Direct Actions of Cocaine on Cardiac Cellular Electrical Activity

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The hypothesis that cocaine has Class I-type antiarrhythmic drug effects was tested in tissues isolated from rabbit heart with standard microelectrode methods. Propranolol (1 μM) was used to block β-adrenergic effects. The actions of cocaine on cellular electrophysiology were concentration- and time-dependent and were reversible. In paced right atrial (RA) and right ventricular papillary (RVP) tissues, cocaine produced a profound prolongation of the effective refractory period (ERP) assessed by either premature stimulation or minimum pacing interval. ERP was increased up to eightfold in RA tissue and doubled in RVP tissue by 60 μM cocaine. This concentration of cocaine depressed action potential phase 0 depolarization 80% in RA tissue and 53% in RVP tissue but had no effect on resting membrane potentials. Automaticity was moderately depressed in sinus node (34% decrease in rate) but not in tricuspid valve cells. Phase 0 depolarization was not altered in these spontaneously active slow-response cells. Repolarization was depressed in RA, tricuspid valve, and sinus node cells leading to a twofold increase in action potential duration during exposure to cocaine. Evidence from the effects on cellular action potentials suggests that cocaine affects both fast Na⁺ channels and repolarizing K⁺ but not Ca²⁺ channels. We conclude that cocaine has Class I-type activity and the effects on ERP are extreme. (Circulation Research 1989;65:185-192)

Cocaine has both local anesthetic and sympathomimetic actions. Both of these actions would be presumed to affect cardiac function with exposure to cocaine. There is, however, little experimental evidence documenting the effects of cocaine on cardiac cells. Cocaine has been shown to have sympathomimetic effects in isolated cardiac tissue preparations. Cocaine has also been shown to have depressant, local anesthetic effects in isolated guinea pig atria. Weidmann demonstrated the local anesthetic effects of cocaine in cardiac Purkinje fibers. In these experiments, cocaine was shown to arrest automaticity and depress action potential phase 0 depolarization. However, the direct actions of cocaine have not been reported for cardiac cells other than Purkinje cells.

Our objective was to determine the direct, local anesthetic actions of cocaine on cardiac cellular electrical activity representative of major types of electrophysiological behavior seen in the mammalian heart. We studied fast upstroke action potentials characteristic of both atrial and ventricular myocardium and slow upstroke, spontaneous action potentials characteristic of sinus node and tricuspid valve tissues isolated from rabbit hearts. We determined the effects of cocaine on action potential configuration, refractory period, membrane potential, maximum rate of phase 0 depolarization (Vmax), and automaticity. Because our objective was to determine the direct actions of cocaine on different myocardial cells, we used propranolol in all experiments to block the β-adrenergic effects of cocaine.

Materials and Methods

Male New Zealand rabbits, 1.5–2.5 kg, were anesthetized by an intravenous dose of sodium pentobarbital (50 mg/kg). Hearts were rapidly removed and immersed in and perfused by way of the aorta with heparinized, chilled, and oxygenated (95% O₂, 5% CO₂) bicarbonate buffered salt solution. The composition of the solution, which was used throughout these studies, was (mM) NaCl 125.2, KCl 5.6, NaHCO₃ 25, MgSO₄ 1, CaCl₂ 2.2, and dextrose 10 (Sigma, St. Louis, Missouri). All solutions contained 1 μM propranolol. The buffered salt solution maintained a pH of 7.4 in our tissue chamber within the temperature range of our experiments, 32–36°C. Bath temperature remained constant (±0.5°C) throughout each experiment. A majority of experiments were conducted at 35°C.

Tissues

Four different tissue preparations were used. Each tissue preparation was obtained from a differ-
ent heart. Tissues were immersed in oxygenated, chilled buffer throughout the dissection. Right ventricular papillary (RVP) muscles were typically 4–5 mm and selected for a diameter at the base of less than 1 mm. Right atrial (RA) strips (2×5 mm) were cut from the posterior free wall between the crista terminalis and the atrioventricular ring. Sinoatrial node sections were trimmed to 3×3 mm. Posterior tricuspid valve (TCV) leaflets were trimmed at the atrioventricular ring. Tissue preparations were mounted with stainless steel pins to the silastic floor of an 8-ml recording chamber. The chamber was gradually warmed, and tissues were allowed to stabilize for 1 hour. The bath was continuously gassed and renewed with fresh buffer at 20-minute intervals throughout the stabilization and experimental periods.

