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Original Article

Modern approaches for diagnosing transformations of the heart in qualified athletes

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Abstract
Background: The lack of clear standards for medical supervision of athletes considerably limits the ability to diagnose and prevent overstrain of the cardiovascular system. To date, in the Republic of Kazakhstan, an assessment of the significance of early cardiomarkers, reflecting the state of maladjustment of the heart to physical exertion among highly qualified athletes involved in martial arts, has not been performed. **Aims:** The aim of this study is to determine the level and diagnostic significance of cardiac biomarker IL1RL1 (sST2 - serum-soluble) and the role of psychological stress on the risk of cardiovascular disease in qualified sport veterans engaged in speed–strength sports. **Methods:** A prospective study on wrestlers was performed at the Centre for Sports Medicine and Rehabilitation (Almaty, Republic of Kazakhstan). All participants (n = 30) were males aged 30 to 44 years s, masters of sports of international class, and honoured masters of sports). The control group consisted of volunteers (VO) (n = 30). The sST2 level was determined before (BT) and immediately after (AT) training. Anthropometric and hemodynamic parameters of athletes were studied along with electrocardiography and echocardiography tests. **Results:** The average age of 30 athletes was 36.3 ± 0.5 years; the largest proportion of athletes was 35–39 years old (66.7%, n = 20); 6 sports veterans (20%) were 30–34 years old; the smallest proportion of athletes was under 40–44 years old (13.3%, n = 5). According to the electrocardiography (ECG) data, minor deviations from the norm (16.6 %) and abnormal ECG (30%) were identified. The echo-CG data showed "moderate" and "pronounced changes" in 40.0% and 60.0% of cases, respectively.The sST2 level of VO (337.1 ± 61.8 pg/mL) was lower than that of BT (570.1 ± 32.6 pg/mL) and AT (768.7 ± 71.6 pg/mL) ($p < 0.05$).IL1RL1 (ST2) showed high sensitivity in determining the maladaptation of the cardiovascular system to physical exertion in highly qualified sports veterans ($p > 0.05$). **Conclusion**: Athletes' sST2 levels exceeded thresholds both before and after training. Our findings indicate that the elevated sST2 concentrations in athletes can be used as the predictive valueshow maladaptation of the cardiovascular. However, it requires further intensive studies.
Keywords: IL1RL1\soluble ST2; exercise; cardiac biomarker;athletes; heart hypertrophy

Introduction

Regular exercise lasting up to 150 min per week reduces the risk of cardiovascular disease by 30% and increases the adaptive reserve capacity of the body, which improves the quality of life and life expectancy of the population (Shiroma EJ, 2010). Thus, owing to physical activity, both instantaneous and long-term changes occur in the cardiovascular system (Dirk J Duncker 1, 2008). Instantaneous changes after physical exercise include not only an increase in HR and RR but also an increase in inflammatory markers, B-type naturetic peptide, and myocardial necrosis marker (cTnI) (Scharhag J, 2008). These changes in biomarkers are not constant, and the normalization of their concentration occurs within 24–72 h. (Scherr J, 2011) However, according to a meta-analysis conducted in 2016, the mechanism of release of the abovementioned changes in biomarkers is physiological, and the clinical significance is still unknown. (Gresslien T, 2016)

In the cohort of all athletes, owing to the discrepancy between the intensity and duration of the impact of stressful factors of sports activity on the adaptive capabilities of the body, in 40% of highly qualified athletes, changes in the myocardium occur from the category of adaptive pass to the rank of pathologic. (Yakovleva L. V., 2013)(A recent systematic review has reported an increase in the prevalence of myocardial fibrosis in endurance athletes. (Schoor FR, 2016) This hypothesis suggests that prolonged endurance training, especially without adequate recovery, predisposes to myocardial fibrosis, regardless of whether the athlete is active or a

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veteran of the sport (Małek, 2020). Myocardial fibrosis (MF) is a common occurrence in the late stages of heart failure and is a predictor of sudden cardiac death. MF is a complex process, which is characterized by an increase in the volume of collagen in the myocardium owing to damage to the heart muscle during inflammation, remodelling of the heart during hypertonic overload, or ischemia (hypoxia) of the myocardium. (E.N., 2005). To date, MF is diagnosed using magnetic resonance imaging of the heart; however, the prognostic value of MRI of the heart remains unclear. According to a study conducted by the University of Tueben in Germany, MRI of the heart cannot be recommended for regular comprehensive functional examination of athletes because this method was useful in detecting cardiovascular diseases in only 5% of all athletes (E., 2013).

