

# Electrophysiologic Properties of Isolated Preparations of Human Atrial Myocardium

By Henry Gelband, Harry L. Bush, Michael R. Rosen,  
Robert J. Myerburg, and Brian F. Hoffman

## ABSTRACT

The electrophysiologic properties of human atrium were studied with intracellular microelectrodes in 22 preparations of human right atrial tissue obtained at the time of corrective open heart surgery. Two types of fibers were identified: the first had electrical characteristics typical of atrial contractile cells and the second those of atrial specialized fibers. Automaticity developed only in the latter type of cell. In 36 impalements of specialized atrial fibers, resting membrane potential was  $-86 \pm 5$  mv (mean  $\pm$  SD), transmembrane action potential amplitude was  $102 \pm 12$  mv, transmembrane action potential overshoot was  $16 \pm 4$  mv. Similar results were obtained in 49 impalements of contractile fibers. Conduction velocity measured 0.28–0.33 m/sec in contractile fibers and 0.41–0.45 m/sec in specialized atrial fibers. Action potential duration of specialized atrial fibers was linearly related to the basic cycle length between 200 and 1000 msec. At cycle lengths greater than 1000 msec the increase in action potential duration was no longer linear. There was a decrease of 58 mv in resting membrane potential of specialized atrial fibers when exposed to a tenfold increase in extracellular  $[K^+]$ . This decrease occurred in a linear fashion in  $[K^+]$  above 5 mM. These experiments provide reference values for future studies dealing with electrophysiology of human atrial tissue.

**KEY WORDS** membrane responsiveness resting membrane potential transmembrane action potential conduction velocity latent pacemaker phase 4 depolarization extracellular  $K^+$  concentration automaticity action potential duration

■ Although extensive electrophysiologic investigations utilizing intracellular microelectrode techniques have been carried out on the hearts of lower mammals, there are only a few published papers dealing with human cardiac tissue. Investigators have utilized flexibly mounted microelectrodes to study ventricular muscle of exposed contracting human hearts during surgery (1, 2). Trautwein et al. (3)

were among the first to record transmembrane action potentials from isolated human atrial and ventricular myocardium. They reported the results of five experiments. In two of these, atrial samples from young patients with atrial septal defects, mean resting membrane potential was  $-70$  mv (range  $-60$  to  $-80$  mv), and action potential amplitude was 75 mv (range 64 to 90 mv). The other specimens, from older patients with valvular disease showed lower resting membrane potential and amplitude. Other electrophysiologic experiments have been concerned with excitation-contraction coupling in human atrial tissue (4, 5) or excitation of the human fetal heart (6). Sleator and de Gubareff conducted a series of studies on human atrium at a temperature range of 24–27°C, and electrophysiologic properties within the physiologic temperature range were not reported (4). All patients in Prasad's report were over 50 and had

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From the Department of Pharmacology, College of Physicians and Surgeons, Columbia University, New York, New York 10032.

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rheumatic heart disease (5). In seven atrial samples which evinced spontaneous rhythm, mean resting membrane potential was  $-43.5$  mv and amplitude 44 mv. In 15 specimens which showed no automaticity, mean resting membrane potential was  $-83.2$  mv, and amplitude 104.4 mv. Because of the variability in results obtained from these studies and the limited data on electrophysiologic properties of normal human atrial cells, we conducted a systematic investigation on human atrial tissue taken from patients with no electrical or hemodynamic evidence of atrial disease. Our primary objective was to obtain control data for future electrophysiologic studies utilizing human atria. In addition, we wished to ascertain if there are any major differences between the electrophysiologic properties of human atrial tissue and atria from other species.

### Methods

Small pieces ( $< 1$  cm<sup>2</sup>) of atrial myocardium from the anterior free wall of the right atrium were excised from the hearts of 22 patients undergoing corrective open heart surgery as part of the cannulation technique for cardiopulmonary bypass. All patients were under 16 years of age. Fourteen had ventricular septal defects and 8 congenital aortic stenosis. To ensure that the preparations of atrial tissue were physiologically normal, the following criteria were employed. No patient had been in congestive heart failure and none had received any cardiotonic, antiarrhythmic or diuretic medication. Preoperative electrocardiograms in all patients revealed normal values for P-R interval, P-wave amplitude and P-wave duration. No patient had a history or electrocardiographic evidence of cardiac arrhythmia. Cardiac catheterization revealed normal right atrial pressures and no evidence of interatrial shunting.

