THE VOLTAGE DEPENDENCE OF THE
CARDIAC MEMBRANE CONDUCTANCE

D. NOBLE

From the Department of Physiology, University College, London, England

ABSTRACT   Solutions have been computed for the point polarization of a sheet-like membrane obeying the equations used previously (Noble, 1960, 1962) to reproduce the Purkinje fiber action potential. It was found that, in spite of the gross non-linearity of the membrane current-voltage relations, the relations between total polarizing current and displacement of membrane potential at various distances from the polarizing electrode are remarkably linear. It is therefore concluded that Johnson and Tille's (1960, 1961) results showing linear polarizing current-voltage relations obtained by passing current through the membrane from a microelectrode during the plateau of the rabbit ventricular action potential do not conflict with the Hodgkin-Huxley theory of electrical activity.

INTRODUCTION

The action potential of cardiac muscle differs from those of skeletal muscle and nerve in that the initial fast depolarization is followed by a very slow repolarization of the membrane, usually consisting of a plateau lasting several hundred milliseconds which is terminated by a slightly faster phase of repolarization. The available experimental evidence indicates that the potassium conductance of the cardiac membrane is low during the plateau (Hutter and Noble, 1960; Carmeliet, 1961; Lorber, 1962). The maintenance of the plateau therefore probably results from a combination of this fall in potassium conductance and the residual increase in sodium conductance predicted by the Hodgkin-Huxley sodium current equations (FitzHugh, 1960; Noble, 1960, 1962). During the return to the resting potential, the conductances may be supposed to return to their resting values.

The question whether these changes in ionic conductance during repolarization are dependent on voltage and time as in the Hodgkin-Huxley nerve equations (Hodgkin and Huxley, 1952) or on time only is, however, disputed. In the case of Purkinje fibers, there is little doubt that the conductances are voltage-dependent. Weidmann (1951, 1956) has shown that the current-voltage relation during the plateau in these fibers is non-linear and that a large enough repolarizing current will initiate an all-or-nothing repolarization. This phenomenon

has also been demonstrated by Chang and Schmidt (1960) and it indicates that the current-voltage relation is not only non-linear but that it also includes a region of negative conductance. In the case of ventricular muscle the situation is not so clear. Cranefield and Hoffman (1958) have shown that in some circumstances (low extracellular calcium concentration) all-or-nothing repolarization may be initiated in cat and dog papillary muscles using external polarizing electrodes. However, Johnson and Tille (1960, 1961) have recently described experiments in which they found no detectable non-linearity in the relation between polarizing current and displacement of membrane potential at an intracellular microelectrode during the plateau in rabbit ventricular muscle. On the basis of this result they have concluded that the ionic conductance of the membrane does not depend on the value of the membrane potential, and George and Johnson (1962) and Woodbury (1962) have formulated models for repolarization in which the conductances are only time-dependent. Both of these models involve substantial qualitative departures from the Hodgkin-Huxley (1952) theory of electrical activity, and it is therefore important to decide whether Johnson and Tille's conclusion necessarily follows from their results.

The computations described in this paper show that virtually linear polarizing current-voltage relations are to be expected in the conditions of Johnson and Tille's experiments even if the membrane current-voltage relation is non-linear and includes a range of voltages over which the conductance is negative.

THEORY

In the method used by Johnson and Tille, current is passed across the membrane through one barrel of a double-barrelled microelectrode while the change in potential is recorded with the other barrel. The preparation is the wall of the rabbit ventricle so that, provided that the electrode is not placed too close to the edge of the preparation, current will spread in all directions away from the electrode. Woodbury and Crill (1961) have investigated a similar situation in experiments using microelectrodes to polarize the wall of the atrium and they have shown that if the surface membrane is assumed to resemble a continuous sheet separating a layer of intracellular fluid from the extracellular fluid then the relation between the steady-state voltage deflection, V, and distance, r, from the polarizing electrode should obey the following equation:

$$\frac{d^2 V}{dr^2} + \frac{1}{r}\frac{dV}{dr} - (R_i/R_m) \cdot V = 0 \tag{1}$$

where R_m = resistance per unit area of membrane and R_i = resistance of unit length and breadth of myoplasm. If a current, I, is applied through the microelectrode at $r = 0$ then for a membrane having a linear current-voltage relation we obtain:

$$V = \frac{IR_i}{4} jH_0^{(1)}[jr/\lambda] \tag{2}$$

where $\lambda = \sqrt{(R_m/R_i)}$, $j = \sqrt{-1}$ and $H_0^{(1)}$ is a tabulated Bessel function (Jahnke and Emde, 1945).

