Electrophysiology of the Normal-to-Hypoxic Transition Zone

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SUMMARY. The "normal-to-hypoxic" transition zone was modeled after the chamber technique for perpendicular and parallel orientation with respect to the direction of fiber axis. The evidence obtained from the recording of the transmembrane action potentials suggests the presence of a preservation phenomenon in the hypoxic area, based on the utilization of energy stores of the normoxic area. The preservation phenomenon is enhanced with improvement of the intercellular communication. Better intercellular coupling in longitudinal than in transverse fiber direction results in the anisotropic properties of the preservation phenomenon. The preservation phenomenon provides a basis for the existence of critical size of the viable hypoxic area compared to the size of the transitional zone. The crucial role of electrotonic coupling was demonstrated, as well as the possible contribution to the preservation phenomenon mechanism of the cell-to-cell diffusion of metabolites. (Circ Res 51:321-329, 1982)

THE transitional zone between the normal and ischemic myocardium is of great interest in terms of the development of the myocardial infarction zone, the survival of the boundary area, and the onset of ischemic arrhythmias. Considerable progress in getting insight into the biochemical properties of the transitional zone has been made in recent years (Hearse et al., 1977; Janse et al., 1979).

Thus, by taking minute local specimens, it was possible to show that there exists a difference in biochemical properties, with a clear-cut 2- to 4-mm wide boundary between the normal and injured zones (Hearse et al., 1977). The employment of histochemical and fluorescent techniques demonstrated that the boundary area was still narrower (Barlow and Chance, 1976; Harken et al., 1978, Janse et al., 1979). However, the mechanisms underlying the development of the transitional zone still remain unclear. Because of the importance of intercellular junctions in the interaction between the normal and ischemic myocardium, we focused on the role of cell-to-cell coupling in the formation of the transitional zone.

In the present study, we used hypoxia with no glucose in the medium as a model of ischemia. This model reflects the biochemical and electrophysiological properties of the ischemic tissues (Morena et al., 1980).

Methods

In all, 49 experiments were performed on isolated trabecular preparations from rabbit atrium. Conventional microelectrode technique was employed to record transmembrane action potentials (AP) of the myocardial fibers. Cathodal electric pulses of twice threshold intensity and 2 msec long were delivered via a bipolar Ag-AgCl electrode. Normally, the preparations were perfused with normoxic Tyrode's solution of the following composition (mm): NaCl, 136; KCl, 2.7; CaCl₂, 1.8; MgCl₂, 0.5; NaH₂PO₄, 4.6; NaHCO₃, 14.0; glucose, 5.0 (at 37°C and pH 7.35). To maintain hypoxic conditions, the saline was gassed continuously with 95% N₂ + 5% CO₂ without glucose. The Po₂ of the normoxic saline was 500 mm Hg, whereas that of the hypoxic one was only 20–30 mm Hg.

Hypoxic conditions were achieved either by producing general hypoxia of the whole preparation, or by using the chamber technique. All experiments commenced with perfusion of a preparation with normoxic Tyrode's solution for at least 1 hour. The experimental arrangements used in the chamber technique for modeling the normal-hypoxic (N-H) transition zone are shown, for the two directions of fiber axis, in Figure 1, A and B. Preparations were pulled through a rectangular scoop in the chamber partition (1), which was then closed by letting a movable fluoroplastic rectangular plate about 200 μm thick (2) drop through grooves in the partition. A and B show the respective arrangements with fibers running perpendicular and parallel with respect to the partition. The fiber direction is shown by the dashed lines. The left compartment of the chamber was bathed with normoxic Tyrode's solution, while the right one was perfused with hypoxic saline.

