Effect of Hypoxia on the Sinoatrial Node, Atrium, and Atrioventricular Node in the Rabbit Heart

JOCHEN SENGES, TETSUO MIZUTANI, DIETER PELZER, JOHANNES BRACHMANN, UDO SONNHOF, AND WOLFGANG KÜBLER

SUMMARY We used intracellular microelectrodes to study the effects of hypoxia on the isolated, superfused sinoatrial (SA) node, atrium, and atrioventricular (AV) node of the rabbit heart. Hypoxia decreased the rate of spontaneous impulse initiation in SA nodal fibers by decreasing the slope of diastolic depolarization. With gradually decreasing $P_0$, the sinus rate was reduced; concomitantly, the corrected sinus node recovery time after rapid atrial stimulation was much less affected demonstrating marked prolongation only under severe anoxic conditions. Hypoxia decreased the amplitude of action potentials of the SA node and of the AV node but not of the atrium. SA and AV nodal conduction were slowed by hypoxia; intraatrial conduction was not significantly affected. AV nodal conduction block occurred at lower atrial rates, and the effective refractory period of the AV node was prolonged. Inhomogeneity of SA and AV nodal impulse propagation often was observed in the presence of hypoxia. This was associated with concealed reentry within both nodal areas. The extracellular $K^+$ concentration of the atrial tissue was measured with ion-sensitive microelectrodes. $[K^+]_o$ remained unchanged even after prolonged periods of severe hypoxia. These results are consistent with the hypothesis that acute hypoxia predominantly inhibits slow response activity but has only little effect on the fast inward sodium current. Circ Res 44: 866-863, 1979

IN MAN and in animals, the common response to acute systemic hypoxia is an increase in the heart rate (Korner, 1971). With progressive anoxia, however, an intense bradycardia develops (Litwin and Skolasinski, 1966). Available evidence supports the concept that autonomic reflex factors including $\beta$-adrenergic and cholinergic mechanisms contribute importantly to the regulation of cardiac rate during hypoxia (Dowing, 1972). The effects of anoxia on the isolated sinoatrial (SA) nodal action potential have been described recently (Kohlhardt et al., 1977). However, the hypoxic alterations of various parameters of SA nodal automaticity, including slow diastolic depolarization, sinus rate, and poststimulatory SA nodal recovery time, have not been analyzed and little information is available on the direct action of oxygen deficiency on conduction within the isolated atrioventricular (AV) node.

The purpose of this study was to determine the effects of hypoxia on the electrophysiological properties of the nodal tissues as compared with the right atrium. Therefore, action potentials were recorded simultaneously from nodal and atrial fibers. The results indicate that hypoxia selectively depresses automaticity and conduction in the SA and AV nodes, but has only little effect on the electrical activity of the atrium.

Methods

Rabbits, weighing 2-3 kg, were stunned by concussion. The heart was rapidly removed and dissected in a modified Tyrode’s solution (Bretag, 1969) containing (millimolar concentrations): NaCl, 107.7; KCl, 3.48; CaCl$_2$, 1.53; MgSO$_4$, 0.69; NaHCO$_3$, 26.2; NaH$_2$PO$_4$, 1.67; Na gluconate, 9.64; glucose, 5.55; and sucrose, 7.6, which was equilibrated with 95% O$_2$ and 5% CO$_2$. The endocardial surface of the right atrium was exposed by an incision that extended from the free wall of the right ventricle through the AV groove and followed the anterior border of the right appendage terminating as a longitudinal cut in the anterior wall of the superior vena cava (Paes de Carvalho, et al., 1959). The preparation consisted of SA node, crista terminalis, pectinate muscles of the atrial appendage, intra-atrial septum, coronary sinus, AV node, and His bundle; for studies on the AV node, the SA node was excised.

