Original article

Left atrial remodeling, early repolarization pattern, and inflammatory cytokines in professional soccer players

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A R T I C L E   I N F O

Article history:
Received 24 March 2015
Received in revised form 16 August 2015
Accepted 20 August 2015
Available online 21 November 2015

Keywords:
Athletes
Atrial remodeling
Inflammation
Interleukin-6
Soccer

A B S T R A C T

Objectives: Although regular physical exercise clearly reduces cardiovascular morbidity risk, long-term endurance sports practice has been recognized as a risk factor for atrial fibrillation (AF). However, the mechanisms how endurance sports can lead to AF are not yet clear. The aim of our present study was to investigate the influence of long-term endurance training on vagal tone, atrial size, and inflammatory profile in professional elite soccer players.

Methods: A total of 25 professional major league soccer players (mean age 24 ± 4 years) and 20 sedentary controls (mean age 26 ± 3 years) were included in the study and consecutively examined. All subjects underwent a sports cardiology check-up with physical examination, electrocardiography, echocardiography, exercise testing on a bicycle ergometer, and laboratory analysis [standard laboratory and cytokine profile: interleukin (IL)-6, tumor necrosis factor (TNF)-α, IL-8, IL-10].

Results: Athletes were divided into two groups according to presence or absence of an early repolarization (ER) pattern, defined as a ST-segment elevation at the J-point (STE) ≥0.1 mm in 2 leads. Athletes with an ER pattern showed significantly lower heart rate and an increased E/e’ ratio compared to athletes without an ER pattern. STE significantly correlated with E/e’ ratio as well as with left atrial (LA) volume. The pro-inflammatory cytokines IL-6, IL-8, TNF-α as well as the anti-inflammatory cytokine IL-10 were significantly elevated in all soccer players. However, athletes with an ER pattern had significantly higher IL-6 plasma levels than athletes without ER pattern. Furthermore, athletes with “high” level IL-6 had significantly larger LA volumes than players with “low” level IL-6.

Conclusions: Athletes with an ER pattern had significantly higher E/e’ ratios, reflecting higher atrial filling pressures, higher LA volume, and higher IL-6 plasma levels. All these factors may contribute to atrial remodeling over time and thus increase the risk of AF in long-term endurance sports.

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Introduction

Physical exercise has been shown to have a protective effect against mortality from all causes, primarily atherosclerosis, diabetes, and even cancer [1,2]. In addition, physical training has been shown to be effective in treating patients with coronary artery disease, heart failure (HF), and arterial hypertension [3,4]. Although regular physical exercise clearly reduces cardiovascular morbidity risk, long-term endurance sports practice has been recognized as a risk factor for atrial fibrillation (AF). A meta-analysis by Abdulla and Nielsen [5] demonstrated that the overall risk for AF was significantly higher in athletes than in non-athlete controls. In 1998, Karjalainen et al. evaluated the presence of AF in veteran male orienteers (cross-country runners) and compared this with AF prevalence in a matched control group. Lone AF was diagnosed in 12 orienteers (5.3%) vs. 2 control subjects (0.9%) [6]. Heidbuchel et al. assessed the influence of sports activity on the risk of AF after ablation of atrial flutter [7]. They could show that a history of competitive sports practice was associated with a higher post-ablation risk of developing AF. Furthermore, ongoing
practice of endurance sport after the ablation also increased the risk of AF. In another study Elosua et al. reported that current practice of sports with lifetime practice >1500 h was associated with AF [8]. The type of sports practiced was also a risk factor according to a few studies [9,10]. As opposed to other causes of AF, lone AF is generally benign. However, results reporting mortality data in athletes with AF are scarce and inconsistent [11,12].

The mechanism of AF in athletes is multifactorial. One of the major mechanisms for the generation of lone AF is considered to be increased vagal tone. According to the GIRAF study, vagal AF is a more common form of lone AF demonstrating that 70% of consecutive patients with lone AF had vagal AF [13]. In this context experimental data could show that vagal stimulation led to an increased left atrial pressure [14]. An increased left atrial pressure possibly leads to left atrial enlargement and remodeling. In particular, endurance sports athletes often have a high vagal tone with prolonged PQ time and 1st-degree atrioventricular-block [15]. The early repolarization (ER) pattern is a common alteration in the athlete’s electrocardiogram (ECG) and is thought to be a surrogate for an increased vagal tone [16–18].