When r is small compared to λ, equation (2) may be simplified to give

$$V = -\frac{IR_i}{2\pi} \ln (r/\lambda) \tag{3}$$

From this equation it is clear that when r is very small, as in Johnson and Tille's experiments, the voltage displacement will be very insensitive to changes in R_m. Thus, even if r is as large as $\lambda/10$, a fourfold increase in R_m (twofold increase in λ) would produce only a 30 per cent increase in V.

The detection of changes in R_m due to polarization of a membrane having a non-linear current-voltage relation should be even more difficult since the change in R_m is then non-uniform and less extensive. It is quite possible, therefore, that the method would fail to detect even fairly large non-linearities in the membrane current-voltage relation. Johnson and Tille's failure to obtain all-or-nothing re-polarization as observed by Weidmann (1951) and Cranefield and Hoffman (1958) may also be accounted for, since when the hyperpolarizing current is terminated, local circuit currents will flow in such a direction as to help to bring the potential at the polarizing electrode back to the plateau; *i.e.*, the negative conductance is shunted by the positive conductances of the intracellular fluid and those areas of membrane which have not been polarized sufficiently to reach the potential at which the conductance becomes negative. This effect is of course also present in a cable-like membrane but it should be much greater in the case of a sheet membrane since the local circuit current will be supplied from all directions whereas in the cable case the current is supplied from only two directions. This difference may be seen more clearly when it is realised that to simulate the cable situation in a sheet membrane the polarizing current would have to be supplied not from a point but from a "line" electrode traversing the entire sheet, which would clearly require more current to displace the potential at the electrode by the same amount but which would do so across a greater area of membrane.

This difficulty does not apply to the same extent to Cranefield and Hoffman's experiments since they used much larger external electrodes for applying the polarizing current. A larger proportion of the membrane must have been po-larized in their experiments and the situation probably approximated more closely to the line polarization case than to point polarization. They would therefore be more likely to detect non-linearities and, if the conditions were sufficiently favour-able, to show all-or-nothing repolarization.

In order to test this explanation of Johnson and Tille's results, I have computed steady-state relations between polarizing current and voltage displacement for

the point polarization of a sheet membrane obeying the equations which I have used previously to reproduce the Purkinje fiber action potential (Noble, 1960, 1962). Two points during the plateau were chosen: one at 100 msec. after the initiation of the action potential (about the middle of the plateau) and one at 200 msec. (towards the end of the plateau). The sodium current at each potential was equated to the steady-state current given by

$$I_{Na} = (400 m^3 h + 0.14)(E_m - 40) \qquad (4)$$

$$m = \alpha_m/(\alpha_m + \beta_m) \qquad (5)$$

$$h = \alpha_h/(\alpha_h + \beta_h) \qquad (6)$$

$$\alpha_m = \frac{0.1(-E_m - 48)}{\exp\left[(-E_m - 48)/15\right] - 1} \qquad (7)$$

$$\beta_m = \frac{0.12(E_m + 8)}{\exp\left[(E_m + 8)/5\right] - 1} \qquad (8)$$

$$\alpha_h = 0.17 \exp\left[(-E_m - 90)/20\right] \qquad (9)$$

$$\beta_h = \left[\exp\left[(-E_m - 42)/10\right] + 1\right]^{-1} \qquad (10)$$

where E_m is the membrane potential expressed as the intracellular potential minus the extracellular potential.