**Pacing**

Tissue pacing and premature stimulation were achieved with 2-msec duration, constant current, rectangular pulses generated by a stimulus isolation buffer and digital timing device (Digitimer, Medical Systems, Greenvale, New York). Papillary muscles were stimulated through the exposed tips of insulated platinum wire electrodes in contact with the tissue near the basal end. A glass capillary suction electrode (cathode, filled with the buffered salt solution) with a remote anode was used in RA and TCV preparations. Atrial and papillary muscle preparations were paced at a basic cycle length of 1,400 msec. The TCV leaflets all exhibited rhythmic spontaneous activity with rates ranging from 60 to 180 per minute. These tissues were paced at intervals 50–100 msec shorter than the spontaneous cycle length. Sinus node preparations were studied at their spontaneous rate (120–200/min).

Refractory periods in RA, RVP, and TCV tissues were determined by the systematic application of premature stimuli during the basic cycle. Recovery periods of at least 10 basic cycles were instituted after each premature response. Stimulus intensity for both the basic cycle and the premature stimuli were maintained at three times the minimum needed to elicit an action potential at the basic cycle. The effective refractory period (ERP) was measured as the interval between the upstrokes of a basic cycle action potential and the earliest premature action potential that propagated. Premature stimulus intervals were tested at 10-msec increments during the first 100 msec after repolarization and at 20-msec increments between 100 and 500 msec after repolarization. Refractory periods greater than 500 msec were tested at 50-msec increments.

In addition to ERP determination by single premature stimulus, we also determined papillary muscle refractory periods using a rapid pacing protocol. This protocol consisted of shortening the cycle length by 100 msec between successive stimuli until the tissue failed to respond. The cycle length was then increased 100 msec and successively shortened by 10-msec increments until the tissue again failed to respond. This was usually achieved within a 1-minute span. This protocol allowed us to scan the refractory period at maximum paced rates with only a brief period of rapid pacing and thereby prevented tissue rundown.

We redetermined stimulation threshold at the basic cycle length throughout the course of each experiment to be certain that the prolonged ERPs that we recorded during cocaine exposure were not a result of changes in stimulating electrode properties. All data were obtained at three times threshold stimulus intensity.

**Action Potential Configuration**

Cellular action potentials were obtained by standard intracellular (transmembrane) recording techniques with glass microelectrodes (inner filament, WP Instruments, New Haven, Connecticut) filled with 3 M KCl. Electrodes selected for use had tip resistances of 15–30 MΩ. Analog signals were recorded on a strip chart (Brush model 220, Gould Instruments, Cleveland, Ohio), monitored on an oscilloscope, and recorded and analyzed digitally with a computer-based data acquisition and signal analysis system (DASA 9000 Gould).

$V_{\text{max}}$ was calculated by an arithmetic program from digital data captured at a frequency of 50 kHz. Other action potential configuration parameters were determined from digital data captured at a frequency of 1 kHz. Action potential duration ($\text{APD}_{90}$) was measured as the elapsed time from the point of $V_{\text{max}}$ to the point of phase 3 repolarization corresponding to 90% repolarization. Action potential configuration data were taken from steady-state responses at the basic cycle length.

The desired concentrations of cocaine in the tissue bath were obtained by addition of appropriate aliquots of a 1 mM cocaine HCl (Mallinckrodt, St. Louis, Missouri) stock solution. The cocaine stock solution contained $10^{-1}$ M NaH$_2$PO$_4$ and $10^{-3}$ M ascorbate. The stock solution was prepared on the day of the experiment and stored on ice in a sealed, foil-covered container. Cocaine was rapidly mixed in the bath solution by the action of vigorous gas bubbling.

We are reporting data for cocaine concentrations of 18, 30, and 60 μM. Concentrations greater than 60 μM resulted in concentration- and time-dependent action potential depression and, ultimately, arrest. Because the maximum response to cocaine in all tissues was arrest, we present data as either absolute levels of the electrophysiological parameters or as relative changes from control levels.