Thus, it is necessary to understand how to improve the diagnosis of maladaptation changes in the heart (myocardial fibrosis) to minimize the frequency of overstrain of CVS of athletes. According to a 2017 meta-analysis conducted by the Harvard Clinical Research Institute (Boston, MA), the interleukin-1 receptor (IL1RL1\ST2) encoded gene is an independent single- and serial-measured predictive cardiac biomarker of myocardial fibrosis in patients with heart failure (Aimo A, 2017). ST2 [(supression of tumorogenicity 2), growth stimulation expressed gene 2, stimulating growth factor expressed by gene 2 (IL1RL-1)] is a member of the interleukin-1 receptor superfamily. (Pascual-Figal DA, 2015). There are 2 isoforms of ST2, i.e., the ST2L transmembrane receptor and the soluble ST2 trap receptor (both forms are expressed from the same gene). sST2 is an IL-33 receptor; it is released by cardiomyocytes and fibroblasts. (Sanada S, 2007). It has been shown that the concentration of sST2 in the blood increases in many inflammatory diseases (Mueller, 2015). For example, Weinberg et al. have shown that the levels of circulating serum sST2 may be employed to assess patients with chronic severe heart failure (Shah RV, 2010). Aengevaeren et al. have showed that the change in the concentration of sST2 in the blood can be used as a predictor of cardiovascular disease in runners (before and after exercising) (Aengevaeren, 2019). However, of note, this study did not compare the level of this biomarker in people who are not involved in sports. Thus, this biomarker is formed in the heart in response to pathological changes caused by chronic diseases and acute injuries, which reflects the process of ventricular remodelling and myocardial fibrosis.

The aim of this study was to determine the basic and exercise-induced level as well as the diagnostic significance of the cardiac biomarker ILRL1 (sST2) in sports veterans. Sports veteran is an individual who has reached a certain age and has finished his professional career, systematically engaged in physical culture and sports, and participated in competitions organized for such persons.

Materials and Methods

This study is the first work to assess the maladaptation of the cardiovascular system in highly qualified sport veterans in the Republic of Kazakhstan.

Ethical Issues

This study was approved by the Ethics Committee of the Kazakh Medical University of Continuing Education, Almaty, Kazakhstan (protocol of the Local Ethics Commission No. 3 of 17.03.2020).

This study was a prospective study of 30 athletes who were 30–44 years, all male, with long-term (i.e., 10–20 years) experience in Greco–Roman wrestling, whose sports qualifications were masters of sports (MS), masters of sports of international class (MSIC), and honoured masters of sports (HMS); this study was performed at the Center of Sports Medicine and Rehabilitation "PROSPORT" in the Olympic CenterAkbulak (Almaty region, Republic of Kazakhstan). Participation of athletes in the study was possible only with written informed consent. To objectify the results of the study, the inclusion criteria were defined such as the availability of written voluntary informed consent to participate in the study. Exclusion criteria were injuries to the musculoskeletal system during the last 6 months, exacerbation of chronic diseases, refusal to participate in the study or lack of informed consent, participation in any clinical studies during the last month or at the time of examination, acquired and congenital immunodeficiency, mental disorders, and connective tissue diseases.

After a thorough history of the disease, all subjects underwent a standard physical examination, assessment of anthropometric parameters (height, body weight), calculation of body mass index, electrocardiography (BTL CardioPoint) and echocardiography (Siemens Acuson S1000) evaluations. The weight and height of each subject was measured using InBody 770 and BSM 370 Quick Reference (Seoul, Korea).The level of systolic and diastolic blood pressure (BP) at rest was determined according to the ACC/AHA guidelines (Drawz, 2020); pulse rate at rest was determined according to a previous study (Alexis, 2010).ECG data were analysed at the Research Institute of Cardiology and Internal Medicine (Almaty, Kazakhstan) by two independent cardiologists and divided into three subgroups (normal, mildly abnormal, and abnormal) according to a previous study (Koch, 2014).

