THE NEW ARMENIAN MEDICAL JOURNAL
Volume16 (2022), Issue 4 p.54-63

DOI: https://doi.org/10.56936/18290825-2022.16.4-54

CALCIUM-REGULATING HORMONAL SYSTEM IN CARDIAC FUNCTIONAL ACTIVITY

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Received 26.05.2022; accepted for printing 18.08.2022

Abstract

The variance of calcium homeostasis is known as a risk factor for the development of heart failure. A study of calcium-regulating hormones is a crucial element to understand underlying pathophysiological mechanisms of heart failure. Pro-inflammatory factors, released during mechanical, hypoxic or bacterial damage of myocardial cells, lead to an imbalance of calcium and disrupt to heart function. The investigation of mentioned factors influence mechanism on the heart, is an urgent solution for preventing the development of heart failure.

Present study aimed to reveal the role of calcium-regulating hormones in heart functional activity and their possible involvement in the development of heart failure. The pharmacological analysis of the action mechanism of bacterial lipopolysaccharides on heart functional activity was carried out using a calcium channel blocker.

The concentrations of calcium-regulating hormones in blood serum in patients suffering from heart failure was determined by immunoassay enzyme method, and ionized calcium and inorganic phosphate concentrations - by spectrophotometric method. The photoelectrical method was used to determine the direct effect of calcium-regulating hormones and possible calcium-dependent action mechanism of bacterial lipopolysaccharides on the isolated frog's heart.

Clinical findings show that chronic heart failure is accompanied by shifts in the calcium-regulating hormonal system and blood electrolyte balance. In vitro experiments on isolated frog hearts have shown the potentiating effect of parathyroid hormone, its related protein, calcitonin, and vitamin D_3 on myocardial contractility. It has been shown, that bacterial lipopolysaccharides suppress the contractile and rhythmogenic functions of the myocardium, and their action can be mediated through a calcium-dependent mechanism.

The increase of parathyroid hormone in chronic heart failure has a protective significance aimed at maintaining the contractile ability of a weakened myocardium and preserving cardiac output. Bacterial lipopolysaccharides are able to suppress functional activity of the heart by calcium-dependent mechanism.

Keywords: *chronic heart failure, isolated heart, parathyroid hormone, parathyroid hormone-related protein, vitamin D, calcitonin, calcium, bacterial lipopolysaccharides.*

Introduction

Calcium-regulating hormonal system includes parathyroid hormone (PTH), vitamin D_3 and calcitonin (CT). The disbalance of calcium homeostasis leads to dysfunctions of the heart conductive system, myocardial hypertrophy, calcification of the heart valves, ischemia, arterial and renal hyperten-

Cite This Article as:

Harutyunyan K.R., Melkumyan K.V., Abrahamyan H.T., Adamyan S.H., Khudaverdyan D.N., Ter-Markosyan A.S.(2022). Calcium-regulating hormonal system in cardiac functional activity. The New Armenian Medical Journal, 16(4): 54-63, https://doi.org/10.56936/18290825-2022.16.4-54

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sion [*Fischer E et al., 2014*]. Meta-analysis indicated that increased PTH level (hyperparathyroidism) is independently associated with an increased risk of heart failure in the general population [*Meng F et al., 2016*]. This risk is more pronounced among older men. However, it is suggested that a well-designed randomized controlled trial should be carried out to evaluate whether reducing the levels of PTH will decrease heart failure risk or attenuate the disease progression.

Amplification of calcium current and maintenance of heart contractility by parathyroid hormone were revealed in experimentally-induced myocarditis in rats [*Wu G et al., 2018*]. Immunohistochemical analysis established the activation of reparative and remodeling properties of damaged heart cells in the post-infarction period by parathyroid hormone [*Peguero-Rivera A, Corder C, 1992; Brunner S et al., 2012*]. Increased sensitivity of cardiomyocytes to calcium ions and an increase in contractility and energy supply to the rat myocardium during systemic administration of PTH are found [*Jansen J et al., 2003*].

