Monitoring of Antiarrhythmic Drugs with the Monophasic Action Potential and the Ventricular Evoked Response

B. MERKELY, L. GELLÉR, A. JUKAS-NAGY
Department of Cardiovascular Surgery, Semmelweis Medical University, Budapest, Hungary

V. LANG, J.P. STRÖBEL, A. BOLZ, M. SCHALDACH
Department of Biomedical Engineering, Friedrich-Alexander-University, Erlangen, Germany

Summary

Intracardial electrocardiograms (IECG) are a standard tool for investigating the conduction system of the heart and its pathological changes during electrophysiological investigations. But using new electrode materials like fractally coated Iridium the low-frequency components of the IECG are also available with implantable leads. Alterations of the ion currents across the cardiac cell membrane are observable using the bipolar measured monophasic action potential (MAP) and the unipolar recorded ventricular evoked response (VER). This article demonstrates the frequency effects and the influence of antiarrhythmic drugs on both signals simultaneously recorded in dog. At higher stimulation rates MAP and VER shortened (60 ppm: MAPd90: 285±19 ms, 180 ppm: MAPd90: 202±16 ms). The T^+-duration lied between MAPd50 and MAPd90. VER duration was 23-28% longer. The effects of 2 mg/kg isoproterenol to the intrinsic rhythm and MAP duration of mongrel dogs were the same as reported in literature (MAPd90-shortening: 175±7 to 157±11 ms, MAPd50: 160±9 to 110±23 ms). The VER-morphology altered comparable (180 ppm: VER-T^+: 180±8 to 170±14 ms). Following i.v. bolus of 0.5 mg/kg sotalol in MAP and VER equivalent results were also achieved. Both signals show a strong correlation (MAPd90-VERd90: $p<0.0001$; MAPd90-T^+ amplitude: $p<0.0018$) indicating that the MAP and VER reflects the effects of these drugs on the transmembrane ion-currents of cardiac cells equivalently. The arrangement of the MAP electrodes with small distance to each other implies that the MAP is a local signal with a high spatial resolution. The VER as a unipolar recorded signal sums the action potential over a bigger area of cells. Lead with Ir-coated electrodes allows to record both signal with the same lead and therefore depending on aim of the investigations the change of the transmembrane ion currents can be monitored either with the global VER or the local MAP. Using these materials for implantable leads together with a pacemaker with high-resolution-IECG-telemetry the therapeutic effects of cardiac drugs are observable without catheter examinations. Thus, monitoring of the effects of antiarrhythmic drugs has been made available using methods known from invasive catheter procedures with a higher time-resolution for optimizing the specific drug therapy for each patient.

Key Words

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

Introduction

The strength and duration of the transmembrane ion currents adjust on cellular basis the velocity of the excitation wave and the contractility of each cell by the electromechanical coupling process. The cellular action potential (CAP) reflects the transmembrane ion currents[1]. Therefore, the morphology of the cardiac action potential includes all information about the myocardial status. The CAP controls the excitation velocity in the cardiac conduction system and muscle fibers, the contractiliy and adjusts preload, inotropy, dromotropy and chronotropy[2]. Sensors measuring the electrical properties of the cardiac cells which do not influence this complex system are a perfect tool to monitor the activity of the heart, diagnose pathological changes and control therapeutic interventions[3,4].

For monitoring the functionality of the heart the recording of the surface electrocardiogram (ECG) was

developed 1903 by Einthoven[5] and is now a diagnostic standard tool. But the limitation of the surface ECG is that only the representation of the electrical vectorfield of the heart which is based mainly on the leftventricular muscle is measured. Therefore only few or no information about the properties of the atrial refractory period or conduction fibers like HIS-bundles are achievable. For such investigations the local electrical field has to be analyzed and therefore intracardial measurements (IECG) are indispensable.

Implantable sensors for intracardial measurements have to fulfill several requirements. In a wide frequency range between 0 and 1 kHz the cardiac signals must be measured with small impedance and without frequency-dependent damping[2,4,6]. Low-polarisability is also required to measure directly after a stimulus without disturbing artifact[6]. The electrode material has to be biocompatible with an excellent long-term stability[7].

