

New Insights Into Application of Cardiac Monophasic Action Potential

S.-G. YANG¹, O. KITTNAR¹

¹Institute of Physiology, First Faculty of Medicine, Charles University, Prague, Czech Republic

Received July 21, 2009

Accepted January 15, 2010

On-line April 20, 2010

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 performed 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 electrophysiological research in cardiology. Its crucial importance is based upon 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. This can be particularly helpful in the case of arrhythmias. There are no doubts that physiological MAP recording accuracy is almost the same as transmembrane AP as was recently confirmed by anisotropic bidomain model of the cardiac tissue. MAP recording devices provide precise information not only on the local activation time but also on the entire local repolarization time course. Although the MAP does not reflect the absolute amplitude or upstroke velocity of transmembrane APs, it delivers highly accurate information on 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 a variety of electrophysiological phenomena in the *in situ* heart (including effects of cycle length changes and antiarrhythmic drugs on AP duration).

Key words

Monophasic action potential • Electrocardiography

Corresponding author

Otomar Kittnar, Institute of Physiology, Charles University, First Faculty of Medicine, Albertov 5, 128 00 Prague 2, Czech Republic.
E-mail: okittnar@lf1.cuni.cz

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 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 were 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 whose form was very similar to the cellular action potential later obtained by the cellular impalement technique with microelectrodes. This technique (known from the late 1930s from the giant axon of the squid) was applied to the cardiac cell by Coraboeuf and Weidmann (1949) and by Woodbury *et al.* (1950). Thanks to those experiments, many of the theories developed for the giant axon of the squid could also be applied to cardiac cells, elucidating the role of Na^+ , K^+ , and Ca^{2+} in the processes underlying electrical changes in the myocardial cells (Coraboeuf and Weidmann 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 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). Unfortunately, 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. Franz *et al.* (1986) have revealed the forgotten paper of the Jochim's team and based on its observations they have produced an electrode-catheter, 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 *et al.* (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. However, suction presented the risks of air embolism and irreversible mechanical myocardial lesion (Olsson 1972) and thus the contact electrode technique was once again considered to be a useful tool for experimental and clinical cardiac electrophysiology.

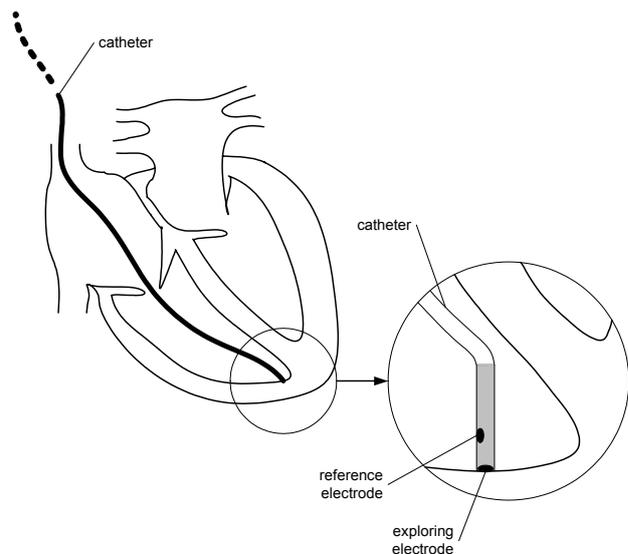


Fig. 1. The MAP catheter is introduced through femoral vein to right ventricle. In the detail: the situation of the electrodes in relation to the myocardium.

The 'contact electrode technique' for clinical use was developed between 1980 and 1983 by Franz and coworkers. 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 the heart

exposure. 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 for 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 was found (Gravilescu and Luca 1978). 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 (Slaviček *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 (Ruan *et al.* 2007). However, cardiac hypertrophy is associated in a reverse process with increased mechanical stretch, electrical remodeling and arrhythmogenesis (Michael *et al.* 2009).
- 2) *Ischemia and reperfusion*: Acute ischemia opens ATP-sensitive potassium channels (K_{ATP}) and causes acidosis with hypoxia/anoxia in cardiac muscle. The ensuing repolarizing potassium efflux shortens the 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 $\text{I}_{\text{Ca-L}}$ (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 antiarrhythmic 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 channel behavior. Assessment of potential drugs 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 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 depolarizing 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, 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).

There is no doubt that physiological MAP recording accuracy is almost the same as transmembrane action potential what was confirmed 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 consider 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 to 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 *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 also found repolarization gradients over the atrial endocardium. MAP recordings can also be used as a validation of other electrophysiological mapping procedures, e.g. a non-contact mapping (Yue *et 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 or 3D endocardial mapping by MAPs.

