REACTIVITY OF CORONARY ARTERIES AND CORONARY VASOCONSTRICTOR ACTION OF SERUM IN HYPERCHOLESTEREMIA AND ATHEROSCLEROSIS

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In experiments on the isolated hearts of rabbits receiving cholesterol an increase in the coronary vasoconstrictor action of serum of patients with coronary atherosclerosis and serum of rabbits with experimental atherosclerosis was found.

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Investigations conducted on isolated organs have demonstrated increased reactivity (with a tendency toward development of spastic states) of vessels, including the coronary vessels, in experimental cholesterol atherosclerosis [2, 5, 7, 8, 10, 12-14]. Changes in reactivity of the coronary arteries of the isolated heart of human patients with atherosclerosis, dying from various causes, have also been found [1].

The metabolic disturbances in atherosclerosis may not only modify vascular reactivity but may also cause the appearance (or accumulation) of humoral factors possessing a vasoconstrictor action in the blood Human serum has a moderate coronary vasoconstrictor effect on the isolated rabbit's heart; the serum of patients with angina pectoris has a stronger action [3, 4, 15].

We have studied the action of serum from patients with atherosclerosis and rabbits fed with cholestrol on the isolated heart of healthy rabbits and rabbits with experimental atherosclerosis. By using an autologous serum the nonspecific action of heterologous, and even homologous serum could be eliminated.

EXPERIMENTAL METHOD

The isolated heart was taken from 63 male rabbits weighing 1.8-2.8 kg, of which 21 animals were controls, and 42 had previously been fed with cholesterol in a daily dose of 0.3 g/kg with the diet (vegetables or bran with sunflower oil) for various periods.

Serum was taken from the control and experimental rabbits and also from 41 patients with coronary atherosclerosis (15 with an anginal syndrome, and 26 with myocardial infarction), and from 18 persons not affected with atherosclerosis (control group).

In experiments on the contracting isolated (by Langendorff's method) heart changes in the lumen of the coronary vessels were judged from the volume of effluent fluid. Perfusion was performed with Ringer – Locke solution enriched with oxygen, at a pressure of 900 mm water at 38°. After the rate of outflow had become initially stabilized, the test serum was added to the perfusion fluid for 1 min (1 : 5 – 1 : 60) after which normal perfusion was resumed. Five types of serum were used: autologous serum (from the rabbit whose heart was isolated), the serum of another rabbit homologous) not receiving cholesterol, homologous serum of a rabbit receiving cholesterol, serum of a patient with atherosclerosis, and serum from the human controls. The volume of fluid passing through the coronary vessels in the course of 15 min after treatment with serum (V) was compared with the theoretical outflow (V_0), the latter being calculated by multiplying the initial minute volume by 15 and taken as 100%. Changes in the outflow under the influence of serum (R) were determined from the formula:

$$R = \frac{V - V_0}{V_0} \times 100\%.$$

A negative value of R indicates a decrease in outflow, a positive value an increase.

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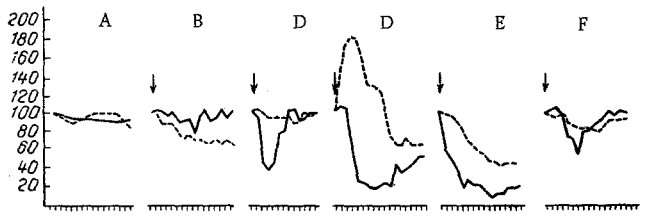

Fig. 1. Coronary outflow (continuous line) and heart rate (broken line). Abscissa) time (in min); ordinate) outflow and heart rate (in % of initial values). Arrow denotes injection of serum. A) Experiment without injection of serum; B) control rabbit (injection of autologous serum); C – E) rabbits receiving cholesterol (injection of autologous serum); F) isolated heart of control rabbits (injection of control homologous serum).

EXPERIMENTAL RESULTS

A series of biochemical changes was found in the rabbits receiving cholesterol, characteristic of atherosclerosis (the blood cholesterol concentration rose considerably (on the average by 5 times the initial level, etc.), and these were accompanied by changes in the ECG and atherosclerotic lesions of the aorta and coronary arteries, and by a decrease in the lecithin/cholesterol ratio.

In most experiments 2-5 min after injection of serum into the perfusion fluid, the outflow diminished, but the degree and duration of this effect varied. No parallel was observed between the changes in outflow and in heart rate. Each successive injection of serum began after establishment of a new initial level of outflow (but not less than 15 min after the previous injection of serum). The order of administration of the sera was varied, so that when the results were assessed the possibility that the differences were dependent on repetition or on duration of work of the isolated heart could be ruled out.

