure monitoring. The left anterior descending (LAD) branch of the coronary artery was dissected free close to its origin and an electromagnetic flow probe (Statham SP 2201, Carolina Electronics, USA) of appropriate size was placed around the vessel. Right ventricular endocardial and left ventricular epicardial MAP signals were recorded by quadripolar endocardial Ag-AgCl catheters, as well as by bipolar or quadripolar fractal Ir-coated endocardial and bipolar epicardial leads (Synox, MulitCath 4F, AlCath S; all from Biotronik). A low dose (30 pmol/min) of intracoronary ET-1 was administered. The dose of ET-1 was increased to 60 pmol/min if spontaneous arrhythmias did not occur after 30 min. Four control dogs received an intracoronary saline infusion.

Clinical Application

To study the arrhythmia mechanism, MAP recording was carried out during an electrophysiologic study of a patient suffering from long QT syndrome. Following puncture of the right internal jugular vein, Ag-AgCl and fractal Ir-coated (Multicath 4F) catheters were used to record the right ventricular MAP signals. The same number of catheters was used as during a routine electrophysiologic study. The two catheters were placed in the apical, septal, lateral wall, and outflow tract positions in order to determine the MAP dispersion. After the routine programmed electrical stimulation had been completed, the MAP signals were simultaneously recorded from two sites in the right ventricle during spontaneous heart rate, pacing at 80, 100, 120 beats/min, and programmed stimulation.

MAP and VER Evaluation

Recordings were amplified with a DC-coupled isolation amplifier (with an adjustable amplification in the range from ± 5 to ± 250 mV), digitized (at a 500-Hz sampling rate and 12-bit resolution), and stored on a PC. Afterwards the standardized parameters for the MAP (MAP duration at 50 and 90 % repolarization time: MAPd50 and MAPd90, amplitude, cycle length, repolarization velocity) and the VER (duration and amplitude of R^-, R^+, and T^+ waves from surface ECG nomenclature; VER duration at 90 % repolarization time: VERd90) were evaluated using a semiautomatic MAP/VER evaluation program [2,4]. Correct triggering of the onset of each MAP and the calculation of the MAP duration were manually proved and corrected using the MAP evaluation program. The correlation of the MAP signals, recorded with both the Ag-AgCl and Ir-coated leads, was calculated at the MAPd90, MAPd50, and plateau amplitude.

