The Electromotive Force of the Ventricular Free Wall and Papillary Muscle Preparations

Saburo Mashima, Kan Takayanagi, Georg Schmidt, and Akira Nozaki

SUMMARY. The electromotive force of the ventricular tissues with different anatomy and activation patterns was studied. The left ventricular wall was perfused with Tyrode's solution from the circumflex branch of the left coronary artery and was stimulated first at an epicardial and then endocardial site to induce ectopic beats. The early QRS voltage was compared with the activated area at the same instant. In other experiments, the whole heart was perfused from the aorta, and the anterior papillary muscle of the right ventricle was introduced into a small separate chamber. Different locations were stimulated to induce longitudinal and transverse activation, and the remote potential was measured with leads in both directions. By means of a calibration system with artificial dipoles, the strength of the double layer was expressed in terms of mA-cm per unit area of the activation wave front. The results indicated that epicardial stimulation of the left ventricular wall produced voltage proportional to the activated area; the average moment was found to be 0.11 mA-cm per unit area. The potential curve produced by endocardial stimulation of the same preparation was characterized by an initial low-voltage phase, followed by a sharp upstroke. The right ventricular papillary muscle produced a larger double layer moment during activation in the longitudinal direction, but voltage due to transverse activation was several times smaller. (Circ Res 56: 851-856, 1985)

THE extracellular potential field of myocardial tissue was studied in our previous report (Mashima et al., 1978). Using the isolated dog heart, we determined the effectiveness of the activation wave front as a current generating the double layer in terms of mA-cm per unit area. Although our experiments measured the average amount of the double layer extending over layers of ventricular muscle, contributions from different portions probably vary, depending on local structures and activation patterns of the tissue. Some evidence indicates that the strength of the double layer depends on the local activation sequence with respect to the orientation of fibers (Corbin and Scher, 1977; Spach et al., 1979; Colli-Franzone et al., 1982). Whereas the direction of the fibers varies with muscle layers of different depths, the apical portion of the papillary muscle consists of nearly parallel fibers (Myerburg et al., 1978), which provides an opportunity for investigation of different patterns of the activation process. Patterns of activation in subendocardial layers of the ventricle containing specialized fibers may be different from those in subepicardial layers.

This work was undertaken to extend our previous studies to include different tissues and activation sequences. Utilizing preparations perfused from a coronary artery, we examined the effect of an activation wave on remote potential by stimulating the left ventricular wall at epicardial and endocardial sites. The potential produced by the anterior papillary muscle of the right ventricle was measured during activation proceeding along and across the long axis of the preparation.

Methods

Twenty mongrel dogs were used in this study. The hearts were isolated and perfused with Tyrode's solution at 37°C. For experiments with the left ventricular wall, the circumflex branch of the left coronary artery was selectively perfused, and portions of the ventricle, perfused from other branches, including the right ventricle and interventricular septum, were removed. The free wall obtained from the left ventricle was supported by a stiff wire to make a plate-like configuration and was suspended in a cubic box filled with Tyrode's solution. Stimulating electrodes were attached to the midportion of the preparation at corresponding sites on the epicardial and endocardial surfaces.

The recording system is similar to that described in our previous paper (Mashima et al., 1978) and will be mentioned here only briefly. The preparation was immersed in Tyrode's solution in a cubic container (edge length, 12 cm). Five silver electrodes attached at each of the surfaces of the container were connected through equal resistors making a remote lead with a uniform lead field. The potential in the lead perpendicular to the preparation was amplified and observed on an oscilloscope with photographic recording, or was written directly with an ink-jet recorder (Nihon-Koden model R1108-4S). There were no significant differences in the results obtained by these two methods.

The local activation time was determined at many epicardial and endocardial sites. On the epicardial surface, a cross-shaped electrode holder with 80 electrodes, 20 on
each of the four arms, was attached for the measurement of activation time. On the endocardial surface, a bipolar search electrode or one of the arms of the electrode holder described above was used. In addition, the intramural activation time was determined by electrode needles with 10 small electrodes having an interelectrode distance of 1.0 mm. The needles were inserted into the preparation at 8–14 locations successively around the stimulating electrodes. On the endocardial surface, deflections due to the activation of Purkinje fibers and the ventricular muscle were sometimes observed. In these instances, the latter was used for the determination of local activation time.

Within a short time after stimulation, the activation wave was confined to the inside of the preparation without breaking through the opposite surface. During this period, the area of the activation wave front was estimated by the activated area on the epicardial or endocardial surface. Voltage and area measurements were performed at 5-msec intervals and were compared to calculate the average voltage per unit area of the activation wave front.