Since the time constants of the time-dependent component of the potassium conductance (g_{K_2}) are very long, this may be regarded as a constant and was given the values which it attains at each point during the normal action potential. I_K is therefore given by

$$I_K = (g_{K_1} + g_{K_2})(E_m + 100) \qquad (11)$$

$$g_{K_1} = 1.2 \exp\left[(-E_m - 90)/50\right] + 0.015 \exp\left[(E_m + 90)/60\right] \qquad (12)$$

$$g_{K_2} = 1.2 n^4 \quad \text{where} \quad n_{100\ msec.} = 0.582 \qquad (13)$$

$$n_{200\ msec.} = 0.687$$

The membrane current-voltage relations described by equations (4)–(13) are grossly non-linear and are shown in Fig. 1.

The relation applying at 100 msec. is the continuous curve while the curve applying at 200 msec. is interrupted. The most positive values of E_m at which I_m (= $I_{Na} + I_K$) = 0 are −4.746 at 100 msec. and −14.56 at 200 msec. Voltage displacements (V) from the plateau are therefore equal to $E_m + 4.746$ at 100 msec. and $E_m + 14.56$ at 200 msec. Both curves have two regions of positive slope conductance (dI_m/dV); one at the plateau and another at the resting potential. Between these regions, the slope conductance is negative. Both curves

have a range of potentials, which is more extensive at 200 msec. than at 100 msec., over which the direction of the membrane current is reversed, when the membrane is acting as a source of current. This region of negative conductance is also greater in magnitude at 200 msec. when the maximum reversed current is greater than the maximum current in the region of positive conductance near the plateau.

These relations apply for the *uniform* polarization of a membrane obeying these equations and in these circumstances a large enough current would switch the membrane potential to the other stable point (the resting potential). To reproduce Johnson and Tille's experimental situation we now have to consider the behaviour of the system for the case of *non-uniform* polarization with a point electrode.
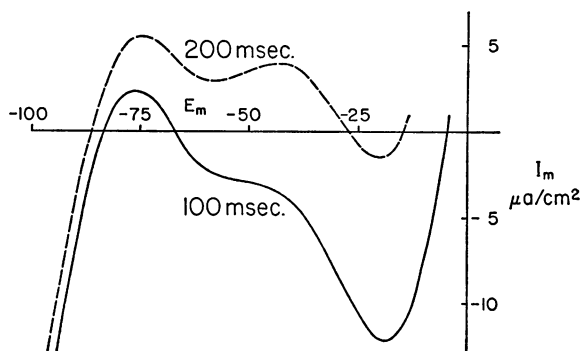

FIGURE 1   Membrane current-voltage relations given by equations used to reproduce the Purkinje fiber action potential (Noble, 1962). Abscissa: Membrane potential in millivolts. Ordinate: Total membrane current ($I_{Na} + I_K$) given by steady-state sodium current and the potassium current obtained by assuming the slow time-dependent component of g_K to be constant. These are the relations which would be expected for uniform polarization of the membrane. The continuous curve is the relation applying at 100 msec. after the initiation of the action potential; the interrupted curve applies at 200 msec. Note that both curves have a region of negative conductance and that this is larger in range and magnitude at 200 msec. than at 100 msec.

COMPUTATION

Since R_m is not constant, the equation to be solved is

$$\frac{d^2 V}{dr^2} = R_i I_m - \frac{1}{r} \frac{dV}{dr} \tag{14}$$

where I_m is the function of V given by equations (4)–(13). The initial conditions were obtained by choosing a point at a distance 3 λ away from the polarizing electrode where the voltage displacement may be made small enough for R_m to be regarded as a constant. Differentiation of equation (2) gives an equation

for dV/dr:

$$\frac{dV}{dr} = \frac{IR_i}{4} H_1^{(1)}(jr/\lambda) \tag{15}$$

where $H_1^{(1)}$ is another Bessel function. From (2) and (15) we obtain:

$$\frac{dV/dr}{V} = \frac{1}{\lambda} \frac{H_1^{(1)}(jr/\lambda)}{jH_0^{(1)}(jr/\lambda)} \tag{16}$$

When $r = 3\lambda$ this ratio is $-1.1555/\lambda$.

