Transmembrane potential changes caused by monophasic and biphasic shocks

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Zhou, Xiaohong, William M. Smith, Robert K. Justice, James L. Wayland, and Raymond E. Ideker. Transmembrane potential changes caused by monophasic and biphasic shocks. Am. J. Physiol. 275 (Heart Circ. Physiol. 44): H1798–H1807, 1998.—Transmembrane potential change (ΔVm) during shocks was recorded by a double-barrel microelectrode in 12 isolated guinea pig papillary muscles. After 10 S1 stimuli, square-wave S2 shocks of both polarities were given consisting of 10-ms monophasic and 10/10-ms and 5/5-ms biphasic waveforms that created potential gradients from 1.1 ± 0.3 to 11.9 ± 0.4 V/cm. S2 shocks were applied with 30, 60- to 70-, and 90- to 130-ms S1-S2 coupling intervals so that they occurred during the plateau, late portion of the plateau, and phase 3 of the action potential, respectively. Some shocks were given across as well as along the fiber orientation. The shocks caused hyperpolarization with one polarity and depolarization with the opposite polarity. The ratio of the magnitude of hyperpolarization to that of depolarization at the three S1-S2 coupling intervals was 1.5 ± 0.3, 1.1 ± 0.2, and 0.5 ± 0.2, respectively. ΔVm during the shock was significantly greater for the monophasic than for the two biphasic shocks. The prolongation of total repolarizing time (TRT) was significantly greater for monophasic (119.8 ± 19.1%) and 10/10-ms biphasic (120.5 ± 18.2%) than for 5/5-ms biphasic (113.0 ± 12.9%) waveforms. The dispersion of the normalized TRT between instances of hyperpolarization and depolarization caused by the two shock polarities was 7.4 ± 7.1% for monophasic, 3.0 ± 4.1% for 10/10-ms biphasic, and 2.8 ± 3.1% for 5/5-ms biphasic shocks (P < 0.05 for monophasic vs. biphasic). Shock fields along fibers produced a larger ΔVm and prolongation of TRT than those across fibers. We conclude that 1) a change in shock polarity causes an asymmetrical change in membrane polarization depending on shock timing; 2) the 5/5-ms biphasic waveform causes the smallest ΔVm prolongs repolarization the least, and causes the smallest polarity-dependent dispersion; and 3) the changes in transmembrane potential and repolarization are influenced by fiber orientation. depolarization; hyperpolarization; action potential duration; defibrillation

The response of myocardial cells to an electrical shock occurs in several steps. The initial step is a change in the transmembrane potential (ΔVm) caused by the shock. This change includes depolarization and/or hyperpolarization depending on local shock strength, shock polarity, and fiber orientation (2, 4, 14, 29). Because many ionic channels in the cell membrane are voltage dependent, the ΔVm caused by the shock affects the activation state of voltage-dependent channels. These channels in turn affect excitability, action potential duration, and the refractory period following the shock. Many studies of defibrillation mechanisms have investigated the changes in action potential duration, refractory period, and excitability of myocardium after a shock (2, 19–22, 32).

Recently, studies have reported the ΔVm caused by a shock (4, 7, 13, 14, 29, 31). Optical recording techniques have been used to study ΔVm during a shock in single isolated myocardial cells (13), in a layer of myocardial cells (7), and in isolated perfused rabbit hearts (1, 2, 4, 14, 29). Because ΔVm during the shock recorded in isolated hearts by optical techniques represents the averaged potential changes from many cells (2, 29), a double-barrel microelectrode that can record from a single cell and can minimize the shock artifact has also been used to record the transmembrane potential during a shock (31). Both optical and microelectrode recording techniques have found that hyperpolarization is greater than depolarization when a shock is delivered during the action potential plateau (4, 7, 13, 29, 31). A recent report shows that the magnitude of hyperpolarization and depolarization is not significantly different when the shock is given during the later portion of the plateau (7). It is not clear how the transmembrane potential changes when the shock is delivered during phase 3, a portion of the action potential thought to be crucial for defibrillation and for the electrical induction of fibrillation.

Another approach to study the ΔVm caused by a shock is the use of mathematical models to predict the relation between the shock strength and the response of the transmembrane potential, but some of the results of these models are conflicting (17, 23). Recently, computer models have also been used to explain the reasons for unsuccessful defibrillation (10, 11, 16) and to predict better monophasic and biphasic waveforms for defibrillation (25). More experimental data are required to test the predictions of the mathematical models and to establish the values of certain parameters used in these models.