For experiments with papillary muscle, the whole heart was perfused from the aorta. The right coronary artery was ligated and the right ventricle was opened. The anterior papillary muscle of the right ventricle, which was perfused from the anterior descending branch, was exposed, and the valvular attachment was cut free after being ligated with a thread. As shown in Figure 1, the papillary muscle was introduced into a small cubic box (edge length, 19 mm), which had a hole 8 mm in diameter at the bottom. Longitudinal potential measurements were made with a lead from two loops of silver wire at the bottom and at a height of 12 mm. The box had another pair of silver plates on the inside surface to form the transverse lead (Fig. 1). To activate the preparation longitudinally, a remote epicardial site outside the small box was stimulated electrically. To obtain transverse activation, two small pairs of stimulating electrodes were applied to the side of the muscle, at a site near the bottom and at about one-third the distance from the apex of the papillary muscle. On both occasions, local activation time was determined at many sites on the epicardial surface of the preparation to confirm nearly longitudinal or transverse directions of activation. With longitudinal activation, the area of the activation wave was considered as the transverse section of the muscle, which was calculated from the long and short diameters of the muscle at the level of the midpoint between the base and apex. The area of the transverse activation wave varied with time. The maximal value was estimated by multiplying the height of the muscle by thickness. Since the potential due to transverse activation usually was small, the peak voltage was compared with the maximal cross-sectional area estimated as stated above.

In order to express the effectiveness of the myocardial generator in terms of dipole moment in mA-cm, each measurement system was calibrated with artificial dipoles.

The lead system for the left ventricular wall was calibrated with an artificial dipole placed at several locations within the region corresponding to the preparation. The effect was found to be nearly uniform over the region, with less than 10% errors. In the small box for the papillary muscle experiments, the transverse lead was also practically uniform, but the longitudinal lead showed slightly different sensitivity to dipoles of different locations. The average sensitivity to several dipole locations was used for this lead.

Because of the differences in the resistivity of Tyrode’s solution and ventricular muscle, a dipole inserted into the tissue was more effective than that in the solution with the same moment. The ratio of their effectiveness was determined by comparison of a needle dipole inserted into the preparation and the same needle in the solution, as described previously (Mashima et al., 1978). For the papillary muscle, two directions of the needle, longitudinal and transverse, were examined. For the left ventricular preparation, the direction perpendicular to the wall was selected.

**Results**

**Left Ventricular Wall**

Examples of recorded potential curves are shown in Figure 2. The spread of activation from epicardial and endocardial sites is shown in Fig. 3, where the surface measurements (top) and intramural activation times (bottom) are shown. With epicardial stimulation, arrival of the activation at the endocardial surface was usually more than 30 msec after stimulation. The spread of activation was faster with endocardial stimulation, and the breakthrough at the epicardial surface was sometimes less than 20 msec after stimulation. However, the activation front was generally confined within the intramural region to 20 msec, and since measurements at the earlier time were susceptible to errors, the voltage...
was read at 20 msec after endocardial stimulation and at 20 and 30 msec after epicardial stimulation. At the same instants, the activated area on the corresponding surface was determined. Dividing the voltage by area, the strength of the double layer was expressed in terms of mV/cm². This value was compared with the effectiveness of an artificial dipole with known moment inserted into the preparation. Thus, the absolute moment of the double layer was obtained in terms of mA-cm per unit area of the activation wave front. The results are shown in Table 1. It can be seen that values at 20 and 30 msec after the epicardial stimulation are not significantly different. At 20 msec, endocardial activation produced a smaller voltage.

The potential curves in Figure 2 show that endocardial stimulation was characterized, as compared with epicardial stimulation, by initial low voltages, which were followed by a sharp rise. The timing of the sharp upstroke differed from preparation to preparation, ranging from 15–25 msec. Sometimes a delay of the upstroke was noticed after prolonged experimental procedures in the same preparation. Since an accurate area measurement was difficult at times before 20 msec, the amplitude of the voltage at 10 and 15 msec relative to the value at 20 msec standardized as unity was plotted as shown in Figure 4. The solid line indicates the curve of the square of elapsed time. Epicardial potentials were almost on the line; that is, the potential was nearly proportional to the square of time. In contrast, the endocardial potentials were significantly lower than the line in Figure 4. At 20 msec, the double layer moment due to endocardial stimulation was already about 60% that of epicardial stimulation (Table 1). Earlier voltages were even smaller.

**Papillary Muscle**

Figure 5 shows the activation time on the surface of two papillary muscle preparations. The left panel shows the longitudinal activation induced by a stimulus applied to a remote site, indicating that activation was not perfectly longitudinal. However, since the voltage in the longitudinal lead was due to the longitudinal component of the double layer, the voltage was compared with the cross-sectional area of the papillary muscle as the projection of the activation wave on the plane perpendicular to the long axis of the preparation. The preparation on the right-hand side in Figure 5 is an example of transverse activation. Even with stimulation of one location, the spread of activation was faster in the longitudinal direction and the activation on the whole proceeded in the transverse direction.