The choice of λ for ventricular muscle must at present be a somewhat arbitrary one as no experimental information is available. Woodbury and Crill (1961) have shown that treatment of the atrial wall as a flat sheet membrane gives a value of 0.1 mm for λ. It seems likely that λ is larger than this value in the ventricle. The ventricular wall is much thicker than that of the atrium so that the value of R_i required to fit the flat sheet membrane equations is likely to be smaller. In fact, the thickness of the ventricular wall is such that the flat sheet model is almost certainly a very inaccurate representation of the situation. However, it will be argued later (see Discussion) that a more accurate model would not substantially modify the results and would in fact make non-linearities in the membrane current-voltage relation even less evident in the polarizing current-voltage relation.

Fortunately, the choice of λ does not seriously affect the present computations. The value of λ simply determines the scale of the distance axis and the magnitude of the total polarizing current (if λ is reduced, for example, the area of membrane polarized decreases and less current is required). A choice of $\lambda = 1$ mm for small voltage displacements at 100 msec. gives values for the total polarizing current which are of the same order of magnitude as those used by Johnson and Tille. At 200 msec. λ increases to about 1.8 mm.

Various values for the voltage deflection at $r = 3\lambda$ were chosen and the corresponding values for dV/dr were calculated from equation (16). The computations were done on the London University digital computer (Mercury), equation (14) being solved as two simultaneous differential equations:

$$\frac{dV}{dr} = Y$$

$$\frac{dY}{dr} = R_i I_m - \frac{Y}{r}$$

using the Runge-Kutta numerical approximation. From $r/\lambda = 3$ to $r = 0.4$ mm a step length, δr, of -0.02 mm was used. Between $r = 0.4$ mm and $r = 0.01$ mm, δr was reduced to -0.005 mm.

The intracellular current was calculated at each stage from the relation

$$I_i = -(2\pi r/R_i) \cdot dV/dr \tag{17}$$

As *r* approaches zero, I_t approaches a limit which is the total polarizing current.

RESULTS

Fig. 2 shows the solutions obtained at 100 and 200 msec. for closely similar total polarizing currents (-1.623 μa at 100 msec., -1.602 μa at 200 msec.). In both cases, as *r* decreases, the magnitude of V rises, slowly at first, but as $r = 0$
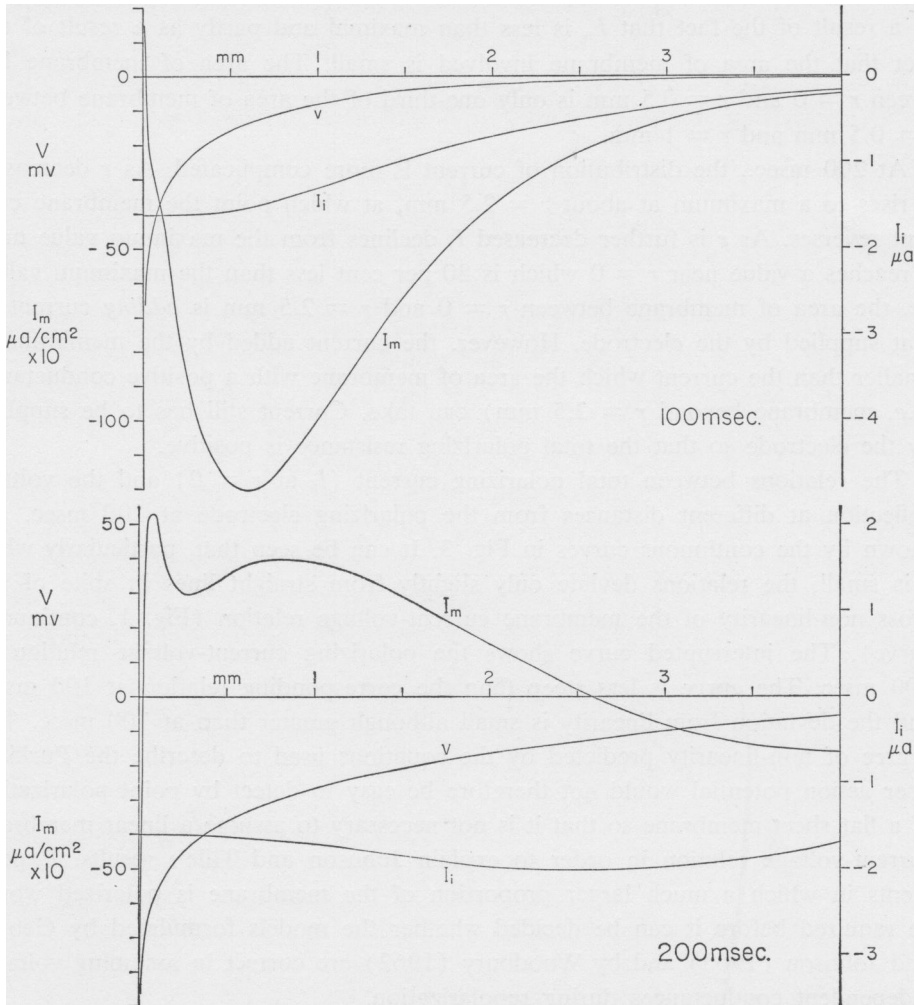