Transmembrane action potentials were recorded simultaneously from both sides of the preparation with two microelectrodes at varying distances from the partition and varying durations of hypoxia. Experiments were carried out on preparations with intact intercellular junctions in the normal-hypoxic zone as well as on those with injuries by deliberately squeezing the zone with the movable rectangular plate [(2) in Fig. 18]. In the latter case, for a better recovery of the preparation after crushing, 1.5 hours were allowed to elapse, and the experiments were started after the action potential was restored, in the area of the partition. Squeezing usually would bring about a complete conduction block between the zones. The criteria for absence of intercellular interaction were as follows: (1) lack of the electrotonic spread between the zones, linked to the action potentials generated asynchronously in both zones, (2) lack of the electrotonic spread between the zones at imposed
myocardial units (Trautwein et al., 1954; Girardier, changes under hypoxic conditions are presented in the effects of hypoxia on action potentials of the resting potential values and the action potential durations and heights are displayed in Figure 2, B–D, as a function of the distance from the partition in the control zone, but rapidly shortens with increasing distance. For simplicity, the phenomenon of a slower decrease of the action potential duration will henceforth be referred to as “preservation phenomenon.” The averaged action potential duration data as a function of the distance of hypoxia and the remoteness of the hypoxic area with respect to the partition, are plotted in Figure 4, for intact (A, C) and damaged (B, D) cell-to-cell communication. There is a decline in the action potential duration with increasing duration of hypoxia, with the least changes recorded nearest the partition (x = 0). Yet, at a distance as small as 4 mm, the relationship is much like that of general hypoxia (Fig. 4A, B, dashed line). It is obvious, from a comparison of Figure 4, A and B, that a violation of cell-to-cell communication brings about a clear-cut increase in the rate of action potential shortening and broadens the action potential duration range in the transition zone. In the control zone, the action potential shortening occurs to a lesser degree (the data for curve N in Figure 4, A and B, were obtained at the point beside the partition in the nor-

Results

Impact of General Hypoxia on Physiology of the Rabbit Atrium

There are quite a number of reports available about the effects of hypoxia on action potentials of the myocardial units (Trautwein et al., 1954; Girardier, 1971–72). However, we felt it was necessary for us to run a series of these experiments ourselves, so that we could determine the most appropriate electrophysiological parameter for evaluating the effect of hypoxia, and the relationships between such a parameter and the duration of hypoxia, in order to serve later as a reference.

In this series, 12 experiments were carried out. Transmembrane action potentials were recorded from both the epicardial and endocardial sides of a preparation. Sample recordings showing action potential changes under hypoxic conditions are presented in Figure 2A. Only a slight hypoxic effect was evident in the resting potential (RP) and the action potential upstroke slope; however, there was a marked decrease in the action potential height and duration. After 40–60 minutes of hypoxia, response conduction was blocked and excitability faded. The averaged data for the resting potential values and the action potential durations and heights are displayed in Figure 2, B–D, as a function of the duration of hypoxia. It can be seen that 1 hour of hypoxia had almost no effect on the resting potential, whereas there was a marked decrease in the action potential height and duration.

Thus, the parameters most sensitive to hypoxic conditions were the action potential height and duration. The action potential height strongly depends upon the resting potential and the quality of a cell’s impalement with the microelectrode, which gives scattered values, and hence causes certain difficulties in evaluation of this parameter. In contrast, the action potential duration is considerably less affected by the above-mentioned factors. The AP shape and duration display negligible distortions even when the recording is performed with suction electrodes (Olsson, 1971).

On the basis of this evidence, we have selected, for this study, the action potential duration (APD) as the index of the effect of hypoxia.

Electrophysiology of the Normal-to-Hypoxic Transition Zone: Chamber Technique

The chamber technique was used to study the longitudinal and transverse positions of the axis of the fibers in the N–H transition zone to assess the role of myocardial anisotropy in the formation of the transitional zone.

This approach enabled us to evaluate the importance of cell-to-cell coupling for individual parameters of the transitional zone, since, depending on fiber positioning, one deals either with good (longitudinal positioning—along trabeculae direction) or poor (transverse positioning) intercellular interaction (Bukauskas et al., 1976).

The two cases are considered in detail below.

Case 1. The Normal-to-Hypoxic Transition Zone is Perpendicular to the Fiber Axis (Fig. 1A)

