THE INFLUENCE OF THE EXTRACARDIAC NERVOUS SYSTEM ON THE FUNCTIONAL STATE OF THE HEART IN EXPERIMENTAL MYOCARDIAL INFARCTION

COMMUNICATION II. THE EFFECT OF REPEATED ELEVATION OF THE TONUS OF THE VAGUS NERVE CENTER ON THE COURSE OF EXPERIMENTAL MYOCARDIAL INFARCTION

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Laboratory investigations on dogs with experimental myocardial infarction have shown that an increase in the tonus of the vagus nerve center by the injection of adrenalin against a background of the action of morphine, or stimulation of the peripheral cut end of the vagus nerve by means of an induction coil, strengthening the contractions of the ventricles of the heart, leads to a lack of correlation between the strength of the contractions and the blood supply of the myocardium. The ensuing functional overload brings about the more rapid and extensive development of myocardial infarction of the ventricles of the heart [8, 9]. The importance of the factor of functional overload is confirmed by the work of several authors [1, 2, 11, 12].

Studies of the pathogenesis of myocardial infarction have shown that in the first days after ligation of the descending branch of the left coronary artery, polytopic ventricular extrasystoles develop, to a large extend associated with the influence of the vagus nerve on the heart [8]. The role of the vagus nerve in the production of extrasystoles has been pointed out by other workers [3, 6, 13, 15, 16].

In the most recent investigations in the laboratory it has been found that, during the first 5-6 days after the onset of experimental myocardial infarction, an increase in the tonus of the vagus center does not cause a slowing of the rhythm, but increases the extrasystoles of the ventricles of the heart. On the 5th-6th day after operation, the inhibitory action of the vagus nerve on the heart is restored, and this coincides with disappearance of the extrasystoles [10]. A change in the reactions of the heart in response to stimulation of the vagus nerve, in association with myocardial damage, has also been observed by other workers [5, 6, 14].

These findings enabled an approach to be made to the study of the action of the heart and of the effect of an increase in the tonus of the vagus center on the heart in the later stages of development of experimental myocardial infarction in dogs of different ages. This question is dealt with in the present paper.

EXPERIMENTAL METHOD

Chronic experiments were conducted on 5 healthy dogs of different ages. In order to produce an experimental myocardial infarct in these animals, the descending branch of the left coronary artery was ligated. The operations were performed in sterile conditions under morphine-urethane or morphine-kemithal anesthesia. The development of an infarct was confirmed electrocardiographically and by subsequent morphological examinations. The tone of the vagus center was raised in the chronic experiments by injection of morphine and calcium chloride.

Morphine was injected subcutaneously (1-2 ml of a 1% solution), and the calcium chloride intravenously in the form of a 10% solution, the dose being 0.05 g/kg body weight. The chronic experiments on the dogs Donor and Lysyi concluded with acute experiments under morphine-kemithal anesthesia, in which both vagus nerves were divided and their peripheral cut ends were stimulated by an induction current.

Recordings were made of the electrocardiograph of all the experimental animals using the 3 standard leads, and using lead II for prolonged observations on the action of the heart. Needle electrodes were introduced subcutaneously. The heart rate was counted and the heart sounds and murmurs auscultated during the experiments. In the chronic experiments the dogs were made to stand on the apparatus, and in the acute experiments the arterial pressure was recorded with a mercury manometer. The peripheral cut end of the vagus stimulated by means of a DuBois-Reymond induction apparatus from a 5v accumulator.

EXPERIMENTAL RESULTS

We give a brief description of the results of the experiments on the dogs Donor, Volchok, Starik, Lysyi and Rek.

The dog Donor. Male, weight 28 kg, age 4 years. Mobile, balanced. on January 20, 1958 the descending branch of the left coronary artery was ligated in its middle third. The dog was kept under observation for 114 days. After operation, polytopic ventricular extrasystoles appeared, lasting 8 days. Raising the tonus of the vagus center on the 9th day caused considerable left ventricular extrasystoles. On the 11th day an attack of paroxysmal ventricular tachycardia was observed, which lasted about 24 hours. On subsequent days an increase in the tonus of the vagus nerve center led to slowing of the cardiac contractions; there were no extrasystoles. Throught the whole period of observation on the dog there was no change in its behavior. The heart rate was between 100 and 120 beats per minute. In the acute experiment, in response to stimulation of the peripheral cut end of the vagus nerve on the 114th day a slowing of the rate was observed, with isolated extrasystoles, which continued after cessation of the stimulation.