Figure 6 shows the potential curves of longitudinal and transverse leads, which were obtained during longitudinal activation of the preparation. In this experiment, activation was confined almost entirely within the papillary muscle between 55 and 65
TABLE 1
Double Layer Moment of the Activation Wavefront Measured with Left Ventricular Free Wall
and Anterior Papillary Muscle of the Right Ventricle

<table>
<thead>
<tr>
<th></th>
<th>No. of preparations</th>
<th>mA cm per unit area</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left ventricular wall</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epicardial stimulation</td>
<td>20 msec 13</td>
<td>0.10 ± 0.042</td>
</tr>
<tr>
<td>Endocardial stimulation</td>
<td>30 msec 15</td>
<td>0.11 ± 0.039</td>
</tr>
<tr>
<td></td>
<td>20 msec 13</td>
<td>0.06 ± 0.031</td>
</tr>
<tr>
<td>Right ventricular papillary muscle</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Longitudinal activation</td>
<td>mean 9</td>
<td>0.17 ± 0.041</td>
</tr>
<tr>
<td></td>
<td>peak 10</td>
<td>0.18 ± 0.044</td>
</tr>
<tr>
<td>Transverse activation</td>
<td>6</td>
<td>0.021 ± 0.009</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± sd.

msec. Hence, the mean voltage during this period was measured as the representative value of the voltage. In addition, the peak voltage was used for calculation, since tapering of the preparation, as well as the width of the activation wave, may cause reduction of the voltage. For comparison with the peak voltage, the thickest cross-section of the preparation was used. The results are also shown in Table 1.

Transverse activation of the papillary muscle was usually induced by simultaneous stimulation of two locations, one at the base and the other near the apex. We used only those experiments in which variations of the activation time along the long axis on the line opposed to the stimulated side were within 5 msec. The peak voltage in the transverse lead was measured and compared with the projection area of the preparation on the plane perpendicular to the lead. Hence, the results (Table 1) are not strictly from the simultaneous voltage and area measurements. However, it is obvious that transverse activation was associated with much smaller moment. At the same time, the longitudinal lead in Figure 7 also recorded certain deflections due to local longitudinal activation processes, indicating that activation was not completely transverse. The voltage in the longitudinal lead was quite small compared with the potential due to longitudinal activation.

Discussion

The electromotive force of ventricular tissue is based not only on the membrane potential of individual fibers, but also, on the mode of impulse conduction in tissue. So that the electromotive force associated with different structures and activation patterns could be investigated, special preparations were designed in this study. The isolated left ventricular wall was perfused from the circumflex artery to keep the intramural layers in active physiological condition. The anterior papillary muscle of the right ventricle was similarly perfused from the anterior

![Figure 4](upstroke_of_the_potential_curves_of_epicardial_epi_and_endocardial_endo_stimulation_with_standardization_of_the_value_at_20_msec_as_unity_a_solid_line_indicates_the_square_function_of_time.png)

**Figure 4.** Upstroke of the potential curves of epicardial (epi) and endocardial (endo) stimulation with standardization of the value at 20 msec as unity. A solid line indicates the square function of time.

![Figure 5](examples_of_the_activation_spread_in_two_papillary_muscle_preparations_stimulated_at_a_remote_side_left_and_at_the_side_of_the_preparation_right_numbers_indicate_the_time_after_the_stimulus_in_msec.png)

**Figure 5.** Examples of the activation spread in two papillary muscle preparations stimulated at a remote site (left) and at the side of the preparation (right). Numbers indicate the time after the stimulus in msec.
descending artery, and the potential measurements were performed in a separate chamber. Longitudinal and transverse leads in the chamber were practically insensitive to outside events, if the level of the solution was kept below the edge of the small box and there was no electrical connection to the outside solution over the edge.

The results of the experiments with the left ventricular wall indicated that epicardial stimulation produced a double layer with the moment of 0.11 mA·cm per unit area. Comparable values at 20 and 30 msec after stimulation indicate that the strength of the double layer was proportional to the activated area on the epicardial surface, which was in accord with our previous results (Mashima et al., 1978), and supported the view that the moment was representative of ventricular tissue with muscle conduction. The value 0.11 mA·cm was somewhat smaller than that of the previous study with the whole heart, but individual variations were rather large and the differences were not significant. A systematic difference may exist, as implied by the same values at 20 and 30 msec in this study. Differences in the preparations may be the cause.