The investigation of local electrical properties during electrophysiological investigations is a standard procedure during diagnosis of cardiac rhythm disorders for years[5]. But the available electrodes analyze only the frequency range over 5 Hz due to the limited electrical properties of the electrode-tissue interface[6]. The development of the contact electrode technique with the Ag/AgCl electrode allows to measure the low-frequency part of the cellular action potential and the analysis of the action potential for clinical usage has been made available[3]. The monophasic action potential (MAP) is a summed signal of the cellular action potential (CAP) as widely investigated and reflects the strength and duration of the transmembrane currents of the cells directly under the different electrode[2]. Therefore every change of the CAP due to arrhythmias, neurohumoral influences, and cardiac drugs are reflected in morphological changes of the MAP. The MAP allows for the first time the monitoring of the effects of antiarrhythmic drugs on the cellular ion currents in man[3]. The ventricular evoked response (VER) represents also a sum signal of the cellular action potential. But due to the unipolar measuring of the VER between electrode tip and indifferent electrode outside of the heart it characterizes the sum signal of the CAP over a wide range of the ventricle instead of a small area as MAP measurements and reflects the velocity of the excitation wave (Figure 1).

Registration of MAP's and VER's implies non-polarisable leads with a wide frequency response. Ag/AgCl electrodes fulfill these electrical requirements but the stability of the Ag/AgCl electrodes allows only temporary measurements during electrophysiological investigations. Fractally coated leads fulfill also the electrical requirements for measuring MAP, but their also proofed long-term-stability allows implantable MAP/VER leads[6,3].

This article shows the correlation of the MAP and the VER simultaneously recorded using Ag/AgCl and fractally coated leads during overstimulation and therapeutic interventions using antiarrhythmic drugs.

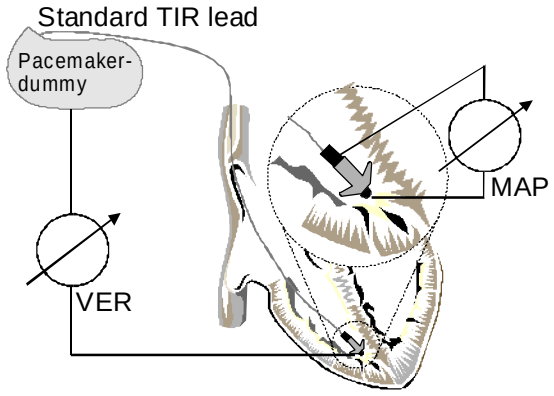

Figure 1. *Experimental onset for measurement of the bipolar MAP and the unipolar VER.*

Methods

The endocardial MAP was recorded with a Ag/AgCl-catheter (EP Technologies, USA) and with a bipolar fractally coated pacing lead (TIR 60 BP, BIOTRONIK, Germany). The VER was measured using a standard unipolar pacing lead with fractal coating (TIR 60, BIOTRONIK). The MAP and VER were measured using an isolation amplifier with adjustable amplification (Range ±5 to ±250 mV), digitized (500 Hz sampling frequency, 12 bit resolution) and stored on PC. The standardized parameters of MAP and VER were then evaluated off-line using a semi-automatic MAP/VER evaluation program afterwards (Figure 2)[2,8].

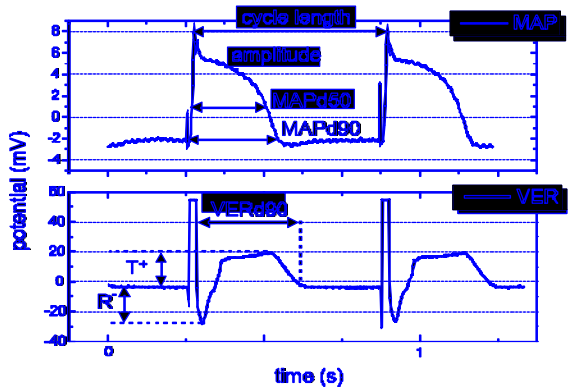

Figure 2. *MAP and VER parameters .*

The measurements were only performed if a constant baseline, indicating a stable position, was achieved.

Seven mongrel dogs were anesthetized with pentobarbital (30 mg/kg i.v.). Two MAP-catheters and one VER-lead were placed in the right ventricle at the apex and the anterior wall. The MAPs were recorded bipolary using the first ring of the catheter as indifferent electrode. The VER were recorded using the electrode tip as different and a pacemaker dummy as the indifferent electrode positioned at a classical pacemaker implantation position at the right side of the chest. The effects of i.v. boli of 2 µg/kg isoproterenol, 1 mg/kg sotalol were investigated during intrinsic rhythm and during a stimulation protocol with 10 consecutive beats with 250 and 300 ms cycle length. The AV-node of 3 dogs was ablated using a high frequency ablation system (AbControl, BIOTRONIK). Afterwards the effects of isoproterenol and sotalol on these dogs were investigated during stimulation with 60-180 ppm. The VER lead was taken for the stimulation using an external pacemaker (EP 20, BIOTRONIK).

