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CHANGES IN AREA OF INJURY OF THE NORMAL, NONISCHEMIC MYOCARDIUM ADJACENT TO THE INFARCTION "RISK ZONE" DURING PERMANENT AND TRANSIENT CORONARY OCCLUSION

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UDC 616.12-005.4-02:616.132.2-007.271]-07:616.127-005.8-036.3-076

KEY WORDS: infarction, zone of real damage, peri-infarction zone, ischemia

A so-called "risk zone" of development of a myocardial infarct (IRZ) has been described in the literature [5, 6, 10], and it menans an area of myocardium, identifiable soon after coronary occlusion, which undergoes primary ischemia (i.e., its arterial system is nonfunctioning). The ratio of the size of IRZ to that of the zone of real damage (ZRD) can be used as a measure of involvement of the normal nonischemic myocardium, adjacent to IRZ, in the pathological process. The zone of normal myocardium around IRZ, corresponds most closely to the concept of a peri-infraction zone (PIZ). The area of the latter can be calculated by subtracting the area of IRZ from the area of ZRD.

There is evidence that in the comparatively early stages of development of infarction (3-6 h after coronary occlusion) ZED is no larger than IRZ and, consequently, there is no PIZ [5, 6, 10]. Meanwhile some workers [3, 4] have given morphological evidence in support of the presence of PIZ.

EXPERIMENTAL METHOD

Permanent and transient coronary occlusion ischemia was produced in noninbred male rats by ligation of the left coronary artery 3-4 mm below the left angle of the base of the infundibulum, by the methods described in [1, 2]. The group of animals was killed by inhalation of ether 10 min after coronary occlusion and the initial area of myocardial ischemia, corresponding to IRZ, was determined. For this purpose, the coronary vessels were injected with a suspension of latex microspheres (LM), stained blue with a 1% solution of trypan blue, post mortem through a cannula introduced through the right carotid artery into the aorta. The diameter of LM as a rule was 4.35-8 μ and their concentration 2.5×10^6-3.1×10^6/mm^3. After the vessels had been injected the heart was removed, cut into segments 2 mm thick starting from the apex, and subjected to segmental morphometry by the technique described for the reaction with nitro-blue tetrazolium (nitro-BT [2]). IRZ, unlike the normal myocardium, did

Department of Pathophysiology and Department of Pharmacology, I. M. Sechenov First Moscow Medical Institute. Translated from Byulleten' Eksperimental'noi Biologii i Meditsiny, Vol. 100, No. 12, pp. 758-760, December, 1985. Original article submitted April 20, 1985.