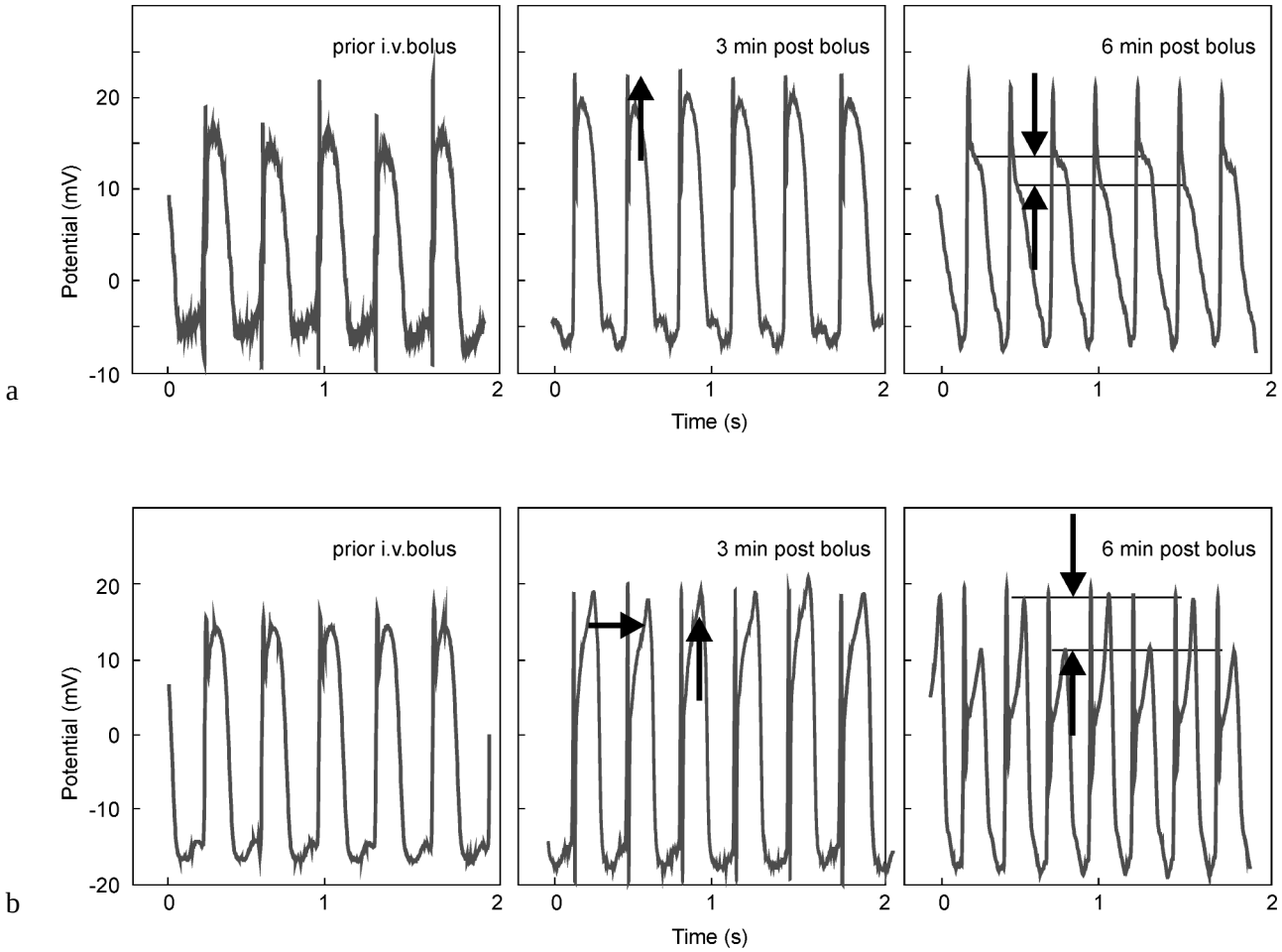

Figure 1. Monophasic action potential recorded with an Ag-AgCl electrode (panel a) and a fractal Ir coated electrode (panel b) following i.v. bolus of isoproterenol.

Statistical Analysis

Mean values and standard deviations were calculated for each parameter. Statistical significance was assessed at the 95 % confidence level by using variance analysis (ANOVA) followed by Bonferroni's t-test. Pearson's r-coefficient of correlation was calculated as well as the corresponding p-value for statistical significance of $|r| > 0$.

Results

Experimental Results

MAP recordings: The basic morphology of the MAP signals recorded with Ag-AgCl and Ir-coated leads were comparable but differed between individual dogs (Figure 1). The amplitudes of the MAP showed no statistical difference (Ag-AgCl: 15 ± 7 mV; Ir: 13 ± 8 mV). The MAP in the endocardial recording positions showed a stable amplitude up to 3 hours. Then a decrease of amplitude was observed due to micro-dislocation of the tip electrode because of the mechanical irritation of the beating heart. The MAP signals recorded in AV-ablated dogs were more stable due to the lower heart rate. The MAP duration shortened with higher heart rates. The MAPd50 and MAPd90 decrease, measured with Ag-AgCl and Ir-coated electrodes, showed a strong correlation (MAPd50: r = 0.97; MAPd90: r = 0.98).

Following an i.v. bolus of 2 mg/kg isoproterenol, the spontaneous rate increased (from 175 ± 18 to 245 ± 25 beats/min) in the dogs with an intact AV node. The MAP duration shortened (MAPd90: AgCl:

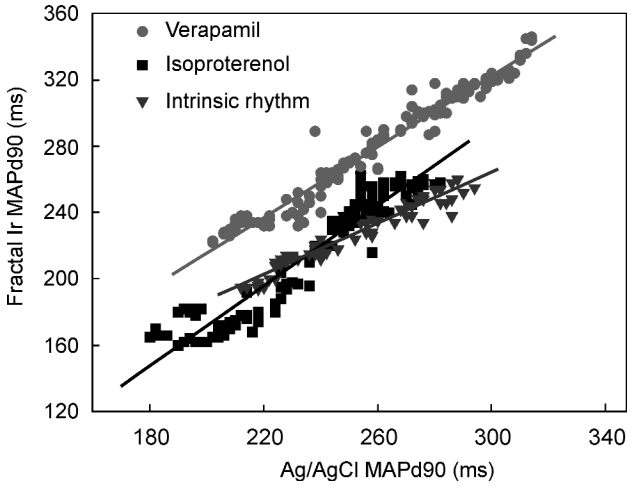

Figure 2. Correlation between monophasic action potential duration at 90 % repolarization time (MAPd90) recorded using Ag-AgCl and Ir catheters at different rates (intact AV node) and following bolus of isoproterenol and verapamil (ablated AV node, VVI pacing).