The synthesis of parathyroid hormone-related protein (PTH-rP) is stimulated in the myocardium in violation of its blood supply in chronic heart failure [*Ogino K et al., 2002*]. PTH-rP can enhance myocardial contractile function under experimentally induced hypoxia [*Lütteke D et al., 2005*]. The amount of PTH and PTH-rP in the blood can be considered a biomarker for the diagnosis of ischemia, which can lead to the progression of chronic heart failure [*Kubiak G et al., 2017*].

It is also assumed that vitamin D prevents the development of atherosclerosis, cardiac muscle hypertrophy and fibrosis of heart valves [*Franczyk A et al., 2014*] and its chronic deficiency can increase the risk of mortality caused by hypertension, coronary heart disease, cardiomyopathy, chronic heart and kidney failure [*Tamayo M et al., 2017*].

Despite numerous studies elucidating the role of calcium-regulating hormonal system in the regulation of cardiac activity [*Ogino K et al., 2002; Brunner S et al., 2012; Franczyk A et al., 2014; Tamayo M et al., 2017*], the effect of CT is still unclear. A unique study indicates that CT has a dose-dependent suppressive effect on the inotropic-chronotropic activity of isolated cardiomyocytes in the rat. Moreover, its negative inotropic-chronotropic effect was more pronounced in atrial sections than in the ventricular [*Chiba S, Himori N, 1977*]. At the same time, other authors [*Peguero-Rivera A, Corder C, 1992*] observed a slight increase in the mean arterial pressure after systemic administration of CT to animals.

Inflammatory processes of various etiologies (septic myocarditis, ischemic hypoxia, hypertrophic or idiopathic cardiomyopathy, etc.) often lead to the development of chronic heart failure [*Tzeng H et al., 2008; Asavarut P et al., 2013*]. Inflammatory mediators of damage-associated and pathogen-associated molecular patterns groups are combined into a group of immunity alarmins [*Shauer A et al., 2013; Lin L, Knowlton A, 2014*]. Excessive secretion of immunity alarmins disturbs calcium homeostasis, mitochondrial respiration, etc., as a result of which contractile function of the heart and blood ejection fraction suffer, which eventually lead to the development of chronic heart failure [*Drosatos K et al., 2015; Cai Z et al., 2020a; Adamyan S et al., 2021*].

The above testifies in favor of monitoring the status of the calcium-regulating hormonal system and the blood electrolyte (calcium, phosphorus) composition in patients suffering from chronic heart failure. The examination of physiological concentrations of individual components calcium-regulating hormonal system in the regulation of pacemaker and contractile activity of the heart is also relevant.

As already noted, pro-inflammatory factors may be involved in the pathological process of the development of heart failure. Some immunity alarmins (eg, S/100A8-9, HSP60, HSP70) have a calcium-binding ability and provoke chronic heart failure as a result of prolonged and excessive activation [*Shauer A et al., 2013; Drosatos K et al., 2015; Xia C et al., 2018; Cai Z et al., 2020b*]. PTH is able to exhibit a protective effect, aimed at maintenance of pacemaker and contractile activity of the heart during cardiac disorders induced by

To overcome it is possible, due to the uniting the knowledge and will of all doctors in the world

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lipopolysaccharides (LPS) of bacterial origin [*Ter-Markosyan A et al., 2021*]. The cardioprotective effect of PTH against the background of LPS administration is possibly associated with the calcium-regulating ability of the hormone [*Ter-Markosyan A et al., 2017*]. To confirm this hypothesis, a pharmacological analysis of the action mechanism of LPS on the functional parameters of the heart was carried out using verapamil - a calcium channel blocker.

We strongly believe that such a comprehensive approach will help to identify in time the risk of developing heart failure and choose an efficient treatment strategy for patients suffering from this pathology.

MATERIAL AND METHODS

The blood serum of individuals at the age of 40-65 years was examined. The patients, 31 women and 57 men, suffering from chronic heart failure II, III groups according to the New York Heart Association classification were involved in the study. Patients of the II group were under outpatient monitoring. Patients of the III group were in the process of inpatient treatment in the Scientific Research Institute of Cardiology of the Ministry of Health (Armenia). The healthy volunteers (13 women and 26 men, control group) expressed no objective and subjective complaints from the cardio-vascular system and had normal blood pressure, ultrasound and ECG of the heart. According to the provisions of the Institutional Ethics Committee, all patients were warned of ongoing analysis and gave their written consent. Research complied with the principles of the Helsinki Declaration and was controlled by the Ethical Committee of Yerevan State Medical University.

