The investigation described above thus established an important molecular mechanism of protection of hepatocytes against the damaging action of a pathogenetic factor of the terminal process, namely increased activity of nuclear Ca^{2+},Mg^{2+}-dependent liver endonucleases.

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EXPERIMENTAL EVALUATION OF THE HEMODYNAMIC EFFICIENCY OF DYNAMIC CARDIOMYOPLASTY IN THE SURGICAL TREATMENT OF SEVERE LEFT VENTRICULAR FAILURE

V. S. Chekanov, K. V. Shatalov, V. Yu. Merzlyakov, M. V. Tolmachev, and R. R. Movsesyan

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KEY WORDS: dynamic cardiomyoplasty; heart failure; left ventricle

Autologous muscle tissue was used for the first time in heart surgery for indirect revascularization of damaged myocardium in 1935 [8]. Since the end of the 1950s, autologous muscle tissue has been widely used in heart surgery for indirect revascularization and also for plastic replacement of injured myocardium. Progress in the development of electrophysiology and integrated electronic circuitry has led to the development of new trends in the use of skeletal muscles for surgical treatment of the heart. In 1960 [11] it was suggested that stimulated skeletal muscle be used not only for plastic, but also for dynamic replacement of the infarcted myocardium. In different countries of the world more than 100 operations have now been performed by the method of dynamic cardiomyoplasty (DCMP), including more than 15 such operations in the USSR [1, 2, 4, 7, 9, 12].

The aim of this investigation was a comprehensive experimental study of the hemodynamic status of the circulatory system in the immediate and late stages after performance of DCMP on the damaged heart.

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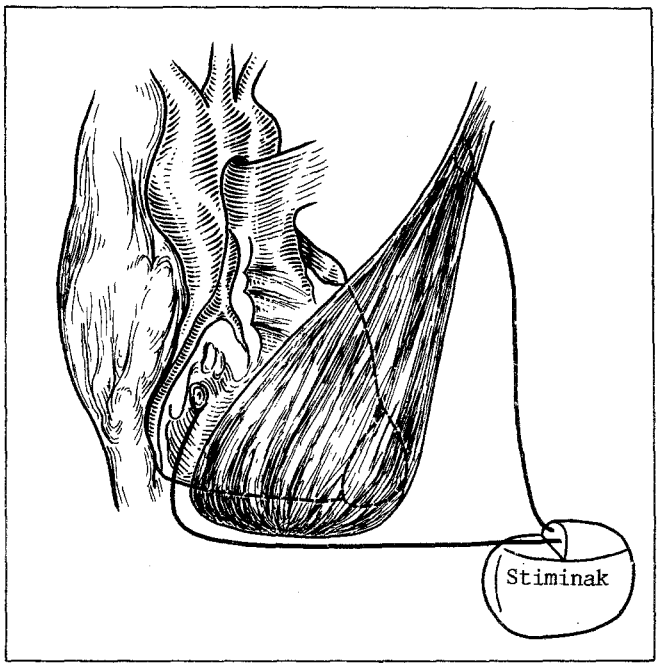

Fig. 1. Diagram of experimental model of operation of dynamic myoventriculoplasty on artificial aneurysm of the left ventricle.

