The monophasic action potential upstroke: a means of characterizing local conduction

JOSEPH H. LEVINE, M.D., E. NEIL MOORE, D.V.M., PHD. ALAN H. KADISH, M.D., THOMAS GUARNIERI, M.D., AND JOSEPH F. SPEAR, PHD.

ABSTRACT The upstrokes of monophasic action potentials (MAPs) recorded with an extracellular pressure electrode were characterized in isolated canine tissue preparations in vitro. The characteristics of the MAP upstroke were compared with those of the local action potential foot as well as with the characteristics of approaching electrical activation during uniform and asynchronous conduction. The upstroke of the MAP was exponential during uniform conduction. The time constant of rise of the MAP upstroke (TMAP) correlated with that of the action potential foot (Tfoot): TMAP = 1.01 Tfoot + 0.50; r² = .80. Furthermore, changes in Tfoot with alterations in cycle length were associated with similar changes in TMAP. Tfoot = 1.06 TMAP − 0.11; r² = .78. In addition, TMAP and Tfoot both deviated from exponential during asynchronous activation; the inflections that developed in the MAP upstroke correlated in time with intracellular action potential upstrokes that were asynchronous in onset in these tissues. Finally, the field of view of the MAP was determined and was found to be dependent in part on tissue architecture and the space constant. Specifically, the field of view of the MAP was found to be greater parallel compared with transverse to fiber orientation (6.02 ± 1.74 vs 3.03 ± 1.10 mm; p < .01). These data suggest that the MAP upstroke may be used to define and characterize local electrical activation. The relatively large field of view of the MAP suggests that this technique may be a sensitive means to record focal membrane phenomena in vivo.


MONOPHASIC action potentials (MAPs) have been recorded from the surface of myocardium in animals and man with extracellular electrodes that induce local injury via suction or pressure.1–7 The close correlation between the time courses of repolarization of intracellular and monophasic action potentials during electrolyte and cycle length changes has been confirmed in vitro.1,3,7 The upstroke of the MAP, however, has received little attention. Although it is well known that its rate of rise is significantly slower than that of neighboring action potentials,1 its characteristics and determinants during both uniform and asynchronous conduction have not been well studied. In addition, the “field of view” of monophasic action potentials, that is, the distance from the recording electrode that an electrophysiologic event can be recorded, has not been determined. This is of importance if this technique is to be applied to record focal events such as afterdepolarizations3–4 from human or animal myocardium.

The present experiments in vitro were performed to (1) define the characteristics and determinants of the MAP as upstroke and demonstrate how it reflects local activity and (2) determine the field of view of the MAP and document its relationship to tissue architecture.

Methods

Experiments were performed on 33 tissues removed from 28 adult mongrel dogs weighing between 8 and 16 kg. The animals were anesthetized with intravenous sodium pentobarbital (30 mg/kg), their chests were opened via a left lateral thoracotomy, and their hearts were removed. Endocardial or epicardial tissues from the left and right ventricles 1 to 2 mm thick, 2 cm wide, and 2 to 3 cm long were removed and placed in a 100 ml tissue bath filled with oxygenated Tyrode’s solution (standard unless otherwise stated). Epicardial tissues were removed so that their longitudinal axis was parallel to the superficial fiber orientation. The methods used as well as the validity of fiber orientation determination have been described previously.8,9 The tissues were paced at a basic cycle length of 1000 msec with a bipolar stimulating electrode consisting of two Teflon-coated silver wires positioned at one end of the tissue. Constant current rectangular wave pulses of 2 msec duration and twice diastolic threshold intensity were used.

Monophasic action potential and transmembrane poten-
tial recordings. Monophasic action potentials were recorded with a pressure electrode with a silver-silver chloride recording tip (1.5 mm in diameter). A distal bath ground was used as the reference electrode. The unipolar signals were DC amplified (WPI, input impedance 10^{13} \Omega). The electrode was mounted on a micromanipulator to allow for stable, long-term recordings from a single site. MAP signals maintained their amplitude and configuration for greater than 1 hr with these methods.

