# DESCRIBING THE ELECTROCARDIOGRAPHIC CHANGES IN DOGS WITH EXPERIMENTAL ATHEROSCLEROSIS UNDER CONDITIONS OF LONG OBSERVATION

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The definite ideas recently formulated as to the morphology and morphogenesis of atherosclerosis are chiefly based on the widely known and accepted research of Russian pathologists [1, 2, 4, 5, 8]. These works stress experimental reproduction of atherosclerosis in animals and systematic comparison of the morphological data obtained experimentally with the corresponding changes in man at different stages in the development of the pathologic condition. But, although these works on the problem of atherosclerosis are of great significance, extensive exploitation of the physiological experiment is needed to explain the primary pathogenic mechanisms of its development.

Besides the choice of animal, one must also take into account in reproducing a biological model of atherosclerosis the slow and gradual character of the development of this process in man. The initial insidious stage in the development of atherosclerosis, primarily associated with disturbances in the area of nervous regulations [4, 14], undoubtedly deserves particular attention and requires special experimental methods for its demonstration.

In experiments on dogs, the use of large cholesterol loads combined with strong influences on the metabolic processes (suppression of thyroid gland function) seems to give results which differ greatly from the functional changes which take place in the organism during the natural development of atherosclerosis, especially in the initial stages. In this respect, it would seem that the experimental pathologic condition could be more efficiently created by employing pathologic influences on the organism which are milder, but of longer duration. One can also assume that compensatory changes would be more apparent under conditions of slowly developing pathologic changes, making it possible to study at the same time the dynamics of the functional disorders and the mechanisms of their compensation.

Our work, which was based on the above ideas, consisted of pathologic-anatomical examination of the material after two and three-year systematic functional investigations, performed on the same groups of dogs throughout, during the development of experimental atherosclerosis in the animals.

The influences employed in the work to induce atherosclerotic changes in the dogs' cardiovascular systems were relatively mild.

We were particularly interested in the possibility of comparing the functional changes which occurred in these investigations with the known facts concerning the morphogenesis of atherosclerosis which indicate the variable course of this pathologic condition [1, 2, 4, 5, 8, 14]. It seems rational to assume that the fluctuations and cycles in the morphological picture of atherosclerosis are connected with the changes in the mechanisms which regulate the physiological functions of the organisms and the variations in the metabolic processes at different stages in the development of the pathologic condition.

This article reports some results of electrocardiographic research performed on dogs with experimental atherosclerosis. We were largely concerned with the changes in the cardiac activity of the animals which could be detected with the aid of extra stimulations (intravenous adrenalin injection) at a stage in the experiments when the resting electrocardiogram did not yet show pathologic changes.

## EXPERIMENTAL METHODS

The experiments were performed on five dogs aged 5-7 years and weighing 7-10 kg. Methylthiouracil was administered enterally to the dogs daily throughout the investigations in gradually decreasing doses, beginning with 1 g during the first 1-2 months of the experiment and subsequently decreasing to 0.3 g. Chol-

esterol was administered with the food (without being first dissolved in oil) in a daily dose of 2-3 g. Periodically, generally during 10 months of the first 1½ years of observation, the animals each received 30,000-50,000 units daily of vitamin D. An intravenous infusion (into the anteroexternal vein of a posterior extremity) of a 1:10,000 solution of adrenalin in a dose of 0.2-0.6 ml was used as one of the functional tests. The adrenalin administration was accompanied by a continously recorded electrocardiogram (taken with an ÉKP-5 apparatus in the second standard lead with the dog standing) and was used at least thrice monthly under chamber conditions; the experimental setup was kept strictly constant throughout the two and three-year investigations. We used the electrocardiograms of five intact dogs, recorded on a background of the adrenalin test, as the control.

## EXPERIMENTAL RESULTS

With the adrenalin test, the first changes on the electrocardiogram were apparent in individual dogs the 5th-6th and 8th months of the administration of the preparations inducing the development of atherosclerosis in the animals. As the experiment continued, the pathologic reactions of the heart increased in degree and duration, as well as in the speed with which they were manifested after the administration of adrenalin to the animal. These disturbances lasted 1-2 minutes and were distinguished by pronounced polymorphism. Some of the disturbances in myocardial automatism and conductivity which we observed in the experiments with the administration of adrenalin to the dogs are shown in Figs. 1, 2, and 3.

