

Impact of connective tissue dysplasia on heart adaptation to exercise stress in young athletes

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Abstract. This study addresses the contribution of connective tissue dysplasia (CTD) to the cardiac function in young athletes. Thirty-three cross-country skiers aged 15 underwent maximum stress-ECG and TTE before and immediately after stress-test. Global and regional function of LV was evaluated with the use of further image processing. We found that 87.9 % of athletes had phenotypic markers of CTD ranged from 12 to 26 score points. Parameters of LV global function at rest in all studied athletes corresponded to normal age-gender values but markers of regional function showed high degree of mechanical asynchrony that depended on extent of CTD. All athletes passed stress-test successfully and demonstrated a high level of exercise performance. Meanwhile, the variables of LV pump-function and mechanical asynchrony close correlated with CTD extent. Obtained results imply that the increase of CTD extent was accompanied by the decrease of scale of heart adaptation to physical loads.

1 Introduction

Connective tissue dysplasia (CTD) relates to inherited defects of fiber structure [1]. Collagen synthesis impairment is accompanied with the decrease of tissue elastic properties and may result in impairment of human organs and systems forming [2]. For instance, heart manifestation of CTD is the appearance of anomalous structures – false tendons that are not connected to the heart valve apparatus [3-7]. Among other pathologies associated with CTD are also considered scoliosis, flat feet, increased bone fragility, myopia etc. [8].

Despite CTD is widely spread in population and may come up to 70-80 % of youths and adults, the rate of its distribution is higher in young athletes, than in non-athletic individuals of the same age [9, 10]. Generally, subjects with CTD have asthenic type, high height and joint hypermobility [11]. Notably, these features provide certain advantages for selection in professional sports.

Numerous studies have showed that intensive exercise loads were associated with increased risk of sudden cardiac events [12-14]. According to pathomorphologic observations, the CTD phenotypic markers were revealed in most cases of young athletes, who died suddenly during exercise activity [15]. This fact indirectly points at the negative impact of CTD on the heart adaptation to exercise stresses.

The aim of present study focuses on the search for possible relationships between the extent of CTD and features of the heart mechanical response to exercise loads in young athletes.

2 Materials and Methods

Thirty-three cross-country skiers aged 15 with training experience more than 5 years were enrolled into the study. Mean height of the athletes was 174.1 ± 8.6 (156.0-190.0) cm, weight – 63.1 ± 7.4 (48.0-76.0) kg, body mass index – 20.8 ± 1.9 (16.0-24.1) kg/m². All recruited individuals were free of any confirmed genetic or cardiovascular disease, had no restrictions from participation in trainings and competitive activity in accordance to ESC guidelines. Athletes and their parents were given the comprehensive description on the purpose, methods and possible risks of the research before their parents' written consent was obtained. The study conforms to the principles of the Helsinki Declaration of WHO and was approved by the Ural Federal University Ethics Committee.

Registration of phenotypic markers and the extent of CTD severity in athletes were based on data from physical and laboratory examination, undertaken by pediatrician and functional diagnostics specialist. The extent of CTD was estimated in accordance with algorithms proposed by the National Guidelines and expressed in points (CTD score) [2]. Additional information concerning features of CTD phenotype was obtained with the use of Gents' criteria scale revised by Loeys [16] as well as Beighton scale of joint hypermobility [17].

Each athlete underwent cycle exercise stress ECG. Exercise stress ECG was undertaken by maximal RAMP protocol with the use of Schiller stress system (Cardiovit-AT, cycle ergometer Ergosana 911, Schiller AG, Switzerland) according to ACC/AHA Guideline Update for Exercise Testing (2002) [18].