from 160 ± 11 to 148 ± 12 ms; Ir: from 158 ± 18 to 148 ± 15 ms) during stimulation with a 250-ms cycle length. The maximum of the plateau phase of the MAP signals recorded with an Ir catheter shifted (from 71 ± 3 to 102 ± 10 ms). These alterations were not observed in the recordings using the Ag-AgCl electrodes (Figure 1). Following the plateau shift, maximum beat-to-beat oscillations in amplitude appeared, which were more pronounced in the Ir recordings (AgCl: 10 %, Ir: 25 %). Immediately following administration of the bolus (Figure 1), an elevation of the plateau amplitude by up to 25 % was observed in all recordings. Early afterdepolarizations (EAD) occurred in five cases 2 – 4 min after the bolus. After 20 min the rate decreased to the former values, and the shortening of the MAP duration vanished. In the AV-ablated dogs, the ventricular rate increased from under 80 beats/min to over 104 ± 23 beats/min, limiting the recording at pacing rates below 100 beats/min. The maximum shortening was observed 2 – 3 min following administration of the bolus. During isoproterenol medication, the MAPd90 recorded with Ag-AgCl and Ir-coated leads also showed a strong correlation (Figure 2: intact AV node: r = 0.96; ablated AV node: r = 0.97).

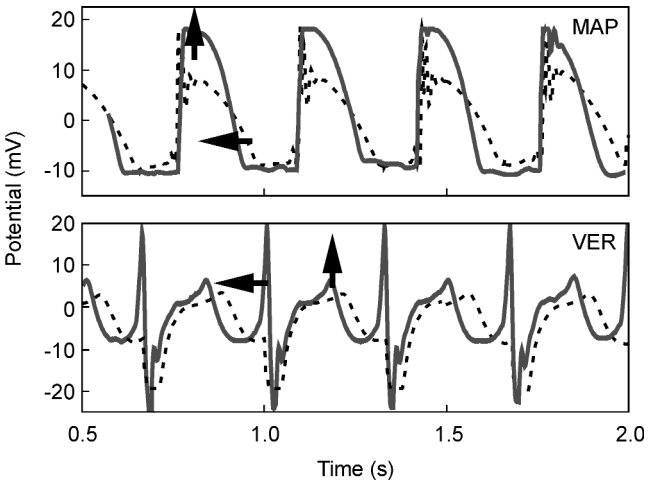

Figure 3. Effects of i.v. bolus of isoproterenol on monophasic action potential (MAP) and ventricular evoked response (VER). Curves were recorded before (dashed line) and 60s following the bolus (solid line).

An i.v. bolus of 0.2 mg/kg verapamil decreased the spontaneous rate (from 167 ± 11 to 104 ± 23 beats/min) and lengthened the MAPd90 (AgCl: from 225 ± 5 to 240 ± 13 ms; Ir: from 232 ± 10 to 246 ± 21 ms; p-values < 0.0001). A good correlation (r = 0.96) was observed between the MAPd90 of the Ag-AgCl and Ir-coated electrodes during treatment with verapamil (Figure 2). Consequently, during all measurements there was a strong correlation between the durations of the MAP recorded with the different types of electrodes used.