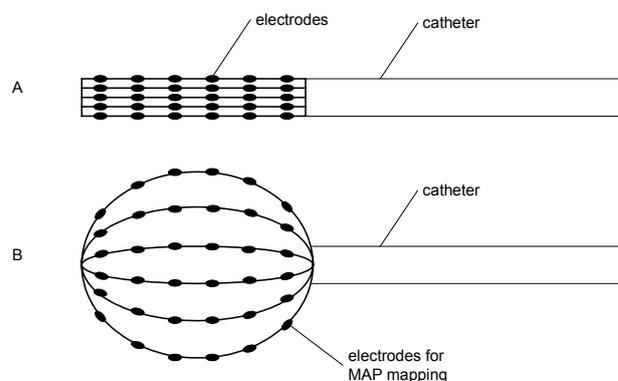


Fig. 2. The 'Lantern Catheter' is used for transpercutaneous catheterization followed by three-dimensional mapping of the endomyocardial MAPs. The catheter in close (A) and open (B) positions.

For real-time endocardial mapping of MAPs a Lantern Catheter was designed recently (Cui and Sen 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-AgCl 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 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 (APD₉₀), the slowest action potential repolarization and/or depolarization (dv/dt), and/or other parameters can be determined very precisely. 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.

Conclusions

The monophasic action potential method represents a very efficient tool for the research in both experimental and clinical cardiology. It enables the study of the myocardial action potentials in vivo and, therefore, the study of the dynamic relation of this potential with all the organism variables. Thus MAP recordings offer the

opportunity to study, in the *in situ* heart, a variety of electrophysiological phenomena including effects of cycle length changes, action potential alternans, and antiarrhythmic drugs on electrical processes in myocardium. The recordings can provide systematic data for the design and interpretation of arrhythmia studies in animal models as well as for a mathematical modeling of ionic currents and corresponding electrical events in myocardial cells. As the recordings may reflect cellular calcium abnormalities the method seems to be also a potential source of a marker for identification of patients before heart failure decompensation or at risk for severe arrhythmias. Therefore it can be supposed that the application and interest in the MAP technique are only at its beginning.

Conflict of Interest

There is no conflict of interest.

Acknowledgements

This study is supported by grant GAAV 1ET201210527.

References

- AIDONIDIS I, POYATZI A, STAMATIOU G, LYMBERI M, MOLYVDAS PA: Assessment of local atrial repolarization in a porcine acetylcholine model of atrial flutter and fibrillation. *Acta Cardiol* **64**: 59-64, 2009.
- BURDON-SANDERSON J, PAGE FJM: On the electrical phenomena of the excitatory process in the heart of the frog and of the tortoise, as investigated photographically. *J Physiol Lond* **4**: 327-338, 1883.
- BURGEN ASV, TERROUX KG: The membrane resting and action potentials of the cat auricle. *J Physiol Lond* **119**: 139-152, 1953.
- COLLI FRANZONE P, PAVARINO LF, SCACCHI S, TACCARD B: Monophasic action potentials generated by bidomain modeling as a tool for detecting cardiac repolarization times. *Am J Physiol* **293**: H2771-H2785, 2007.
- CORABOEF E, WEIDMANN S: Potentials d'action du muscle cardiaque obtenus à l'aide de microelectrodes intracellulaires. Présence d'une inversion de potentiel. *Car Soc Biol Paris* **143**: 1360-1361, 1949.
- CUI G, SEN L (inventors): An apparatus and method for optimization of cardiac resynchronization therapy. App. No.: PCT/US2007/076543, Pub. No. WO/2008/024857, <http://www.wipo.int/pctdb/en/wo.jsp?IA=WO2008024857>, 2008.
- FRANZ MR, BURKHOF D, SPURGEON H, WEISFELDT ML, LAKATTA EG: In vitro validation of a new cardiac catheter technique for recording monophasic action potentials. *Eur Heart J* **7**: 34-41, 1986.
- FRANZ MR, BARGHEER K, RAFFLENBEUL W, HAVERICH A, LICHTLEN PR: Monophasic action potential mapping in human subjects with normal electrocardiograms: direct evidence for the genesis of the T wave. *Circulation* **75**: 379-386, 1987.
- FRANZ MR: Method and theory of monophasic action potential recording. *Prog Cardiovasc Dis* **33**: 347-368, 1991.
- GAO Z, XIONG Q, SUN H, LI M: Desensitization of chemical activation by auxiliary subunits. *J Biol Chem* **283**: 22649-22658, 2008.
- GRAVILESCU S, LUCA C: Right ventricular monophasic action potentials in patients with long QT syndrome. *Br Heart J* **40**: 1014-1018, 1978.