EXPERIMENTAL METHOD

Altogether 108 experiments were carried out on male and female mongrel dogs weighing from 16 to 32 kg. The experiments were divided into three series. In series I (13 experiments) the optimal surgical technique was worked out on a model of aneurysm of the apical region of the left ventricle (LV), followed by application of a muscle graft taken from the latissimus dorsi muscle (LDM). During this procedure great attention was paid to the choice of optimal parameters and conditions of stimulation of the autologous muscle graft, from the point of view of its effect on the cardiac hemodynamics. In series II (52 acute experiments), on the basis of analysis of the intracardiac and systemic hemodynamics, the effect of the stimulated untrained LDM graft, applied around LV with an experimental model of aneurysm, on the hemodynamic status of the animals was studied immediately after the operation. In series III (43 chronic experiments) the long-term (from 3 to 6 months) effects of the heart–skeletal autologous muscle graft complex on the hemodynamics was studied. The function of the graft–heart system was maintained continuously throughout the period of observation by the usual methods of stimulation [3, 5, 7, 9, 10, 12]. All the surgical procedures were carried out after premedication with ketamine (10-15 mg/kg). Artificial ventilation of the lungs was carried out by means of a "Jaeger" apparatus (West Germany) on moderate hyperventilation mode. The hemodynamics was monitored on the "Mingograf-7" apparatus Siemens Elema, Sweden) and an SP-2201 flowmeter ("Statham-Gould, Inc.," USA). Basal anesthesia was maintained by a combination of neuroleptanalgesia and a 2.5% solution of hexobarbital. Muscle relaxants were not used at any stage of the operation because of their uncontrollable action on skeletal muscle. Cardiac stimulants were not given during recording of the hemodynamic parameters. All hemodynamic parameters obtained by the usual formulas were subjected to statistical analysis by the method of paired comparison of variances. The homogeneity of most of the data was confirmed statistically: the standard error for each experiment and for all groups as a whole did not exceed 15%; mean values of functions were estimated with an error of not more than 10%. Multiprogrammed electrical stimulators of muscular blood pumps of the "Stiminak" type, developed at the Department of Electronics of the Moscow Institute of Physiological Instrumentation (I. A. Dubrovskii and A. N. Ryzhikh), were used for the investigation. The course of the operation was as follows: the left latissimus dorsi muscle (LDM) was totally mobilized through a broad skin incision on the left side at the level of the 6th intercostal space by blunt and sharp dissection, and the tendinous fixation point of the muscle in the region of the humerus was preserved. A strip of the tendon fixing LDM to the spines of the vertebrae was detached in such a way that it could be used later as "padding" during aneurysm formation. In the region of bifurcation of the thoracodorsal nerve (nerve to the latissimus dorsi), at its point of

