EFFECT OF HYPOXIA ON CELLULAR INTERACTION IN THE MYOCARDIUM

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UDC 616-008.922.1.04-092.9-07: 616.127-018.1-076.5

Passive electrical properties in the papillary muscle of the rabbit heart were investigated under (control) and hypoxic conditions. The input resistance and the length constant of electronic decay were measured. With the use of a two-dimensional model of the anisotropic syncytium and the results of measurement of the length constant and input resistance it was shown that the resistance of the electrogenic membrane is reduced by 1.4 times after 10 min of hypoxia, whereas the resistance of the intracellular medium of the syncytium in the longitudinal (ρ_x) and transverse (ρ_y) directions of the fibers is increased by 1.39 and 1.3 times respectively. The increases ρ_x and ρ_y are due to an increase in resistance of the contacting membranes. Disturbance of cellular interaction during hypoxia is important to the understanding of the mechanism of the cardiac arrhythmias arising in ischemia of the heart and myocardial infarction.

KEY WORDS: length constant; input resistance; hypoxia; cellular interaction in the myocardium.

Hypoxia is one of the commonest causes of a disturbance of normal function of the myocardium. In ischemia and myocardial infarction cardiac arrhythmias and blocks to the transmission of excitation in different parts of the conducting system of the heart frequently arise [7, 10, 13]. There are two possible mechanisms of these arrhythmias and disturbances of the conduction of excitation: depression of the excitability of the electrogenic membranes and a disturbance of cellular interaction.

Many experimental studies have revealed depression of the excitability of the myocardial fibers during hypoxia [12, 14]. Ultrastructural investigations have shown a disturbance of intercellular contacts during hypoxia [2, 11]. However, there is still a lack of direct evidence of an impairment of cellular interaction based on the study of the passive electrical properties of the myocardium.

The object of this investigation was to study the effect of hypoxia on intercellular connections in the myocardium.

EXPERIMENTAL METHOD

Experiments were carried out on the papillary muscle of the rabbit heart. The preparation was perfused with oxygenated Tyrode solution. The temperature of the solution was $37 \pm 0.5°C$ and its pH 7.35. To produce hypoxia a solution not containing glucose and saturated with a gas mixture consisting of 95% N_2 and 5% CO_2 was used. The partial pressure of oxygen in the hypoxic solution was reduced to 10-15 mm Hg.

The length constant (λ) and input resistance (R_{in}) was measured in the experiments under normal and hypoxic conditions. During the measurement of λ a suction electrode [6] was used for intracellular polarization. Electrotonic decay was investigated in the longitudinal and transverse directions of the fibers from the suction electrode. During the measurement of R_{in}, double microelectrodes were used; a pulse of current of 10^{-8} A was applied through one electrode and the other was used for recording. The total number of experiments was 21.

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Department of Clinical Surgery, Kaunas Medical Institute. Research Institute of Physiology and Pathology of the Cardiovascular System, Kaunas Medical Institute. Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 82, No. 7, pp. 819-821, July, 1976. Original article submitted June 3, 1975.

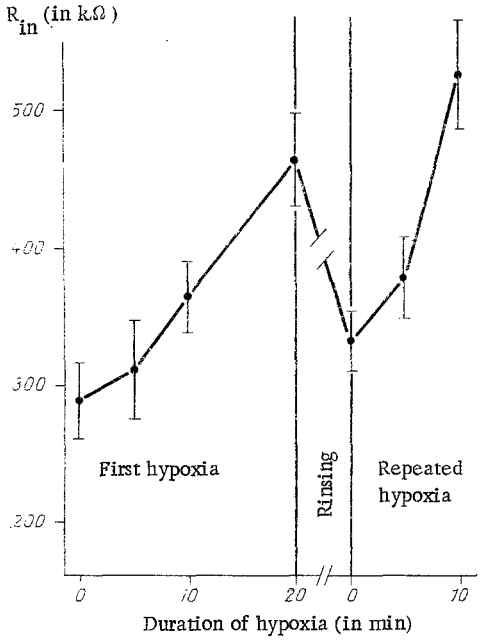

Fig. 1. Dependence of input resistance (R_{in}) of myocardial syncytium on exposure of preparation under hypoxic conditions.

EXPERIMENTAL RESULTS AND DISCUSSION

The dependence of R_{in} on exposure of the preparation under hypoxic conditions is illustrated in Fig. 1, which shows that R_{in} increased with an increase in the degree of hypoxia. Repeated hypoxia led to an even sharper increase in R_{in}. The experimental measurements of R_{in} and the length constant in longitudinal (λ_{xe}) and transverse (λ_{ye}) direction of the fibers are given in Table 1. The measurements were made under control conditions (oxygenated solution) and after 10 min of hypoxia.

