Cardiac arrest, produced by an increased extracellular potassium concentration, was first observed by Hering in 1907. Recent studies with microelectrodes have revealed that an increased potassium concentration decreases the transmembrane potential of fibers of atrium, ventricle, and the Purkinje system. Sensitivity to potassium, however, differs for the several tissues. Conduction fails earlier in atrial fibers than in ventricular tissue. The specialized fibers of the sino-atrial and atrio-ventricular node and the crista terminals are less sensitive to potassium than the atrial fibers. The most resistant fibers are apparently those of the bundle of His, which remained excitable when other types of cardiac fibers are inexcitable. The loss of excitability and the failure of conduction which lead to cardiac arrest have been attributed to the fall of the resting potential below a critical level.

We observed that isolated rabbit hearts could be arrested by the rapid replacement of a potassium deficient perfusion fluid with one containing a physiological concentration of potassium. The shortening of the ventricular action potential and subsequent arrest may have resulted from the sudden change in the potassium gradient across the cell membrane. At that time we were not aware that similar observations had been made in the past. Arrest of frog's heart after a change of the medium from a potassium-free Ringer to normal Ringer solution was described by Zwaardemaker in 1920. Subsequently, Libbrecht confirmed the observation of Zwaardemaker, and noted that not only the mechanical but also the electrical activity of the ventricles was inhibited. He also found that, during arrest, spontaneous atrial activity was maintained and the stimulated ventricles showed normal contractility and excitability. Libbrecht termed this phenomenon a paradox which he attributed to an adaptation of the heart to new conditions. Lenzi and Caniggia called attention to the "Zwaardemaker and Libbrecht paradoxical phenomenon" because they felt that it offered supporting evidence for the ionic theory of excitation. Our renewed interest in this type of cardiac arrest arose during a study designed to correlate the effects of high and low [K] on the transmembrane action potential and the electrocardiogram. We noted significant differences between the effect produced by high [K] and that elicited by a rapid shift from low to normal [K] on the ventricular and atrial action potential and the electrocardiogram. This paper describes these differences in order to emphasize that the Zwaardemaker-Libbrecht phenomenon has an entirely different mechanism from the arrest caused by high extracellular K concentration.

Methods

The method of perfusion of isolated rabbit hearts, the recording of monophasic action potentials (MAP) with suction electrodes and the recording of electrocardiograms was previously described. The perfusing Krebs-Henseleit solution (control) contained 145 mM Na, 4.8 mM K, 2.5 mM Ca and 1.2 mM Mg in 1 liter. The potassium concentration in the low-K solution was 0.8 mM/L.
and in the high-K solution 12.0 mM/L. The temperature of the perfusing solution was 37°C and the pH ranged between 7.3 and 7.5.

Transmembrane potentials were recorded with flexibly mounted microelectrodes with an outer tip diameter of less than 0.5 micron and filled with 3M KCl. The resistance of microelectrodes was 10-30 megohms. The recording system consisted of a cathode follower, a Grass P7 D-C preamplifier and either an Electronics for Medicine (EfM) D-C amplifier and oscilloscope or a Dumont 403 oscilloscope. The records photographed from both oscilloscopes simultaneously showed identical amplitudes and contours. Electrocardiogram, contractile force and ventricular and atrial action potentials obtained with suction electrodes also were registered simultaneously on a four-channel Sanborn Poly-Viso Electrocardiograph at a paper speed of 50 mm/sec. We recorded the tracings obtained with suction electrodes and microelectrodes during the same experiment because of the difficulty in maintaining a microelectrode in a single fiber of a beating heart for prolonged periods of time. Usually, we were able to observe the uninterrupted sequence of changes in the shape and duration of the action potential more clearly on those records obtained with suction electrodes.

