# Medication Therapy Control by MAP Monitoring

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### *Summary*

*The monophasic action potential (MAP) represents a summed signal of action potentials of myocardial cells surrounding the tissue electrode. Therefore, the MAP reflects the electrophysiological changes on the cellular level, e.g. caused by medication therapy. The efficacy of drugs can be detected and controlled by continuous MAP-recording and analysis. An important prerequisite for a medication therapy control by MAP monitoring is the reliable long-term recording of the MAP ensured by the use of implantable Ir-coated leads and special designed monitoring pacemakers. The influence of different drugs (orciprenaline, esmolol, dopamin, verapamil) on the MAP measured with Ir-coated leads (BIOTRONIK) is discussed in detail.*

### Key Words

monophasic action potential, medication therapy control, Ir-coated lead

## Introduction

The monophasic action potential (MAP) representing a summed signal of action potentials surrounding the tissue electrode allows the exact analysis of the myocardial repolarisation process. Therefore, the MAP has been used in a variety of methods to monitor the effects of drugs on the cellular level of the heart[4,7]. Sympatholytics, parasympatholytics, beta blockers, antiarrhythmics, and other drugs were shown to influence the repolarization in a significant manner. It was found that the efficacy of the drugs can be observed by their alterations of the MAP morphology, e.g. of the MAP duration[12].

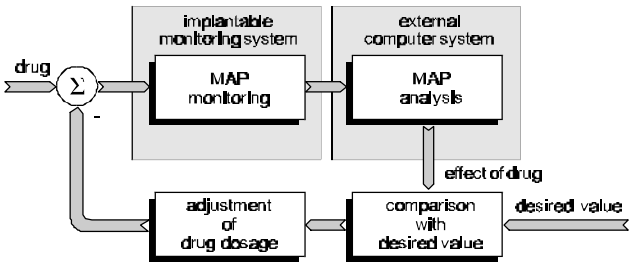


***Figure 1.*** *Flow chart of medication therapy control by MAP monitoring.*

The effects of several drugs were widely investigated in animals and man with temporary Ag/AgCl electrodes since years[5,6]. But a long-term medication therapy control by MAP analysis (see figure 1) providing an improved medication and dosage requires MAP monitoring with implantable leads and monitoring devices.

This article demonstrates the effects of various drugs on the MAP detected with Ir-coated leads, which guarantee biocompatibility and long-term stability of their electrical properties[1]. Therefore, these leads allow chronic implantation and MAP monitoring using an implantable device.

### *Effects of esmolol and orciprenaline*

Medication by beta blockers is a typical therapy for treatment of arrhythmias and hypertension[3]. Beta adrenergic receptors are blocked by these drugs. The opposite effect, the stimulation of adrenergic receptors, can be reached by sympathomimetics. The

reflection of beta adrenergic receptor modulation on the MAP was analyzed during electrophysiological investigations using a beta blocker and a sympathomimetic with short-term effects. The reflection of beta blockage by drugs for long-term medication therapy of arrhythmias and hypertension is expected to be the same.

## Methods

The endocardial ventricular MAP was recorded with fractally Ir-coated leads (BIOTRONIK) in 11 patients (4 female, 7 male, mean age: 62±11 years) during electrophysiological investigations[11]. For analyzing the influence of a beta blocker the ventricular MAP was monitored during and after an infusion of esmolol (0.5 µg/kg/min). The influence of a sympathomimetic was analyzed by ventricular MAP monitoring before, during and after an infusion of orciprenaline (0.5 µg/kg/min). The MAP duration at a level of 90% repolarization (MAPd90), the maximum MAP amplitude and the heart rate were calculated by a computerized data analysis.

### Results

The influence of esmolol on the ventricular MAP is shown in figure 2.

