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Correction of Disturbances of Cardiac Electrical Stability in Postinfarction Cardiosclerosis with a Polyunsaturated Fatty Acid-Enriched Diet

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It has been shown previously that polyunsaturated fatty acids (PUFA) added to the rat diet as eiconol preparation with a high content of docosahexaenoic and eicosapentaenoic acids reduce mortality for acute myocardial infarction sevenfold. This result has been achieved mainly due to suppression of ischemic and reperfusion arrhythmias and, particular, heart fibrillation [1,7]. These facts agree with the results of epidemiological and clinical investigations that have shown fish oil consumption to reduce mortality in myocardial infarction [3,8]. The influence of a PUFA-enriched diet on the contractility and electrical stability of the heart during postinfarction cardiosclerosis (PIC) has not yet been investigated. Meanwhile, millions of people surviving infarction suffer from PIC, posing an urgent problem in clinical cardiology. A considerable proportion of these people die from severe arrhythmia culminating in fibrillation [2,6].

The aim of the present study was to assess the effect of a PUFA-enriched diet on spontaneous arrhythmia and the main parameters of the electrical stability of the heart in animals with PIC.

MATERIALS AND METHODS

Experiments were carried out on Wistar male rats weighing 300±10 g. The animals were divided into four groups: group 1 comprised intact animals (control); group 2 consisted of animals receiving an eiconol-containing diet for 50 days; group 3 comprised animals with a 30-day myocardial infarction (i.e., with PIC) receiving the standard diet; group 4 comprised animals in which myocardial infarction was created after they had received an eiconol-containing diet during 15-23 days, after which they were kept on the same diet for another 30 days. Myocardial infarction was reproduced after Selye. Eiconol

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TABLE 1. Effect of Eiconol on the Electrical Stability of the Heart in Rats with Postinfarction Cardiosclerosis ($M \pm m$)

Series of experiments	Heart fibrillation threshold, mA	Percent of animals with spontaneous fibrillation, %	Number of extrasystoles during stimulation of vagus (number of thresholds)		Total number of extrasystoles in each group
			2	4	
Control ($n=15$)	7.0±0.5	0	4	0	4
Eiconol($n=10$)	7.5±0.4	0	5	0	5
PIC	2.3±0.5 ($n=8$)	45 ($n=20$)	10.7±3.9 ($n=9$)	47±12.2 ($n=9$)	420
Eiconol+PIC	3.5±0.6** ($n=8$)	15 ($n=20$)	0.4±0.4** ($n=8$)	21±7.6* ($n=8$)	168

Note: n: number of animals in each series of experiments. *: reliability of differences for $p<0.05$.

(TU 400 SP "A" - 1145-118-90 of Trinita, Moscow) contained 18% eicosapentaenoic acid, up to 12% docosahexaenoic, 18.1% oleic acid, 18.2% linoleic acid, and 18.3% linolenic acid, as well as saturated and monounsaturated fatty acids. The degree of eiconol unsaturation (iodine number) reached 190. Eiconol in a dose of 1.3 g/day was added to the standard diet.

The investigations were conducted in two stages, the electrical stability of the heart being studied in the first stage. The frequency of spontaneous arrhythmia and the level of ectopic activity of the heart were assessed in the intact thorax of narcotized animals (thiopental, 50 mg/kg). To suppress the automatism of the sinus node, electrostimulation of the distal end of the right vagus nerve was performed with a strength from 1 to 4 thresholds (in the range of 0.16-0.64 V on the average, frequency 20 Hz, duration 2 msec, delay 5 msec) for 30 sec. Thoracotomy was then performed, and the ventricular threshold of fibrillation (mA) was measured under artificial respiration with air [5]. For this purpose the heart was stimulated with single preliminary pulses (duration 10 msec) with the aid of a coaxial electrode inserted in the apex of the right ventricle; stimulation was performed with a SEN-3201 Nihon-Kohden electronic stimulator (Japan) triggered by the R-wave of the ECG recorded on an RM-6000 polygraph (the same firm). In the second stage, the contractile function of the heart was assessed according to a pressure curve recorded in the left ventricle with the aid of a Siemens-Elema Mingograf-34 electromanometer (Germany). Heart rate (HR), systolic, diastolic, and developed pressure, maximal rate of contraction and relaxation reflecting the rate of rise and drop of the pressure (mm Hg), and functional intensity of the structures (FIS) calculated as a product of HR (n) and developed pressure per unit weight of the left ventricle (mm Hg×n/mg) were determined. It should be mentioned that the weight of the left ventricle for FIS determination was calculated without scar tissue weight; thus, FIS reflected the function only of myocardium left ventricle mass that remained intact and was viable. The results were subjected to statistical analysis using the Student test.

