PREVENTION BY CURANTIL OF DAMAGE TO THE MYOCARDIUM BY ISOPROTERENOL

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Experiments on sexually mature albino rats showed that a single subcutaneous injection of isoproterenol caused electrocardiographic and ultrastructural changes in the myocardium characteristic of ischemia and necrosis of the heart muscle and disturbances of its contractile function. Preliminary administration of curantil for 3 days to sexually mature rats in a dose of 10 mg/kg had a marked protective action on the myocardium against damage produced by isoproterenol.
KEY WORDS: *myocardium; damage caused by isoproterenol; protective action of curantil; electrocardiogram; ultrastructural analysis.*

In recent years the drug isoproterenol has been widely used for the experimental simulation of myocardial infarction [2, 4, 10]. At the same time it has been shown that certain coronary dilators and, in particular, curantil, appreciably improve the collateral circulation of the myocardium, exert a positive inotropic action, and so protect the heart muscle against damage by isoproterenol [1, 3, 5, 7-9, 11-14].

The object of the present investigation was to undertake an electron-microscopic and electrocardiographic study of morphological and functional changes reflecting the protective action of curantil against damage caused by isoproterenol.

EXPERIMENTAL METHOD

Experiments were carried out on 48 sexually mature albino rats of both sexes weighing 180-200 g, divided into two groups. The animals of group 1 (30 rats) received a single subcutaneous injection of isoproterenol in a dose of 80 mg/kg to disturb the integrity of the myocardium [10]. Before and 15, 30 and 45 min and 1, 2, 4, 6, and 12 h after injection of isoproterenol the ECG of the animals was recorded in three standard leads: The 18 animals of group 2 received a single subcutaneous injection of curantil (dipyridamole) (dose 10 mg/kg) before receiving 3 daily injections of isoproterenol [15]. Before this injection and 2, 4 and 18 h thereafter, the ECG was recorded. The numerical data were subjected to statistical analysis. For the morphological investigations of the myocardium six animals were killed at each time. The material was fixed in 1% OsO_4 solution in Caulfield's buffer, stained with a 2% aqueous solution of uranyl acetate, embedded in a mixture of Epon and Araldite, and examined in the UÉMV-100V electron microscope.

EXPERIMENTAL RESULTS

In the ECG of the animals of group 1 in standard lead II 1, 2, 3, 4, 6, and 12 h after injection of isoproterenol the heart rate was significantly reduced ($P < 0.05$-$P < 0.02$) and the systolic index was increased ($P < 0.001$-$P < 0.05$), evidence of a disturbance of the contractile function of the myocardium. In most animals 1, 2, 3, and 4 h after injection of isoproterenol, the ECG in standard lead II showed evidence of ischemia and necrosis of the myocardium. A shift of the initial part of the S-T interval below the isoelectric line and a high dome-shaped T wave (Fig. 1B). The most marked changes in the myocardium in the animals of this group were observed 4 h after injection of isoproterenol. Analysis of the electron-microscopic data showed that by this time (4 h) considerable swelling of the cytoplasm of the endothelial cells was observed in the myocardial capillaries, causing constriction of the lumen of the microvessels (Fig. 2). The nuclei of the endothelial cells were enlarged.

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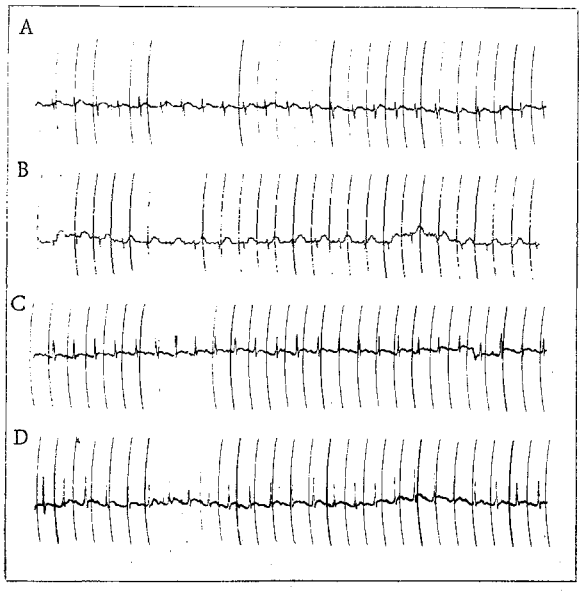

