Effects of Dimebon on Coronary Blood Flow and Myocardial Contractility

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Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 121, No. 5, pp. 506-508, May, 1996
Original article submitted February 12, 1996

The antihistamine Dimebon, which is an H_1-receptor blocker, is shown to act as a moderate coronary vasodilator without exerting a marked effect on myocardial contractility.

Key Words: *Dimebon; coronary blood flow; myocardial contractility*

A major problem in cardiology is sudden cardiac death, which is often preceded by ventricular arrhythmias due to inadequate coronary circulation [7]. Recently, we reported evidence that the Russian-made antihistamine Dimebon (H_1-receptor blocker) exhibits, in various animal models, an antiarrhythmic activity superior to that of quinidine, Ethmosine, Bonnecor, and verapamil [2]. Our present study is the first in which Dimebon was tested for its effects on coronary blood flow (CBF) and myocardial contractility.

MATERIALS AND METHODS

Phasic changes in CBF were examined in five dogs with open chest [4] after an intravenous injection of Dimebon at 2.5 mg/kg body weight. The following parameters were measured: heart rate, left ventricular and aortic pressures, perfusion pressure in coronary vessels at the end of diastole, stroke systolic CBF, stroke diastolic CBF, coronary index (ratio of the stroke diastolic CBF to the stroke systolic CBF), stroke CBF, minute CBF, and resistance of coronary vessels at the end of diastole. Myocardial contractility was evaluated from the level of intraventricular pressure and the rate of its change ($\Delta P/\Delta t_{max}$) and also by measuring the acceleration developed by the myocardium [5].

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The effect of intravenous Dimebon (2.5 mg/kg) on myocardial contractility was tested on seven artificially ventilated cats with β-adrenoceptors blocked by Obsidan (1 mg/kg intravenously). In these cats we additionally determined the phasic structure of the cardiac cycle by measuring the lengths of the asynchronous contraction phase, isometric contraction phase, tension period, ejection period, total systole, and left ventricular diastole [3].

The effect of Dimebon on the electrical and contractile properties of coronary vessels was examined *in vitro* using 12 isolated segments of porcine coronary arteries [6] exposed to a hyperpotassic solution or to serotonin.

The data were statistically analyzed as described by Belen'kii [1].

RESULTS

Dimebon administration to dogs led to significant rises in the heart rate by 3.7%, stroke systolic CBF by 68.8%, stroke diastolic CBF by 42.2%, stroke CBF by 49.5%, and minute CBF by 52.6%, and to a 48.6% increase in the acceleration developed by the myocardium; the aortic and perfusion pressures significantly decreased by 6.9% and 12.3%, respectively (Fig. 1).

Variations in the other two parameters (coronary index and $\Delta P/\Delta t_{max}$) in response to Dimebon were insignificant, which should be interpreted as an indication of its beneficial cardiotropic action. It is