To study the biomarker, the subjects' blood serum (obtained by centrifugation) was used. Blood sampling was performed according to the established standards, i.e., strictly in the morning on an empty stomach. The samples were analysed using a spectrophotometer designed for enzyme immunoassay (ELISA) (ChemWell Elisa); the calibration curves were plotted using the software that is specified to the device and according to the instructions attached to the kits.The analysis was performed in a certified (ISO 15189-2015) scientific clinical diagnostic laboratory of the Scientific Research Institute of FPM named after I. B. Atchabarova (Almaty, Kazakhstan).

In this study, we used Cloud-Clone Corp. kits. (China), which are intended for the quantitative determination of markers by the sandwich method of ELISA in the patient's blood serum. The range of determination of the indicator IL1RL1 (ST2) is 62.5–4000.0 pg/mL (the minimum detectable concentration is 22.3 pg/mL) (Chen W, 2018). At each point of the sample, 10 mL of blood was collected from the ante-cubital vein. All venous blood was collected in serum-gel vacutainer tubes; after centrifugation, the serum was frozen and stored at −80°C for later analysis. The analysis was performed over a single day using the same calibration and setup. As a control group (VO), the study included 30 volunteers (20–34 years old), who are not involved in professional sports.

Statistical analysis

Statistical analysis was performed using SPSS Statistics 25 (SPSS Inc., Chicago, Illinois, USA); the $p < 0.05$ value was considered statistically significant. All data were summarized using descriptive statistics methods. All parameters were visually checked for normality and also tested using the Shapiro–Vilk normality test. Parametric variables were compared using Student's t-test for normally distributed data and the Mann–Whitney test for abnormally distributed data. Bivariate associations of variables were evaluated using Pearson correlation coefficients. Continuous variables were recorded as the mean value ± SD in the usual distribution, or as the median (interquartile range), as Me [Q1; Q4], where Me is the median, [Q1; Q4] is the upper bound of the 1st and lower bound of the 4th quartiles. Qualitative data were summarized by calculating the proportion of observations (in the form of percentages) of a specific category in the sample under study.

Results

The average age of athletes was 36.3 ± 0.5 years; the largest proportion of athletes was 35–39 years (66.7%, n = 20); 6 sports veterans (20%) were 30–34 years old, and the smallest proportion of athletes was under 40–44 years old (13.3%, n = 5) (Table 1). According to anthropometric data, the average weight and height were equal to 79.4 ± 2.4 kg and 173.1 ± 1.1 cm, respectively; BMI was 26.4 ± 0.8 kg/m^2.The SBP level was 121 ± 1.4 mm Hg; DBP was 80 ± 1.3 mm Hg; the pulse rate was 66.6 ± 1.7 beats/min.
In the sports category, the masters of sports of international class were most prevalent and accounted for 76.7 ± 7.72% (n = 23); the rest of the athletes were masters of sports [30 ± 7.3% (n = 9)] and honoured masters of sports [6.7%±3.26 (n = 2)].

Table 1 – General characteristics of all investigated subjects

Parameter	Subjects (n = 30)
Age	36.3 (±0.5)
Weight	79.4 (±2.4)
Growth	173.1 (±1.1)
BMI (body mass index)	26.4 (±0.8)
Systolic blood pressure	121 (±1.4)
Diastolic blood pressure	80 (±1.3)
Pulse	66.6 (±1.7)

According to the international standard for ECG interpretation (Drezner JA S. S., 2017), sports veterans were divided into 3 groups, and their impulse conduction disturbances of various nature were identified: sinus bradycardia – 23.3% (±7.72); atrioventricular block I degree – 3.3% (±3.26); right bundle branch block – 3.3% (±3.3). Signs of left ventricular myocardial hypertrophy were diagnosed in 36.7% (±8.8) of the athletes, and impaired myocardial repolarization processes were diagnosed in 16.7% (±6.81) of the athletes. According to the ECG data, minor deviations from the norm (16,6 %) and abnormal ECG (30 %) were identified (Table 2).

