EXPERIMENTAL MYOCARDIAL INFARCTION IN CERTAIN PHYSIOLOGICAL AND PATHOLOGICAL CONDITIONS

PART I. EFFECT OF PHYSICAL STRESS ON FORMATION, COURSE, AND HEALING OF EXPERIMENTAL MYOCARDIAL INFARCTION*

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(Received June 24, 1955. Presented by A. L. Myasnikov, Member Acad. Med. Sci. USSR)

There is, in connection with the successful experimental solution of a number of problems of the physiology and pathology of the coronary circulation, an indubitable interest in the experimental study of the significance of various physiological and pathological states of the organism in determining the course and the outcome of myocardial infarction.

In this connection, we performed a series of experiments in which myocardial infarct due to interference with coronary circulation was studied in conjunction with conditions of muscular work loading, acute hemodynamic load on the left ventricle, hypertension, and atherosclerosis.

We present below our basic findings on the effect of graduated physical effort on animals suffering from experimental myocardial infarction. A separate communication will be devoted to a detailed clinical-morphological analysis of our experimental material.

The theoretical basis of the work described in the present paper lies in the well-known beneficial effect of active movements on the metabolism and general tonus in both health and sickness, and also in the existence of definite physiological evidence of the existence of vasodilator proprioceptive impulses acting on the coronary vessels, and arising in muscles during their active contraction. We could not, however, exclude from consideration the possibility that physical exertion may have an adverse effect on the cardiovascular system, in particular during the early stages of development of an infarct, owing to the imbalance between the raised oxygen requirements of the myocardium and its inadequate blood supply in the parts affected by coronary insufficiency.

There can be no doubt as to the practical importance of the question of the effect of moderate physical effort on development and healing of a myocardial infarct. This problem has not been subjected to experimental study, although in clinical practice physiotherapy is sometimes started as early as the 15-20th day after the incidence of a myocardial infarct [5], i.e. at a time when the organization of the infarct and the consolidation of the scar are not in all cases completed; with broad infarcts, fairly large portions of necrotic tissue may persist in the central zones of the infarct.

It was necessary for our investigation to produce areas of necrosis of the myocardium, of standard size and location. It has been shown in an earlier paper [1] that for the production of such standard infarcts one of the most convenient methods consists in ligation of coronary arteries, as practiced by G. F. Ivanov [3], E. S. Shakhbazyan [10], A. I. Smirnov [7], B. V. Ognev, and others. However, a serious shortcoming of this procedure is the superimposition of the serious traumatic effect of thoracotomy, which must undoubtedly influence the dimensions

* Presented at the Jubilee Scientific Session in honor of the Bicentenary of the Order of Lenin I Moscow Institute, May 14, 1955.

and the nature of the myocardial process, and which prevents the animals from making any active movements. Some authors [10] and others have effected the ligation in two stages, placing a loop of the ligature round the coronary arteries, with the free ends at the skin surface, and drawing the knot tight after healing of the wound on the chest wall. Mendlowitz, Schauer, and Gross [12] have suggested the use of a "double sliding knot" for this purpose. However, the proximity to each other of the free ends of the ligature prevents the knot from being drawn tight, and the heart is fixed to the anterior wall of the thorax by this procedure. The use of a glass cannula, proposed by Sutton [13] for externalizing the free ends of the ligature, is applicable only to acute experiments, since such a cannula must be considered to be a foreign body of considerable size, and a portal of infection.

EXPERIMENTAL METHODS

The following procedure was adopted, in order to exclude the above shortcomings. Anterior thoracotomy was performed without entering the pleural space, and the ends of the ligature, after placing a loose knot on the descending branch of the left coronary artery, were passed through the soft tissues at the margins of the incision into the chest wall (Fig. 1). After 6-7 days, when the wound was fully healed, the ligature was pulled tight, closing the coronary artery. The operation was performed under aseptic conditions, with mixed general and local anesthesia (intravenous Barbamyl, with local procaine and cocaine), and was followed by a single dose of 150,000 units of penicillin.