The penetrations were performed on the surface of the right ventricle and we attempted to record from the same area throughout an experiment. The difficulty in maintaining an electrode inside the cardiac fiber was partly obviated by immobilizing the area studied with a few subepicardial sutures. The immobilization procedure did not change the characteristics of the records. Our criteria for acceptance of the transmembrane action potential records were described elsewhere.14

Results

Perfusion with low K solution produced typical changes in the shape, duration and amplitude of the ventricular transmembrane potential and in the pattern of the ECG.10,14 These changes are illustrated in figures 1B and 3 (B and C). Continued perfusion resulted in development of supraventricular and ventricular ectopic beats, ectopic tachycardias, and finally, ventricular fibrillation. The time of onset of ventricular fibrillation ranged from 5 to 45 minutes and fibrillation continued after a change to control solution. If, however, a change to control solution was made prior to the development of ventricular fibrillation, the Zwaardemaker-Libbrecht effect was observed (figs. 1 and 3). Cardiac arrest lasting for 2-30 seconds occurred almost instantaneously after the control solution reached the heart. In most instances only one or few supraventricular impulses were conducted to the ventricles after arrest, and they were followed by a second period of arrest lasting for several seconds. This in turn was followed by bradycardia and a gradual return to control rate within one to two minutes. The tracings recorded immediately after arrest and between the first and second period of arrest were studied in detail, and compared with tracings made during perfusion with high K solution. The effects of high K solution on the shape, duration and amplitude of the ventricular transmembrane potential and ECG pattern have been described elsewhere.14 Typical changes are illustrated in figures 2 and 3 (G, H, and I).

Atrial monophasic action potentials recorded immediately after a change from low K to control solution had a shorter duration and a slightly lower amplitude than the controls (fig. 3D). We have not compared the magnitude of the atrial resting membrane potential before and after arrest. The appearance of the atrial action potential immediately after the change from low K to control solution contrasted with the appearance of the atrial action potential recorded during perfusion with high K solution. During this perfusion the monophasic action potential rapidly decreased in amplitude until it could be recognized only as a small rounded deflection (fig. 3 H and I). The P wave disappeared at the time when the ventricular action potential and the ventricular complex in the ECG were still well defined (fig. 3 I).

Ventricular action potentials had an increased amplitude during perfusion with low K solution (fig. 1B). Immediately after the change from low-K to control solution the amplitude of the action potential decreased by 20-30 millivolts. This decrease resulted in an amplitude which was only slightly lower than the control amplitude. The return to control amplitude occurred rapidly (fig. 1E). The resting membrane potential immediately
after arrest was lower than during the low K perfusion but slightly higher than the control. Thus, the overshoot of the action potential immediately after the arrest was lower than during low K perfusion but slightly higher than the control (fig. 1C). The resting and action potential were always significantly higher immediately after arrest than during perfusion with high-K solution (fig. 2). The recorded maximal upstroke velocity of the action potential after arrest was unchanged in contrast to a marked slowing during perfusion with high-K solution. The duration of the ventricular action potential decreased about threefold although the heart rate was slower. The action potential immediately after arrest and between two periods of arrest was shorter than the control and shorter than the action potential during perfusion with high-K solution (figs. 1 and 2). The shortening of the action potential was caused by an increased velocity of the phase 3 since phase 2 had already disappeared prior to the change to control solution. Thus, the ventricular action potential had a marked resemblance to a normal atrial action potential (figs. 1 and 3). Electrocardiograms recorded immediately after arrest reflected the change in shape and duration of the action potential. The Q-T interval was very short, the S-T segment was
absent, and the T wave was very short. Thus, the ECG pattern resembled the electrocardiographic pattern of hypercalcemia in rabbit and man (figs. 1C and 3D). The duration of the QRS complex immediately after arrest was either unchanged or slightly decreased in contrast to a marked increase in the QRS duration during perfusion with high-K solution (figs. 2 and 3 H and I). The rhythm immediately after the arrest which followed the change from low-K to control solution was either sinus or A-V nodal. Figure 3 demonstrates that immediately after arrest the ventricles are capable of responding at a rate of at least 300 per minute and the atria at a rate of at least 250 per minute. This suggests that the refractory period of the ventricles and atria is very short as expected from the duration of the action potentials. The first impulse after both periods of arrest in figure 3D appears to originate in the A-V node because the configuration of the ventricular complex in the ECG is normal, and the atrial and ventricular action potentials have the same time of onset. The second atrial impulse in both instances is most likely conducted in a retrograde fashion from the ventricle or the A-V node. The exact interpretation of the mechanism of both short bursts of atrial and ventricular activity following the arrest may be difficult but the events suggest that not only could the ventricles and the atria be excited at rapid rates but also that the rapid conduction between the atria and the ventricles could occur immediately after arrest. Occasionally the conduction between the atria and the ventricles was delayed as evidenced by a prolonged P-R interval of the beats immediately after arrest (fig. 1C). In a few instances we have observed a ventricular arrest with a maintenance of regular but slow atrial activity.

