DIASTOLIC RIGIDITY OF THE MYOCARDIUM IN CHRONIC ADRIAMYCIN CARDIOMYOPATHY

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An increase in the diastolic rigidity of the myocardium is a common pathogenetic feature of many diseases of the human heart, including in various types of cardiomyopathy [4, 5, 10]. One of these, frequently combined with congestive heart failure, is the cardiomyopathy arising during long-term treatment of neoplastic diseases with adriamycin. The cause of the increased rigidity of the myocardium is usually considered to be fibrosis, which develops at the site of foci of micronecrosis [2, 10]. At the same time, diastolic rigidity is known to increase also in the presence of an acute disturbance of energy formation in myocardial cells [4, 5].

In the investigation described below, which was conducted on the isolated hearts of rats receiving long-term adriamycin treatment, the compliance and rigidity of the myocardium were studied in order to shed light on the character of disturbance in this form of pathology.

EXPERIMENTAL METHOD

Rats weighing 200 g were given adriamycin in an ultimate cumulative dose of 20 mg/kg over a period of 10 days [7]. About one-quarter of the animals died, and the hearts were removed from the surviving rats, under urethane anesthesia, and perfused with Krebs' solution at 37°C through the left atrium. The resistance pressure was 80 cm water, and the filling pressure varied between 5 and 25 cm water. In the course of the experiment the pressure in the aorta and left ventricle was recorded on the "Gould 2600S" recorder (through a needle introduced into the lumen of the ventricle) with ordinary and high amplification (0.4 mm Hg/mm), the first derivative of pressure was recorded by means of a differentiator, and the cardiac output was measured by means of an electromagnetic flowmeter (from Caroline Medical Electronics, type 501D). The following parameters were calculated: the diastolic rigidity of the ventricle — as the ratio between the increase of pressure during diastole and the increase in volume of the ventricle, equal to the stroke volume, and the diastolic rigidity of the myocardium — by dividing the above-mentioned value by the end-diastolic pressure [4, 5]. In other experiments the heart was perfused through the aorta at a constant rate of about 10 ml/min·g, and a latex balloon was introduced into the left ventricle. During a gradual increase in the volume, the increase in pressure in the balloon was recorded, and in that way some idea could be obtained of the compliance of the left ventricle. The right atria were taken from the hearts of some animals, placed in a chamber containing Krebs' solution at 29°C, and stimulated at the rate of 30 stimuli/min. After perfusion for 1 h the atria were gradually flexed by increasing the load, and changes in length under these circumstances were recorded by means of an MTI KD-100 light-sensitive transducer.

EXPERIMENTAL RESULTS

In experiments on the isolated hearts an increase in filling pressure had an about equal action on the increase in cardiac output: the maximal values of cardiac output in the control animals and those receiving adriamycin (31 ± 1 and 28 ± 3 ml/min, respectively) did not differ significantly from each other. The rise of the end-diastolic pressure (EDP) in the left ventricle under these circumstances was significantly greater in the hearts of the rats receiving adriamycin (Fig. 1a). The parameters of diastolic rigidity of the ventricle was sig-

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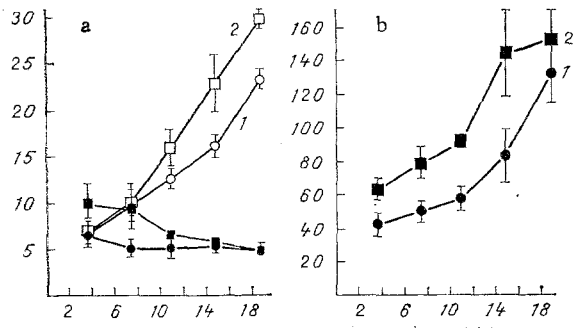

Fig. 1

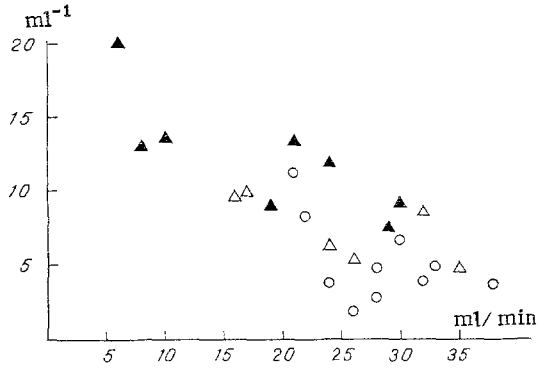

Fig. 2

Fig. 1. Effect of filling pressure on parameters of function of isolated hearts of control rats (1) and rats receiving adriamycin (2). Abscissa, filling pressure (in mm Hg). a) Time course of EDP (in mm Hg, empty symbols) and of parameter of diastolic rigidity of myocardium (in ml^{-1}, filled symbols); b) time course of parameters of diastolic rigidity of left ventricle (in mm Hg/ml, M ± m).