RESULTS

The mortality for acute myocardial infarction in the animals which preliminarily received an eiconol-containing diet for 15-23 days was only half as high compared to the animals not receiving eiconol (16.0 and 39.7%, respectively). This shows that the effect of eiconol on mortality in myocardial infarction after a short-term consumption is not as strong as after a 60-day consumption, when animal mortality decreased sevenfold [1]. The degree of left ventricle

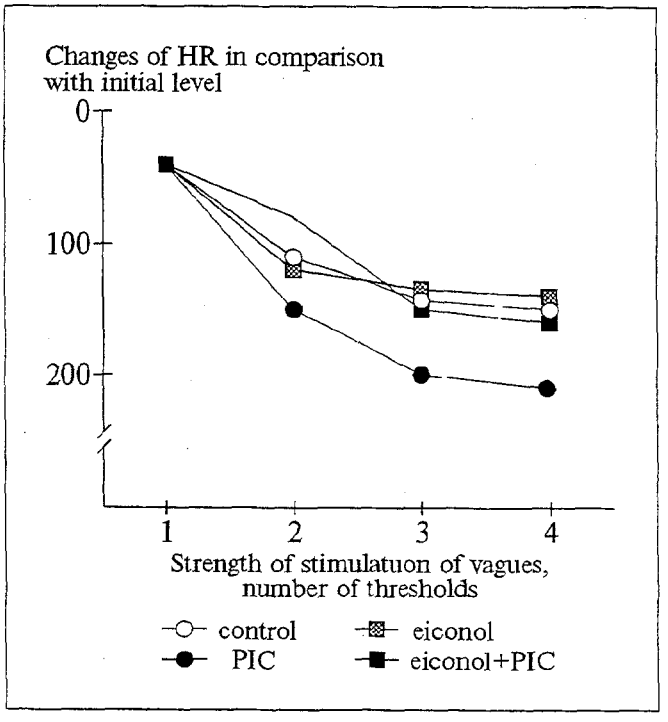

Fig. 1. Effect of eiconol on degree of vagal bradycardia in rats with postinfarction cardiosclerosis.

TABLE 2. Effect of Eiconol on Myocardial Contractility during Postinfarction Cardiosclerosis ($M \pm m$)

Series of experiments	HR (n), beats per min	Diastolic pressure, mm Hg	Developed pressure, mm Hg	Intensity of structure functioning, mm Hg×n/mg	Rate of contraction, mm Hg/sec	Rate of relaxation, mm Hg/sec
Control (15)	352±8	2.3±1.2	122±4.5	76±3.9	7950±617	3051±211
Eiconol (8)	380±10	2.7±0.7	140±8.2	94±7.4	9000±275	3999±259*
PIC (7)	289±20	3.2±0.8	66±6.3	40±5.2	3272±472	1927±423
Eiconol+PIC (10)	320±17	3.3±0.6	71±6.2	56±4.4*	3461±323	2429±388

Note: figures in the parentheses: number of animals; n: HR. *: reliable differences ($p<0.05$).

hypertrophy in animals receiving and not receiving eiconol were similar and constituted 12%. Eiconol did not affect the scar weight either; the specific weight of the latter in the left ventricle weight in the groups compared was 22.1±2.3 and 16.5±2.4%, respectively ($p>0.1$).

The results of the study of heart electrical stability are presented in Table 1; as is seen from the table, the ventricular fibrillation threshold fell sharply (by 68%) in the animals with PIC as against the control. Eiconol raised the fibrillation threshold in animals with PIC 1.5 times. Significant differences were revealed in the frequency of spontaneous extrasystole in narcotized animals. As Table 1 shows, eiconol decreased the frequency of spontaneous arrhythmia 3-fold.