With standard 3M potassium-filled microelectrodes, action potentials referenced to the bath ground were recorded from Purkinje fibers or superficial muscle cells within 7 mm of the contact electrode. Both MAP and microelectrode recordings were displayed on a memory oscilloscope (Tektronix) and were recorded on an electrostatic paper recorder (Gould) at paper speeds of 25 to 250 mm/sec or photographed on 35 mm film. In all cases, the action potentials were simultaneously recorded with the corresponding MAP. The MAP and action potential variables were measured to the nearest millivolt and 0.07 msec by projecting the 35 mm film onto a GTCO 1117 manual digitizer interfaced with a Hewlett Packard 9836 computer. Action potential duration during pacing was measured manually to the nearest 5 msec from the electrostatic paper recordings (100 mm/sec).

Anisotropy experiments. A wavefront conducts slower when moving transverse to myocardial fiber orientation than when moving longitudinal to it because of differences in internal axial resistances in the two directions. We used this normal anisotropic property of myocardium to study the relationships between the MAP upstroke and locally recorded transmembrane potentials during uniform conduction in 20 tissues. Conduction was longitudinal in 11 tissues, transverse in one tissue, and both longitudinal and transverse sequentially in eight tissues. Figure 1 presents the experimental arrangement. The pressure electrode for recording the MAP was positioned in one quadrant of the tissue. Two bipolar stimulating electrodes applied to the surface of the tissue were used to evoke wavefronts approaching the pressure electrode from either the transverse or longitudinal directions relative to the superficial myocardial fiber orientation. Longitudinal or transverse propagation was confirmed by recording unipolar electrograms and documenting from its morphology that uniform propagation in the stated direction was present. The position of the pressure electrode was altered when changing wavefront orientation to ensure stable MAP recordings in each direction. During each of these pacing modes, four to 10 transmembrane potentials were recorded in a straight line between the pacing wire and the wall of the extracellular electrode. Thus, the characteristics of multiple transmembrane potentials could be compared with those of the MAP. In addition, the influence of myocardial fiber orientation on the field of view of the MAP was studied in this model by altering the direction of conduction. Conduction velocity of the wavefront was determined by plotting the onset of activity at each of the multiple impalements against the position of the impalement. The location of each impalement was determined by observing the dimple midpoint produced at the site of impalement. An optical micrometer with a resolution of 0.08 mm was used to measure distances. The activation time of a site was measured at the time difference between the stimulus artifact or an upstroke of a single impalement and the time of the maximum rate of depolarization of a second action potential measured with a roving microelectrode. Since the slope of the regression is used to determine conduction velocity, this method is independent of stimulus latency. The entire MAP upstroke and the initial 10 mV deviation of the foot of the action potentials were manually digitized and displayed as a semilogarithmic plot of voltage vs time. In this way the time constants of the foot of the action potential (T<sub>foot</sub>) and of the MAP upstroke (T<sub>MAP</sub>) could be compared.

The relationship between T<sub>foot</sub>, the space constant (λ), conduction velocity (θ), and the time constant of the membrane (T<sub>m</sub>) has been described by Tasaki and Hagiyara

\[ T_{foot} = (\lambda/\theta)^2 (T_m)^{-1} \]

Since T<sub>foot</sub> and θ were measured and T<sub>m</sub> is independent of direction of conduction, the space constant ratio for transverse (T) and longitudinal (L) conduction can be calculated in the eight tissues in which the “field of view” of the MAP was measured in both directions (Table 1). The space constant ratio is:

\[ \lambda_T/\lambda_L = (\theta_T/\theta_L) (T_{foot} T_{foot L})^{-1} \]

In two tissues, the effect of pacing rate on the characteristics of the MAP upstroke and the action potential foot were compared. The tissues were paced at the following cycle lengths: 2000, 1000, 900, 800, 700, 600, 500, 400, 350, and 300 msec. The time constant of rise of the MAP upstroke and the action potential foot at each cycle length were compared.

Experiments to induce asynchrony.

Cold storage experiments. Four epicardial and four endocardial tissues were exposed to cold storage before being studied in order to induce depression in their electrophysiologic responses and were subjected to the following protocol: After removal from the heart, the tissues were placed in a tissue bath maintained at 27° C for a period of 2 to 4 hr. The tissues were then placed in a tissue bath maintained at 37° C and were studied immediately at this temperature while being driven at a cycle length of 1000 msec. All experiments were completed within a period of 1 hr. This technique allowed for the development of automatic activity and impaired impulse conduction during the period of time in which the tissue reequilibrated. MAPs and microelectrode recordings were obtained as described above during this early recovery period and electrophysiologic abnormalities noted in each. The microelectrode recordings were made from three to seven sites within a 2 mm radius of the extracellular pressure electrode.