Since early basic research by Jones et al. (8, 9) showed beneficial effects of biphasic waveforms for defibrillation, some biphasic waveforms have been demonstrated to be more efficient than monophasic waveforms for successful defibrillation (5, 6, 18). Hypotheses for the higher efficacy of defibrillation of biphasic shocks usually involve differences in excitation threshold and prolongation of action potential duration and refractoriness for monophasic and biphasic waveforms (9, 19, 21, 22, 32). For example, extensive experimental studies and computer models from Jones et al. (9, 11, 19, 22) have demonstrated that a biphasic waveform produces greater prolongation of action potential duration and smaller dispersion of action potential prolonga-
ion than a monophasic waveform at low shock intensities, which they postulated is crucial for a successful defibrillation. Although the $\Delta V_m$ caused by the shock has been recorded during monophasic shocks (1, 7, 13, 29–31), no experimental data have been reported to show $\Delta V_m$ recordings during biphasic shocks. Investigation of $\Delta V_m$ caused by shocks should furnish more experimental data for computer models (10, 11, 16, 25) and help elucidate the basic mechanisms of defibrillation.

The main purpose of this study was to determine the $\Delta V_m$ caused by monophasic and biphasic field stimulation during different phases of the action potential by using double-barrel microelectrode recordings in guinea pig papillary muscles. Because a minimum shock potential gradient of 4–6 V/cm is thought to be necessary for defibrillation (28), potential gradients lower than, equal to, and greater than this were examined, with an emphasis on the lower potential gradients.

**METHODS**

Tissue preparation. Twelve guinea pig papillary muscles were used. Guinea pigs weighing ~300 g were injected with Nembutal (75 mg in 1.5 ml saline) via the abdomen. The hearts were rapidly excised through a median sternotomy and immersed in cold Tyrode solution. The Tyrode solution had the following formula (mM): 129 NaCl, 1.8 CaCl₂, 1.1 MgCl₂, 4.5 KCl, 1 Na₂HPO₄, 20 NaHCO₃, and 11 glucose. The left ventricular anterior papillary muscle, ~4-mm long, was removed and pinned on silicon rubber in the center of a 2 × 2-cm tissue bath. The tissue was then continuously superfused with Tyrode solution bubbled with a 95% O₂-5% CO₂ mixture, giving a pH range of 7.35–7.40. Solution temperature was maintained in the range of 35–36°C. The cardiac tissue was paced at one end via two extracellular 0.1-mm-diameter electrodes with a stimulator controlled by a Macintosh II computer. In seven guinea pig papillary muscles, two mesh platinum shock electrodes (16 × 10 mm) were placed on opposite sides of the tissue bath and immersed in the Tyrode solution to generate an electric field through the tissue bath that was along the longitudinal direction of the tissue. In this way, the fiber orientation of the papillary muscle was parallel to the electrical field vector. In another five guinea pig papillary muscles, a mesh platinum shock electrode (10 × 6 mm) was placed on each of the four sides of the tissue bath so that the electrical field vector could be generated either parallel or perpendicular to the longitudinal direction of the tissue, depending on which electrode pair was used. In this way, the influence of the fiber orientation on the $\Delta V_m$ during a shock could be studied.

Two extracellular recording electrodes fixed on the silicon rubber were just beside the tissue near the double-barrel microelectrode to record the extracellular potentials generated by the shock. The distance between these two extracellular recording electrodes was ~1 mm and was measured to the nearest 0.1 mm with a dissecting microscope. The electrodes were aligned so that an imaginary line between the two electrodes was parallel to the shock potential gradient. The potential between the two electrodes was recorded differentially with a data acquisition system. The potential gradient generated at the tissue by the shock was obtained by dividing the potential difference generated by the shock between the two extracellular electrodes by the distance between them.

Signal recordings. The technique of recording the signals has been published previously (31). To make a double-barrel microelectrode, two single glass capillaries (Glass 1BBL W/FIL 1.0 mm, WPI, Sarasota, FL) were glued together except in the region where the tips were to be formed and were pulled by a horizontal micropipette puller (Industrial Science Associates, Ridgewood, NY). The capillary tubes were pulled to have an impedance of ~10 MΩ for each tip when filled with 3 M KCl. The distance between the microelectrode tips measured under the light microscope varied from several micrometers to several tens of micrometers. Only those double-barrel microelectrodes with a 15- to 50-µm distance between the tips were used. Each double-barrel microelectrode was mounted on a motorized micromanipulator (DC3001, WPI). Each barrel of the double-barrel microelectrode was connected to the input of a differential preamplifier (Duo 773 Dual Microprobe System, WPI) with an Ag-AgCl wire. Capacitor compensation within the preamplifier was used to eliminate capacitive coupling between the two tips. The signals were recorded differentially as a voltage between the two double-barrel microelectrode tips. After preamplification, the signal was recorded with direct-current coupling using a data acquisition system. Signals were recorded digitally with 12-bit accuracy at a rate of 8,000 samples/s.

