EFFECT OF CORDANUM AND PROPRANOLOL ON CORONARY RESISTANCE

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Propranolol is the most widely used β-adrenoblocker. It has been shown to reduce the heart rate (HR) and the force of the cardiac contractions [1, 3, 4, 7, 9]. Some workers have observed a decrease [5, 6], but others an increase [3, 4] in the coronary blood flow following administration of propranolol. Recently selective β_1-adrenoblockers have been extensively used in clinical and experimental medicine, in particular cordanum (talinolol). However, the effect of cordanum on the resistance of the coronary vessels has virtually not been studied.

The aim of this investigation was to study the effect of cordanum and propranolol on coronary resistance.

EXPERIMENTAL METHODS

Experiments were carried out under pentobarbital anesthesia (30-40 mg/kg) on 30 isolated cats' hearts, perfused under constant pressure (80-100 mm Hg) with blood from a donor. The flow of blood into the coronary arteries was recorded by the electromagnetic transducer of an MF-46 flowmeter (Nihon Kohden, Japan). The pressure in the right atrium and the left ventricle and the perfusion pressure were recorded by electromanometric transducers (EMT-746; Siemens-Elema, Sweden). The parameters obtained were recorded on a Mingograf-82 instrument (Siemens-Elema).

Coronary blood flowing into the left side of the heart was drained through a catheter in the apex of the left ventricle, thus ensuring low values of intraventricular pressure. For this reason changes in activity of the isolated heart could be judged from HR.

The coronary resistance was calculated as the ratio of the difference between the perfusion pressure and pressure in the right atrium, on the one hand, and the volume velocity of the coronary blood flow (in mm Hg/ml/min) on the other hand. Coronary vascular tone was assessed by the degree of reactive hyperemia in response to ischemia for 10 sec.

Cordanum in doses of $0.7 \cdot 10^{-5}$ to $1.0 \cdot 10^{-5}$ g/ml and propranolol in doses of $0.7 \cdot 10^{-5}$ to $1.0 \cdot 10^{-5}$ g/ml were injected through the stabilizing perfusion vessel.

EXPERIMENTAL RESULTS

After injection of cordanum two types of changes in coronary resistance were discovered: 1) a decrease (35.3%) and 2) an increase (64.7%). In reactions of type 1 (Figs. 1 and 2a) the resistance of the coronary vessels decreased in the first minute, the greatest decrease being observed after 61.0 ± 4.5 sec (by 26.3 ± 7.1% of the initial value; $p < 0.02$). The coronary resistance thereafter increased and stabilized after 232.0 ± 20.9 sec at values which did not differ from the initial values. The decrease in HR began 30.0 ± 12.3 sec after the decrease of the coronary resistance. On average, changes in HR were not significant ($p > 0.1$).

In reactions of type 2 (Fig. 2b) there was a gradual increase in coronary resistance, which stabilized after 203.0 ± 22.6 sec, when it was 13.5 ± 5.2% higher than the initial value ($p < 0.05$). HR began to fall simultaneously with the rise of coronary resistance. On average the changes in HR were not significant ($p > 0.1$). No significant differences were found in the resistance (3.9 ± 0.5 and 5.0 ± 0.4 mm Hg/ml/min, $p > 0.1$) and tone of the coronary vessels (reactive hyperemia 42.0 ± 13.0% and 80.0 ± 16.3%, $p > 0.1$) in reactions of types 1 and 2.

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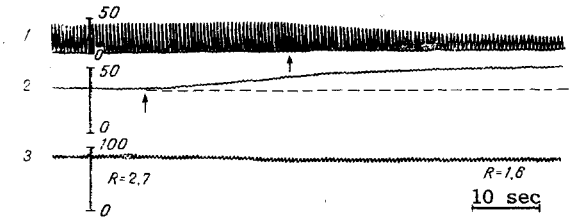

Fig. 1. Decrease of coronary resistance following injection of cordanum. 1) Pressure in left ventricle (in mm Hg); 2) blood flow into coronary arteries (in ml/min); 3) perfusion pressure. Broken line) initial value of coronary blood flow. Arrows indicate beginning of decrease of coronary resistance and weakening of cardiac activity. R) Value of coronary resistance.

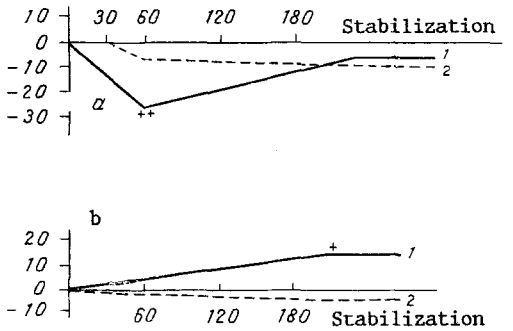

Fig. 2. Two types (a, b) of change in coronary resistance following injection of cordanum. Abscissa) time from beginning of reaction (in sec); ordinate: 1) changes in coronary resistance (in percent of initial value); 2) changes in HR (in percent of initial value). *p < 0.05; **p < 0.02.