MAP and VER recordings: The basic MAP and VER morphologies were found to be different, but significant points of the signals showed good correlation. The first negative VER deflection (VER R^- amplitude) correlated with the peak maximum of the MAP; the first relative VER maximum (VER R^+ amplitude) correlated with the plateau maximum of the MAP. The MAP duration is represented by the maximal positive VER deflection (VER T^+ amplitude). The VERd90 was about 25 % longer than the MAPd90 and was approximately the sum of the MAPd90 and the local activation time. The MAP and VER recorded with the Ir-coated leads showed comparable amplitudes of 10 – 25 mV. The MAPd90 and VER T^+ duration decreased at the higher rates. The MAP amplitude did not change significantly, but the VER T^+ amplitude increased by 15 % when the pacing rate was changed from 80 to 180 beats/min. The MAP signals recorded with Ir-coated leads correlated with those recorded with the reference Ag-AgCl MAP catheter (MAPd90: r = 0.99; MAPd50: r = 0.97; amplitude: r = 0.91).

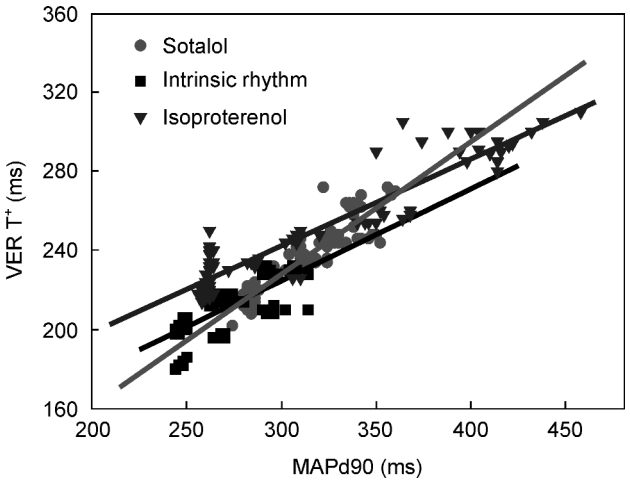

Figure 4. Correlation between monophasic action potential duration at 90 % repolarization time (MAPd90) and duration of the ventricular evoked response T+ wave (VER T+) at different rates (intact AV node) and following bolus of isoproterenol and sotalol (ablated AV node, VVI pacing).

MAP and VER signals were recorded simultaneously before, during, and following an i.v. bolus of isoproterenol (Figure 3). In the first 60 s following the bolus, the spontaneous ventricular rate rose to 104 ± 23 beats/min; this, in turn, limited the recording of the VER at lower rates immediately after the bolus. The MAP and VER amplitudes increased significantly, and the duration decreased at all fixed pacing rates. The morphological alterations of the signals were comparable. In the first minute, MAP and VER duration decreased by -15% and -11%, respectively. The MAP amplitudes increased by 30 %. The VER T+ amplitudes showed equivalent variations of 28 %. In addition, the MAP recordings in Figure 3 show that the plateau of the MAP after administration of isoproterenol was more pronounced, and the repolarization velocity, represented by a tangent in the late repolarization phase, increased. All parameters reached statistical significance of p-value < 0.001, compared with the values recorded before and 3 min following the bolus. After 15 min, no effects of the drug on MAP and VER were observed.

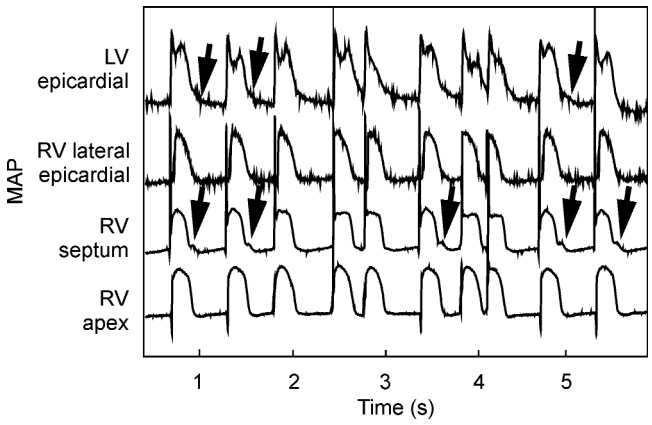

Figure 5. Early afterdepolarizations (indicated by arrows) induced by low dose intracoronary endothelin-1 infusion. Four-channel digital monophasic action patential (MAP) recording from left ventricle (LV) and right ventricle positions.