The data were stored on optical disks for later computer analysis. Experimental protocols. The double-barrel microelectrode was slowly lowered into the Tyrode solution just above the tissue with a motorized micromanipulator. It was then rotated until the potential difference was almost undetectable on the monitoring oscilloscope during shocks that created a shock field of ~10 V/cm. The double-barrel microelectrode was then lowered into the tissue until an action potential was seen in the differential recording between the two barrels shown on a monitoring oscilloscope. The location of the recording site was ~1 mm away from one end of the papillary muscle. After 10 S1 stimuli at twice diastolic threshold were given through the pacing wires with a 300-ms S1-S1 interval, an S2 shock was given through the shock electrodes to produce different levels of potential gradient in the papillary muscle at the double-barrel microelectrode. Each S2 shock was a symmetrical square wave consisting of a 10-ms monophasic, 10/10-ms biphasic, or 5/5-ms biphasic waveform. The shape of the shock waveform was programmed by a Macintosh II computer. The electrometer and computer programs sent the waveform information to a current-source arbitrary waveform generator that was connected to the shock electrodes and created the required waveform across the tissue bath.

In seven papillary muscles, three shock strengths created potential gradients of ~3, 6, and 12 V/cm. Each shock level with the same S1-S2 coupling interval was given twice, the second time with the electrode polarity reversed. The S2 shock was given with three S1-S2 coupling intervals, i.e., 30, 60–70, and 90–110 ms, so that the S2 shocks were delivered during the plateau, the late portion of the plateau, and phase 3 of the 10th S1-induced action potential, respectively. When the S2 shock was delivered during the action potential plateau with a 30-ms S1-S2 coupling interval, all three levels of shock potential gradients were given. When the S2 shock was delivered with longer S1-S2 coupling intervals, i.e., 60–70 and 90–110 ms, only a medium level of shock potential gradient (~6 V/cm) was used. The order of S2 testing of each waveform, polarity, and S1-S2 coupling interval was determined randomly. All recordings were made from the same impalement for each papillary muscle.

In another five papillary muscles, shocks creating five levels of potential gradients ranging from 1.1 ± 0.3 to 4.3 ± 0.5 V/cm were given during phase 3 of the action potential with a 90- to 130-ms S1-S2 coupling interval. Each shock level was given twice, the second time with the reversed shock.
and was called the normalized TRT. The term total repolarizing time, instead of APD\textsubscript{90}, was used because the shock given during phase 3 of the action potential sometimes produced a new action potential. Resting membrane potential (RP) is the voltage difference between the extracellular potential and the diastolic intracellular potential. The extracellular potential (Fig. 1) was obtained by withdrawing the microelectrode tip from the intracellular space to the extracellular space after all S2 shocks had been given.

For monophasic shocks, $\Delta V_m$ is the absolute value of the maximum voltage difference between the membrane potential just before the shock and that just before the end of the shock, i.e., the potential difference between arrows 1 and 2 in the top tracing in Fig. 1. Because a biphasic shock caused biphasic changes in the transmembrane potential, $\Delta V_m$ was determined both at the end of the first phase (voltage difference between arrows 1 and 2 in the bottom 2 tracings in Fig. 1) and at the end of the second phase, which was called the net $\Delta V_m$ (voltage difference between arrows 1 and 3 in the bottom 2 tracings in Fig. 1). The difference between the $\Delta V_m$ at the end of the first phase and the $\Delta V_m$ at the end of the second phase was also determined and was called the reversal $\Delta V_m$ (voltage difference between arrows 2 and 3 in the bottom 2 tracings in Fig. 1). The net $\Delta V_m$ and the reversal $\Delta V_m$ for biphasic shocks were said to indicate depolarization when the potential at arrow 3 was greater than at arrow 2 (dashed tracings in Fig. 1) and were said to indicate hyperpolarization when the potential at arrow 3 was less than at arrow 2 (solid tracings in Fig. 1). Shock membrane potential was determined as the membrane potential immediately before the S2 shock, as indicated by arrow 1 in Fig. 1. Spontaneous repolarization was determined as the amount of repolarization of the 9th control action potential during the interval (horizontal bars in 9th S1 action potentials in Fig. 1) when the shock was given during the 10th test action potential. This was assumed to indicate the amount the membrane potential would have changed during the shock if the shock had not been given.

