It will be evident that the combined use of HBO and of antioxidant preparations preventing the development of LPO would allow the beneficial action of HBO to be manifested to the full.

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INHIBITION OF SUPEROXIDE DISMUTASE AS A FACTOR PROMOTING MYOCARDIAL DYSFUNCTION IN OXYGEN LOADING

A. M. Gerasimov, V. I. Mil'chakov, E. A. Demurov, Yu. B. Koloskov, and S. N. Efuni*

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Diethyldithiocarbamate (DEDTC) is an inhibitor of superoxide dismutase (SOD), an enzyme controlling the intracellular level of superoxide radicals (O_2^-) in aerobic organisms [8]. If DEDTC is administered to animals, the SOD activity of their heart is reduced [5, 6].

The writers showed previously that injection of DEDTC into rabbits with hypertrophy of the heart not only inhibits SOD activity but also seriously impairs the contractility and pumping function of the heart in the presence of an excess of O_2^- caused by sessions of hyperbaric oxygenation (HBO) [3]. Meanwhile in experimental myocarditis induced by injection of adrenalin, an SOD preparation had a protective action on cardiac function and prevented the disturbance of contractility due to more intensive oxidation [4].

Beneficial effects of other substances with antioxidant action on cardiac function during stimulation of free-radical injury to the heart have been described [7]. These observations indicate that one condition for manifestation of the toxic action of oxygen on the heart is inadequate capacity of its antioxidant defensive systems. To confirm this hypothesis directly it was decided to study the effect of DEDTC on myocardial contractile function under conditions stimulating O_2^- formation.

EXPERIMENTAL METHOD

Experiments were carried out on Chinchilla rabbits weighing 2.5-3.3 kg. DEDTC was injected intraperitioneally twice a day into intact animals in a dose of 0.5 g/kg, and into animals with adrenalin-induced cardiac damage (AICD) in a dose of 0.25 g/kg daily for 3 days. AICD was produced by slow intravenous injection of 1% caffeine solution (20 mg/kg) and 0.1%

*Corresponding Member, Academy of Medical Sciences of the USSR.

Department of Hyperbaric Oxygenation, All-Union Scientific Center for Surgery, Academy of Medical Sciences of the USSR. Laboratory of Biochemistry, N. I. Priorov Central Institute of Traumatology and Orthopaedics, Ministry of Health of the USSR, Moscow.

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TABLE 1. Effect of DEDTC and SOD in Conjunction with Hyperbaric Oxygenation (HBO) on Contractile Function of the Heart in Intact Rabbits and Rabbits with Adrenalin-Induced Cardiac Damage (M ± m)

Parameter	Experimental conditions	Stage of experiment		
		relative rest	cardiac stimulation	compression of aorta
Heart rate, beats/min	Control	228±4,6	300	212±5,5
	DEDTC	210±7,9*	300	204±6,9
	DEDTC + HBO	188±9,8*	270	183±6,1
	DEDTC + HBO + SOD	215±4,3*	300	211±5,1
	AICD	213±13,4*	300	210±10,4
	AICD + DEDTC	209±7,8	300	194±6,5
	AICD + DECTC + HBO	202±9,4	270	190±5,6
Stroke ejection, ml	Control	1,42±0,06	0,95±0,06	—
	DEDTC	1,44±0,08	0,86±0,03	—
	DEDTC + HBO	1,18±0,06*	0,64±0,03*	—
	DEDTC + HBO + SOD	1,71±0,07*	1,10±0,06	—
	AICD	1,20±0,08*	0,72±0,06*	—
	AICD + DEDTC	1,30±0,05	0,80±0,05	—
	AICD + DEDTC + HBO	0,84±0,04**	0,46±0,04**	—
Developed pressure, mm Hg	Control	107±5,2	94±4,6	209±6,2
	DEDTC	102±4,5	79±4,3*	195±8,4
	DEDTC + HBO	79±6,6*	62±4,5*	159±9,5*
	DEDTC + HBO + SOD	104±5,1	92±5,0	195±4,7
	AICD	103±5,9	72±4,8*	187±9,0*
	AICD + DEDTC	93±5,3	69±3,7*	178±6,9*
	AICD + DEDTC + HBO	82±4,9**	50±3,6**	141±5,7**
Velocity of contraction, mm Hg/sec	Control	2883±184	2196±127	3920±144
	DEDTC	2807±143	1922±109	3587±211
	DEDTC + HBO	2230±91*	1026±87*	3008±122*
	DEDTC + HBO + SOD	2706±157	1745±143*	3028±129*
	AICD	2378±198*	1435±120*	3315±180*
	AICD + DEDTC	1852±104	1291±75	2748±127
	AICD + DEDTC + HBO	1481±90**	906—54**	2253±116**
Velocity of relaxation, mm Hg/sec	Control	2096±112	1805±99	2824±179
	DEDTC	2081±178	1525±94*	2572±160
	DEDTC + HBO	1384±184*	792±81*	1946±120*
	DEDTC + HBO + SOD	1916±103	1429±141*	2350±175*
	AICD	1879±109	1237±127*	2377±107*
	AICD + DEDTC	1367±95	988±46	1967±107
	AICD + DEDTC + HBO	926±72**	644±50**	1551±90**
Total peripheral resistance, dynes · sec · cm^{-5}	Control	22 400±900	22 200±1100	—
	DEDTC	22 200±900	21 600±900	—
	DEDTC + HBO	25 200±600*	26 000±900*	—
	DEDTC + HBO + SOD	21 100±900	21 000±1100	—
	AICD	22 900±1700	25 700±2500	—
	AICD + DEDTC	—	—	—
	AICD + DEDTC + HBO	—	—	—

