New Insights into Application of Cardiac Monophasic Action Potential

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Summary

Monophasic action potential (MAP) recording plays an important role in a more direct view of human myocardial electrophysiology under both physiological and pathological conditions. The procedure of MAP measuring can be simply realized using the Seldinger technique, when MAP catheter is inserted through femoral vein into the right ventricle or through femoral artery to the left ventricle. The MAP method represents a very useful tool for an electrophysiological research in cardiology. Its crucial importance lies in the fact that it enables the study of the action potential (AP) of myocardial cell in vivo and, therefore, the study of the dynamic relation of this potential with all the organism variables what can be particularly helpful in the case of arrhythmias. It is undoubtable that physiological MAP recording accuracy is almost the same as transmembrane AP what was reproved recently by anisotropic bidomain model of the cardiac tissue. MAP recording devices provide precise information not only of the local activation time but of the entire local repolarization time course as well. Although the MAP does not reflect the absolute amplitude or upstroke velocity of transmembrane APs, it delivers highly accurate information on the AP duration and configuration, including early afterdepolarizations as well as relative changes in transmembrane diastolic and systolic potential changes. Based on available data, the MAP probably reflects the transmembrane voltage of cells within a few millimeters of the exploring electrode. Thus MAP recordings offer the opportunity to study, in the in situ heart, a variety of electrophysiological phenomena including effects of cycle length changes and antiarrhythmic drugs on AP duration.

Key words: Monophasic action potential, electrocardiography

Introduction

Electrocardiography (ECG) is the best-known and the most popular procedure of recording of the electrical activity of myocardium. However, ECG detects just body surface projection of the electrical heart field and can not reveal heart´s local information such as actual cellular depolarization and repolarization process of myocardial tissue. The standard surface electrocardiogram as well as the intracavitary electrocardiographic recordings are not able to provide more precise and more locally oriented information as they represent just the summation of an electric activity of many myocardial cells from relatively big regions of the heart. Moreover the obtained picture of the electric heart field is distorted by different conductivities and resistances of tissues situated between the source of an electric activity and measuring electrodes. In many situations an advanced knowledge of the entire temporal extension of cellular action potentials would be very helpful what is related particularly to the study of arrhythmias pathogenesis and of mechanisms of antiarrhythmic drugs actions. For such purposes only two methods are available: the cellular impalement technique and the monophasic action potential (MAP) method. Thus, MAP recording plays an important role in a more direct view of human myocardial electrophysiology under both physiological and pathological conditions.

MAP history and definition

The history of MAP started in 1883 when the potentials generated by frog cardiac beats where continuously recorded (Burdon-Sanderson and Page, 1883). In one of the described observations one electrode was placed on the intact surface of the heart while the other one on an injured region. Transitory monophasic potential (with only one polarity) was then recorded. Monophasic was the potential in comparison to the (at that time already known) transitory multiphase recordings that have got both positive and negative polarities. This was the origin of the term monophasic action potential (MAP), whose form was very similar to the cellular action potential later obtained by the cellular impalement technique with microelectrodes. In 1949, the cellular impalement technique (known from the late 1930s from the giant axon of the squid) was applied to the cardiac cell by Coraboeuf and Wiedmann (1949) and one year later by Woodbury et al (1950). Thanks to those experiments, many of the theories developed for the giant axon of the squid could be applied also to cardiac cells, elucidating the role of Na^+, K^+, and Ca^{2+} in the processes underlying electrical changes in the myocardial cells (Coraboeuf and Wiedmann, 1949, Burgen and Terroux, 1953, Orkand and

Niedergerk, 1964).

The first non-traumatic method for recording of MAPs was developed and published by Jochim et al. (1934). These authors demonstrated that MAPs can be obtained simply by pressing an electrode against the epicardium of the toad´s ventricle while another electrode merely touched the nearby epicardium. They also demonstrated that the MAP is positive with respect to zero if the pressure electrode is the active one (connected to the positive amplifier input). Unfortunatelly their important observations went largely unnoticed for many years. However, the procedures used in their study were both in methodology and interpretation surprisingly similar to the current principle of recording MAPs by contact electrode. Only in 1986, Franz et al. have revealed the forgotten paper of the Jochim´s team and based on its observations they have produced an electrodecatheter, that using just simple contact with the myocardium, obtained a stable and high-quality MAP, eliminating the risks of suction. Suction electrode that captured monophasic potentials with great simplicity, not requiring the production of a specific myocardial lesion, because this was already caused by the suction itself, was introduced by Korsgren (1966). In this way, the right ventricle MAP of a patient could be recorded, which revealed a clinical application for the technique of MAP recording. Suction, however, presented the risks of air embolism and irreversible mechanical myocardial lesion (Olsson, 1972) and thus only the contact electrode technique was once again considered to be a useful tool for experimental and clinical cardiac electrophysiology.

