# **Original Article**

# Masked hypertension and cardiac remodeling in middle-aged endurance athletes

Lukas D. Trachsel\*, Frederik Carlen\*, Nicolas Brugger, Christian Seiler, and Matthias Wilhelm

**Objectives:** Extensive endurance training and arterial hypertension are established risk factors for atrial fibrillation. We aimed to assess the proportion of masked hypertension in endurance athletes and the impact on cardiac remodeling, mechanics, and supraventricular tachycardias (SVT).

**Methods:** Male participants of a 10-mile race were recruited and included if office blood pressure was normal (<140/90 mmHg). Athletes were stratified into a masked hypertension and normotension group by ambulatory blood pressure. Primary endpoint was diastolic function, expressed as peak early diastolic mitral annulus velocity (*E*'). Left ventricular global strain, left ventricular mass/ volume ratio, left atrial volume index, signal-averaged P-wave duration (SAPWD), and SVT during 24-h Holter monitoring were recorded.

Results: From 108 runners recruited, 87 were included in the final analysis. Thirty-three (38%) had masked hypertension. The mean age was  $42 \pm 8$  years. Groups did not differ with respect to age, body composition, cumulative training hours, and 10-mile race time. Athletes with masked hypertension had a lower E' and a higher left ventricular mass/volume ratio. Left ventricular global strain, left atrial volume index, SAPWD, and SVT showed no significant differences between the groups. In multiple linear regression analysis, masked hypertension was independently associated with E' (beta = -0.270, P = 0.004) and left ventricular mass/volume ratio (beta = 0.206, P = 0.049). Cumulative training hours was the only independent predictor for left atrial volume index (beta = 0.474, P < 0.001) and SAPWD (beta = 0.481, P<0.001).

**Conclusion:** In our study, a relevant proportion of middleaged athletes had masked hypertension, associated with a lower diastolic function and a higher left ventricular mass/ volume ratio, but unrelated to left ventricular systolic function, atrial remodeling, or SVT.

**Keywords:** ambulatory blood pressure, atrial arrhythmias, diastolic function, left atrial volume index, left ventricular mass/volume ratio

**Abbreviations:** A', peak late diastolic mitral annulus velocity; BP, blood pressure; E', peak early diastolic mitral annulus velocity; PAC, premature atrial contraction; SAPWD, signal-averaged P-wave duration

# INTRODUCTION

ompared to the general population, middle-aged endurance athletes have an approximately five-fold increased risk of developing atrial fibrillation [1]. Atrial remodeling due to repetitive episodes of volume overload, atrial stretching and inflammation, an elevated vagal tone, and premature atrial contractions are suggested contributing factors [2], recently confirmed in an animal model of exercising rats [3]. Arterial hypertension is the most prevalent risk factor in athletes [4], and a potent risk factor for atrial fibrillation [5]. In collegiate American-style football players, a postseasonal increase in blood pressure (BP) has been reported. Forty-seven percent of athletes met criteria for prehypertension and 14% for stage 1 hypertension. In linemen, the increase in BP was associated with an increase in left ventricular mass and concentric left ventricular remodeling [6]. For a comparable amount of training and performance, male endurance athletes had a significantly higher BP compared to their female counterparts. The higher BP in male athletes was associated with concentric left ventricular remodeling, an altered diastolic function, a more pronounced left atrial remodeling, and a higher proportion of paroxysmal atrial fibrillation [7]. The higher BP in male athletes may, at least in part, explain the striking male predominance of atrial fibrillation in athletes [1]. Masked hypertension is defined as a normal office BP in the presence of an elevated BP during the 24-h BP measurement [8]. It receives increasing attention since it has been assigned a nearly similar risk of cardiovascular morbidity as sustained hypertension [8,9]. In the general population, the prevalence lies in the range of 8-20%, but can be up to 50% in the treated hypertensive patients [8]. The prevalence of masked hypertension in athletes is unknown. The aim of our study was to assess the proportion of masked hypertension in male endurance athletes and the impact on

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cardiac morphology, mechanics, and supraventricular tachycardias (SVT). We hypothesized that masked hypertension would be an independent predictor of a reduced diastolic function and increased cardiac remodeling, thus acting as a risk factor for atrial fibrillation [10,11].

# **METHODS**

#### **Participants and protocol**

The Grand Prix of Bern is one of the most popular 10-mile races in Switzerland with over 25000 participants. Male runners, aged 30 years and older, were recruited for a study on cardiac remodeling by an open letter of invitation published on the homepage of the 2011th events [12,13]. The term 'hypertension' was not mentioned in the invitation letter to minimize selection bias. All athletes applied via electronic mail. Athletes were classified based on their experience in endurance competitions in three categories: leisure-time runners (no or up to one previous marathon participation), marathon runners (more than one marathon participation), and ultraendurance athletes (participation in 78 or 100-km races or long-distance triathlons). An equal number of athletes were randomly selected from each category. Analyses were performed from July 2011 to June 2012, at least 4 weeks after a competition. All athletes provided written informed consent and the protocol was approved by the local ethics committee.

