Left atrial dyssynchrony in veteran endurance athletes with and without paroxysmal atrial fibrillation

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Abstract

Background: Prolonged endurance exercise is associated with an increased risk of atrial fibrillation (AF) in men. Left atrial (LA) dilation is a marker of pathological atrial remodeling and associated with AF in the general population. In athletes, however, atrial dilation is part of a physiological response to exercise, and functional parameters may help separate physiological from pathological atrial remodeling in this group. LA mechanical dispersion (LA MD) is a novel marker of LA mechanical dyssynchrony associated with AF in the general population. The associations between prolonged endurance exercise, LA MD and AF are yet to be investigated. Purpose: To investigate LA MD in male veteran athletes who had regularly participated in an annual 54-kilometer cross-country (XC) ski race in Norway with and without paroxysmal AF and to investigate the ability of LA MD to identify veteran athletes with paroxysmal AF. Methods: Two hundred and ninety-three men from four groups, veteran XC skiers with (n=57) and without (n=87) AF, and men from a non-athletic population with (n=61) and without AF (n=88) underwent an echocardiographic exam while in sinus rhythm. Using speckle-tracking echocardiography, LA strain was measured in each of the six atrial segments in an atrial-focused apical four-chamber view. We defined LA MD as the standard deviation of time-to-peak strain (SD-TPS) and report the average from three consecutive loops. Results: XC-skiers (mean age 70.9 $\pm$ 5.7 years) reported an average of 40-50 years of regular endurance exercise and an average of 16 completed annual Birkebeiner XC ski races. LA volumes were associated with both AF and athletic status ($p<0.001$). SD-TPS was associated with AF ($p<0.001$), but not with athletic status ($p=0.173$). We found no significant trend between years of endurance exercise and SD-TPS in individuals without AF ($p=0.846$). SD-TPS did not add incremental value in identifying athletes with AF in addition to clinical markers, QRS width, LA volume, and LA reservoir strain ($p=0.056$). Conclusion: LA MD was associated with paroxysmal AF regardless of athletic status. However, it was not associated with years of performing endurance exercise, suggesting LA MD could be a promising marker of pathological atrial remodeling in endurance athletes, less affected by physiological exercise-induced atrial remodeling than absolute volumetric measurements. We found no incremental value of LA MD in identifying veteran athletes with paroxysmal AF when LA reservoir strain was included in the model.

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Abstract:*Background:* Prolonged endurance exercise is associated with an increased risk of atrial fibrillation (AF) in men. Left atrial (LA) dilation is a marker of pathological atrial remodeling and associated with AF in the general population. In athletes, however, atrial dilation is part of a physiological response to exercise, and functional parameters may help separate physiological from pathological atrial remodeling in this group. LA mechanical dispersion (LA MD) is a novel marker of LA mechanical dyssynchrony associated with AF in the general population. The associations between prolonged endurance exercise, LA MD and AF are yet to be investigated.

Purpose: To investigate LA MD in male veteran athletes who had regularly participated in an annual 54-kilometer cross-country (XC) ski race in Norway with and without paroxysmal AF and to investigate the ability of LA MD to identify veteran athletes with paroxysmal AF.*Methods:* Two hundred and ninety-three men from four groups, veteran XC skiers with (n=57) and without (n=87) AF, and men from a non-athletic population with (n=61) and without AF (n=88) underwent an echocardiographic exam while in sinus rhythm. Using speckle-tracking echocardiography, LA strain was measured in each of the six atrial segments in an atrial-focused apical four-chamber view. We defined LA MD as the standard deviation of time-to-peak strain (SD-TPS) and report the average from three consecutive loops.*Results:* XC-skiers (mean age 70.9 ± 5.7 years) reported an average of 40-50 years of regular endurance exercise and an average of 16 completed annual Birkebeiner XC ski races. LA volumes were associated with both AF and athletic status ($p<0.001$). SD-TPS was associated with AF ($p<0.001$), but not with athletic status ($p=0.173$). We found no significant trend between years of endurance exercise and SD-TPS in individuals without AF ($p=0.846$). SD-TPS did not add incremental value in identifying athletes with AF in addition to clinical markers, QRS width, LA volume, and LA reservoir strain ($p=0.056$).