Venous blood of patients and volunteers was centrifuged at 3000*g* for 15 minutes at 4°C and after separating the blood cells, the obtained serum was frozen and stored at -70°C. The immunoassay enzyme method was used to determine the concentrations of vitamin D (kit from Global Diagnostics B, Belgium), calcitonin (kit from DRG International, Germany), PTH (kit from DRG International, Germany) in the blood serum. The concentrations of ionized calcium and inorganic phosphate were determined by a spectrophotometric method (kit from Biosystems, Spain).

Model experiments were performed on isolated hearts of frogs (*Rana temporaria*). The maintenance and use of experimental animals were correspondent to the provisions of the Institutional Committee of Bioethics. All stages of experiments were directly controlled by the Ethical Committee of Yerevan State Medical University. The choice of isolated organ methods allows for studying the mechanisms of direct influence of biologically active substances *in vitro* without the influence of other factors, such as neuronal, hormonal etc. [*Olejnikova V et al., 2015*]. The frog's heart is a convenient object of study due to the presence of multiple ion channels (voltage-gated and mechano-gated, ligand-sensitive). At the same time, being a cold-blooded animal, frog metabolism is energy efficient, so its heart can be contracted for a long time [*Burggren W, Warburton S, 2007*]. For *in vitro* studies, a frog's heart was surgically removed from a body, after the animal was euthanized by ether. The isolated heart was placed in a photoelectric device chamber with Ringer's solution for cold-blooded animals (0.65% NaCl, 0.018% KCl, 0.02% $CaCl_2$, 0.03% NaH_2PO_4, pH = 7.4, t = 15-18°C).

In the I series of experiments PTH, PTH-rP, vitamin D_3 (1-25 dihydroxy-vitamin D_3,) or CT (all from Sigma, USA) were added in different sets of experiments and final concentrations of mentioned hormones in the incubation medium were equal to physiological, 10^{-10} *M*.

In the II series of experiments, LPS (Sigma) at a dose of 10 *μg/ml* or LPS in combination with a calcium channel blocker verapamil (10^{-5} *M*) (Sigma), were added into the incubation medium, where an isolated frog heart is located.

Registration of the heart functional activity (pacemaker rhythm, amplitude of heart contractions) was performed by the specific photoelectric device (LLC BioArt, Armenia) that works according to the principle of dispersion of the luminous flux. Heart contraction changed the angular distribution of the light beam and led to a corresponding change in the indices of the photodetector. The semiconductor laser (MOD HLDPM10–650–3, Huey Jann Electronics, China) was used as a radiation source, and a FD-256 silicon (Si) photodiode (Russia) was used to estimate the light intensity. After amplification, the photo-detector signals were

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subjected to analogue-to-digital conversion (Takfly communications co. Ltd, China) and stored. The sampling time for analogue-to-digital conversion was 10 *ms*. The custom-developed software (in the LabView environment) allowed visualization and subsequent analysis of the recorded signals. The amplitude and frequency of the frog's heart contractile activity were evaluated. Averaged amplitude and time-frequency curves of the contractile activity of the heart were plotted for each series of studies (15-20 animals in each series). To unify the amplitude distributions of the functional activity of the heart, the initial values of their registration were taken as 100%. The frequency of contractions is expressed in absolute values. The analysis of the recorded signals was carried out in two stages. First, to assess the changes in the amplitude of the heart contractions in dynamics, the curves of the recorded signals were plotted. Second, to analyze the frequency of heart contractions, the signals were normalized by the calculated current amplitude of contractions and their peak values were distinguished by the amplitude discrimination method. Statistical analysis of the obtained data was performed by using "Origin 8.5" software.

Clinical data were statistically processed using the "Statistica 10" software. Results are expressed as the mean value (M) ± standard deviation (SD). The differences between groups were determined by Student's *t*-test with a significance of 0.05.