Table 2 – Distribution of study participants into three subgroups according to ECG data

Normal ECG/minor Normal ECG n – 16		**Mildly abnormal Mildly abnormal ECG n – 5**		**Distinctly abnormal Distinctly abnormal ECG n – 9**	
R or S wave 25–29 mm	19 (63.3)	R or S wave 30–34 mm	2(6.7)	R or S wave _35 mm	9 (30)
ST segment elevation	0	Flat/tall T wave	5 (16.7)	T wave inversion	0
Incomplete RBBB	1 (3.3)	Q wave 2–3 mm	3	Q wave _4 mm	0
PR interval >0.20 s	1 (3.3)	Incomplete R wave progression V1 to V3	0	30° ≤ QRS axis ≥ 110°	0
Sinus bradycardia <60 bpm	7(23.3)	PQ interval ≤0.12 s	0	LBBB	0
		RBBB	0	WPW	0

Values, n (%); Incomplete RBB, incomplete right bundle branch block; RBBB, right bundle branch block; LAD, left axis deviation; RAD, right axis deviation; WPW, Wolff–Parkinson–White syndrome

The results of echocardiography in athletes (Table 3) showed that the meansize of interventricular septum (IVS) was 1.1 ± 0.19 cm, and the thickness of posterior wall (PW) was 1.0 ± 0.12 cm. The EF percentage was 65 ± 3.08%. The average left ventricular mass (LV mass) was 184 ± 35.5 gr, and LVM was 107.5 ± 24.7 gr/m^2 (Table 3). According to the guidelines from the British Society of Echocardiography (Harkness A, 2020), which is used to assess echocardiographic parameters in sports veterans, eccentric and concentric remodelling of the myocardium was revealed in 12 athletes.

Table 3 – Results of the comparative analysis of echocardiographic parameters

Parameter	Me	Q1	Q4
IVS_cm	1,1000	0,9750	1,3000
PW_cm	1,0000	0,9000	1,1250
EF	65,0000	63,7500	65,0000
LV_mass_gr	184,0000	164,7500	214,0000
LVMi_grm2	107,5000	83,7500	124,7500

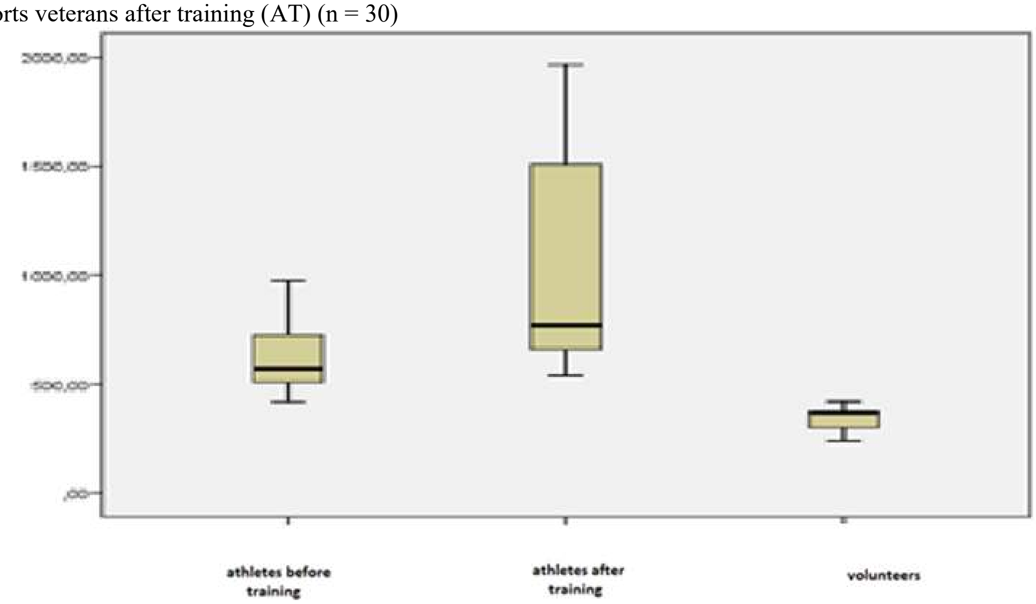
To test the distribution for normality, the Shapiro–Wilk test was applied, which indicated that the distribution was statistically significantly different from normal ($p < 0.05$). In this connection, the Wilcoxon signed rank test was applied for related samples, which was equal to 0.01. Thus, the average value of the marker in sports veterans at rest was 570.1± 32.6 pg/mL and 768.7± 71.6pg/mL after exercising(Table 4).