In experiments on the isolated heart of healthy rabbits (see Fig. 1, F), a moderate coronary vasoconstrictor action of the homologous healthy rabbit serum (mean value $R = -23 \pm 4\%$; $P < 0.01$), and also of the control human serum ($R = -14.4 \pm 2.7\%$; $P < 0.001$) was found [3, 4, 11, 15]. At the same time, autologous healthy rabbit's serum had no significant effect on the coronary outflow ($R = -1.8 \pm 3.1\%$; $P > 0.5$; see Fig. 1, B). In this series of experiments no significant difference could be found between the coronary vasodilator action of the serum of patients with atherosclerosis (or rabbits with experimental atherosclerosis), and the human (or rabbit) serum of the control group. The results were different during perfusion of the heart from a rabbit previously fed with cholesterol (see Table 1). Autologous serum considerably reduced the outflow (see Fig. 1, C – E). Homologous serum from a rabbit receiving cholesterol had a stronger action than homologous serum of a healthy rabbit; the serum of patients with atherosclerosis was more active than serum from the human control group. Consequently, the coronary vessels of the rabbit became more sensitive as a result of cholesterol feeding, and because of this, the increase in the coronary vasoconstrictor properties of the serum resulting from atherosclerosis could be clearly revealed. Human control serum and serum from healthy rabbits had an action on the isolated heart of the rabbits receiving cholesterol which was no stronger than their action on the "control" heart.

The vascular reactivity is increased in the early stages of experimental atherosclerosis [7-9], a factor possibly dependent on the direct action of cholesterol on the blood vessels [17]. In our experiments the sensitivity of the coronary arteries increased after administration of cholesterol for one month, coinciding in time with the development of hypercholesteremia. The increase in coronary vasoconstrictor properties of the serum evidently takes place later in the course of administration of cholesterol to the rabbit. Table 1 shows that the serum of patients with atherosclerosis had a marked action on the isolated rabbit's heart even in the early stages of cholesterol feeding, whereas the effect of autologous serum did not appear until after two months. Evidently, time is required for more profound changes in metabolism to appear in the course of development of experimental atherosclerosis. Several biochemical changes (especially concerning glucoproteins) cannot be detected in the animals until the second month of cholesterol feeding

TABLE 1. Changes in Outflow in Experiments on Isolated Rabbits' Heart (M±m)

	Mean change in outflow under influence of autologous serum	Mean difference between effects of "atherosclerotic" and control sera	
		rabbit (homologous serum)	mean
Heart of animals not receiving cholesterol (control)	−1,8±3,1	+6,4±3,3	+0,5±2,3
Heart of animals receiving cholesterol for one month	−0,2±6,1		−28,6±3,6 $P_1<0,01$ $P_2<0,001$
2 months	−32,5±8,4 $P_1<0,01$ $P_2<0,001$	−19,2±6,5 $P_1<0,05$ $P_2<0,01$	−14,8±4,1 $P_1<0,01$ $P_2<0,001$
3—4 months	−29,4±5,4 $P_1<0,01$ $P_2<0,001$	−19,9±11,0 $P_2<0,02$	−16,6±2,7 $P_1<0,001$ $P_2<0,001$
five months and more	−24,8±4,8 $P_1<0,01$ $P_2<0,001$	−3,9±6,9	−3,3±2,7

Legend: P_1 denotes a statistically significant effect, P_2 denotes significance of difference between action of serum on heart of rabbit receiving cholesterol and of control.

(according to some reports [3, 4], the coronary vasoconstrictor substance in the serum is a glucoprotein in its chemical nature). Other evidence that the coronary vasoconstrictor effect is dependent on the intensity of the biochemical changes is given by the greater decrease in outflow in the experiments with autologous serum with a low lecithin/cholesterol ratio.

It may, nevertheless, be concluded that the coronary vasoconstrictor effect of serum in atherosclerosis is not directly associated with the hypercholesteremia (despite an indication in the literature that cholesterol may have a direct vasoconstrictor action [16]). Despite the marked hypercholesteremia, autologous serum did not diminish the outflow in rabbits receiving cholesterol for one month; on the other hand, in later stages of the experiment, despite the progression of the hypercholesteremia, the effect of autologous and homologous sera did not increase, but actually diminished (see Table 1).

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