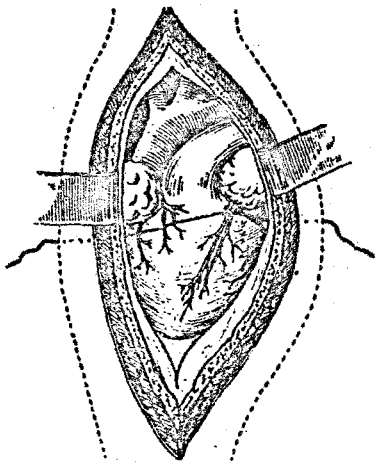

Fig. 1. Two-stage ligation of a coronary artery, with externalization of the free ends of the ligature at a distance from the margins of the chest incision. The dotted line represents the line along which the free ends pass through the soft tissues.

The experimental animals were male rabbits, weighing 2000-2500 g.

The animals were exercised, at various times after ligation and impairment of the coronary supply, twice a day for several days. The exercise consisted of moderately active running for 4 minutes in a treadwheel rotating at a rate of 5-6 rpm, which amounted, for a circumference of 2.5 m, to a speed of 12-15 m per minute.

In all, 34 rabbits were operated on, and of these 4 died during the operation, and 5 within a week of it, before tightening the knot. The ligature around the descending branch of the left coronary artery was tightened in the surviving 25 animals, after they had fully recovered from the operation. As a result, an infarct of the anterior wall of the left ventricle developed in 22 of the animals.

Two animals were exercised before tightening the knot, 3 on the 2nd-3rd day after, 2 on the 5th-7th day, 2 on the 8th-10th day, 2 on the 16th-20th day, and 2 on the 26th-30th day. Control, unexercised animals were examined at the same times after tightening the ligature, using 3, 2, 2, 1, and 1 rabbits, respectively. Two control animals in which the ligature was applied but not tightened were exercised, and two were not.

Electrocardiograms were taken for about half the rabbits before and after tightening the ligature, and at various times after development of an infarct. Blood pressure was measured in the femoral artery of 6 rabbits at the moment of tightening the knot. Respiration was measured before and after interrupting coronary circulation. The animals were killed an hour after being last exercised, and the heart was embedded in paraffin-celloidin and histopographic sections were examined. In addition to the usual histological techniques, we applied Gomory silver impregnation, and staining with toluidine blue for chromotropic substance.

EXPERIMENTAL RESULTS

Our experimental material showed that the placing of the ligature around the coronary artery did not by itself lead to any marked circulatory disturbances of the myocardium. A connective tissue reaction appears around the ligature, with presence of giant cells, and restricted scar formation takes place; muscle fiber bundles damaged by the ligature perish. Changes characteristic of myocardial infarction take place after interference with coronary

circulation, caused by tightening the ligature previously applied to the descending branch of the left coronary artery. The resulting necrosis is confined to a limited area of the anterior wall of the left ventricle, the anterior papillary muscle, and the anterior part of the ventricular septum. The infarct is always smaller than the region supplied by the ligated artery, pointing to the presence of a well-developed collateral circulation.

The changes in the electrocardiogram are typical of those found in ischemia and necrosis of the anterior wall of the ventricle (Fig. 2).