The electrophysiological parameters of primary concern in this study, action potential $V_{\text{max}}$, resting or maximum diastolic membrane potential, action potential duration, and relative refractory period vary from cell to cell within each region. Thus, to accurately assess the effects of cocaine on these...
parameters, all of the data we report were derived from continuous and stable impalements of the same cell during control and exposure to cocaine. In most experiments impalements were sustained beyond the cocaine exposure period and include the cocaine washout period. In a majority of experiments two concentrations of cocaine were evaluated cumulatively in sequence before washout.

**Data Analysis**

A minimum of at least three preparations for each tissue type was evaluated at each cocaine concentration. Data were recorded continuously from only one cell in each preparation; thus, in all cases paired control and experimental data were obtained from the same cell. Statistical analyses were performed using paired Student’s *t* test. Values of *p*<0.05 were considered significant. Grouped data are presented as the mean±SEM. The significance of dose dependency was determined by analysis of variance on the means of groups exposed to different cocaine concentrations. Control values from individual groups exposed to the various cocaine concentrations were not significantly different by analysis of variance and thus have been pooled in the presentation of results.

**Results**

After the addition of cocaine to the tissue bath, we found rapid onset (within 1 minute) of effects that continued to develop toward a steady state at approximately 20 minutes. Thus, we report, as representative of the concentration-dependent effects of cocaine, data obtained between 20 and 25 minutes of exposure. Electrophysiological parameters returned to control levels after drug washout for 20-60 minutes.

**Right Atrial Tissue**

Representative records from a single RA cell before and during exposure to 60 μM cocaine are presented in Figure 1 (top tracing). Cocaine reduced the rate of phase 0 depolarization and caused a broadening of the RA action potential at all levels of repolarization. Recovery of excitability, which normally is coupled to repolarization, was delayed by cocaine for extended periods beyond full repolarization.

The data from RA cells presented in Figure 2 show that cocaine caused a significant, concentration-dependent prolongation of ERP. The APD<sub>90</sub> was also significantly increased at the three cocaine levels tested. The average precocaine values for APD<sub>90</sub> and ERP were 107±12 msec and 167±23 msec (n=6), respectively. The data in Figure 2 also show that RA ERP is progressively increased beyond action potential repolarization in a concentration-dependent manner. Thus, the increase in ERP was not associated with a similar increase in APD<sub>90</sub>. The pronounced increase in RA ERP produced by cocaine was accompanied by a decrease in the RA V<sub>max</sub> (Figure 3).

Cocaine exposure did not change the resting membrane potential (Figure 3) or overshoot.

**Right Ventricular Papillary Muscle**

Representative action potentials recorded from RVP cells during exposure to 60 μM cocaine are shown in the middle tracings of Figure 1. The average precocaine values for APD<sub>90</sub> and ERP were 217±9 msec and 246±10 msec (n=10), respectively. As shown in Figure 2, cocaine caused a significant increase in RVP APD<sub>90</sub> only at 30 μM. In one of five RVP cells tested at 60 μM cocaine, APD<sub>90</sub> decreased 26 msec during drug exposure. The maximum rate of repolarization (phase 3) was not significantly affected by cocaine at any of the three concentrations studied. The ERP was significantly increased by cocaine in a dose-dependent manner (Figure 2). Cocaine also caused a decrease in the RVP V<sub>max</sub> with no change in resting membrane potential. These data are shown in Figure 3. Compared with RA cells under identical conditions, RVP cells exhibited smaller absolute increases in ERP at each concentration (Figure 2).
and correspondingly less depression of $V_{\text{max}}$ (Figure 3). At 60 $\mu$M cocaine, the average ERP in RA cells was approximately 900 msec compared with approximately 500 msec in RVP.

**Evaluation of Papillary Muscle Response to Rapid Pacing**

Because papillary muscle action potential duration and refractory period are rate-dependent, we wanted to know if the pronounced increases in refractory period that we observed were unique to our slow pacing protocol. To examine this, we evaluated the effect of 30 $\mu$M cocaine on papillary muscle response to rapid pacing. Three RVP preparations were tested.

The RVP refractory period determined during rapid pacing was 210±5 msec during control and 319±21 msec after 20-minute exposure to 30 $\mu$M cocaine. This difference was significant. During cocaine exposure, $\text{APD}_{90}$ was 202±10 msec at the minimum pacing interval (319 msec). Thus, rapidly paced RVP preparations remained refractory 117 msec beyond repolarization during cocaine exposure.