The experiments were performed with intact (ten experiments) as well as damaged (eight experiments) intercellular contacts in the transition zone. The representative recordings of the action potential shape as a function of the distance from the partition on the 30th minute are shown in Figure 3. As one can see, the action potential displays only minor changes in the vicinity of the partition, but rapidly shortens with increasing distance. For simplicity, the phenomenon of a slower decrease of the action potential duration will henceforth be referred to as “preservation phenomenon.” The averaged action potential duration data as a function of the distance of hypoxia and the remoteness of the hypoxic area with respect to the partition, are plotted in Figure 4, for intact (A, C) and damaged (B, D) cell-to-cell communication. There is a decline in the action potential duration with increasing duration of hypoxia, with the least changes recorded nearest the partition (x = 0). Yet, at a distance as small as 4 mm, the relationship is much like that of general hypoxia (Fig. 4A, B, dashed line). It is obvious, from a comparison of Figure 4, A and B, that a violation of cell-to-cell communication brings about a clear-cut increase in the rate of action potential shortening and broadens the action potential duration range in the transition zone. In the control zone, the action potential shortening occurs to a lesser degree (the data for curve N in Figure 4, A and B, were obtained at the point beside the partition in the nor-
moxic zone). The families of curves in Figure 4, C and D, were derived from the curves in A and B, and they show the action potential duration as a function of the distance from the partition at fixed time intervals from the onset of hypoxia. It can be seen that deterioration of cell-to-cell coupling results in accentuation of action potential duration changes in the hypoxic area and in stabilization of the parameter in the control zone. Although diminished, the preservation phenomenon persists (see Fig. 5), and the possibility of a contribution to the phenomenon by the extracellular space cannot be excluded. In the cases of intact intercellular contacts, a prolonged bathing (for 3–4 hours) of a preparation in the hypoxic solution suppresses excitability (Figure 5, A and B). Delineated is a boundary for alteration of electrophysiological properties of the zone which is characterized by a drastic change of the resting potential from −70 to −80 mV up to −8 to 0 mV, over as small a distance as 0.5 mm. Such a phenomenon is observed only in the hypoxic area farther from the partition, and is possibly due to the injury of intercellular junctions. A further prolongation of hypoxia causes the narrowing of the transitional zone and its subsequent shift.
Figure 4. The action potential duration as a function of the hypoxia duration and the distance to the partition perpendicular to the direction of the fibers. A: Family of curves showing relationship between the action potential duration and the duration of hypoxia in the transitional zone with normal cell-to-cell coupling. Averaged data. Each curve shows the relationship for a given recording site (0, 0.5, 1, 2, 4 mm from the partition). All action potential duration values are in relative units. C stands for the recording site close to the partition and situated on the normoxic side of the preparation, the dashed curve, GH, shows the relationship characteristic of general hypoxia. B: The same as in A, for the case of damaged intercellular junctions. C: Family of curves showing relationship between the action potential duration and the recording site in the transitional zone with normal cell-to-cell coupling. Averaged data. Each curve shows the relationship for a given duration of hypoxia (10, 20, 40, 60, and 120 minutes). All action potential duration values are in relative units. The values for infinite duration come from the experiments with general hypoxia. D: The same as in A, for the case of damaged intercellular junctions.

toward the normal area (Figure 4, C and D; Figure 5).

In nine experiments in which 2,4,6-chloromethoxy carbonyl cyanide phenylhydrazone was used instead of hypoxia the action potential shortening occurred about 30 times more rapidly than with hypoxia (Figure 6C). In Figure 6A, averaged data are presented, showing the character of dependence of the action potential duration on the 2,4,6-chloromethoxy carbonyl cyanide phenylhydrazone action duration for the first minute of incubation at four separate recording sites shown in Figure 6B. The action potential duration vs. the incubation in the 2,4,6-chloromethoxy carbonyl cyanide phenylhydrazone time plot shows no difference, in qualitative terms, between the respective action potential duration changes at individual recording sites under hypoxic conditions and with 2,4,6-chloromethoxy carbonyl cyanide phenylhydrazone (cf. Figure 4A). A prolonged incubation (to 100 minutes) in 2,4,6-chloromethoxy carbonyl cyanide phenylhydrazone leads to a complete suppression of excitation and a very marked depolarization in 20–30 minutes (Figure 7B). In the control zone, the action potential is shortened by 60–80% in 20 minutes of 2,4,6-chloromethoxy carbonyl cyanide phenylhydrazone action, thereafter starting to expand gradually to the control level (Figure 7A), vs. the background of negligible decrease of the resting potential. The action potential duration restoration to the control level starts at the onset of complete suppression of the excitation in the 2,4,6-chloromethoxy carbonyl cya-
FIGURE 5. The action potential shape as a function of the recording site and duration of hypoxia. Note the build-up, with increasing duration, of a non-excitable zone (see A, 150 and 300 minutes; B, 90 and 220 minutes) characterized by a tendency to extend toward the normal area. A and B stand for recording sets from two experiments. The bottom of the action potential upstrokes were positioned to match respective recording sites (heavy dots) on the bottom diagrams.

nide phenylhydrazone zone. This evidence suggests a functional disconnection of the latter, from the control zone.