The ‘contact electrode technique’ for clinical use was developed between 1980 and 1983 by Franz et al. Besides being simple and more clinically safe, the contact electrode method provides MAP recordings that, due to lack of myocardial injury, are stable over time. This allows clinical electrophysiologists to monitor MAPs over periods of several hours from the same endocardial site to assess, for instance, the effects of antiarrhythmic drugs or cycle length changes on local myocardial repolarization. With the contact electrode technique, MAP recordings can be obtained from the human endocardium or epicardium without suction but rather by pressing a nonpolarizable electrode gently against the endocardium or epicardium. Catheters and probes for endocardial and epicardial MAP recording were developed both for clinical and experimental studies. The application of the epicardial electrode requires direct contact with the epicardium and, consequently, needs a surgical incision for a heart exposition. However, the endocardial electrode can be fixed to the tip of a catheter and installed to the endocardium through blood vessels (Fig. 1), enabling its clinical utilization with a minimum risk to the patient (Leirner and Cestari, 1999).

Many interesting results also in the field of theoretical electrocardiography were

obtained by the MAP method, for instance an evidence for the hypothesis of opposite directions of ventricular depolarization and repolarization (Franz et al. 1987) thanks to the measurements of MAPs from different left ventricular endocardial and epicardial sites during cardiac surgery and catheterization.

Potential applications of the MAP

Two hypotheses have been advanced to explain the generation of MAP recordings. One hypothesis suggests that MAP corresponds to a local electrical activity flowing from the active to inactive regions near the tip of the inactive electrode. An alternative hypothesis suggests that the MAP "indifferent electrode" actually records active myocardial tissue from a wide field-of-view. In any case the MAP method represents a very useful and agile tool for an electrophysiological research in cardiology. Its crucial importance lies in the fact that it enables the study of the action potential of myocardial cell in vivo and, therefore, the study of the dynamic relation of this potential with all the organism variables (Leirner and Cestari, 1999). As mentioned earlier it can be particularly helpful in the case of arrhythmias. Using the MAP measurement an association between the arrhythmias accompanying the long QT syndrome and the anomalies of duration and temporal dispersion of the MAPs, as well as the presence of postpotentials (Gravilescu and Luca, 1978) was found. A possible relation of postpotentials to cardiac arrhythmias as well as their developing mechanisms were largely studied using MAPs by Zipes (1991). Nevertheless the myocardial action potential can be affected by many other factors (Slavicek et al. 1998):

1. Cellular hypertrophy: The development of ventricular arrhythmias was recently found to be correlated with electrophysiological remodeling in isolated ventricular myocytes, including action potential prolongation, increased sodium-calcium exchanger activity, reduced outward potassium currents, sarcoplasmic reticulum Ca^{2+}defects, and loss of protein kinase A-dependent phospholamban phosphorylation (Hongmei et al. 2007). However, cardiac hypertrophy is associated in a reverse process with increased mechanical stretch, electrical remodeling and arrhythmogenesis (Michael, 2009).

2. Ischemia and re-perfusion: Acute ischemia opens ATP-sensitive potassium channels (K_{ATP}) and causes acidosis with hypoxia/anoxia in cardiac muscle. The ensuing repolarising potassium efflux shortens an action potential. Moreover, accumulation of extracellular potassium is able to partially depolarize the membrane, reducing the upstroke velocity of the action potential and thereby impairing impulse conduction. Both mechanisms are believed to

be involved in the development of reentrant arrhythmias during cardiac ischemia (Liu et al., 2007). On the other hand, the ischemia-reperfusion can induce significant down-regulation of I_{Na} (sodium current) and I_{to} (transient outward potassium current) and up-regulation of $I_{Ca\text{-}L}$ (L-type calcium current), which may underlie the altered electrical activity and long abnormal transmembrane action potential duration of the surviving ventricular myocytes, thus contributing to ventricular arrhythmias during acute ischemia-reperfusion period (Gao et al. 2008).