Discussion

Increased extracellular K concentration affects the cardiac transmembrane action potential in two ways: (1) by decreasing the resting potential, and (2) by increasing the velocity of repolarization. The decrease in the resting membrane potential is responsible for the decreased upstroke velocity of the action potential; this results in a slow conduction and a decreased excitability. The rapid repolarization shortens the duration of the action potential. This effect is attributed to an increased potassium permeability.

Our observation suggests that the two effects of increased extracellular K concentration are dissociated in the Zwaardemaker-Libbrecht phenomenon. The increased velocity of repolarization and the resulting shortening of the action potential are very pronounced while the changes in the resting potential are slight and the upstroke velocity of the action potential is unchanged. Cardiac arrest in the potassium-depleted heart after a sudden in-
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FIGURE 3
Retraced ventricular monophasic action potential (Ventr.), atrial monophasic action potential (A.tr.) and electrocardiogram (ECG) recorded simultaneously at a paper speed 50 mm/sec. A: Control. Note that the atria and the ventricles are excited simultaneously which was interpreted as an A-V nodal rhythm. B: After two minutes and 30 seconds of perfusion with low-K solution. Note the increased duration of the ventricular and atrial action potential (AP) and the typical ECG changes. C: After perfusion for 17 minutes with low K solution, immediately before the change to control solution. Note further increase in the duration of the ventricular and atrial AP. Excitation of the atria occurs after the excitation of the ventricles; this was interpreted as a delay in the retrograde conduction. D: On the left the first three beats after 22 seconds of arrest following a change from low K to control solution. Note the decreased duration of the ventricular and atrial AP. In the first beat the atria and the ventricles are excited simultaneously, in the second beat the atria are excited before the ventricles, and in the third beat transmission to the atria is blocked. On the right, two beats after a second arrest of 10 seconds duration. In the first beat the atria and the ventricles are excited simultaneously, and in the second beat the ventricles are excited before the atria. E: Two minutes and F: 25 minutes following the change from low K to control solution. Note the sinus A-V nodal rhythm and a normal shape of the ventricular and atrial AP. G: Ten minutes of perfusion with high-K solution. Note the change to sinus rhythm. H: Twenty minutes of perfusion with high-K solution. Note the decreased amplitude of the atrial (A) and ventricular AP. The beginning of the ventricular AP is deformed by a superimposed QRS artifact. The QRS duration is increased and the P-R interval is prolonged. I: Twenty-five minutes of perfusion with high-K solution immediately before return to control solution. Note further decrease in the amplitude of the atrial AP which is transformed into a small round deflection (A) and of the ventricular AP. The latter is deformed by the QRS artifact. Note further decrease in heart rate, an increase in the duration of the QRS complex, and absence of P wave. J: One minute and 30 seconds after return to the control solution. The sinus rhythm persists but the shape of the ventricular and atrial AP and the ECG have returned to normal.