Case 2. The Transition Normal-to-Hypoxic Zone is Parallel to the Fiber Axis (Figure 1B)

In this instance, the normal and hypoxic zones interact through side intercellular junctions. Figure 8A shows averaged curves for action potential duration as a function of hypoxia duration (the figures on the curves indicate the recording sites). The action potential duration at site 7 changes likewise in case of total hypoxia. With the recording site approaching the partition, the preservation phenomenon is more marked, even though it is less pronounced, in quantitative terms, than in case 1 (cf. Figure 4A). The family of curves in Figure 8B was derived from the curve family in Figure 8A and shows the dependence of the action potential duration on the distance to the transition zone on the 10th, 20th, 40th, 60th, and 120th minute of hypoxia.

Discussion

The data obtained point out that, with cell-to-cell coupling of good quality, there is a gradual change in values of electrophysiological parameters between one zone and another. A slower time-course of the APD decrease in the hypoxic zone near the partition, as compared with that observed with general hypoxia, was termed a "preservation phenomenon." In order to understand the mechanism of this, some factors of major importance should be given proper concern. They are (1) electrotonic coupling, (2) cell-to-cell diffusion of ions and molecules due to a concentration gradient, and (3) diffusion in the extracellular compartment.

Electrotonic Coupling

In 2,4,6-chloromethoxy carbonyl cyanide phenylhydrazone experiments, no phase shifts were found between the curves for the action potential duration as a function of the duration of the drug's action, at
any of the recording sites used. This finding suggests that the time needed for triggering the mechanism underlying the preservation phenomenon should be less than the time for the action potential duration decrease, i.e., it should be less than 10 seconds. Since the time for electrotonic coupling in the myocardium is within the range of 5–20 msec, it thus meets the above requirement and points to the involvement of electrotonic processes in the mechanisms underlying the preservation phenomenon. This is favored by quite a large decay length constant (1 mm on the average) for electrotonic spread along the atrial trabeculae (Bukauskas et al., 1976). With increasing duration of hypoxia, the decay length constant decreases (Bredikis et al., 1976; Wojtczak, 1979) and this should diminish the preservation phenomenon. This is probably one of the major causes of the "narrowing" of the normal-to-hypoxic transition zone with sustained hypoxia.

**Cell-to-Cell Diffusion**

Hypoxia inhibits the pumping ability of the electrogenic membrane and thus leads to a potassium loss and Na⁺ accumulation by the cell. Concurrently, as a result of suppression of the oxidative phosphorylation and due to activation of the glycolysis, there builds up an intracellular deficiency in high-energy compounds and a redundancy of products of the glycolysis (Williamson et al., 1977). Thus an intracellular gradient for a variety of compounds arises, as well as the diffusional forces directed toward diminishing this gradient. Weidmann (1966) has shown the intercellular junctions to be highly permeable to K⁺ and other ions. Intercellular exchange with macromolecules (ATP, creatine phosphate, lactates) is also possible (Imanaga, 1974; Pollack, 1976). By utilizing the
chamber technique, these investigators were able to obtain evidence for intercellular diffusion of compounds with large molecules (with molecular weight up to 700) several millimeters from the site of their application. Recently, there has been growing evidence that the specialized junctions (nexuses), with pores of up to 10-15 Å, are the sites at which the overwhelming majority of the diffusional macromolecular exchange occurs (McNutt and Weinstein, 1973). It remains to be determined however, how powerful and far-reaching the intercellular diffusional flow of metabolities is. By utilizing the equation for free intercellular diffusion (Weingard, 1974), we can find that a compound with a diffusion coefficient of $10^{-7}$ cm/sec takes 2 minutes to travel 1 mm. Temporal parameters for diffusion are 3 or 4 orders of magnitude larger than those for electrotonic processes. For this reason, in 2,4,6-chloromethoxy carbonyl cyanide phenylhydrazine experiments, only the electrotonic processes had enough time to make their contribution to the preservation phenomenon, whereas, with the agents that bring about injury after more than ten minutes (e.g., hypoxia), the diffusional phenomena also should have had an effect.