The effects of sotalol on the TAP were also demonstrated with simultaneous recordings of MAP and VER (Figure 4). After an i.v. bolus of 0.5 mg/kg sotalol, the MAPd90 and VER T+ duration increased significantly (p-value < 0.001) within the first 20 min. In strong correlation with the temporal variations of MAP and VER duration, the VER T+ amplitude decreased by – 15 % and reached its minimum 20 min after the start of medication. The MAP amplitude did not change significantly, but the repolarization velocity of the MAP slowed after sotalol therapy. About 60 min following the bolus, no effects of sotalol were observed. The variations in duration and amplitude of VER and MAP returned to the former values. In five out of ten cases, early afterdepolarizations (EADs) [5] were seen in the repolarization course of the MAP signals 15 to 25 min following the bolus. The MAP duration was lengthened by the distortions in the repolarization phase of the MAP. Following an EAD, MAP signals with shorter intervals were observed with 25 % shorter MAP duration. Onset and amplitude of the EADs were not stable. Early afterdepolarizations were primarily observed only at one MAP recording site and in epicardial positions in three of the five cases. In contrast to the MAP recordings, EADs could not be observed in any of the VER traces.

As is obvious from Figure 4, the VER T+ duration showed excellent correlation with the MAPd90 duration at different rates (r = 0.97) and following bolus of isoproterenol (r = 0.96) and sotalol (r = 0.96). No statistical difference was seen between the correlation coefficients of the recordings during different interventions. The MAPd90 and VER T+ duration decreased

at the higher rates showing an almost linear correlation to the heart rate (sotalol: r = 0.94, intrinsic rhythm: r = 0.96, isoproterenol: r = 0.96).
The correlation between the MAP duration and the VER amplitudes (MAPd90 vs. VER R^-: r = 0.91 with corresponding p-value < 0.0013; MAPd90 vs. VER T^+: r = 0.96 with corresponding p-value < 0.0018) demonstrates that the VER amplitude also reflects changes of the TAP. Sotalol and isoproterenol alter the repolarization velocity of the MAP. The correlation of this with the VER T^+ amplitude was calculated as r = 0.96 with corresponding p-value < 0.001.

Induced arrhythmias: In the AV-ablated dogs, ventricular arrhythmias developed in six cases after intracoronary administration of 30 pmol/min ET-1, and in eight cases following intracoronary infusion of 60 pmol/min ET-1. ET-1 administration led to the onset of premature ventricular contractions and short non-sustained salvos after 20 – 30 min of administration. Later on, episodes of non-sustained tachycardias (nsVT) often followed each other in an incessant way. Non-sustained salvos often showed polymorphism. Sustained ventricular tachycardias (sVT) were observed within 30 – 40 min. In 86 % of the cases, monomorphic and polymorphic ventricular tachycardias occurred alternately. Spontaneous sVTs developed in nine dogs. In the other five dogs, longer ventricular salvos occurred. Ventricular tachycardias spontaneously accelerated into ventricular fibrillation (VF) at termination in 12 (86 %) cases out of 14. No ventricular arrhythmias developed in the control group. Despite repeated programmed electrical stimulation, induced sVTs were observed only in two cases, and VF, in one case.
At the time of the appearance of premature beats, no signs of myocardial ischemia were observed on the ECG. Nevertheless coronary blood flow decreased moderately (21 ± 2 ml/min vs. 16 ± 2 ml/min, p-value < 0.01). ET-1 treatment resulted in a significant prolongation of QT time (325 ± 13 vs. 358 ± 14 ms, p-value < 0.01), endocar-dial MAPd90 (255 ± 9 vs. 290 ± 8 ms, p-value < 0.01), and epicardial MAPd90 (244 ± 10 vs. 292 ± 12 ms, p-value < 0.05). Ventricular effective refractory period, P-P interval and blood pressure did not change significantly.
In eight dogs (57 %), ET-1-induced EADs could be recorded using MAP electrodes (seven cases endocardial, four cases epicardial). Figure 5 shows EADs on the descending part of repolarization in the epicardial and endocardial MAP recordings. The mechanism of the couplet shown in the tracing seems to be based on EAD.