Immediately after excision, the tissue was immersed in cool Tyrode's solution and taken to the laboratory. Within 10 minutes after excision, the atrial preparations were mounted in an acrylic perfusion chamber; stainless steel pins secured them to the wax bottom of the chamber. The tissue was perfused at a rate of 8 ml/min with Tyrode's solution composed of (in mM): NaCl 137, NaHCO<sub>3</sub> 12, dextrose 5.5, NaH<sub>2</sub>PO<sub>4</sub> 1.8, MgCl<sub>2</sub> 0.5, CaCl<sub>2</sub> 2.7, and KCl 4. The KCl concentration was varied for certain experiments. The Tyrode solution was gassed with a 95% O<sub>2</sub>-5% CO<sub>2</sub> mixture which maintained the pH at

$7.36 \pm 0.04$ . A glass heat exchanger was used to maintain temperature at  $37 \pm 0.5^\circ\text{C}$ .

External driving stimuli were delivered to the preparation by Teflon-coated bipolar silver electrodes. Stimuli were initiated using pulse and wave-form generators (Tektronix Models 161 and 162, respectively) and stimulus isolation units (Bioelectric Instruments). The method for delivering a basic drive stimulus (S<sub>1</sub>) and test stimuli (S<sub>2</sub>) has been previously described (7). S<sub>1</sub> was generally 2 msec in duration with amplitude one to two times threshold; S<sub>2</sub> was generally 3-4 msec in duration with an amplitude two to three times threshold. S<sub>2</sub> was used to determine membrane responsiveness.

Microelectrodes were machine-pulled from capillary glass and filled by boiling in 3M KCl. Tip diameter was less than  $1\mu$ , and resistance ranged from 10 to 30 megohms. The electrodes were coupled by a 3M KCl interface to an Ag-AgCl bar which led to an amplifier with high input impedance and capacity neutralization (Bioelectric Instruments NF-1). The output was displayed in the upper beam of a cathode ray oscilloscope (Tektronix Model 565) and was led into an operational amplifier (Tektronix Type 0), which provided a differentiated signal to be displayed on the lower beam of the same oscilloscope. This permitted electronic calibration and monitoring of maximum rate of rise of phase 0 of the action potential (dv/dt) by methods previously described (7). Values for dv/dt and membrane potential were obtained directly from a digital counter (United Systems Digitec, Model 275) using the method of Gelband et al. (8). Membrane responsiveness curves were determined by expressing dv/dt of a prematurely induced action potential as a function of the membrane potential from which the action potential was elicited. Action potential duration was studied by displaying the action potential on an oscilloscope (Tektronix Model 502A) and measuring to the point of 70% repolarization by a technique previously described (9). Recordings were photographed with a Polaroid camera.

For studies of conduction velocity, an external stimulus was applied to a linear pectinate muscle or to small strands of tissue connecting the pectinate muscles. These strands were similar in appearance to false tendons of the canine ventricular conduction system. Transmembrane action potentials recorded from these latter areas invariably demonstrated a prominent plateau. Time for passage of the action potential between two intracellular microelectrodes was recorded. Conduction time was measured between the midpoints of the action potential upstrokes, with an accuracy of  $\pm 0.1$  msec, using the method of

Myerburg et al. (9). Distance between microelectrodes was measured at a magnification of 10 $\times$ . Automaticity was induced in preparations stimulated at a slow rate (cycle length of 2000 msec) by overstretching or hypoxia or both (10).