The preparation was pinned to a paraffin bed in a 10-ml tissue bath and superfused with the modified Tyrode’s solution at 36°C. A mixture of 95% O$_2$ and 5% CO$_2$ was admitted directly to the chamber through a sintered glass disc and also to the Ty-
rode's solution. After 2 hours of equilibration, hypoxia was induced by substituting either 95% N₂-5% CO₂ or intermediate mixtures (60% O₂-35% N₂-5% CO₂ and 35% O₂-60% N₂-5% CO₂) for the control gas. Measurements of Po₂, Pco₂, and pH were made by withdrawing samples of Tyrode's solution from the vicinity of the tissue preparation and analyzing them with a pH/gas analyzer (Radiometer, Copenhagen). The pH (7.4 ± 0.02; n = 20) and Pco₂ (40 ± 1.8 mm Hg) were measured before and after superfusion. The calibration curves were reproducible and calibrated, both before and after each experiment, with solutions containing 150 mM NaCl. The resistance of the ISM's ranged between 3 and 6 × 10⁷ Ω and that of the reference micropipettes was filled with 150 mM NaCl. The resistance of the ISM's was measured by a K concentration near the physiological range (3.6 mM). The calibration curves were reproducible and, after electronic subtraction, gave a pure potassium signal. The ISM's were calibrated, both before and after each experiment, with solutions containing 150 mM NaCl and different concentrations of KCl, ranging from 1.5 to 96 mM. The calibration curves were reproducible and, at KCl concentrations between 7 and 96 mM, showed a slope of 42–50 mV per 10-fold change in potassium concentration (Sonnhof et al., 1977). At a K concentration near the physiological range (3.6 mM), the selectivity coefficient for Na relative to K was between 10⁻² and 2 × 10⁻³ corresponding to earlier results (Lux and Neher, 1973). Simultaneously, interstitial Po₂ was measured directly with microelectrodes whose tips were membranized with Epoxilite using a polarizing voltage of 550 mV. For Po₂-sensitive electrodes, glass-insulated platinum wires were used (Lübbers et al., 1968).

Transmembrane action potentials were recorded from two sites in the preparation by means of floating microelectrodes. An extracellular His bundle electrogram was recorded through a close bipolar electrode. For experiments on the SA node, transmembrane action potentials were recorded from different SA nodal cells within an identifiable small area before and after hypoxic superfusion. The following parameters of the pacemaker action potentials were measured: total amplitude (maximum diastolic potential-peak overshoot of the action potential), slope of diastolic potential (maximum diastolic potential-threshold potential/duration of diastole (Goupil and Lenfant, 1976)), sinus rate. For measuring the retrograde sinoatrial conduction time, the atrium was stimulated through electrodes placed on the right atrial appendage at a constant cycle length of 330 msec. The stimulus was a rectangular pulse 2 msec in duration and twice threshold amplitude. Sinus node recovery time was measured following suppression of the SA nodal pacemaker by atrial stimulation at a cycle length of 330 msec for 1 minute. The corrected sinus node recovery time was defined as the recovery interval in excess of the basic sinus cycle.

Atrial transmembrane action potentials were recorded from single fibers of the crista terminalis. The atrium was stimulated at a constant cycle length of 330 msec, and action potential amplitude and repolarization time to 95% were determined. Intra-atrial conduction was measured as the interval between the upstroke of the action potential recorded from the upper part of the crista terminalis and the atrial electrogram near the AV node.

The effects of hypoxia on the AV node were studied after excision of the SA node. Transmembrane action potentials were recorded from various portions of the AV node as identified by action potential configuration and anatomic location (Paes de Carvalho and De Almeida, 1960). However, since transition from one region to the other is quite gradual, the terms AN, N and NH have been used loosely, indicating primarily upper, middle, and lower node, respectively. For measuring AV nodal conduction as a function of atrial rate, the atria were stimulated at decreasing cycle lengths until an impulse failed to conduct to the His bundle. Total AV nodal conduction was determined at each cycle length by measuring the interval between atrial and His deflections in the extracellular His bundle electrogram. Conduction of premature impulses through the AV node was determined at a constant atrial cycle length (660 msec). Premature atrial stimuli of 4 times rheobasic strength and 2-msec duration were introduced after every eighth basic drive stimulus. The interval of the atrial test impulse was progressively decreased, until the most premature atrial action potential which was conducted to the His bundle was identified. At each atrial coupling interval, the conduction time of the premature impulse through the AV node was measured.

For statistical analysis, the respective electrical parameters were determined immediately before and 30 to 45 minutes after exposure to hypoxia. All statistical data in this study are means ± SD, and significance of the difference of means was determined by Student's t-test.