Conclusion: LA MD was associated with paroxysmal AF regardless of athletic status. However, it was not associated with years of performing endurance exercise, suggesting LA MD could be a promising marker of pathological atrial remodeling in endurance athletes, less affected by physiological exercise-induced atrial

remodeling than absolute volumetric measurements. We found no incremental value of LA MD in identifying veteran athletes with paroxysmal AF when LA reservoir strain was included in the model.

Keywords: Atrial fibrillation, dyssynchrony, left atrium, exercise, echocardiography

Abbreviations: AF, atrial fibrillation; LA, left atrium; $LAVI_{max,}$ maximal left atrial volume indexed; LA MD, left atrial mechanical dispersion; SD-TPS, standard deviation of time-to-peak strain; LASr, left atrial reservoir strain; LV, left ventricle/left ventricular; GLS, global longitudinal strain; XC, cross-country;

Introduction:

Exercise is beneficial for a wide range of diseases and associated with lower cardiovascular morbidity and mortality.[1, 2] When it comes to atrial fibrillation (AF), however, the effect of exercise is ambiguous. While exercise of low and moderate intensity and duration lowers the risk of AF, prolonged endurance exercise is associated with an increased risk of AF in men.[3-6] To accommodate the increased demands of exercise, endurance athletes experience structural, functional, and electrical cardiac remodeling referred to as the "athlete's heart".[7] While cardiac remodeling is a physiological response to exercise, the athlete's heart shares several common features with pathologically remodeled hearts, and to separate physiological from pathological atrial remodeling in athletes is a challenging task.[8, 9] Current knowledge indicates that functional measures obtained by speckle-tracking echocardiography could be more helpful than mere size when trying to differentiate physiological from pathological atrial remodeling in veteran endurance athletes. However, data is sparse and somewhat conflicting.[9-12] Studies assessing atrial function in athletes with AF have focused on left atrial (LA) strain values.[10-13] Speckle-tracking echocardiography can also be used to measure the timing of atrial contraction. LA mechanical dispersion (LA MD), defined by the standard deviation of time-to-peak strain (SD-TPS), is a marker of electromechanical atrial function. It is reported to be a novel predictor of AF in the general population, linked to the recurrence of AF after catheter ablation, and associated with stroke among AF patients.[14-17] Watanabe et al. found an association between increased LA MD and low voltage zones recognized by voltage mapping in paroxysmal AF patients indicating regional fibrosis in the LA wall.[18] There has also been a report of increased atrial fibrosis assessed by magnetic resonance imaging (MRI) in a group of healthy veteran endurance athletes, linking long-term endurance exercise to increased atrial fibrosis.[19] Still, the impact of long-term endurance exercise on LA MD, the interplay between AF, endurance exercise, aging, and LA MD, and the ability of LA MD to identify athletes with paroxysmal AF in sinus rhythm have yet to be investigated.

The main aim of this study was to investigate LA MD in veteran endurance athletes with and without AF and to evaluate the ability of LA MD to identify veteran athletes with paroxysmal AF when in sinus rhythm.

Material and methods:

Study population:

Cross-country (XC) skiing ranks among the sports with the highest cardiovascular demands and profound cardiac remodeling.[20] The Norwegian Birkebeiner XC ski race is one of the world's most demanding XC ski races, with a course length of 54 km, covering approximately 1000 altitude meters. Previous studies have demonstrated how participation in the Birkebeiner XC ski race is associated with athletic cardiac remodeling and an increased risk of AF.[4, 13, 21] To cover the whole range of physical activity in the population, the Birkebeiner Atrial Fibrillation study (2012) comprised two independent cohorts; one cohort consisting of persons who had completed the Birkebeiner XC ski race, and another cohort of individuals that had participated in a population-based health survey (The Oslo Health study).[4] With the aim to investigate athletic cardiac remodeling in relation to AF, we invited 520 former participants in the Birkebeiner Atrial Fibrillation study to participate in a cross-sectional clinical study performed between January 2019 and October 2020. All veteran skiers with AF living within a 2-hour perimeter from the study site were invited. Participants with supraventricular tachycardia other than AF, prior open-heart surgery, heart failure (EF <35%), or clinically significant valvular disease were excluded. Veteran skiers without AF, age-matched to the included skiers with AF, were invited until reaching the same number of included skiers with and without a history of AF. Age-matched participants from the non-athletic cohort with and without a history of AF were consecutively invited until reaching the same number of included individuals in all four groups. Because the original study cohort lacked age-matched non-athletic controls, the group of non-athletes with AF was supplemented by male patients visiting the AF outpatient clinic at Diakonhjemmet Hospital between May and September 2020. All patients were screened, and men of the proper age were consecutively invited to participate. Participants with AF during the examination, paced rhythm, or left bundle branch block were excluded from the current analysis (Figure 1). The methods of the study have been described in detail earlier.[10]

All participants answered a questionnaire and underwent physical examination by the main investigator (ES). Data from the questionnaire (age, sex, history of heart failure, hypertension, stroke, coronary heart disease, and diabetes mellitus) were used to estimate the CHA_2DS_2-VASc score as a marker of cardiovascular risk.[22] Regular endurance exercise was self-reported in the questionnaire on an eight-level ordinal scale. To evaluate the dose-response relationship between years of endurance exercise and LA MD, we condensed this scale into four categories in the same matter used previously.[13]

A 12-lead electrocardiogram (ECG) was obtained and exported in digital format for offline processing using standard Glasgow algorithm with automatic identification of fiducial points, intervals and amplitudes of the components of the PQRST-complex.[23] We affirmed the history of AF by review of medical journals, adjudicating AF according to guidelines.[24] In 13 participants (5 athletes and 8 non-athletes), it was challenging to differentiate paroxysmal AF from persistent AF, these were included as having paroxysmal AF.

The study complies with the Declaration of Helsinki and was approved by the Regional Committee for Medical and Health Research Ethics (ref.nr: 2016/565). All participants gave written consent.

Transthoracic echocardiography:

Resting echocardiograms were recorded in the left lateral decubitus position by the main investigator (ES) using the same digital ultrasound scanner in all participants (Vivid E9, GE Vingmed Ultrasound, Horten, Norway). We obtained 2D-greyscale, tissue Doppler, and color Doppler images in parasternal and apical views according to recommendations.[25] Three to five consecutive loops were obtained and saved in cine loop format, including 200 milliseconds (ms) before and after all beats.

The main investigator (ES) performed all analysis offline (Echo PAC version 203, GE Vingmed Ultrasound, Horten, Norway), blinded to the patients' other data.

Conventional parameters of left ventricular (LV) size were obtained, calculated, and indexed to body surface area according to recommendations.[25] We obtained LA 2D acquisitions from atria-focused apical views. LA volumes were calculated by the summation of discs in apical four- and two-chamber views.[25]Atrial volumes were indexed to body surface areas, and an average from three consecutive loops was computed.

Strain analysis:

We assessed strain parameters by speckle-tracking echocardiography. LV global longitudinal strain (GLS) was computed from apical four-chamber, two-chamber, and long-axis views using the 18-segment model.[26] GLS was defined as the peak negative strain during systole.

LA strain was obtained from LA-focused apical four-chamber 2D views at frame rates >60 frames per second. The LA border was traced along the endocardium from one side of the mitral annulus to the other, and a region of interest was automatically defined, then adjusted manually as recommended to fit the thickness of the LA wall.[27] The software divided the LA into six segments, scoring tracking quality with the possibility of manual correction. Zero strain reference was set at LV end-diastole, defined by the frame prior to mitral valve closure. LA strain values were computed as the average of accepted atrial segments averaged over three heart cycles and stated as LA reservoir strain (LASr), LA conduit strain (LAScd), and LA contractile strain (LASct).[27] SD-TPS was calculated as the mean value of the time-to-peak strain in the six atrial segments. SD-TPS was calculated separately in three consecutive loops, and an average of these values is reported.