Table 4 – Results of comparative analysis at rest and induced by physical activity

Parameter		sST2 before	sST2 after
Me		570.1000	768,7000
IQR	Q1	506,1750	652,0000
	Q4	727,4750	1509,2500

For the reference range of IL1RL1 concentration, the biomarker value was determined in the range of 337.1 ± 61.8 pg/mL (IQR 237.6-419.6), after which a comparative assessment was performed with the biomarker level of sports veterans. To assess the uniformity of variance between samples, the Levin test was applied, which indicated that the equality of variance was not assumed. Then, when performing the Mann–Whitney test for independent samples, a statistically significant deviation of the ILRL1 marker was determined to be $p < 0.05$.

Figure 1. Analysis of serum ST2 levels in volunteers (VO) (n = 30), sports veterans before (BT) (n = 30), and sports veterans after training (AT) (n = 30)



In addition, an increase in the level of the marker was identified in athletes with an increased myocardial mass and wall thickness of the interventricular septum ($p > 0.01$) according to Spearman's Rank-Order Correlation. In addition, the indicators of the marker in athletes were analysed depending on the experience of Greco–Roman wrestling. It was determined that when the total experience of athletes increased, there was a statistically significant increase in the ST2 indicator ($p = 0.02$ according to Spearman).

Discussion

This study is the first in the Republic of Kazakhstan to determine heart strain in highly qualified athletes using new biomarkers of myocardial fibrosis.

The results of a comparative study of general clinical manifestations and data from functional studies indicated a significant variability in the response of CVS in some sports veterans to physical activity.

After determining the reference range of IL1RL1 concentration, i.e., 337.1 pg/mL (±61.8), a comparative assessment of the biomarker level in highly qualified athletes was performed. When comparing the ST2 level before and after exercising, a statistically significantly higher amount after exercising was determined. (Aengevaeren VL, 2019). In addition, it was determined that individuals with signs of maladjustment had a higher amount of marker compared to athletes with optimal cardiovascular function ($p = 0.00$, Wilcoxon signed rank criteria for related samples); this fact is confirmed by previously published studies (Khaletskaya A.I., 2018). This result indicates the high sensitivity of sST2 biomarker in patients with cardiovascular diseases.

Adaptive mechanisms that develop during intense physical exertion lead to functional and structural changes in the cardiovascular system. Moreover, the thickness of both the septum and posterior wall of the heart increases to the same extent as the internal volume. The mass to volume ratio and, therefore, the maximum systolic wall stress remains constant compared to the pathological forms of hypertrophy (Dickhuth, 2004). These results indicate the need for dynamic monitoring of the state of cardiovascular system of athletes. In our work, distinctly abnormal changes in ECG were detected, and echocardiographic results had a statistically significant relationship with an increase in sST2 concentration ($p > 0.05$).

The use of international criteria for ECG interpretation compared with the Seattle criteria is more sensitive for the diagnosis of false-positive ECGs and can be a useful tool when combined with the diagnosis of CVS maladjustment. (Hyde N, 2019)

When analysing the indicators of the marker in athletes depending on the experience of Greco–Roman wrestling, it was determined that with an increase in the total experience of athletes, there was a statistically significant increase in the ST2 indicator ($p = 0.02$, according to Spearman).

Study limitations

This study has several limitations. Because the main goal was to assess the maladaptation of the heart to physical activity, in this study, functional methods of research were not performed during and after exercising.

Conclusions

Our data showed that athletes' sST2 levels exceeded thresholds both before and after exercising. According to the obtained results, changes in hemodynamic parameters, even within the range of compensatory capabilities, also require careful medical monitoring to assess the development of the risk of cardiovascular complications in qualified athletes. Therefore, there is a need to use in practice a combination of traditional instrumental methods of research (e.g., ECG, EchoCG, and new cardiomarkers) as methods of monitoring the timely detection of weak links of adaptation in the body of each individual athlete.sST2 concentration is associated with cardiopulmonary stress induced by the cumulative exercise dose; thus, the role of elevated sST2 level in athletes under stress requires further intensive studies.

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