The heart at autopsy: in the anterior wall of the left ventricle there is a whitish scar, measuring 5 × 5 cm; thickness of the left ventricle 1.5 cm, of the right ventricle 0.5 cm.

The dog Starik. Male, weight 16 kg, age about 12 years. Tranquil, inhibited, sluggish. The dog remained under observation for 42 days. On March 26, 1958 the descending branch of the left coronary artery was ligated in its upper third. Only 40 minutes after operation low-voltage extrasystoles appeared; the heart rate quickened. On the 7th day, intravenous injection of calcium chloride against a background of the action of morphine led to continuous extrasystoles which lasted one hour. Electrocardiogram on the 9th day: T_1—negative, $T_{2,3}$—above the isoelectric level, T_3—high, coronary, monophasic curve. Elevation of the tonus of the vagus center on the 10th day was accompanied by extrasystoles and by atrioventricular block. The monophasic curve persisted in this experiment; on the following days the T wave reached the same value as the R wave (Fig. 1, a) and isolated extrasystoles of different voltages and shapes were present. Injection of morphine on the 14th day caused bigeminy, but after the intravenous injection of calcium chloride, against a background of slow contractions (54 per minute), attacks of paroxysmal tachycardia appeared, lasting 10-15 seconds, which then changed into continuous paroxysmal ventricular tachycardia (see Fig. 1, a,b,c). The attack of paroxysmal tachycardia continued for over 24 hours. On auscultation a systolic murmur and alternation were heard. On the 16th day the attack of paroxysmal ventricular tachycardia came to and end, leaving only solitary extrasystoles; T_3—high, trigeminy.

On the 17th day the T wave became low, and on the 31st day—negative, and T_2 remained high, with bigeminy. An increase in the tonus of the vagus center on the following days led to a slowing of the pulse rate, to the appearance of extrasystoles, to atrioventricular block (see Fig. 1, d) and to elevation of the T_2 wave. Increase in the tonus of the vagus center on the 42nd day caused atrioventricular block; the T_2 wave was considerably elevated. Ventricular fibrillation—sudden death of cardiac origin—supervened 25 minutes after injection of calcium chloride.

The heart at autopsy: in the anterior wall of the left ventricle there is a whitish, stretched scar, triangular in shape, measuring 4 × 2.5 × 2.5 cm; the wall of the left ventricle in the region of the scar is thinned and translucent.

The dog Volchok. Female, weight 15 kg, age 5 years. Very mobile, spirited. On April 21, 1958 the descending branch of the left coronary artery was ligated in its upper third. The dog was under observation in the