In addition to crude SD-TPS in ms, SD-TPS was also corrected by the cycle length and expressed as a percentage of the cardiac cycle SD-TPS (%) = ($\frac{SD-TPS(ms)}{Cycle\ length(ms)}$ X 100). A higher value of SD-TPS reflects a higher degree of LA MD (Figure 2).

Statistical analysis:

Normally distributed continuous variables are reported as mean ± standard deviation, other continuous variables are reported as median (25^{th}-75^{th} percentile). Categorical variables are reported using frequencies and percentages.

Reproducibility analyses were conducted offline on 15 randomly selected anonymized recordings using a two-way mixed model with absolute agreement between measures. The main investigator (ES) performed intra-observer analysis with a two-week interval between measurements. Rater two (MGS) conducted inter-rater analysis, separated in time and place from rater one, on the same set of recordings from each participant. The raters could select different pictures and loops randomly for analysis and re-analysis.

To explore the interplay between AF, athletic status, and echocardiographic values, we conducted a two-way between-groups analysis of variance with athletic status and AF status as independent variables. In addition, a one-way analysis of variance with polynomial contrasts investigating for a linear trend between SD-TPS and years of regular exercise was performed in all participants without a history of AF to explore the associations between prolonged endurance exercise and LA MD.

To assess the association between AF and SD-TPS, we performed a logistic regression analysis with AF as the dependent variable, adjusting for weight, height, CHA_2DS_2-VASc score, GLS, QRS width, and indexed maximal LA volume ($LAVI_{max}$) in all participants and in athletes. We also performed a hierarchical logistic regression adding LASr to the model to evaluate the independent incremental value of SD-TPS in identifying athletes with AF.

Tests with P -values <0.05 were considered statistically significant. All analyses were performed using SPSS Statistics version 26 (IBM, Armonk, NY).

Results:

Of 520 invited individuals, 394 (76%) met for examination. After exclusions, 57 athletes with paroxysmal AF, 87 athletes without AF, 88 non-athletes without AF, and 61 non-athletes with paroxysmal AF were included (Figure 1).

Baseline characteristics: All participants were men, with a mean age of 70.7 ± 6.7 years. Athletes with and without AF reported a median of 40-50 years of performing regular endurance exercise and a median of 16 completed annual Birkebeiner XC-races. Eighty-six participants had never practiced regular endurance exercise, whereas 49 participants had practiced regular endurance exercise for 1 to 20 years, 43 participants for 20 to 40 years, and 115 participants for >40 years. Almost 80% of the athletes still participated in regular endurance exercise at the time of examination. Athletes had a very low comorbidity burden, a lower BMI and a lower resting heart rate than non-athletes. Blood pressure was similar between all four groups. Individuals with AF were taller than those without AF. The AF burden was low in both AF groups, with more than three out of four individuals experiencing paroxysms of AF less than once a month. While a higher proportion of athletes had performed AF ablation, the use of antiarrhythmic drugs was higher among non-athletes (Table 1).

Echocardiographic parameters: LA echocardiographic parameters are presented in Table 2, and LV echocardiographic values are presented as supplemental material (Table S1). There was no significant interaction between athletic status and AF status regarding atrial parameters. LA size was associated both with athletic status and AF status. SD-TPS stated in ms was associated with AF status but not athletic status. When correcting SD-TPS by the R-R interval, we found SD-TPS (%) to be associated with both athletic and AF status. LASr, LAScd, and LASct were lower in the AF groups regardless of athletic status. As opposed to

$LAVI_{max,}$ we could not identify any significant trend between years of performing endurance exercise and SD-TPS in individuals without a history of AF (p=0.893) (Figure 3).