Barium chloride. Three epicardial tissues were exposed to
barium chloride (10^{-7} M) to induce asynchronous activation. In addition, early afterdepolarizations and phase 4 diastolic depolarization were noted. MAPs were recorded from a given site and intracellular action potentials were recorded with one or two roving microelectrodes impaled in cells up to 2 mm from the extracellular pressure electrode. The microelectrode recordings were made from three to seven sites impaled sequentially.

Ischemia. In one tissue, asynchronous activation was induced after a brief ischemic period followed by a recovery period in situ before harvesting of tissue. In this animal, intravenous pentobarbital (30 mg/kg) was administered, mechanical ventilation was instituted, and the chest opened. The anterior descending artery was occluded for 15 min and a 20 min reflow period followed. The heart was then removed and epicardial tissues prepared in the manner described above. Simultaneous MAP and intracellular recordings were made. Action potentials were sampled with a roving microelectrode at distances up to 5 mm from the extracellular electrode in a direction parallel to the superficial fiber orientation.

Statistical methods. All tabular data are expressed as means ± SDs. Comparisons of means were made by the Student t test. A p value of .05 or less was considered significant. Linear fits were made by linear regression. For the conduction velocity determinations, an r^2 value greater than .90 was considered acceptable and indicated a uniform conduction velocity. Exponential fits were made by linear regression of the semilogarithmic transform of the data. An r^2 value greater than .97 for the foot of the action potential and the MAP upstroke was considered acceptable and indicated an exponential relationship. An r^2 value greater than .70 indicated a positive correlation between variables.

Results

Characteristics of the upstroke of the MAP. An example of an MAP and a simultaneous intracellular action potential are shown in figure 2. Note that the time course of repolarization of the intracellular recording is accurately depicted by the MAP. The amplitude of the MAP, on the other hand, is significantly lower than that of the intracellular action potential. In addition, the characteristics as well as the rate of rise of the upstroke of the MAP differ significantly from that of the intracellular action potential.

The upstroke of MAPs and intracellular recordings were displayed on an oscilloscope, photographed on 35 mm film, and digitized to compare their characteristics. An example of a semilogarithmic plot of voltage vs time of the digitized recordings of an MAP upstroke (right circles) and the intracellular potential recorded from a cell 5.1 mm from the wall of the pressure electrode (left circles) is shown in figure 3, A. The onset of MAP activity was defined as the first point at which the MAP voltage deviated from baseline by 0.1 mV (left vertical dashed line). The termination of the upstroke was defined as the first point at which the upstroke became nonexponential (right vertical dashed line). In all but one case this represented a point whose voltage was greater than 75% of the total MAP amplitude. Note that the absolute voltage of the MAP (right) was less than that of the intracellular recording (left), that the MAP rate of rise was slower, and that unlike the intracellular action potential in which only the foot rises exponentially, the majority of the MAP upstroke was exponential. These characteristics were consistently found in each experiment during uniform conduction and were independent of the direction of the wavefront relative to fiber orientation.

The pressure electrode recorded MAPs that reflected approaching electrical activity at a considerable distance. To determine the position of the leading edge of electrical activity relative to the extracellular electrode at which time the MAP first deviated from baseline (i.e., its “field of view”), a plot of distance vs time for local activation was constructed with intracellular action potential recordings and this plot was then compared with the MAP time course for each experiment (figure 3, B). The position of the approaching electrical activation at the time corresponding to a deviation of the MAP from baseline of 0.1 mV, the onset (a) and the position at the time at which the MAP upstroke became nonexponential (b) were extrapolated from

![FIGURE 2](http://circ.ahajournals.org/)

Analog recordings of an MAP and a simultaneously recorded intracellular action potential (IAP). Note that the time course of repolarization of the MAP closely approximates that of the intracellular recording. The amplitude and overshoot of the MAP, however, differ from those of the intracellular recording.

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these plots. The distance of the leading edge of electrical activity from the pressure electrode at the time the MAP deviation from baseline was 0.1 mV (arrow — a) defined its field of view. These data for all the tissues are presented in table 1. This distance was related to fiber orientation and was greater in the longitudinal direction than in the transverse direction. The onset of the MAP occurred when the approaching edge of electrical activity was 6.02 ± 1.74 mm away from the contact electrode in the longitudinal direction and 3.03 ± 1.10 mm away from the electrode in the transverse direction (p < .01).