Results

Monitoring of the calcium-regulating hormonal system status in patients suffering from chronic heart failure revealed the gender-depended changes of examined parameters. We observed significant shifts in all studied parameters in women suffering from chronic heart failure, compared with the control group (Table 1). In men, only calcium and vitamin D concentrations were significantly changed (Table 2). However, the general trend of changes in the indices in men and women was similar, except for the calcium and PTH concentrations. Unlike men, in women with chronic heart failure, the concentration of calcium was lower, and PTH was above the norm.

Interestingly, the concentration of the vitamin D was significantly lower than the standard norm (25-80 *ng/ml*) both in healthy volunteers and in patients suffering from heart failure. A negative shift of CT and a positive one of inorganic phosphate concentrations with varying degrees of significance were observed in patients of both genders.

To confirm the role of the calcium-regulating hormonal system in the regulation of the functional activity of the heart, further experiments (I series) were carried out on an isolated frog heart. The dynamics of changes in the functional activity of the heart (amplitude and heart rate) under the action of PTH, PTH-rP, vitamin D_3, and CT *in vitro* are presented in Figure 1. In the control group experiments, when a physiological solution was added to the incubation medium, cardiac activity decreased. Then, in different series of experiments, PTH, PTH-rP, vitamin D_3 or CT was introduced into the incubation medium. In general, the trend of the amplitude shifts of heart contractions under the action of these substances was unidirectional, however, shifted in time (Fig. 1A). PTH increased the strength of the heart contractions to 130% at the 40th minute of the experiment (Fig. 1A). Unlike other components of the calcium-regulating hormonal system, PTH rather maintained the contractile function of the heart, causing an inotropic-sta-

Table I.

Blood serum electyrolites and hormones in healthy individuals and patients with chronic heart failure

Investigated parameters	Women		Men	
	Control n=13	CHF n=31	Control n=26	CHF n=57
Ionized calcium (*mmol/l*)	0.79 ± 0.04	0.53 ± 0.09**	0.64 ± 0.11	0.79 ± 0.21*
Inorganic phosphate (*mmol/l*)	1.19 ± 0.25	1.64 ± 0.16**	1.29 ± 0.18	1.47 ± 0.33
Parathyroid hormone (*pg/ml*)	35.74 ± 1.14	40.26 ± 3.12*	37.18 ± 2.88	35.15 ± 1.46
Vitamin D (*ng/ml*)	14.68 ± 2.83	11.22 ± 1.62*	16.83 ± 3.71	13.14 ± 2.83*
Calcitonin (*pg/ml*)	5.44±1.10	2.54 ± 1.59*	6.01 ± 1.61	5.47 ± 3.92

*Notes: All data are shown as mean ± SD, * significance at p<0.05; ** significance at p<0.01*

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bilizing effect, while PTH-rP initiated a biphasic increase in inotropic activity (Fig.1. A). The initial peak was observed within 10-20 min of introduction of PTH-rP and caused the increase of the amplitude up to 260%, then the amplitude of contractions slightly decreased, but did not reach the initial level. The second peak was recorded at the 40-50th minute and reached up to 280%. Big (within 230%) amplitude of heart contractions in the interpeak intervals indicates a cardio-potentiating effect of PTH-rP.

Vitamin D_3 increased the amplitude of the heart contractions up to 147% after 10 minutes of its introduction, and then the index decayed to 50% and increased again to the maximum value - of 148% at the 100th minute (Fig. 1A).

CT had the highest and fastest inotropic activity, causing a threefold increase of the heart contraction amplitude (300%) within 10 minutes after introduction (Fig.1 A). This was followed by a gradually decreased of this parameter that reached approximately 55% at the 50-60th minute.

Heart rate (Fig. 1B) had an initial tendency to decrease (mainly during the first 30 minutes), and then to increase in different time intervals under the action of these drugs, except for PTH (Fig. 1B). The effect of PTH appeared as a smooth increase in chronotropic activity, peaking at the 50th minute of the introduction. The fact of prolongation of the isolated heart functioning under the influence of calcium-regulating hormones is important and indicates the maintenance of its viability.