Legend. *P < 0.05 compared with control, **P < 0.05 compared with AICD. Number of animals in control 7, in all other cases 6.

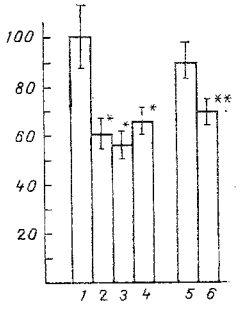

Fig. 1. SOD activity in left ventricle of rabbit heart. 1) Control, 2) DEDTC, 3) DEDTC + HBO, 4) DEDTC + HBO + SOD, 5) AICD + HBO, 6) AICD + DEDTC + HBO. *P < 0.05 compared with control, **P < 0.05 compared with AICD + HBO. Ordinate, SOD activity (in % of control).

adrenalin solution (0.2 ml) at an interval of 2 min. Control animals received an injection of physiological saline. HBO sessions were given daily for 3 days (2 atm. 1 h). To study the effect of exogenous SOD, a preparation isolated from bovine blood by a modified method in [11] was injected intraperitoneally into rabbits in a dose of 1 mg/kg 30 min before the HBO sessions.

Endogenous SOD activity was determined by a method based on ability of the enzyme to inhibit O_2^--mediated self-oxidation of adrenalin [1]. Homogenates for determination of SOD activity were prepared as described previously [4]. Protein was determined by Lowry's method [10]. The contractile function of the left ventricle was assessed by recording the intraventricular pressure manometrically with a Mingograf-82 apparatus, under conditions of relative rest, with rhythm binding and compression of the aorta for 5 sec.

EXPERIMENTAL RESULTS

On the 3rd day of daily injection of DEDTC the contractile and pumping functions of the heart were disturbed (Table 1) and SOD activity in the tissue of the left ventricle was reduced (Fig. 1). At rest this disturbance was not apparent except for the heart rate, which was reduced a little. However, during rhythm binding the developed pressure and, in particular, the rate of relaxation were reduced. During isometric loading induced by compression of the aorta for 5 sec, the parameters of cardiac function remained close to their control values.

A combination of DEDTC with HBO sessions, which by themselves do not depress cardiac function [2], lowered the parameters of cardiac function both at relative rest and during work (Table 1). There was also a significant increase in the total peripheral resistance.

Animals with AICD receiving the SOD inhibitor in a dose of 0.5 mg/kg died during the HBO sessions. Injection of half the dose of DEDTC into animals with a combination of AICD and HBO caused total impairment of the contractile and pumping functions of the heart both at rest and during work. Reduced binding of the imposed frequency of stimulation and a marked decrease in the contractile function of the heart were characteristic.