We excluded athletes with a history of cardiovascular disease, medication intake, ergogenic aids usage, or an office BP at least 140/90 mmHg at the initial visit. Office BP was defined as optimal (<120/80 mmHg), normal (120/80–129/84 mmHg), and high-normal (130/85–139/89 mmHg) [9]. The 24-h ambulatory BP monitoring was performed. Also, 24-h, daytime, and night-time SBP and DBP were recorded. Masked hypertension was diagnosed if 24-h and/or daytime BP were above the established cut-off values (mean SBP  $\geq$ 130 and/or mean DBP  $\geq$ 80 mmHg, daytime SBP  $\geq$ 135 and/or daytime DBP  $\geq$ 85 mmHg) [9]. The athletes were then stratified into a normotension and a masked hypertension group.

Assessment included transthoracic echocardiography with Doppler tissue imaging and two-dimensional speckle tracking, signal-averaged analysis of the ECG, and 24-h ambulatory Holter monitoring. Before the tests, the athletes were asked to abstain from food, and caffeine-containing substances ( $\geq$ 3 h) and alcohol ( $\geq$  24 h), and they were told to refrain from vigorous exercise training for 24 h before the tests. All measurements were performed on the same day, starting with office BP measurement, followed by signalaveraged ECG, transthoracic echocardiography, and preparation for 24-h BP and Holter monitoring. In case of an ambulatory BP monitoring with insufficient data quality, the measurement was repeated within 1 week.

Primary endpoint was diastolic function, expressed as peak early diastolic mitral annulus velocity (*E*). Secondary endpoints included parameters of left ventricular systolic function (left ventricular global strain), left ventricular remodeling (left ventricular mass/volume ratio), left atrial remodeling [left atrial volume index and signal-averaged Pwave duration (SAPWD)], premature atrial contractions (PACs), and SVT during 24-h Holter monitoring.

#### Office blood pressure

Resting BP was measured three times in the right arm with an oscillometric device (Dinamap XL; Criticon Inc., Tampa, Florida, USA) after a 10-min rest in supine position. The cuff size was adjusted to the arm's circumference. The first measurement was discarded and the mean of the two last measurements was used for data analysis.

## **Sports history**

A comprehensive questionnaire was used to assess personal and sports histories. Lifetime training hours were based on the athletes' training diaries and/or estimations, and were calculated as follows: average endurance and strength training hours per week multiplied by 52 weeks multiplied by training years after the age of 18 [12,14]. Furthermore, cumulative lifetime competitions were assessed and expressed as marathon equivalents: 10 km race  $\times$  0.24, 10 mile race  $\times$  0.38, half marathon  $\times$  0.5, marathon  $\times$  1.0, mountain marathon  $\times$  1.3, 78 km race  $\times$  1.8, ironman triathlon race  $\times$  2.5, and 100 km race  $\times$  2.5.

## Ambulatory blood pressure

A 24-h BP measurement was performed using a certified oscillometric device (Ultralite 90217; Spacelabs Healthcare) and following the guidelines of the European Society of Hypertension [9]. Daytime and night-time hours were defined based on the athletes' diary. Four daytime and two night-time measures per hour were performed. A valid recording was defined as at least 90% of correct measurements. Invalid recordings were repeated, if possible. Mean 24-h, daytime, and night-time values of the SBP and DBP were extracted using the ABP Report Management System (Spacelabs Healthcare).

## Transthoracic echocardiography

Standard transthoracic echocardiography was performed on a Phillips iE33 System (X5-1 transducer; Phillips Medical Systems, Zurich, Switzerland). Left ventricular diastolic function was evaluated using standard parameters. Peak early and late diastolic velocities at the septal and lateral side of the mitral annulus were recorded, and the mean value was calculated and defined as E' mean and A' mean [15]. Diastolic dysfunction was defined as E' septal less than 8 cm/s and/or E' lateral less than 10 cm/s [15]. Maximal left atrial volume was calculated using the biplane summed disc method [16]. A markedly enlarged left atrium was defined as left atrial volume index at least 34 ml/m<sup>2</sup> [16]. Left ventricular dimensions and wall thickness were measured using M-mode, and the left ventricular mass and relative wall thickness were calculated. Left ventricular volumes were obtained using the biplane summed discs method, and the left ventricular mass/volume ratio and ejection fraction were derived [16,17]. Mass and volume parameters were indexed for the body surface area. Strain analysis of the left ventricle (LV) was performed by two-dimensional speckletracking echocardiography in apical four, two, and threechamber views [18]. High frame loops (70-80 Hz) were acquired during breath hold for five cardiac cycles and were analyzed off-line using the QLAB CMQ software (Philips Medical Systems, Zurich, Switzerland). All measurements

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were taken by the same operator. When selecting three points in the endocardium, the software automatically traces the endocardium and epicardium of the left ventricular wall for each view and divides the septum and LV-free wall into basal, middle, and apical segments. The peak negative systolic strain was calculated from the six segments of each view, in inferoseptal and anterolateral walls (fourchamber view), inferior and anterior walls (two chamber view), and inferolateral and anteroseptal walls (threechamber view). The left ventricular global strain was determined by averaging all values of the 18 segments of the three views. For intraobserver variability, a comparison of the left ventricular global strain was performed in 25 athletes, as described previously [13].