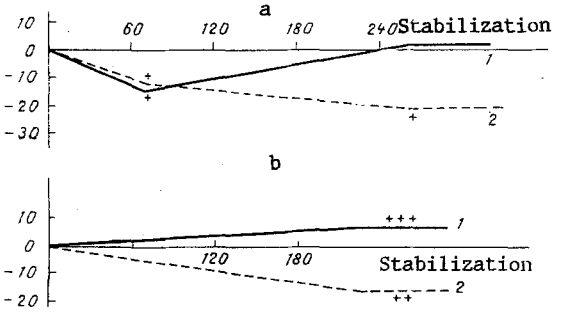

Fig. 3. Two types (a, b) of change of coronary resistance following injection of propranolol. *p < 0.01, ***p < 0.02. Remainder of legend as to Fig. 2.

It can be concluded from these results that the beginning of the fall of resistance in response to injection of cordanum is due to the primary action of the drug on the coronary vessels, for the work of the heart began to weaken 30 sec later (Fig. 1). The change in pressure in the left ventrical on the curve displayed suggests that on the whole weakening of activity of the isolated heart was more marked than that determined from HR, more especially because, according to data obtained by other workers [1, 2], cordanum reduces the force of contraction by a greater degree than the heart rate. However, as the curve shows, the decrease of pressure in the left ventricle began significantly later than the decrease in

coronary resistance confirming the conclusion that cordanum has a primary dilator action on the coronary vessels in reactions of this type.

The increase in coronary resistance in reactions of type 2 took place parallel with weakening of cardiac activity and, consequently, it may have been due to secondary coronary constriction as a result of reduction of the myocardial oxygen demand. The reduction of extravascular compression in that case is probably less important because of the relatively high initial tone of the coronary vessels.

After injection of propranolol two types of changes of the coronary resistance also were found: 1) a decrease (80.8%), 2) an increase (19.2%). In type 1 reactions (Fig. 3a) the resistance of the coronary vessels fell after 1 min, and the greatest decrease was observed after 69.0 ± 4.8 sec, by 14.1 ± 1.4% ($p < 0.001$) from the initial value. The coronary resistance later increased and stabilized after 263.0 ± 17.3 sec at values which did not differ from those observed initially. HR began to fall simultaneously with the coronary resistance, falling by 12.2 ± 2.2% ($p < 0.001$) toward the end of the dilator phase, and by 20.3 ± 2.7% ($p < 0.001$) from the initial values toward the end of the reaction.

In type 2 reactions (Fig. 3b) there was a gradual increase in coronary resistance, which stabilized after 225.0 ± 36.7 sec, when it was 7.7 ± 2.0% higher than initially ($p < 0.02$). HR began to fall simultaneously with the rise of the coronary resistance, and toward the end of the reaction it was reduced by 15.2 ± 3.1% ($p < 0.01$) below the initial value.

No differences were found in the resistance (3.1 ± 0.1 and 3.1 ± 0.3 mm Hg/ml/min) and tone of the coronary vessels (reactive hyperemia was 27.0 ± 2.8 and 26.0 ± 12.4%) in reactions of types 1 and 2.

After injection of propranolol there was thus in most cases a short-term fall of the coronary resistance, which was accompanied by weakening of cardiac activity. We know [8] that the low initial tone of the coronary vessels is responsible for the determinative role of an extravascular mechanical factor in the changes in coronary resistance. Since the decrease of resistance after injection of propranolol took place against the background of the low initial tone of the coronary vessels, this suggests that it is due to a decrease in extravascular compression during weakening of cardiac activity.

The following conclusion can be drawn from these results as a whole. After injection of cordanum or propranolol both a decrease and an increase in coronary resistance may be observed. In most cases changes in the coronary resistance take place parallel with weakening of cardiac activity and, consequently, they are largely determined by the relationship between two opposing factors: reduction of extravascular compression and reduction of myocardial oxygen demand. The determining role of each of these factors depends on the initial tone of the coronary vessels, and this evidently explains the predominance of an increase in coronary resistance after injection of cordanum (high initial tone) and a decrease in coronary resistance after injection of propranolol (low initial tone). Moreover, after injection of cordanum a short-term decrease in coronary resistance is observed in some cases, which precedes the change in work of the heart and which, consequently, may be due to the primary action of cordanum on the coronary vessels.

LITERATURE CITED

1. V. B. Brin and B. Ya. Zonis, Kardiologiya, 23, No. 4, 104 (1983).
2. V. B. Brin and V. A. Kapliev, Vopr. Okhr. Mat., 29, No. 11, 52 (1984).
3. R. A. Karsenovich, Sh. B. Irgashev, and S. Z. Kostko, Problems in Clinical and Experimental Pharmacology and the Side Effect of Drugs [in Russian], Tbilisi (1983), pp. 33-35.
4. S. Z. Kostko and A. Sh. Kasimkhodzhaev, Med. Zh. Uzbek. No. 11, 17 (1980).
5. M. D. Mashkovskii, Therapeutic Substances: Textbook of Pharmacotherapy for Physicians, 9th ed., Revised and Enlarged [in Russian], Vol. 1, Moscow (1984).
6. V. I. Metelitsa, The Cardiologist's Guide to Clinical Pharmacology [in Russian], Moscow (1980).
7. S. A. Nikolaenko and V. A. Navarenko, Byull. Vses, Kardiol. Nauch. Tsentra, 4, No. 2, 93 (1981).
8. E. N. Novikova, Kardiologiya, 10, No. 4, 44 (1970).
9. R. Urbanich, B. M. Shargorodskii, A. Kovach, and M. E. Raiskina, Kardiologiya, 20, No. 10, 78 (1980).