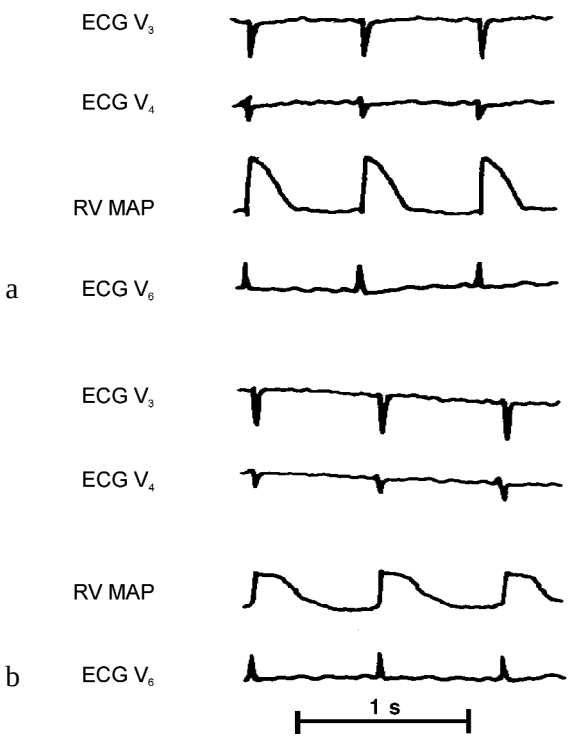

Figure 6. Increased dispersion (200 ms) of the right ventricular monophasic action potential (RV MAP) in a patient suffering from congenital (panel a) and acquired long QT syndrome (panel b)

Clinical Results
We made continuous MAP recordings during the electrophysiologic study of patients suffering from congenital or acquired long QT syndrome (Figure 6). A 40-year-old woman with rheumatic heart disease and chronic atrial fibrillation (AF) was admitted with congestive heart disease. The ECG showed AF with a ventricular rate of 100 – 120 beats/min. The QT-intervals were normal. A spontaneous VF episode was observed in the intensive care unit. Intravenous amiodarone was applied. 19 hours after amiodarone administration, recurring torsade de pointes (TdP) and VTs were observed. Some deteriorated into VF or flutter, requiring electrical cardioversion. At this

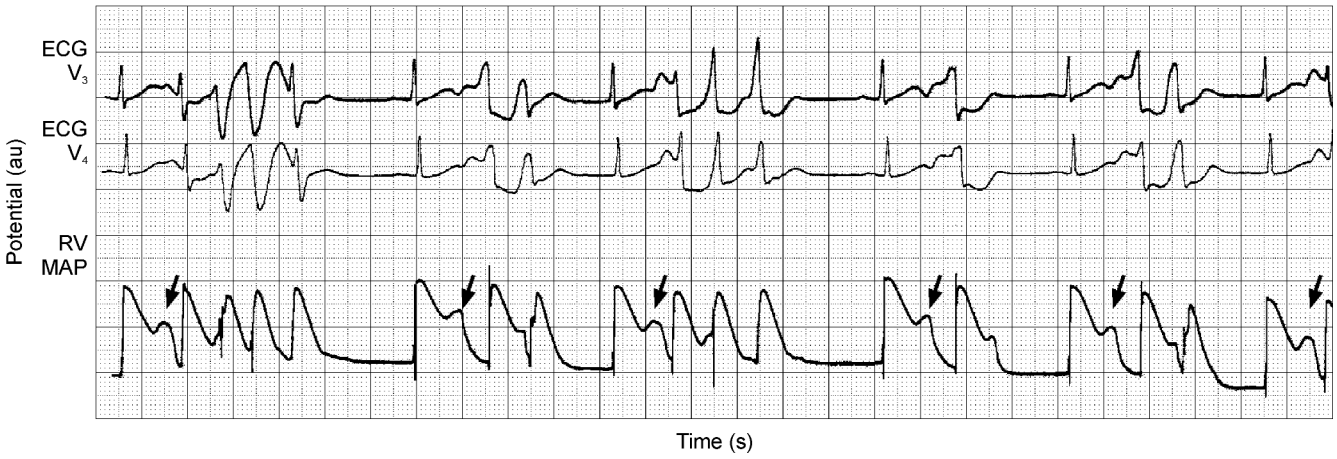

Figure 7. Surface ECG and right ventricular momophasic action potential (RV MAP) recorded 19 h after amiodarone proarrhythmia administration. Early afterdepolarization induced couplets and triplets are seen. au = arbitrary units.

time, the serum K^+ was 4.3 mmol/l. Intravenous Mg^{2+} was given, and a temporary atrial pacemaker lead was introduced. Pauses resulting from pacemaker malfunction caused recurrent TdP again. At this point, a fractal coated MAP electrode was positioned into the right ventricular apex for pacing and for recording of MAP signals. The right ventricular MAP revealed pause-related, high amplitude EADs (Figure 7). Both digoxin and amiodarone were discontinued. One year later, the patient is in sinus rhythm with brief episodes of asymptomatic non sVTs.