# Twenty-four-hour Holter monitoring

A three-channel ECG was recorded with a Lifecard CF digital recorder (Spacelabs Healthcare) and manually analysed and interpreted using the Pathfinder Software (Spacelabs Healthcare). PAC and SVT (three or more consecutive PACs) were classified according to onset and QRS morphology. Spectral power analysis of heart rate variability was performed and the high-frequency/low-frequency power ratio was used as a surrogate of the sympatho-vagal balance [19].

# Signal-averaged ECG and analysis of P wave

A 12-lead ECG was recorded at a paper speed of 25 mm/s with the athlete in the supine position (MAC5500; GE Healthcare, Glattbrugg, Switzerland). The method for recording and analyzing a signal-averaged ECG P-wave has been described previously [7].

# Data analysis

The data were analyzed with SPSS Software for Windows (Version 17.0, SPSS Inc., Chicago, Illinois, USA). The normality of the quantitative variables was verified with the Shapiro-Wilk test. Normally distributed data were presented as mean  $\pm$  SD, and variables with skewed distribution were shown as median (minimum, maximum). Continuous variables were compared with the Student's ttest or Mann–Whitney *U* test, as appropriate. A chi-square test was used to compare the categorical data. Multiple linear regression analyses were performed to determine predictor for primary and secondary endpoints. Independent variables were masked hypertension, cumulative training hours, and age. Dependent variables were parameters of diastolic function (E' mean), left ventricular remodeling (left ventricular volume/mass ratio), and left atrial remodeling (left atrial volume index and SAPWD). P value of less than 0.05 was considered to indicate statistical significance. Relative risk and 95% confidence intervals (CIs) for having masked hypertension was calculated for athletes with optimal vs. nonoptimal office BP.

Sample size calculation (G-Power Version 3.1.9.2, University of Düsseldorf, Germany) for the primary endpoint (*E'*) was based on a previous study in male, middle-aged amateur athletes with a mean *E'* of  $12.9 \pm 1.7$  cm/s [14]. We assumed a 10% lower *E'* ( $11.6 \pm 1.5$  cm/s) in the masked hypertension group to be clinically meaningful (effect size 0.81). With an alpha of 0.05 (one-sided) and a power of

80%, we calculated a necessary sample size of 20 athletes per group. Assuming a prevalence of masked hypertension in our population of 20% [8], 100 athletes had to be included. Assuming that 90% of recruited athletes would meet inclusion criteria and have sufficient data quality, we aimed to include approximately 110 athletes.

# RESULTS

# Participants' characteristics

A total of 208 runners applied for participation and were classified according to the predefined three categories. Athletes of each category were ordered according to electronic mail entry date. On the basis of the sample size calculation, 36 athletes had to be selected from each category. The total number of applicants per category was divided by 36, and accordingly every second or third athlete was selected. Twelve athletes had to be excluded because of systemic arterial hypertension, and one because of treated hypercholesterolemia. Eight athletes had insufficient 24-h BP measurements; thus 87 were included in the final analysis. Thirty-three athletes (38%) showed elevated 24-h and/or daytime BP measurements and were allocated to the masked hypertension group.

Mean age was  $42 \pm 8$  years, with no significant differences between groups. Additionally to ambulatory BP, office BP was significantly higher in the masked hypertension group, compared to the normotension group (Table 1). The relative risk of having masked hypertension with a nonoptimal office BP was 2.03 (95% CI 1.39–2.96).

The spectrum of recruited athletes reached from leisuretime runners with no experience in competitions to semiprofessional ultraendurance athletes with a maximum of 23 endurance training hours per week, and 82 marathon equivalents of competitions. Mean exercise training years, median endurance and strength training hours, the athletic category, and participation in competitions were balanced between the groups, and there were no differences with regard to parameters of body composition and race performance (Table 1).

# Left ventricular mechanics and morphology

In athletes with masked hypertension, E' mean and the E'/A'ratio were significantly lower, and the E/E' ratio and left ventricular mass/volume ratio were significantly higher, compared to normotensive athletes. Left ventricular mass index showed a tendency towards higher values. Left ventricular global strain and other parameters of left ventricular function and morphology showed no group differences (Fig. 1 and Table 2). Intraclass correlation coefficient for left ventricular global strain was 0.867, which is a very good agreement. The proportion of athletes with diastolic dysfunction was not different between the normotension and the masked hypertension group (9.3 vs. 12.1%; P = 0.466). There was a significant correlation of the left ventricular mass/volume ratio with E' mean in an univariate model (R = 0.265, P = 0.013). However, the association was lost when age was entered as an independent variable. Age and masked hypertension were independent predictors of E' mean and the left ventricular mass/volume ratio in multivariate models (Fig. 2, Table 3).

