Prediction of the Onset of Atrial Fibrillation after Cardiac Surgery Using the Monophasic Action Potential

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Summary

The major cause of patient morbidity and hospital cost after routine cardiac operations is the development of rhythm disturbances, mainly supraventricular in origin. This work was directed to show that the monophasic action potential (MAP) recorded continuously from human epicardium may be used to predict the imminent onset of these cardiac arrhythmias during the days following surgery. During an average observation period of 7 days (±2.7, 4-14 days) 7 episodes of atrial fibrillation (AF) were seen in 6 of a first group of 22 patients. Prior to the arrhythmia specific alterations of the MAP morphology were reproducibly observed. The MAP shortened (25±4 % 60 min prior to AF), developed a triangular shape and the plateau amplitude decreased from 5.3±1.2 mV to 2±0.2 mV in 5 of 7 cases. In the 2 remaining cases the beat-to-beat variability of cycle length and MAPd90 was seen to increase from 24±8 ms and 12±8 ms (24 h prior to AF) to 156±23 ms and 56±11 ms (30 min prior to AF) respectively. Atrial arrhythmias were successfully treated by the administration of the b-blocker sotalol in 3 and a combination of verapamil, digoxin, and quinidine in a further 2 cases. The previously observed changes of MAPd90 and MAP morphology were seen to regress. The mechanisms underlying these arrhythmias appear similar to those found in other patient populations. On the basis of this first series of observations the continuous and intermediate term recording of the MAP from atrial and ventricular epicardium seems a valid tool for the detection of imminent arrhythmias after cardiac surgery with a sensitivity of 100 % and a specificy of 87.5 %. Thus dosage optimized treatment may selectively be given for prophylaxis.

Key Words

atrial fibrillation, supraventricular arrhythmias, monophasic action potential, postoperative management

Introduction

Patients suffering from cardiac arrhythmias consume a significant proportion of medical resources[1,2]. Of all the supraventricular tachycardias atrial fibrillation is by far the most common and the most important. It effects up to 4 % of individuals aged above the age of 70 years[1]. Similarly the major cause of morbidity and hospital cost following routine cardiac operations is the development of rhythm disturbances, mainly of supraventricular origin[2]. The incidence averages around 26.7 %[3]. The pathophysiological mechanisms in this specific patient population are presently a matter of discussion. In contrast, in the case of „ordinary“ atrial fibrillation, different forms of re-entry mechanisms are being made responsible[4,5].

The aim of clinical research must therefore be on one hand to elucidate the mechanism of post-operative arrhythmias. On the other hand the clinician needs to be in a position to identify those patients that will develop arrhythmias and to implement a specific prophylactic therapy. In order to predict the onset of arrhythmias a detailed instantaneous knowledge of the electrical activity of the myocytes would be required. The behavior of the individual cardiac myocytes as well as the heart as an organ is governed by the strength and duration of the transmembrane ion currents[6]. Therefore, the cellular action potential (CAP), which reflects these ion currents allows the monitoring of physiological and pathological proc-

esses as well as the effects of pharmacological interventions[7].

Recording of the cellular action potential is up to the present a time limited invasive procedure resulting in cellular damage[8]. For long-term use in the clinical setting a non-cell damaging method is required. The monophasic action potential (MAP) represents a potential candidate[9]. It is a summed signal of the CAP's of a defined number of electrically active cells surrounding the different electrode[8]. The limitations of MAP recording techniques up to the present time have been the lack of long term stability of the signal using the traditional Ag/AgCl-electrodes (<3 h)[7,9]. With the advent of modern electrode coating techniques it was possible to develop a long-term stable and biocompatible electrode material[10,11]. Fractally coated electrodes with low impedance, no frequency-dependent damping, and a low polarisability allow to measure the MAP reliably over a prolonged time period[11]. A comparison of the signals obtained with an Ag/AgCl electrode and the fractally coated lead at the same location endocardially have shown a nearly perfect correlation (r=0.99)[12].

The underlying hypothesis of the work presented here is that the electrical alterations that cumulate in the occurrence of postoperative atrial arrhythmias are reflected by morphological changes of the atrial MAP.

Thus this study aims to show that monophasic action potential from human epicardium my be used to predict the imminent onset of cardiac arrhythmias during the days following aortic valve replacements.

Methods

Following aortic valve replacements bipolar epicardial MAP electrodes[10,13] (BIOTRONIK, Germany) were attached to the lateral aspect of the right atrium and the apex of the right ventricle using three 6/0 prolene sutures. Alike the conventional temporary pacing wires the leads were brought out transcutaneously. From the time the patients arrived on the intensive care unit the MAP's were registered continuously using an isolation amplifier with adjustable amplification (range: ±5 to ±250 mV), digitized (500 Hz sampling frequency, 12 bit resolution) and stored on PC. For the duration of the in-patient stay the signals were recorded almost continuously. Before discharging the patients the MAP leads were removed by traction.