From the data presented, it is evident that the pathologic changes in the electrocardiographic elements occurred on a background of a sometimes extremely pronounced central effect induced by the adrenalin and, therefore, were to a definite degree associated with changes in the experimental animals of the functional condition of the cardiac center of the vagus nerves. The same doses of adrenalin sometimes retarded the rate of the cardiac contractions in the intact dogs, but this retardation was never as great as in the animals with developing experimental atherosclerosis. At first, the pathologic changes in the electrocardiogram observed with the adrenalin test were brief, the curve returning to its original form at the 40th-60th second of the recording. Besides the retardation of the rate of the cardiac contractions observed during the first 10-20 seconds of the recording, the electrocardiogram also showed changes in the form and direction of the T wave and considerable changes in atrioventricular conductivity, usually tending to retard the latter. Soon, single ventricular and blocked atrial contractions, ventricular extrasystoles, or premature blocked atrial contractions began to attend the administration of adrenalin.

At subsequent stages of the investigation, the disturbances of the principal myocardial functions induced

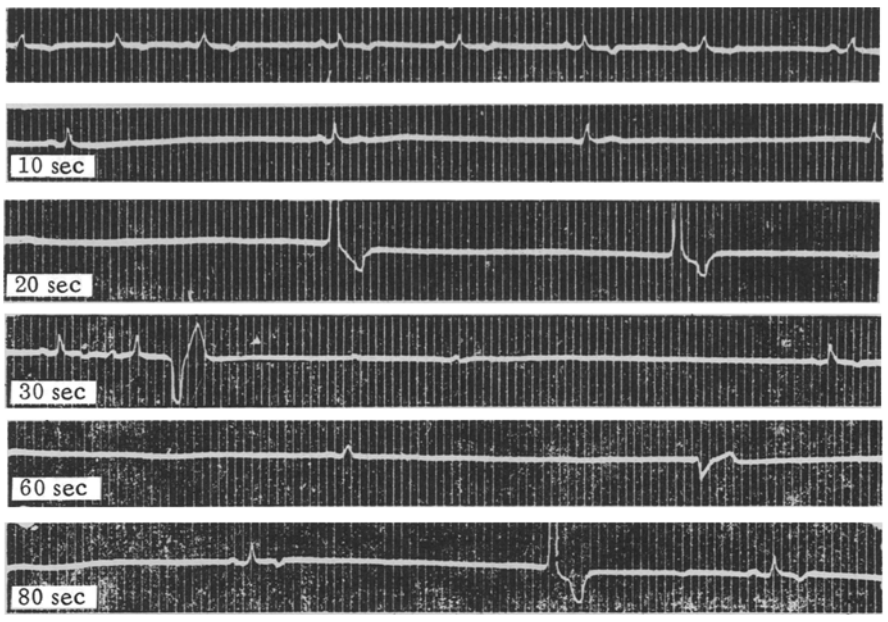


Fig. 1. Electrocardiogram of dog Damka taken April 13, 1957. Top) Initial recording; below) subsequent recordings at different times after the administration of 0.4 ml of the adrenalin solution (1:10,000). Before infusion: RR) 0.55-0.90 sec; PQ) 0.10-0.11 sec; QRS) 0.05-0.06 sec; QT) 0.22-0.23 sec. After infusion: RR) 0.55-2.6 sec; PQ) 0.08-0.15 sec; QRS) 0.06-0.07 sec; QT) 0.21-0.25 sec. Tenth second-change in direction of T wave; starting 20th second-periods of idioventricular rhythm and wandering pacemaker, single ventricular extrasystoles.