TABLE 1. Baseline characteristics o	f endurance athletes, stratifie	d according to 24-h ambulator	y blood pressure measurement
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Variable	Normotension (n = 54)	Masked hypertension ( <i>n</i> = 33)	P value
Age (years)	42±8	42±8	0.794
BMI (kg/m <sup>2</sup> )	$22.9 \pm 1.8$	23.4±1.8	0.240
Body surface area (m <sup>2</sup> )	1.9 ± 0.1	1.9±0.1	0.256
Office SBP (mmHg)	$119.1 \pm 8.4$	127.2 ± 6.9	< 0.001
Office DBP (mmHg)	$77.2 \pm 5.5$	83.1±4.9	< 0.001
Office BP <120/80 mmHg (n)	30 (55.6%)	7 (21.2%)	0.003
Office BP 120/80 to 129/84 mmHg (n)	18 (33.3%)	11 (33.3%)	
Office BP 130/85 to 139/89 mmHg (n)	6 (11.1%)	15 (45.5%)	
24-h SBP (mmHg)	$119.5 \pm 5.4$	130.1 ± 7.3	< 0.001
24-h DBP (mmHg)	$76.5 \pm 3.4$	84.2±3.6	< 0.001
Daytime SBP (mmHg)	121.8±5.7	133.2 ± 7.6	< 0.001
Daytime DBP (mmHg)	$78.5\pm3.5$	86.9 ± 3.7	< 0.001
Night-time SBP (mmHg)	$105.3 \pm 6.2$	113.1±6.8	< 0.001
Night-time DBP (mmHg)	63.7±4.8	69.8±4.8	< 0.001
Training volume			
Exercise training (years)	$14.5 \pm 10.2$	12.8±6.8	0.343
Endurance training (hours : min/week) <sup>a</sup>	4:00 (1:00, 23:00)	4:30 (0:30, 13:00)	0.719
Strength training (hours : min/week) <sup>a</sup>	0:37 (0:00, 3:00)	0:30 (0:00, 3:00)	0.399
Cumulative lifetime training (h) <sup>b</sup>	2171 (0, 14872)	2340 (0, 16640)	0.431
Athletic category and participation in competitions			
Leisure time runners (n)	21 (38.9%)	14 (42.4%)	0.498
Marathon runners (n)	21 (38.9%)	9 (27.3%)	
Ultraendurance athletes (n)	12 (22.2%)	10 (30.3%)	
Marathon equivalents ( <i>n</i> ) <sup>c</sup>	2.0 (0, 82)	2.0 (0, 65)	0.510
Performance			
10-mile race time (hours:min)	1:10±0:10	1:09±0:09	0.933

Data are expressed as mean  $\pm$  SD, median (minimum, maximum) or %. BP, blood pressure.

<sup>a</sup>Estimated averages of the past 3 months. <sup>b</sup>Average total endurance and strength training hours per week × 52 × training years.

<sup>1</sup>O-km races × 0.24, 10-mile race × 0.38, half marathon × 0.5, flat marathon × 1.0, mountain marathon × 1.3, 78-km race × 1.8, Ironman triathlon race × 2.5, and 100-km race × 2.5.

# Left atrial remodeling and supraventricular tachycardias

The left atrial volume index and parameters of signalaveraged P-wave analysis showed no significant differences between the groups (Fig. 1 and Table 4). The proportion of athletes with a markedly enlarged left atrium (>34 ml/m<sup>2</sup>) was not statistically significantly different between the normotension and the masked hypertension group (40.7 vs. 30.3%, respectively; P=0.327). Cumulative training hours was the only independent predictor of the left atrial volume index and the SAPWD in the multivariate models (Table 3). PACs occurred significantly more frequently in the normotension group and were inversely correlated with the low-frequency/high-frequency power ratio (R=-0.297, P=0.005). The burden of SVT was low and showed no significant differences between the groups (Table 4).

#### DISCUSSION

In our sample of middle-aged endurance athletes, the proportion of athletes with masked hypertension was substantially higher (38%) than estimates from the general population (8–20%) [8], but comparable to male professional football players [20]. Importantly, the prevalence of masked hypertension depends on the definition. Asayama *et al.* [21] demonstrated in a middle-aged untreated population an increase of the prevalence from 9.7 to 15.0% and 19% if 24-h BP, 24-h or daytime BP, or 24-h, daytime or night-time BP, respectively, had been used. In our study, we used the criterion of 24-h or daytime BP. Inclusion of night-time BP would have increased the prevalence to 40% without a significant impact on the primary endpoint *E*'.