APA, TRT (or APD\textsubscript{90}), $\Delta V_m$, reversal $\Delta V_m$, net $\Delta V_m$, and spontaneous repolarization were measured using a computer.
RESULTS

For the control ninth action potential, APA was $130 \pm 9$ mV, $APD_{90}$ was $127 \pm 20$ ms, and $RP = -87 \pm 5$ mV. The spontaneous repolarization of the ninth S1-induced control action potential during the time corresponding to the S2 shock interval was $4.8 \pm 2.1$, $9.1 \pm 2.6$, and $19.5 \pm 6.6$ mV at S1-S2 coupling intervals of 30, 60–70, and 90–130 ms, respectively, for 10-ms monophasic and 5/5-ms biphasic shocks and was $10.1 \pm 5.1$, $19.9 \pm 5.5$, and $38.1 \pm 12.7$ mV, respectively, at the above three S1-S2 coupling intervals for 10/10-ms biphasic shocks.

$\Delta V_m$ caused by shocks during action potential plateau. The three levels of potential gradient generated by the shock at the tissue were $3.1 \pm 0.2$, $6.1 \pm 0.2$, and $11.9 \pm 0.3$ V/cm, and all three potential gradients were applied during the action potential plateau. Figure 2 shows examples of the $\Delta V_m$ caused by shocks all from the same impalement. One shock polarity induced depolarization (Fig. 2, left), whereas the opposite polarity induced hyperpolarization (Fig. 2, right). An asymmetrical response, i.e., hyperpolarization greater than depolarization, existed for the monophasic waveforms and the first phase of the biphasic waveforms at each of the three levels of potential gradient. As the potential gradient increased, $\Delta V_m$ during the shock increased monotonically but not linearly. Increasing the potential gradient from 5.9 to 12.2 V/cm did not double the magnitude of $\Delta V_m$. For the same shock strength, $\Delta V_m$ caused by the monophasic waveform was almost the same as that caused by the first phase of the 10/10-ms biphasic waveform but greater than that caused by the first phase of the 5/5-ms biphasic waveform, especially for the hyperpolarization response. At the reversal of the two phases of a biphasic shock, hyperpolarization (Fig. 2, left) and depolarization (Fig. 2, right) were greater than the corresponding changes caused by the first phase of the biphasic shock.
For all three levels of shock potential gradients delivered with a 30-ms S1-S2 coupling interval, the magnitude of hyperpolarization caused by the monophasic shock and the first phase of the biphasic shocks was 1.6 ± 0.4 times greater than that of depolarization caused by the same shock strength but with the opposite polarity (P < 0.001), indicating that the ΔVm caused by shocks during the action potential plateau was asymmetrical.

Figure 3 shows ΔVm caused by monophasic and biphasic shocks. The net ΔVm was larger for the monophasic than for the biphasic shocks (Fig. 3A). The reversal ΔVm caused by a 10/10-ms biphasic shock with either polarity was greater than the ΔVm caused by the monophasic shock or the reversal ΔVm of the 5/5-ms biphasic shock at the same potential gradient (Fig. 3B). The depolarization of the reversal ΔVm caused by the 5/5-ms shock was significantly greater than the depolarization caused by the corresponding monophasic shocks (Fig. 3B). There was no difference in the magnitude of hyperpolarization of the reversal ΔVm caused by 5/5-ms biphasic shocks and the ΔVm caused by 10-ms monophasic shocks. Thus, although the reversal ΔVm was greater for biphasic than for monophasic shocks, the net ΔVm at the end of the shock was smaller for biphasic than for monophasic shocks.

ΔVm caused by shocks during different phases of action potential. The membrane potential just before the shocks of 6.1 ± 0.2 V/cm strength was +30.0 ± 8.5, +12.3 ± 8.9, and −25.7 ± 9.5 mV for the S1-S2 coupling intervals of 30, 60–70, and 90–110 ms, respectively. For the monophasic and the first phase of the biphasic waveforms, shocks causing depolarization caused a larger response as the shock was given later during the action potential (dotted tracings in Fig. 4). Conversely, for shocks causing hyperpolarization, ΔVm became smaller as the shock was given later during the action potential (dotted tracings in Fig. 4). The responses immediately...
after the shock were also different for shocks given during different phases of the action potential. Immediately after shocks given early during the action potential plateau, repolarization appeared to continue (30-ms S1–S2 in Fig. 4). For shocks given later during the plateau of the action potential, a local response appeared to occur (70-ms S1–S2 in Fig. 4) because the membrane potential immediately after the shock was more positive than that just before the shock, suggesting the initiation of active processes by the shock even though it was given during the refractory period. When shocks were given during phase 3 of the action potential, the response resembled a premature action potential (110-ms S1–S2 in Fig. 4). This can be seen most clearly for the hyperpolarizing monophasic shock and the depolarizing biphasic shocks in which the membrane was first partially depolarized at the end of the shock and then initiated a new action potential (110-ms S1–S2 in Fig. 4).