FIGURE 2 Computed variation in V, I_m, and I_t at 100 msec. (upper curves) and 200 msec. (lower curves) for total polarizing currents (I_t at $r = 0$) of almost equal magnitude (-1.623 μa at 100 msec.; -1.602 μa at 200 msec.). Description in text. Note that the voltage displacement near the electrode is greater at 200 msec. than at 100 msec.; the polarization resistance increases by about 30 per cent between these two times.

is approached, it increases very rapidly to values at $r = 0.01$ mm of -66.4 mv at 100 msec. and -86.03 mv at 200 msec. At this interelectrode distance therefore, the polarization resistance rises by about 30 per cent during the second half of the plateau.

At 100 msec., as r decreases, the intracellular current rises to a maximum which is nearly reached at $r = 0.5$ mm, before $|V|$ has exceeded 20 mv. Very little of the current crosses the membrane between $r = 0$ and $r = 0.5$ mm, partly as a result of the fact that I_m is less than maximal and partly as a result of the fact that the area of membrane involved is small. The area of membrane between $r = 0$ and $r = 0.5$ mm is only one-third of the area of membrane between $r = 0.5$ mm and $r = 1$ mm.

At 200 msec., the distribution of current is more complicated. As r decreases, I_i rises to a maximum at about $r = 2.5$ mm, at which point the membrane current reverses. As r is further decreased I_i declines from the maximum value until it reaches a value near $r = 0$ which is 20 per cent less than the maximum value, *i.e.* the area of membrane between $r = 0$ and $r = 2.5$ mm is *adding* current to that supplied by the electrode. However, the current added by the membrane is smaller than the current which the area of membrane with a positive conductance (*i.e.* membrane beyond $r = 2.5$ mm) can take. Current still has to be supplied by the electrode so that the total polarizing resistance is positive.

The relations between total polarizing current (I_i at $r = 0$) and the voltage deflection at different distances from the polarizing electrode at 100 msec. are shown by the continuous curves in Fig. 3. It can be seen that, particularly when r is small, the relations deviate only slightly from straight lines in spite of the gross non-linearity of the membrane current-voltage relation (Fig. 1, continuous curve). The interrupted curve shows the polarizing current-voltage relation at 200 msec. The curve is less steep than the corresponding relation at 100 msec. and the deviation from linearity is small although greater than at 100 msec. The degree of non-linearity predicted by the equations used to describe the Purkinje fiber action potential would not therefore be easy to detect by point polarization of a flat sheet membrane so that it is not necessary to assume a linear membrane current-voltage relation in order to explain Johnson and Tille's results. Experiments in which a much larger proportion of the membrane is polarized would be required before it can be decided whether the models formulated by George and Johnson (1962) and by Woodbury (1962) are correct in assuming voltage-independent conductances during repolarization.

