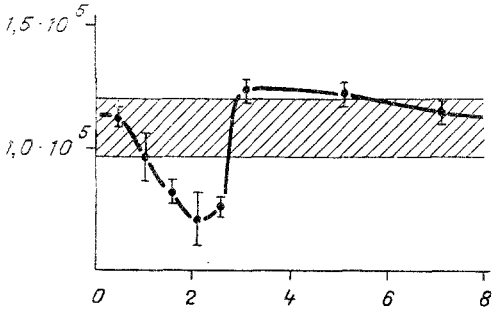

Fig. 3. Strength of left ventricular wall at different times of experimental MI during successive tests. Legend as to Fig. 1.

Under normal conditions the rat heart is thus characterized by high reserves of strength, and in uncomplicated MI, even in the stage of marked necrotic changes in the myocardium in the zone of infarction, strength is not reduced. The mechanisms whereby this strength is maintained include an increase in the ischemic phase and an early onset of repair, following necrotic changes.

LITERATURE CITED

1. L. T. Malaya, V. A. Pilipenko, G. G. Avtandilov, et al., Sov. Med., No. 4, 11 (1984).
2. A. V. Smol'yannikov and T. A. Haddachina, Klin. Med., No. 8, 79 (1968).
3. Problems in Morphology and Pathogenesis of Infarction (Myocardium, Lungs, Kidneys, Spleen), A. I. Struchkov, ed. [in Russian], Moscow (1959).
4. N. I. Yabluchanskii, G. G. Avtandilov, V. A. Pilipenko, et al., Sud.-Med. Ékspert., No. 4, 26 (1982).
5. R. H. German, C. S. Apstein, H. M. Kagan, et al., Circulat. Res., 53, 378 (1983).
6. G. Weissman, J. E. Smolen, and S. Hoffstein, J. Invest. Derm., 71, 95 (1978).

PREVENTION OF ISCHEMIC AND REOXYGENATION ARRHYTHMIAS AND VENTRICULAR FIBRILLATION WITH THE ANTIOXIDANT IONOL

F. Z. Meerson and L. M. Belkina

UDC 616.12-005.4-06:616.12-008.318-085.243.4-039.71

KEY WORDS: ventricular fibrillation; transient myocardial ischemia; reperfusion of the myocardium; antioxidants.

Reoxygenation after hypoxia or ischemia of the myocardium leads to activation of lipid peroxidation (LPO) [2, 6], which plays an important role in reoxygenation injury to membranes of the myocardium [2, 5] and disturbance of its contractile function [2, 3, 6]. These phenomena can be prevented by antioxidants [1, 2, 5, 13]. Recent investigations have shown that induction of LPO in the myocardium regularly leads to bradyarrhythmia and cardiac arrest, which can also be prevented by antioxidants [4]. These facts are important because relatively transient ischemia followed by reperfusion (RP) and reoxygenation constitute an unavoidable stage of the process in any coronary attack, in the course of which reduction or cessation of the coronary blood flow is followed by reactive hyperemia, adenosine-induced in its origin [7]. Under these circumstances cardiac arrhythmias and fibrillation may develop [9, 12]. The role of activation of LPO in the genesis of these arrhythmias is highly prob-

Research Institute of General Pathology and Pathological Physiology, Academy of Medical Sciences of the USSR, Moscow. (Presented by Academician of the Academy of Medical Sciences of the USSR P. D. Gorizontov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 101, No. 6, pp. 662-664, June, 1986. Original article submitted March 22, 1985.

TABLE 1. Effect of Antioxidant Ionol on Arrhythmias Induced by Occlusion of Coronary Artery for 10 Min and Subsequent Reperfusion

Experimental conditions	Fibrillation		Tachycardia		Extrasystoles	
	No. of animals	duration, sec	number of animals	Duration, sec	number of animals	Duration, sec
			Ischemia			
Control	2	30±20	8	23,2±8,1	20	16,4±3,5
Ionol	0	—	0	—	12	3,6±1,6*
			Reperfusion			
Control	12	90±29	22	35,2±7,9	20	22,7±9,2
Ionol	0	—	12	6,6±2,1*	12	3,2±1,5*

Legend. In each series of experiments 24 rats wre used. *P < 0.001.

able, although no attempt has been made to study the possibility of preventing them by means of antioxidants.

The aim of this investigation was to assess the effects of the synthetic antioxidant ionol (2,6-di-tert-butyl-4-methylphenol) on cardiac arrhythmias and fibrillation arising during transient ischemia followed by reoxygenation of the myocardium.