Results

The VER was only measurable using the Ir-coated electrodes, because the post-stimulus signal of the Ag/AgCl electrodes shows an polarisation artifact disturbing the VER signal significantly. The amplitudes of MAP recorded with both electrode types depend on the recording position and were in ventricle between 10-30 mV and in atrium 5-12 mV respectively. The VER amplitudes were insignificantly higher (15-40 mV). The signal-to-noise ratio was -23 dB in all measurements. At a stable base line the amplitudes of MAP decreased with time and had to be repositioned. This is effected by the mechanical dislocation of the catheter tip due to the heart beat. The stability of MAPs recorded in dogs with intrinsic rhythm of 200 bpm was significantly lower than in AV-node-ablated dogs (ventricular rhythm: 50 bpm). The VER amplitudes remain constant and therefore their amplitudes were analyzed as well.

1. Effects of Stimulation

During stimulation with 60-180 ppm the MAP- and VER-duration showed a shortening with higher rates in the AV-ablated dogs (Table 1). The T^+-duration of the VER ranged between MAPd50 and MAPd90 and showed comparable shortening with higher rates

	60 ppm	80 ppm	100 ppm	120 ppm	150 ppm	180 ppm
MAPd50 [ms]	245±11	245±10	226±8	208±13	195±15	167±8
MAPd90 [ms]	285±19	283±11	267±15	247±10	227±9	202±16
T^+ [ms]	268±12	264±17	253±14	241±22	217±18	185±11
VERd90 [ms]	365±21	352±16	332±19	310±19	278±17	265±16

Table 1. *Duration of MAP and VER during stimulation at several rates*

	60 ppm	80 ppm	100 ppm	120 ppm	150 ppm	180 ppm
base-R^- [mV]	17.0±1.3	18.1±2.1	17.7±2.3	18.1±1.8	16.7±2.3	16.1±1.9
base-T^+ [mV]	17.1±1.2	17.5±1.5	18.5±1.9	19.7±1.7	20.0±2.1	22.0±1.9
R^--T^+ [mV]	29.4±1.0	30.8±1.4	32.7±1.2	33.1±0.9	34.0±2.0	36.7±2.3

***Table** 2. Amplitude of VER during stimulation at several rates*

(Table 1). The VER duration (VERd90) is 23-28% longer than the MAPd90. The amplitude of R^--wave did not change significantly except at the highest rates. The T^+-wave and the difference T^+-R^- increases with higher rate significantly (Table 2).

The shortening of the MAP and the VER reflects the shortening of the cellular action potential due to the faster turn-over of the ion-currents especially these of the K^+-channels at higher rates[1]. The VER duration is longer than the MAP duration, because it reflects as a unipolar measurement setup the duration of the CAP and the delay due to the excitation velocity along the ventricle.

2. Effects of Isoproterenol

After i.v. bolus of 2 µg/kg isoproterenol the intrinsic rate of the dogs rose from 170±14 bpm to 225±9 bpm within 4 min to return to original rate after 12 min. During intrinsic rhythm the MAP duration shortened by 35±14 ms within the first minutes. During stimulation protocol with 250 ms cycle length the MAP duration shortened (MAPd90: 175±7 to 157±11 ms, MAPd50: 160±9 to 110±23 ms). The maximal reduction was seen after 8-15 min. Following the bolus of isoproterenol the repolarisation phase of the MAP's changed significantly. The MAP recorded with Ir-coated lead showed a shift in the plateau-maximum 2-4 min after the bolus (71±3 ms to 102±10 ms) in 6 of 7 cases. In all cases beat-to-beat-oscillations of the plateau amplitude (AgAgCl: 10%, Ir: 30 %) were seen 4-7 min following the bolus. The oscillations of plateau phase is a secondary effect of the extremely high increased K^+ outward current which influences the Ca^{2+} current during plateau phase. These oscillations were seen before appearance of extrasystoles in single cell preparations[9] and during these experiments. Before the oscillations the plateau-maximum shifted to the later repolarisation phase indicating a prolonged Ca^{2+} inward current and/or a delay of the K^+ current. Secondary the Ca^{2+} overload produces the oscillations and starts the arrhythmogenic extrasystoles in the repolarisation phase.

The effects of isoproterenol on VER were investigated with AV-node ablated dogs at different stimulation rates. To compare the results with MAP both signals were recorded simultaneously (Figure 3).