The longest time of an isolated heart activity was observed when vitamin D_3 was introduced into the incubation medium: the active mode of the heart lasted more than 100 minutes.

A pharmacological analysis of the action mechanism of LPS on the functional parameters (pacemaker rhythm, contractility) of the heart was carried out in the II series of experiments. The data obtained indicate the suppression of the pacemaker and contractile function of the heart by lipopolysaccharide (Fig. 2 A, B). The isolated heart functioned during 10-20 minutes., The amplitude of heart contractions dropped to 23% compared to the control (100%) (Fig. 2 A), and the frequency – from 48 *beat/min* to 42 *beat/min* (Fig. 2 B). The combined action of LPS with verapamil slowed down the development of negative inotropic and chronotropic effects. Reducing the strength of heart contractions up to 23% compared to control (100%) was recorded only at the 30-40th minute of the experiment. The maximum shift in the frequency of contractions was 30 beats/min versus 42 beats/min - under the influence of LPS.

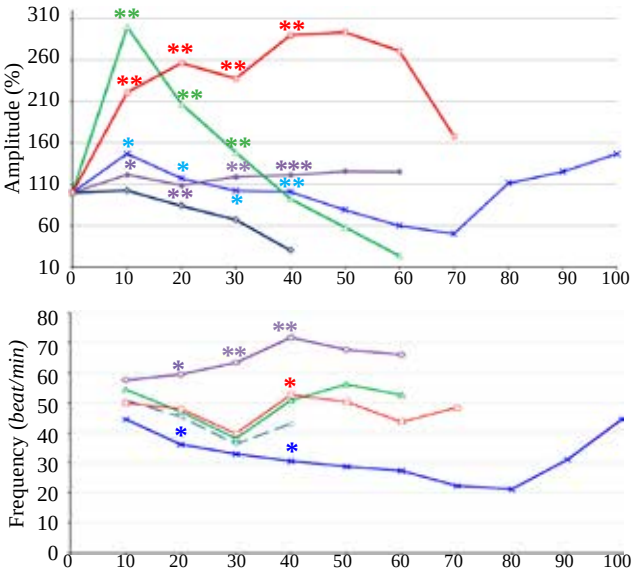

FIGURE 1. *Dynamics of amplitude changes (as a percentage of the initial level, A) and frequency (in beat/min, B) in the presence of: ■ parathyroid hormone (PTH); ■ parathyroid hormone related protein (PTH-rP); ■ vitamin D_3 and ■ calcitonin (CT) compared with ■ control. (Significance *- p<0.05, **-p < 0.01)*

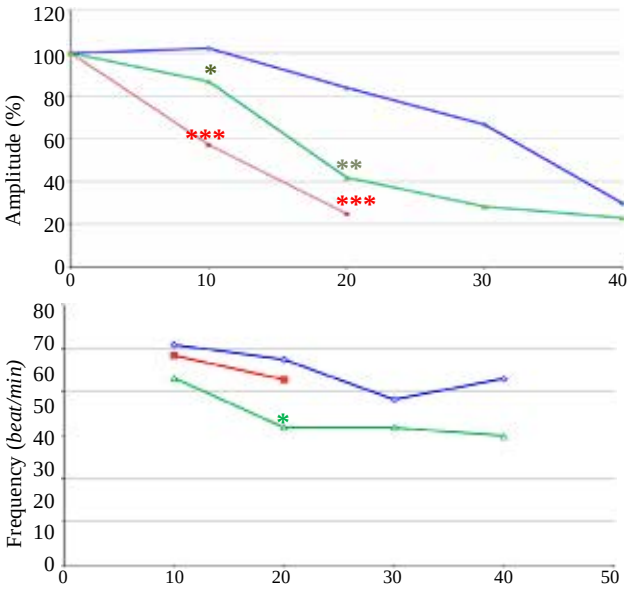

FIGURE 2. *Dynamics of amplitude changes (as a percentage of the initial level, A) and frequency (in beat / min, B) in ■ control, in the presence of ■ LPS (10 μg/ml) and ■ LPS with verapamil (10^{-5}M). (Significance *- p<0.05, **-p < 0.01)*