Fig. 2. Relationship between cardiac output (in ml/min) and parameter of diastolic rigidity of myocardium (in ml^{-1}) in experiments on hearts of control rats (circles) and rats receiving adriamycin (triangles), at frequency of spontaneous contractions (empty symbols) and of contractions imposed by electrical stimulation. (solid symbols).

nificantly raised compared with the control values at all filling pressures except maximal (Fig. 1b). It was raised even when EDP was at the normal level observed at a low filling pressure. However, the diastonic rigidity of the myocardium, determined from the ratio between them, was virtually normal over the whole range of filling pressure (Fig. 1a).

The frequency of contractions in animals receiving long-term adriamycin treatment, incidentally, was consistently reduced by 16%, whereas the diastolic pause was increased from 99 ± 6 msec in the control to 122 ± 7 msec ($P < 0.05$). The lengthened diastole could facilitate filling of the ventricle. If, however, the frequency of contractions was increased by electrical stimulation from the spontaneous level of 200 ± 16/min to the control level of 240/min, and the effect of lengthened diastole was thereby canceled out, the diastolic rigidity of the myocardium of animals receiving adriamycin rose significantly — from 7.8 ± 0.6 to 13.3 ± 1.6 ml^{-1} ($P < 0.01$). Meanwhile an increase in the parameter of diastolic rigidity of the ventricle by more than 50% and a decrease in cardiac output from 28 ± 3 to 18 ± 3 ml ($P < 0.05$) were observed, while the filling pressure remained stable at 15 cm water. Close negative correlation was observed between the values of diastolic rigidity of the myocardium and cardiac output (Fig. 2, $r = -0.76$). These results are evidence that increased diastolic rigidity of the ventricle in rats receiving adriamycin is the resultant of two components: stable and dynamic. The first component is observed whatever the filling pressure, the second arises when the intensity of function is increased.

In the experiments of series II the compliance of the ventricular and atrial myocardium was assessed after long-term administration of adriamycin. The weight of the hearts and that of the atria was approximately equal, and the ratio between pressure in the balloon and the increase in its volume did not differ significantly in the two groups (Fig. 3a). The ratio between the load stretching the atrium and the increase in its length also was identical (Fig. 3b). These results show that compliance of the myocardium changes only a little after long-term adriamycin treatment, at least under these experimental conditions.

The increased diastolic rigidity of the ventricle over a wide range of filling pressures (Fig. 1b) can thus hardly be explained by a disturbance of myocardial compliance. It is more likely to be the result of constant dilatation of the ventricle because of a possible disturbance of myocardial contractility. It increases even more if the frequency of contractions is increased, when increased demands are presented to the systems of ion transport and energy formation of the myocardial cells. We know that under the influence of adriamycin permeability of the mitochondria to Ca^{++} increases significantly [8] and Ca^{++}-Na^{+} exchange through the sarcolemma is inhibited [3]. Regardless of which of these possible causes is the principal one

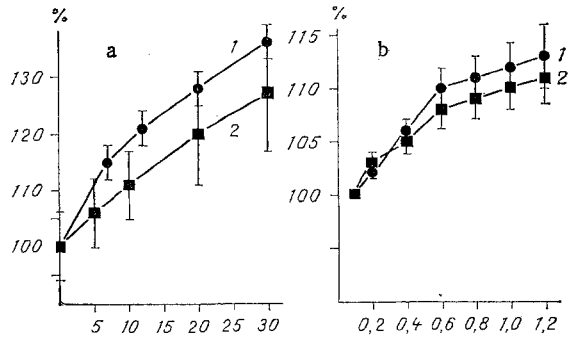

Fig. 3. Comparison of compliance of left ventricle (a) and right atrium (b) of control rats (1) and rats receiving adriamycin (2). Abscissa: a) pressure (in mm Hg); b) load (in g). a) Ratio between pressure in balloon (in mm Hg) and its volume (in %); b) ratio between stretching load and increase in length of atrium (in % of length with minimal load).

in the development of increased diastolic rigidity of the myocardium, it has to be pointed out that the presence of bradycardia helps to prevent failure of the pumping function of the isolated heart, for under these circumstances the energy expenditure is reduced, the duration of the rest period of the cells is increased, and atrial systole is strengthened due to increased stretching of the atrium. As a result, filling of the left ventricle, essential to maintain ejection, is facilitated. This form of "mechanical" compensation of the depressed inotropism is usual both in acute experiments [9] and in various forms of dilatation cardiomyopathy arising in the presence of insufficiency of the inotropic function of the heart [1, 10].

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