Discussion

Our in-vivo results showing the effects of pacing and antiarrhythmic drugs on MAP correlated well with the results of in-vitro experimental studies [7]. Higher rates shorten the duration of TAP and thus MAPd50 and MAPd90 by increasing the K^+ inward current [7]. An excellent correlation between MAP shortening recorded with Ag-AgCl and Ir-coated leads was found. VER signals also showed the same shortening at higher rates, indicating that these signals also reflect the described changes of the transmembrane ion currents.

Isoproterenol effects adrenergic receptors at the heart and increases Ca^{2+} inward current [8], resulting in the increase of the plateau amplitude of the TAP. Moreover, isoproterenol increases K^+ outward currents, thus shortening the repolarization and causing a shorter TAP duration [7,8]. In excellent accordance to theory, these alterations were observed in the MAP traces, indicating that this extracellular waveform reflects the effects of isoproterenol on the TAP.

The calcium channel blocker verapamil prolongs the duration of the TAP. The MAP recordings reflected the increase of the total refractory period with both types of leads.

The class III antiarrhythmic drug d,l-sotalol slows the K^+ outward current during late repolarization phase and therefore prolongs the duration of the TAP [9]. This increase of the total refractory period was reflected by MAP duration prolongation as well as by the lengthening of the VER T^+-wave. The local EADs observed in MAP recordings during sotalol therapy are already described in the literature [10]. In the global VER, morphological changes referring to the EADs were not documented [10], for VER reflects the TAP of a larger area of cells and the VER morphology is also effected by the excitation course.

The presented results show that Ag-AgCl and Ir-coated electrodes are suitable for acute MAP recording and reliably reflect the expected changes of the TAP under all investigated interventions [11]. However, only the Ir-coated electrodes can be used as chronically implantable leads. Using implantable MAP leads in combination with an implant with high-resolution telemetry of the intracardiac signals, monitoring and controlling of drug therapy with a higher time reso-

lution becomes available without the limitations of catheter examinations [12-14]. Depending on the aim of the investigation, either the local MAP or the global VER can be used as the diagnostic tool of choice.

Our in vivo results enlarge the scope of previous reports [6,15] by showing that low dose intracoronary administration of ET-1 causes spontaneous ventricular arrhythmias before signs of myocardial ischemia appear [16-21]. These arrhythmias result in VF and death in most of the animals, so ventricular arrhythmias caused by ET-1 could be the prototype of rhythm disturbances leading to sudden cardiac death. Permanent bradycardia promotes the development of sustained VTs. In our study, low dose intracoronary ET-1 infusion resulted in a significant prolongation of QT time and of the epi- and endocardial MAPd90. In response to intracoronary infusion of ET-1, EADs could be recorded in 50 % of the cases. The results appear to show that ET-1 has a direct arrhythmogenic effect that is based on prolonging the duration of the action potential and on the development of EADs. Our experimental setup can serve as a pathophysiologic model for inducing triggered activity VTs. This model is also suitable for antiarrhythmic drug testing.

We were the first to continuously record MAPs during routine electrophysiologic studies using fractal-coated electrodes. We documented the pathogenic role of EADs in amiodarone proarrhythmia using MAP recording. On the basis of our findings we can assume the role of triggered activity in the formation of amiodarone-induced ventricular arrhythmias [22].

In the future, MAP recording could be a method of great importance in the analysis of the patho-mechanism of atrial and ventricular arrhythmias, and in the evaluation of the effectiveness and possible proarrhythmic effects of medical treatment. Using implantable MAP leads in combination with an implant that offers high-resolution telemetry of the intracardiac signals, monitoring and controlling of drug therapy with a higher time resolution could become available.

Acknowledgement

This paper is a short version of the work that was awarded the International Virchow Prize in 1999. It is dedicated to the memory of Professor Dr. Max Schaldach.

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