Rational Drug Correction of Systemic Inflammatory Response Syndrome in Severe Experimental Heart Failure

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A course of adenocine (cardiotonic drug with a pronounced cardioprotective effect) for severe experimental heart failure caused by toxic allergic myocarditis (for 10 days) more effectively restored the systolic and diastolic function of the heart and arrested systemic inflammatory response syndrome than traditional therapy with angiotensin-converting enzyme inhibitors, β-adrenoblockers, or diuretics in combination with neoton. Adenocine is characterized by a synergistic effect, and none of its ingredients alone (nicotinamide adenine dinucleotide, inosine, β-acetyldigoxin, oxyfedrine) exhibits similar effect.

Key Words: *heart failure; central hemodynamics; systemic inflammatory response syndrome; adenocine*

Systemic inflammatory response syndrome (SIRS) and its key factors (endotoxemia, tissue dysoxia, and dysfunction of the defense systems of the body) trigger and maintain the vicious circle of the development and progress of many diseases, for example, myocardial infarction and coronary heart disease, atherosclerosis, arterial hypertension, chronic heart failure (HF) irrespective of the etiology, osteoarthrosis deformans, gestosis, radiation sickness, and chronic intoxication [1,4]. At the beginning of SIRS development, toxins and metabolites are released into the blood, lymph, interstitial fluid from the pathological focus (inflammation, trauma, tumors, *etc.*). If the defense systems neutralize these substances, it is possible that no clinical symptoms will manifest, though a latent or transitory SIRS is presumably a component of any disease [1,4,5]. Decompensation of the defense and regulatory systems (secretory, detoxification (microsomal oxidation, conjugation), or mononuclear macrophageal) triggers accumulation of endogenous toxins (the stage of accumulation of primary affect products). Tissue dysoxia serves as the basis for the formation of an abnormal mechanism of oxygen extraction by peripheral tissues because of insufficient desaturation of hemoglobin in capillaries. Systemic release of cytokines, catecholamines, angiotensin II, and prostaglandins promotes the formation of a tissue shunt with reduced perfusion [1,2,4].

We studied the efficiency of adenocine, an original drug with a nanotechnological effect, for SIRS arrest in HF.

MATERIALS AND METHODS

Experimental toxic allergic myocarditis served as the model of SIRS with predominating severe HF.

The study was carried out on 120 Chinchilla rabbits (2.4-4.1 kg) during autumn and winter. Of these, 21 animals were intact and 99 had severe HF caused by 10-day toxic allergic myocarditis [6] and received the following treatment: controls (injected with 2 ml saline, n=13), adenocine (90.875 mg/kg intravenously once daily, n=14), standard therapy

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(nonsteroid antiinflammatory drugs, angiotensin-converting enzyme inhibitor, diuretics, *n*=12) fortified by neoton, inosine (80 mg/kg, *n*=9), NAD (0.5 mg/kg, *n*=7), NAD+β-acetyldigoxin (0.5 mg/kg and 0.075 mg/kg, respectively, *n*=9), NAD+oxyfedrine (0.5 mg/kg and 0.3 mg/kg, respectively, *n*=9), and oxyfedrine (0.3 mg/kg, *n*=7). Drug therapy was started 5 days after administration of the resolving dose of staphylococcal toxin and was carried out for 5 days. The animals were kept in a vivarium under standard conditions on standard rations. Euthanasia was carried out under hexenal narcosis. In experimental rabbits, body weight, heart rate, respiration rate, ECG in three standard and thoracic leads, and intensity of congestion symptoms at the periphery were evaluated during the experiment. Intracardiac hemodynamics was studied under conditions of regulated respiration with atmospheric air in rabbits narcotized with urethane and chloralose (200 and 50 mg/kg, respectively) with droperidol-diphenhydramine-atropine premedication (0.5 ml of 0.25, 1.0, and 0.1% solutions, respectively). The thorax was opened, the pericardium dissected, and a catheter connected to a EMT-118 monometric pickup and a EMT-34 mingograph amplifier (Siemens-Elema) was introduced into the left ventricle. The dynamics of pressure rise and drop in the left ventricle and ECG in standard lead II were recorded. The systolic pressure developed by the left ventricle (P_{lv}), maximum rates of pressure rise (dP/dt_{max}) and drop (dP/dt_{min}), and end-diastolic pressure (EDP) were estimated by the intraventricular pressure curve and its first derivative [5]. The severity of SIRS was evaluated by the increase in the content of medium-molecular-weight molecules in the plasma and erythrocytes [5]. Histamine and serotonin concentrations were measured by the fluorometric method, proinflammatory IL-6 and IL-1β and antiinflammatory IL-10 were assayed by ELISA using the BioSource International test system, lactate by the Lactic Acid REA Tdx kit (Abbott), vascular cell adhesion molecule (VCAM-1c) by spectrofluorometry using highly sensitive EIA, histamine, and serotonin.