**Results**

**Effect of Hypoxia on the SA Node**

The most prominent effect of hypoxia on the SA node was a marked decrease in the sinus rate.
Figure 1 Relationship between sinus rate, corrected sinus node recovery time (CSRT), and PO2. Values are means ± SD from five experiments determined 30-45 minutes after exposure to graded hypoxia.

Figure 1 shows the relationship between the PO2 of the Tyrode's solution and both the sinus rate and the corrected sinus node recovery time (CSRT) after rapid atrial stimulation. As PO2 decreased, the spontaneous sinus rate slowed. On the contrary, the CSRT was only moderately increased following reduction of the PO2 from 460 to 130 mm Hg and was abruptly prolonged at 40 mm Hg PO2. The SA nodal pacemaker always had the shortest recovery time following suppression by atrial stimulation and, even in severe hypoxic preparations with markedly prolonged CSRT, no escape of subsidiary pacemakers was observed (Fig. 2).

Recordings of SA nodal action potentials before and after exposure to hypoxia (PO2 40 mm Hg) are shown in Figure 3. In 10 experiments, the most striking changes were a decrease in the diastolic depolarization rate from 40 ± 10 to 8 ± 2 mV/sec (P < 0.001) and a reduction of action potential amplitude from 73 ± 11 to 42 ± 16 mV (P < 0.001).

Changes in antegrade SA conduction were difficult to evaluate because of the frequent shifts in the site of the pacemaker. However, in the presence of hypoxia, antegrade sinoatrial conduction times which markedly exceeded the control range occasionally were observed (see below). Retrograde SA conduction was prolonged significantly from 38 ± 16 msec control values to 74 ± 36 msec (P < 0.01) during hypoxia (Fig. 4). These anoxic changes in sinus rate and in SA nodal action potential parameters initially occurred abruptly, but then developed more gradually after 15-20 minutes. Therefore, the present data were determined after exposure to hypoxia for 30-45 minutes. Periods of oxygen deficiency exceeding 1 to 2 hours caused only a little further slowing in sinus rate accompanied occasionally by a short-lasting irregular failure of impulse propagation.
Effect of Hypoxia on the Right Atrium

The action potentials recorded from atrial muscle fibers (Fig. 4) were much less affected by hypoxia (P<sub>O</sub>2 40 mm Hg) than was the SA node. The control values of the action potential amplitude (96 ± 11 mV; n = 10) were not significantly altered after 30 minutes of oxygen deficiency (94 ± 10 mV; n = 10). The only consistent change was a small decrease of the action potential duration from 143 ± 25 to 122 ± 23 msec, which was not significant (P > 0.05) when all results were summarized because of the big standard deviation. Intra-atrial conduction was not significantly changed before (26 ± 7 msec; n = 10) and after exposure to hypoxia (31 ± 8 msec; Fig. 4).

Effect of Hypoxia on the AV Node.

Figures 5 and 6 show the effects of hypoxia on the action potentials of AV nodal cells recorded from the same single fibers before and after exposure to a superfusate with low P<sub>O</sub>2 (40 mm Hg). The most striking changes were a reduction in action potential amplitude and a marked decrease in the slope of diastolic depolarization (Fig. 5). Qualitatively similar results were obtained in six additional experiments in which multiple impalements of different fibers in various AV nodal regions were made. However, statistical evaluation of the effects of hypoxia on action potential parameters in the various nodal layers has been omitted, since one is dealing with nonuniform groups exhibiting gradually changing characteristics. The decrease in amplitude during hypoxia sometimes was associated with the appearance of notches on the upstroke of the action potential (Fig. 6) or the occurrence of a second action potential peak during the repolarization phase (Fig. 5). All changes were readily reversible on reoxygenation.

Atrioventricular conduction was impaired consistently in the presence of hypoxia. At a constant atrial cycle length (660 msec) lowering the P<sub>O</sub>2 from 460 to 40 mm Hg resulted in prolongation of the AV conduction. After reoxygenation, normal SA nodal function was restored within 20-40 minutes.