3. Chemical effects: In addition to anti-arrhythmic drugs a lot of other chemical substances can also change the cardiac action potential. These chemical substrates change cardiac action potential by an alteration of cardiac ion channels behavior. Potential drugs assessment and disclosure of their action mechanisms has been one of the most frequent uses of the MAP method for a few last years.

4. Thermal effects: The electrical excitability of the cardiac myocytes is determined by sarcolemmal ion currents which flow through ion specific channels. Since function of the ion channels is dependent on temperature, low temperatures are expected to reduce sarcolemmal ion currents and therefore compromise excitability and conductivity of the cardiac myocytes. The changes in the depolarizating sodium current (I_{Na}) tend to maintain adequate excitability in the cold, while increased intensity of the rectifying potassium current (I_{Kr}) will prevent excessive lengthening of action potential duration in the cold.

5. Mechanical effects: The electrical activity of the cardiac cell is usually understood to be triggering the mechanical activity in a single direction. However, there is an evidence of an inverse pathway; in other words, the mechanical activity could also cause changes in the electrical potential of the cells. This process is called mechano-electrical feedback (Lab, 1991). For instance an isovolumetric contractions against an infinite afterload is causing evident changes in the action potential (Leirner, 1992).

It is undoubtable that physiological MAP recording accuracy is almost the same as transmembrane action potential what was reproved recently by anisotropic bidomain model of the cardiac tissue (Colli et al., 2007). To understand why MAP recordings register an approximation of the transmembrane voltage, an ideal system can be described: first it is necessary to start by considering the potential at the contact electrode as ground. The transmembrane voltage of the region under the electrode is also constant and thus, the intracellular potential is fixed. To reach the indifferent electrode, a path has be followed that goes on intracellularly under the electrode and then across the membrane which has a time-

varying voltage. Therefore, relative to the intracellular potential that is fixed with respect to ground, the extracellular potential will move with the transmembrane voltage (Vigmond, 2005). Although the MAP does not reflect the absolute amplitude or upstroke velocity of transmembrane APs, it delivers highly accurate information on the AP duration and configuration, including early afterdepolarizations as well as relative changes in transmembrane diastolic and systolic potential changes. It also documents regional electrophysiological phenomena of the heart without interrupting the intrinsic organization of the tissue, and also documents the normal or pathological interrelations between the heart and the body. Thus MAP recordings offer the opportunity to study, in the in situ heart, a variety of electrophysiological phenomena including effects of cycle length changes and antiarrhythmic drugs on AP duration (Franz, 1991).

MAPs measurement has many interesting applications but two fields dominate: 1. Research of arrhythmias and mechanisms underlying their origin and maintenance and 2. drugs assessment (particularly antiarrhythmic drugs) and their action mechanisms.
For instance, investigation of atrial fibrillation using MAPs of the atrial myocardium has a very long tradition. Olsson et al. (1971) described changes of action potential duration in patients with higher risk of atrial fibrillation relapses after cardioversion almost 40 years ago and research in this field has been continuing till today (Aidonidis et al., 2009). Similar tradition can be found in the research of myocardial action potential alterations caused by antiarrhythmic drugs (Vaughan Williams, 1984, Franz, 1991, Osaka T et al., 2009). In last few years many studies have used the MAP method for endocardial and epicardial mapping of electrophysiological events in the heart. For instance Kongstad et al. (2005) have measured the activation time, MAP duration and end of repolarization time in healthy pigs and they have described both endo- and epicardial dispersion of ventricular repolarization. The same team (Li et al., 2002) has found also a repolarization gradients over the atrial endocardium. MAP recordings can be used also as a validation of other electrophysiological mapping procedures, for instance of a noncontact mapping (Yue te al. 2004).

