BLOOD SUPPLY TO THE HEART AND CORONARY VASODILATOR RESERVES IN EXPERIMENTAL MYOCARDIAL HYPERTROPHY

N. P. Stroganova and V. I. Kovalenko

UDC 616.127-007.61-008.46-008.64-092.9

KEY WORDS: myocardial hypertrophy, contractile function of the heart, coronary blood flow, coronary vasodilator reserves.

The work of Soviet researchers has led to the formulation of some principles of adaptation of the heart to an increased load, to the distinction of three basic stages of development of compensatory hypertrophy of the myocardium, and to the elucidation of some molecular mechanisms of hypertrophy and failure of the heart [1-3]. One cause of early functional insufficiency of the hypertrophied heart may be disparity between the increased weight of the myocardium and the ability of the coronary circulation to supply sufficient blood to the heart when the latter requires an increased blood supply [6]. Meanwhile many problems concerning the state of the coronary circulation and possible mechanisms of relative coronary insufficiency during hypertrophy of the myocardium remain disputed.

The aim of this investigation was to study the state of the coronary circulation and the coronary vasodilator reserves in the stage of stable myocardial hypertrophy, produced experimentally in dogs by coarctation of the aorta.

EXPERIMENTAL METHOD

Experiments were carried out on heparinized mongrel dogs weighing 15-25 kg, anesthetized with pentobarbital (25-30 mg/kg, intraperitoneally). After wide thoracotomy and with controlled respiration (the RO-2 apparatus), the ascending part of the thoracic aorta and the left ventricle were catheterized, and this was followed by electromanometric (EMT-31, Elema-Sweden) measurement of the systemic arterial pressure (SAP), the pressure in the left ventricle (LV), the maximal systolic (LVP) and end-diastolic (LVEDP) pressures, and also the first derivative (dP/dt) of intraventricular pressure (by the EMT-63 differentiator, from Elema). To assess the contractile function of the heart, force (LVP and P — dP/dt_{max}), velocity (positive and negative dP/dt_{max}), and temporal (time taken to reach dP/dt_{max}; t — dP/dt_{max}) parameters were used. The cardiac output (CO) and coronary blood flow (CBF) were measured by means of an electromagnetic flowmeter (Nihon Kohden, Japan), the slip-on transducers of which were located at the root of the pulmonary artery and in the proximal part of the circumflex branch of the left coronary artery. The coronary vasodilator reserves were estimated by the degree of reactive hyperemia arising on restoration of the blood flow after 5-10 sec of its total cessation in the circumflex branch of the left coronary artery; the maximal reactive flow (R_K), corresponding to the greatest decrease in hydraulic resistance in the territory supplied by this branch of the coronary artery, the absolute magnitude of the increase in CBF at the height of the hyperemic response, and also certain relative values, notably the index of reactivity (I_r) [8]. Calculated parameters of the general hemodynamics and cardiodynamics, such as the systolic blood volume (SV), the total peripheral resistance (PPR), the external work (A) of LV, and the index of efficiency of work (IEW) of LV, and Veragut's index (V_v) were calculated by the usual equations. To estimate the blood (oxygen) supply required by the heart, the tension-time index (TTI [12]) was used, and as the parameter characterizing the hemodynamic conditions of diastolic perfusion of the myocardium, the diastolic pressure time index (DPTI) was calculated [7]. The ratio DPTI/TTI was regarded as an indirect parameter of the adequacy of the coronary blood supply to the heart and of the transmural distribution of CBF [7, 9, 14, 15]. SAP, LVP, CO, dP/dt, and CBF were recorded synchronously on the 6NEK30 automatic writer at a speed of 25 mm/sec. Data obtained in the control series of experiments

Academician N. D. Strazhesko Kiev Research Institute of Cardiology. (Presented by Academician of the Academy of Medical Sciences of the USSR N. N. Gorev.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 100, No. 9, pp. 266-268, September, 1985. Original article submitted July 18, 1984.

 0007-4888/85/0009-1156$09.50

TABLE 1. Basic Parameters of General Hemodynamics and Cardiodynamics in Animals with Experimental Myocardial Hypertrophy

Parameter meaured	Control animals, n = 21	Animals with experimental myocardial hypertrophy (n = 9)	P
SAP, kPa:			
systolic	7,96±0,33	11,52±0,59	<0,01
diastolic	5,26±0,48	8,89±0,64	<0,01
LVP, kPa	8,19±0,68	11,67±0,87	<0,01
LVEDP, kPa	0,62±0,02	1,75±0,08	<0,01
CO, liters/min	1,16±0,13	1,09±0,14	NS
HR, beats/min	166,0±8,4	158,0±16,7	NS
SV, ml	6,9±0,3	6,93±0,95	NS
TPR, kPa/liter/min	678,8±37,5	875,8±21,9	<0,01
A, J	7,85±0,35	12,19±1,32	<0,01
IEW	1,61±0,13	1,12±0,09	<0,01
TTI	49,8±11,2	111,15±13,3	<0,01
$+dP/dt_{max}$, kPa/sec	159,3±16,4	139,9±13,6	NS
$P-dP/dt_{max}$, kPa	6,01±0,34	7,14±0,46	<0,05
$t=dP/dt_{max}$, msec	4,5±0,2	5,5±0,18	<0,05
V_v, sec^{-1}	26,51±4,82	20,69±5,96	NS
$-dP/dt_{max}$, kPa/sec	132,8±26,75	92,9±10,8	NS