METHODS

Experiments were carried out on male Wistar rats weighing 250-300 g, anesthetized with urethane (160 mg/kg), on which thoracotomy was performed, followed by artificial ventilation with air. The animals were divided into two groups: the animals of group 1 (control) were given sunflower oil (0.05 ml/100 g, *per os*) once daily for 4 days before the experiment, and the rats of group 2 were given ionol (6 mg/100 g), dissolved in the same volume of sunflower oil, by the same scheme. The ECG was recorded in standard leads I, II, and III, on a Mingograf-34 instrument (Siemens-Elema, Sweden) together with the left intraventricular pressure. The systolic and diastolic pressure, and the maximal rate of rise and fall of pressure (dp/dt), which reflect the rate of contraction and relaxation of the myocardium respectively, were calculated from the pressure curve. The heart rate (HR) and the intensity of functioning of structures (IFS) — the product of the developed pressure and HR, divided by the weight of the left ventricle — also were determined. The experiments were conducted in two stages: After recording of the parameters in a state of relative physiological rest, the descending branch of the left coronary artery was ligated for 10 min and the ECG and parameters of cardiac contractility were recorded during ischemia; the ligature on the artery was then released and the response of the heart to RP was estimated for 5 min, for arrhythmias always appeared during the first minute of RP only.

RESULTS

The study of the effect of ischemia and RP on cardiac contractility and on the development of arrhythmias showed that ischemia for 10 min caused significant depression of cardiac contractility. For instance, after 10 min of occlusion the systolic pressure fell from 92 ± 7.3 to 72 ± 7 mm Hg and the rate of contraction from 4733 ± 200 to 3400 ± 733 mm Hg/sec and the rate of relaxation from 3133 ± 733 to 2200 ± 333 mm Hg/sec. The diastolic pressure and HR during this period did not change significantly. On restoration of the blood supply all parameters recovered quickly, and after 5 min of RP they regained their original level.

Data on the arrhythmogenic effect of ischemia and RP are given in Table 1. It will be clear from Table 1 that RP caused much more severe disturbances of rhythm than ischemia. In fact, during ischemia ventricular fibrillation (VF) occurred in only two of 24 animals, compared with 12 during RP; in four of them, moreover, fibrillation caused cardiac arrest. Other types of arrhythmia; during RP also occurred much more often than during ischemia. Incidentally, during ischemia disturbances of rhythm developed mainly 5-6 min after the beginning of occlusion, whereas reperfusion arrhythmias occurred almost immediately after re-

moval of occlusion (after 5-10 sec). It can be tentatively suggested that these outwardly similar arrhythmias are based on different mechanisms.

Investigation of the effect of ionol on cardiac contractility and on the development of arrhythmias during ischemia and RP showed that ionol increases some parameters of cardiac contractility in a state of relative physiological rest. For instance, the systolic pressure was significantly increased by 39% (128 ± 10.1 mm Hg), whereas HR was at the control level (377 ± 5 beats/min), as a result of which IFS was increased also by 39% (64 ± 5.3 and 90 ± 7.8 mm Hg·min/mg respectively). The rate of contraction under the influence of the antioxidant was increased under these circumstances by 36%, but the rate of relaxation was the same as in the control.

Ionol had no significant effect on depression of cardiac contractility during ischemia or on its recovery during RP.

Before turning to the analysis of the effect of ionol on cardiac arrhythmias, it will be noted that the duration of the QT interval in the preischemic period in animals receiving ionol was 12% less than in the control (80.2 ± 2.4 msec). In the modern view the duration of QT reflects the degree of dispersion of myocardial excitation [8, 12], and its shortening may be a sign of increased resistance of the heart to arrhythmogenic influences. Characteristically, ionol had a strong antiarrhythmic action during the period of ischemia and, in particular, on restoration of the blood supply (Table 1). During ischemia, in the animals receiving ionol, there was not a single case of ventricular tachycardia: The number of cases of extrasystoles fell from 83 to 50%, and the duration of the extrasystoles was reduced by 4.6 times. During RP, ionol completely prevented the development of VF and, at the same time, it reduced the number of cases of ventricular tachycardia from 91 to 50%, and of extrasystoles from 83 to 50%; it also shortened the duration of tachycardia and of extrasystoles by 5.3 and 7 times respectively compared with the control. Hence it follows that ionol has a marked antifibrillating action, and it largely prevents the development of other types of arrhythmias.

In a discussion of the possible mechanisms of the arrhythmic and, in particular, the antifibrillatory action of ionol, the first point to note is that during ischemia and, in particular, during RF, ionol as an antioxidant limits the degree of injury to cell membranes [2, 3] and, consequently, it limits the disturbance of ionic transport, which is an essential prerequisite for disturbance of the electrical stability of the heart. Thus the membrane-stabilizing action of ionol must lead to blocking of mechanisms inducing arrhythmias.

We know that VF and ventricular tachycardia may arise through a re-entry mechanism, the condition for the formation of which is a critical increase in the degree of heterogeneity of the myocardium relative to its conduction patterns [8, 14].

It can accordingly be postulated that ionol reduces the degree of heterogeneity of the myocardium which, in turn, prevents the development of arrhythmias of re-entry type. Our results agree withthe fact established previously that the xanthine oxidase inhibitor, allopurinol, depressed the arrhythmogenic action of transient ischemia and subsequent RP [10]. On the whole, the phenomenon thus discovered is evidende of the important role of activation of LPO in the pathogenesis of ischemic and reoxygenation arrhythmias, so that there are good prospects for the use of antioxidants for the clinical treatment of arrhythmias.