- JOCHIM K, KATZ LN, MAYNE W: The monophasic electrogram obtained from the mammalian heart. *Am J Physiol* **111**: 177-186, 1934.
- KONGSTADT O, XIA Y, LIANG Y, HERTEVIG E, LJUNGSTRÖM E, OLSSON SB, YUAN S: Epicardial and endocardial dispersion of ventricular repolarization. A study of monophasic action potential mapping in healthy pigs. *Scand Cardiovasc J* **39**: 342-347, 2005.
- KORSGRÉN M, LESKINEN E, SJOSTRAND U, VARNAUSKAS E: Intracardiac recordings of monophasic action potentials in human heart. *Scand J Clin Lab Invest* **18**: 561-564, 1966.
- LAB MJ: Monophasic action potentials and the detection and significance of mechanoelectric feedback in vivo. *Prog Cardiovasc Dis* **34**: 29-35, 1991.
- LEIRNER AA: Monophasic action potential of a cardiac muscle. *The system for experimental data measurement and evaluation*. (Doctoral Theses). In Portuguese. FMUSP, São Paulo, 1992, 52 p.
- LEIRNER AA, CESTARI IA: Monophasic action potential. New uses for an old technique. *Arq Bras Cardiol* **72**: 237-242, 1999.
- LI Z, HERTEVIG E, KONGSTADT O, HOLM M, GRINS E, OLSSON SB, YUAN S: Global repolarization sequence of the right atrium: monophasic action potential mapping in health pigs. *Pacing Clin Electrophysiol* **26**: 1803-1808, 2003.
- LIU XS, JIANG M, ZHANG M, TANG D, HIGGINS RS, CLEMO SH, TSENG GN: Electrical remodeling in a canine model of ischemic cardiomyopathy. *Am J Physiol* **292**: H560-H571, 2007.
- MICHAEL G, XIAO L, QI X-Y, DOBREV D, NATTEL S: Remodelling of cardiac repolarization: how homeostatic responses can lead to arrhythmogenesis. *Cardiovasc Res* **81**: 491-499, 2009.
- OLSSON SB: Right ventricular monophasic action potential during regular rhythm. *Acta Med Scand* **191**: 145-157, 1972.
- OLSSON SB, COTOI S, VARNAUSKAS E: Monophasic action potential and sinus rhythm stability after conversion of atrial fibrillation. *Acta Med Scand* **190**: 381-387, 1971.
- ORKAND RK, NIEDERGERK R: Heart action potential. Dependence on external calcium and sodium ions. *Science* **146**: 1176-1177, 1964.
- OSAKA T, YOKOYAMA E, KUSHIYAMA Y, HASEBE H, KURODA Y, SUZUKI T, KODAMA I: Opposing effects of bepridil on ventricular repolarization in humans. Inhomogeneous prolongation of the action potential duration vs flattening of its restitution kinetics. *Circ J* **73**: 1612-1618, 2009.
- RUAN H, MITCHELL S, VAINORIENE M, LOU Q, XIE L-H, REN S, GOLDHABER JI, WANG Y: Gial-mediated cardiac electrophysiological remodeling and arrhythmia in hypertrophic cardiomyopathy. *Circulation* **116**: 596-605, 2007.
- SLAVÍČEK J, KRŮŠEK J, KITTNAR O, VYSKOČIL F, TROJAN S: Monophasic action potential in frog and rat heart and its possible origin. *J Physiol Lond* 511P: 86P, 1998.
- TSALIKAKIS DG, FOTIADIS DI, KOLETIS T, MICHALIS LK: Automated system for the analysis of heart monophasic action potentials. *Comput Cardiol* **30**: 339-342, 2003.
- VAUGHAN WILLIAMS EM: A classification of antiarrhythmic actions reassessed after a decade of new drugs. *J Clin Pharmacol* **24**: 129-147, 1984.
- VIGMOND EJ: The electrophysiological basis of MAP recordings. *Cardiovasc Res* **68**: 502-503, 2005.
- WOODBURY LA, WOODBURY JW, HECHT HH: Membrane resting and action potentials of single cardiac muscle fibers. *Circulation* **1**: 264-266, 1950.
- YUE AM, PAISEY JR, ROBINSON S, BETTS TR, ROBERTS PR, MORGAN JM: Determination of human ventricular repolarization by noncontact mapping: validation with monophasic action potential recordings. *Circulation* **110**: 1343-1350, 2004.
- ZIPES DZ: Monophasic action potentials in the diagnosis of triggered arrhythmias. *Prog Cardiovasc Dis* **23**: 385-396, 1991.