Global LV function was estimated by means of transthoracic echocardiography (TTE) with the use of ultrasound system "Samsung Medison HM70" (Samsung, Korea), at rest and immediately after test (within 3 minutes of recovery period) according to ACC/AHA Guidelines for the Clinical Application of Echocardiography (2013) [19]. The following parameters were chosen as measures of global function: end-diastolic volume (EDV, ml), stroke volume (SV, ml), ejection fraction (EF, %), end-diastolic index (EDI, ml/m²), stroke index (SI, ml/m²) [20-23].

Regional contractile function [24] was assessed by means of the frame-by-frame image processing of LV long-axis section in the course of complete cardiac cycle. LV endocardial contour was outlined with the use of semi-automated method based on the speckle tracing techniques "Dicor" software [25]. The area of LV delineated figure was divided into 12 sectors using radii connecting to the center of mass of the respective LV section. Finally, 12 triangles were obtained, and the relative area change of triangle in the course of complete cardiac cycle was used to characterize the myocardium regional function. The duration of regional systolic motion was estimated for each region as a time between the LV end-diastole and the maximum of regional relative area change. The root-mean-square (RMS) of 12 durations (dT) were calculated. To evaluate the contribution of individual regions to global EF of LV, the value of relative area change at the end-systole of LV for each region was measured. Thus, 12 regional EF (r-EF) were determined, and the variation coefficient of r-EF (Cv r-EF) was defined. Variation coefficient was calculated as the RMS deviation of the parameter used, divided by its average value, and multiplied by 100%. The values of Cv r-EF (%) and dT (ms) served as a measure of LV mechanical asynchrony [4, 24, 26].

The obtained values of all assessed parameters before and after stress test were further analyzed. Impact of exercise load on LV mechanical function was assessed by the increment (Δ) in corresponding parameters before and after stress-test.

The statistic software packages Microsoft Office Excel 2017 and SPSS Statistics 23.0 were used for statistical analysis. For descriptive analysis all data were expressed as mean (M) \pm standard deviation (SD). The variables were investigated using Shapiro Wilk's test to determine whether or not they were normally distributed. Differences between the groups were further evaluated by analysis of variance (one-way ANOVA). To find possible interrelations between the parameters Spearman correlations were calculated. The level of significance was set at $p < 0.05$.

3 Results and Discussion

The phenotypic markers of CTD were obtained in 87.9 % ($n = 29$) athletes. The extent of CTD severity varied within a wide range – from 12 to 26 score points. Notably, TTE data showed that these athletes had false tendons (FT) in LV from one to five units per LV. FTs were mainly localized in the medium and medium-apical portions of LV. As usual, FTs were fixed to interventricular septum (IVS) and LV free wall, and were oriented perpendicular or at an angle to LV long axis. The peculiarities of FTs topology in LV were not taken into account to calculate the extent of CTD.

According to ultrasound examination, the variables of LV pump-function in young skiers at rest corresponded to the normal age-gender values for athletes [27, 28]. Obtained results are in good agreement with the data of our previous studies [4, 7, 26] as well as findings by other researchers [9]. At the same time, the analysis of LV regional function at rest pointed at high level of the mechanical inhomogeneity in athletes. It was confirmed by major values of the variation coefficient by 12 LV regional ejection fractions ($C_v r\text{-EF} = 30.6 \pm 18.7\%$), and the RMS (root-mean-square) by 12 LV regional durations of systolic motion ($dT = 42.7 \pm 27.8$ ms).

Based on the detailed analysis of LV regional motion in the course of complete cardiac cycle, we found that the inhomogeneity phenomenon was associated with time desynchronization between IVS and LV free wall motion. In particular, at the beginning of LV systole the motion of the free wall regions was delayed for 40.1 ± 30.3 ms relatively to the IVS regions. At the beginning of LV diastole, the delay of 56.6 ± 39.5 ms took place as well. Generally, the inhomogeneity of regional mechanics in space and time reflects the LV mechanical asynchrony [26, 29]. According to our earlier studies, we assume that high scale of LV asynchrony in the studied group may be associated with the presence of FTs in LV in the major part of the observed athletes [4, 26].