### Results

**Transmembrane Action Potential Configuration.**—Two distinctly different atrial transmembrane action potentials (TAP) were recorded from nine of the preparations (Fig. 1). Panel A demonstrates the typical TAP recorded from what we believe to be a specialized atrial fiber. Following the initial rapid upstroke of the TAP, there appears a brief repolarization (phase 1). Subsequently there is a plateau (phase 2) and fairly rapid repolarization during phase 3. In contrast, panel B shows a typical TAP recorded from a fiber belonging to the mass of atrial pectinate muscles in the human atria. Repolarization proceeds to completion with only minor change in slope. The recovery limb of the TAP is concave and separate phases 2 and 3 cannot be identified. In both types of fibers, however, the terminal phase of repolarization is characterized by an extremely slow return of the TAP to its resting value. Spontaneous phase 4 depolarization (Fig. 2) developed only in specialized atrial fibers, i.e., those whose TAP showed a prominent plateau. To demonstrate phase 4 depolarization, it was necessary to stimulate these fibers at a cycle length of 2000 msec or longer, and usually stretch or hypoxia

or both were necessary to induce spontaneous activity. Phase 4 depolarization did not occur in contractile fibers of the pectinate muscles at any time under similar conditions.

**Transmembrane Action Potential Characteristics.**—Resting membrane potential (RMP), TAP amplitude, and TAP overshoot were recorded in 85 successful microelectrode impalements (36 in specialized atrial fibers and 49 in contractile fibers). In specialized atrial fibers, RMP was  $-86 \pm 5$  mv (mean  $\pm$  SD), TAP amplitude  $102 \pm 12$  mv and TAP overshoot  $16 \pm 4$  mv; in atrial contractile fibers the values recorded were RMP  $83 \pm 6$  mv, TAP amplitude  $97 \pm 8$  mv and TAP overshoot  $12 \pm 8$  mv. For each of these three characteristics, no significant differences were present ( $P > 0.05$ ) (11) between the two types of fibers. RMP was quite constant during phase 4 except under conditions of stretch or hypoxia, hence maximum diastolic potential was equal to RMP.

**Action Potential Duration.**—Action potential duration (APD) measured to 70% repolarization was recorded for 49 contractile and 36 specialized atrial fibers at a basic cycle length of 1000 msec. APD was  $210 \pm 12$  msec for the specialized fibers. For contractile fibers, APD was considerably shorter, measuring  $138 \pm 21$  msec. The shorter APD of the contractile fibers was due to the absence of a plateau phase during repolarization.

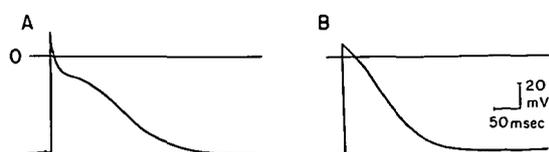


FIGURE 1

*Transmembrane action potentials (TAP) recorded from two types of atrial fibers. Top trace in each panel is line of zero potential. A: Typical TAP recorded from an atrial specialized fiber. There is a prominent overshoot, followed by a period of rapid repolarization and then a prolonged phase of slow repolarization (plateau). B: TAP from an atrial contractile fiber. In contrast to A, separate phases of repolarization cannot be distinguished in contractile fibers.*

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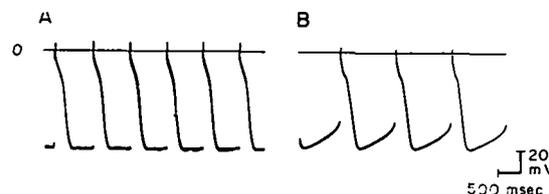


FIGURE 2

*Development of automaticity in an atrial specialized fiber. A: Preparation was stimulated at a cycle length of 800 msec. Resting potential is stable. B: TAP from the same cell after discontinuing the driving stimulus and subjecting the preparation to stretch. Automaticity of the fiber at a rate of 38/min has developed and is associated with a prominent increase in the slope of diastolic depolarization (phase 4). Some decrease in the amplitude of the overshoot is present.*

In seven experiments the basic cycle length was varied from 200 msec to 2000 msec at 37°C. Between cycle lengths of 200 to 1000 msec, APD increased in a linear fashion; this relationship is graphically demonstrated in Figure 3. At cycle lengths greater than 1000 msec there appeared to be a further increase in APD but it no longer was linearly related to cycle length. When the preparations were driven at cycles longer than 2000 msec, automaticity usually developed secondary to enhanced phase 4 depolarization.