The degree to which the geometry of the sheet membrane situation masks non-linearities in the membrane current-voltage relation is rather surprising and calls for further explanation. The effect is brought about by a redistribution of current. When R_m increases in the region of the polarizing electrode a smaller proportion of the total polarizing current crosses the membrane in this region and a larger pro-
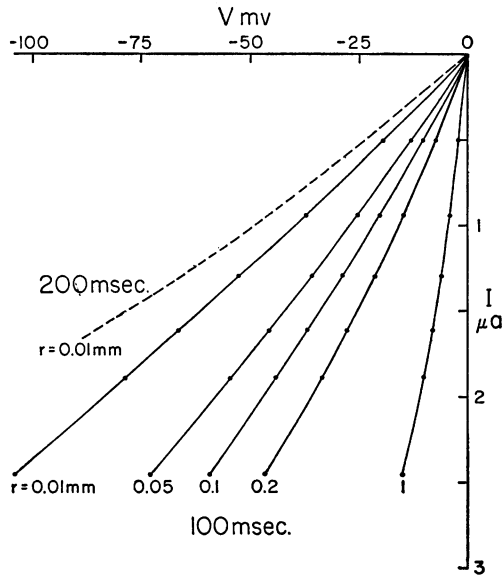
FIGURE 3 Continuous curves: Computed relations between total polarizing current applied through a point electrode at $r = 0$ and the membrane voltage displacement at different distances away from the current electrode at 100 msec. Interrupted curve: Computed relation for smallest interelectrode distance at 200 msec. For small interelectrode distances the curves are nearly linear. The relation applying at 200 msec. differs from the corresponding relation at 100 msec. in that it is slightly less linear and the polarization resistance is greater.

portion crosses the membrane in distant regions where the change in R_m is smaller because the voltage deflection is smaller. Thus the resistance changes in the region of membrane close to the electrode are shunted out by the nearly constant resistance of the outer regions of membrane and the constant intracellular resistance in series with it. The potential across the membrane near the electrode therefore changes by much less than it would have done if the current were applied uniformly.

This redistribution of current is shown in Fig. 4 in which $[dI_i/d(r/\lambda)]/I$ (*i.e.* the rate at which the intracellular current is proportionately reduced by current crossing the membrane) is plotted against r/λ. Fig. 4a shows the curves computed for two values of the total polarizing current, $I = -0.5$ μa and $I = -2.45$ μa, at 100 msec. It can be seen that when $I = -2.45$ μa very much less of the current crosses the membrane between $r = 0$ and $r = 0.5$ mm than when $I = 0.5$ μa. The greater part of the current crosses the membrane beyond $r = 1$ mm where the voltage displacement is less than 15 mv. Fig. 4b shows the redistribution of current which occurs at 200 msec. when the polarizing current is increased from -0.61 μa to -1.59 μa. At the larger current strength, all the current crosses the membrane beyond $r = 2.4$ mm while the area of membrane between this point and the electrode acts as a source of current in addition to the electrode.
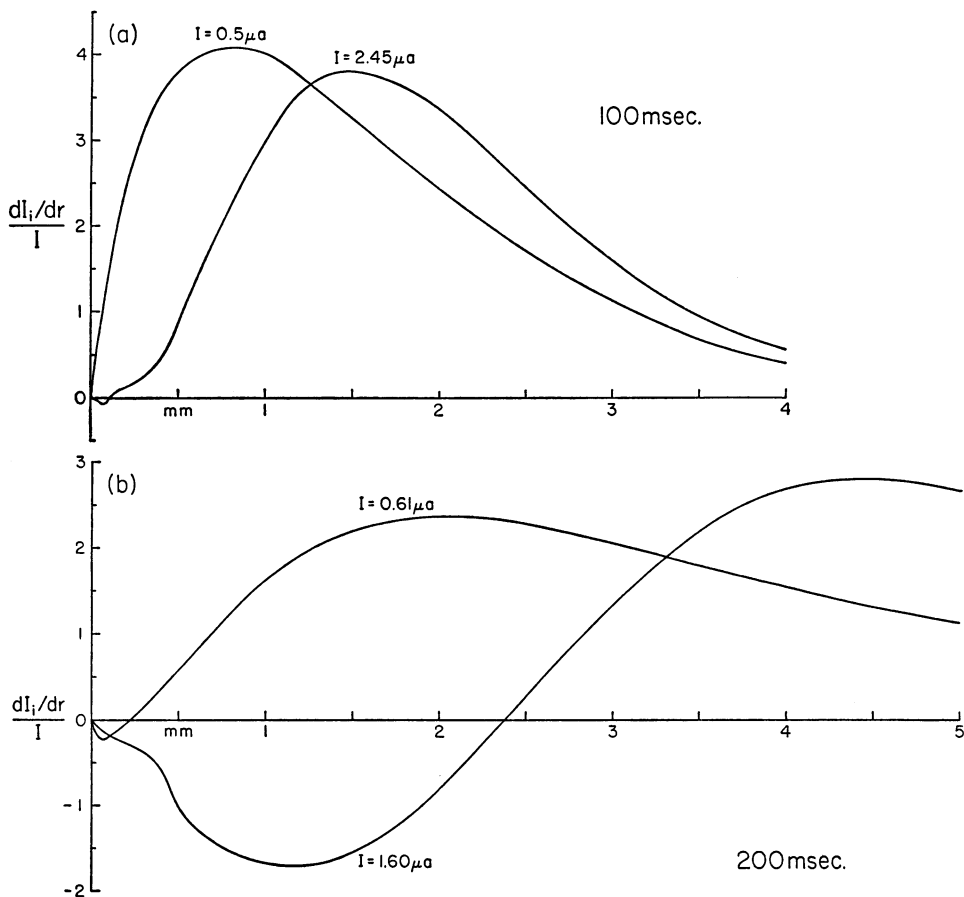
FIGURE 4a   Distribution of current for weak ($I = 0.5$ μa) and strong ($I = 2.45$ μa) polarizing currents at 100 msec. Ordinate: Proportionate rate of reduction of I_t, $(dI_t/dr)/I$. Abscissa: r. Note that at the larger current strength, only a small proportion of the current passes through the region of membrane close to the polarizing electrode.