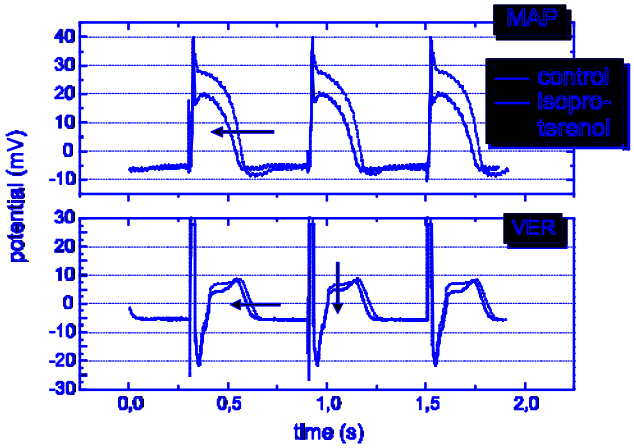

Figure 3. *Effects of isoproterenol on MAP and VER.*

The shortening of the intracardial signals seen during intrinsic rhythm was also observed after AV-node ablation in MAP and VER (60 ppm: MAPd90: 250±11 to 220±9 ms, VER-T^+: 249±8 to 190±13 ms; 180 ppm: MAPd90: 204±13 to 169±8 ms, VER-T^+: 180±8 to 170±14 ms). During shortening of the MAP and the VER the T^+-amplitude increased (60 ppm: 22±3.2 to 27±4.1 mV, 180 ppm: 24±2.2 to 30±2.3 mV). Following the isoproterenol bolus the R^+-amplitude decreased significantly by 2.2±0.4 mV. 18-21 min after the bolus the MAP duration returns to the former values but the reduction of MAP amplitude (Figure 3) did not disappear. Therefore, this might be an effect of isoproterenol or due to the mechanical instability of the MAP electrodes of the Ag/AgCl-catheter. The duration and amplitudes of the VER returned to former values after 10-15 min. The reversible amplitude changes of the VER R^+- and T^+-wave and its ratio following isoproterenol are much higher than the amplitude changes during overstimulation (Table 2). Therefore amplitude and morphology of the VER are parameters for drug monitoring as well as the duration of T^+-wave or the VERd90.

3. Effects of sotalol

The effects of sotalol, which is used for termination of supraventricular arrhythmia, were demonstrated with simultaneous recordings of MAP and VER. After i.v. bolus of 0.5 mg/kg sotalol the MAPd90 increased (60 ppm: MAPd90: 280±15 to 350±29 ms) within 25 min. The MAP recorded with Ag/AgCl and Ir-coated

electrodes show an excellent correlation during the sotalol experiments (Figure 4).

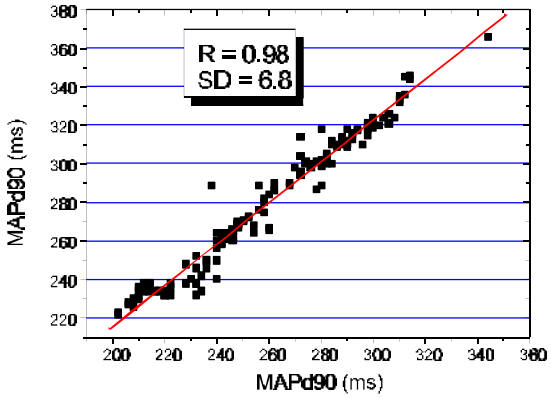

Figure 4. *Correlation between MAP duration recorded with Ag/AgCl (x-axis) and Ir-coated (y-axis) electrodes before, during, and after sotalol bolus .*

The T^+-wave showed a comparable increase while the T^+-amplitude decreased significantly (60 ppm: 20±2.0 to 17±4.1 mV). This alterations were maximized after 8-15 min and reversed to original values 60 min afterwards. The K^+ inward current (I_K) during late repolarisation phase is slowed by the ß-blocker sotalol and therefore the duration of the CAP prolonged, which is reflected by the MAP and VER [11,12]. The reversible amplitude changes following sotalol bolus point to the opposite direction compared to during increase of the stimulation rate (Table 2). This indicates that the amplitude of the VER is a more significant sensor for the effects of sotalol than the duration because the VER length is also influenced by the heart rate (Table 1).

4. Correlation between MAP and VER

The VER duration correlate well with these of MAP signals (Figure 5). Due to the unipolar recording method the VER duration is 23-28 % longer than the MAP duration because the VER reflects the CAP of a larger area of cells and the duration is then also influenced by the excitation velocity. The change of duration of the CAP is visible in both signals.