In four experiments APD of specialized cells was measured when the preparations were cooled to 29°C at a cycle length of 1000 msec. At this temperature APD lengthened by 92–105 msec. The contour of the action potential was changed in such a way that a smooth prolongation of the entire repolarization limb occurred (Fig. 4). There were no changes in RMP or TAP amplitude on cooling.

**Conduction Velocity.**—Conduction velocity was measured for nine preparations. In two, two specialized atrial fibers 5–7 mm apart in a single longitudinal strand of atrial tissue were impaled. Conduction velocity measured 0.45 and 0.41 m/sec. Results obtained from the

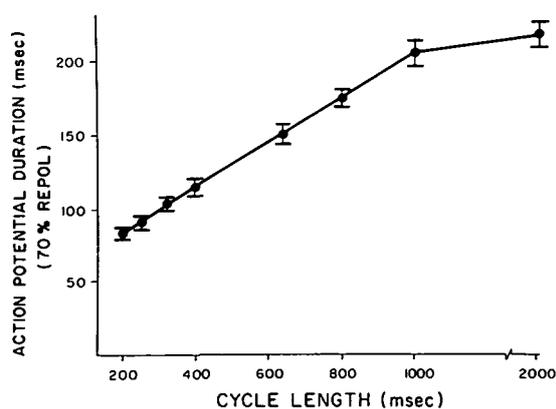


FIGURE 3

Relation between action potential duration (APD) and basic cycle length of specialized atrial fibers in seven experiments. *sd* is shown. There is a linear increase in APD as the cycle length is increased from 200 to 1000 msec. At a cycle length greater than 1000, the increase in APD no longer is linear but apparently reaches a plateau.

impalement of contractile fibers in nine preparations ranged from 0.28 m/sec to 0.33 m/sec. Although conduction velocity was measured in only two preparations of atrial fibers possessing specialized characteristics, they apparently conduct at a higher velocity than ordinary atrial fibers.

**Effect of Varying Extracellular  $K^+$  Concentration.**—The RMP of cardiac tissue is primarily determined by the ratio of intracellular  $[K^+]$  to extracellular  $[K^+]$ . Figure 5 demonstrates the effect of increasing extracellular  $[K^+]$ . In six experiments Tyrode's solution containing the desired  $[K^+]$  was infused and allowed to equilibrate for 30 minutes before results were recorded. As extracellular  $[K^+]$  was increased from 5 to 50 mM (Fig. 5, A through F) there was a decrease in RMP from  $-78$  mv to  $-14$  mv, which was accompanied by a decrease in the TAP amplitude and overshoot and a change in TAP configuration. When the RMP was less than 60 mv (panel C), the overshoot disappeared and the driving stimuli elicited responses which propagated only a short distance. Atrial electrograms, recorded through Teflon-coated bipolar silver wires positioned 6–10 mm distal to a recording microelectrode showed no propagation of electrical activity when extracellular  $[K^+]$  was greater than 10 mM. This indicates a failure of conduction from stimulus site to electrogram recording site although a local TAP of decreased amplitude is inscribed.

The change in the RMP was related to the logarithm of the extracellular  $[K^+]$  in an

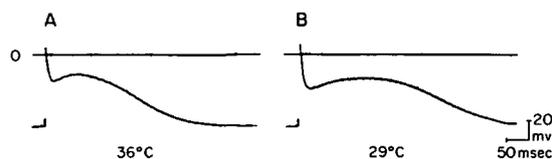


FIGURE 4

Effect of temperature on the transmembrane action potential of a single specialized atrial fiber. A and B show the same atrial cell at 36°C and 29°C, respectively. Cooling of the preparation caused a symmetrical prolongation of the entire repolarization limb. Action potential duration increased from 358 msec to 461 msec.