Besides alterations in the autonomic nervous system inflammatory mechanisms also appear to play a role in AF. Epidemiologic studies have noted an association between elevated C-reactive protein (CRP) and interleukin (IL)-6 levels and the risk for developing AF [19,20]. Psychari et al. found CRP to be an independent predictor of AF, and both CRP and IL-6 to be positively related to left atrial diameter and negatively related to left ventricular function [21]. Therefore, inflammatory mediators appear to play a role in the evolution of AF as well as in structural atrial remodeling.

Regular physical exercise has been shown to reduce inflammatory markers, while high-intensity endurance training may induce a sustained inflammatory response [11,22].

However, it is not clear whether such a sustained, chronic systemic inflammation could influence the evolution of AF in endurance sports athletes.

The aim of our study was to examine the associations between signs of a high vagal tone, left atrial size, left atrial filling pressure as well as inflammatory mediators in a group of elite soccer players.

Methods

From May to August 2009 consecutive professional soccer players underwent cardiovascular screening including routine history, physical examination, electrocardiography, echocardiography, and exercise testing on a bicycle ergometer as part of their preparticipation screening for the national soccer league. Examinations were performed in the morning, 24 h after the last strenuous training. All players had similar training schedules, although there was some variability based on a player’s position. All players were engaged in professional soccer for at least 2 years.

A control group of 20 sedentary but otherwise healthy subjects was recruited. Written informed consent was obtained from each participant, and the study was approved by the University of Erlangen Ethics Committees, Erlangen, Germany.

Diagnostics

Twelve-lead ECGs were obtained with a subject in supine position and recorded at 50 mm/s (CardioSoft 5, GE Medical Systems, Freiburg, Germany). Heart rate at rest was determined after 1 min in a supine position. Electrocardiographic patterns were evaluated according to commonly adopted clinical criteria [23]. The ER pattern was defined as an upward ST-segment elevation 0.1 mV in 2 peripheral or precordial leads, beginning from an elevated J-point [24]. For linear comparisons, average ST-segment elevation at the J-point (STE) was calculated from leads I, II, III, aVF, aVL, and V. The Sokolov index was calculated from the S- and R-wave voltages in leads V1 and V5 or V6. Average precordial T-wave amplitude was calculated from leads V2 to V6.

Exercise testing was conducted according to recommendations of the American Heart Association [25]. Cycle ergometry (Ergoline ERG 900, Bitz, Germany) was performed in the upright position. The exercise protocol included 3 min of cycling at 50 W and progressive loadings of 50 W every 3 min to exhaustion. Participants were encouraged to reach 85% of predicted maximal achievable heart rate (220 minus age in years). Midway through each stage of exercise, at peak exercise, and 1 min to 3 min after cessation of exercise, data on symptoms, heart rate, blood pressure (as measured by indirect arm-cuff sphygmomanometry), and estimated workload (as determined from standard tables) in METs (1 MET equals 3.5 ml of oxygen uptake per kilogram of body weight per minute) were collected.

Standard transthoracic echocardiography was performed according to recommendations of the European Association of Echocardiography [26] on a Vivid 7 Dimension machine (GE Vingmed, Horton, Norway; M3S 2.5–MHz transducer). Images were stored digitally and analyzed off-line (EchoPac PC, GE Vingmed). For all measurements 3 beats were stored and analyzed. Left atrial and ventricular volumes, left ventricular (LV) end-diastolic diameter, and LV mass were calculated according to current recommendations and indexed for body surface area [27]. Pulse-wave Doppler was performed in the apical 4-chamber view to obtain peak early filling (E wave) and late diastolic filling (A wave) velocities, E/A ratio, deceleration time of the early filling wave, and the isovolumic relaxation time. Pulse-wave tissue Doppler imaging was performed in the apical 4-chamber view to acquire peak septal (e’ septal) and lateral (e’ lateral) mitral annular velocities and to calculate the average mitral annulus velocity (e’). The frame rate for tissue Doppler imaging measurements was 100 frames/s. Timings of aortic valve opening, peak systolic contraction, and aortic valve closure were measured in relation to the beginning of the QRS complex. Methods of image acquisition and post-processing of strain measurement with 2-dimensional speckle tracking have been described previously [28]. Global longitudinal strain and global systolic and diastolic strain rates were calculated for the entire U-shaped length of the LV myocardium (basal, mid, and apical segments of 2 opposite walls in each view). All images were obtained at a frame rate of 60–80 frames/s.

Peripheral venous blood was drawn into blood collection tubes in a standardized manner. All blood samples were collected under minimal tourniquet pressure from the antecubital vein using a wide caliber puncture needle (21-gauge) under resting conditions (subjects had rested for more than 15 min). All blood tubes were immediately transferred to the laboratory. Platelets were stained within 30 min of blood collection. A separate aliquot of blood without any additives was allowed to clot for 1 h before centrifugation (1000 × g and 4°C for 15 min). The serum supernatant was stored at −80°C until analysis. Samples were thawed only once.