Up to the present stage 22 patients (7 female, 15 male, 64±12, 29-85 years) have been included in the study after giving informed consent. Exclusion criterion was the presence of electrically non-convertible atrial fibrillation or flutter at the end of the period of extracor-

poral circulation. Furthermore patients receiving coronary artery bypass grafts or mitral valve replacements were not included.

The standard MAP parameters (cycle length, $MAPd_{50/25/90}$, plateau amplitude)[7,8] were evaluated retrospectively using a semiautomatic MAP evaluation software (figure 1).

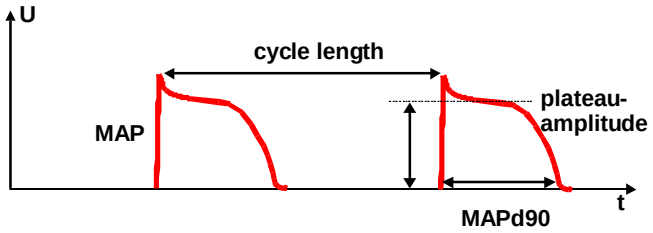

Figure 1. *Analysed MAP parameters using the semiautomatic evaluation program.*

From these the MAP duration normalised for cycle length (nMAPd90=MAPd90/cycle length) and the difference between nMAPd25 and nMAPd90 were calculated. Furthermore the beat-to-beat variability of cycle length (ΔCL) and MAP duration (ΔMAPd) were determined.

The appearance of atrial fibrillation was correlated with nMAPd, nMAPd90-25, the plateau amplitude, and the variability parameters. In those patients where sinus rhythm was successfully reestablished, the MAPs were compared to those prior to the onset of AF. Measurements were only accepted if a constant baseline indicated a stable position of the electrode. On the occurrence of atrial arrhythmias the patients received one of the institution's standard antiarrhythmic drug regimens (verapamil/digoxin ± quinidine or sotalol monotherapy).

Results

MAPs were recorded in 22 patients with a signal-to-noise ratio >26 dB (figure 2). The plateau amplitude started at 5.3 ±1.2 mV in the atrium (n=21) and 15 ±7 mV in the ventricle (n=5). After an average time period of 48 hours the amplitude stabilised at 40-60 % of the initial value. This development was correlated with the cessation of fluid loss over the pericardial drains. The longest recording period was 14 days in a

patient who remained in hospital for pulmonary reasons. At that time the atrial signal measured was 2.3 mV. All other patients left the unit after the usual time period of 5 to 10 days.

During the cumulative recording period of 170.1 days (average 7.0 ± 2.7 (4-14) days) 7 episodes of atrial arrhythmias were observed. In 6 cases these occurred within the first 48 h after surgery.

Prior to the occurrence of supraventricular arrhythmias the atrial MAP morphology changed significantly. In 5 of 7 cases the MAP developed a triangular shape (figure 2).

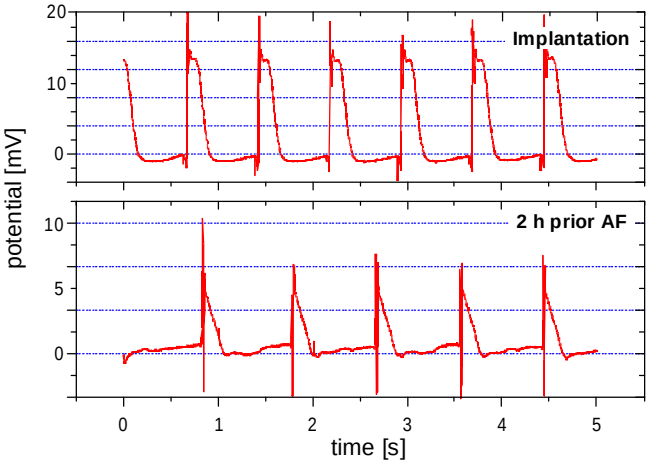

Figure 2. *Atrial MAP before atrial fibrillation.*

A heart rate independent shortening of MAPd90 and MAPd50 was observed (nMAPd90: -25±4 %, nMAPd50: 22%+- 60-180 min prior to AF). The difference nMAPd90-nMAPd25, which reflects the triangularity of the MAP, increased by 23±9%. The plateau amplitude of the atrial MAP decreased from 5.3±1.2 mV to 2±0.2 mV (figure 2).

In the other 2 cases the beat-to-beat changes in cycle length (ΔCL) and MAP duration (ΔMAPd) increased significantly (Table 3) with a concurrent appearance of a bigeminal picture (figure 3).