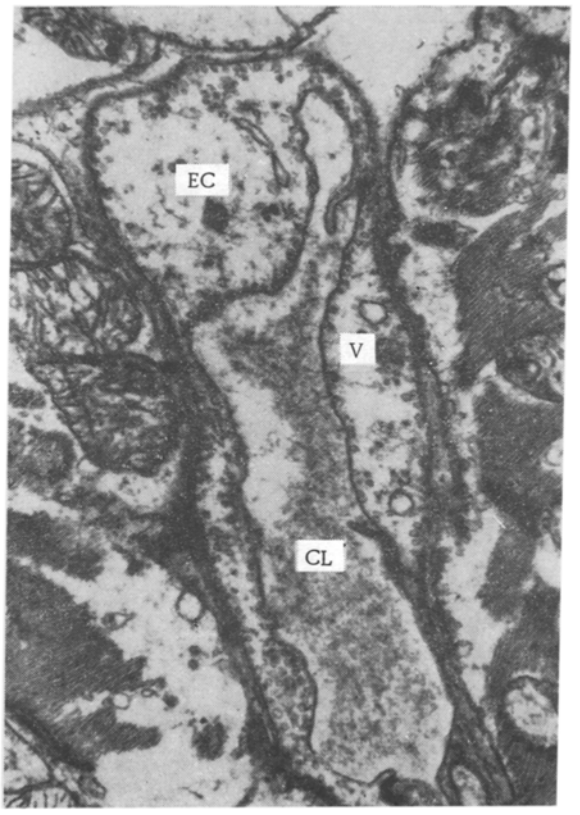

Fig. 1 Fig. 2

Fig. 1. Changes in ECG of rats under the influence of isoproterenol and curantil. A) Before injection of isoproterenol; B) 4 h after injection of isoproterenol; C) before injection of curantil; D) 4 h after injection of isoproterenol but after preliminary administration of curantil for 3 days.

Fig. 2. Ultrastructural changes in myocardial capillaries of albino rats following administration of isoproterenol (16,000×). CL) Capillary lumen; EC) endothelial cell; V) vacuole.

The mitochondria were located mainly in the perinuclear zone and their matrix was pale. The lamellar complex appeared to consist of dilated vacuoles and vesicles. The basal layer of the capillaries was irregularly widened. Marked changes also were observed in the cardiomyocytes surrounding the capillaries. The mitochondria became swollen and their isomorphism was disturbed. In some areas homogenization of the myofilaments or even their destruction was observed, accompanied by marked intracellular and intercellular edema, evidence of hypoxia.

In the animals of group 2, according to the ECG 2 and 4 h after injection of isoproterenol there was no significant change in heart rate ($P > 0.5$-$P > 0.1$); 2, 4, and 18 h after injection of isoproterenol no statistically significant change likewise was observed in the systolic index ($P > 0.1$, $P > 0.1$, and $P > 0.5$ respectively). In all three standard leads the ECG of all the animals showed a marked increase in voltage of the R wave; the S-T interval likewise did not fall below the isoelectric line (Fig. 1D). Electron-microscopic investigation of the myocardium showed that in the animals of this group the subcellular changes in the heart muscle were less marked than in the rats of group 1; the capillary lumen differed in shape, in some parts the cytoplasm of the endothelial cells of the capillaries was condensed, although no special changes were found in its organoids (Fig. 3). The ultrastructure of the cardiomyocytes was close to normal again.

The results described above are in agreement with the observations of Eichbaum et al. [11], who concluded from their light-optical investigations that curantil causes a marked decrease in the accumulation of monocytes and histiocytes in the interstices of the myocardium during the formation of isoproterenol necrosis, and also inter- and intrafibrillary

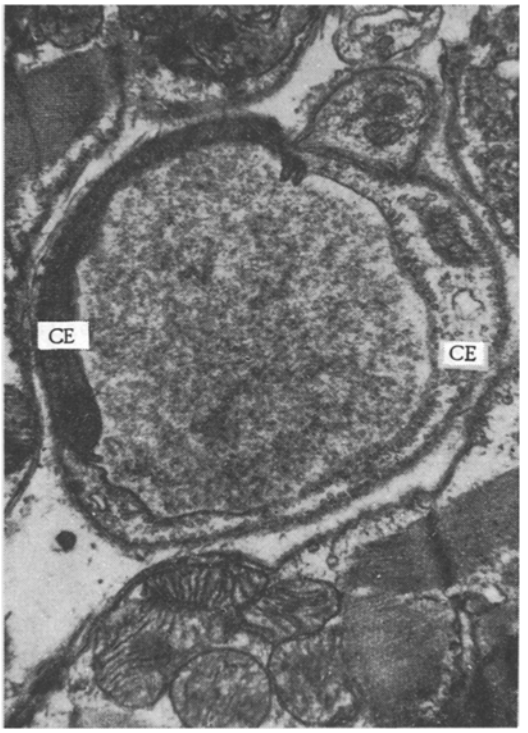

Fig. 3. Structural changes in components of myocardial capillary in response to isoproterenol following preliminary administration of curantil for 3 days (10,000×). CE) Cytoplasm of endothelial cells — condensed.

edema and focal necrotic lesions of the cardiomyocytes. The protective effect of curantil observed in the present experiments can be explained by its action on the microcirculation and also by its ability to improve the development of a collateral circulation in the myocardium.

The results of this study of the functional state and ultrastructure of the myocardium confirmed the protective action of the drug morphologically. The results are thus evidence that curantil can be given with advantage not only therapeutically, but also prophylactically in patients with ischemic heart disease.

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