Monitoring Cellular Electrical Activity - Monophasic Action Potential and Ventricular Evoked Response

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Summary

Recordings of the transmembrane action potential (TAP) of cardiac cells are limited to in-vitro experiments. Summed potentials of the TAP like the monophasic action potential (MAP) and the ventricular evoked response (VER) reflect the effects of antiarrhythmic drugs on the TAP and my be measured long term stable with implantable fractally coated leads now. This article demonstrates the alterations of the TAP detected by analyzing using MAP and VER recorded in AV ablated dogs. Rate dependent shortening of MAP and VER were observed and showed a almost a linear correlation between MAP and VER duration and heart rate. The T^+-interval lay between MAPd50 and MAPd90. VER duration was 23-28% longer than the MAPd90 and was approximately the sum of MAPd90 and the activation time. Infusion of 2 μg/kg isoproterenol increased MAP amplitude up to 30 % corresponding with a shortening of the duration by -15 %. Following i.v. bolus of 0.5 mg/kg sotalol MAP amplitudes did not alter but a lengthening of MAPd90 by 18 % was observed. VER was duration lengthen strongly correlated with MAP (r=0.97) and in contrast to the MAP amplitude the VER amplitude decreased. Both signals showed a strong correlation during all investigated interventions (MAPd90-VERd90: r=0.96 with p<0.001; MAPd90-T^+ amplitude: r=0.94 with p<0.0018). This indicates that MAP and VER reflect the effects of these drugs on the transmembrane ion currents of cardiac cells. The arrangement of the MAP electrodes with small distance to each other implies that the MAP measures local repolarization with a high spatial resolution. The VER sums up the TAP over a larger area of cells and reflects the global repolarization of the heart. Depending on the aim of the investigations the change of the TAP can be monitored either with the global VER or the local MAP. Using implantable leads together with a pacemaker with high-resolution-IEGM-telemetry the therapeutic effects of cardiac drugs on the TAP are observable without catheter examinations.

Key Words

Monophasic action potential, ventricular evoked response, sotalol, isoproterenol, drug monitoring

Introduction

The transmembrane action potential (TAP) of the myocytes reflects the strength and duration of the ion currents crossing the cell membrane[1]. They adjust on a cellular basis the velocity of the excitation wave and the contractility of the cells by the electromechanical coupling process[1]. Thus, the morphology of the cardiac action potential includes all information on the electrophysiological status of the heart. Since TAP recordings require the impalement of an individual cardiac cell by a microglass electrode, they are limited to in-vitro preparations[2]. The monophasic action potential (MAP) and the ventricular evoked response (VER) are recorded on extracellular side that reproduce the time course of the TAP[3,4]. MAP and VER can be recorded from the endo- or epicardium in vivo from the beating heart. This technique is suitable for studying characteristics of the myocardial repolariza-

tion in the clinical setting[5]. The MAP is recorded with a bipolar electrode configuration with small distance between tip and ring electrodes to each other (Figure 1)[2]. The MAP represents a summed signal of the TAP of a small volume of cells surrounding the tip and includes information of the local repolarization course[5]. The unipolar VER recorded between the tip and an indifferent electrode outside the heart characterizes not only the TAP of almost the whole ventricular muscle but also the excitation course in the ventricle (Figure 1)[6,7].

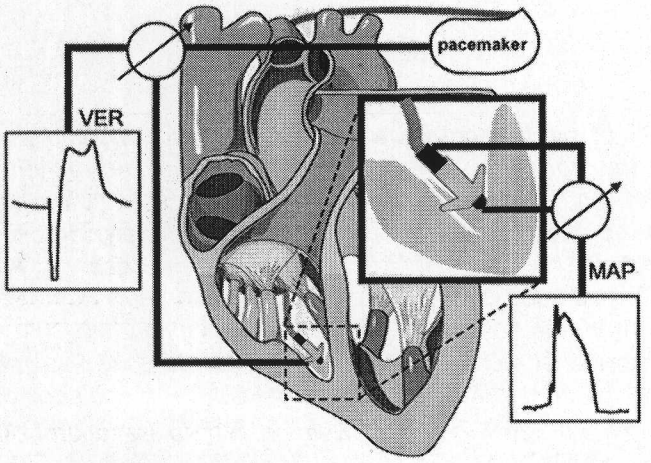

Figure 1. *Bipolar measurement configuration provides MAP with high spatial resolution. Unipolar configuration leads to VER which represents the global repolarization of the heart*