Routine laboratory tests including serum electrolytes, glucose, total cholesterol (TC), high-density lipoprotein (HDL), TC/HDL ratio, and triglycerides were determined by standard laboratory methods. Serum levels of interleukin (IL)-6, tumor necrosis factor (TNF)-α, IL-8, and IL-10 were measured using commercially available enzyme-linked immunosorbent assay (ELISA) kits (R&D Systems, Minneapolis, MN, USA), according to the manufacturers’ instructions. All kits had the following sandwich ELISA format: microtiter plates already precoated with a murine monoclonal antibody against the human cytokine being measured. Standards of the analyte and serum samples in duplicate were added along
with another antibody against another epitope of the analyte conjugated to horseradish peroxidase (HRP) for TNF-α and conjugated to alkaline phosphatase for IL-10 (high-sensitivity assay kit) measurements. The samples were incubated for 2 h. Finally, the chromogen TMB was added and incubated for 20 min in the dark. After the addition of 2N H₂SO₄, the optical densities at 450 nm (reference filter 570 nm) were read and standard curves were plotted in a Spectramax Plus (Molecular Devices, Sunnyvale, CA, USA) microplate reader. The intra-assay and interassay coefficients of variation were below 8% for all ELISA assays.

Statistics

Data were analyzed with SPSS 17.0 Windows (SPSS, Inc., Chicago, IL, USA). We evaluated numerical data for a normal distribution using the Kolmogorov–Smirnov test. Parametric data are presented as mean ± SD. Statistical comparisons of parametric data were made with Student's t-test for 2-group comparisons. Simple linear regression analysis was performed to determine the relation between pairs of continuous variables. In addition, a multivariate, stepwise linear regression analysis was performed to identify independent determinants of left atrial volume. A 2-sided p-value < 0.05 was considered to indicate statistical significance.

Results

We included 25 professional football players with a mean age of 24.2 ± 4.3 years in this study. All subjects were asymptomatic without a history of atrial fibrillation or physical illness.

ECG showed mild abnormalities in 16 (64%) athletes. Three (15%) showed a first-degree atrioventricular block, 9 (36%) had an intraventricular conduction delay, 5 (20%) showed a positive Sokolov-Lyon-index as a criteria for LV hypertrophy, 6 (24%) had sinus bradycardia, and 13 (52%) had an ER pattern. In the age-matched control group, none of the subjects showed an ER pattern. In order to exclude that ER pattern in our athletes is only a temporary phenomenon, we controlled ECG 3 months later and could show that athletes with ER pattern at the first visit still had an ER pattern.

Athletes with an ER pattern had a significantly shorter QTc interval as compared to athletes without an ER pattern (Table 1). The heart rate in athletes with ER pattern tended to be lower; however, there was no statistical significance (64.1 ± 4.7 vs. 69.3 ± 8.1, p = 0.060, Table 1).

The exercise test showed no significant differences concerning baseline and maximum heart rate, and maximum workload between groups.

In echocardiographic examinations, mild LV hypertrophy (LV mass index >115 g/m²) was present in 4 athletes (16%) and moderate LV hypertrophy (LV mass index >131 g/m²) in one athlete (4%). Eight (32%) athletes had a mildly abnormal ejection fraction (<55%) (Table 1). Concerning diastolic function, the E/e’ ratio as well as the diastolic stiffness index were within normal limits in all athletes (Table 1). However, athletes with an ER pattern showed a significant increased E/e’ ratio (median 5.2, 25th 4.7, 75th 5.5 vs. 6.3, 25th 5.3, 75th 6.9, p < 0.05, Fig. 1). Furthermore, athletes with ER pattern had significantly higher LV end-diastolic diameter (52.3 ± 3.9 mm vs. 48.5 ± 3.9 mm, p < 0.05, Table 1) and higher LV mass index (106.7 ± 12.4 g/m² vs. 92.7 ± 13.1 g/m², p < 0.05, Table 1).

Multivariate regression analysis revealed significant correlations between STE and left atrial volume (r = 0.557, p < 0.005, Fig. 2B) and between STE and E/e’ (r = 0.513, p < 0.01, Fig. 2A).

In the laboratory examinations electrolytes, glucose, uric acid, and liver enzymes were within the normal range; creatine kinase (CK) activity was 4-fold elevated to normal range.