For a qualitative evaluation of a contribution to the preservation phenomenon by the diffusion of metabolites across the intercellular junctions, we used an "end-to-end" model for two, "normal" and "hypoxic", cylindrical cells. We can estimate the amount of creatine phosphate (CP), one of the key energetic substances (Rosenshtraukh et al., 1976), which passes across the junctional membrane and the molecular weight above, i.e., 5 mm/liter. By making use of the relationship during one cardiac cycle approximately. Let us suppose that the "normal" cell is functioning at a normal level and the creatine phosphate concentration in it, $C_N$, is 10 mM/liter (Rodenroth et al., 1973), whereas the "hypoxic" cell is subject to hypoxia and the creatine phosphate level, $C_h$, is one half of the above, i.e., 5 mM/liter. By making use of the relationship between the cell-to-cell molecular permeability of the junctional membrane and the molecular weight (Pollack, 1976), we find, for creatine phosphate molecules, a value of $4 \times 10^7$ $\mu$m/min. If we also assume the cell diameter and length equal to 20 $\mu$m and 40 $\mu$m, respectively, and use the following relationship

$$I = P \times S \times (C_N - C_h)$$

where I is the CP flow across the junctional membrane per unit time and S is the cross-sectional area, we obtain a value of $4.2 \times 10^{-14}$ M for the amount of creatine phosphate passing, by diffusion, from the "normal" to the "hypoxic" cell per one cardiac cycle. Under normal conditions, the creatine phosphate level in the cell is $2.5 \times 10^{-13}$ M. A beating heart cell wastes $5 \times 10^{-14}$ M of high-energy molecules per cardiac cycle, whereas the corresponding value for a resting cell is $6 \times 10^{-16}$ M (Pool et al., 1969). Thus, the amount of creatine phosphate translocated by diffusion exceeds the amount of high-energy molecules utilized during a contraction by nearly an order of magnitude. Even though the above model is still far from reality, it points out the necessity for accounting for cell-to-cell diffusion in the analysis of interaction between the normal and the injured myocardium.

The role of cell-to-cell diffusion is not limited by the effect of flow of high-energy molecules to hypoxia-injured cells. Not less important, for the latter, are other effects, such as a "wash-out" of noxious metabolic intermediates, a restoration of normal acid-base and ion equilibrium [$Ca^{++}$ particularly, since its accumulation inside the cell is associated with disastrous effects on vital functions, destructive lesions and uncoupling (De Mello, 1976)].

Thus, the junctional structures are the real morphological basis that can account for the preservation phenomenon via reequilibration, by diffusion, of electrolytes and compensation for a shortage of high-energy compounds in injured cells by those supplied by the normal units.

**Extracellular Diffusion**

As shown by the evidence obtained from the experiments of impaired cell-to-cell coupling in the normal-to-hypoxic transition zone, extracellular diffusion cannot be eliminated as a possible contributor to the preservation phenomenon. Under such conditions, the preservation phenomenon is considerably weakened, yet not abolished. Since the cells are electrotonically uncoupled in this paradigm, only the extracellular diffusion of molecules should be given concern. The extracellular space, which makes up as much as 25% of the total volume of the tissue (Prasad et al., 1974), apparently provides the basis for the diffusion of oxygen molecules and reequilibration of electrolyte levels.

**The Role of Intercellular Coupling in the Interaction between Hypoxic and Normal Myocardium**

Cardiac structures, especially atrial trabeculae, are known to display marked anisotropic electrical properties. The transversal intercellular coupling in the rabbit atrial trabeculae is 7 to 10 times less effective than the longitudinal coupling (Bukauskas et al., 1974). The evidence obtained made it possible for us to evaluate the formation of the transitional zone at three different levels of intercellular interaction: (1) good (longitudinal direction), (2) mediocre (transverse direction), and (3) no interaction, due to a mechanical damage of the transitional zone. As one can see from Figures 4, A and B, and 5A, with the intercellular interaction impaired, the preservation phenomenon is less pronounced and the transitional zone is narrower. Figure 9 shows the corresponding action potential duration differences in the three cases, between both sides of the partition on the 20th, 40th, and 80th minute of hypoxia. As could be expected, the difference was smallest with efficient coupling and the largest with no coupling. With increasing duration of hypoxia, the differences in the APD became more evident and the transition zone narrower. This may be due to progressive derrangement of the intercel-
Critical Size of Hypoxic Area

Electrical and diffusional cell-to-cell links make it possible for a healthy myocardium to compensate for the energy deficit of the hypoxic area. It is possible that there is a critical size for the hypoxic area which is still sufficient to safeguard the tissue from necrosis by virtue of compensatory processes. It should be much like the size of the normal-to-hypoxic transition zone.