Interestingly, in the study by Asayama *et al.*, the masked hypertension group had a higher daytime SBP, compared to our athletic population  $(139.1 \pm 10.0 \text{ vs. } 133.2 \pm 7.6 \text{ mmHg})$ , whereas the daytime DBP was lower  $(84.9 \pm 7.6 \text{ vs. } 86.9 \pm 3.7 \text{ mmHg})$  in their population. This may be due to the fact that 24 out of our 33 athletes (73%) qualified for the masked hypertension group using the DBP criterion. Participants in the study by Asayama *et al.* were slightly older, and more obese, and it can be speculated that the pathophysiology of masked hypertension may be different from a normal-weight athletic population.

Although exercise training in general may prevent hypertension by positively affecting endothelial function and arterial stiffness [22,23], repetitive episodes of high-intensity strength or endurance exercise may contribute to a rise in BP, possibly by an increased sympathetic activity [6,20]. However, our study was not intended to demonstrate a causal relationship between endurance sports practice and masked hypertension. Masked hypertension was associated with a lower diastolic function and a higher left ventricular mass/volume ratio, indicating a more pronounced structural remodeling of the LV, consistent with a study in American-style football players [6]. However, the percentage of diastolic dysfunction was low and equally distributed between the groups, and only two athletes (one in the normotension and one in the masked hypertension group) presented with an E/E' ratio of at least 9, suggestive of an elevated left atrial pressure [15].

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FIGURE 1 Characteristics of the normotension and the masked hypertension group with regard to parameters of LV diastolic function (E' mean), systolic function (LV global strain), LV remodeling (LV mass/volume ratio), and LA remodeling (LA volume index). Columns represent means and bars represent 2 standard errors. LA, left atrial; LV, left ventricular.

#### TABLE 2. Echocardiography

Variable	Normotension ( <i>n</i> = 54)	Masked hypertension ( <i>n</i> = 33)	P value
Mean heart rate during examination (b.p.m.)	53±7	53±7	0.878
LVEDVI (ml/m <sup>2</sup> )	$62\pm10$	$59\pm9$	0.210
LVESVI (ml/m <sup>2</sup> )	$21\pm4$	21±4	0.542
LV ejection fraction (%)	$66\pm5$	$65\pm5$	0.625
LVMI (g/m <sup>2</sup> )	$100 \pm 18$	$104 \pm 19$	0.258
Relative wall thickness	$0.38 \pm \pm 0.06$	$0.38 \pm 0.06$	0.897
Peak E (cm/s)	$70.0 \pm 10.5$	71.0±13.2	0.694
Peak A (cm/s)	43.9±10.2	47.5±9.9	0.120
E/A ratio	$1.66 \pm 0.44$	$1.54 \pm 0.38$	0.197
DT (ms)	$179\pm31$	182±31	0.654
IVRT (ms)	79±11	82 ± 6	0.329
A' mean (cm/s)	9.4±2.0	10.6 ± 4.7	0.114
E'/A' ratio	$1.38 \pm 0.36$	$1.16 \pm 0.34$	0.008
E/E' ratio	6.0±1.3	$6.6\pm1.2$	0.046

Data are expressed as mean ± SD. A' mean, peak late diastolic septal and lateral mitral annulus velocity; DT, deceleration time; *E/E'*, peak early mitral inflow velocity to peak early diastolic mitral annulus velocity ratio; IVRT, isovolumic relaxation time; LVEDVI, left ventricular end diastolic volume index; LVESVI, left ventricular end systolic volume index; LVMI, left ventricular mass index.

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FIGURE 2 Impact of age and masked hypertension on the primary endpoint (E').

Left ventricular global strain as a marker of left ventricular systolic function showed no significant group differences. Values were comparable with data from a study including healthy and normotensive power-endurance athletes [24]. For patients with high-normal BP or hypertension, both significantly lower values for left ventricular global strain [24,25] and values comparable to normotensive patients [26] have been published. Probably, the time course of BP elevation plays an important role for the impact on left ventricular mechanics. Athletes in our study were younger compared to patients with high-normal BP and reduced left ventricular global strain ( $42\pm8$  vs.  $47\pm7$  years, respectively) [25]. An elevated BP may induce a deterioration of diastolic function that precedes the reduction of systolic function.

Consistent with the relatively low E/E' ratio in the masked hypertension, we found no association of masked hypertension with parameters of left atrial remodeling. Despite the fact that the left atrium was markedly dilated in 32 athletes (36.8%), this was only attributable to the cumulative lifetime training hours. Also the SAPWD, a surrogate marker for atrial fibrosis, was only associated with cumulative lifetime training hours. Interestingly, the SAPWD was substantially longer in our cohort compared to reference values from an age-matched nonathletic population ( $140 \pm 13$  vs.  $117 \pm 12$  ms, respectively) [27]. Values above 130 ms have been associated with a higher risk of

atrial fibrillation [28]. Nevertheless, the burden of SVT during 24-h Holter monitoring was low in our study and equally distributed between the groups. Interestingly, PACs occurred more frequently in the normotension groups and showed an inverse correlation with markers of the sympatho-vagal balance, suggesting an association with vagal activity.