The difference in the field of view of the MAP during conduction transverse or longitudinal to fiber orientation was related to differences in the space constant in these directions. The Tfoot for each tissue is also presented in table 1. The space constant ratio was calculated as described in the methods. The calculated space constant ratio was correlated with the ratio of the field of view of the MAP in the transverse and longitudinal directions on the ordinate. The equation of the regression and the r² value are shown.

![Figure 3](https://example.com/figure3.png)

**Figure 3.** A, Examples of an MAP and a simultaneous intracellular action potential photographed on 35 mm film and then digitized. Potential vs time is plotted on a semilogarithmic scale. Note the amplitude of the MAP is lower and the upstroke slower than that of the action potential. Note also that nearly the entire MAP upstroke is exponential and that its time constant (TMAP) approximates that of the action potential foot (Tfoot). B, Field of view of the MAP. The time at which the MAP deviated from baseline by 0.1 mV, conveniently obtained as the x-axis intercept from the semilogarithmic plot, and the time at which the MAP became nonexponential were identified on the corresponding conduction velocity plot. In this way the position of the leading edge of electrical activation at both of these times could be extrapolated and the field of view of the MAP determined. Note also that the true edge of the contact electrode (arrow) was nearly the same as the extrapolated location of the electrical activity at the time the MAP became nonexponential. See text for details.

![Figure 4](https://example.com/figure4.png)

**Figure 4.** The space constant ratio derived from the foot of the action potential comparing transverse (T) and longitudinal (L) directions is correlated with the ratio of the field of view of the MAP in these directions. The space constant ratio (T/L) is displayed on the abscissa and the ratio of the field of view of the MAP in the transverse and longitudinal directions on the ordinate. The graph of these results as well as the regression equation are presented in figure 4.
whose rate of rise is not dependent on local sodium channel activation but rather is determined by approaching electrical activity, i.e., the action potential foot. To determine whether the MAP upstroke and the action potential foot are related, their time constants of rise were compared. These data are shown in table 1. A correlation between these measured variables was present. In figure 5 is the regression between the time constant of rise of the action potential foot and that of the MAP upstroke in the 28 experiments. Note that not only are the two values related but that they are close in magnitude. Note also that the magnitude and direction of change in Tfoot were the same as those in TMAP when comparing measurements made in the longitudinal and transverse directions in each tissue (table 1).

To strengthen the evidence for the relationship between Tfoot and TMAP, two tissues were stimulated at varying cycle lengths and Tfoot and TMAP were compared during longitudinal conduction. In this way, changes in TMAP induced by changing membrane properties (the effect of cycle length on conduction and sodium conductance) could be evaluated and compared with the changes in Tfoot. Results from one tissue are shown in figure 6. Both TMAP and Tfoot increased at decreasing

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2.22 ± 1.28
2.74 ± 1.44

\( p < .01 \)

Experiments 12, 20; 13, 21; 14, 22; 15, 23; 16, 24; 17, 25; 18, 26; and 19, 27 were performed in the same tissue at different sites during longitudinal and transverse conduction.

\( T_{foot} \) = time constant of the foot of the action potential, mean value of five to 10 measurements; \( T_{MAP} \) = time constant of the MAP upstroke; \( L \) = longitudinal; \( T \) = transverse; \( \theta \) = conduction velocity.

*By paired t test.
pacings cycle lengths. As shown in the figure, these changes were closely correlated and of nearly the same magnitude.

Asynchronous activation and electrotonic phenomena. We have characterized the properties of the MAP upstroke during uniform conduction and have demonstrated that the upstroke is exponential under these circumstances. In epicardial tissues in which slow conduction and asynchronous activation were present associated with cold storage depression, ischemia, or exposure to barium chloride, the upstroke of the MAP became discontinuous and in some cases exhibited multiple inflections. In tissues in which a relatively small degree of asynchrony was present, deviation from the exponential nature of the MAP was best demonstrated in semilogarithmic plot of voltage vs time. An example of this, as well as an analogous changes in nearby action potential foot recordings from the same tissue are shown in figure 7. Note that the semilogarithmic plots were nonlinear for both the action potential foot and the MAP upstroke, which is in contrast to what was noted during uniform conduction (figure 3).