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Discussion

Our results of clinical observations demonstrated an alteration of calcium-phosphorus homeostasis and calcium-regulating hormonal system status in patients with chronic heart failure. Increased level of PTH in women probably is the result of a compensatory stimulation of its synthesis as a response to hypocalcemia. This phenomenon has a cardioprotective effect, aimed at maintaining the contractile function of a weakened myocardium. A similar conclusion was also made by us based on the results of previous clinical studies [*Arakelyan K et al., 2007; Ter-Markosyan A et al., 2018; Adamyan S et al., 2021*] and proved by other authors [*Khudaverdyan D, Ter-Markosyan A, 2000; Brunner S et al., 2012; Sugimoto T et al., 2014*]. We have found that in women suffering from chronic heart failure, the concentration of PTH-rP and its related protein increased in the I to IV group by New York Heart Association. These changes were significant only in group IV in men. Concentrations of blood electrolytes, including sodium and potassium ions, also showed gender-dependent changes [*Arakelyan KP et al., 2007*].

In the present study, we have observed the positive shift of PTH in the blood serum of patients with chronic heart failure that was accompanied by a decrease in the CT concentration, and, most importantly, a significant decrease in the level of vitamin D in patients of both sexes. A similar phenomenon was presented by other authors [*Polat V et al., 2015*]. Comparing our results with the clinical observations of other researchers [*Nitsa A et al., 2018*] relative to the cardioprotective value of vitamin D, it is assumed that its deficiency in chronic heart failure may be a factor in the further escalation of the disease. Moreover, due to the activating effect on the reparative remodeling functions of cardiomyocytes, vitamin D promotes the survival of patients with myocardial infarction and prevents the development of chronic heart failure [*Saponaro F et al., 2017*].

We have observed an increase in PTH levels in the blood of patients suffering from chronic heart failure, which could represent a compensatory mechanism aimed at maintaining the pacemaker and contractile activity of the weakened heart muscle. This is in agreement with the opinion of other authors [*Brunner S et al., 2012*]. At the same time, low levels of PTH, vitamin D could be considered factors for unfavorable prognosis of myocardial infarction and chronic heart failure [*Brunner S et al., 2012; Nitsa A et al., 2018*]. In chronic heart failure the calcium-regulating hormones have crucial significance because of their exclusive action on cardiac functional activity.

Parathyroid hormone has a positive inotropic and chronotropic effect on the isolated heart. It is noteworthy that the action of PTH appears to stabilize the inotropy and may have a protective/modulatory value, aimed at maintaining the contractile function of the heart, but at the same time, protecting the heart from excessive stress [*Brunner S et al., 2012; Wu G et al., 2018*].

PTH-rP and vitamin D_3 cause biphasic changes in cardiac activity, however, they prolong the time of functioning of an isolated heart more than other hormones of calcium-regulating hormonal system. A similar effect ("U"-shape effect) of vitamin D_3 was observed in experiments conducted on isolated cardiomyocytes of mice [*Meng F et al., 2016*], and cells of hypophysis [*Tornquist K, Tashjian A, 1989*]. We also found a similar biphasic effect of PTH in neurons [*Kostyuk P et al., 1992*]. Moreover, the "fast" phase of the action of PTH was mediated by direct activation of the calcium current, and the slow one, protein kinase C, eventually again initiating the calcium mechanism [*Khudaverdyan D, Ter-Markosyan A, 2000*].

CT has a rapid but short-term inotropic-activating effect. At the same time, the chronotropic activity of the heart is initially suppressed and then activated later. Interestingly, CT is an antagonist to PTH and vitamin D_3 in the regulation of calcium homeostasis but shows a synergistic cardio-potentiating effect during the first 10-20 minutes of action. In this aspect, our finding contradicts the literature data indicating the suppressive effect of CT on inotropic and chronotropic cardiac activity [*Chiba S, Himori N, 1977*].