Effect of Hypoxia on the Right Atrium

The action potentials recorded from atrial muscle fibers (Fig. 4) were much less affected by hypoxia (P<sub>O</sub>2 40 mm Hg) than was the SA node. The control values of the action potential amplitude (96 ± 11 mV; n = 10) were not significantly altered after 30 minutes of oxygen deficiency (94 ± 10 mV; n = 10). The only consistent change was a small decrease of the action potential duration from 143 ± 25 to 122 ± 23 msec, which was not significant (P > 0.05) when all results were summarized because of the big standard deviation. Intra-atrial conduction was not significantly changed before (26 ± 7 msec; n = 10) and after exposure to hypoxia (31 ± 8 msec; Fig. 4).

Effect of Hypoxia on the AV Node.

Figures 5 and 6 show the effects of hypoxia on the action potentials of AV nodal cells recorded from the same single fibers before and after exposure to a superfusate with low P<sub>O</sub>2 (40 mm Hg). The most striking changes were a reduction in action potential amplitude and a marked decrease in the slope of diastolic depolarization (Fig. 5). Qualitatively similar results were obtained in six additional experiments in which multiple impalements of different fibers in various AV nodal regions were made. However, statistical evaluation of the effects of hypoxia on action potential parameters in the various nodal layers has been omitted, since one is dealing with nonuniform groups exhibiting gradually changing characteristics. The decrease in amplitude during hypoxia sometimes was associated with the appearance of notches on the upstroke of the action potential (Fig. 6) or the occurrence of a second action potential peak during the repolarization phase (Fig. 5). All changes were readily reversible on reoxygenation.

Atrioventricular conduction was impaired consistently in the presence of hypoxia. At a constant atrial cycle length (660 msec) lowering the P<sub>O</sub>2 from 460 to 40 mm Hg resulted in prolongation of the AV conduction. After reoxygenation, normal SA nodal function was restored within 20-40 minutes.
nodal conduction time from a control of 62 ± 26 msec to 108 ± 29 msec (P < 0.005; n = 8; Figs. 5, 6). Periods of anoxia (Po2 40 mm Hg) exceeding 1 to 2 hours often caused complete AV nodal block. The propagation of premature impulses through the AV node was slowed at all atrial coupling intervals in the presence of hypoxia (Fig. 7), and the effective refractory period of the AV node was significantly increased from 140 ± 34 to 340 ± 180 msec (P < 0.005; n = 6) at a constant atrial cycle length.

To determine the cycle length at which conduction block first occurred in the AV node, the frequency of atrial stimulation was increased gradually. Under hypoxic conditions (Po2 40 mm Hg) AV nodal conduction time was prolonged at all cycle lengths as compared with control values (Fig. 8), and the cycle length at which 1:1 conduction failed was significantly lengthened from 210 ± 32 to 480 ± 170 msec (P < 0.001; n = 6). This rate-dependent depression of AV nodal conduction in the presence of hypoxia resulted in transient complete AV block during sinus rhythm. Figure 3 shows that after 10 minutes of hypoxia, sinus rate was 73/min and was associated with normal intraatrial conduction, but impulse transmission through the AV node had failed. However, following 30 minutes of hypoxia, sinus rate was depressed further to 55/min, and 1:1 conduction through the AV node appeared paradoxically to be restored.

Arrhythmogenic Effects of Hypoxia

In the presence of hypoxia, SA nodal automaticity was depressed in all experiments resulting in marked bradycardia. However, in some preparations, irregular premature SA and AV nodal depolarizations were observed associated with a marked slowing of nodal conduction. A typical example is shown in Figure 9: 10 minutes after exposure to hypoxia (Po2 40 mm Hg) the antegrade SA conduction time is prolonged to 260 msec as compared with a 40-msec control value. The SA nodal pacemaker is slightly arrhythmic but 1:1 conduction to the atrium still occurs. Following every atrial impulse, a second smaller action potential peak appears in the SA node; 5 minutes later, complete antegrade SA block has occurred, as indicated by the irregular sinus rhythm associated with a slower but constant atrial rate (Fig. 9B). However, a more or less pronounced second action potential peak still appears in the SA node. The variations in amplitude of this irregular nodal depolarization seem to depend on the interval between the SA nodal and atrial impulses: when both action potentials occur almost simultaneously, the resulting nodal response is a single depolarization of large am-

![Figure 7](image)

**Figure 7** Effect of hypoxia (Po2 40 mm Hg) on conduction of premature atrial impulses in the AV node. All values were obtained in the same experiment. Abscissa: coupling interval between the last basic atrial impulse (A1) and the premature test impulse (A2). Ordinate: conduction time of the premature impulse between atrium and His bundle (A1-H2). Asterisk shows A1-A2 interval at which conduction block first occurred. Basic atrial cycle length 660 msec.