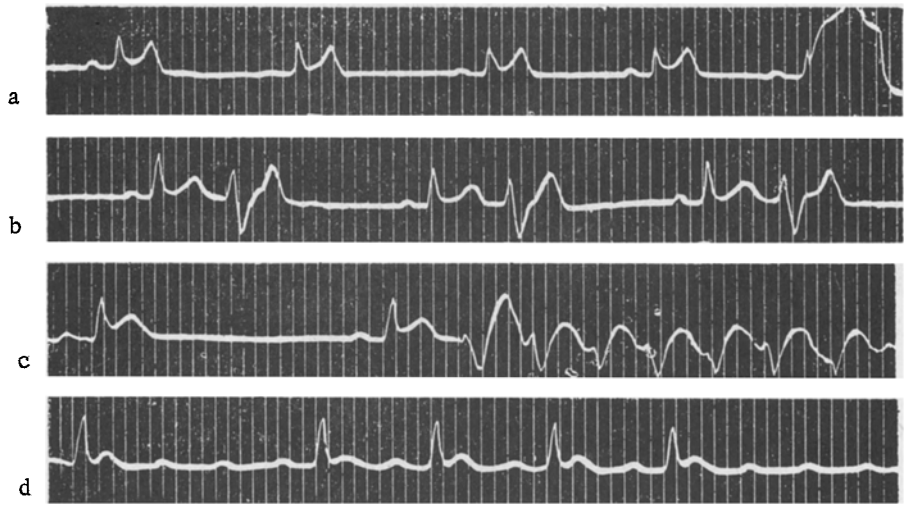

Fig. 1. Changes in the excitation of the heart with elevation of the tonus of the vagus nerve center in the dog Starik . a) Experiment on April 7, 1958, electrocardiogram (lead II) on the 14th day after ligation of the descending branch of the left coronary artery, before injection of morphine—monophasic curve; b) the same experiment, electrocardiogram (lead II) after injection of morphia—bigeminy; c) the same experiment, electrocardiogram (lead II) after the intraveous injection of calcium chloride—attack of paroxysmal ventricular tachycardia against a background of slow contractions of the heart; d) experiment on April 17, 1958, 24th day after ligation of the descending branch of the left coronary artery, electrocardiogram (lead II) after intravenous injection of calcium chloride—atrioventricular block.

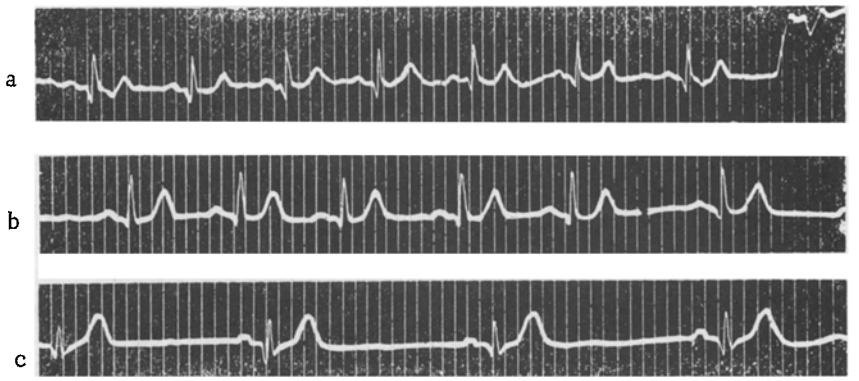

Fig. 2. Changes in the T_2 wave after elevation of the tonus of the vagus venter in the dog Volchok (16th day after ligation of the descending branch of the left coronary artery). a) Electrocardiogram (lead II) before injection of morphine, pulse 130 per minute; b) electrocardiogram (lead II) after injection od 2 ml of a 1 % solution of morphine , pulse 110 per minute; c) electrocardiogram (lead II) after injection (intravenously) of 10 ml of a 10 % solution of calcium chloride, pulse 76 per minute.

laboratory for 60 days. In the first 24 hours extrasystoles appeared, polytopic or in the form of bigeminy, and continued for 4 days. On the 5th day, after the tonus of the vagus center had been raised by injection of morphine , single left ventricular extrasystoles appeared; after the intravenous injection of calcium chloride considerable polytopic extrasystoles were observed, with elevation of the T wave, respiratory arrhythmia, slowing of the heart

rate from 100 to 56 per minute, increased heart sounds and a systolic murmur. On the 6th day the polytopic ventricular extrasystoles were still present. On the following days no extrasystoles were observed, Q_1 was very deep and T_3 below the isoelectric level.

On subsequent days (16th, 19th, 23rd, 25th, 29th) an increase in the tonus of the vagus center caused ventricular extrasystoles, sometimes polytopic and predominantly right ventricular, sometimes in the form of bigeminy, considerable elevation of the T_2 wave, respiratory arrhythmia and a slowing of the heart rate. The appearance of extrasystoles and elevation of the T_2 wave were observed after injection of morphine alone, but more especially after the intravenous injection of calcium chloride (Fig. 2). The T_2 wave reached the height of the R_2 wave, and sometimes even exceeded it. At the end of the experiment (after 1-1½ hours) the T_2 wave returned to its original magnitude. On the 36th, 43rd and 46th days, elecation of the tonus of the vagus nerve center led to the changes already mentioned and, in addition, atrioventricular block was observed after injection of calcium chloride.