The procedure of MAP measuring can be simply realized using the Seldinger technique, when MAP catheter is inserted through femoral vein into the right ventricle or through femoral artery to the left ventricle. The tip electrode has to be nearly perpendicular to endocardium what allows flexions back and forth with each cardiac contraction-relaxation cycle. The MAP catheter lead is connected to an electrophysiologic recording system and the signal can be analyzed by automated computer system (Tsalikakis et al., 2003) what allows to

calculate 2D (2-dimensionally) or 3D (three-dimensionally) an endocardial mapping by MAPs.

For real-time endocardial mapping of MAPs a Lantern Catheter was designed recently (Cui et al., 2008). The Lantern Catheter devised according to the invention is used for transpercutaneous catheterization followed by three-dimensional mapping of the endomyocardial MAP. Preferably at least 64 points (Ag-AgCI plated electrodes) of MAP are recorded simultaneously and the data analyzed by a conventional electrophysiological (EP) analysis system (Fig. 2). The pattern and/or the magnitude or size of the alteration of the action potential, changes in the action potential duration and/or the site or sites of 90% of the action potential duration (APD_{90}), the slowest action potential repolarization and/or depolarization (dv/dt), and/or other parameters can be determined very preciously. Using this real-time 3D mapping, the site and sites of the myocardium with maximum dispersion of these parameters among 64 or more recording sites are supposed to be identified that could enable to identify the pathology of the myocardium, even in an early disease stage.