FIGURE 4b   Distribution of current for weak ($I = 0.61$ μa) and strong ($I = 1.60$ μa) polarizing currents at 200 msec. Note that at the larger current strength, the area of membrane between the electrode and $r = 2.4$ mm is adding current to that supplied by the electrode.

DISCUSSION

It is clear from the computations described in this paper that the results obtained by Johnson and Tille would be expected for the point polarization of a sheet membrane. It might however be argued that the sheet model is not an accurate representation of the experimental situation for two reasons.

First, the wall of the ventricle is a relatively thick structure so that current

will not only spread in all directions in the plane of the surface but also into the depth of the preparation. It would therefore be better to use a 3-dimensional model. However, this would make the detection of non-linearities in the electrical characteristics of the membrane even more difficult. Current would be redistributed in 3 dimensions so that the resistance of the region of membrane close to the electrode would be shunted out by an even larger area of membrane in regions distant from the electrode.

Secondly, the representation of the surface membrane by a continuous sheet does not take account of the syncytial arrangement of the cells. The importance of this deficiency in the model depends on the dimensions of the cells. If the dimensions of the cells were of the same order of magnitude as the space constant then for small interelectrode distances the situation would approximate more closely to the cable situation and membrane resistance changes should be much easier to detect. During the spike of the action potential, when R_m is presumably very small, this may well be the case and Johnson and Tille are probably correct in assuming the polarization resistance at this time to be small. However, if the space constant is large compared to the dimensions of the individual cells, as is likely to be the case during the plateau of the action potential, the syncytial arrangement should not make much difference. In the outer regions it would simply have the effect of apparently increasing R_i. In the region close to the electrode, the effects will in any case be very small since the proportion of current crossing the membrane in this region is small (Fig. 4).

There seems no reason therefore to doubt that a more accurate representation of the experimental situation would give a substantially similar result and it might in fact make the detection of non-linearities even more unlikely than in the 2-dimensional model used in this paper.

Another deficiency in the computations described in this paper is that no account is taken of the capacity current. During the plateau itself, this is justifiable since the rate of repolarization (and therefore also the capacity current) is very small. During the more rapid phase of repolarization the membrane capacity becomes more important. In fact, at times beyond about 220 msec. the current-voltage relation given by the steady-state sodium current and the instantaneous potassium current no longer has a stable point in the region of the plateau (Noble, 1962, Fig. 9). Computations of the type described here are not therefore possible during the more rapid phase of repolarization. If the voltage is expressed with respect to a zero at the remaining stable point (the resting potential) the membrane resistance is now always positive and the subsequent process of repolarization is simply the discharging of the membrane capacity through a non-linear resistance. Hyperpolarizing currents applied during the rapid phase of repolarization would only speed up this process, and it has been shown elsewhere (Noble, 1962, Fig. 10) that Weidmann's (1951) impedance record for

Purkinje fibers, which included polarizing currents during the rapid phase of repolarization, may be accounted for, at least qualitatively, even when the equations for uniform polarization are used.