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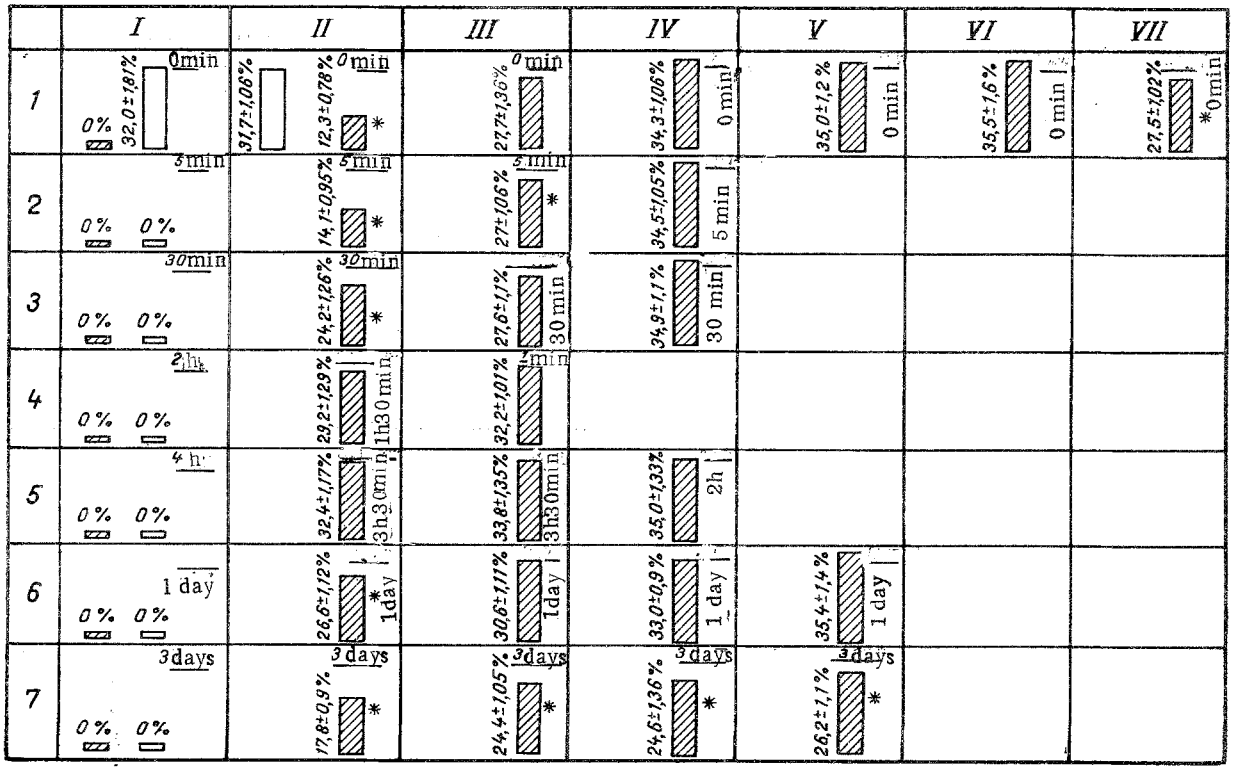

Fig. 1. Time course of area of zone of injury compared with original area of IRZ of myocardium. I-VII) Duration of ischemia 10 and 30 min, 1, 2, and 4 h, and 1 and 3 days respectively. Unshaded columns — IRZ corresponds to original unperfused zone, detectable 10 min after coronary occlusion; shaded columns — ZRD and ZRD. cardium in early stages after coronary occlusion. *P < 0.05 between IRZ and ZRD. Number of animals in individual experiments varied from six to 10. Areas of zones given in % of total area of ischemic left ventricle. Duration of perfusion indicated in top right hand corner in each square of figure.

not stain blue. To determine the area of ZRD at different times after coronary occlusion (in the case of permanent ischemia, after 30 min, 1, 2, and 4 h, and 1 and 3 days; in the case of transient ischemia after 5 and 30 min, 1, 1.5 and 2-3.5 h, and 1 and 3 days) the animals of the corresponding groups were killed by inhalation of ether. The heart was removed and, just as when determining IRZ, it was cut into transverse segments 2 mm thick, starting from the apex. These were then incubated with 0.1% nitro-BT solution for 15 min at 37°C, which was followed by segmental morphometry [2]. ZRD in the reaction with nitro-BT, unlike normal myocardium, did not stain blue. The area of PIZ was calculated by subtracting the area of IRZ from that of ZRD. The area of IRZ and ZRD was measured initially in absolute units segment by segment, and the area of the ischemic left ventricle was measured simultaneously, also segment by segment. After corresponding summation of the areas of the segments, the area of IRZ and ZRD was calculated as a percentage of the total area of the left ventricle. The MBS-1 sterioscopic microscope, fitted with ocular micrometer, was used for the morphometric measurements. Experiments were carried out on 286 noninbred male albino rats weighing 180-220 g. The number of animals in the groups varied from 8 to 10.