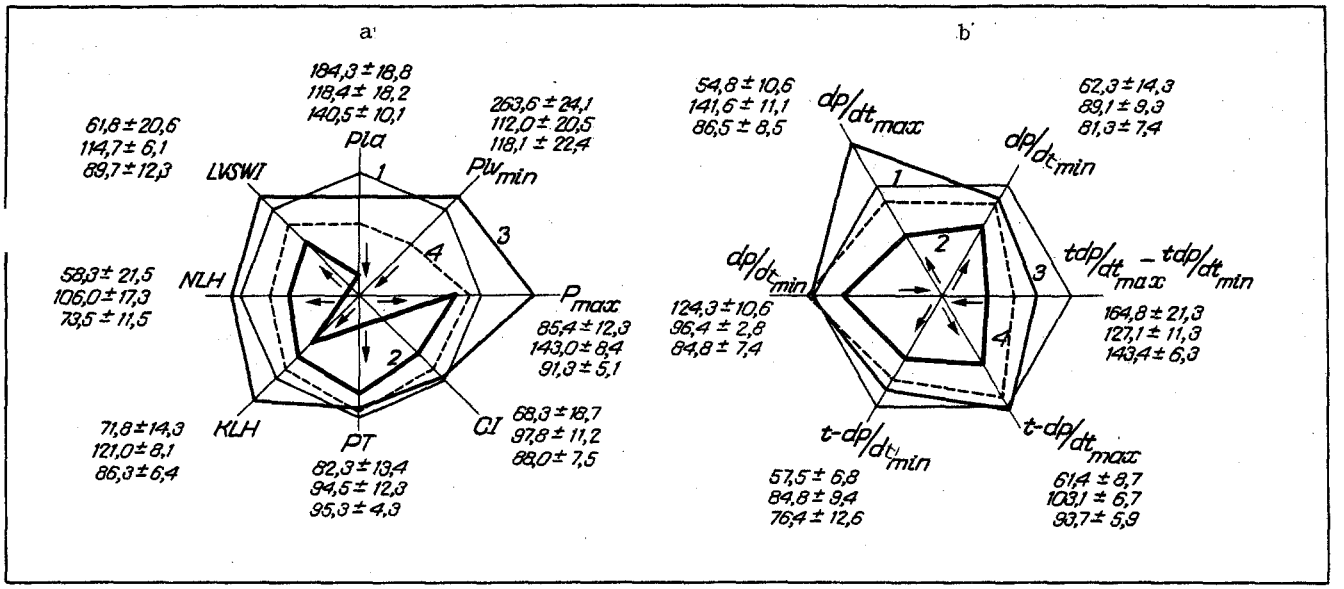

Fig. 2. Hemodynamic status of experimental animals in initial state (1: intact hearts — 100%, n = 52) after operation to create model of LV aneurysm (2: n = 52), in immediate (3: n = 50) and late (4: n = 43) stages after operation. a) pumping capacity of heart (relative percentages). PLA) mean pressure in left atrium; PLV_{min}) end-diastolic pressure in LV; PLV_{max}) systolic pressure in LV; CI) cardiac index; PV) central venous pressure; KLH) pumping coefficient of left heart; NLH) power of left heart; LVSWI) left ventricular stroke work index; b) contractility of heart (relative percentages). dp/dt_{max}) maximal rate of rise of pressure in LV; dp/dt_{min}) maximal rate of fall of pressure in LV; $tdp/dt_{max} - tdp/dt_{min}$) duration of period of ejection from LV; $t - dp/dt_{max}$) time of active contraction of LV; $t - dp/dt_{min}$) time of active relaxation of LV; dp/dt_{min-0}) time of passive filling of LV.

emergence from the common neurovascular bundle, a muscle stimulating electrode was implanted. A left-sided anterolateral thoracotomy was next performed along the 6th left intercostal space and a window formed in the third intercostal space through which LDM could enter the thorax. The pericardium was opened along the longest possible perimeter, in order to obtain a pericardial "patch," subsequently to be used to produce a model of an aneurysm. The cardiac electrode through which the R wave of the ECG was derived to control the stimulator was implanted into the region of the outlet of the right ventricle. Transducers for monitoring the left atrial and left ventricular pressure were applied, and the transducer of a flowmeter was applied to the aorta. The apical part of the left ventricle was isolated by compression with forceps of "Satinsky" type. Without using an artificial circulation, the myocardium of the working heart was excised down to the level of the base of the papillary muscles, equivalent on average to about 12-15% of the active mass of the left ventricle. The pericardial patch was attached by means of a continuous "Prolen 4.0" purse-string suture around the border of the myocardial defect thus produced. The forceps were removed after careful control of hemostasis. A three-dimensional zone of dyskinesia, identical with a saccular aneurysm of the left ventricle, was formed in the apical region of LV. The graft of LVM, buried in the thoracic cavity, was fixed by 6 interrupted U-shaped "Mersilen 2.0" sutures to the myocardium in the form of a loop. In this way a new apical part of the left ventricle with inner autopericardial layer was formed (Fig. 1). After relative stabilization of the hemodynamics, the control stage of the experiment was carried out.

EXPERIMENTAL RESULTS

After formation of a model aneurysm of LV signs of left-ventricular failure, refractory to pharmacotherapy were clearly revealed. An extensive zone of acute infarction was identified electrocardiographically in the region of the apex.

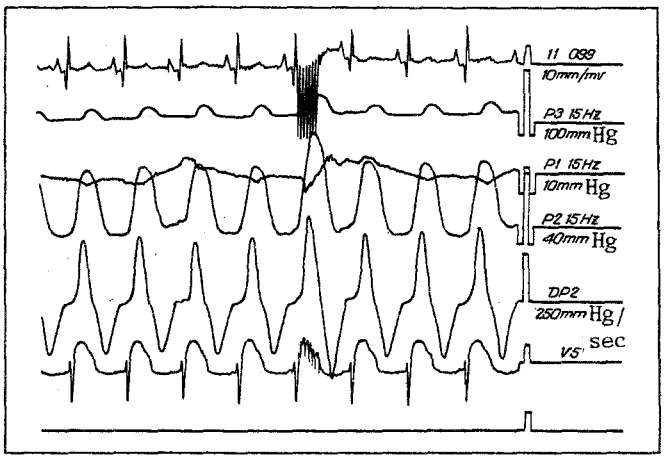

Fig. 3. Structure of curves of pressure in chambers of heart and ACG of experimental animal with functioning "heart-stimulated autologous muscle" complex during stimulation of autologous muscle graft applied to LV. P3) pressure in femoral artery; P1) average venous pressure; P2) pressure in LV; DP) first differential derivative of pressure in LV; 11 and V5) ECG leads.

The systolic pressure in LV (PLV_{max}) at this stage was lowered on average to 76.4 mm Hg (85.4% of the initial value); the end-diastolic pressure in LV (PLV_{min}) was significantly raised under these circumstances to 22.8 mm Hg on average, or 263.6% of the initial level. The pressure in the left atrium (PLA) was increased on average to 28.7 mm Hg (184.3% of the initial level). The cardiac index (CI) fell on average by 31.7%. Values of the pumping coefficient (KLH) and power of the left heart (NLH) were lowered by 28.2% and by 41.7% respectively. The left ventricular stroke work index fell by 38.2% (Fig. 2a).