In two tissues subjected to cold storage depression and in one tissue exposed to barium chloride, activation became even more asynchronous and frank discontinuity of the upstroke was noted. An example is shown in figure 8 from a tissue subjected to cold storage depression. In this case, microelectrode recordings from multiple sites at close approximation to the contact MAP electrode identified action potentials whose upstrokes corresponded in time to each phase of the asynchronous MAP upstroke, thereby documenting the composite nature of the upstroke of the MAP.

In some regions of the asynchronously activated tissues, intracellular action potentials were preceded by electrotonic prepotentials. The prepotentials were also apparent in monophasic action potentials. An example is shown in figure 9. The action potential was recorded at a distance of 1.5 mm from the pressure...
LABORATORY INVESTIGATION—ELECTROPHYSIOLOGY

FIGURE 8. Asynchronous activation detected by MAPs recorded in an epicardial tissue subjected to cold-storage depression. Note the asynchronous upstroke of the MAP. Note also that the onset of action potential 1 and 2 correspond to different portions of the MAP upstroke. IAP = intracellular action potential. See text for details.

electrode. Note that the time course of the MAP accurately reflects that of the action potential; that is, its onset of activity (dotted lines) and its duration are similar to those of the recorded action potential. Note also that the presence or absence of the prepotential (small arrow) in the intracellular action potential is recorded in the MAP. Finally, phase 4 depolarization present in the microelectrode recording is also recorded in the MAP (large arrow).

Discussion

The major finding in this study is that MAPs recorded with an extracellular pressure electrode result from electrical activity at a distance from the recording site. The field of view of this technique, and hence its sensitivity to record focal events such as afterdepolarizations, has been defined. In addition, the MAP upstroke has been characterized and has been shown to be analogous to the action potential foot and hence may be used to derive information of passive membrane properties that relate to conduction. Furthermore, discontinuities in conduction were demonstrated as inflections in the upstroke. Thus the MAP upstroke appears to give qualitative and quantitative information on the nature of local conduction.

MAPs can be recorded from cardiac tissue that has been injured by suction or pressure. The cells directly beneath the electrode are injured and hence do not generate active responses. Therefore, the potential changes sensed by the extracellular electrode must represent potential changes generated by activity elsewhere in the preparation and represent a fraction of the transmembrane potential as determined by the shunt resistance between the intracellular and extracellular space. As such, the distance from the electrode at which electrical activity is detected depends on the passive properties of the tissue (i.e., the space con-

FIGURE 9. After exposure to cold storage, electrotonic prepotentials (small arrows) were present in both the transmembrane and monophasic recordings. Note that in the third beat, the prepotential was no longer present in either record and that the onset of the action potential (left dotted line) and the prepotential (right dotted line) were coincidental in the two recordings. Note also that enhanced phase 4 depolarization (large arrow) was present and was accurately detected by the contact electrode. IAP = intracellular action potential.
stant) that in turn affect the feed-in of currents from surrounding active tissues. This is supported by the finding that nearly the entire MAP upstroke during uniform conduction resulted from activity at a distance from the extracellular electrode. In addition, the field of view of the MAP was found to be greater during longitudinal compared with transverse conduction and was found to correlate with a calculated space constant. It is known that a difference in internal resistance exists in the longitudinal and transverse directions.\textsuperscript{10-14, 16, 17} This has been attributed to fewer low-resistance intercellular connections and hence a decreased space constant in the transverse direction.\textsuperscript{12, 13} It is of interest that the semilogarithmic plot of voltage vs time of the MAP upstroke remained linear until that time corresponding to the activation of the normal cells nearest to the extracellular electrode. At this time, the rate of rise of the MAP upstroke decelerated as did the slope of the semilogarithmic plot. This is also consistent with the notion that the genesis of the MAP is dependent in part on the space constant, since at this time the space constant would decrease significantly because of the increase in sodium conductance in the rim of active cells immediately adjacent to the electrode. Thus the MAP does not just record a fraction of the activity of the rim of cells in immediate contact with the extracellular electrode but rather detects activity occurring at a distance from the extracellular electrode that is determined at least in part by passive membrane properties. Therefore the determinants of the MAP are not significantly different from those leading to that part of an intracellular action potential not dependent on sodium current activation, i.e., the action potential foot.