The contact technique to measure the monophasic action potential with Ag-AgCl chloride electrodes has been in clinical use for several years[2,5]. But it is limited to short term recordings using catheters during electrophysiological investigations. This condition did not allow monitoring the effects of antiarrhythmic drugs on the TAP using MAP recordings on a long-term basis[10]. Controlling of antiarrhythmic drug therapy using intracardial signals require frequent recordings without the inconvenience of catheter examinations. Fractally coated leads allow to record the intracardiac signals with low impedance, without frequency-dependent damping, and with low polarization to measure even directly after a stimulus without disturbing artifact[8,9].

This article discusses the use of the MAP and VER for monitoring the effects antiarrhythmic therapy on the TAP.

Methods

10 mongrel dogs (18±3 kg, 2-5 years) were anesthetized with pentobarbital (30 mg/kg i.v.). MAP and VER leads were placed epi- and endocardially in the right ventricle and epicardially at the left respectively. The measurements were only performed if a constant baseline, indicating a stable position of the electrodes, was achieved. After HF ablation of the AV-node the effects of i.v. boli of 2 µg/kg isoproterenol and 0.5 mg/kg sotalol were investigated during VVI stimulation with 80-180 ppm. The VER lead was taken for the stimulation using an external pacemaker (EP 20, BIOTRONIK). MAP were recorded with bipolar active and passive fixable fractally coated pacing leads (TIR and Synox 60 BP, BIOTRONIK, Germany). VER were measured using a standard unipolar pacing lead (TIR 60, BIOTRONIK). For reference recordings MAP measurements were performed using an Ag-AgCl catheter (EP technol., U.S.A.). MAP and VER were DC-coupled amplified (adjustable amplification in the range ±5 to ±250 mV), digitized (500 Hz sampling frequency, 12 bit resolution), and stored on PC. The standardized parameters of MAP (MAPd90, MAPd50, amplitude, cycle length, repolarization velocity) and VER (time and amplitude of R^-, R^+, T^+ wave, VERd90) were evaluated using a semiautomatic MAP/VER evaluation program afterwards (Figure 2)[6,9].

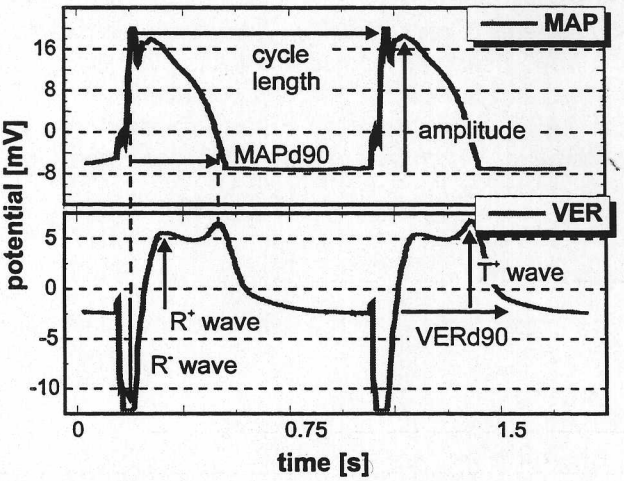

Figure 2*: MAP and VER parameters*[6,10]