TABLE 2. Basic Parameters of the State of the Coronary Circulation in Animals with Experimental Myocardial Hypertrophy

Parameter measured	Control animals, n = 21	Animals with experimental myocardial hypertrophy (n = 9)	P
CBF, ml/min	47,2±8,2	88,8±11,7	<0,01
EPP, kPa	4,64±0,1	7,1±0,14	<0,01
R_K, kPa/ml/min	0,98±0,04	0,79±0,07	<0,01
DPTI	62,3±7,1	75,66±11,7	<0,01
DPTI/TTI	1,21±0,04	0,76±0,03	<0,01
Maximal reactive flow, ml/min	95,34±12,9	145,55±22,8	<0,05
Δ KK at peak of reactive hyperemia, ml/min	48,2±11,8	58,78±12,5	NS
R_K at peak of reactive hyperemia, kPa/ml/min	0,49±0,1	0,48±0,11	NS
I_r	1,02±0,02	0,68±0,03	<0,01

Legend. EPP) Effective perfusion pressure in coronary vessels, equal to diastolic pressure in aorta — LVEDP; R_K) calculated hydraulic resistance of coronary vessels.

(n = 21) and in experiments with the model of myocardial hypertrophy (n = 9), namely coarctation of the abdominal aorta in the region of origin of the renal arteries from it, were compared. The degree of narrowing of the aorta was characterized by a pressure gradient of 2.25-3.38 kPa, and by the time of its development, which was 7-12 months.

EXPERIMENTAL RESULTS

Chronic pressure loading of the heart led to the development of moderate myocardial hypertrophy: the ratio of the weight of LV, including the septum (in grams) to the body weight (in kilograms) in the group of animals with stable and long-lasting elevation of SAP was increased on average by 37.2% compared with the control.

Data on the changes in the general hemodynamics and cardiodynamics, summarized in Table 1, agreed with data in the literature and are evidence of an increase in SAP, LVP, LVEDP, TPR, and A, and this fact was combined with an increase in TTI, an index which is the energetic equiva-

lent of the work of LV, and reflects an increase in the blood (oxygen) supply required by LV. Changes in heart rate (HR), CO, and SV, while observed in individual experiments, were not significant and irregular, and this was reflected in the absence of any statistically significant differences between these parameters in animals of the groups compared. In animals with experimental myocardial hypertrophy a certain tendency was observed for the velocity parameters of contraction and relaxation to decrease, and combined with lengthening of t-dP/dt, this can be regarded as evidence of some decrease in the rate of development of the active state, despite its sufficiently complete development, maintaining a satisfactory level of intensity of contraction of the hypertrophied myocardium. Attention must be drawn to the decrease in efficiency of work of LV in animals with experimental myocardial hypertrophy.

In agreement with data in the literature [7, 14, 15], we found an increase in CBF in animals with myocardial hypertrophy, caused hemodynamically by a fall in the resting R_K, and in conjunction with an increase in the effective perfusion pressure, this led to an increase in throughput of the coronary vessels. One result of the increase in the effective perfusion pressure, while HR and, in particular, the duration of diastole remained unchanged, was an increase in DPTI (Table 2).

The increase in the real CBF under conditions of myocardial hypertrophy and its normal value, calculated per gram of tissue [10, 14, 15] (CBF was not calculated per gram weight of myocardium in the present experiments, for we measured the volume velocity of the blood flow in one – circumflex – branch of the left coronary artery) does not rule out the possibility that adaptive reactions of the coronary system can be limited, and changes in CBF will be inadequate to meet the increased blood supply demanded by the hypertrophied heart. It is generally accepted that the basic mechanism ensuring optimization of CBF relative to the oxygen demand of the heart is realization of the coronary vasodilator reserves [4, 5]. The use of a test reaction with transient occlusion of the circumflex branch of the left coronary artery in the present experiments showed that absolute values of the maximal reactive flow and of the increase in the blood flow at the height of the hyperemic reaction in the experimental animals were greater than in the control; it was found, however, that the increase was 101.9% in the control and only 68.3% in animals with experimental hypertrophy ($P < 0.01$). The minimal hydraulic resistance, determined at the peak of reactive hyperemia, was practically equal in the animals of both groups. The presence of adequate coronary vasodilator reserves was combined, in animals with experimental hypertrophy, with limitation of the degree of realization of the adaptive powers of the coronary vessels, as shown by a decrease in the range of changes of hydraulic resistance of these vessels, a decrease in the reactivity index and the DPTI/TTI ratio, a fall of which below 0.8-0.7 coincided with reduction of the diastolic fraction of CBF and a decrease in the endocardial flow/epicardial flow ratio below 0.65. The latter reflects worsening of perfusion of the deep layers of the myocardium [7, 15] and was combined with an increase in the risk of development of ischemia of the subendocardium in the course of any physiological procedure leading to an increase in the blood supply demanded by the heart.