**Tricuspid Valve Tissue**

In TCV cells, we found that cocaine caused concentration-dependent increases in $\text{APD}_{90}$. Changes in $\text{APD}_{90}$ were accompanied by a prolongation of ERP. We found no significant change in TCV $V_{\text{max}}$, overshoot, or spontaneous rate during cocaine exposure. Maximum diastolic potential was decreased by cocaine. Paced and spontaneous action potentials exhibited identical changes with cocaine.

Representative examples of cocaine-induced changes in TCV action potential configuration are shown in the lower tracings of Figure 1 for paced tissues and in the tracings of Figure 4 for spontaneous tissues. At 60 $\mu$M, cocaine caused a retardation of phase 3 repolarization and eliminated the early portion of phase 4 (diastolic) depolarization. Phase 0 $V_{\text{max}}$ was not significantly depressed by cocaine (Figure 3). Maximum diastolic potential (presented as membrane potential in Figure 3) was significantly decreased by 60 $\mu$M cocaine in TCV cells.

The magnitude of the increased ERP due to cocaine in paced TCV corresponds to a prolongation of the action potential. The time elapsed between repolarization at 90% and the earliest premature response in TCV was significantly decreased by cocaine at 60 $\mu$M (Figure 2).

The altered qualitative relation between refractoriness and repolarization during TCV exposure to cocaine is shown in the experiment presented in Figure 5. Before cocaine exposure, the earliest premature action potentials can be evoked only after complete repolarization (i.e., the attainment of maximum diastolic potential; Figure 5, top). However, as shown in the lower tracings of Figure 5, during exposure to cocaine, cells were excitable in the latter, prolonged phase of repolarization. The
membrane potential at the takeoff of the earliest premature response in control is more negative than in the presence of cocaine.

We found that cocaine had no significant effect on TCV spontaneous rate at any of the three concentrations tested. There was no change in spontaneous rate in any tissue exposed to 18 or 30 μM cocaine. Variable effects on rate were observed in three tissues exposed to 60 μM cocaine. One tissue exhibited an increase, one a decrease, and one no change in spontaneous rate (see Figure 4). As in paced preparations, all concentrations of cocaine caused an increase in action potential duration, which resulted in a decrease in the length of the phase 4 depolarization period. As shown in Figure 4, we found a decreased duration of phase 4 depolarization in TCV preparations that exhibited both an increase and a decrease in spontaneous cycle length. The cocaine-induced shortening of the phase 4 depolarization period appears to result from the elimination of the early, fast period of phase 4 depolarization. The later, linear portion of phase 4 was not significantly affected by cocaine.

Sinus Node

Continuous records were obtained from seven sinus node cells during control and cocaine exposure. Four of these cells exhibited characteristics of pacemakers. Three cells appeared to be following a faster pace as they exhibited an abrupt transition from phase 4 to phase 0 depolarization. These three cells also had a V_max that was significantly faster than the four pacemaker cells. The effects of cocaine on these two groups of sinus node cells were evaluated independently; however, the results were similar (see Table 1).

We found that 18 μM cocaine had no effect on action potential configuration or the spontaneous rate recorded from sinus node preparations. At higher levels of cocaine, we found significant changes in APD90, spontaneous interval, and maximum diastolic potential. Action potential overshoot was not significantly affected, but the takeoff potential was decreased in all cells by cocaine. Figure 6 shows representative records obtained from sinus node pacemaker and follower cells exposed to 60 μM cocaine. We found that the increase in spontaneous interval was coupled to the increase in action potential duration; that is, the duration of the period of phase 4 depolarization was not changed by cocaine. However, as shown in Figure 6, cells exposed to 60 μM cocaine exhibited accelerating depolarization in the diastolic period rather than the characteristic linear phase 4 depolarization.

Discussion

Cocaine produced significant, dose-dependent changes in both fast and slow upstroke cardiac

![Figure 4](image1.png)

**Figure 4.** Tracings of spontaneous action potentials recorded from tricuspid valve cells. Control and cocaine-exposed (60 μM, indicated by arrows) records from the same cell are shown superimposed. The top tracings were recorded from a tissue exhibiting a slight increase in rate during cocaine exposure. Lower tracings are from a tissue exhibiting depression of rate during cocaine exposure. Vertical calibrations are from 0 to −70 mV. Horizontal bar, 200 msec.