The results were statistically processed using SPSS 10. The significance of differences was evaluated using Student's *t* test.

RESULTS

After three days, the peak of erythrocyte optical density increased 2.87 times ($p<0.001$) and reached 0.82±0.04, plasma extinction increased 4-fold ($p<0.001$) and reached 1.23±0.15 (due to release of biochemical substrates of endogenous intoxication, substances of catabolic origin, lipid peroxides, products of cells degradation, *etc.* into plasma). Hence, 3 days after injection of staphylococcal toxin, toxic products not only accumulated in the myocardium (target organ): inflammatory and mosaic focal degenerative necrotic involvement with secondary hyperergic allergic reaction developed. On day 10, plasma extinction 3.9 times and erythrocyte extinction 2.9 times surpassed the normal (Table 1). Changes in spectrograms together with almost 2-fold increase in the content of VCAM-1c confirmed the persistent release of medium-molecular-weight molecules from the focus of aggression and their adsorption on the glycocalyx or in erythrocytes (Table 1). In animals with HF, the systemic antiinflammatory response to allergens manifested by elevated level of inflammation markers (histamine content increased more than 2-fold, serotonin level increased 3.5 times; Table 2) and by shifts in se-

TABLE 1. Changes in Optical Density of Plasma and Erythrocytes as an Integral SIRS Index in HF

Group	dP/dt_{max}, mm Hg×sec^{-1}	dP/dt_{min}, mm Hg×sec^{-1}	EDP, mm Hg	Erythrocytes, λ=258 nm	Plasma, λ=282 nm
Basal level	1350±55	1650±120	4.8±0.4	0.56±0.05	0.23±0.04
Control	899±98**	836±79***	12±2***	1.61±0.09***	0.95±0.07***
HF+TT	1000±65*	924±92**	10.4±0.5***	1.52±0.05***	0.75±0.08**+
HF+adenocine	1180±87	1435±92	4.4±0.5	0.52±0.05	0.25±0.08
HF+inosine	980±25**	1007±35*+	8.9±0.8*+	1.07±0.08*+	0.75±0.08*
HF+NAD+β-AD	1521±96+++	1494±106+	6.5±0.4*+	0.78±0.05*+	0.59±0.06*+
HF+NAD+β-AD+oxyfedrine	1456±87+++	1238±37*+	5.9±0.3*++	0.72±0.07*++	0.51±0.05++
HF+β-AD	1160±107*+	1167±90*+	6.8±0.3*+	0.85±0.07*+	0.88±0.06*
HF+oxyfedrine	1000±43*+	1234±40*+	8.9±0.8*+	0.89±0.05**+	0.79±0.07*

Note. Here and in Tables 2, 3: TT: traditional therapy; β-AD: β-acetyldigoxin. *$p<0.05$, **$p<0.01$, ***$p<0.001$ compared to basal level; +$p<0.05$, ++$p<0.01$, +++$p<0.001$ compared to control.

TABLE 2. Dynamics of Inflammation Markers (Serotonin and Histamine) in Heart Failure Caused by Toxic Allergic Myocarditis

Group	Histamine, nmol/liter	Serotonin, nmol/liter
Basal level	35±4	0.26±0.03
Control	78±8***	1.32±0.14***
HF+TT	70±6***	1.09±0.10***
HF+adenocine	42±3++	0.35±0.04+++
HF+inosine	48±5+	0.97±0.08***+
HF+NAD+β-AD	52±6*+	1.04±0.06**+
HF+NAD+ β-AD+oxyfedrine	56±7**+	0.38±0.03*+
HF+β-AD	58±7*+	0.87±0.07**++
HF+oxyfedrine	59±6*+	0.93±0.12**++

condary inflammation factors (content of proinflammatory IL increased almost 2-fold in comparison with the control; Table 3).