Depolarization became larger, whereas hyperpolarization became smaller when the S1–S2 coupling interval was increased for all three shock waveforms (Table 1). For the monophasic shock and the first phase of the biphasic shock delivered during the plateau of the action potential, depolarization was significantly smaller than hyperpolarization (P < 0.05), whereas depolarization was significantly larger than hyperpolarization (P < 0.05) when the same shock strength was given during phase 3 of the action potential. For shocks delivered late during the plateau of the action potential, the magnitude of depolarization was not significantly different from that of hyperpolarization. The ratio of hyperpolarization to depolarization at the S1–S2 coupling intervals of 30, 60–70, and 90–110 ms was 1.6 ± 0.4, 1.1 ± 0.1, and 0.5 ± 0.2, respectively, for the 10-ms monophasic waveform, 1.6 ± 0.3, 1.1 ± 0.2, and 0.5 ± 0.1, respectively, for the 10/10-ms biphasic waveform, and 1.3 ± 0.2, 0.9 ± 0.2, and 0.5 ± 0.2, respectively, for the 5/5-ms biphasic waveform [P = not significant (NS) among 3 waveforms at the same coupling interval]. Thus not only could shocks cause asymmetrical ΔV_m responses, but their response changed as the phase of the action potential changed.

Table 1. Mean ΔV_m caused by shocks given with different S1–S2 coupling intervals

<table>
<thead>
<tr>
<th>S1–S2 Coupling Interval, ms</th>
<th>30</th>
<th>60–70</th>
<th>90–110</th>
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<tr>
<td>Depolarizing response</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>10-ms Mono</td>
<td>49 ± 9†</td>
<td>60 ± 10</td>
<td>86 ± 8‡</td>
</tr>
<tr>
<td>10/10-ms Bi</td>
<td>49 ± 9†</td>
<td>59 ± 9</td>
<td>84 ± 10†</td>
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<tr>
<td>5/5-ms Bi</td>
<td>41 ± 7‡</td>
<td>51 ± 10</td>
<td>68 ± 9‡</td>
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<tr>
<td>Hyperpolarizing response</td>
<td></td>
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</tr>
<tr>
<td>10-ms Mono</td>
<td>77 ± 7</td>
<td>65 ± 15</td>
<td>41 ± 13‡</td>
</tr>
<tr>
<td>10/10-ms Bi</td>
<td>77 ± 6</td>
<td>67 ± 16</td>
<td>40 ± 12†</td>
</tr>
<tr>
<td>5/5-ms Bi</td>
<td>53 ± 9</td>
<td>48 ± 11</td>
<td>32 ± 12†</td>
</tr>
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</table>

Values, in millivolts, are means ± SD. ΔV_m, transmembrane potential change; Mono, monophasic waveform; Bi, 1st phase of biphasic waveform. *P < 0.05 between the 3 coupling intervals (Student-Newman-Keuls test); †P < 0.05 vs. other 2 coupling intervals (Student-Newman-Keuls test); ‡P < 0.05 vs. hyperpolarizing response to the same shock waveform.

Action potential prolongation by shock. Action potential prolongation was characterized by the extension of TRT after the shock. For shocks of 6.1 ± 0.2 V/cm, the normalized TRT was not significantly prolonged (P > 0.05) in comparison with the control value (100% for 9th action potential) for any of the three waveforms with a 30-ms S1–S2 coupling interval, e.g., 103 ± 6% for 10 ms monophasic, 103 ± 8% for 10/10-ms biphasic and 102 ± 2% for 5/5-ms biphasic waveform. For S1–S2 coupling intervals of 60–70 ms, the normalized TRT was significantly prolonged (P < 0.05) for all waveforms, e.g., 114 ± 7% for 10-ms monophasic, 117 ± 9% for 10/10-ms biphasic, and 109 ± 5% for 5/5-ms biphasic waveforms. The normalized TRT for 10-ms monophasic and 10/10-ms biphasic waveforms was not significantly different, but both were significantly greater than that for the 5/5-ms biphasic waveform (P < 0.05). The normalized TRT was significantly prolonged for shocks with 90- to 110-ms S1–S2 coupling intervals, e.g., 142 ± 12% for 10-ms monophasic, 141 ± 11% for 10/10-ms biphasic, and 128 ± 9% for 5/5-ms biphasic waveforms. The 5/5-ms biphasic shocks produced less prolongation of TRT than 10-ms monophasic and 10/10-ms biphasic waveforms (P < 0.05). Neither shock polarity significantly prolonged the repolarization time of the action potential more than the other (P = NS), even though a hyperpolarizing shock usually, but not always, caused a longer prolongation than a depolarizing shock.