Results

The basic morphology of the MAP is comparable to the TAP. The MAP recorded with fractally coated leads were correlated with those recorded with the

reference Ag-AgCl MAP catheter (correlation MAPd90: r=0.99; MAPd50: r=0.97; amplitude: r=0.91). The basic morphologies of MAP and VER differ, but significant points of both signals are correlated. The first negative deflection of the VER was correlated with the peak maximum of the MAP, the VER R^+ wave as the first relative maximum correlates with the plateau maximum of the MAP. The MAP duration is represented by the maximal positive deflection (T^+ wave) of the VER. The VERd90 was 23-28% longer than MAPd90 and was approximately the sum of MAPd90 and the activation time. The unipolar recorded VER reflects the TAP of larger area of cells and the VER morphology is also effected by the excitation course. The MAP and VER recorded with the fractally coated leads showed comparable amplitudes of 10-25 mV (Figure 2). With higher rates the MAP and VER duration decreased showing almost a linear correlation between rate and duration (r=0.94). The MAP amplitude did not change significantly but the VER amplitude increased by 15% by changing the stimulation rate from 80 to 180 ppm.

MAP and VER were recorded simultaneously before, during, and following i.v. bolus of isoproterenol (Figure 3). The MAP and VER amplitude increased and the duration shortened at all fixed stimulation rates. In the first 60 s following the bolus the spontaneous rate in ventricle rose to 104±23 bpm limiting the recording of the evoked response at lower rates. The morphological alterations of both signals were comparable indicating that both signals reflect the effects of the drugs on the transmembrane potential.

The time course of the MAP and VER duration and amplitudes are presented in Table 1. In the first two minutes MAP and VER duration decreased by -15 % and -11 % respectively. The MAP amplitudes increased by 30 %. The VER amplitudes showed equivalent variations. In addition the MAP recordings in Figure 3 show, that the plateau of the MAP after isoproterenol medication was more pronounced and the repolarization velocity increased. All parameters reached statistical significance of $p<0.001$ in comparison of the values recorded before and 3 min following the bolus. After 15 min the former values were reached again and no effects of the drug on MAP and VER were observable any more.

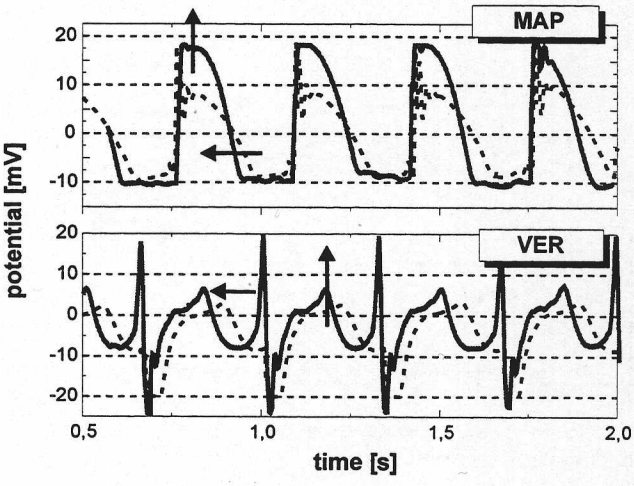

***Figure 3**: Effects of i.v. bolus of isoproterenol on MAP and VER*

The effects of sotalol on the TAP were also demonstrated with simultaneous recordings of MAP and VER. In Figure 4 the time course of MAP and VER duration and amplitude is shown at a stimulation rate of 100 ppm. After i.v. bolus of 0.5 mg/kg sotalol the MAPd90 and VER-T^+ duration increased significantly

time after bolus of isoproterenol [min]	MAPd90 [ms]	VER T^+ [ms]	MAP amplitude [mV]	VER amplitude [mV]
0	205±10	195±6	20.5±1.4	24.3±2.3
2	175±7	175±12	22.1±0.9	29.5±4.1
3	169±6	170±17	29.2±1.8	30.3±5.6
5	185±6	180±10	27.6±1.0	30.2±6.7
10	200±12	190±10	20.0±3.4	26.8±5.6
15	205±8	190±8	21.3±2.2	23.9±3.4

***Table 1**. Time course of MAP and VER parameters at 150 ppm stimulation rate following i.v. bolus of isoproterenol*

(p<0.001) within the first 20 min. In strong correlation to the temporal variations of MAP and VER duration the amplitude of the VER decreased by -15 % and reached the minimum 20 min after the start of medication, too. The MAP amplitude did not changed significantly but the repolarization velocity of the MAP slowed after sotalol therapy. About 60 min following the bolus no effects of sotalol were observed any more. The variations in duration and amplitude of VER and MAP returned to the former values.