Taken together, atrial remodeling in our cohort of endurance athletes was related solely to cumulative training hours, which is consistent with other studies [14,29]. One could speculate that repetitive episodes of volume overload during training and competition, associated with atrial stretching, elevated atrial wall tension, and parameters of inflammation [30], would contribute substantially more to structural remodeling of the left atrium than a mildly altered diastolic function, especially when the left atrial pressure is not substantially elevated.

In contrast to a recently published meta-analysis of athletes with atrial fibrillation, our participants were much younger  $(51 \pm 9 \text{ vs. } 42 \pm 8 \text{ years}, \text{ respectively})$  [1]. Diastolic function declines with age [15], consistent with the strong inverse association of E' mean with age in our cohort. Although it has been suggested that the age-related decline of ventricular compliance may be mitigated by endurance training [31], an elevated BP could abolish this positive effect or even aggravate the age-related decline. On the long term, uncontrolled masked hypertension in athletes could promote diastolic dysfunction with elevated left atrial pressures like demonstrated in a nonathletic population [32], and contribute to atrial remodeling and atrial fibrillation later in life.

#### Limitations

We included male endurance runners and triathletes; thus, our findings cannot be generalized to athletes of other types of sports or female athletes. We cannot exclude that unreported analgesic use or alcohol consumption may have contributed to masked hypertension [33]. We did not perform a laboratory test to rule out kidney dysfunction. Office BP was measured only in the right arm, so a possibly higher BP in the left arm was not taken into account. Due to our rather small sample size, the results should be confirmed in a larger population. The determination of the left ventricular mass/volume ratio may be imprecise using two-dimensional echocardiography. Three-dimensional techniques have a better reproducibility [34], but were not available

TABLE 5. Independent breaktors for barancers reneative of cardiac removement
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	Beta coefficient	Standard error beta	Standardized $\beta$	P value
$E'$ mean ( $R^2 = 0.293$ )				
Age	-0.108	0.024	-0.425	< 0.001
Masked hypertension	-1.122	0.384	-0.270	0.004
LV mass/volume ratio ( $R^2 = 0.119$ )				
Age	0.010	0.004	0.250	0.018
Masked hypertension	0.137	0.069	0.206	0.049
LA volume index ( $R^2 = 0.241$ )				
Cumulative training hours	0.001	0.000	0.474	< 0.001
SAPWD ( $R^2 = 0.288$ ) Cumulative training hours	0.002	0.000	0.481	<0.001

Multiple linear regression analysis including masked hypertension (0 = no, 1 = yes), cumulative training hours, and age. Only significant associations are displayed. E' mean, peak early diastolic septal and lateral mitral annulus velocity; LA, left atrial; LV, left ventricular; SAPWD, signal-averaged P-wave duration.

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#### TABLE 4. Signal-averaged ECG and 24-h Holter monitoring

Variable	Normotension (n = 54)	Masked hypertension ( <i>n</i> = 33)	P value
Signal-averaged ECG			
SAPWD (ms)	$141 \pm 14$	138±9	0.259
Integral P wave (µVs)	882±310	786±223	0.604
RMS 20 (µV)	4.3±2.1	4.6 ± 2.2	0.136
24-h Holter monitoring			
Premature atrial contractions (n)	92 (0, 1870)	9 (0, 99)	0.023
SV arrhythmias (n)	0 (0, 4)	0 (0, 4)	0.112
Premature ventricular contractions (n)	14 (0, 173)	8 (0, 75)	0.486
Mean HR (b.p.m.)	64 (46, 86)	65 (49, 78)	0.462
Minimal HR (b.p.m.)	44 (31, 58)	45 (33, 57)	0.536
Maximum HR (b.p.m.)	127 (83, 184)	128 (83, 177)	0.746

Data are expressed as mean ± SD or median (minimum, maximum). b.p.m., Beats per minute; HR, heart rate; RMS 20, root mean squares voltage in terminal 20 ms of the P wave; SAPWD, signal-averaged P-wave duration; SV, supraventricular.

at the time of the study measurements. The low arrhythmic burden and absence of sustained SVT could be due to the low-risk participants included in the study. Further, nondetection of SVT may have been related to the short monitoring period of only 24 h. Seven days of Holter monitoring would have been more appropriate to rule out paroxysmal atrial fibrillation [35], but was impractical for athletes in preparation of competitions. The study was not powered to detect differences in arrhythmic burden between the groups.

#### Perspectives

In our study, a relevant proportion of middle-aged endurance athletes had masked hypertension, associated with a lower diastolic function and a higher left ventricular mass/ volume ratio, but unrelated to left ventricular systolic function, atrial remodeling, or SVT. However, uncontrolled masked hypertension has a potential to contribute to atrial remodeling and atrial fibrillation in the long term.