We determined the difference between the normalized TRT caused by a depolarizing shock and that caused by a hyperpolarizing shock of the same strength but opposite polarity. This difference, called the polarity-dependent dispersion in the TRT, was significantly larger (P < 0.05) for the 10-ms monophasic waveform (7.4 ± 7.1%) than for either the 10/10-ms biphasic waveform (3.0 ± 4.1%) or the 5/5-ms biphasic waveform (2.8 ± 3.1%) for all coupling intervals together. An example of the dependence of repolarization prolongation on the polarity is also shown in Fig. 4. Thus the two shock polarities for biphasic waveforms caused less dispersion of the action potential prolongation than did the monophasic waveform.

Effects of low shock strengths and field direction on ΔV_m. The membrane potential just before the shocks was −23 ± 9 mV. The five levels of shock potential gradients were 1.1 ± 0.3, 1.7 ± 0.3, 2.4 ± 0.3, 3.4 ± 0.5, and 4.3 ± 0.5 V/cm for the shock fields along the fiber orientation and 1.1 ± 0.3, 1.7 ± 0.3, 2.3 ± 0.2, 3.2 ± 0.3, and 4.2 ± 0.4 V/cm for the shock fields across the fiber orientation. Figure 5 shows the transmembrane potentials during shocks that were given along and across the longitudinal axis of one papillary muscle during early phase 3 of the action potential. All recordings were made from the same impalement with the line of the two microelectrode tips perpendicular to the longitudinal axis of the papillary muscle. Only recordings for the lowest, middle, and highest potential gradients are shown in Fig. 5. The response of the transmembrane potential to the shock becomes larger with the increase in the shock potential gradients, which were either along or across the fiber orientation. However, at
the same level of shock potential gradient the \( \Delta V_m \) for shock fields along the fiber orientation were obviously larger than that for shock fields across the fiber orientation. Because the line of two double-barrel microelectrode tips was parallel to the shock potential gradient vector, which was across the fiber orientation, each recording shows a shock artifact with a fast, clear direct-current offset. The \( \Delta V_m \) between the fast onset and offset of the shock artifact was smaller than the \( \Delta V_m \) for shock fields along the fiber orientation. Figure 6 shows the mean values of the \( \Delta V_m \) caused by the 10-ms monophasic and the first phase of the biphasic shocks with different strengths along and across the fiber orientation. For all three waveforms, the \( \Delta V_m \) caused by shocks along the fiber orientation was significantly greater than that caused by shocks across the fiber orientation. This phenomenon occurred at all five levels of shock strengths with either depolarizing or hyperpolarizing shocks.

Figure 5 also shows the action potential prolongation by shocks of different strengths, polarities, and waveforms. Shocks of higher strength produced larger action potential prolongation than shocks of lower strength. Even shocks with a low strength of 1.1 V/cm caused action potential prolongation, especially for 10-ms monophasic and 10/10-ms biphasic waveforms. The changes in the action potential prolongation are also different for shock fields along versus across the fiber orientation. Compared with the control APD\(_{90}\) indicated by a dashed line in each tracing, the action potential prolongation was larger for shock fields along than for shock fields across the fiber orientation. In addition, the difference in the magnitude of the action potential prolongation between one shock polarity and the reversed polarity was smaller for shock fields along the fiber orientation than for shock fields across the fiber orientation. Table 2 shows the mean values of the prolongation of TRT caused by the shock. TRT was significantly prolonged by all three waveforms with both shock polarities at all five levels of potential gradients. Again, 10-ms monophasic and 10/10-ms biphasic waveforms caused a significantly greater prolongation of TRT than the 5/5-ms biphasic waveform at higher shock potential gradients. At several potential gradients, the prolongation of TRT was significantly greater for shock fields along than across the fiber orientation (Table 2).