SD-TPS remained significantly associated with AF after adjusting for height, weight, CHA_2DS_2-VASc score, $LAVI_{max}$, GLS, and QRS width in all participants and the athletic group alone (Table S2 and S3). However, SD-TPS did not remain significantly associated with AF in athletes when LASr was included in the model (p=0.06) (Table S4). Hence, in a hierarchical logistic regression model, SD-TPS did not add independent incremental value in identifying individuals with AF on top of clinical characteristics, CHA_2DS_2-VASc score, QRS width, standard echocardiographic values, and LASr (Figure 4).

Athletes had larger left ventricles and slightly lower GLS and E/e' than non-athletes. There were no significant interactions between AF and athletic status regarding LV values except for LV mass index. GLS was not significantly affected by AF status.

Reproducibility:

For SD-TPS intra-observer intraclass correlation coefficient (ICC) was 0.935 (0.812-0.978), and the inter-observer ICC was 0.932 (0.803-0.977). $LAVI_{max}$ intra-observer ICC was 0.985 (0.957-0.995) and inter-observer ICC 0.984 (0.954-0.995). For $LAVI_{min,}$ the corresponding numbers were 0.980 (0.922-0.994) and 0.959 (0.881-0.986). For LASr, intra-observer ICC was 0.846 (0.543-0.948) and inter-observer ICC 0.893 (0.676-0.964). LAScd intra-observer ICC was 0.872 (0.614-0.956), inter-observer ICC 0.854 (0.557-0.951), and for LASct the intra-observer ICC was 0.869(0.614-0.956) and the inter-observer ICC 0.820 (0.452-0.940).

Discussion: The main finding of this study is that LA MD was associated with paroxysmal AF regardless of athletic status and not associated with years of performing endurance exercise, despite extensive cardiac remodeling among those reporting the longest history of endurance exercise. However, LA MD had no independent incremental value in identifying veteran athletes with a history of AF on top of clinical markers, other relevant echocardiographic variables, and LASr.

Due to promising results in its ability to identify patients with paroxysmal AF when in sinus rhythm, association with atrial fibrosis on MRI, and ability to identify electrical remodeling regardless of LA size, LA MD has emerged as an interesting marker when evaluating LA remodeling in athletes.[18, 28, 29] The present study is the first to investigate the associations between LA MD, prolonged endurance and AF in a large group of veteran endurance athletes.

Most studies of LA MD have defined the parameter as SD-TPS corrected by the R-R interval (%) instead of the crude SD-TPS value in ms.[14, 17, 28, 30] Endurance athletes experience exercise-induced bradycardia and as expected, the athletes in the present study had a lower resting heart rate than the non-athletic group.[31] Hence, we introduced an association between athletic status and LA MD when correcting SD-TPS by the R-R interval. Consequently, we chose to focus on SD-TPS in ms in this study and suggest stating the crude SD-TPS values in ms as well as SD-TPS (%) when investigating LA MD in endurance athletes.

An MRI study by Peritz et al. suggested an association between long-term endurance exercise and atrial fibrosis among a small group of healthy athletes, and LA MD has been demonstrated to associate with LA fibrosis on MRI.[19, 29] We found no association between years of reported endurance exercise and LA MD in this study, despite increasing atrial volumes by years of exercise, indicating that athletic remodeling per se has little effect on LA MD measured by echocardiography.

We found a highly significant association between paroxysmal AF and LA MD irrespective of athletic status, suggesting LA MD assessed by SD-TPS could be a promising marker of pathological atrial remodeling in endurance athletes, less affected by physiological exercise-induced cardiac remodeling than absolute volumetric measurements. However, SD-TPS did not add an independent incremental value in identifying veteran athletes with AF when including LASr in the model. This questions the clinical utility of LA MD in veteran athletes, especially considering novel software with automated function imaging of the LA, making LA strain measurements more feasible without including LA MD measurements as an option. Several studies in non-athletic cohorts have demonstrated LA MD to have an independent incremental value at identifying individuals with AF on top of LASr and to predict the recurrence of AF post ablation.[14, 16] Current knowledge indicates that LA MD increases with increasing age in healthy individuals.[32] As the mean age in this study is 70 years, we must assume age-induced alterations in electromechanical function are present and affect LA MD. As LA MD is perceived to increase as associated with the pathophysiology of healthy aging, prospective studies and studies in younger endurance athletes will have to answer whether LA MD is an independent predictor of AF in endurance athletes and if it adds incremental value to LASr when trying to identify younger athletes with AF.