That the MAP upstroke and the portion of the intracellular recording dependent on approaching electrical activity rather than sodium channel activation (i.e., the action potential foot) are analogous is supported by data from our experiments. First, the time constants of rise of the MAP upstroke and the action potential foot were closely correlated and close in absolute magnitude (figure 5). Second, changes in T\textsubscript{foot} caused by pacing at shorter cycle lengths were reflected by similar changes in T\textsubscript{MAP} (figure 6). Finally, the deviation from an exponential relationship of the action potential foot during asynchronous activation was reflected by similar changes in the MAP upstroke (figure 7). Thus the characteristics of the MAP upstroke under a wide variety of conditions are analogous to those of the action potential foot.

Although T\textsubscript{MAP} and T\textsubscript{foot} were strongly correlated and close in absolute value, T\textsubscript{MAP} was consistently some-what larger than T\textsubscript{foot} (table 1). The reasons for this are unclear. These changes may be caused by tissue injury induced with the contact electrode. Alternatively, it is likely that the seal between the contact electrode and the tissue is not perfect. This may result in a low-resistance shunt between the extracellular space and the tissue bath resulting in an increase in T\textsubscript{MAP}. Another possibility is that a difference exists between the way a microelectrode (a point source) and the contact electrode (a finite cylinder) sense an approaching wavefront. Specifically, the relative position of the leading edge of the activity and the different portions of the edge of the contact electrode may influence the voltage measured by the contact electrode at each position of the wavefront and hence may alter its upstroke characteristics. Finally, T\textsubscript{foot} in table 1 is a mean value. There was a variability in this value even among close points (coefficient of variance, range .10 to .46; mean ± SD .25 ± .08). The degree to which T\textsubscript{MAP} varied from mean T\textsubscript{foot} is within this range.

In our experiments, the mean values of T\textsubscript{foot} were greater for transverse than for longitudinal conduction. Others have noted either no change\textsuperscript{14} or a decrease in T\textsubscript{foot} for transverse relative to longitudinal conduction\textsuperscript{12, 13} Differences in our results from others as well as differences between results of others likely are a result of changing MAP recording sites, microelectrode impalement sites, and stimulation sites in these tissues (our experiments were not designed to directly determine the effects of changes in direction of conduction on T\textsubscript{foot} at a given site).

The properties of the MAP upstroke may be used to characterize local conduction. During uniform conduction, the MAP upstroke was exponential in all cases. However, during nonuniform conduction and asynchronous activation, the MAP upstroke became nonexponential and inflections developed (figure 7). In addition, when gross asynchrony was present, even larger and more prominent inflections developed and frank discontinuity was apparent (figure 8). Each inflection correlated in time with the onset of a local intracellular action potential. Thus a quantitative estimate of the degree of asynchrony among cells within the field of view of the MAP is available. Finally, prepotentials were occasionally noted (figure 9). It is of interest that the tissue injury that is a prerequisite for the development of MAPs did not itself lead to artifacts simulating electrotonic phenomena. This supports the notion that the contact electrode records phenomena from normal cells at a distance from the contact electrode. Nevertheless, in no case were prepotentials or asynchronous activation noted spuriously in MAPs.
when not present in action potentials recorded at a site in close approximation to the contact electrode. Thus the properties of the MAP upstroke may be used to characterize the nature of local conduction and may be analogous to those of fractionated unipolar electrograms, which can also be recorded from areas of exhibiting asynchronous activation.18

The findings in our study are clinically relevant. Current electrophysiologic techniques do not allow for adequate identification of arrhythmic mechanisms in man. We have recently demonstrated that afterdepolarizations can be recorded in MAPs and therefore we may be able to characterize abnormal impulse initiation in the catheterization laboratory.3, 4 The sensitivity of this technique to record focal events such as afterdepolarizations was unknown. The present study defines the field of view of the MAP technique and has demonstrated that this is determined in part by tissue architecture and the space constant. In addition, the MAP upstroke can be used to characterize the nature of local conduction. Uniform and asynchronous activation can be differentiated by determining whether the MAP upstroke remains exponential. The degree of asynchrony can be estimated from the time course of the inflections, each of which correlates with local cellular excitation. Furthermore, the time constant of rise of the MAP upstroke may be used in the same way as the time constant of rise of the action potential foot to approximate changes in conduction and passive membrane properties in vivo.

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The monophasic action potential upstroke: a means of characterizing local conduction.

J H Levine, E N Moore, A H Kadish, T Guarnieri and J F Spear

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