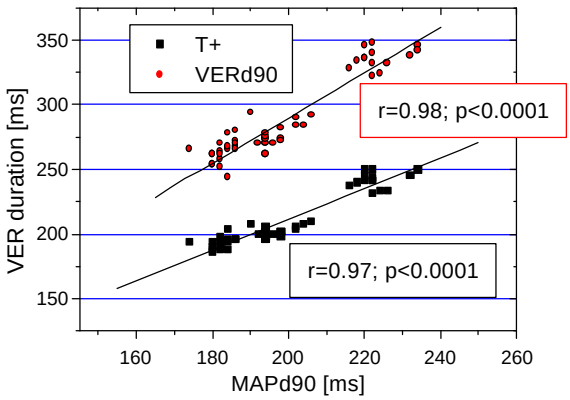

Figure 5. *Correlation between MAP duration and VER duration before, during, and after sotalol bolus.*

The strong correlation between the MAP duration and the amplitude of the VER (MAPd90-R^-: $p<0.0013$; MAPd90-T^+: $p<0.0018$) demonstrates that not only the duration but also the morphology has to be taken into account for diagnostic use.

Discussion

The effects of stimulation and antiarrhythmic drugs on MAP were the same as investigated at single cell preparations. After the bolus of isoproterenol the increase of intrinsic rate and shortening of the MAP duration was seen as described in literature [6]. The results achieved following the bolus of sotalol were also in excellent accordance to the literature[11,12]. Sotalol lengthens the CAP which is effected by the slower opening of the K^+ outward currents. By lengthening the VER/MAP and thus the effective refractory period the overall non-excitable regions of the cardiac muscle increase and arrhythmias underlying re-entry mechanisms and dispersions are terminated[2,10,11]. During all measurements a strong correlation between the MAP duration and the VER duration was observed. The analogous changes of both signals after the boli of sotalol and isoproterenol proof that both signals reflect the variations of the CAP during therapeutic intervention with these antiarrhythmic drugs.

The analogous alterations of MAP and VER in duration following intervention with antiarrhythmic drugs are in contrast to the changes in amplitude. MAP amplitudes decreased with time while the VER amplitudes remained constant during all experiments or showed reversible changes following the interven-

tion with drugs. The MAP recordings are very local measurements due to the close arrangement of the indifferent electrode to the catheter tip. Therefore, small dislocations of one of the two MAP electrodes lead to big changes in the MAP amplitude. During spontaneous beat of the heart (about 200 bpm) the stability of the MAP was much lower than during ventricular rate after AV-node ablation (<50 bpm) because the mechanical stress per time unit is significantly higher. The VER represents the CAP over a wide range of the ventricle due to the unipolar measurement setup. Thus, small dislocations of the electrode, which were suppressed by the standard tines of the TIR-lead, are not as important as during MAP recordings.

However, the reversible and reproducible changes of the VER amplitude offer in addition to the VER duration like T^+-wave or VERd90 more parameters to control the effects of antiarrhythmic drugs. This may be used for cross-checking the results or increasing the sensitivity of drug monitoring.

Non-stable MAP amplitudes forbid the usage of the absolute value for monitoring. But the morphological changes of the MAP plateau-phase like shifting or oscillating following the bolus of isoproterenol show that the influence of pathological changes and cardiac drugs on specific ion channels can not be classified only by evaluation of MAP duration or amplitude. The specific changes of the morphology offer also information about strength and duration of specific ion currents across the cell membrane.

In all experiments was demonstrated that MAP and VER reflect the changes of the CAP by altering the duration, the amplitude and the morphology. The local setup of the electrodes with a small distance to each other during MAP recordings implies that a local area of the cardiac muscle can be observed. The VER reflects a bigger area of the ventricle and therefore the spatial resolution is lower. 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. Since Ir-electrodes measure in contrast to Ag/AgCl-electrodes the IECG without any post-stimulus polarization artifact both signals are available with a single lead only by changing the indifferent electrode. Thus local changes of the CAP and their over-all effects on the ventricular muscle can be monitored without changes of lead configuration.

This advantage of Ir-electrodes in combination with their proofed long-term stability and biocompatibility makes implantable systems for recording of MAP and VER with the same device available now[6]. Together with a pacemaker with high-resolution IECG telemetry like Physios CTM 01[13] or Logos (both BIOTRONIK) drug monitoring with an implantable device becomes reality. Now, control and individual adjustment of the dose of antiarrhythmic drugs needs no longer to be performed during invasive catheter operation. Drug monitoring using the usual non-invasive pacemaker telemetry is already in clinical use.

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