To analyze the results and assess the changes in cellular interaction during hypoxia, a two-dimensional model of the anisotropic syncytium may be used [1]. The distribution of electrotonous (V) in the model is described by the equation:

$$\lambda_x^2 \frac{\delta^2 V}{\delta x^2} + \lambda_y^2 \frac{\delta^2 V}{\delta y^2} = V. \tag{1}$$

For convenience of examination, the above-mentioned model was slightly modified, and in addition the resistance of the myoplasm during the distribution of the intracellular current in the transverse direction of the fibers will be taken into account. In that case:

$$\lambda_x = \sqrt{K \frac{R_m}{\rho_x}}, \tag{2}$$

$$\lambda_y = \sqrt{K \frac{R_m}{\rho_y}}, \tag{3}$$

where R_m is the specific resistance of the electrogenic membrane, K a coefficient, and ρ_x and ρ_y the specific resistances of the intracellular medium in the longitudinal and transverse directions of the fibers, including the resistance of the myoplasm and the contacting membranes.

R_{in} in the model, when measured with the microelectrode, is described by the following equation:

$$R_{in} = K_1 \sqrt{\rho_x \rho_y} \ln \frac{\lambda_x}{x_0}, \tag{4}$$

where K_1 is a coefficient and x_0 the dimensions of the electrode.

TABLE 1. Changes in Passive Electrical Properties of the Myocardium under Hypoxic Conditions

Experimental conditions	λ_{xe}, μ	λ_{ye}, μ	R_{in}, kΩ	λ_x, μ	λ_y, μ
Control	339±36 (n=20)	152±30 (n=12)	288±28 (n=30)	590	200
After 10 min of hypoxia	263±65 (n=11)	117±46 (n=7)	364±26 (n=38)	420	148

Legend. λ_{xe} and λ_{ye}, λ_x, and λ_y represent values of length constant measured experimentally and determined with the aid of the model respectively; n) number of measurements.

Measured experimentally with the aid of the suction electrode, λ_{xe} and λ_{ye}, were always smaller than the true values of the length constant (λ_x and λ_y). Knowing the diameter of the suction electrode x_0, by means of the model [5] it is possible to find λ_x and λ_y from the measurements of λ_{xe} and λ_{ye}; the results of the calculation are given in Table 1.

By the use of the equations (2), (3), and (4) and the results of measurement of λ_x, λ_y, and R_{in}, it is easy to show that under hypoxic conditions R_m is reduced by 1.4 times, whereas ρ_x and ρ_y are increased by 1.39 and 1.3 times respectively.

During hypoxia, R_m is thus reduced. This result correlates well with data showing an increase in permeability for K^+ ions [9]. Considering that the resistance of the myoplasm shows little or no change after hypoxia for 10 min, the increase in ρ_x and ρ_y must be attributed mainly to an increase in the resistance of the contacting membrane.

Confirmation of the disturbance of cellular interaction in hypoxia is given by morphological data obtained with the light and electron microscopes [2, 11]. Widening of the intercalated disks, enlargement of the intercellular space [2, 11], and dissociation of the tissue into individual cells [3] are observed in the zone of ischemia and myocardial infarction. Under hypoxic conditions a fall is observed in both the stationary and the nonstationary velocity of conduction of excitation down to the development of complete block at various levels of the conducting system of the heart [8, 14]. The weakening of cellular interaction may be the main cause of the onset of these disturbances.

In hypoxia there is an increased risk of the development of cardiac arrhythmias. The question arises: What is the role of the weakening of intercellular connections in the development of these hypoxic arrhythmias? When the conduction of excitation from cell to cell is disturbed, the conditions are facilitated for the accumulation of the long latencies necessary for re-entry formation [4]. It follows from the model concepts that re-entry takes place only in the case of rupture of the excitation wave-front as a result both of the heterogeneity of the refractory periods and thresholds of excitation and the geometrical characteristics, and also of the characteristic electrical anisotropy of the myocardium [6]. It follows directly from the model of re-entry arising through anisotropy that its formation is facilitated when cellular interaction is weakened.

There is no doubt that a disturbance of intercellular contacts is one of the main causes of the disorganization of the electrical activity of the heart which arises in general and local myocardial hypoxia. Unfortunately, the antiarrhythmic drugs available at present for clinical use are known only for their action on the excitability of electrogenic membranes and no drugs acting at the level of the contacting membranes have yet been produced.

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