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<th>Table 1: Characteristics of study participants.</th>
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Values are mean ± Standard error of the mean (SEM). Statistical significant (p < 0.05).

Compared with the control group of 20 sedentary and healthy age-matched subjects, soccer players showed significantly increased plasma levels of the pro-inflammatory cytokines TNF-α (median 10.8 pg/ml, 25th 9.8 pg/ml, 75th 34.8 pg/ml vs. 8.7 pg/ml, 25th 7.7 pg/ml, 75th 11.0 pg/ml, p = 0.016, Fig. 3A), IL-6 (median 50.0 pg/ml, 25th 30.0 pg/ml, 75th 82.5 pg/ml vs. 15.4 pg/ml, 25th 12.0 pg/ml, 75th 29.8 pg/ml, p < 0.001, Fig. 3B), and IL-8 (median 98.0 pg/ml, 25th 66.1 pg/ml, 75th 242.5 pg/ml vs. 27.4 pg/ml, 25th 19.0 pg/ml, 75th 43.9 pg/ml, p < 0.001, Fig. 3C). The anti-inflammatory cytokine IL-10 was also significantly enhanced in soccer players.
players compared to the sedentary controls (Fig. 3D). When comparing the inflammatory 'profiles', given as the ratio of TNF-α to IL-10, there was no significant difference between soccer players and sedentary controls (0.85 ± 0.4 vs. 1.0 ± 0.6, p = 0.87).

When comparing IL-8 cytokine levels with the enhanced CK levels, especially athletes with highest CK levels also showed the highest plasma levels of IL-8 (CK levels were divided in tertiles: T1: CK < 175 U/L; T2: CK 175–280 U/L; T3: CK > 280 U/L, Fig. 4A). In a multivariate regression analysis a significant correlation between

![Fig. 1. Influence of presence or absence of early repolarization (ER) pattern on E/e' ratio.](image)

![Fig. 2. (A) Correlation between ST elevation at the J-point and E/e' ratio (r = 0.513, p < 0.01). (B) Correlation between ST elevation at the J-point and left atrial (LA) volume (r = 0.557, p < 0.005).](image)

![Fig. 3. Cytokine profiles in professional soccer players vs. sedentary controls: (A) Tumor necrosis factor (TNF)-α; (B) interleukin (IL)-6; (C) IL-8; (D) IL-10.](image)
levels of IL-8 and CK could be detected (Fig. 4B). In contrast to IL-8, the pro-inflammatory cytokine IL-6 however showed a different regulation. Athletes with an ER pattern had significantly higher IL-6 levels than athletes without an ER pattern (median 36.5 pg/ml, 25th 28.5 pg/ml, 75th 50.0 pg/ml vs. 70.6 pg/ml, 25th 48.8 pg/ml, 75th 187.0 pg/ml, p < 0.05, Fig. 5A). Furthermore, we observed that soccer players with “high” IL-6 levels (defined as >50 pg/ml) had significantly higher LA volumes than players with “low” IL-6 levels (median 20.5 ml/m², 25th 19.2 ml/m², 75th 22.5 ml/m² vs. 24.9 ml/m², 25th 21.9 ml/m², 75th 27.0 ml/m², p < 0.05, Fig. 5B).

Discussion

Regular physical activity is a recommended strategy in the primary and secondary prevention of cardiovascular disease, as it both prevents and helps to treat many established atherosclerotic risk factors, including elevated blood pressure, insulin resistance and elevated cholesterol concentrations [29]. Although regular physical activity clearly reduces cardiovascular risk, long-term endurance sport has been recognized as a risk factor for AF [7]. AF is the most common arrhythmia in athletes and is more frequently detected in middle-aged than in young athletes [30]. Anatomic adaptation, chronic systemic inflammation, and alterations in the autonomic system are discussed as possible explanations for the increased prevalence of this arrhythmia in endurance sports. In our study, we could confirm that endurance training is associated with left atrial enlargement. In particular, soccer players with an ER pattern in the ECG had significantly higher LA volume than players without ER pattern. Generally, the ER pattern is a surrogate for an increased vagal tone [17,18]. Based on this, players with an ER pattern had a significantly shorter QTc interval. The heart rate tended to be lower in athletes with ER pattern; however, these results did not reach statistical significance. Furthermore, the ER pattern was associated with a significantly higher E/e’ ratio in the echocardiographic evaluation. We could find a significant correlation between the average ST-segment elevation at the J-Point (STE) and the E/e’ ratio. Nagueh et al. has already shown a good correlation between the E/e’ ratio and pulmonary capillary wedge pressure and thus left atrial filling pressure [31]. A higher vagal tone may thus contribute to a higher left atrial filling pressure and to left atrial enlargement over time.