On the 60th day the dog's general condition was satisfactory. On the electrocardiogram Q_1 was sharply pronounced and T_3 was below the isoelectric level. After injection of morphine the dog remained mobile and spirited, came into the laboratory by itself, jumped on to the bench and then, 2 minutes later, unexpectedly hung limp in its straps—sudden death of cardiac origin supervened (ventricular fibrillation).

The heart at autopsy: in the anterior wall of the left ventricle, below the site of the ligature, an aneurysm measuring 3 x 3 x 3 cm is seen; in this situation the wall of the left ventricle is grossly thinned, translucent and flabby; the thickness of the left ventricle is 2 cm, and of the right, 0.5 cm ; the lungs , liver and kidneys are congested.

The dog Lysyi. Male, weight 20 kg, age about 15 years (canine and incisor teeth sharpened, fur lacking in lustre , cornea cloudy). Relatively immobile, sluggish. On May 22, 1958 the descending branch of the left coronary artery was ligated in its upper third. The dog was kept under observation for 30 days. In the first few days after operation polytopic ventricular extrasystoles appeared and the heart rate was quickened to 120-140 per minute. On the 5th day, in order to raise the tonus of the vagus center, calcium chloride was injected intravenously against a background of the action of morphine . The initial state of the dog was satisfactory. The pulse rate was 108 per minute; solitary extrasystoles were present.

In the first minutes after the injection of calcium chloride the animal's condition deteriorated sharply : weakness of the action of the heart developed and the dog hung limp in its straps, showing signs of severe dyspnea; on auscultation the heart sounds were muted and there was a systolic murmur. On the electrocardiogram there was a significant increase in polytopic ventricular extrasystoles (mainly right ventricular), gross changes were present in the PQRST complex (lagging and ill-defined P wave, splitting of the apex of the R wave, T wave sometimes positive and sometimes negative, and so on). The elevation of the T_2 wave must be particularly mentioned. A gradual slowing of the heart rate (to 50 per minute) was observed 30-40 minutes after injection of calcium chloride. Parallel with this, the changes in the PQRST complex disappeared and the condition of the dog improved. On the 6th day no extrasystoles were observed and the pulse rate was 100 per minute; the general condition was satisfactory. On the 9th, 13th, 27th and 29th days after operation, elevation of the tonus of the vagus center led to the appearance of ventricular extrasystoles and to slowing of the cardiac contractions. Under these circumstances elevation of the T_2 wave was observed to appear occasionally after injection of morphine, and particularly of calcium chloride. The T_2 wave reached the height of the R_2 wave or even exceeded it. In the acute experiment, on the 30th day stimulation of the peripheral cut end of the vagus nerve led to the appearance of single left ventricular extrasystoles against a background of the ordinary action of the vagus nerve. Extrasystoles were also observed after stimulation had ceased.

The heart at autopsy: below the site of the ligature there is a whitish scar measuring 5.5 x 2.5 cm, oval in shape; there are recent hemorrhages beneath the endocardium of the left ventricle; the thickness of the wall of the left ventricle is 1.5 cm, and of the right , 0.8 cm; the heart muscle is flabby.

The dog Rek. Male, weight 25 kg, age 6-8 years. Balanced. On May 29, 1958 the descending branch of the left coronary artery was ligated in its upper third. On the second day continuous polytopic ventricular extrasystoles appeared and the heart rate was quickened to 150-160 per minute. On the 6th day the extrasystoles gradually diminished and the heart rate reached its original value—70-80 per minute. On the 7th day the polytopic ventricular extrasystoles disappeared. Elevation of the tonus of the vagus center on the 7th and subsequent days did not cause extrasystoles, but led to slowing of the heart rate (to 52 per minute).

The young dogs tolerated experimental myocardial infarction quite well. The disturbance of cardiac activity was shown in these animals by the appearance of polytopic ventricular extrasystoles on the first or second day after operation, continuing usually for 5-6 days. During this time the vagus nerve did not exert its action on the heart in the form of slowing of the rate of contraction; elevation of the tonus of the vagus center led to intensification of the extrasystoles. Depending on the development of the collateral blood supply of the heart, its functional state gradually recovered, the extrasystoles disappeared and , on the 5th-6th day, the ordinary inhibitory influence of the vagus nerve on the heart reappeared. An example of this is the dog Rek , whose polytopic ventricular extrasystoles appeared on the second day after ligation of the descending branch of the left coronary artery, and lasted for 6 days . On the following days, elevation of the tonus of the vagus center caused merely a slowing of the heart's contractions. In the dog Donor, the extrasystoles lasted a little longer—8 days . On the 9th day, elevation of the tonus of the vagus center led to extrasystoles , and on the 11th day an attack of paroxysmal tachycardia was observed, which lasted about a week. On the following days, on raising the tonus of the vagus center, the usual action of the vagus nerve on the heart was observed. In the dogs Rek and Donor, thanks to the development of collateral coronary vessels, the cardiac activity was restored to normal.