EXPERIMENTAL RESULTS

The results show (Fig. 1) that in permanent coronary-occlusion ischemia a PIZ can be detected continuously 2 and 4 h and also 1 day after occlusion, but its size is extremely small, namely 2.3-3.5 % of the total area of the ischemic left ventricle, or 7.2-10.1% of the total area of IRZ. The difference between the area of ZRD and IRZ was not statistically significant (P > 0.05) and, consequently, the area of PIZ, calculated as the difference between the areas of ZID and IRZ, likewise was not significant. However, since PIZ, while admittedly extremely small in size, was constantly detected during the period from 2 h to 24 h after coronary occlusion, this suggests that its formation was a regular feature. At an earlier stage after permanent coronary occlusion (30 min), and also at a later stage

(after 3 days) the dimensions of ZRD were 19.4 and 4.5% respectively less than those of IRZ ($P < 0.05$), evidence of the absence of a PIZ at these times. During reperfusion after ischemia lasting 30 min, ZRD as a rule was smaller than IRZ. Consequently, under these conditions no PIZ as a rule was absent and, consequenently, normal myocardium was not subjected to injury. Deviations observed in the case of reperfusion after 1 and 3 h, when PIZ was between +0.6 and +2.1% of the total area of the ischemic left ventricle, or 1.1-6.5% pf the area of IRZ, were not significant ($P > 0.05$). During perfusion after the cessation of coronary occlusion, a PIZ of exceedingly small size was constantly discovered: it amounted to between +1 and +3% of the area of the ischemic left ventricle, or 3.1-9.3% of the area of IRZ ($P > 0.05$). By the end of the 3rd day after the beginning of reperfusion and against the background of ischemia lasting 30 min-4 h, ZRD became 5.8-14.2% smaller than IRZ ($P < 0.05$). A difficult problem emerges from these data. In permanent coronary occlusion ischemia, the area of PIZ after 24 h is 3.5% of the area of the ischemic left ventricle, but by the end of the 3rd day the PIZ has disappeared. Moreover, its size becomes negative: -4.5% of the area of the left ventricle, or -14% of IRZ ($P < 0.05$), which apparently suggests spontaneous (without treatment) reversibility of the necrotic manifestations which have lasted 24 h. Such an assumption is possible if it is accepted that the myocardium, which gives a negative reaction with nitro-BT 24 h after the beginning of permanent coronary occlusion ischemia (indicating absence of dehydrogenase activity), is in fact not necrotic, but is in a kind of anabiotic (dormant) state, which protects it against hypoxic damage. However, this has naturally to be proved. In support of the above hypothesis on partial reversibility of the damage there is some evidence which indicates that the size of ZRD and IRZ is considerably reduced during the first few days after coronary occlusion under the influence of certain drugs. For example, according to our own data, at the end of the first day of coronary occlusion the β-adrenoblocker atenolol reduces the area of the zone of damage and of the unperfused zone by 13.5 and 5.9% respectively of the total area of the ischemic left ventricle, or by 38.1 and 21.2% compared with the corresponding zones of the untreated control infarct ($P < 0.05$). A reduction in size of ZRD and IRZ also was observed 3-6 h after coronary occlusion under the influence of amiodarone [6], molsidomine [10] and flurbiprofen [5]. The possibility cannot be ruled out that the spontaneous reversibility of damge mentioned above is due at least partly to the fact that on the 3rd day after coronary occlusion the zone of infarction is invaded by growth of granulations, which react positively with nitro-BT and can invade blood vessels. The data showing the very small size of PIZ are in agreement with the results of ultrastructural investigations [11], which showed that by 1 h after coronary occlusion in rats the unperfused zone is bounded on the side of the perfused myocardium by 1-5 rows of damaged cardiomyocytes. The results of the investigation are relevant to the discussion of the so-called limiting (reversibly damaged) zone in the region of a myocardial infarct. They do not directly answer the question of the absence [7] or presence of such a zone [9], but they indicate that the contribution of the damaged (normal) nonischemic myocardium adjacent to IRZ to the possible formation of such a zone is exceedingly small or close to zero.

The results and some data in the literature thus indicate that the zone of injury to normal nonischemic myocardium adjacent to the "risk zone" of development of infarction (as revealed by the dehydrogenase test) is extreemely small in size or absent altogether in both permanent and transient ischemia.

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