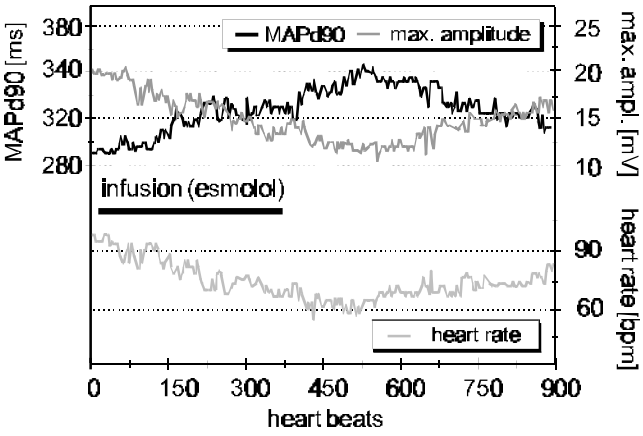


***Figure 2.*** *Effects of esmolol (0.5 µg/kg/min) on MAPd90, heart rate and maximum MAP amplitude.*

The intrinsic heart rate decreased by 37±18%, the MAP duration was prolonged by 16±14% and the maximum amplitude of the MAP was reduced. The prolonged MAP duration is explained by reduced outward $K^+$ currents of the myocytes as a result of decreased intrinsic heart rate and of decreased $K^+$ conductivity as a direct result of adrenergic blockage by esmolol. The reduced maximum amplitude is a result of decreased inward $Ca^{2+}$ current into the myocardial cells caused by beta adrenergic blockage[10].

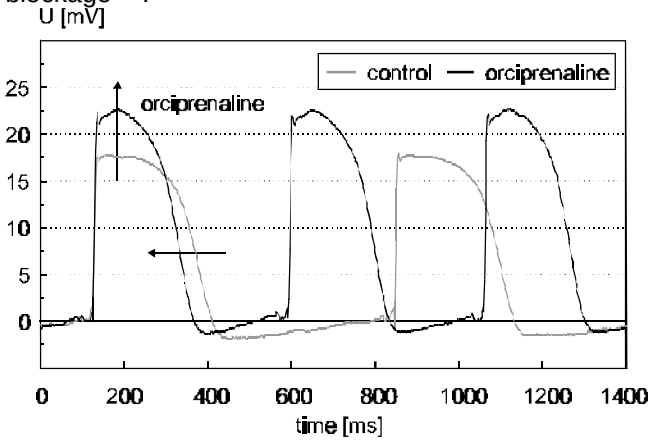


***Figure 3.*** *Influence of orciprenaline (0.5 µg/kg/min) on the ventricular MAP.*

Figure 3 demonstrates the opposite effects on the MAP caused by adrenergic stimulation with orciprenaline. The heart rate increased by 55±9%, the MAP duration was shortened by 21±12% and the plateau voltage of the MAP was elevated.

In conclusion, these results confirm the expectation that beta adrenergic receptor modulation caused by drugs is reflected on the MAP.

## *Effects of dopamine*

Dopamine effects as a positive inotrope drug. It acts primarily on the $\alpha_1$- and $\beta_1$-adrenergic receptors, increasing systemic vascular resistance and exerting a positive inotropic effect on the heart. Dopamine is commonly used to treat hypotension associated with cardiogenic shock at low cardic output states[8].

### Methods

In 18 patients (11 male, 7 female, 66±13 years) following aortic valve replacement epicardial fractally Ir-coated MAP leads (MAPOX, BIOTRONIK) were implanted at the lateral aspect of the right atrium and the apex of the right ventricle. During in-patient stay the MAP was recorded continuously[9]. The effects of hemodynamic drugs like dopamine were observed

using the atrial and ventricular MAP lead and compared with simultaneously recorded mean atrial blood pressure (MABP) during institutions standard regimen.

### Results

After bolus of 6 mg/kg/min dopamine the intrinsic rate increased by 57±5 %, the MAP duration shortened (MAPd90: 15±11 %; MAPd50: 18±11 %) and the MABP increased by 15±8 %. (see figure 4).