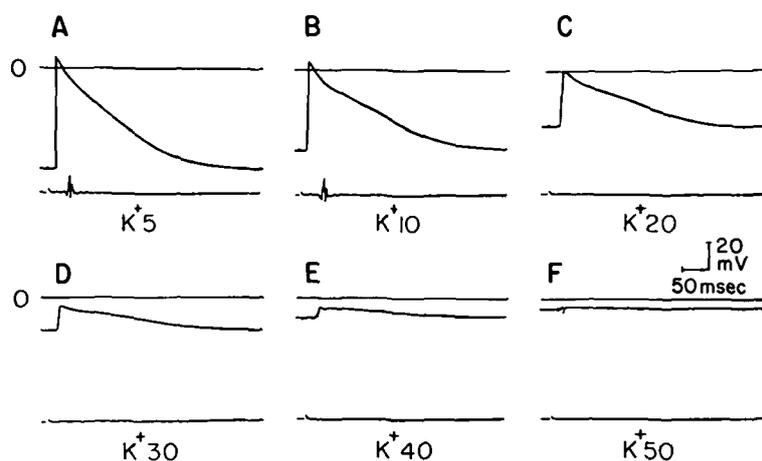


FIGURE 5

Effect of increasing extracellular  $[K^+]$  on the electrical activity of a human atrial cell. Transmembrane potentials shown in panels A through F were recorded from a single impalement. Top trace in each panel represents line of zero potential. Bottom trace of each panel is an atrial electrogram positioned 7 mm distal to the recording microelectrode. Extracellular  $[K^+]$  in mM is indicated under each panel. As extracellular  $[K^+]$  was increased from 5 mM to 50 mM, there was a decrease in resting membrane potential from  $-78$  mv to  $-14$  mv. The absence of an atrial electrogram in panel C, when the  $[K^+]$  was 20 mM suggests that the action potential was not conducted to the electrogram recording site.

approximately linear manner (Fig. 6) (12). Increasingly extracellular  $[K^+]$  from 5 to 50 mM resulted in a decrease in RMP from  $-80 \pm 1.6$  mv (mean  $\pm$  SD) to  $-21 \pm 8$  mv; RMP thus decreased 58 mv per tenfold increase in external  $[K^+]$ . This is slightly less than the 61.4 mv predicted by the Nernst equation for  $37^\circ\text{C}$ . When the extracellular  $[K^+]$  was decreased below 5 mM in successive steps to 1 mM there was a slight increase in RMP. The increase in RMP deviated widely from the predicted slope. At  $[K^+]$  less than 1 mM (0.4 mM) spontaneous activity occurred in all preparations and phase 4 depolarization was recorded from specialized fibers.

**Maximum Rate of Rise of Phase 0 ( $dv/dt$ ) and Membrane Responsiveness.**—Membrane responsiveness, defined as the relationship between  $dv/dt$  of a premature TAP and the membrane potential from which the TAP was elicited, was measured for specialized fibers in eight experiments. The observations in each experiment were made from a single impalement. When stimuli were applied during phase 3 at different levels of membrane

potential, data which constructed a typical sigmoid membrane response curve were obtained (Fig. 7). The  $dv/dt$  ranged from 202 to 244 v/sec with a mean of  $226 \pm 14$  v/sec (mean  $\pm$  SD) at a peak membrane potential of  $-86 \pm 5.7$  mv. The minimum transmembrane potential at which a response could be elicited ranged from  $-54$  mv to  $-59$  mv with a mean of  $-56 \pm 1.6$  mv. The  $dv/dt$  measured at these levels of RMP ranged from 12 to 22 v/sec. The take-off potential for which the rate of voltage change during phase 0 was half maximal was noted. This value was  $-68 \pm 2.2$  mv with a range of  $-65$  to  $-72$  mv. The  $dv/dt$  measured for atrial contractile fibers in 18 preparations ranged from 110 to 152 v/sec. Membrane responsiveness curves were not recorded for these fibers.

