Membrane Excitation in Cardiac Muscle

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The contributions made during the past 10 years are reviewed. Intracellular recording has made it possible to state absolute values for the cardiac resting potential (90 mv., inside negative to outside) and the "overshoot" during activity (30 mv., inside positive to outside). The surface membrane of a resting fiber is considered to be predominately permeable to K ions. During activity, Na conductance increases and K conductance decreases. The latter process is thought to be essential for explaining the high membrane resistance that is measured during the long-lasting "plateau" found with cardiac muscle. A hypothesis is presented that would account for the termination of the plateau and the beginning of repolarization.

It is the plan of the present survey to begin with a description of the electrical events during cardiac activity; to continue with their interpretation in terms of the movements of ions; and to close by treating a more special problem: the possible reasons for the long-lasting action potential that is typical for cardiac muscle.

Intracellular Recording

It was in 1949 that Ling and Gerard, working in Chicago, described a new tool that stimulated electrophysiologic research in almost all its branches: the capillary microelectrode. Two people who had been taught the technic by Ling were to become responsible for extending the method from skeletal to cardiac muscle: J. W. Woodbury, then working at Salt Lake City, and A. L. Hodgkin of Cambridge, England. I can well remember the day of July 16th, 1949. Having learned the microelectrode technic at Cambridge and having been rather unsuccessful in prodding around in different tissues of the frog, I became a heart physiologist by 2-fold chance: from 5 to 6 p.m. Dr. Feldberg had demonstrated a Starling preparation to the medical students and allowed me to cut out the dog's heart; and my wife agreed that I need not be home for supper at 6:30.

Now, what is the advantage of the new technic? The suction electrode, introduced and widely used by Schütz, had revealed the time course of the cardiac action potential with a fair amount of accuracy. Only by the use of the Ling-Gerard electrode, however, was it possible to record the full amount of the potential difference existing between the inside and the outside of a cardiac fiber.

Figure 1 illustrates the potential changes that can be observed when a microelectrode is introduced into a rhythmically driven preparation (sheep ventricle). The "zero line" or "reference potential" is first recorded between two extracellular electrodes (see drawing upper right). One of the electrodes then is moved into the preparation. Touching and penetrating the endocardial layer causes minor potential changes (first arrow). The penetration of a muscle fiber by the electrode tip (second arrow) is signaled by the occurrence of large potential changes synchronous with the contractions. In diastole the potential difference is constant (resting potential, here 85 mv.). On pulling back the electrode the potential drops to the reference level. When viewed on a faster time base (fig. 1, lower records), the transmembrane action potential shows an extremely rapid upstroke (1 msec.) followed by a plateau and a moderately rapid downstroke (repolarization).

The upstroke would coincide with the QRS complex and the downstroke with the T wave of a surface ECG.

The Distribution of Ions

In heart muscle, as in other living cells, the ionic composition of the inside differs marked-
ly from that of the extracellular space. There are different views on how the inside composition is maintained in spite of the established fact that the membrane is permeable to all the ionic species that have to be considered (fig. 2). One of the simplest hypotheses is this: Na ions leave the cell by some "pump" process of an unknown nature. Na outflux takes place against an electrical gradient and a concentration gradient; for thermodynamic reasons it requires metabolic energy. K and Cl ions may be looked upon as being passively distributed. In the case of K ions the force from the concentration gradient (outward) would be balanced by the force from the electrical potential gradient (inward for a positive ion). It may be stated that the ratio of the K concentrations, 30:1 (inside:outside), and possibly also that of the Cl concentrations 1:30 (1) are in good agreement with the measured potential difference of about 90 mv. (for references see Weidmann5 and Hoffman and Cranefield.6).

**Figure 2**  
Distribution of ions between the inside and the outside of a muscle fiber. Exchange at rest for various ions is indicated with arrows of different length.

**The Movement of Ions**  
If the inner surface of a cell membrane is to become more positive, as during the upstroke of an action potential, the positive charge must be shifted from outside inward. During repolarization, on the other hand, the positive charge must leave the cell. Identification of the ionic species that carry the charge has been accomplished on a quantitative scale for the giant nerve fibers of the squid, mainly by the "Cambridge group." Experiments on cardiac tissue then revealed many similarities (for references see Hoffman...
and Cranefield\(^6\)). Thus it is generally agreed that the movements indicated by figure 3 are responsible for the cardiac action potential: inward movement of Na ions for depolarization, outward movement of K ions for repolarization. These shifts may be "passive," that is, they may be brought about by a succession of permeability changes: first a transitory increase of Na permeability, then a slight increase of K permeability.

The state of ionic concentration differences represents stored energy and makes it possible for strong ionic currents to flow during the action potential. At the end of activity, the inside of the fibers will have gained a minute quantity of Na ions and lost a similar quantity of K ions. If ionic order is to be maintained over a longer period, Na ions must be ejected and K ions accumulated during the time between the two action potentials.

**Evidence for an Increase in Na Permeability During the Action Potential**

Since the work of Overton\(^5\) it has been known that Na ions are necessary for cardiac excitation. Figure 4 shows an experiment of the type that led to the conclusions expressed in the preceding section. Replacement of 80 per cent of the normal NaCl by choline chloride—choline being a nonpenetrating ion—has the following effects: (a) the resting potential remains unaltered, suggesting that the resting membrane is but sparingly permeable to Na ions; (b) the amplitude of the action potential and its duration decrease, suggesting that normally there is an inward Na current during activity. Furthermore, the upstroke velocity of the action potential can be shown to be roughly proportional to the extracellular Na concentration\(^5,10\) suggesting that during the initial phase of activity Na ions are the main carriers of charge.