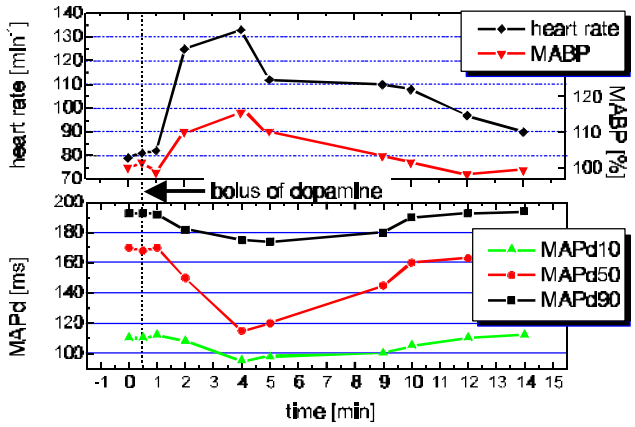


***Figure 4**. Effects of dopamine on heart rate, MABP, and rate-corrected MAP duration.*

The course of heart rate, MAP-duration and MABP following the bolus of dopamine reflects the onset of 2 min and the duration of 10-15 min of this drug as described in literature[8]. Using the monophasic action potential the effects of dopamine on the heart can be monitored on cellular level and the dose of the drug can be adjusted directly. This provides a more specific control of dopamine and cross-checks simultaneously the effects of the drug monitored by the MABP or the cardiac output. This procedure was already proved in clinical practice in more than 15 patients.

### Effects of verapamil

The most important application of verapamil is to control the ventricular rate during supraventricular tachycardias. It effects as a class IV antiarrhythmic drug[2,12] mainly on the sinus and the AV-node. On the one hand it reduces the sinoidal rate and on the other hand it generates high AV-blocks to avoid 1:1 conduction of the high atrial rate in the ventricle.

### Methods

Seven mongrel dogs were anesthetized with pentobarbital (30 mg/kg i.v.). Ir-coated MAP-catheters (MULTICATH 4/F, BIOTRONIK) were placed in the right ventricle at the apex and the anterior wall. The effects of i.v. boli of 0.01 mg/kg verapamil were investigated during intrinsic rhythm and during a stimulation protocol with 10 consecutive beats with 300 ms cycle length.

### Results

Following a bolus of 0.01mg/kg verapamil the spontaneous rate slowed by 33±11%. During the stimulation with 10 consecutive beats of 300 ms cycle length the MAP duration MAPd90 lengthened 15 min after the bolus by 23±11% (Figure 5).

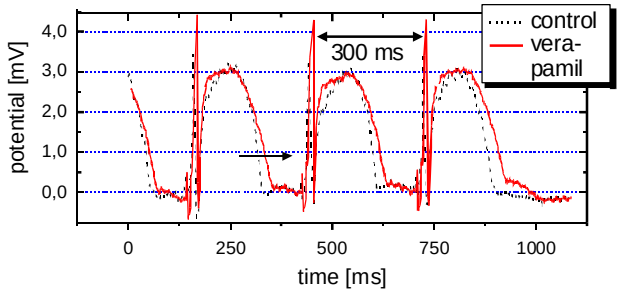


***Figure 5**. Effects of verapamil on the monophasic action potential.*

60 min afterwards the duration returns to the pre-experimental values. The results were in good accordance to the literature[2]. The prolongation of the spontaneous rate and the lengthening on MAP was demonstrated.
The verapamil effects sensitively the AV-node and may generate a total AV-Block if the dose is not well and patient specific adjusted. Thus controlling the effects of verapamil on cellular level using the monophasic action potential the risk of these drug by producing a total AV-block may reduced significantly.

### Conclusions

Analyzing the monophasic action potential the effects of different drugs on the heart can be reproducable monitored on cellular level. Using an implantable system consisting of fractally Ir-coated leads and special designed monitoring pacemakers an reliable medication therapy control is enabled. This allows a more specific control of the drug dosage and

therefore an optimization of the medication therapy resulting in a reduction of patients risk.

**Literature**

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