When the function of the sinus node during PIC was suppressed by stimulation of the vagus, eiconol markedly reduced the ectopic activity. For instance, at a nerve stimulation strength of 2 thresholds 96 extrasystoles were registered in animals with PIC kept on the standard diet, whereas extrasystole was practically absent in the animals with PIC which received eiconol. The total number of extrasystoles arising during a 4-threshold stimulation of the vagus nerve was 2.5 times reduced by eiconol. Fig. 1 shows the degree of vagal bradycardia in the groups compared and demonstrates that in the intact animals eiconol itself did not affect the intensity of bradycardia, but markedly restricted bradycardia in animals with PIC. The differences between the groups were more pronounced at a stimulation strength of two thresholds, while in the eiconol-fed animals with PIC the HR increased by 45%.

Hence, eiconol to a certain extent prevented the disturbances of heart electrical stability during PIC, this being manifested as a decrease of the frequency of spontaneous and induced extrasystoles, an increase of sinus node resistance to stimulation of the vagus, and, last, a decreased probability of fibrillation.

At the same time, the cardioprotective effect of eiconol proved to be less pronounced (Table 2). Eiconol reduced the depression of heart contractility in the physiologically resting state. Thus, the rate of functional activity of the structures was 40% higher in eiconol-fed animals with PIC than in the animals not receiving eiconol (56±4.4 and 40±5.2 mm Hg×n/mg, respectively; $p<0.05$). The results thereby provide evidence that eiconol quite effectively restricts disturbances of heart electrical stability and to a lesser degree repairs disturbances of contractility in PIC.

As shown by analysis of the results, the main noteworthy fact is that the PUFA-enriched diet did not alter cardiac activity when this was profoundly disturbed, although it increased the main functional parameters of the heart in the control. Just one parameter, FIS, most representative of the integrated contractility of the surviving parts of the myocardium, increased reliably (by 40%, mainly due to the increase of HR and the slight increase of developed pressure).

On the other hand, the effect of eiconol on all parameters of the electrical stability of the heart was markedly pronounced. It sharply increased the heart fibrillation threshold, three times reduced the number of animals with spontaneous extrasystole, and diminished the ectopic activity during suppression of automatism of the sinus node. This almost selective antiarrhythmic effect of eiconol, leading to a normalization of the electrical stability of the heart, is most significant. In our view, this clinically important fact is probably explained by a PUFA-enriched diet-induced increase of PUFA in all membranes in general and in the membranes of the cardiomyocytes in particular [4]. Such alterations in the neighboring lipids may activate membrane-bound proteins, primarily Na,K-ATPase and Ca-ATPase. This, in turn, may result in a higher resting potential and greater conduction velocity of the action potential, and, as a consequence, an increase of the electrical stability of the heart. This hypothesis, of course, must be verified by studies of bioelectrical activity of cardiomyocytes in the working heart.

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Reduced Vasoconstriction and Enhanced Vasodilation of the Isolated Resistive Artery during Adaptation to Periodic Hypoxia

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The myogenic tone of resistive blood vessels is known to drop during adaptation to periodic hypoxia [6], inhibiting hereditary hypertension in SHR rats [4], the pathogenesis of this condition being similar to that in humans. This adaptation lowers arterial pressure in the initial stages of essential hypertension [5]. However, many aspects of the antihypertensive effect of adaptation to periodic hypoxia have not yet been clarified. For example, the effect of this adaptation on the α- and β-adrenergic responses of resistive arteries is unclear, although their increased tone is known to be an important factor in the development of hypertension.

The aim of the present work was to study the effect of adaptation to periodic hypoxia on the reactions mediated by the α- and β-adrenergic receptors of the isolated rat caudal artery, as well as on the level of the endothelium-dependent relaxation induced by acetylcholine.

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MATERIALS AND METHODS

Experiments were carried out on Wistar male rats weighing 350-400 g. Adaptation to periodic hypoxia was carried out in a pressure chamber for 30 days, four hours daily, at an "altitude" of 5000 m. The course of adaptation was started at 1000 m and the "altitude" was gradually increasedover five days.

An arterial segment approximately 8 mm long was taken from the proximal end of the caudal artery of decapitated rats. Cannulas were inserted in both ends of the segment, which was then placed in an incubation chamber. Perfusion with Krebs-Henseleit solution (37°C) was performed at a constant flow rate (2 ml/min) [1]. The reactions of the perfused vessel were assessed by the changes in the perfusion pressure recorded with a KSP-4 potentiometer with the aid of a Statham pressure sensor (USA).

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