Thus in the stage of stable myocardial hypertrophy, ensuring adequate hemodynamic output of the heart, signs of latent insufficiency of the coronary circulation were found; their discovery is facilitated by estimation of the coronary vasodilator reserves and the indirect parameter of a change in the transmural distribution of CBF, namely the DPTI/TTI ratio.

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MECHANISM OF THE ANTISTRESS ACTION OF D-ALA^2-LEU^5-ARG^6-ENKEPHALIN

Yu. B. Lishmanov, L. N. Maslov, and M. I. Titov

UDC 612.82.015.2:547.943]-08

KEY WORDS: Leu-enkephalin analog; blood hormones; cAMP; stress.

The literature on peptide regulators contains information on activation of the system of endorphins and enkephalins in stress [8, 9], and it suggests that it may be possible in principle to use analogs of endogenous opioids to regulate the severity of stress changes in the body pharmacologically. However, opportunities for testing this hypothesis in practice have been limited by the very short half-life of opioid peptides *in vivo*. Progress toward overcoming this difficulty has been due largely to increasing their resistance to enzymic degradation by substituting glycine in position 2 of the oligopeptide chain for alanine [11]. The writers have shown that a stable analog of Leu-enkephalin has a marked antistress protective effect [3]. However, the mechanisms of this phenomenon have not yet been explained.

The aim of this investigation was to study the effect of the arginine-containing hexapeptide analog of Leu-enkephalin — D-Ala^2-Leu^5-Arg^6-enkephalin (henceforward called enkephalin) on blood plasma levels of ACTH, cortisol, and hormones of the pituitary-thyroid complex, and the cAMP concentration in adrenal and thymus tissues during stress induced by crushing the soft tissues (CST).

EXPERIMENTAL METHOD

Experiments were carried out on noninbred male albino rats weighing 160-180 g. CST was reproduced by the method in [1]. Half of all the rats were given an intraperitoneal injection of enkephalin (the product was obtained in the Laboratory of Peptide Synthesis, All-Union Cardiologic Scientific Center, Academy of Medical Sciences of the USSR, by Dr. of Chem. Sci. M. I. Titov), and the remaining animals received physiological saline (control). The rats were decapitated in groups of 8-10 at a time, 60 and 300 min after CST and immediately after decompression, under ether anesthesia, blood was taken, the thymus and adrenals were quickly removed with cold scissors on ice, and pieces of the tissues were frozen in liquid nitrogen, weighed, and homogenized in cold absolute alcohol. After centrifugation, the cAMP concentration in the supernatant was determined by the competitive protein binding method, using kits from Amersham Corporation (England). The plasma ACTH and cortisol levels were determined by radioimmunoassay using kits from CEA-Sorin (France), thyroxine (T_4) and tri-iodothyronine (T_3) were determined with kits from Byk Mallinckrodt (West Germany), and pituitary thyrotropic hormone (TTH) by a kit from Corning (USA). A Tracor Analytic Gamma-spectrometer (USA) and Mark III Beta-scintillation counter (USA) were used. The results were subjected to statistical analysis with the aid of Strelkov's tables [7] and by calculation of the Wilcoxon-Mann-Whitney nonparameteric criterion (P_u).

EXPERIMENTAL RESULTS

During preliminary experiments the optimal dose of enkephalin (1.25 nmole/kg body weight), giving an antistress effect [3], was chosen. CST for 60 min caused a marked increase in ACTH and cortisol concentrations in the plasma of the experimental rats and in the cAMP concentration in the adrenal tissue (Table 1). The cAMP level in thymus tissue after 60 min of CST also was raised, evidently due to stress-induced hypercatecholaminemia, for the lymphocyte membranes are richly supplied with adrenoreceptors [13]. Of the thyroid hormones, a sig-

Laboratory of Radionuclide Methods of Investigation, Siberian Branch, All-Union Cardiologic Scientific Center, Academy of Medical Sciences of the USSR, Tomsk. (Presented by Academician of the Academy of Medical Sciences of the USSR R. S. Karpov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 100, No. 9, pp. 268-270, September, 1985. Original article submitted October 31, 1984.