The comparative analysis of TTE data obtained before and right after the stress-test showed the increment of main parameters of LV global function: $\Delta SI - 18.2 \pm 7.0$ ml/m², $\Delta EDI - 17.3 \pm 8.8$ ml/m², $\Delta EF - 9.1 \pm 6.5$ %. The results obtained are in good agreement with the known data. The most interesting observation is a considerable increase of LV regional function variables after stress-test. In particular, the values of ΔdT came up to 25.7 ± 19.2 ms, and $\Delta C_v r\text{-EF} - 19.2 \pm 13.8$ %.

Results of correlation analysis showed significant positive relationship between the extent of CTD and the increment of EDI (ΔEDI) under exercise load ($r = 0.468$, $p < 0.01$). The results of one-way ANOVA confirmed the impact of CTD on the increase of SI ($p = 0.0000000006$, $F = 5.79$) and the increase of EDI ($p = 0.003$, $F = 2.65$) in athletes immediately after stress-test. Therefore, the obtained data imply that the increase of CTD extent accompanies by the increase of LV pump-function to maintain a high level of exercise stress. In other words, the more pronounced CTD the greater is involvement of the Starling adaptation.

Data of correlation analysis between the extent of CTD and parameters of LV mechanical asynchrony are present in Table 1. One can see that higher extent of CTD was

associated with higher increase of mechanical asynchrony level. This conclusion is valid for both states at rest and after exercise.

Table 1. Correlation between the extent of CTD and the parameters of LV mechanical asynchrony

Parameter	Coefficient of correlation	p
C_v r-EF (at rest), %	0.56	< 0.01
dT (at rest), ms	0.53	< 0.01
ΔC_v r-EF, %	0.40	< 0.05
ΔdT , ms	0.52	< 0.01

* C_v r-EF – variation coefficient of 12 r-EF, dT – RMS by 12 LV regional durations of systolic motion, ΔC_v r-EF – increment between C_v r-EF before and after exercise-test, ΔdT – increment between dT before and after exercise test.

Results of one-way ANOVA analysis also confirmed impact of the CTD extent on the increase of mechanical asynchrony under exercise stress – ΔC_v r-EF ($p = 0.000008$, $F = 9.07$) and ΔdT ($p = 0.000000005$, $F = 4.90$).

In general, the scale of mechanical asynchrony in LV reflects the level of heart’s functional reserve, i.e. an ability of heart to maintain pump-function adequate to the increasing load. The increase of mechanical asynchrony in LV results in the decrease of the heart’s functional reserve [24]. We have demonstrated that CTD determines the scale of asynchrony in young athletes so that the more the extent of dysplasia the more was the scale of asynchrony (see Table 1). This result implies that initially (at rest) the athletes had a different level of the heart’s functional reserve, therefore, a different ability to maintain adequate pump-function in response to an increased load.

In the present study, all athletes passed stress-test successfully and demonstrated a high level of the exercise performance. Let us take into account the fact that initially the athletes had a different level of heart functional reserve. Then we may assume that to perform approximately the same physical activity, athletes need to set adaptation mechanisms to varying degrees. Consequently, athletes with a greater extent of CTD involve adaptation mechanisms largely. Significant correlations between the extent of CTD and increments of the LV pump-function or the LV regional function parameters as a response of young athletes to the exercise stress are supporting this assumption.

4 Conclusion

At rest, the parameters of LV global function in all studied athletes corresponded to normal age-gender values but LV regional function demonstrated high scale of mechanical asynchrony that depended on the extent of CTD. All athletes had a high level of the exercise performance. Meanwhile, the variables of LV pump-function and mechanical asynchrony close correlated with the CTD extent. Obtained results imply that the increase of CTD extent accompanies by the decrease of scale of heart adaptation to physical loads.

Thus, the results obtained in this study may serve as additional arguments in support of known facts on the negative role of connective tissue dysplasia in the appearance of sudden cardiac death in athletes.

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