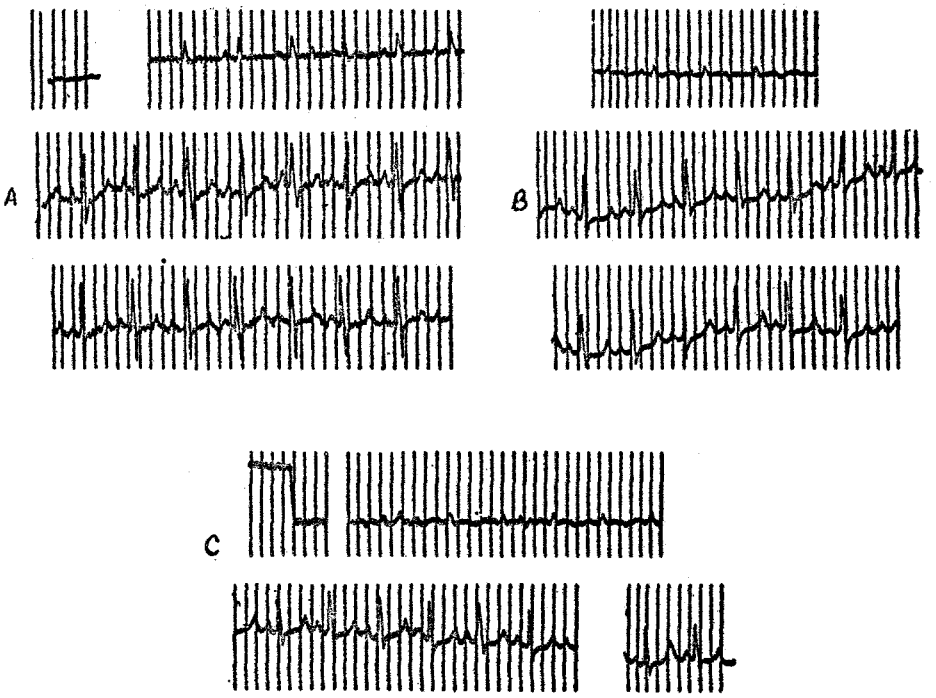

Fig. 2. Electrocardiograms taken from Rabbit No. 15. A) before tightening the ligature applied to the descending branch of the left coronary artery; B) 10 minutes after tightening the ligature (note lowering of the T_1 wave, change in the ST_1 segment, which assumes the form of a convex arc, which undergoes transition to the negative T_1 spike. The ST_2 and ST_3 intervals are below the isoelectric line; T_2 and T_3 are high); C) 30 minutes after tightening the ligature (the same changes, with more pronounced depression of the ST_2 and ST_3 intervals).

On the succeeding days the ST_2 and ST_3 intervals remain below the isoelectric level. In some cases, where there is involvement of the ventricular septum, changes in the QRS complex, which assumes a W form, are evident. With time, the excitability of the myocardium gradually recovers, the Q wave becomes less prominent, the R_1 wave appears, and the T_1 wave reappears; these effects are evidence of regenerative processes in the myocardium, with formation of scar tissue. There was very little change in blood pressure after tightening the ligature, although a transient rise was sometimes observed.

Histological examination of the zone of infarction reveals a picture of marked circulatory disturbances, with irregular filling of vessels, dilation of the smaller vessels, stases, minor extravasations, and large hemorrhagic foci. All stages of dystrophic change of the muscle fibers are evident, from changes in staining properties of the protoplasm, with cloudy swelling and fatty degeneration of the fibers, to total loss of structure, with discoid degeneration. Foci of myomalacia begin to spread on the 2nd-3rd day, and are accompanied by a massive cellular reaction; at first, round cells, macrophages, and polymorphonuclears are seen, and are later replaced by juvenile connective tissue cells. Silver impregnation at this stage reveals a newly formed reticulum of delicate fibers, which very quickly becomes collagenized. Fuchsinophilic collagen fibers, rich in chromatropic substance, are seen among the newly formed argyrophilic fibrils on the 4th-5th day.

Examination of the histotopographic sections of the heart showed that graduated physical effort applied at various times during the 14-20 days after formation of the infarct in general increases the extent of the infarct, by formation of additional disseminated confluent foci of necrosis, infiltration, and vascular dystrophy (Fig. 3).

