CHANGES IN HEMODYNAMIC INDICES OF DOGS WITH EXPERIMENTAL CHOLESTEROL ATHEROSCLEROSIS

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We have established that considerable hypercholesterolemia and weight changes are observed in young male dogs receiving by simultaneous enteral administration a solution of cholesterol in sunflower oil and 6-methylthiouracil in powder form for a period of 120 days. No persistent increase in the arterial pressure was observed under these conditions.

At morphological examination of the dogs, sacrificed 150 days after the beginning of feeding, the most pronounced changes were found in the coronary arteries of the heart and in the arteries at the base of the brain, i.e., in those parts of the cardiovascular system which are most commonly and most severely affected by arteriosclerosis in man.

Because of this resemblance, in the present research we made a dynamic study of the functional changes in the circulation of the blood during experimental cholesterol atherosclerosis in dogs.

EXPERIMENTAL METHOD

We used electrocardiography and the method of ballistocardiography, which enables the state of the contractile function of the myocardium to be assessed and is being used in experimental and clinical practice on an increasingly wide scale. An essential condition for the recording of the ballistocardiogram (BCG) is the provision of the most complete possible muscular rest of the animal. In acute experiments this difficulty is easily overcome by anesthesia [4], but in chronic experiments in which large numbers of repeated observations have to be made, the use of anesthesia is for obvious reasons undesirable.

The technique which we have devised [8] enables the BCG to be recorded by a direct method in chronic experiments on dogs without the use of anesthesia and fixation of the animal. Of the 12 dogs included in the experiment, the BCG was recorded regularly in ten. Two dogs were so excitable that, in spite of prolonged training, it was impossible to develop a pose reflex in them and to record the BCG and, moreover, when these animals were subsequently fed with cholesterol and 6-methylthiouracil, epileptic fits were observed.

Besides the BCG of velocity and the ECG, recorded in three standard leads by means of subcutaneous needle electrodes, determinations were also made of the velocity of spread of the pulse wave, which is known from clinical findings [2] to be increased in atherosclerosis. The pulse waves were recorded by means of two piezoelectric pickups, one of which was fixed to the left common carotid artery, exteriorized in a skin flap by operation, and the other was applied to the proximal segment of the left femoral artery. The distance between the pickups was determined as follows. The distance from the sternal notch to the carotid artery, from the carotid artery to the umbilicus and from the umbilicus to the point of registration of the pulse in the femoral artery was measured in the dog. We added the values of these segments and subtracted from the total obtained twice the distance from the sternal notch to the carotid artery, since the blood flow in the ascending aorta and the carotid artery is directed in an opposite manner to that in the femoral artery, and the distance from the sternum to the carotid artery practically corresponds to the length of the ascending portion of the aorta and also to the distance from the aorta to the carotid artery. Measurements on cadavers have shown that the distance, calculated in this way, from the heart to the femoral artery differs from the true distance by only 1-3 cm, which is negligible when the velocity of spread of the pulse wave is high [2].

The velocity of spread of the pulse wave was determined by simple arithmetical calculation from the time of delay in the appearance of the femoral pulse after the pulse in the carotid artery.

These indices were recorded at the same time as a tracing of the respiration, which is needed for interpretation of the BCG as well as for giving an idea of the animal's general condition. For recording the respiration, we used a piezoelectric pickup, fixed to the animal's chest wall.

Bearing in mind that moderate physical effort (running on a treadmill for 5 min at a velocity of movement of the belt of 6.5 km/hr) places increased demands on the heart, we considered that this would enable us to detect latent signs of failure of the coronary circulation, and

to give a better picture of the obvious signs. We therefore recorded all the indices (BCG, ECG, pulse waves and external respiration) before and after physical effort. The pickups and electrodes were connected by means of screened leads to the input of the amplifier of a 4-channel ink-recording apparatus for functional diagnosis, type 4-PFD-7. The calibration signal was of 500 μv. The pulse waves were recorded on paper moving at the rate of 6 cm/sec, and the ECG and BCG on paper moving at the rate of 3 cm/sec.

EXPERIMENTAL RESULTS

The experiments on the dogs were carried out in the morning, before the animals were fed, in standard conditions and in the prone position; before the animals were fed with cholesterol and 6-methylthiouracil they were kept under preliminary observation for 1½ -3 months. The heart rate of the dogs under these circumstances was 70-120/min, and slight respiratory arrhythmia and moderate tachycardia were observed after physical effort.

In the ECG at this period, the T wave in three dogs was positive and in one it was negative in all leads; in four dogs it was negative on lead I only; in one dog the ST interval in lead I was below the isoelectric line.