While most endurance athletes at risk for atrial fibrillation would feel reluctant to reduce their training volume to prevent atrial remodeling, arterial hypertension is an easily modifiable risk factor. Current guidelines recommend office BP measurements for middle-aged athletes, engaged in high-intensity activities [36]. Our data suggest that the relative risk of having masked hypertension is two-fold increased in the presence of a nonoptimal office BP ( $\geq$ 120/80 mmHg), which is consistent with studies including nonathletes [37]. Ambulatory BP measurements may be indicated is these athletes to rule out uncontrolled masked hypertension.

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#### **Conflicts of interest**

There are no conflicts of interest.

#### REFERENCES

1. Abdulla J, Nielsen JR. Is the risk of atrial fibrillation higher in athletes than in the general population? A systematic review and meta-analysis. *Europace* 2009; 11:1156–1159.

- Wilhelm M. Atrial fibrillation in endurance athletes. *Eur J Prev Cardiol* 2013; 21:1040–1048.
- Guasch E, Benito B, Qi X, Cifelli C, Naud P, Shi Y, *et al.* Atrial fibrillation promotion by endurance exercise: demonstration and mechanistic exploration in an animal model. *J Am Coll Cardiol* 2013; 62:68–77.
- De Matos LD, Caldeira Nde A, Perlingeiro Pde S, dos Santos IL, Negrao CE, Azevedo LF. Cardiovascular risk and clinical factors in athletes: 10 years of evaluation. *Med Sci Sports Exerc* 2011; 43:943–950.
- 5. Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. *JAMA* 1994; 271:840–844.
- 6. Weiner RB, Wang F, Isaacs SK, Malhotra R, Berkstresser B, Kim JH, *et al.* Blood pressure and left ventricular hypertrophy during american-style football participation. *Circulation* 2013; 128:524–531.
- Wilhelm M, Roten L, Tanner H, Wilhelm I, Schmid JP, Saner H. Gender differences of atrial and ventricular remodeling and autonomic tone in nonelite athletes. *Am J Cardiol* 2011; 108:1489–1495.
- Bobrie G, Clerson P, Menard J, Postel-Vinay N, Chatellier G, Plouin PF. Masked hypertension: a systematic review. *J Hypertens* 2008; 26:1715– 1725.
- 9. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M, *et al.* 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J* 2013; 34:2159–2219.
- 10. Mont L, Tamborero D, Elosua R, Molina I, Coll-Vinent B, Sitges M, *et al.* Physical activity, height, and left atrial size are independent risk factors for lone atrial fibrillation in middle-aged healthy individuals. *Europace* 2008; 10:15–20.
- Rosenberg MA, Gottdiener JS, Heckbert SR, Mukamal KJ. Echocardiographic diastolic parameters and risk of atrial fibrillation: the Cardiovascular Health Study. *Eur Heart J* 2012; 33:904–912.
- Brugger N, Krause R, Carlen F, Rimensberger C, Hille R, Steck H, et al. Effect of lifetime endurance training on left atrial mechanical function and on the risk of atrial fibrillation. Int J Cardiol 2014, 170:419–425.
- Rimensberger C, Carlen F, Brugger N, Seiler C, Wilhelm M. Right ventricular adaptations and arrhythmias in amateur ultra-endurance athletes. *Br J Sports Med* 2014; 48:1179–1184.
- Wilhelm M, Roten L, Tanner H, Wilhelm I, Schmid JP, Saner H. Atrial remodeling, autonomic tone, and lifetime training hours in nonelite athletes. *Am J Cardiol* 2011; 108:580–585.
- Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. Eur J Echocardiogr 2009; 10:165–193.
- Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, *et al.* Recommendations for chamber quantification. *Eur J Echocardiogr* 2006; 7:79–108.
- 17. Buakhamsri A, Popovic ZB, Lin J, Lim P, Greenberg NL, Borowski AG, *et al.* Impact of left ventricular volume/mass ratio on diastolic function. *Eur Heart J* 2009; 30:1213–1221.
- Mor-Avi V, Lang RM, Badano LP, Belohlavek M, Cardim NM, Derumeaux G, *et al.* Current and evolving echocardiographic techniques for the quantitative evaluation of cardiac mechanics: ASE/EAE consensus statement on methodology and indications endorsed by the Japanese Society of Echocardiography. *Eur J Echocardiogr* 2011; 12:167–205.