The deficiencies in the present computations make any quantitative comparison between the change in polarization resistance during the second half of the plateau predicted by these equations and that recorded experimentally by Johnson and Tille rather meaningless. It is however encouraging to note that the predicted increase is of the right order of magnitude. The fact that this change in resistance may be detected while changes in resistance due to non-linearities in the membrane current-voltage relation are less easy to detect is a result of the fact that the changes in resistance during the plateau are taking place in *all* areas of the membrane. Although it is still true that some redistribution of current will occur as R_m changes, the effect will not be as great, so that it is possible for the method to detect uniform changes in R_m with time while failing to detect non-uniform changes in R_m dependent on voltage.

REFERENCES

CARMELIET, E., 1961, Chloride ions and the membrane potential of Purkinje fibres, *J. Physiol.,* **156,** 375.

CHANG, J. J., and SCHMIDT, R. F., 1960, Prolonged action potentials and regenerative repolarizing responses in Purkinje fibers of mammalian heart, *Arch. ges. Physiol.,* **272,** 127.

CRANEFIELD, P. F., and HOFFMAN, B. F., 1958, Propagated repolarization in heart muscle, *J. Gen. Physiol.,* **41,** 633.

FITZHUGH, R., 1960, Thresholds and plateaus in the Hodgkin-Huxley nerve equations, *J. Gen. Physiol.,* **43,** 867.

GEORGE, E. P., and JOHNSON, E. A., 1962, in press, cited by JOHNSON, E. A. *in* the Proceedings of the XXII International Congress of Physiological Sciences, Symposium on Electrophysiology of Cardiac Muscle, *Excerpta Med.*

HODGKIN, A. L., and HUXLEY, A. F., 1952, A quantitative description of the membrane current and its application to conduction and excitation in nerve, *J. Physiol.,* **117,** 500.

HUTTER, O. F., and NOBLE, D., 1960, Rectifying properties of cardiac muscle, *Nature,* **188,** 495.

JAHNKE, E., and EMDE, F., 1945, Tables of Functions, New York, Dover Publications, 4th edition, 236.

JOHNSON, E. A., and TILLE, J., 1960, Changes in polarization resistance during the repolarization phase of the rabbit ventricular action potential, *Australian J. Exp. Biol. and Med. Sc.,* **38,** 509.

JOHNSON, E. A., and TILLE, J., 1961, Evidence for independence of voltage of the membrane conductance of rabbit ventricular fibres, *Nature,* **192,** 663.

LORBER, V., 1962, *in* Proceedings of the XXII International Congress of Physiological Sciences, Symposium on Electrophysiology of Heart Muscle, *Excerpta Med.*

NOBLE, D., 1960, Cardiac action and pacemaker potentials based on the Hodgkin-Huxley equations, *Nature,* **188,** 495.

NOBLE, D., 1962, A modification of the Hodgkin-Huxley equations applicable to Purkinje fibre action and pacemaker potentials, *J. Physiol.,* **160,** 317.

WEIDMANN, S., 1951, Effect of current flow on the membrane potential of cardiac muscle, *J. Physiol.*, **115**, 227.

WEIDMANN, S., 1956, Elektrophysiologie der Herzmuskelfaser, Bern, Huber.

WOODBURY, J. W., 1962, in press, cited by WOODBURY, J. W. *in* the Proceedings of the XXII International Congress of Physiological Sciences, Symposium on Electrophysiology of Heart Muscle, *Excerpta Med.*

WOODBURY, J. W., and CRILL, W. E., 1961, On the problem of impulse conduction in the atrium, *in* Nervous Inhibition, (E. Florey, editor), New York, Pergamon Press.