**The Plateau of the Cardiac Action Potential**

In a nerve fiber, the action potential is ended in less than a millisecond; in the mammalian ventricle, activity lasts for a few tenths

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resistance during the plateau is relatively high (fig. 5). This is an important finding, which indicates that the increase of the Na permeability causing the upstroke of the action potential is at least partially reversed, while the permeability to other ions remains constant or even decreases.

Data of a more quantitative nature have been obtained for Purkinje fibers of the sheep heart (fig. 6).\(^*\) The action potential of Purkinje fibers regularly shows an initial spike and thus a comparatively "low" plateau; as a rule there is some potential drop during diastole, which is typical for all membranes with pacemaker properties. The figures attached to the tracing indicate that the resistance is even higher during activity than at rest.

The behavior of the nerve membrane was adequately described by Hodgkin and Huxley\(^7\) with the aid of a set of empirical equations. Briefly, it was assumed that depolarization causes a transitory increase of Na conductance (G\(_{Na}\)) and a long-lasting but somewhat delayed increase of K conductance (G\(_{K}\)). The increase of G\(_{Na}\) would be responsible for the inward current, causing depolarization; the decrease of G\(_{Na}\) with a simultaneous increase of G\(_{K}\) would provide the outward current, causing repolarization.

An attempt to "produce" a Purkinje-fiber action potential by applying the Hodgkin-Huxley equations was recently made by Noble\(^14\) (fig. 7).\(^*\) In choosing appropriate parameters, the high membrane resistance of Purkinje fibers during the plateau could be simulated only if G\(_{K}\) was allowed to fall as a consequence of depolarization. The conductance changes computed by Noble's machine are seen in figure 8.\(^*\) G\(_{Na}\) rises as a consequence of depolarization; after the initial spike it settles down at about 8 times its resting value. G\(_{K}\) by contrast falls as the driving force for K\(^+\) outflux increases.


\(^*\)Figures 7 (left) reproduced from Draper and Weidmann: J. Physiol. 115: 74, 1951; and figures 7 (right) and 8 from Noble: Nature 188: 495, 1960. By permission of the Journal of Physiology and of Nature.
Convincing experimental evidence is available in the case of the nerve membrane to show that $G_K$ rises as a consequence of depolarization. It is important then to provide experimental evidence for the suggested drop of $G_K$ in Purkinje fibers. With this intention, membrane resistance was measured over a large range of membrane potentials.

To minimize the contribution of Na ions, the experiments were performed in choline chloride (Hutter and Noble; Carmeliet); to eliminate even chloride ions, as carriers of charge, a solution of choline acetylglycinate was used. Under such experimental conditions, the membrane current practically has to be carried by K ions.

Figure 9 reveals that the membrane resistance corresponding to a membrane potential of $-40 \text{ mv.}$ (plateau level) is indeed 3 to 4 times higher than that corresponding to $-90 \text{ mv.}$ (resting level). This is taken to suggest that the assumption of a low $G_K$ during the plateau is well justified.

**The Changes Responsible for Repolarization**

Applying long pulses of depolarizing current to a Purkinje fiber in a Na-free solution, Hutter and Noble found a slow decrease of membrane resistance that was complete at the end of a few tenths of a second. This change

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*Figure 7*

Left. Recorded action potential of a dog Purkinje fiber. (From Draper and Weidmann.) Right. Similar action potential, computed with the aid of the Hodgkin-Huxley equations. (From Noble.)

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*Figure 8*

A. Computed action potential, same as in figure 7. The integration was started by displacing the membrane potential to $-50 \text{ mv.}$ B. Time course of membrane conductance plotted on a logarithmic scale. $G_K$ denotes potassium conductance. $G_Na$ sodium conductance. The potassium and sodium equilibrium potentials were set up $-100 \text{ mv.}$ and $+40 \text{ mv.}$ respectively. (From Noble.)
might indeed be responsible for repolarization if it is attributed to a rise of \( G_K \), thus resulting in a stronger outward current of K ions.

The finding of a strong outward current of tracer potassium (\(^{42}\)K) during the phase of membrane repolarization\(^{18} \) would seem to be in line with the electrical data.

Finally: do we know of any possible reason for which \( G_K \) might increase as a function of time when the membrane is held at a constant potential in the region of the plateau? In this connection let me recall that a rapid rise of the extracellular K concentration induces a "premature" repolarization (fig. 10). One of the suggested mechanisms for this observation was recently tested by Carmeliet.\(^{19} \)

He was able to demonstrate that an increase in the extracellular K concentration causes a drop in membrane resistance that may be interpreted as a rise of \( G_K \) (fig. 9). The effect is most pronounced near \(-40 \text{ mV}\), i.e., in the region of the plateau of the action potential of a Purkinje fiber.

Furthermore, Carmeliet\(^{19} \) measured the inward outflux of radio-K using extracellular solutions of different K concentrations. He could indeed establish that the rate of influx as well as that of outflux became larger when the outside K concentration was increased, again suggesting a rise of \( G_K \).

It seems not unlikely, therefore, that the plateau is brought to an end by the following mechanism: (a) outflux of K ions during the plateau; (b) accumulation of K ions in a narrow space around the fibers; (c) increase of \( G_K \) as a consequence of the rising extracellular K concentration; (d) increase in the rate of K outflux. This is a regenerative process and might well be responsible for terminating the cardiac action potential.
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References
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