It was shown in our laboratory that elevation of the tonus of the vagus center causes not only a slowing of the rate but also a strengthening of the contractions of the ventricles of the heart [7] . In consequence of this, during the development of myocardial infarction, disproportion may arise between the strength of the cardiac contractions and the blood supply of the myocardium, which considerably complicates the course of the infarct and even leads to sudden death of cardiac origin. This was clearly seen in the experiments on the dogs Volchok and Starik. Volchok was middle-aged and very mobile, and at first withstood the myocardial infarction with ease. As a result of repeated elevation of the tonus of the vagus center (10 times) the state of the cardiac activity was sharply altered. After elevation of the tonus of the vagus center on the 46th day, extrasystoles appeared and there was a considerable elevation of the T_2 wave. In subsequent experiments atrioventricular block took place. On the 60th day, elevation of the tonus of the vagus center, in conjunction with considerable physical effort (after receiving an injection of morphine, the dog ran, jumped on to the bench), led to sudden death—ventricular fibrillation supervened. In Starik , with atherosclerotic changes in the coronary vessels (age 12 years), as also in Volchok, after raising the tonus of the vagus center extrasystoles appeared, sometimes polytopic, sometimes in the form of bigeminy or trigeminy, together with atrioventricular block and elevation of the T_2 wave. In addition, attacks of paroxysmal ventricular tachycardia were observed, against a background of slow contractions. The tonus of the vagus center was raised 6 times in Starik; the last elevation, on the 42nd day, led to ventricular fibrillation.

The importance of the functional strain factor was confirmed also by the experiments with the old dog, Lysyi. This animal almost died from an attack of cardiac weakness when, on the 5th day after ligation of the descending branch of the left coronary artery, the tonus of the vagus center was elevated.

It is clear from these experiments that when the functional condition of the heart is altered (myocardial infarction), elevation of the tonus of the vagus nerve center in the dogs Volchok, Starik and Lysyi caused changes in the excitation of the specific musculature; this was manifest as a disorder of the cardiac action—as extrasystoles, paroxysmal ventricular tachycardia, atrioventricular block and ventricular fibrillation.

Stress must be laid on the trend of the T wave in Volchok, Starik and Lysyi: on raising the tonus of the vagus center, besides the disturbance of the cardiac rhythm, elevation of the T wave was observed, reaching the level of the R wave and sometimes exceeding it. This elevation of the T wave demonstrates the influence of elevation of the tonus of the vagus center on the restorative biochemical processes in the myocardium of the ventricles of the heart.

Repeated elevation of the tonus of the vagus center during experimental myocardial infarction, mainly in old dogs , may thus lead to complication of the course of the myocardial infarct by causing disturbances of the rhythmic activity of the heart and changes in the biochemical processes in the heart.

SUMMARY

Experimental myocardial infarction was induced in dogs of various ages. A rise of the vagus center tone was provoked by intravenous injection of calcium chloride solution against the background of morphine action at various periods following ligation of the descending branch of the left coronary artery. Notwithstanding their

briskness, cardiac arrhythmia is observed in the animals, especially old ones, for the period of several days after ligation. It manifests itself in the form of polytopic ventricular extrasystole, bigeminy, trigeminy, ventricular paroxysmal tachycardia or atrioventricular block, with even an occasional ventricular fibrillation, terminating in sudden death. With the rise of the vagus nerve center tone in dogs suffering from experimental myocardial infarction the biochemical processes of the ventricular myocardium become changed. This becomes clearly apparent in some dogs and manifests itself in considerable changes of the T wave which approaches the R wave in its size or even exceeds it.

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