An increase in the amplitude of heart contractions under the action of individual components of the calcium-regulating hormonal system has a positive significance for the maintenance of the heart activity in chronic heart failure and argues in favor of their cardioprotective role [*Muscogiuri G et al., 2017; Nitsa A et al., 2018*]. However, the biphasic fluctuations of the cardiotropic effects of vitamin

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D_3 which we observed in our experiments are not always desirable in clinics. For example, enhanced sensitization of cardiomyocytes to calcium ions can lead to hyper-contractility of the myocardium and sudden death in cardiomyopathy [*Ren X et al., 2018*].

According to the data presented in the literature [*Shauer A et al., 2013; Lin L, Knowlton A, 2014*], the development of chronic heart failure may be conditioned by excessive activation of immunity alarmins of the damage-associated and pathogen-associated molecular patterns groups. In *in vivo* experiments, we revealed significant violations of ECG parameters (particularly, PR and QT intervals), as well as disorders of contractile and pacemaker activity of the heart in condition of intraperitoneal administration of LPS to animals [*Harutyunyan K et al., 2022*]. However, these shifts were more smoothed out, and heart activity was maintained much longer if the administration of LPS was combined with a physiological concentration of 1-34 fragment of PTH [*Ter-Markosyan A et al., 2021*].

The obtained phenomenon proves the protective role of PTH during disturbances of the rhythmogenic and contractile functions of the heart under the influence of LPS. It is well known, that PTH is the main regulator of calcium homeostasis in the organism. According to our data, PTH ensures cardioprotective effect by regulation of calcium flow in the myocardium [*Ter-Markosyan A et al., 2017*], which corresponds to the literature data [*Jansen J et al., 2003; Toribio R et al., 2005; Brunner S et al., 2012; Gruson D et al., 2014*]. The foregoing allows us to assume that the effect of LPS on the heart is related to calcium disbalance in the cardiac tissue [*Rattis B et al., 2021*]. For this purpose, we investigated the mechanism of LPS action on the pacemaker and contractile activity of the heart *in vitro*, using a calcium channel blocker verapamil. An alone application of LPS led to negative chronotropic and inotropic effects. In combined application of LPS with verapamil, these shifts were manifested later. In condition of blockade of calcium channels with verapamil, a sharp decrease of the pacemaker activity of the heart, compared with alone action of LPS, was revealed. This indicates the involvement of a calcium-dependent factor in the mechanism of action of LPS. At the same time, against the background of calcium channel blockade, the suppression of the contractile function of the heart by lipopolysaccharide was less expressed. The literature data shows the weakening of the negative inotropic effect of LPS by verapamil during the shock in rats conditioned by endotoxins [*Rattis B et al., 2021; Sermsappasuk P et al., 2008*]. Thus, comparing the obtained results with literature data, we assume that a calcium-dependent mechanism is involved in the action mechanisms of LPS on the heart.

CONCLUSION

Chronic heart failure is accompanied by shifts in calcium-regulating hormonal system and electrolyte balance of the blood. These changes depend on the patients' gender and are more significant in women.

In chronic heart failure the increased PTH have a protective significance, aimed at maintaining the contractile ability of a weakened myocardium and preserving cardiac output. At the same time, a deficiency of vitamin D may cause a further escalation of the disease.

Positive cardiotropic effect of physiological concentrations of PTH, its related protein, vitamin D_3 and CT was revealed on isolated frog heart *in vitro*, promoting the long-term maintenance of the isolated heart functioning. Moreover, PTH mostly exhibits a cardio-stabilizing effect.

Lipopolysaccharide suppresses pacemaker and contractile functions of the heart by calcium-dependent mechanism.

This work was supported by the State Committee of Science, Ministry of Education, Science, Culture and Sport of the Republic of Armenia, in the frames of the research projects №. 15T-3A074, 18T-3A054, and 21T-3A112

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THE NEW ARMENIAN MEDICAL JOURNAL
Volume16 (2022). Issue 4

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THE NEW ARMENIAN MEDICAL JOURNAL

Volume16 (2022). Issue 4

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Our journal is registered in the databases of Scopus, EBSCO and Thomson Reuters (in the registration process)

SCOPUS EBSCO REUTERS

Copy editor: Tatevik R. Movsisyan

Printed in "VARM" LLC
Director: Ruzanna Arakelyan
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