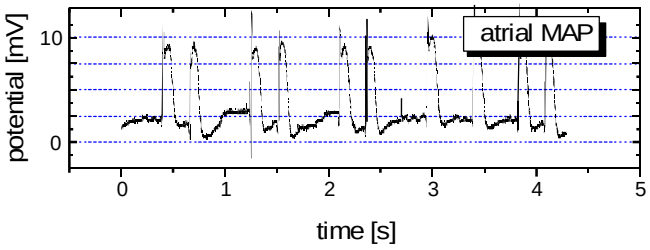

Figure 3. *Atrial MAP before atrial fibrillation.*

t before AF [h]	-24 h	-3 h	-30 min
Δ CL [ms]	24±8	136±24	156±23
Δ MAPd90 [ms]	12±8	23±13	56±11

Table 1. *Average changes of cycle length and MAPd90 before atrial fibrillation.*

Atrial arrhythmias were successfully treated by the administration of sotalol in 3 and the combination of verapamil/digoxin ± quinidine in 2 cases. Two of the patients were still in AF at the end of the observation interval.

Following atrial fibrillation a triangular shape of the MAP with a short duration was seen in all cases (figure 4 upper trace). The MAP plateau phase returns 4-12 h after the conversion to sinus rhythm (figure 4 lower trace).

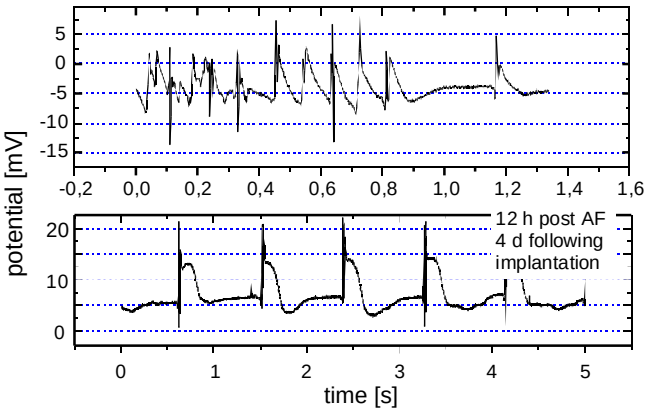

Figure 4. *Atrial MAP following atrial fibrillation.*

The previously observed reduction of nMAPd90 was seen to regress (30 min after AF: -20±12%, 60 min after: -19±5%, 3 h after: -11±3%). The rate corrected

MAP duration of those patients where AF was treated successfully with sotalol showed a prolongation greater than the former values (nMAPd90: +11 %).

The majority of patients did not experience sustained atrial or ventricular arrhythmias during the observation period. The beat-to-beat changes of the cycle length and the MAPd90 did not exceed ΔCL=50 ms and ΔMAPd=18 ms as compared to those cases where AF developed (table 1). Morphological alterations to a triangular shape was observed in 2 of these patients without following atrial arrhythmias.

Discussion

Using the new fractally coated leads long term recordings of the MAP of up to 14 days with an acceptable signal-to-noise ratio were reported for the first time elsewhere[10,13]. The morphology and MAP parameters of the potentials measured with the fractally coated leads are similar to those recorded with Ag/AgCl electrodes[12]. For all patients a decrease in signal amplitude was observed. This is assumed to be caused by alterations in the constitution of the pericardial fluid around the different electrode. Samples of this fluid collected from the pericardial drains deviates in terms of ionic concentrations from extracellular fluids of up to one order of magnitude. A more detailed investigation of this phenomenon is presently underway. The morphology of the MAP recorded with the fractally coated leads maintains its congruence with the traditional MAP despite the decrease in amplitude[10,13]. The normalisation procedure used for MAP duration in this paper to allow for a comparison at different heart rates is based on the finding that in the range of 50 to 120 bpm the correlation between $MAPd_{90}$ and heart rate is linear[8,14].

One consequence of the initial drop in signal size with time is that the marked decline in plateau amplitude observed prior to the onset of AF becomes a less specific predictor for arrhythmias. This is of course more pronounced during the first 48 hours than at a later stage, for example in the case of an implantable device. That a decrease in MAP duration is seen in the presence of a pro-arrhythmic substrate has been demonstrated numerous times[7,20].

Prior to atrial flutter and fibrillation the atrial MAPs shortened significantly with a concomitant loss of the plateau phase in 5 of the 7 cases observed. In the remaining 15 patients only 2 showed similar changes of their atrial MAP's without presenting consequently with persistent supraventricular dysrhythmias. In these cases however an increased occurrence of atrial extrasystoles and triplets was documented. It appears, that the morphological changes observed here, represent an indicator of the probability for the atrial rhythm to become unstable. Similar alterations of the morphology have been described in experimental settings, where hypoxic/ischaemic, hypokalaemic (intracellular) and acidotic changes in the extracellular fluid where observed in the connection with the onset of ventricular arrhythmias[6,7,14,15]. In parallel, from clinical experience these factors are well known to encourage the pro-arrhythmic substrate. From this standpoint the long term monitoring of MAPs seems to possibly bridge the gap between in-vitro results and the clinical situation.