Traditional therapy did not promote stabilization of intracardiac hemodynamics, reduction of endotoxemia (Table 1), levels of inflammation markers (Table 2), level of VCAM-1c, and the proportion of pro- to antiinflammatory cytokines (Table 3). A course of inosine (80 mg/kg) in HF led to a 21% reduction of erythrocyte and plasma extinction, 37% reduction of histamine and 26.5% reduction of serotonin levels (Table 2); VCAM-1c content decreased by 19%, content of proinflammatory cytokines by 12.5% (Table 3). Positive shifts in the intracardiac hemodynamic were observed (Table 1). A course of β-acetyldigoxin (0.075 mg/kg) led to a reduction of erythrocyte (1.7 times) and plasma (32%) extinction. Oxyfedrine (0.3 mg/kg) reduced these parameters by 1.85 and 1.3 times, respectively. The content of histamine decreased by 25.6 and 26%, of serotonin by 38 and 30%, of VCAM-1c by 21 and 21% after β-acetyldigoxin and oxyfedrine treatment, respectively; the level of IL-6 decreased by 25% in both cases, while the level of IL-1β did not change under the effect of β-acetyldigoxin and decreased by 25% in response to oxyfedrine (Table 3). β-Acetyldigoxin and oxyfedrine monotherapy led to a drop (by 30 and 32%) or increase (by 29 and 11.2%, respectively) of left-ventricular pressure and to EDP drop (by 43 and 25.8%, respectively). Simultaneous treatment with NAD and β-acetyldigoxin led to an almost 2-fold drop of extinction level without appreciable changes in optical density of the plasma (Table 1). Simultaneous treatment with NAD and β-acetyldigoxin largely accelerated pressure rise and drop in the left ventricle and reduced EDP similarly as β-acetyldigoxin monotherapy (Table 1). Simultaneous treatment with NAD, β-acetyldigoxin, and oxyfedrine more effectively reduced EDP and eliminated symptoms of endotoxemia than monotherapy with each of these drugs (Tables 1-3). Adenocine, containing NAD (0.5 mg), β-acetyldigoxin (0.075 mg), oxyfedrine (0.3 mg), and inosine (80 mg) promoted normalization of the parameters of central hemodynamic and reduction of endotoxemia to levels observed in normal animals (Table 1). Adenocine therapy reduced blood levels of histamine (by 46%) and serotonin (by 73%). A course of adenocine monotherapy eliminated lactatacidosis (disorders in activities of aerobic and anaerobic glycolysis), shifted the pro-/antiinflammatory cytokine proportion towards antiinflammatory cytokines, and significantly reduced production of VCAM-1c (Table 3), which indicated normalization of endothelial function.

Hence, adenocine exhibited a pronounced positive effect on the central hemodynamic parameters in severe HF caused by toxic allergic myocarditis and arrested the development of SIRS more effectively than monotherapy with inosine, NAD, oxyfedrine, or cardiac glycoside β-acetyldigoxine in the same doses or therapy with combination of NAD, β-acetyldigoxin, and oxyfedrine (Tables 1-

TABLE 3. Effect of Adenocine on Biological Markers of Endotoxemia in HF Caused by Toxic Allergic Myocarditis

Group	Lactate	VCAM-1c	IL-6	IL-1β	IL-10
Basal level	1.7±0.2	267±12	42±2	35.6±1.5	13±3
Control	2.9±0.3**+	536±37**	65±9*	56±7*	5±2+
HF+adenocine	1.6±0.2++	285±42+	45±5**	47±5*	15±4++
HF+inosine	2.2±0.3	432±25*+	57±4*	49±4*+	9.5±0.8*+
HF+NAD+β-AD	1.9±0.2*	324±16*+	50±4*+	46±5*	5.4±2.0**
HF+NAD+β-AD+oxyfedrine	1.8±0.2+	305±35+	47±4*	47±4*+	12±3+
HF+β-AD	2.0±0.2*	423±29*+	50±4+	65±8*+	7.7±1.7*+
HF+oxyfedrine	1.9±0.2*	424±36*+	49±4+	50±5*+	7.9±0.5*+

3). These data and data on adenocine use in patients with chronic HF [1] suggest it as the drug of choice for arresting the development of hemostasis systems failure and progress of SIRS to irreversible decompensation phase with polyorgan failure syndrome.

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