### Discussion

For many years it has been assumed that the electrophysiologic properties of atrial tissue from different species were similar (13-16). Previous studies of human tissues utilizing intracellular microelectrode techniques

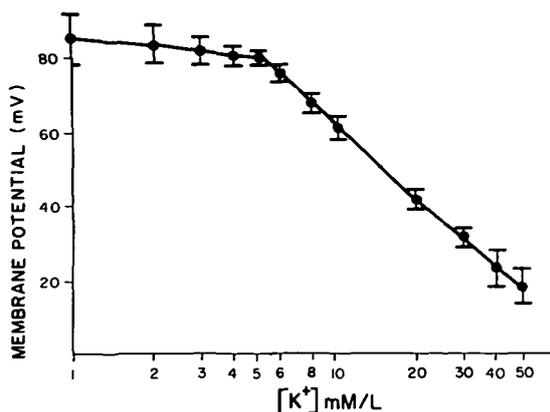


FIGURE 6

Relation between extracellular  $[K^+]$  and the resting membrane potential of single human atrial fibers. Data summarized from six experiments. Means and *SD* are shown. A linear decrease in membrane potential occurred as extracellular  $[K^+]$  was increased from 5 *mM* to 50 *mM*. There was a decrease of 58 *mV* per tenfold increase in  $[K^+]$ . At  $[K^+]$  below 5 *mM*, a slight increase of membrane potential occurred.

have essentially been limited to the study of ventricular myocardium (3, 17-19) or diseased atrium (20). The series dealing with the electrophysiologic properties of human atrium alone have been primarily concerned with the electrophysiology of the fetal atrial myocardium (6), excitation-contraction in human atrial tissue (4, 5), or, more recently, the definition of the membrane permeabilities underlying the two components of the human atrial action potential during hypothermia (21).

Physiologic evidence for specialized atrial fibers has been presented for the rabbit (13) and dog atria (22). James (23) has provided histologic evidence for two distinct fiber types in the human atria, one of which he considers to make up the specialized internodal and interatrial tracts and the other atrial contractile fibers. Utilizing intracellular techniques, investigators have shown that two distinct types of atrial fibers are present in human atrial myocardium. The first has properties typical of atrial contractile fibers described for other species, while the second appears to have an action potential configuration similar

to that of Purkinje fibers, which demonstrates spontaneous pacemaker activity (3, 24). We have shown that these specialized cells are essentially latent pacemaker cells and have the potential to develop pacemaker activity. These tissues show spontaneous phase 4 depolarization (automaticity) at low rates of stimulation and under the influence of stretch or hypoxia and low extracellular  $[K^+]$ . The development of automaticity in these specialized cells may be a prime factor in the genesis of atrial arrhythmias seen clinically. Singer et al. have recently shown that preparations of diseased human right atrial tissue can exhibit atrial parasystole with exit and entrance block (24). Another important functional significance of these fibers is in their capacity, as latent pacemakers, to carry on pacemaker activity when the sinoatrial node is depressed.

It is not unusual to expect not only the sinoatrial node but other specific areas of the atria to be made up of fibers which are

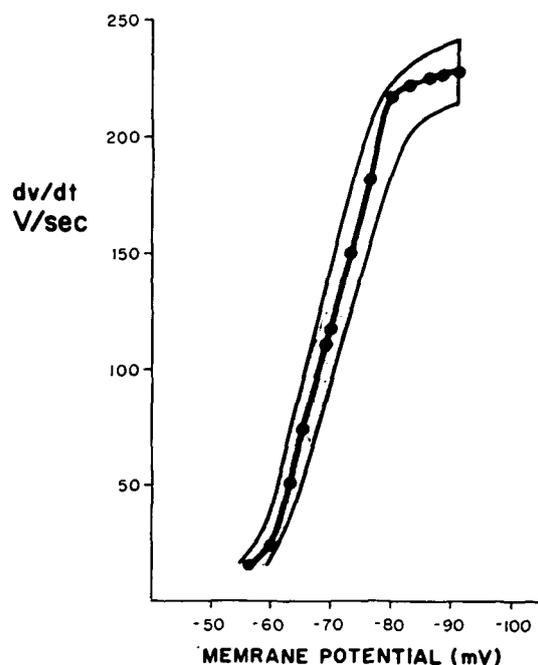


FIGURE 7

Membrane responsiveness curve for human atrial specialized fibers. Circles indicate one representative experiment. Outlined area indicates range of values in seven additional experiments. See text for further discussion.