The "MAP alternans" observed in the other 2 patients, that developed arrhythmias has also been described in the literature to be associated with an increased tendency for the occurrence of dysrhythmias[16].

Thus all observed episodes of supraventricular arrhythmias are preceded either by morphological alterations i.e. a triangular shape or an increased beat-to-beat variability of the cycle length and the MAP duration. In terms of predicting the onset of post-operative arrhythmias in this patient group the rate-corrected MAP duration, the difference MAPd90-25, and the average change of cycle length and MAPd90 may all be used. The prediction threshold for each parameter may be chosen as is depicted in Table 2.

Parameter	Prediction threshold
nMAPd90	reduction by 20 %
MAPd90-25	increase by 20 %
Δ cycle length	increase over 75 ms
Δ MAPd90 [ms]	increase over 20 ms

Table 2. *Parameter limits for prediction of atrial fibrillation of patients following aortic valve replacement.*

Using the limits for the parameters as outlined the sensitivity of the method to predict atrial arrhythmias using the continuously recordings of the monophasic action potential is 100 % with a specificity of 87.5 %.

Following the pharmacological cardioversion in all 4 patients a slow restitution of the initially triangular shape of the MAPs was observed. As the drug regimens, individual dosages and the duration of AF were very different in these cases only a reference is given here to experimental work where similar observations

have been reported in patients converted from atrial fibrillation to a sinus rhythm under MAP monitoring[17,18]. There the conclusion was drawn, that dependent on the duration of AF a process of remodeling takes place. This was felt to be expressed by a short atrial $MAPd_{90}$ following cardioversion that lengthened over a time period which was proportional to the duration of the AF. These results may suggest that a therapeutic intervention to either prevent or else to treat atrial fibrillation early, which is aided by the method presented in this paper, would significantly improve the clinical outcome. The possibility to use the MAP for drug therapy monitoring in this context is well recognised[8].

The two observed kinds of alterations in the atrial MAP namely the triangular shape and the "MAP alternans" indicate that at least two mechanisms underlie the triggering of atrial fibrillation in this group of patients. Due to the focal nature of the method alike to the conventional endocardial MAP recording technique an exact characterization of the triggering event is unlikely to be obtained. Thus to gain a more detailed insight into the triggering procedure and into the mechanism of perpetuation of atrial fibrillation/flutter in-vitro investigations are presently being conducted. A possible mechanism may be the significant dispersion of repolarisation caused by the differences in ionic constitution of endocardial and epicardial environments. Following surgery the composition of the pericardial effusion changes dramatically (own observations). That this may indeed cause a rise of dispersion and consequently an increase in arrhythmic events has been described[19]. If this mechanism forms the basis for postoperative arrhythmias, be it a surface or a transmural phenomenon, it would explain the limited value of the many empirical prophylactic drug trials in the past. The action of every drug would only be expected to modify the dispersion not however to create a uniform electrical behaviour of the atrial myocytes. Thus for every patient a specific treatment should be installed under continuous monitoring.

The authors recognise several limitations of this clinical primarily phenomenological approach to supraventricular arrhythmias. One shortcoming of this technology up to the present moment in time is that the data are evaluated retrospectively. To enable the clinician to apply prophylactic treatment and to monitor the result an on-line evaluation system is required and presently being constructed. Another limitation is that two anti-arrhythmic drug regimens were used. Thus the effects of the drugs on the MAP can not be evaluated due to the small number of cases. In connection with the on-line evaluation system a prospective randomised trial of prophylactic antiarrhythmic therapy is planned. Principally, the significant increase of the MAP duration after sotalol administration reflecting the antiarrhythmic effect by reducing the activity of the K^+ channels [16=20,17=21] indicates that the presented method is useful for drug monitoring[7].

The authors conclude that the intermediate term monitoring of the atrial MAP represents a useful diagnostic tool for the management of patients after cardiac surgery that may aid reduction in morbidity and hospital cost. The results also point to a place for this technology in the evaluation of pharmacological therapy on a long term basis. The mechanisms underlying postoperative arrhythmias and the triggering thereof appear very similar to those reported in the literature for ventricular and atrial arrhythmias under controlled conditions. A more detailed knowledge of the long term changes of the electrical behaviour of the myocytes before and during arrhythmias, as gained with this technology will be useful for the development of all types of antiarrhythmic therapy.

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