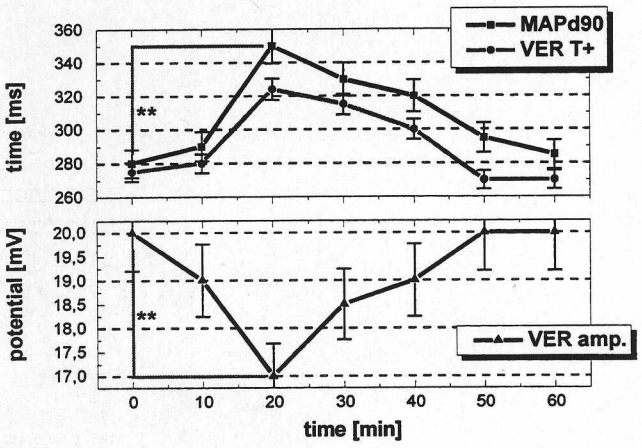

Figure 4. Time course of MAP and VER parameters following i.v. bolus of sotalol

In 5 of 10 cases early after depolarizations (EAD)[10] were seen in the repolarization course 15 to 25 min following the bolus (Figure 5). The MAP duration was lengthened by the distortions in the repolarization phase of the MAP. Following the EAD MAP with shorter R-R intervals were observed with much smaller MAP duration (-25%). Onset and amplitude of the EAD were not stable as depicted in Figure 5.

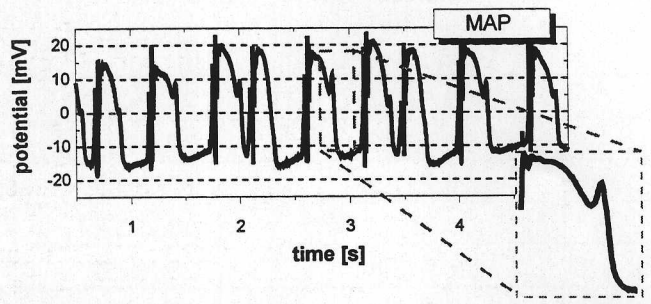

Figure 5. Early depolarizations recorded in the MAP following i.v. bolus of sotalol

EAD were observed mostly only at one MAP recording site and in 3 of the 5 cases in epicardial positions. This indicates that the EAD is a local phenomenon.

In contrast to the MAP recordings, in no VER trace, which reflects the global repolarization course, comparable morphological alterations were observed during the occurrence of the early after depolarizations. This limits the use of the global VER for detecting this local arrhythmogenic process.

In Figure 6 the correlation of the MAP and VER duration is depicted. The duration of the VER T^+-wave showed excellent correlation with the MAP duration at different rates (r=0.97) and following bolus of isoproterenol (r=0.96) and sotalol (r=0.96) (Figure 6). No statistical difference was seen between the correlation coefficients of the recordings during different interventions.

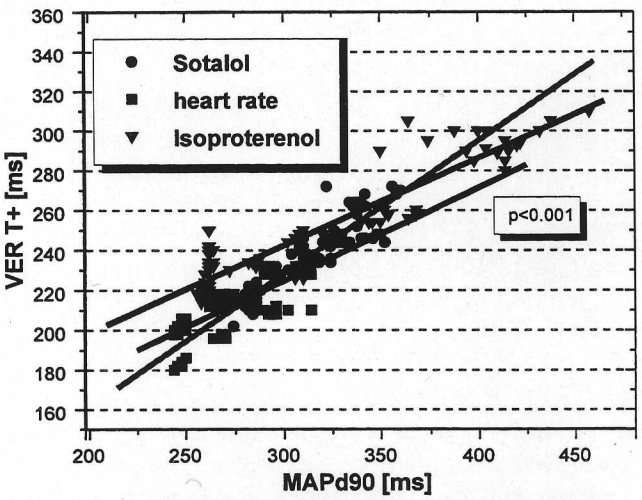

Figure 6. Correlation between MAP and VER duration at different rate and following bolus of isoproterenol and sotalol