potentially pacemakers. Embryologically the sinoatrial node is derived from the sinus venosus, and other remnants of the embryonic sinus venosus are present in several areas of the mammalian heart (25). These areas include the musculature of (a) the superior vena cava, (b) coronary sinus, (c) venous valves, and (d) an area embedded in the proximal sulcus terminalis. Paes de Carvalho et al. (13) have demonstrated that fibers in many of these areas in the rabbit atria show phase 4 depolarization. If these areas could be evaluated in the human heart with microelectrode techniques we would expect similar latent pacemaker activity to be present.

Conduction velocity in human atrial tissue seems to be similar to values found in other mammalian species and essentially equal to that found in human fetal atrium (6). Although the atrium is essentially a syncytium of muscle fibers, we feel that the measurements reported are reliable since conduction velocity was measured in single pectinate muscles or single strands of specialized fibers. Under these conditions we feel that the excitation wave was propagating in a straight line. The few determinations of conduction velocity for specialized fibers seem to indicate that they conduct more rapidly than ordinary atrial fibers, as is the case in canine atrial fibers (26).

The RMP and TAP amplitudes determined for the atrial cells in this study were of generally greater magnitude than those previously reported. A major explanation for this difference may be that all our preparations of atrial tissue were obtained from young patients. None of these patients had clinical evidence of atrial disease. Cardiac arrhythmias were not present either clinically or electrocardiographically, and all patients were free of elevated right atrial pressure or volume overloading. In contrast, in preparations from adults with chronic atrial disease or preparations in which fibrosis and connective tissue proliferation are present, RMP and TAP amplitude may be decreased (27). This is in agreement with Trautwein et al. who were able to obtain electrophysiologic data from

atrial tissue from two patients (ages 6 and 10) but found it difficult to impale and obtain satisfactory results from other preparations obtained from the hearts of adults who had chronic cardiac disease. Automaticity with low membrane potential occurred in these preparations (3).

In a series of experiments utilizing fetal human atrium, Tuganowski and Cekanski reported mean TAP amplitude to be 90 mv, and overshoot, 18 mv (28). The value for overshoot is similar to that noted by us, indicating that the lesser TAP amplitude in their series was due to a lower RMP. This decreased RMP could be explained in part by the higher  $[K^+]$  used by these researchers (4.5 mM) and in part by the immaturity of the fetal tissues.

When human atrial tissue was exposed to increasing  $[K^+]$ , a decrease of 58 mv per tenfold increase in external  $[K^+]$  occurred. The decrease in resting membrane potential when  $K^+$  is increased is expected of a potential which is largely dependent on a  $[K^+]$  ratio across a membrane predominantly permeable to this ion. The change seen in these studies is very close to the expected decrease (61.4 mv) predicted by the Nernst equation for 37°C.

In lower mammals, the atrial RMP usually decreases if the  $[K^+]$  is decreased below physiologic levels (15). This was not the case when human atrial fibers were exposed to  $[K^+]$  less than 5 mM. Usually there was a slight but persistent increase (more negative) in RMP. Others have exposed human fetal ventricular fibers to low  $[K^+]$  and have observed a steady increase in RMP as the  $[K^+]$  was decreased to 1 mM (6). Their as well as our preparations developed automaticity with the expected decrease in membrane potential when  $[K^+]$  less than 1 mM were used. The fact that human atrial fibers do not depolarize at  $[K^+]$  between 5 and 1 mM may provide some protection against arrhythmias since membrane potential is one of the principal determinants of conduction and responsiveness.

The electrophysiologic characteristics of human atrial fibers described in this report do

not significantly differ, except when exposed to low  $[K^+]$ , from those of lower mammals (15). It seems probable that the basic mechanisms underlying the electrical events of the atrial TAP are generally similar for all mammals. The results obtained from this study can be used for "reference" values for future investigations dealing with the electrophysiology of human atrial tissue.

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