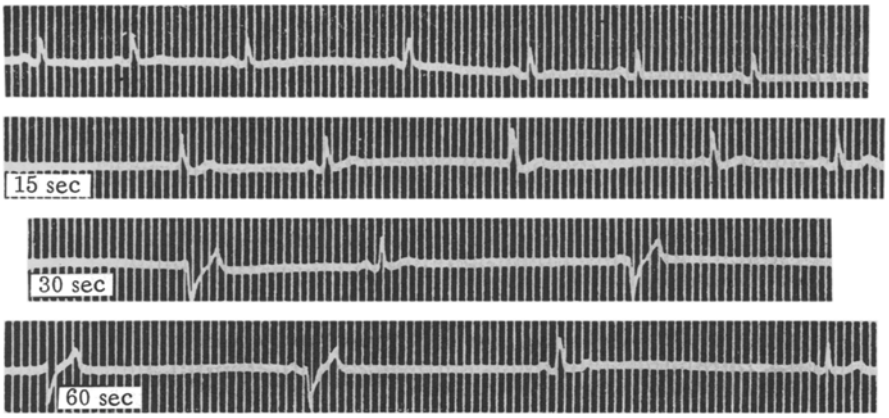


Fig. 2. Electrocardiogram of dog Ryzhka taken January 29, 1957. Top) initial recording, below) subsequent recordings at different times (15, 30 and 60 seconds) after the administration of 0.2 ml of a 1:10,000 adrenalin solution. Fifteenth second: combination of nodal (from middle of atrioventricular node) and sinus rhythms (wandering pacemaker). Subsequently apparent are single ventricular contractions and typical Wolff-Parkinson-White syndrome complexes. PQ) 0.04--0.6 sec; QRS) 0.08 sec.

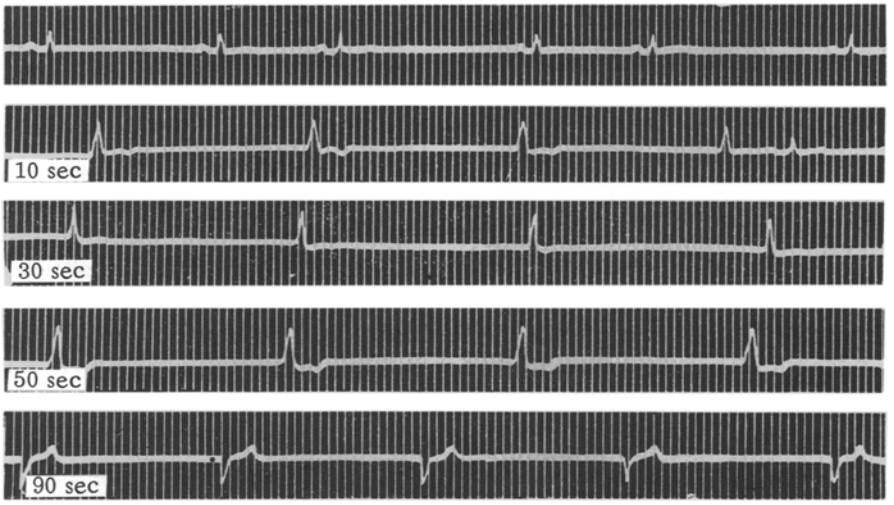


Fig. 3. Portions of electrocardiogram of dog Ryzhka taken March 21, 1957, 10, 30, 50 and 90 seconds after the administration of 0.4 ml of the 1:10,000 adrenalin solution. Successive depression of automatic centers of cardiac excitation with transition to idioventricular rhythm. Pronounced wandering pacemaker. Tenth second: change in direction of T wave. Nodal rhythm with impulses from middle part of atrioventricular node (10th-30th second) combined with intraventricular block. QRS) 0.08 second.

by the adrenalin test became more pronounced and longer lasting, even when the doses of adrenalin were reduced. As well as more pronounced bradycardia, one could observe combinations of complete heart block and ventricular extrasystoles, different types of partial atrioventricular block, periodic coupled rhythm, total depression of the sinus discharges with a gradual dislocation of the focus of stimulation to automatic centers of the II rank (usually nodal rhythm with impulses originating from the middle part of the atrioventricular node), and change-over of the heart to idioventricular rhythm. The wandering pacemaker symptom was extremely pronounced. Particular attention was attracted by the appearance on the electrocardiogram of complexes typical of the Wolff-Parkinson-White syndrome (see Fig. 2), which, in one of the dogs, was often combined with

short periods of paroxysmal tachycardia. As far as is known, this was the first time that this paradoxical disturbance of intraventricular conduction has been clearly observed in classic form under conditions of the development of a pathologic condition in a chronic experiment. The appearance of this electrocardiographic syndrome, the nature of which is still a mystery, was associated with the action of adrenalin on a background of the development in the animals of the given pathologic condition.