0007-4888/96/0005-0459$15.00

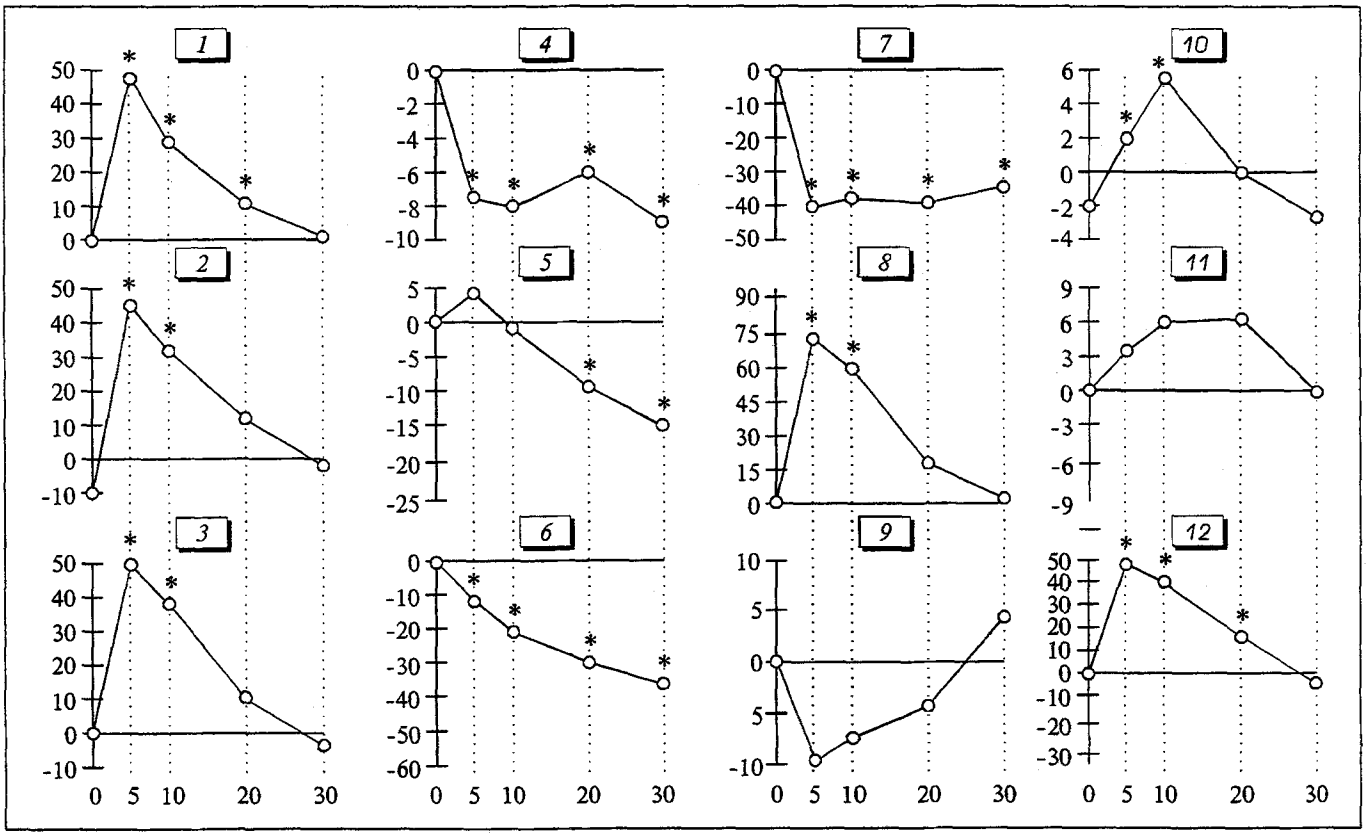

Fig. 1. Effect of Dimebon (2.5 mg/kg intravenously) on phasic changes in the coronary blood flow (CBF) and myocardial contractility in dogs. *1*) stroke diastolic CBF; *2*) stroke CBF; *3*) minute CBF; *4*) aortic pressure; *5*) left ventricular pressure; *6*) end–diastolic perfusion pressure in coronary vessels; *7*) end–diastolic resistance of coronary vessels; *8*) stroke systolic CBF; *9*) coronary index; *10*) heart rate; *11*) $\Delta P/\Delta t_{max}$; *12*) acceleration developed by the myocardium. Ordinate: % changes in the parameters measured. *$p<0.05$ relative to baseline (0).

important to note that the increase in CBF occurred together with a fall in aortic pressure. This observation can only be explained by increased coronary vasodilation but cannot be taken as proof of a direct action of Dimebon on the coronary vessels because the tests were carried out on dogs with preserved neural and humoral regulation of the circulation.

Of interest in this context are the tests with isolated coronary artery segments. These tests showed

TABLE 1. Effects of Dimebon on the Phasic Structure of the Cardiac Cycle and on Myocardial Contractility in Cats with Blocked β-Adrenoceptors (*M±m*)

Parameter	Baseline	Time postinjection, min		
		10	20	30
Cardiac cycle, msec	352.1±11.5	386.9±12.6	387.1±10.6*	376.9±12.4
Asynchronous contraction phase, msec	47.0±3.5	47.4±3.5	45.7±2.6	44.7±1.8
Isometric contraction phase, msec	45.9±7.1	51.0±4.6	49.1±5.3	50.0±5.3
Tension period, msec	94.3±7.9	112.7±5.5*	94.9±5.3	94.7±4.4
Ejection period, msec	126.1±3.5	126.3±3.5	132.4±8.8*	130.0±6.2
Total systole, msec	220.4±1.7	226.3±7.3	227.3±9.7	226.1±7.9
Left ventricular diastole, msec	131.7±10.1	160.6±14.2	159.9±10.6	150.0±15.9
Left ventricular pressure, mm Hg	117.5±11.5	96.2±8.4*	91.6±7.9*	101.4±106.0
$\Delta P/\Delta t_{max}$, mm Hg/sec	2891.7±381.3	2071.4±309.5*	2405.4±200.1*	2700.1±312.4
Acceleration developed by myocardium, mm Hg/sec^2	70157.7±8808.3	45362.4±10396.9*	55853±9946.6*	58325.5±9375.2

Note. *$p<0.05$ relative to baseline.

that Dimebon in a 10^{-5} M dilution had no effect on the resting potential or the basal tone of the coronary arteries, but did lower the contractile response to the hyperpotassic solution and serotonin by 41% and 87%, respectively. The latter two findings are indicative of diminished Ca^{2+} entry via both the potential-dependent and receptor-controlled channels, which provides strong evidence that the drug acts directly on the smooth muscle cells of the coronary arteries.

The time course of contractile myocardial activity in dogs (Fig. 1) appears to reflect two concurrent processes. The first of these is a latent rise in contractility occurring immediately after Dimebon administration and detectable only by the acceleration that the myocardium develops, which has been shown to be the most useful and sensitive index of its contractility [5].

The positive inotropic effect of Dimebon appears to have arisen as a reflex in response to the falls in aortic and perfusion pressures, but it was followed by the gradual emergence of a negative inotropic effect lasting 30 min or longer (Fig. 1, *5* and *12*); the widely used $\Delta P/\Delta t_{max}$ index proved of little value in this situation because of the summation of the two oppositely directed inotropic influences.

This view is supported by the results obtained with cats which were injected with Dimebon after their β-adrenoceptors had been blocked by Obsidan (Table 1). In all cats, changes in the heart rate, in the tension and ejection periods, and in myocardial contractility were clearly negative from the very beginning as a result of the direct action of Dimebon on the conducting and contractile myocardia, although these changes were patently insignificant.

To summarize, the results of this study permit the conclusion that the antihistamine Dimebon, which is also recommended as an antiarrhythmic agent, acts as a moderate coronary vasodilator without exerting a marked effect on myocardial contractility.

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