![Figure 8](image)

**Figure 8** Effect of hypoxia (Po2 40 mm Hg) on conduction of atrial impulses through the AV node at different rates of atrial stimulation. The graph depicts AV nodal conduction time (ordinate) vs. atrial cycle length (abscissa) in the same experiment. Asterisk shows cycle length at which conduction block first occurred.

![Figure 9](image)

**Figure 9** Irregular impulse initiation within the SA node in the presence of hypoxia. The top trace in each section shows records from the SA node, the middle trace shows action potentials from an atrial fiber 2 mm from the SA node, and the bottom trace is the His bundle electrogram. The broken lines indicate the zero voltages for the upper and lower traces. Records were obtained 10 (A) and 15 min (B) after exposure to hypoxia (Po2 40 mm Hg).
Effect of Hypoxia and High Potassium in a Rapidly Superfusing Solution on Atrial Extracellular $K^+$ Concentration ($[K^+]_o$), Extracellular $P_{O_2}$ ($[P_{O_2}]_o$), and Intracellular Resting Potential (RP)

<table>
<thead>
<tr>
<th>Condition</th>
<th>$[K^+]_o$ (mM)</th>
<th>$[P_{O_2}]_o$ (mm Hg)</th>
<th>RP (mV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>3.5 ± 0.1</td>
<td>410 ± 40</td>
<td>78 ± 6</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>3.6 ± 0.2</td>
<td>30 ± 20*</td>
<td>76 ± 6</td>
</tr>
<tr>
<td>10 mM K*</td>
<td>6.8 ± 1.1*</td>
<td>400 ± 30</td>
<td>63 ± 2*</td>
</tr>
</tbody>
</table>

All measurements were performed simultaneously within atrial tissue at a depth of about 100 μm. Values are means ± SD and were obtained immediately before (control) and 1 hour after exchange of $P_{O_2}$ in the superfusing solution from 460 to 40 mm Hg (hypoxia) or 15 minutes after an increase of $K^*$ in the superfusing solution from 3.48 to 10 mM at a constant $P_{O_2}$ (460 mm Hg). Significance ($P$) of the difference of means was determined by Student's $t$-test.

**FIGURE 11** Effect of hypoxia on extracellular potassium concentration ($[K^+]_o$). The membrane potential (MP, middle trace) from a single atrial fiber was recorded with an ink writer (frequency range DC to 15 Hz) resulting in correct and linear reproduction of the resting and/or maximum diastolic potential but not of the amplitude of the action potential; calibration of membrane potential indicates only the linear range of slow changes in resting potential but not of the action potential amplitude (not shown) which remained unchanged at about 105 mV in A. Simultaneously, extracellular $[K^+]_o$ (lower trace) and $[P_{O_2}]_o$ (upper trace) were recorded within the atrial tissue at a depth of 100 μm. $V_o$ represents the extracellular potential registration of the reference barrel of the double-barreled $K^*$-sensitive microelectrode. Note the marked deflection of the $[K^+]_o$ potential caused by intracellular impalement during control period. A: Start and end of superfusion with hypoxic Tyrode's solution ($P_{O_2}$ 40 mm Hg) is indicated by arrows. Note the marked decrease of the interstitial $[P_{O_2}]_o$. B: For comparison, the effect of the increase in $K^+$ concentration of Tyrode's solution from 3.48 to 10 mM at $P_{O_2}$ 460 mm Hg. Note the marked increase in $[K^+]_o$, associated with a decrease in resting potential.
((K\textsuperscript{+}), and extracellular [P O\textsubscript{2}], were determined simultaneously at a depth of about 100 \(\mu\)m within the atrial tissue using ion-sensitive and oxygen-sensitive microelectrodes. The results are summarized in Table 1 and typical records are shown in Figure 11. During insertion of the ion-sensitive microelectrodes into the tissue, marked variations of the (K\textsuperscript{+}) potentials were observed, indicating intracellular potential impalements (Fig. 11). However, after stabilization, the extracellular (K\textsuperscript{+}) potential corresponded closely to those obtained in the Tyrode’s solution when the interstitial P O\textsubscript{2} was moderately reduced. During a 1-hour period of severe hypoxia, the interstitial (P O\textsubscript{2}) was markedly decreased. However, the resting membrane potential was not reduced and, correspondingly, the extracellular K\textsuperscript{+} concentration remained unchanged. On the contrary, an increase in the K\textsuperscript{+} concentration of the solution to 10 mm and equimolar reduction in Na\textsuperscript{+} produced a marked increase of the interstitial (K\textsuperscript{+}), associated with a significant decrease in the resting potential.