In the control group, consisting of two dogs, which received 6-methylthiouracil for 90 days, the T wave was positive in the three standard leads, and apart from a slight fall in the voltage in lead I, we found no changes in the ECG at this period. In the animals of the experimental group, tachycardia appeared 2-2½ months after the beginning of feeding, and was especially marked after physical effort (in some dogs the quickening of the heart rate reached 100%). The voltage of the ventricular complex QRS was decreased, especially in lead I. Changes and inversion of the T wave developed in different leads (most often in lead III), displacement of the ST interval above and below the isoelectric line was observed, especially in leads I and III (Fig. 1). In the course of feeding of the dogs, these phenomena became more pronounced and the T wave in the ECG of some dogs became hardly perceptible, whereas in others it increased in size and equalled in magnitude the height of the R wave. In some dogs the T wave became rounded in shape and the P wave became smaller in size and smoother in shape. In four dogs an extrasystolic arrhythmia appeared, at first coming on before effort and disappearing afterwards; later, however, on the contrary, the extrasystoles appeared most often after physical effort. This phenomenon is evidently explained by the different situation and degree of the developing atherosclerotic changes in the coronary vessels. At first, with slight changes in the arteries of the heart, these vessels were dilated under the influence of physical effort and the blood supply to the myocardium improved. Later, when more advanced changes had developed in the arteries, the vessels were incapable of adequately nourishing the heart to cope with the increased demands made on the cardiac muscle by physical effort, and the conducting system of the heart could not ensure the regular rhythm of the contractions. At this period moderate physical effort became too much for the animals, and they fell on the treadmill after 2-3 min, running only 300-350 m at a velocity of 6.5 km/hr. The ECG showed signs of atrioventricular block, and isolated P waves appeared on a background of the extrasystolic arrhythmia. The ECG changes, especially after physical effort, revealed abnormalities in the dogs similar to those observed in patients with coronary insufficiency [1] and also in dogs with experimental cholesterol atherosclerosis according to the findings of other authors [5]. The opinion is held that the ECG of dogs

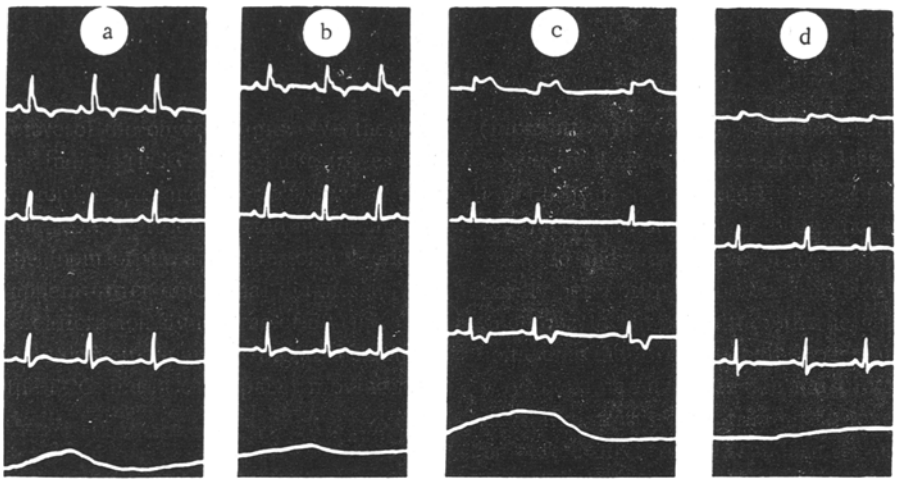

Fig. 1. Electrocardiogram of dog no. 7 in three standard leads. Significance of the curves (from above, down): I, II, III) ECG leads; respiration. a) Before feeding on cholesterol and 6-methylthiouracil, at rest; b) after effort; c) 2 weeks after cessation of feeding, at rest; d) after effort.