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**Fig. 5.** Transmembrane potential recordings during shock fields along and across longitudinal axis of papillary muscle. All shocks were given during early phase 3 of action potential from same impalement. Recordings are shown for 10-ms monophasic (top 2 tracings) and 10/10-ms (middle 2 tracings) and 5/5-ms (bottom 2 tracings) biphasic shocks. Recordings are superimposed for same shock waveform with one shock polarity causing depolarization (solid line) and opposite polarity causing hyperpolarization (dotted line). Shock strengths are given above tracings, with strength in parenthesis for fields across fibers. The 9th control action potential is superimposed on the 10th test action potential. Tracings at far right are extracellular recordings with both microelectrode tips outside cell membrane. Arrows indicate beginning of each shock. Voltage and time scales are given at bottom.

**Fig. 6.** \( \Delta V_m \) caused by monophasic and biphasic shocks along and across fiber orientation. Ordinate is \( \Delta V_m \) caused by shocks given during phase 3 of action potential; abscissa is mean value of shock potential gradient. There is a significant difference between along and across fiber orientation at all 5 levels of potential gradients (\( P < 0.05 \)). Shocks causing depolarization are plotted separately from those causing hyperpolarization.
DISCUSSION

This study confirms previous reports that shocks cause significant changes in the transmembrane action potentials, including depolarization and hyperpolarization, and cause prolongation but not shortening of action potential duration (4, 7, 13, 14, 29, 31). This study also demonstrates that 1) there is a dynamic and asymmetrical change in the $\Delta V_m$ caused by shocks delivered during different phases of the action potential, 2) the $\Delta V_m$ and the prolongation of the repolarization time are greater for shock fields along than across the fiber orientation, and 3) biphasic shocks cause fewer alterations in $\Delta V_m$ at the end of the shock, shorter action potential prolongation, and smaller polarity-dependent dispersion of the prolongation than monophasic shocks of the same or twice the same total shock duration.

Consistent with previous reports (4, 7, 29, 31), this study demonstrates that the response of the $\Delta V_m$ to an electrical shock is asymmetrical depending on the shock timing, with an asymmetrical response of larger hyperpolarization than depolarization for the same shock strength when the shock is given during the plateau of the action potential. This asymmetrical response disappears when the shock is given during the late portion of the plateau of the action potential. The asymmetrical response appears again when the shock is given during phase 3 of the action potential but is reversed with depolarization larger than hyperpolarization. This means that the response of the membrane potential to a shock is not constant but undergoes a dynamic and asymmetrical change as the coupling interval of the shock is changed.

The mechanism for the asymmetrical response of the membrane potential to a shock is not understood, but the phenomenon implies that there may be ionic channel activity during the shock, with a higher impedance to current flow in one direction than the other across the cell membrane, and that the membrane impedance to the current flow changes during different phases of the action potential (12, 26). The major reason for the larger depolarization versus hyperpolarization during phase 3 is probably partial opening of inward-current channels that augment depolarization and hence reduce hyperpolarization. This assumption is supported by the fact that the response of the transmembrane potential after a shock resembles either a new action potential or a graded response (Fig. 4) and both responses involve active membrane processes during the shock. It is not known which channel activity contributes to this response and why active processes can occur at a membrane potential at which inward-current channels are thought to be inactivated.

This study first experimentally demonstrates the larger $\Delta V_m$ caused by a shock field oriented along the fibers than across the fibers at the same shock strength. The larger $\Delta V_m$ caused by a shock field along the fiber orientation has at least two effects. First, a larger depolarization during a shock can cause excitation. This supports the observation of a lower excitation threshold with the fiber orientation parallel to the shock field than perpendicular to the shock field (15, 24). Second, a larger hyperpolarization during a shock can cause more sodium channels to recover as proposed by Jones et al. (10, 11) so that the cell can more easily be excited after the shock. However, the role of the fiber orientation in the mechanism of the electrical defibrillation needs more investigation.

This study experimentally demonstrates that the $\Delta V_m$ caused by biphasic shocks is quite different from that caused by monophasic shocks. The differences in $\Delta V_m$ include 1) a smaller net $\Delta V_m$ for biphasic than for monophasic shocks, indicating that the membrane potential at the end of the shock was closer to the membrane potential just before the shock for biphasic than for monophasic shocks; and 2) a large reversal $\Delta V_m$ for biphasic shocks. The results of the smaller $\Delta V_m$ for biphasic waveforms are consistent with the prediction of the theory and the mathematical models (11, 16, 25). Those models attribute more efficacious defibrillation for the biphasic waveform to the mechanism of removing the excess charge by the second phase of a biphasic shock (11, 16) or of bringing the membrane potential closer to the preshock membrane potential (25). Because the alteration in the membrane potential after a biphasic shock is less in comparison with a monophasic shock, postshock arrhythmias may be less likely to occur, resulting in a higher defibrillation efficacy for certain biphasic waveforms as proposed by J ones and J ones (8). A large $\Delta V_m$ at the reversal of the two phases of a biphasic waveform may help to excite the myocardial cells and hence to defibrillate (27). This hypothesis is confirmed in some studies (27) but not in others (5). Thus, on the one hand, a biphasic shock can cause excitation, whereas on the other hand it can cause fewer alterations in the membrane potential leading to a decreased occurrence of postshock arrhythmias.