**Discussion**

In the present experiments, hypoxia markedly decreased the action potential amplitude in the SA node and in the AV node. In contrast, hypoxia did not significantly affect the action potential amplitude of atrial muscle fibers, and similar results have been reported in ventricular Purkinje fibers (Pozzard, 1975; Pelzer et al., 1977). This difference may be explained by the suggestion that acute hypoxia predominantly inhibits the slow inward current but has very little effect on the fast inward current. That the upstrokes of the action potentials of the SA node and AV node depend on inward current flowing through the slow channel has been suggested by several authors (Lu and Brooks, 1969; Lenfant et al., 1968; Zipes and Mendez, 1973; Zipes et al., 1975; Wit and Cranefield, 1974; Yamagishi and Sano, 1966; Kohlhardt et al., 1972; Hagiwara and Nakajima, 1966; Paes de Carvalho et al., 1969).

In atrial and ventricular fibers, the rate of rise of the action potential is dependent on the activation of a fast Na\textsuperscript{+} inward current (Rougier et al., 1968; Beeler and Reuter, 1970). The effects of hypoxia on the action potential amplitude in the SA node, atrium, and AV node observed in the present experiments resemble very much those obtained in presence of the Ca\textsuperscript{2+}-blocking drug, verapamil (Wit and Cranefield, 1974).

The only consistent change in the atrial action potential during acute hypoxia was a small decrease in the action potential duration. This could be explained by a decrease in the slow inward current, and a similar mechanism has been suggested for the abbreviation of ventricular action potentials in the presence of hypoxia (Watanabe and Besch, 1974; McDonald and MacLeod, 1971; McDonald et al., 1971; Trautwein et al., 1954). It is interesting to note that in the spontaneously beating atrium even 1-hour periods of severe hypoxia associated with marked bradycardia failed to affect significantly either resting membrane potential or interstitial K\textsuperscript{+} concentration. Since the present experiments were not performed at a constant atrial rate, small rate-dependent changes of the interstitial potassium activity in the presence of hypoxia cannot be excluded (Kunze, 1977).

The ionic mechanisms involved in the hypoxic alterations of the slow inward current have not yet been determined. An interesting hypothesis has been advanced by Kohlhardt et al. (1977). They attributed the metabolically induced decrease of the slow inward current to a reduced driving force for Ca\textsuperscript{2+} and/or Na\textsuperscript{+}. This suggestion implies an increase in intracellular free Ca\textsuperscript{2+} and/or Na\textsuperscript{+} concentration due to a hypoxic depletion of cellular ATP content (Blaustein and Hodgkin, 1969; Rojas and Hidalgo, 1968).