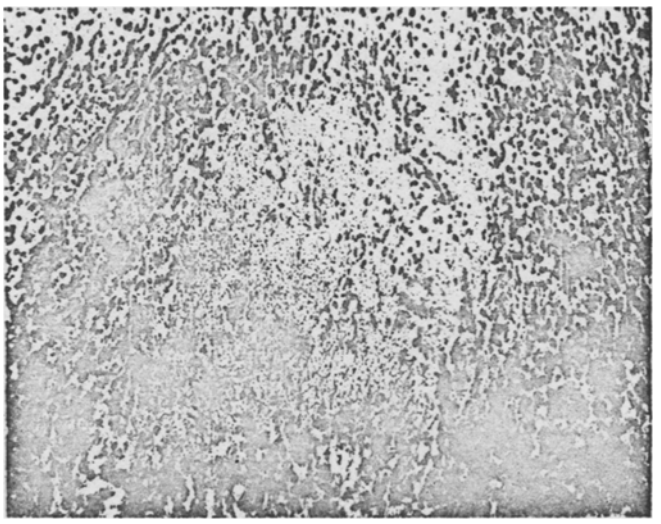

Fig. 3. A necrotic area, located towards the periphery of a myocardial infarct in Rabbit No. 30a. The animal was exercised on the 8th-10th days after tightening the ligature. Hematoxylin-eosin staining.

The circulatory disturbances were particularly prominent, and the infarction most extensive, in 2 animals in which the ligature was drawn tight immediately after physical exertion. In the later stages sclerosis of the myocardium is found in locations other than the site of ligation and of the zone supplied by the ligated artery. Thus, in preparations from exercised animals extensive hemorrhages, fresh patches of proliferation, and small sclerotic areas are found at the apex, in the lateral wall of the left ventricle, in the posterior papillary muscle, and in other parts of the myocardium. The processes of healing and, in particular, those of collagenization of fibrous structures at the margins of the infarct and in secondary necrotic areas, are somewhat retarded in exercised animals, as compared with unexercised controls, in which healing processes are evident by the 4th-5th day. There are also certain qualitative differences in the process of cicatrization. Whereas in unexercised rabbits the fibrous structures forming have a fairly regular orientation of the fibers, and with uniform thickening and collagenization, in exercised animals we see randomly distributed, thick fibers, with non-uniform deposition of collagen, which tends to form aggregates of various sizes. In the control animals in which the ligature was applied, but not tightened, the same physical effort caused no perceptible changes in the myocardium.*

Our experimental results suggest that physical effort has an unfavorable effect on the development and healing of myocardial infarction in rabbits, under our experimental conditions. This effect is evident not only when exercise is done in the early stages of the condition (first week), but also in its later stages (2nd-3rd week).

The formation of scattered regions of infarction in animals subjected to physical effort after tying off the descending branch of the left coronary artery may be regarded as a result of multiple pathological reflex spasms, arising in the diseased heart as a result of physical stress (inverted reaction), or as a result of imbalance between the raised oxygen requirement of the myocardium during physical effort and its diminished blood supply, following ligation of an important branch of the coronary system. The former explanation is supported by the multiple nature and the widely scattered extent of the necrotic and proliferative foci, which are found outside the region supplied by the ligated artery. Evidence of the relative oxygen hunger of the myocardial tissues of exercised

*F. Buchner [11] found that prolonged exercise at high rates of revolution of the treadwheel led to formation of necrotic microfoci in the myocardium.

rabbits is afforded by the more pronounced changes in the argyrophilic fibers and in the chromotropicity of the amorphous substance of the connective tissue of the heart of such animals [4,8]. Electrocardiographic evidence is also given by the accentuation of the T_3 wave after physical effort.

We were not able to discern any effect of physical effort on the healing of experimental myocaridal infarcts in rabbits during the later stages (26-30 days after ligation). By that time, the infarcts were fully healed, and the defects were replaced by connective tissue.

The question as to when physiotherapy should be instituted in patients suffering from myocardial infarct, and what levels of effort should be applied, requires the most careful and thorough clinical and experimental study.

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