With endocardial stimulation of the left ventricular wall, the activation spread was faster, probably due to the existence of the Purkinje network. However, the observed potential was not proportionally larger, at least not in the initial phase. Since the relation between the increase in voltage and the activation front area was not linear and differed from preparation to preparation, the moment at 20 msec listed in Table 1 did not appear to be general. Possible explanations of a smaller moment with endocardial stimulation include island-like activated areas on the endocardial surface in the initial phase, which would cause an overestimation of the activated area. Another possibility is a cancellation effect due to irregularities of the activation wave. Purkinje muscle junctions in deeper layers may create a local radial spread of activation, resulting in the cancellation of forward and backward forces. Opposite possibilities of activation were sometimes observed in intramural activation studies. This was, however, not a constant finding. Besides the existence of Purkinje fibers, the orientation of fibers in subendocardial layers was reported as mainly tangential (Myerburg et al., 1978). Such a structure produces, as indicated by the present experiments with papillary muscle, much smaller voltage in the direction perpendicular to the fiber orientation.

There have been controversies concerning the existence of "electrically silent" subendocardial layers of ventricular wall (Pipberger and Lopez, 1980), and quantitative evaluation of different layers has not been made. According to the present results, endocardial layers are not silent, but are less effective in generating extracellular potential. Configurations of the upstroke of the potential curve suggest that the effect of cancellation or irregularities of the activation process are more marked in the earlier phase. Later, the moment may grow to the level of the epicardial stimulation experiments, although this could not be confirmed due to the breakthrough of activation on the epicardial surface or the wavefront exceeding the measurement area.

The potential produced by longitudinal activation of the papillary muscle was found to be about 50% larger than that of epicardial activation of the left ventricular wall. Uniform orientation of fibers simulates the hypothetic thick fiber considered in our previous study (Mashima et al., 1978). Concerning the effectiveness of generating external potential, a fiber with a cross-sectional area of 1 cm² is equivalent to a dipole with a moment of \(\frac{M}{r_i}\) mA·cm, where \(M\) is the height of the action potential and \(r_i\) intracellular resistivity. If the value 470 ohm·cm is used for \(r_i\) (Weidmann, 1970), the moment of the equivalent dipole is calculated to be about 0.21 mA·cm. The measured moment of the papillary muscle in this study amounted to 80% of the theoretical value, which seemed to be reasonable for tissue containing interstitial space.

Transverse activation of the papillary muscle is another extreme condition. Even the peak voltage in the transverse lead was generally small, and the moment of the activation wave was estimated as several times smaller than that of longitudinal acti-
vation. If the electromotive force of individual fibers is directed along the fiber, a zig-zag course of activation will cause cancellation between opposing forces. The number of branchings and angles with the long axis will determine the net moment of the transverse activation wave.

On the other hand, influences of the anisotropic structure of the myocardium on the electromotive force have received attention in recent years. Dependence of conduction velocity and extracellular potential on the direction of activation spread has been observed in different preparations (Roberts et al., 1979; Spach et al., 1981; Baruffi et al., 1978). For tissue composed of numerous fibers, the remote potential appears to depend on the total intracellular current flow in the direction of the recording lead (Mashima et al., 1978; Spach et al., 1979). In other words, the "effective internal resistance" (Spach et al., 1981) is a principal determinant of the conduction velocity and extracellular potential. With epicardial potential measurements, Roberts and Scher (1982) reported 6 times the internal resistivity in the transverse direction compared with the longitudinal direction. Clerc's (1976) data indicated similarly 9 times the resistivity in the transverse direction. Our results showed that extracellular potential with transverse activation was about one-eighth that with longitudinal activation. The conduction velocity was not accurately determined in this study. However, as shown in Figure 5, the conduction velocity is estimated to be more than twice as fast along the long axis of the preparation. In spite of complex branchings and electrical properties of fibers in three-dimensional living tissue, observed longitudinal and transverse $r$, and conduction velocity seem to be related similarly as expected from the theory with regard to a single fiber, that conduction velocity is inversely proportional to the square root of internal resistivity (Hodgkin, 1954).

Previous studies usually are based on epicardial measurements or observations of excised myocardial strips. Methods of the present study are more physiological, freer from boundary effects and other restrictions, and are therefore suitable for evaluation of the net absolute electromotive force of myocardium as a tissue generator. Underlying cellular mechanisms await further studies, which could explain observed extracellular events.

This study was supported in part by Grant-in-Aid for Scientific Research 56480176 from the Japanese Ministry of Education.

References


Clerc L (1976) Directional differences of impulse spread in trabecular muscle from mammalian heart. J Physiol (Lond) 255: 335–346


INDEX TERMS: Ventricular activation sequence • Equivalent double layer • Subendocardial layer • Myocardial fiber orientation
The electromotive force of the ventricular free wall and papillary muscle preparations.
S Mashima, K Takayanagi, G Schmidt and A Nozaki

Circ Res. 1985;56:851-856
doi: 10.1161/01.RES.56.6.851

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1985 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/56/6/851

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org/subscriptions/