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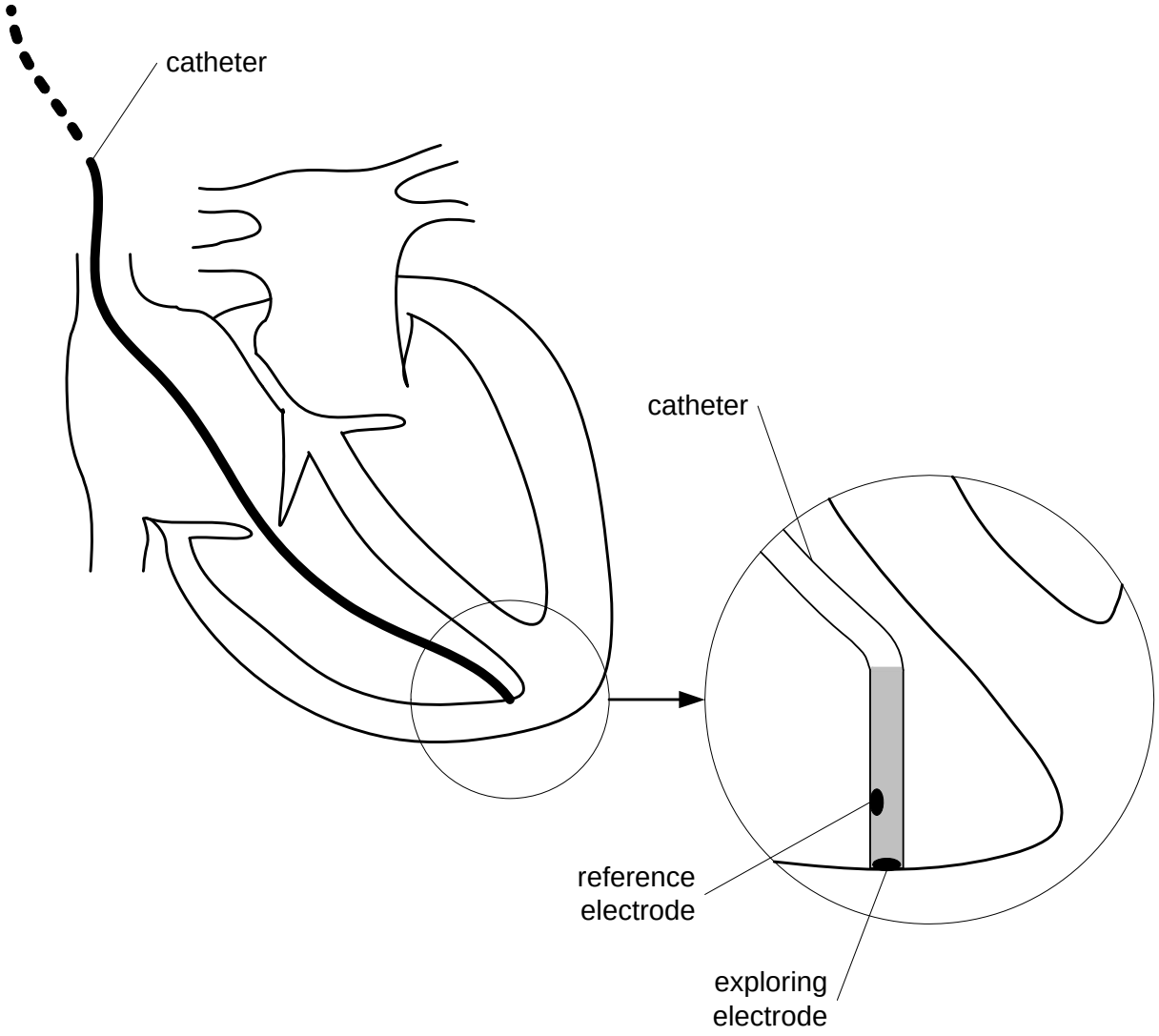
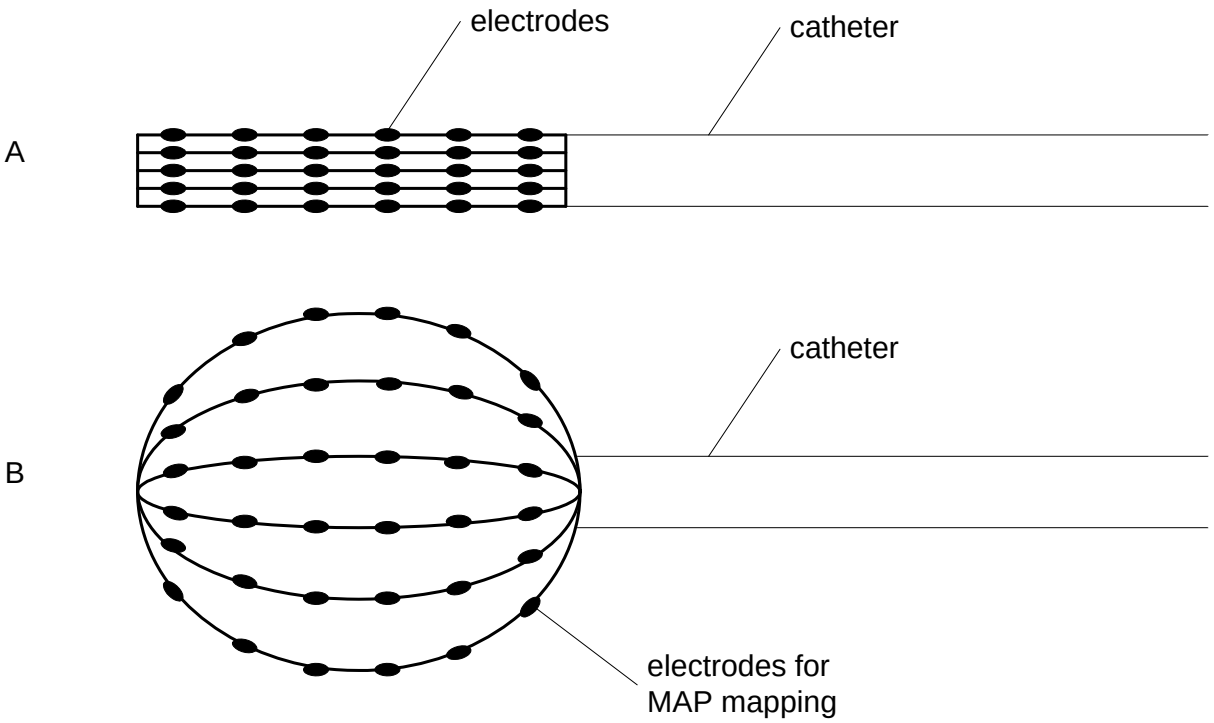
Fig. 1 The MAP catheter is introduced through femoral vein to right ventricle. In the detail: the situation of the electrodes in relation to the myocardium.

Fig. 2 A 'lantern catheter' is used for transpercutaneous catheterization followed by three-dimensionally mapping of the endomyocardial MAPs. The catheter in close (A) and open (B) positions.




A
electrodes
catheter
B
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electrodes for
MAP mapping