Besides the association of higher vagal tone and LA enlargement we could also find an association with the pro-inflammatory cytokine IL-6. Soccer players with ER pattern also had the highest IL-6 plasma levels. Furthermore, athletes with high IL-6 levels also showed larger LA volume than athletes with low levels of IL-6. Epidemiologic studies have noted an association between elevated inflammatory markers and the risk for developing AF [19].
Regular physical exercise is known to reduce inflammatory markers, while high-intensity endurance training may produce a sustained inflammatory response [32,33].

Besides IL-6, we observed significantly elevated levels of the pro-inflammatory cytokines TNF-α and IL-8 in professional, major league soccer players. These results per se appear to represent a paradox in that large amounts of pro-inflammatory cytokines are released during physical exercise, which is generally considered to be health beneficial. There are reports that in relation to an acute bout of exercise, plasma levels of IL-6 increase exponentially with a decline in the post-exercise period [32,33]. In our study, cytokine levels were continuously elevated indicating a persistent or chronic inflammatory state.

Generally, in infections and chronic inflammatory disease states, monocytes are a major source of cytokines, however after strenuous exercise muscles appear to be one major source [34]. Starkie et al. could show that IL-6 mRNA or protein is not increased in circulating monocytes during or following concentric exercise without muscle damage [35]. In cell culture models, it could be shown that muscle cells express several cytokines such as TNF-α, IL-6, IL-8, and IL-15 [36].

Consistent with these observations, we found a significant correlation of IL-8 plasma levels with CK levels suggesting that muscle damage could lead to the release of IL-8 in athletes. Akerstorm et al. showed that exercise induces IL-8 expression in human skeletal muscle [37]. Three hours of ergometer bicycle exercise lead to a marked IL-8 protein expression within muscle biopsy samples. However, the group could not find an increase in systemic plasma concentration of IL-8. Obviously, concentric exercise such as bicycle ergometry or rowing of moderate intensity does not increase plasma IL-8 concentration, whereas exhaustive exercise which involves eccentric muscle contractions, increases systemic IL-8 levels. IL-8 is a chemokine that attracts primarily neutrophils and furthermore acts as an angiogenic factor. It is associated with the CXC receptors 1 and 2. CXCR2 is expressed by human endothelial cells and is the receptor responsible for IL-8 induced angiogenesis. So it is tempting to hypothesize that skeletal muscle-derived IL-8 could stimulate neovascularization.

In contrast to IL-8, TNF-α and IL-6 plasma levels did not correlate with CK levels.

Besides the pro-inflammatory cytokines IL-6, IL-8, and TNF-α, we could also detect significantly elevated levels of the counter-regulatory anti-inflammatory cytokine IL-10. IL-10 is a major inhibitor of cytokine synthesis. It suppresses macrophage function and inhibits the production of pro-inflammatory cytokines as well as matrix metalloproteinases. IL-10 is important in the balance of pro-inflammatory and anti-inflammatory mediators. In 2003, we reported that the TNF-α/IL-10 ratio (TIR) represents a good “tool” for estimating the inflammatory burden in patients with advanced HF [38]. Calculating the inflammatory burden in our study, the TIR in soccer players was not significantly enhanced compared to the non-exercising control group. Obviously, the bout of inflammatory activation with a rise in the cytokine cascade appears to be counterbalanced by a significant rise in the levels of anti-inflammatory cytokine IL-10. The potentially deleterious effects of high cytokine levels could thus be attenuated.

Limitations

Our study had several limitations. The study comprised relatively small, yet homogeneous groups, so our observations need to be verified in large-scale trials. Furthermore, we could not perform longer follow-up periods. The ER pattern and E/e’ ratio are only surrogates for vagal tone and LA pressure. The ER pattern could be the consequence rather than the cause of atrial remodeling.

In conclusion, we could find that athletes with an ER pattern had significantly higher E/e’ ratios, reflecting higher atrial filling pressures, higher LA volume, and higher IL-6 plasma levels. All these factors may contribute to atrial remodeling over time and thus increase the risk of AF in long-term endurance sports.

Whether the levels of circulating cytokines have an impact on atrial conduction and whether athletes really develop AF over time should be examined in a larger study with a follow-up of several years.

Funding

This research received no grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflicts of interest

The authors declare that there is no conflict of interest.

Acknowledgments

The authors wish to thank the participants for volunteering to be a part of this study. There has been no external financial assistance with the project.

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