The correlation between the MAP duration and the amplitude of the VER (MAPd90-R^-: r=0.91 with p<0.0013; MAPd90-T^+: r=0.96 with p<0.0018) demonstrates that the VER amplitude reflects also changes of the TAP. Sotalol and isoproterenol alter the repolarization velocity of the MAP. The correlation of this with the T^+ wave amplitude of the VER was calculated by r=0.96 with p<0.001.

Discussion

The effects of stimulation and antiarrhythmic drugs on MAP were the same as investigated in in-vitro single

cell preparations and reported in literature[1]. Higher rates increase the K^+ inward current effecting shorter duration of TAP and thus, MAPd90[1,4,11]. The same shortening of signal duration with higher rates was observed in the VER recordings indicating that these signals reflect also the described changes of the transmembrane ion currents.

Isoproterenol effects adrenergic receptors at the heart and increases Ca^{2+} inward current [12]. Thus, isoproterenol increases the plateau amplitude of the TAP. Increased K^+ outward currents shortened the repolarization onset effecting a shorter TAP duration[1,12]. These alterations were observed in excellent accordance in the MAP traces indicating that these extracellular waveform reflects the effects of isoproterenol on the TAP. The VER altered also in a strong morphological and temporal correlation to the MAP (r=0.96).

The β-blocker sotalol slows the K^+ outward current (I_K) during late repolarization phase and therefore prolongs the duration of the TAP[13,14]. Thus, atrial arrhythmia carried by re-entry mechanisms are avoided[14]. This increase of the total refractory period is reflected by the MAP duration[4] as well as by the duration of the VER T^+ wave. The MAP amplitudes altered not following the bolus. The observed early afterdepolarizations during sotalol therapy are already described in literature[16]. EAD were seen always as a local phenomenon in our experiments because the EAD were detected only in one trace during the multisite recordings. In the global VER morphological changes were not documented indicating that the VER is limited in detecting this arrhythmogenic phenomenon[16].

In contrast to the MAP the VER recordings showed significant changes of amplitude at different rates and following bolus of sotalol. It is assumed by the authors that the VER is proportional to the first deviation in time of the TAP. This hypothesis is supported by the results that the slowed repolarization velocity effected by the sotalol reduces the VER T^+ amplitudes while the higher repolarization velocity immediately after isoproterenol medication effects higher amplitudes respectively. This explains also the correlation between MAP duration and amplitude of the T^+ wave of the VER, since in our experimental settings the changes of MAP duration was always correlated with a change of the repolarization velocity.

The studies demonstrate that MAP and VER reflect the expected changes of the TAP under all investigated interventions. The local setup of the electrodes with a small distance to each other during MAP recordings implies that only a local area of the cardiac muscle can be observed and thus, the spatial resolution is high. This is important to observe local phenomena like the EAD[9]. The VER reflects a larger area of the ventricle and therefore the spatial resolution is low. The advantage of the VER is that over all changes of the ventricular muscle is represented by only one signal. Thus, for the clinical monitoring e.g. of heart rejection this global signal shall be used[17]. Depending on the aim of the investigation either the local MAP or the global VER has to be used as the diagnostic tool of choice.

Conclusions

MAP and VER reflect reliably the effects of isoproterenol and sotalol on the transmembrane potential. The signals are suitable to control the cellular electrical activity of cardiac cells. Using implantable leads, controlling of drug therapy with a higher time resolution is available without the restrictions of catheter examinations.

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