Parameters reflecting the contractility of LV also were considerably impaired: the maximal rate of rise of pressure in the ventricle (dp/dt_{max}), estimated from the curve of the first derivative of left-ventricular pressure, was reduced virtually by half, dp/dt_{min} was reduced on average by 37.7% (Fig. 2b). The duration of the period of ejection from LV ($tdp/dt_{max} - tdp/dt_{min}$) was increased by 64.8%, due both to an increase in size of LV itself after creation of the aneurysm and to the appearance of a massive zone of akinesia in the wall of LV. The times of active contraction ($t - dp/dt_{max}$) and relaxation ($t - dp/dt_{min}$) of the LV myocardium were reduced by 38.6% and 42.6% respectively. In turn, the passive filling time of LV (dp/dt_{min-0}) was increased on average by 24.3% (Fig. 2b).

It is interesting to note that even after simple application of the muscle to the aneurysm the cardiac index rose by 12% compared with the stage of formation of the LV aneurysm. The end-diastolic pressure fell significantly, the pumping coefficient of the left heart increased by 21.4%, and values of the contractility of the LV myocardium improved, mainly on account of the phase of diastole. The skeletal muscle applied to the aneurysm evidently restricts paradoxical movement of the walls of LV purely mechanically, reduces the end-diastolic volume of the ventricle, and increases the relative rigidity of the myocardium, thereby increasing the efficiency of contraction.

During cardiosynchronized stimulation of the applied muscle the hemodynamics became stabilized, and the hemodynamic status did not differ significantly with respect to a number of parameters from the initial values.

The ECG at this stage of the investigations showed the presence of specific R-dependent "bursts" of impulses recorded in all derivations. Contraction of LDM had a significant effect on the bursts of spikes on the curves of pressure in the chambers of the heart and the great vessels (Fig. 3).

Values of the left ventricular pressure tended toward normal levels or even exceeded the initial values significantly on average by 43% ($p < 0.01$). The end-diastolic pressure in LV and PLA remained significantly higher than normal in this case – on average by 12% and 18% respectively ($p < 0.01$), which, taken together with the estimate of contractility of the myocardium of LV, points to relative insufficiency of LV and to incomplete unloading of the ventricle in the phase of diastole. For instance, the value of dp/dt_{min} was significantly lower than the original values on average by 11% ($p < 0.01$), although if the values of these parameters are compared with the first stage (after formation of an aneurysm of LV), this

parameter was significantly increased on average by 26.8% ($p < 0.001$). The active relaxation time of LV also was increased by 27.3% ($p < 0.001$) compared with the first stage, but this parameter remained 10.9% below its initial values ($p < 0.01$) (Fig. 2).

The actively contracting skeletal muscle applied to LV considerably increased the pumping coefficient, and the power and stroke work index of the left ventricle on average by 50% ($p < 0.01$) compared with the stage of aneurysm formation in LV. The cardiac index differed, but not significantly, from its initial values, at 94.5% ($p > 0.95$). Evidence of improvement of the contractile and pumping capacity of LV at this stage also was indicated by shortening of the period of ejection of blood from the ventricle on average by 37.7% ($p < 0.01$) (Fig. 2).

All the data obtained at the stage of functioning of the autologous muscle graft during cardiomyoplasty after aneurysm formation in LV, in the period immediately after the operation, indicate an adequate effect of the procedure.

The hemodynamic parameters remained sufficiently well stabilized for 3 h. Later, evidently because of exhaustion of the untrained skeletal muscle, considerable weakening of its contractions was observed, and this lead to a sharp reduction of the hemodynamic effect.

The study of the hemodynamic status of the animals in the late stages (3-6 months) after the operation was of great interest. In all the animals of this series of experiments active functioning of the muscle–heart complex was observed. This was confirmed by both visual and instrumental methods of investigation. For instance, during electrocardiography, the presence of specific complexes of cardiac electrical activity, with detectable "bursts" of impulses from the heart muscle stimulator (Fig. 3). No disturbance of work of the stimulator was found in any of the experiments. It is interesting to note that at these times the electrocardiographic signs of myocardial hypoxia were significantly weaker than in the immediate postoperative period. This fact is evidence of the favorable effect of skeletal muscle on revascularization of the affected myocardium.