Sweeney et al. (20) demonstrated that the prolongation of the refractoriness by an electrical shock is related to defibrillation success. Swartz et al. (19) showed prolongation of the action potential by biphasic as well as monophasic shocks. Prolongation has been proposed as one of the mechanisms for ventricular defibrillation. The prolongation of the action potential
duration and hence the prolongation of the refractory period are thought to stop the fibrillating wavefronts when these wavefronts meet refractory tissue, leading to successful defibrillation (2, 19, 20, 32). The results of the present study are consistent with previous reports demonstrating that both monophasic and biphasic shocks can prolong TRT. The extent of the prolongation of TRT depends on 1) shock waveform, 2) timing of the shock, 3) shock polarity, and 4) fiber orientation. Consistent with a previous report (32), the prolongation of TRT was less for the biphasic than for the monophasic waveforms at the same shock strength and coupling interval, especially when the total shock duration was the same, such as 10-ms monophasic vs. 5/5-ms biphasic shocks. This finding is not consistent with results reported by Jones et al. (10, 11, 19), who found a larger prolongation of action potential by a biphasic than by a monophasic shock at low shock strength. This inconsistency may be caused by the use of different tissues, different shock durations, and different S1-S2 coupling intervals of the first phase of the biphasic waveform.

This study also shows that the repolarizing time is influenced by shock polarity, causing a polarity-dependent dispersion in action potential prolongation. This polarity-dependent dispersion is larger for monophasic than for biphasic shocks. A hyperpolarizing shock usually creates a larger postshock response than does a depolarizing shock (Fig. 4), especially during the later portion of the action potential. It is not known from the present study why biphasic shocks cause less action potential prolongation and smaller polarity-dependent dispersion in the prolongation. To answer this question may require investigation of the ionic channel activities during a shock.

Consistent with a previous report (15), a shock field along the fiber orientation causes longer prolongation of the action potential than a shock field across the fiber orientation. Because the \( \Delta V_m \) caused by a shock is larger for the field along than for the field across the fiber orientation, it is quite possible that the \( \Delta V_m \) is related to the action potential prolongation after a shock.

The tissue study shows that the 5/5-ms biphasic waveform causes the smallest \( \Delta V_m \) at the end of the shock and prolongs TRT the least compared with the 10/10-ms biphasic and 10-ms monophasic waveforms. If the smaller \( \Delta V_m \) and action potential prolongation were directly related to the higher defibrillation efficacy of biphasic waveforms, reduction in monophasic shock strength below its defibrillation threshold could also cause a smaller \( \Delta V_m \) and smaller prolongation of action potential. Thus the magnitude of the \( \Delta V_m \) and the action potential prolongation may not be the only shock-induced changes related to defibrillation. Another factor related to successful defibrillation is synchronization of dispersion of repolarization over the ventricles after a shock (2, 3, 21). Results of this study also demonstrate that dispersion in the repolarization time between depolarizing and hyperpolarizing shocks is smaller for biphasic than for monophasic shocks, indicating that a biphasic shock may cause more uniform action potential prolongation than a monophasic shock regardless of polarization.

In conclusion, the dynamic and asymmetrical changes in the \( \Delta V_m \) caused by shocks of different coupling intervals and polarities represent the intrinsic nature of the membrane response, implying that the myocardial response during ventricular defibrillation is complex. A shock field along fibers produces a larger \( \Delta V_m \) and prolongation of repolarization than does a shock field across fibers. The smaller \( \Delta V_m \), the smaller action potential prolongation, and the smaller polarity-dependent dispersion in the action potential prolongation caused by a biphasic shock compared with a monophasic shock may be related to the higher success rate of ventricular defibrillation for certain biphasic shocks than for monophasic shocks. More studies are still required to elucidate the active membrane processes during a shock pulse to better understand the mechanisms of ventricular defibrillation and the higher defibrillation efficacy for biphasic shocks than for monophasic shocks.

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