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- Furholz M, Radtke T, Roten L, Tanner H, Wilhelm I, Schmid JP, *et al.* Training-related modulations of the autonomic nervous system in endurance athletes: is female gender cardioprotective? *Eur J Appl Physiol* 2013; 113:631–640.
- Berge HM, Andersen TE, Solberg EE, Steine K. High ambulatory blood pressure in male professional football players. *Br J Sports Med* 2013; 47:521–525.
- 21. Asayama K, Thijs L, Li Y, Gu YM, Hara A, Liu YP, *et al.* Setting thresholds to varying blood pressure monitoring intervals differentially affects risk estimates associated with white-coat and masked hypertension in the population. *Hypertension* 2014; 64:935–942.
- 22. Rowe GC, Safdar A, Arany Z. Running forward: new frontiers in endurance exercise biology. *Circulation* 2014; 129:798–810.
- Cornelissen VA, Smart NA. Exercise training for blood pressure: a systematic review and meta-analysis. J Am Heart Assoc 2013; 2:e004473.
- 24. Galderisi M, Lomoriello VS, Santoro A, Esposito R, Olibet M, Raia R, et al. Differences of myocardial systolic deformation and correlates of diastolic function in competitive rowers and young hypertensives: a speckle-tracking echocardiography study. JAm Soc Echocardiogr 2010; 23:1190–1198.
- 25. Tadic M, Majstorovic A, Pencic B, Ivanovic B, Neskovic A, Badano L, et al. The impact of high-normal blood pressure on left ventricular mechanics: a three-dimensional and speckle tracking echocardiography study. Int J Cardiovasc Imaging 2014; 30:699–711.
- Narayanan A, Aurigemma GP, Chinali M, Hill JC, Meyer TE, Tighe DA. Cardiac mechanics in mild hypertensive heart disease: a speckle-strain imaging study. *Circ Cardiovasc Imaging* 2009; 2:382–390.
- Ehrlich JR, Zhang GQ, Israel CW, Hohnloser SH. P-wave signal averaging-ECG: normal values and reproducibility. *Z Kardiol* 2001; 90:170– 176.
- Darbar D, Jahangir A, Hammill SC, Gersh BJ. P wave signal-averaged electrocardiography to identify risk for atrial fibrillation. *Pacing Clin Electrophysiol* 2002; 25:1447–1453.
- 29. Molina L, Mont L, Marrugat J, Berruezo A, Brugada J, Bruguera J, *et al.* Long-term endurance sport practice increases the incidence of lone

#### **Reviewers' Summary Evaluations**

#### **Reviewer 1**

The paper 'Masked hypertension and cardiac remodeling in middle-aged endurance athletes' was aimed at investigating the frequency of masked hypertension in middle-aged endurance athletes and its impact on cardiac remodeling, mechanics and supraventricular tachycardia (SVT). This is an interesting study with relevant and novel findings supporting the idea that on long-term, masked hypertension could promote diastolic dysfunction with elevated left atrial pressures and contribute to atrial remodeling and atrial fibrillation later in the life of athletes. Although supported by a proper statistical analysis, the results of this study, coming from a small sample, need to be confirmed by a study performed in a larger population of all types' athletes. atrial fibrillation in men: a follow-up study. *Europace* 2008; 10:618-623.

- 30. Wilhelm M, Zueger T, De Marchi S, Rimoldi SF, Brugger N, Steiner R, *et al.* Inflammation and atrial remodeling after a mountain marathon. *Scand J Med Sci Sports* 2014; 24:519–525.
- Arbab-Zadeh A, Dijk E, Prasad A, Fu Q, Torres P, Zhang R, et al. Effect of aging and physical activity on left ventricular compliance. *Circulation* 2004; 110:1799–1805.
- 32. Komori T, Eguchi K, Kabutoya T, Ishikawa J, Hoshide S, Kario K. Left ventricular diastolic function evaluated by the E/e' ratio is impaired in patients with masked uncontrolled hypertension. *Clin Exp Hypertens* 2014; 36:538–544.
- 33. Camafort M, Coca A. Hypertension and analgesic intake: light and shade on an old problem. *Rev Esp Cardiol* 2010; 63:265–267.
- 34. Caselli S, Di Paolo FM, Pisicchio C, Di Pietro R, Quattrini FM, Di Giacinto B, *et al.* Three-dimensional echocardiographic characterization of left ventricular remodeling in Olympic athletes. *Am J Cardiol* 2011; 108:141–147.
- 35. Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser SH, *et al.* 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. *Eur Heart J* 2012; 33:2719–2747.
- 36. Borjesson M, Urhausen A, Kouidi E, Dugmore D, Sharma S, Halle M, et al. Cardiovascular evaluation of middle-aged/senior individuals engaged in leisure-time sport activities: position stand from the sections of exercise physiology and sports cardiology of the European Association of Cardiovascular Prevention and Rehabilitation. Eur J Cardiovasc Prev Rehabil 2011; 18:446– 458.
- 37. Viera AJ, Lin FC, Tuttle LA, Shimbo D, Diaz KM, Olsson E, et al. Levels of Office Blood Pressure and Their Operating Characteristics for Detecting Masked Hypertension Based on Ambulatory Blood Pressure Monitoring. Am J Hypertens 2015; 28:42–49.

#### **Reviewer 2**

In this manuscript the Authors aimed to assess the proportion of masked hypertension in middle-aged endurance male athletes, and impact of this dysfunction on cardiovascular remodeling. Masked hypertension is an important parameter, associated with a lower diastolic function and a higher left ventricular mass. Uncontrolled masked hypertension could promote atrial remodeling and atrial fibrillation in athletes later in their life. Due to the nature of the present study, it is unclear if the occurrence of masked hypertension higher in endurance athletes vs. general population, and how the main finding of the study applies to female athletes.