LITERATURE CITED

1. P. F. Litvitskii, A. Kh. Kogan, A. N. Kudrin, et al., Byull. Éksp. Biol. Med., No. 3, 115 (1981).
2. F. Z. Meerson, V. E. Kagan, Yu. P. Kozlov, et al., Kardiologiya, No. 2, 81 (1982).
3. F. Z. Meerson, Pathogenesis and Prevention of Stressor and Ischemic Injuries of the Heart [in Russian], Moscow (1984).
4. F. Z. Meerson, V. A. Saltykova, V. V. Didenko, et al., Kardiologiya, No. 5, 61 (1984).
5. R. Ferrari, O. Visioli, C. Guarnieri, et al., Acta Vitaminol. Enzymol., 5, 11 (1983).
6. C. Guarnieri, F. Flamigni, and C. Calderera, J. Mol. Cell. Cardiol., 12, 797 (1980).
7. K. Kroll, J. Schipperheyn, F. Hendriks, et al., Amer. J. Physioll., No. 7/2, H214 (1980).
8. Kuo Chien-Suu, K. Munakata, C. Reddy, et al., Circulation, 67, 1356 (1984).
9. W. Lubbe, P. Daries and L. Opie, Cardiovasc. Res., 12, 212 (1978).

10. A. Manning, J. Coltart, and D. Hearse, Circulat. Re., 55, 545 (1984).
11. A. Manning and D. Hearse, J. Mol. Cell. Cardiol., 16, 497 (1984).
12. A. Moss and P. Schwartz, Mod. Concepts Cardiovasc. Dis., 51, 85 (1982).
13. H. Ohhara, H. Kanaidle, R. Yoshimura, et al., J. Mol. Cell. Cardiol., 13, 65 (1981).
14. C. Reddy, Kuo Chien-Suu, K. Munakata, et al., Amer. J. Cardiol., 49, 934 (1982).

EFFECT OF AN EXCESSIVE OXYGEN SUPPLY ON MYOCARDIAL ENERGY EXPENDITURE

Yu. S. Alyukhin and K. P. Ivanov

UDC 612.172.013.7-06:612.273.1

KEY WORDS: myocardium; oxygen supply.

It is generally considered that the oxygen consumption of the tissues is independent of their oxygen supply, provided that the partial pressure of oxygen within the tissues remains above a certain critical level, which is very low (of the order of 0.1 kPa). However, there are frequent reports in the literature that the oxygen consumption of skeletal muscles and the myocardium rises in response to an increase in the flow of blood or fluid replacing it through the tissue, i.e., when the oxygen supply is increased while at rest or while the level of activity of the organ remains constant [4-8, 10-15]. If these observations are correct, they demand a substantial re-examination of established views on the course of oxidative processes involving oxygen. They are particularly interesting for cardiology, in which the energies of the heart muscle and its oxygen supply are central problems.

Invesitgations have been undertaken in the writers' laboratory using a method of measuring oxygen consumption by the isolated perfused rat heart. Isolation of the organ modifies the conditions of its activity sharply, but allows the oxygen supply to the tissues to be changed at will and to be monitored sufficiently accurately, a matter of the utmost importance for the solution of problems connected with the influence of oxygen supply on energy metabolism. The problem of the influence of oxygen supply on the energetics of the heart has already been examined by the writers previously [2, 3].

In the investigation descxribed below the range of changes in the oxygen supply of the heart was widened and lactate formation in the heart also was measured at different levels of oxygen supply.

METHODS

To simplify interpretation of the results, experiments were carried out on the arrested heart. The basis of the experimental method was described previously [1, 2].

The isolated rat heart was perfused at 37°C with Krebs–Henseleit bicarbonate buffer saturated with a mixture of 95% O_2 and 5% CO_2. The partial pressure of oxygen in perfusion fluid flowing toward the heart was 78-92 kPa. The heart, arrested by excess of potassium, was perfused retrogradely. In each experiment oxygen consumption was calculated only once (3-7 min after cardiac arrest), for the oxygen consumption of the arrested heart changes with time. The rate of perfusion varied from one experiment to another between 40 and 143 ml/g dry weight of myocardium (from now on the parameters are always expressed relative to dry weight of the myocardium) per minute by varying the hydrostatic pressure (7-17 kPa). The rate of lactate formation by the heart was determined in a special additional series of experiments.

The perfused heart was placed in a special chamber connected with two continuous-flow polarographic cells, one of which was placed on the path of inflow of the perfusion fluid into the organ, the other on the outflow path of perfusion fluid, having passed through the

Laboratory of Temperature Regulation and Bioenergetics, I. P. Pavlov Institute of Physiology, Academy of Sciences of the USSR, Leningrad. (Presented by Academician of the Academy of Medical Sciences of the USSR B. I. Tkachenko.) Translated from Byulleten' Eksperimental'noi Biologii i Meditsiny, Vol. 101, No. 6, pp. 664-666, June, 1986. Original article submitted June 29, 1985.

 0007-4888/86/0006-0734$12.50