From a qualitative analysis of the transition zone, one can infer that the area of local hypoxia, still capable of functioning due to the preservation phenomenon, would not exceed 2–3 mm in size. The corollary is that, the stronger the links keeping a cell built in a whole system, the easier it is for it to endure various abnormal conditions, and the larger the critical size of hypoxic area.

If a hypoxic area is large enough, this will ultimately bring about a gradual exhaustion of energy stores around the area. Owing to a permanently existing “source of leakage,” the injured area should gradually expand. However, due to impaired cell-to-cell coupling in hypoxia (Bredikis et al., 1976; Wojtczak, 1979), the injured area becomes isolated from the normal myocardium. Extensive evidence recently gathered points to the key role of calcium ions accumulated inside the cell in controlling this process (De Mello, 1976).

Onset of Hypoxia-Induced Arrhythmias

In a search for mechanisms of hypoxia-induced arrhythmias, the emphasis usually has been placed on findings of marked nonhomogeneity of the action potential duration, which, according to Sano et al. (1972) and Krinskij et al. (1976), can give rise, through reexcitation, to a focus of ectopic beats.

We were not able to observe reexcitation in rabbit atrium preparations even though, in the hypoxic area, a clear-cut depolarizing “hump” was found during the action potential repolarization phase induced by electrotonic interference from the normal zone. To make the excitation mechanism operable, some special requirements may have to be met; those concerning cell-to-cell coupling and accommodation properties are two of the most important (Arita et al., 1976; Sakson et al., 1976). On one hand, intercellular coupling should be strong enough to give rise to effective stimulating local currents; on the other hand, effective intercellular communication is an unfavorable condition for development of considerable action potential duration gradients over short distance. These contradictory effects make reexcitation impossible with either very effective intercellular coupling or complete uncoupling. There is evidently a certain optimum extent in intercellular electrical coupling for the reexcitation mechanism to be put into effect. Normally, atrial and ventricular fibers of the working myocardium exhibit clear-cut accommodative properties. This also hinders reexcitation. In Purkinje fibers, which have poor accommodative properties, and in guinea pig papillary muscle fibers with impaired accommodative properties, due to the action of low-potassium medium and catecholamines, repetitive firing has been reported in response to prolonged injections of a depolarizing current (Arita et al., 1976; Katzung et al., 1975). Therefore, one may suggest that, under ischemic conditions, the impairment of the cell-to-cell coupling and the increased catecholamine release (Valori et al., 1967; Griffits et al., 1971) are the prerequisites due to which the inherent nonhomogeneity of the action potential duration is transformed via the reexcitation mechanism into a source of extrasystoles.

I would like to express my deep appreciation to Professor Jurgis Bredikis for his continuous interest and help in accomplishment of this study and to Doctor Arunas Pakula for his helpful suggestions on the manuscript and his time spent on editing the English text.

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Received May 30, 1979; revised manuscript received May 18, 1981; accepted for publication May 21, 1982.
References


Barlow CH, Chance B (1976) Ischemic areas in perfused rat hearts: Measurements by NADH fluorescence photography. Science 193: 909-910


De Mello WC (1976) Influence of the sodium pump on intercellular communication in heart fibers: Effect of intracellular injection of sodium ion on electrical coupling. J Physiol (Lond) 263: 171-197


Katzung BG, Hondeghem LM, Grant AO (1975) Cardiac ventricular automaticity induced by current of external calcium. Pfluegers Arch 360: 193-197

Knijskij VI, Petsov AM, Reshetilov AN (1976) A plausible mechanism of intercellular interaction resulting in cardiac extrasyso-
toles. In Models of Structural and Functional Organization of Biological systems. Moscow, Dubna (in Russian), p 32


Olsson B (1971) Monophasic action potentials of right heart. Suc-
tion electrode method in clinical investigations. Thesis, Göteborg, Andersens Buktryckeri, p 139

Pollack GH (1976) Intercellular coupling in the atrioventricular node and other tissues of the rabbit heart. J Physiol (Lond) 255: 275-298


Weidmann S (1966) The diffusion of radiopotassium across inter-
calated disks of mammalian cardiac muscle. J Physiol (Lond) 178: 323-342


Wojtczak J (1979) Contractions and increase in internal longitudinal resistance of cow ventricular muscle induced by hypoxia. Circ Res 44: 88-95

INDEX TERMS: Microelectrodes • Action potential • Arrhyth-
mias • Hypoxia • Transitional zone • Intercellular communication