The level of SOD activity fell by about the same degree as in the control animals (Fig. 1) which received the higher dose of inhibitor, possible evidence of a disturbance of the SOD reactivation mechanisms in animals with AICD. Injections of DEDTC into animals with AICD but without HBO also caused depression of cardiac contractility, but by a lesser degree (Table 1).

DEDTC thus caused the appearance of a cardiotoxic action of oxygen in intact animals and enhanced such an action in animals with AICD. Similar results were obtained by the writers previously on a model of myocardial hypertrophy [3]. The results of these model experiments, in our opinion, require a penetrating examination of the possibility that both toxic and therapeutic substances may have an unfavorable action on the antioxidant systems of the myocardium. It is interesting to note that DEDTC is formed *in vivo* from teturam [9]. Potentiation of oxygenation of myocardial tissue or stimulation of free radical processes in it for certain other reasons (inflammation, irradiation, administration of substances with pro-oxidant action, etc.) may act as a provoking factor leading to cardiopathy as a result of relative failure of the antioxidant defense. The results described above, which point to a disturbance of myocardial function in rabbits receiving DEDTC after HBO, and still more, if these factors are combined with AICD, are in our opinion an illustration of the imposition of an oxidative load on a heart less able to withstand it. The possibility cannot be ruled out that a similar principle of myocardial damage also is found in the pathogenesis of certain other forms of heart failure of varied etiology.

Intravenous injection of the SOD preparation before HBO sessions largely prevents the cardiac dysfunction due to the combined action of DEDTC and HBO (Table 1). This was found both at relative rest and when a high frequency of contraction was imposed on the heart and its isometric load was increased. However, the velocity of contraction and relaxation remained lower than in the control. The level of SOD activity in the heart was not restored (Fig. 1), and in our view this is further confirmation of the effect of exogenous SOD on O_2^--mediated processes taking place outside the cariodmyocyte, but leading to a disturbance of its function.

On the whole the protective action of SOD, which the writers demonstrated previously in experimental adrenalin-induced myocarditis [4], and the results of the present investigation obtained with a combination of HBO and DEDTC, demonstrate the important role of O_2^--mediated processes in the genesis of cardiomyopathies and, at the same time, they indicate that SOD may be promising substance for use as a therapeutic agent in cardiology.

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ROLE OF PROSTACYCLINE IN ANTIAGGREGATING ACTIVITY OF THE VASCULAR WALL

É. S. Gabrielyan, S. É. Akopov, and B. G. Balayan

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The antiaggregating activity of the vascular wall is the factor which is largely responsible for preventing the development of intravascular thrombus formation and atherogenesis. A decrease in this activity, under the influence of catecholamines or stress, for example, may be the main cause of development of thrombosis and tissue necrosis [7]. It has been suggested that antiaggregating activity is due to the formation of prostacycline (PGI_2), which has extremely powerful antiaggregating and vasodilator effects [7], in the vascular wall. However, many physiologically active substances which may also affect platelets are formed in a system with such complex organization as the vascular wall. It has been shown, for example, that fibroblasts and smooth-muscle cells release substances which potentiate aggregation [3]. Views ascribing the antiaggregating activity of vessels essentially to PGI_2 synthesis alone may therefore be excessively oversimplified. The aim of the present investigation was to clarify the role of PGI_2 in the realization of the antiaggregating effect of the vascular wall.

EXPERIMENTAL METHOD

Platelet-enriched plasma (PEP) was obtained from fresh citrate-stabilized blood from healthy blood donors. The PEP sample was separated into two parts, to one of which was added crystalline prostacycline (from Upjohn Co., USA) to a final concentration of 1 μg/ml, whereas a segment of a blood vessel was incubated in the other part (5 min, 37°C). The total area of the segment was chosen so that the antiaggregating effect of the isolated vessel corresponded to that in the sample with prostacycline. Samples of 0.5 ml were taken at definite time intervals from these two original samples, and the degree of aggregation induced by ADP (10^{-6} M) was determined in them. Aggregation was measured on an aggregometer of the writers' own design [1]. The vessels for investigation were taken from cadavers of 12 persons with no history of cardiovascular diseases during life, and dying accidentally. The vessels were

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