![Figure 5](image2.png)

**Figure 5.** Top tracing: Three superimposed records of tricuspid valve action potentials with the premature stimuli at different intervals. The earliest and two later premature responses of similar amplitude are shown superimposed. Bottom tracing: Three traces of action potentials and premature responses from the same tricuspid valve cell as in top tracing after the tissue was exposed to 30 μM cocaine. Note that premature responses in top tracings arise after complete repolarization whereas premature responses arise from the trailing phase of repolarization in the cocaine-treated condition in bottom tracings. Horizontal bar, 100 msec.
TABLE 1. Effect of Cocaine on Sinus Node

<table>
<thead>
<tr>
<th>Cocaine exposure</th>
<th>Cocaine exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>in pacemaker</td>
<td>in follower cells</td>
</tr>
<tr>
<td>cells (n=4)</td>
<td>(n=3)</td>
</tr>
<tr>
<td>V_max (V/sec)</td>
<td>0 60 µM</td>
</tr>
<tr>
<td>Maximum diastolic</td>
<td>4.4±0.9 2.5±0.4</td>
</tr>
<tr>
<td>potential (mV)</td>
<td>0 60 mV</td>
</tr>
<tr>
<td>Overshoot (mV)</td>
<td>11±3 6±2</td>
</tr>
<tr>
<td>APD50 (msec)</td>
<td>150±7 291±4*</td>
</tr>
<tr>
<td>Spontaneous</td>
<td>444±39 675±25*</td>
</tr>
<tr>
<td>interval (msec)</td>
<td>519±76 664±62*</td>
</tr>
<tr>
<td>Phase 4 rate of</td>
<td></td>
</tr>
<tr>
<td>depolarization,</td>
<td></td>
</tr>
<tr>
<td>(mV/sec)</td>
<td>60±16 ... 47±22</td>
</tr>
</tbody>
</table>

Values are mean±SEM, n, number of cells; V_max, maximum
rate of phase 0 depolarization; APD50, action potential duration.
*P<0.05.

action potentials. However, the effects of cocaine on fast action potentials were qualitatively different from the effects on slow action potentials.

Fast Upstroke Action Potentials

In RA and RVP cells, cocaine caused a depression of V_max without suppression of overshoot or a change in membrane potential. This action is characteristic of the local anesthetic (Class I) antiarrhythmic agents.4,5 Cocaine has also been shown to depress fast response action potentials recorded from cardiac Purkinje fibers1 and nerve fibers.6,7 Although not confirmed by direct measurements in identified channels in cardiac cells, this action of cocaine appears to be suppression of the fast Na^+ channel conductance.

Cocaine effects on ERP were coupled in time of development and relative magnitude of change to depression of V_max. It has been hypothesized that prolonged refractory periods produced by Class I antiarrhythmic drugs are due to drug interference with Na^+ channel recovery from inactivation.8 This hypothesis is supported by the fact that Class I agents have a higher affinity for inactivated than for activated Na^+ channels.9 In guinea pig papillary muscle, recovery of V_max during diastole has a time constant of 1.5 seconds after block by bupivacaine10 and 5 seconds after block by aprindine.11 If the mechanism of refractory period prolongation by Class I agents is slow dissociation of drug from inactivated channels, then the prominent increase in ERP produced by cocaine would suggest that cocaine dissociation from inactivated Na^+ channels is the slowest yet reported for this group of drugs. Consistent with this idea, Weidmann3 has shown that action potentials recorded from Purkinje fibers exposed to 50 µM cocaine and paced at 1 Hz declined progressively over a 95-minute recording period.

The RA cells exhibited greater depression of upstroke velocity and greater increase in ERP than RVP cells at each cocaine concentration. A similar differential effect on atrial and ventricular ERP has been reported for both quinidine12 and procainamide12 in canine cardiac tissues. When tested at concentrations that produce 30–50% depression of canine cardiac cell V_max,14 neither quinidine nor procainamide was reported to have an effect on ventricular refractory period, but atrial ERP increased between 25 msec12 and 100 msec.13 In our experiments, the 30–50% depression of V_max produced by 30 µM cocaine was accompanied by an average increase in ERP of 200 msec in the ventricle and 400 msec in the atrium. A prominent increase in papillary muscle refractory period was also observed in rapidly paced tissues.