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crease of the extracellular K concentration is probably caused by this selective effect on repolarization. The arrest is probably caused by inhibition of the pacemaker fibers since the conduction and excitability of the atria and the ventricles are normal immediately after arrest.

The normal pacemaker activity is maintained by spontaneous diastolic depolarization which, according to Dudel and Trautwein, is caused by a decreasing K permeability. If, as Weidmann and Carmeliet suggest, K permeability is increased by an increase in extracellular K concentration, then the diastolic depolarization of the pacemaker fibers would be inhibited. Thus, we postulate that in our experiment, the same process that accelerates repolarization in the ventricular fibers inhibits depolarization in the pacemaker fibers. This hypothesis remains to be proven by recording the transmembrane potentials of the pacemaker fibers before, during and after a change from a low-K to control solution.

There remains a possibility that the Zwaardemaker-Libbrecht effect is caused by a greater decrease of the resting potential in the pacemaker fibers than in the atrial and ventricular fibers. This is extremely unlikely. On the contrary, one would expect a lesser effect of increased K concentration on the resting potential of the pacemaker fibers than on the atrial and ventricular fibers. De Mello and Hoffman have shown that the pacemaker fibers are more resistant to high-K concentration because they generate action potentials at the levels of resting potential which do not permit a regenerative response in the myocardial fibers. The vulnerability of the pacemaker fibers under the conditions of our experiment is a puzzling phenomenon. It remains to be determined whether cardiac arrest which occurs when a potassium deficient perfusion fluid is suddenly replaced with one containing a physiological concentration of potassium occurs only in isolated hearts or whether it can occur in an intact animal or man. If such a phenomenon can occur in situ, when the myocardium is depleted of potassium and the plasma K concentration is suddenly raised, the arrest of the heart may result in sudden death.

The Zwaardemaker-Libbrecht effect usually consisted of ventricular and atrial arrest. However, in some instances the atrial activity was maintained similarly to the original observations in the frog heart made by Libbrecht. Ventricular arrest in these instances must be attributed to a failure of the conduction through the A-V node or the conduction system below the A-V node. A delay in conduction through the A-V node also was suggested by an occasional prolongation of the P-R interval following the arrest. However, we have seen many instances of a seemingly normal conduction from the atria to the ventricles and vice versa which suggests that the inhibition of the A-V conduction is not a constant feature of the Zwaardemaker-Libbrecht phenomenon.

Summary

Ventricular arrest occurs in isolated heart perfused with potassium-deficient solution when the extracellular potassium concentration is suddenly raised to a physiological concentration. This is known as a paradoxical phenomenon of Zwaardemaker and Libbrecht. Records of electrocardiograms, and ventricular and atrial transmembrane potentials from perfused rabbit hearts before, during and after this type of arrest revealed that its mechanism differs from the mechanism of cardiac arrest produced by an increase of external [K] above physiological concentration. The Zwaardemaker-Libbrecht phenomenon is associated with a striking increase in the velocity of repolarization while the typical effects of high-K concentration on the resting membrane potential and amplitude and upstroke velocity of the action potential are either very slight or absent. Conduction in the atria, ventricles and between the atria and the ventricles apparently is not disturbed during the Zwaardemaker-Libbrecht phenomenon; therefore, we attribute the cardiac arrest to a selective inhibition of the pacemaker ac-
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Activity. This might be due to an inhibition of the diastolic depolarization of the pacemaker fibers. A speculation is made that the type of imbalance between the intracellular and extracellular K concentration in the myocardium which causes the Zwaardemaker-Libbrecht effect in the isolated heart could occur in situ and cause sudden death.

Acknowledgment

We are grateful to Professor F. Lenzi of the Siena University in Italy for bringing to our attention the original articles of Zwaardemaker and Libbrecht.

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Two Mechanisms of Cardiac Arrest Produced by Potassium
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doi: 10.1161/01.RES.12.4.415
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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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:
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