In the late stages after surgery the effect of the DCMP operation was less marked than in the immediate period. However, compared with the hemodynamic status of the animals after creation of the experimental aneurysm of LV, the hemodynamic status at this stage can be interpreted as compensated. For instance, signs of overloading of LV were observed: values of PLA and PLV_{min} were significantly higher than in the stage of the immediate postoperative period, on average by 22.1% and 69.1% ($p < 0.0l$) respectively, while values of dp/dt_{max} and dp/dt_{min} fell on average by 55.1% and 6.8%, the duration of the period of ejection from LV was increased by 16.3%, and the time of active contraction and relaxation of LV decreased by 9.4% and 8.4% respectively (Fig. 2).

Values of hemodynamic parameters characterizing the pumping capacity of the ventricle with an applied skeletal muscle graft likewise did not reach the original values, but remained significantly lower than in the immediate postoperative period: CI was depressed by 9.8%, KLH by 24.7%, NLH by 32.5%, and LVSWI by 25% ($p < 0.01$) (Fig. 2).

Thus after creation of a model of left-ventricular failure, a perceptible effect of the DCMP operation could be recorded in the immediate stage, but in the late period the degree of alleviation of the hemodynamic status of the experimental animals was insufficient. No consistent explanation of these observations can be given, and it evidently is not simply an imperfection of the experimental technique or the inadequacy of studying the hemodynamic status of animals undergoing the operation.

The main conclusion to be drawn from this investigation is that a brilliant future lies ahead for the surgical procedure of dynamic cardiomyoplasty: in the future it is bound to become a powerful alternative method of surgical treatment of patients with typical heart failure.

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ROLE OF PROSTAGLANDINS OF THE GASTRIC MUCOSA IN ULCER DEVELOPMENT IN CIRRHOSIS OF THE LIVER

R. A Vysotskaya, A. S. Loginov, and Z. D. Kondashova

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-07:616.33-018.73-008 94:577.175.859

KEY WORDS: prostaglandins; cirrhosis of the liver; gastric ulcer.

Among the different effects of prostaglandins (PG) in the digestive system one of the most important is their cytoprotective action on the gastroduodenal mucosa and their antiulcerative effect This cytoprotective effect is connected not only with the inhibition of acid secretion in the stomach, but also with mobilization of protective factors – stimulation of bicarbonate secretion, the formation and secretion of mucoglycoproteinss and mucus, and also the trophic action of PG, etc. [10]. In chronic liver diseases erosive lesions are frequently observed also in the gastroduodenal region, amounting in some cases to the development of so-called "hepatogenic" ulcers in cirrhosis, evidence of lowered resistance of the gastroduodenal mucosa in this pathology. The pathogenetic mechanisms of these lesions have not yet been adequately studied despite their evident urgency. It has recently been shown that disturbances of the function of the gastric mucosa (GM) in chronic liver disease are due to injury of the layer of mucus [6], in the synthesis and secretion of which an active role is paid by PGE and PGI_2 (prostacycline), which are of essential importance in the mechanism of gastric cytoprotection [14]. $PGF_{2\alpha}$ also has recently been shown to have a protective action on the gastroduodenal mucosa [5].

The aim of this investigation was to study the role of PG in the development of ulcers in the gastroduodenal region in cirrhosis of the liver, for which purpose the content of PG of the E, I_2, and $F_{2\alpha}$ groups was studied in GM of patients with cirrhosis of the liver, complicated or uncomplicated by gastric or duodenal ulcer, and also the PGE and $PGF_{2\alpha}$ content in the gastric juice of these patients.

EXPERIMENTAL METHOD

Tests were carried out on 104 patients with chronic liver diseases, divided into four groups. Group 1 (54 patients) had active cirrhosis of the liver of varied etiology: viral (HBsAg+), alcoholic, and primary biliary cirrhosis. The 13 subjects of group 2 and the 12 of group 3 were patients in whom cirrhosis of the liver was complicated by gastric ulcer or ulcer of the duodenal bulb respectively. For greater informativeness, patients with chronic active hepatitis (CAH) of viral and alcoholic etiology also were tested (group 4, 25 subjects). In all cases the diagnosis was confirmed by the usual clinical-biochemical, morphological, roentgenologic, and gastroscopic tests. The control group consisted of six persons with no disturbances of liver function, in whom the GM was unchanged on gastroscopy and on histological investigation, In some patients (10) of group 1 and in those of the control group, PG was determined in biopsy specimens of GM obtained during gastroscopy with direct vision biopsy from the gastric fundus, whereas in patients of groups 2 and 3, the material also was

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