The absolute magnitude of the prolongation of ERP by cocaine, determined by single premature pulses at slow pacing rates or maximum rate pacing, has not been reported for any agent and thus appears to distinguish cocaine among Class I agents. The presence of a methylecgonine ring structure is also unique to cocaine among the local anesthetics. This structure may be responsible for the extreme prolongation of ERP. Slow recovery from block of Na^+ channels by highly lipid-soluble drugs has been suggested to be dependent on drug size.4,15 Our observations with cocaine fit this pattern.

Slow Upstroke Action Potentials

The prominent effect of cocaine on action potentials in slow upstroke cells is a significant increase in APD50. We observed that cocaine depresses repolarization rate in sinus node, TCV, and RA cells. This finding suggests that it may block K^+ (repolarizing) currents. Quinidine,16 tetracaine,17 and bupivacaine18 have been shown to block K^+ currents in cardiac cells. Our finding of an apparent increase in excitability in TCV cells after cocaine exposure (premature action potential before com-
plete repolarization, Figure 5) could be explained by an inhibition of an outward $K^+$ current with no effect on the depolarizing $Ca^{2+}$ current. The lack of a significant effect on repolarization in RVP cells is unexplained. Whether this represents an effect of cocaine in RVP cells that is different from the effect in the other cells or represents different physiology of the cells will require direct study of ionic currents in these tissues.

We conclude from our data that cocaine, at concentrations up to 60 $\mu$M, does not block the $Ca^{2+}$ component of slow upstroke action potentials. Cocaine had no effect on $V_{\text{max}}$ in TCV cells. Cocaine caused a small but statistically insignificant depression of $V_{\text{max}}$ in each of the sinus node preparations tested. The upstroke of TCV cell action potentials are $Ca^{2+}$-dependent and show no tetrodotoxin sensitivity, that is, no apparent voltage-sensitive $Na^+$ channel activity. A lack of tetrodotoxin sensitivity has also been reported in both central sinus node tissue and dispersed pacemaker cells derived from rabbit heart. However, tetrodotoxin sensitivity was observed in peripheral sinus node tissue and in a subpopulation of dispersed cells with $V_{\text{max}}$ greater than 6 V/sec. This variation in apparent $Na^+$ channel activity in the sinus node may account for the slight but consistent depression of $V_{\text{max}}$ by cocaine in our sinus node tissues. Depression of action potential upstroke in both pacemaker and follower cells suggests the presence of $Na^+$ activity in all our sinus node preparations.

**Automaticity**

Although Weidmann has shown that cocaine, at concentrations comparable with those used in the present experiments, blocks Purkinje fiber automaticity, we found no evidence that cocaine causes pacemaker arrest in either sinus node or TCV. Cocaine caused a significant decrease in sinus node rate at the highest concentration (60 $\mu$M). However, these preparations continued to exhibit stable, spontaneous rhythms. The linear period of phase 4 depolarization in sinus node action potentials was qualitatively changed during cocaine exposure. In contrast to this effect on the sinus node, cocaine had no significant effect on linear phase 4 depolarization or diastolic interval in TCV preparations. The comparative effects of cocaine on automaticity in Purkinje fibers (arrest), sinus node (slowing), and TCV (no change) parallel the relative magnitude of tetrodotoxin-sensitive $Na^+$ currents in these tissues. Our findings in rabbit tissue are similar to the moderate depression of sinus rate by cocaine reported in spontaneously beating guinea pig atria.

In summary, the direct effects of cocaine that we have observed in rabbit heart segments suggest that cocaine interacts with $Na^+$ and $K^+$ channels but not with $Ca^{2+}$ channels. Several of the effects of cocaine that we observed on isolated tissues, depression of fast upstroke action potentials, increased atrial action potential duration, and differential sensitivity in atrium and ventricle, are characteristic of the actions of local anesthetic (Class I) antiarrhythmic agents. The extreme prolongation of refractoriness that we found appears to be a unique effect. It will be important to determine the interaction of enhanced $\beta$-adrenergic tone with the direct actions of cocaine in the specific cardiac tissues as well as in the whole heart.

**References**

20. Giles W, van Ginneken A, Shibata EF: Ionic currents underlying cardiac pacemaker activity: A summary of voltage-


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