with experimental atherosclerosis is unchanged [9]. Disturbance of the circulation in the myocardium led to changes in the relationships of the ballistic forces, and was investigated by repeated recording of the BCG. The ballistographic complexes on the initial tracings had a well-marked constancy of shape and amplitude in the phase of expiration, and in inspiration, in consequence of respiratory arrhythmia, were nearly always superimposed on each other. In expiration the H wave was smaller than I, J, and K; the I wave was smaller than J and K; J was smaller than or equal to K. Well-marked atrial and diastolic waves were observed. After physical effort the complexes were unaltered provided that the dogs did not develop severe dyspnea and tachycardia. As feeding of the animals with cholesterol and 6-methylthiouracil continued, their BCG underwent definite changes. The general amplitude of the complexes fell significantly and all the waves became rounded and smoothed. Starting after $1\frac{1}{2}$-2 months, the H wave decreased and then increased in size, and the "early" M waves on the BCG became clearly visible, which was a sign of weakening of the force of contraction of the heart. The I wave was greatly diminished, which also was a sign of the weakening of the contractile function of the myocardium in the phase of expulsion. The J wave was usually split up after physical effort, which was a sign of asynchronism of the expulsion of blood from the right and left ventricles. The K wave was deepened, which also suggested weakening of the expulsion of blood into the aorta. The atrial waves were decreased in size and the diastolic waves were reduced in some dogs and enlarged in others. The character of the changes in the BCG thus demonstrated weakening of the contractile function of the myocardium, which is observed in human subjects in coronary insufficiency [3, 6]. In some dogs the changes in the ECG and BCG developed along parallel lines; in the majority of the animals the changes in the BCG appeared earlier than those in the ECG; the BCG of the control dogs was unchanged.

The velocity of spread of the pulse wave in the period of preliminary observation of the dogs was from 7.05 to 10.8 m/sec, and in the course of the experiment it sometimes (from experiment to experiment) was changed by 10-15%, which could be considered to be physiological variations in the tone of the vessels [2]. The velocity of spread of the pulse wave is almost entirely determined by the degree of elasticity of the aortic compression chamber, and to a lesser degree by the force and rapidity of the expulsion of blood into it from the left ventricle [7]. According to the BCG, findings, the contractile function of the myocardium in the experimental dogs was considerably weakened.

On the other hand, the elasticity of the aorta and the main arteries was unchanged, which is understandable because subsequent morphological investigations of the aorta of the experimental dogs revealed no significant changes in their structure apart from a varying degree of lipoidosis. The increase in the velocity of spread of the pulse wave, frequently observed in clinical practice, must evidently be attributed to the gross morphological changes in the aortic wall with the proliferation of connective tissue, arising at a later stage of atherosclerosis, i.e., when signs of sclerosis are well marked.

The importance attached by clinicians to the velocity of spread of the pulse wave in the diagnosis of the early stages of atherosclerosis [2] is not, therefore, supported by our experimental findings.

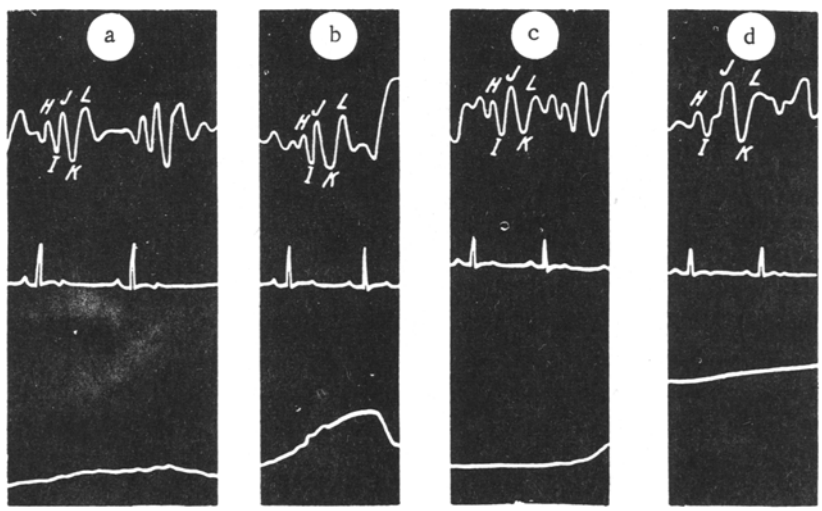

Fig. 2. Direct ballistocardiogram of velocity in dog no. 7. Significance of the curves (from above down): BCG; ECG lead II; respiration. a) Before feeding with cholesterol and 6-methylthiouracil, at rest; b) after effort; c) 2 weeks after cessation of feeding, at rest; d) after effort.

SUMMARY

In dogs with experimental atherosclerosis the decrease of the ECG voltage was greater and occurred more often in the first lead. Changes and inversion of the T wave, displacement of the ST interval above and below the isoelectric lines, extrasystolic arrhythmia, and signs of atrioventricular block were also noted here. The BCG showed a reduction of the total amplitude, sloping of the BCG wave complexes, and early M, splitting of wave I, and deepening of the K. The changes in the ECG and BCG pursued the type observed in patients suffering from coronary insufficiency. The velocity of the pulse wave spread remained unchanged and any alterations therein apparently set in only at the later stages of atherosclerosis.

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