Hypoxia slowed SA and AV nodal conduction but did not significantly affect the intraatrial conduction. These observations are consistent with studies on artificially ventilated dogs deprived of oxygen; differences in atrial conduction may be related to frequent shifts of the atrial pacemaker and consequent changes in conduction pathways in the unpaced animal (Bagdonas et al., 1961). However, two effects of hypoxia on AV and SA nodal conduction merit particular comment. (1) With increasing prolongation of AV nodal conduction, a smaller but distinct second peak appeared in the action potential of AV nodal cells. This finding indicates inhomogeneity of conduction favoring the occurrence of reentry phenomena within the AV node (Mendez and Moe, 1966; Watanabe and Dresius, 1965). Since atrial echoes could not be recorded, the re-excitations were blocked within the nodal area indicating concealed reentry. (2) Premature depolarizations also were observed in the SA node, and were accompanied by prolongation and block of antegrade SA conduction. This could be due to asynchronous firing of two different SA nodal pacemakers and fractionated intranodal conduction. However, the alternative possibility—retrograde sinoatrial conduction in the presence of antegrade sinoatrial block—cannot be excluded when precise timing and sequence of SA nodal and atrial activation are studied.

The reduction of sinus rate by hypoxia may result from a depression of the rate of spontaneous diastolic depolarization or from a shift in the threshold potential to less negative values. Hypoxia-induced shifts in the site of the pacemaker away from the recording site made it difficult to evaluate changes in phase 4 depolarization. However, statistical analysis indicates a marked reduction in the slope of diastolic depolarization recorded from pacemaker cells in the sinus node. Additional changes in threshold potential have been excluded (Kohlhardt et al., 1977). A number of studies agree in attributing diastolic depolarization of SA nodal pacemaker
depolarization to the combined effects of a decline in outward current and an increase in inward current (Brown and Noble, 1969, 1973; Lenfant et al., 1972). The present results do not indicate whether hypoxia affects one or both of these currents.

Acknowledgments

We are grateful to Professor Dr. Reinhardt Riidel and Professor Dr. Wolfgang Trautwein for helpful criticisms and comments and to Karin Bierbaum-Dörff for technical assistance.

References


Beecher GW, Reuter H: Voltage clamp experiments on ventricular myocardial fibers. J Physiol (Lond) 207: 165-170, 1970


Hagiwara S, Nakajima S: Differences in Na and Ca spikes as examined by application of tetrodotoxin, procaine and manganese ions. J Gen Physiol 49: 793-806, 1966


Litwin J, Skolasinski K: On the mechanism for bradycardia induced by acute systemic anoxia in the dog. Pfuegers Arch 289: 109-121, 1966

Lu HH, Brooks CMcC: Role of calcium in cardiac pacemaker cell action (abstr). Bull NY Acad Med 40: 100, 1964


Lux HD, Neher E: The equilibration time course of [K\(^{+}\)]\(_{o}\) in cat cortex. Exp Brain Res 17: 190-205, 1973

McDonald TF, Hunter EG, MacLeod DO: Adenosine-triphosphate partition in cardiac muscle with respect to transmembrane electrical activity. Pfuegers Arch 322: 95-108, 1971

McDonald TF, MacLeod DO: Alxonia-recovery cycle in ventricular muscle: Action potential duration, contractility and ATP content. Pfuegers Arch 321: 305-322, 1971


Paes de Carvalho A, De Almeida DF: Spread of activity through the atrioventricular node. Circ Res 8: 801-809, 1960

Paes de Carvalho A, Hoffman BF, dePaula Carvalho M: Two components of the cardiac action potential. I. Voltage time course and the effect of acetylcholine on atrial and nodal cells of the rabbit heart. J Gen Physiol 54: 607-635, 1969


Watanabe AM, Besch HR: Cyclic adenosine monophosphate modulation of slow calcium influx channels in guine pig hearts. Circ Res 35: 316-324, 1974

Wit AL, Cranefield PF: Effect of verapamil on the sinoatrial and atioventricular nodes of the rabbit and the mechanism by which it arrests reentrant atioventricular nodal tachycardia. Circ Res 35: 413-428, 1974


Zipes DP, Besch HR, Watanabe AM: Role of the slow current in cardiac electrophysiology. Circulation 51: 761-766, 1975
Effect of hypoxia on the sinoatrial node, atrium, and atrioventricular node in the rabbit heart.

J Senges, T Mizutani, D Pelzer, J Brachmann, U Sonnhof and W Kübler

Circ Res. 1979;44:856-863
doi: 10.1161/01.RES.44.6.856

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1979 American Heart Association, Inc. All rights reserved.
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:
http://circres.ahajournals.org/content/44/6/856

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at: http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at: http://circres.ahajournals.org/subscriptions/