In this connection, it is interesting to note that A.V. Lirman [11, 12] observed the Wolff-Parkinson-White syndrome in acute experiments on dogs, stimulating certain sympathetic cardiac ramuli with faradic current. Studying the topography of these ramuli, the author discovered that they take part in the innervation of the atrioventricular system (4th-3rd nerve plexuses and ganglionic areas according to Vorob'ev-Zhuravlev).

Analysis of the electrocardiographic changes described above in the experimental animals under the influence of adrenalin permits the hypothesis that a condition of functional instability of the cardiac conducting system develops in dogs even in the early stages of the atherosclerotic process.

In our experiments, doses of adrenalin which did not cause pathologic changes in the cardiac activity of intact animals, under conditions of the development of atherosclerosis, became extraordinarily stimulating to the organism, even in the initial stages of the experimental condition, causing insidious forms of disturbance of its compensatory mechanisms. These disturbances chiefly affected the intracordal nerve apparatuses and the region of the atrioventricular node in particular, as the Wolff-Parkinson-White phenomenon is, according to experimental data [11, 12, 18], associated with change in the functional condition of the structure elements of the atrioventricular node.

The known facts concerning the considerable change in vascular reactivity, specifically to adrenalin, which occurs in hypercholesteremia and experimental cholesterol atherosclerosis [3, 6, 9, 10, 13, 15, 16, 17] permit the hypothesis that the pathologic changes which develop in the region of the autonomic innervation of the vascular system of the heart disturb the blood supply of various parts of the conducting system by altering their functional condition.

This creates a pathologic background for the extracardial influences (also altered in atherosclerosis) which realize the changes we observed on the electrocardiograms.

The pathologic reactions of the heart to adrenalin in the experiments were striking both for their extraordinary polymorphism and the periodic nature of their manifestation. The electrocardiograms obtained with our systematic use of the adrenalin test throughout the investigations showed the pathologic phenomena to have periods of increase and decrease. In cases of the latter, electrocardiographic disturbances could be induced simply by increasing the dose of adrenalin. In several cases, the functional tests showed a general lack of pathologic changes; specifically, the pathologic changes apparent on the electrocardiogram of the dog Damka taken April 13, 1957 (Fig. 1) were less pronounced on the recordings taken April 27, 1957 and completely absent on May 9 and 27, 1957. Neither was any central adrenalin effect apparent in these instances. The administration of adrenalin to the same dog on May 28, 1957 again induced pathologic changes in the electrocardiogram, which then again gradually disappeared in the subsequent investigations. Towards the end of the 2nd year of observations on this animal, we observed a considerable decrease in the voltage of all the electrocardiogram waves, and the disturbances noted during the functional tests were in most cases confined to variations in the condition of atrioventricular and intraventricular conduction and to changes in the T wave.

The above dynamics of the electrocardiographic indices were observed to varying degrees in all the experimental animals, indicating the fluctuation of the functional condition of the cardiovascular system during the development of experimental atherosclerosis in dogs.

In our investigations, the indices of the lipid-cholesterol metabolism, the blood pressure level, and the condition of the vascular reflexogenic zones [19] also demonstrated a similar picture of phasic functional changes varying in degree and cycles. Comparison of these functional shifts with the data indicating the fluctuating course of the morphological changes in atherosclerosis (also observed on our material [7]) permit one to propose the existence of certain genetic links between them.

## SUMMARY

The author presents data concering the dynamics of the ECG changes occurring in dogs following an intravenous injection of adrenalin under conditions of experimental atherosclerosis. As a result of 2- and 3-year systematic investigations, it was established that the adrenalin test aids in detecting latent forms of disturbed physiological compensatory mechanisms, even at the early stages in the development of experimental atherosclerosis. This was manifested in the ECG by various combinations of pathological rhythms of cardiac activity; the negative cardiac shifts were polymorphic, indicating pronounced functional instability of the cardiac conducting system. As noted, the disturbances of the main functions of the cardiac muscle observed in the adrenal tests are cyclic in character with periods of rise and fall in the negative shifts. This is associated with the varying course of morphological changes occurring in atherosclerosis.

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