Strengths and limitations: This is the first study to explore the relationship between endurance exercise, AF, and LA MD, and it comprises a unique cohort of veteran XC skiers with an average of 40-50 years of performing endurance exercise.

The study may have seemed more appealing to individuals interested in endurance exercise, attracting the fittest members of the non-athletic control cohort, and possibly diluting the effect of training in the athletic group. Finally, this is a single-center study, and due to the low number of female participants in the Birkebeiner study with exercise-related AF, men only were included.

Conclusion: LA MD was associated with paroxysmal AF regardless of athletic status but not associated with years of performing endurance exercise despite considerable atrial remodeling in those reporting the longest history of endurance exercise. These results suggest LA MD could be a relevant marker of pathological atrial remodeling in endurance athletes. However, LA MD did not add incremental value to LASr identifying veteran athletes with AF, questioning its clinical utility in this group.

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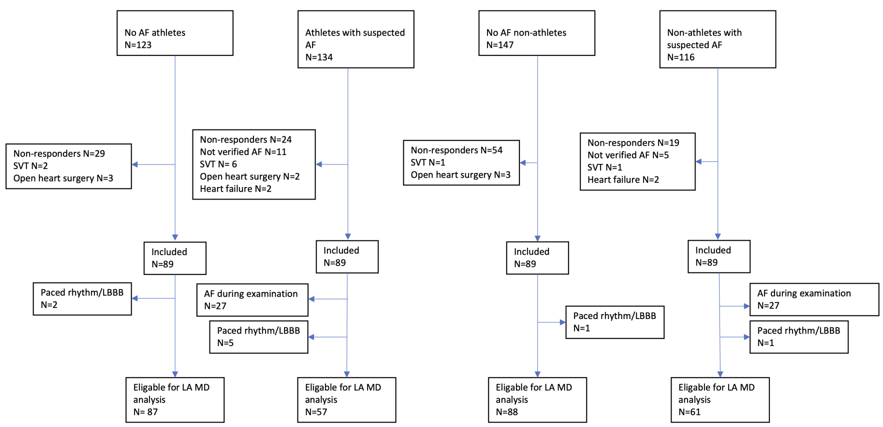
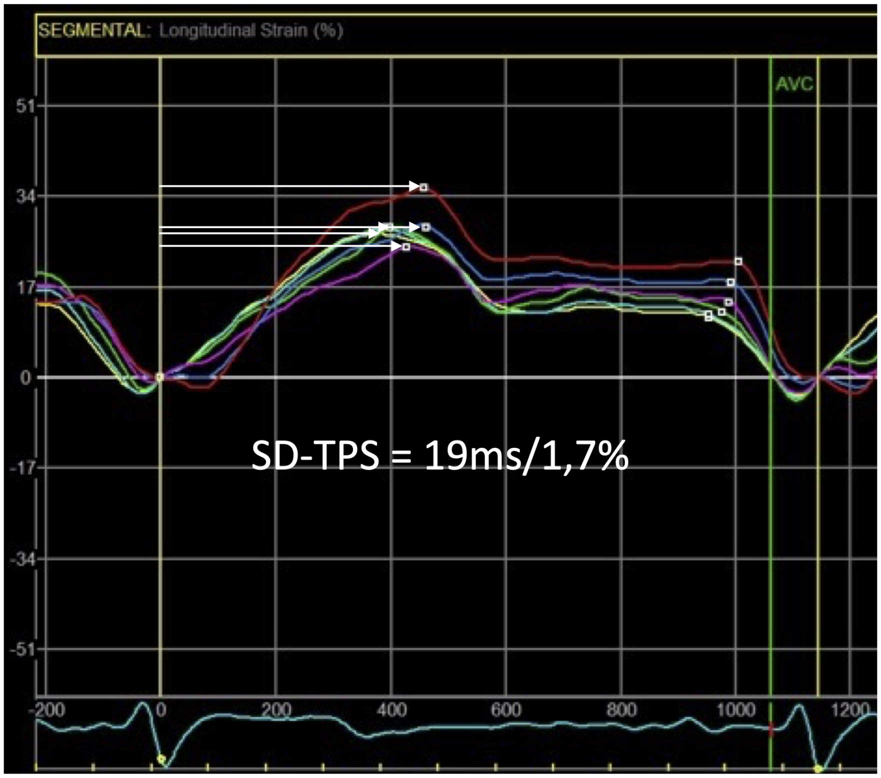
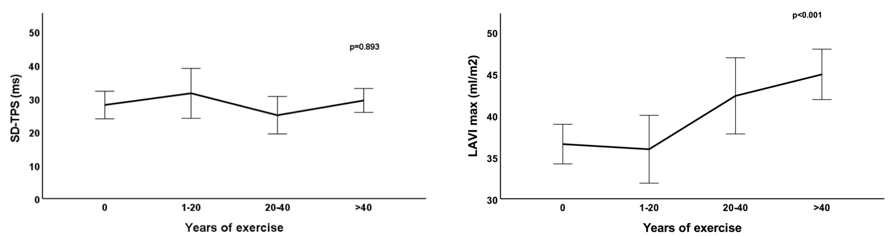
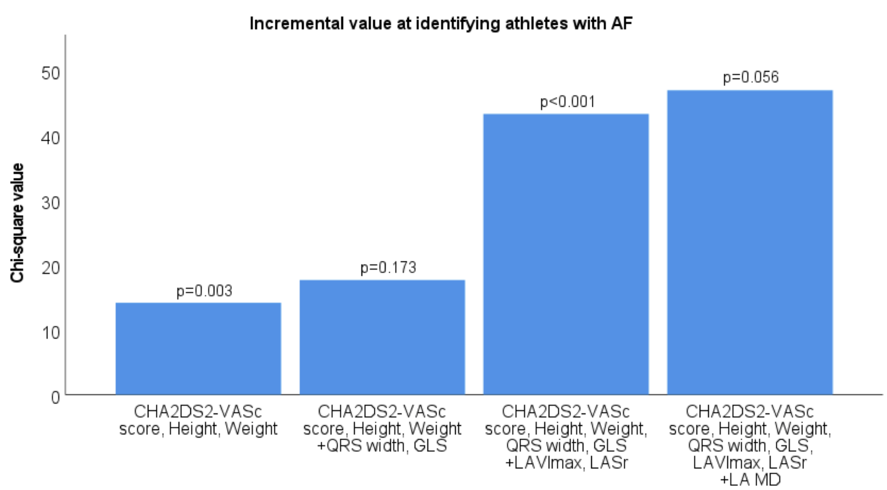



SEGMENTAL: Longitudinal Strain (%)
AVC
SD-TPS = 19ms/1,7%
51
34
17
0
-17
-34
-51
-200
0
200
400
600
800
1000
1200


SD-TPS (ms)
p=0.893
Years of exercise
0
1-20
20-40
>40
LAVI max (ml/m2)
p<0.001
Years of exercise


Incremental value at identifying athletes with AF
Chi-square value
p=0.003
p=0.173
p<0.001
p=0.056
CHA2DS2-VASc score, Height, Weight
CHA2DS2-VASc score, Height, Weight +QRS width, GLS
CHA2DS2-VASc score, Height, Weight, QRS width, GLS +LAVImax, LASr
CHA2DS2-VASc score, Height, Weight, QRS width, GLS, LAVImax, LASr +LA MD

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