Inflammation and atrial remodeling after a mountain marathon

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Middle-aged endurance athletes have an increased risk of atrial fibrillation. We performed a longitudinal study on elite runners of the 2010 Jungfrau Marathon, a Swiss mountain marathon, to determine acute effects of long-distance running on the atrial myocardium. Ten healthy male athletes were included and examined 9 to 1 week prior to the race, immediately after, and 1, 5, and 8 days after the race. Mean age was 34.9 ± 4.2 years, and maximum oxygen consumption was 66.8 ± 5.8 mL/kg•min. Mean race time was 243.9 ± 17.7 min. Electrocardiographic-determined signal-averaged P-wave duration (SAPWD) increased significantly after the race and returned to baseline levels during follow-up (128.7 ± 10.9 vs. 137.6 ± 9.8 vs. 131.5 ± 8.6 ms; P < 0.001). Left and right atrial volumes showed no significant differences over time, and there were no correlations of atrial volumes and SAPWD. Prolongation of the SAPWD was accompanied by a transient increase in levels of high-sensitivity C-reactive protein, proinflammatory cytokines, total leukocytes, neutrophil granulocytes, pro atrial natriuretic peptide and high-sensitivity troponin. In conclusion, marathon running was associated with a transient conduction delay in the atria, acute inflammation and increased atrial wall tension. This may reflect exercise-induced atrial myocardial edema and may contribute to atrial remodeling over time, generating a substrate for atrial arrhythmias.

Materials and methods

Study design and participants

The Jungfrau Marathon, taking place in the Swiss Alps, is one of the most popular mountain marathons with a 1829-m difference in altitude and over 4000 participants. We performed a prospective, single-center observational study at the University Hospital of Bern, Switzerland. Marathon runners listed for the race 2010 were recruited from the publicly available ranking list of the 2009 event, meeting the following criteria: male gender, age 20–40 years, a
finishing time in 2009 of less than 4:30 h and a reasonable travel
time from place of residence to the hospital.

We excluded athletes with evidence of cardiac disease, myocardial
ischemia (assessed by exercise testing), complex arrhyth-
mia (assessed by 24-h Holter monitoring), cardiovascular risk
factors such as smoking, positive family history for myocardial
infarction, hypertension (assessed by 24-h blood pressure mea-
surement), diabetes and dyslipidemia (assessed by fasting blood
sampling), or drug abuse. Each participant gave written informed
consent. The study was approved by the local ethics committee
in Bern, Switzerland and registered on ClinicalTrials.gov
(NCT01179802).

Baseline examinations were conducted on a single day, 9 to 1
week before the race and consisted of a comprehensive question-
naire to ascertain personal and sports history, fasting blood sam-
ping, electrocardiography (ECG) with signal-averaged P-wave
analysis (SAECG), echocardiography, cardiopulmonary exercise
testing, 24-h ambulatory Holter monitoring and 24-h blood pres-
sure measurement. Follow-up measurements were performed
immediately after the race (blood sampling within 15 min,
SAECG within 1 h), 1 day post race (blood sampling), 5 days post race (SAECG) and 8 days post race (blood
sampling, echocardiography), respectively.

Signal-averaged electrocardiogram

Twelve-lead ECGs were performed with the subject in supine
position and recorded at a paper speed of 25 mm/s (MAC5500, GE
Healthcare, Glattbrugg, Switzerland). The methodology for
recording and analyzing a signal-averaged P-wave has been
described previously (Dhala et al., 2002; Wilhelm et al., 2011). In
brief, a signal-averaged P-wave was recorded in a room, free-from
electrical interference. It incorporated three bipolar orthogonal
leads referred to as the X, Y and Z leads, which correspond to those
used for the acquisition of the standard signal-averaged ECG. A
P-wave template was generated and confirmed by the user. Then
250 P-waves that meet the criteria of matching (95%) with the
template P-wave were averaged to form a final template. Averaged
P-wave signals were digitized and filtered using a spectral filter
with a bandwidth of 40–250 Hz and were then combined into a
vector magnitude $[VM = (x^2 + y^2 + z^2)^{1/2}]$. The measurements
computed by the system included the signal-averaged P-wave
duration (SAPWD) in milliseconds and the root mean square
voltage in the terminal 20 ms of the P-wave (RMS20), expressed
in micro-Volts ($\mu$V). In addition, the integral of the P-wave (area
under the vector magnitude curve from P-wave onset to offset,
$\mu$Vs) was computed. Onset and offset of the P-wave were manu-
ally adjusted (Fig. 1).

Blood samples

Blood was collected into lithium heparin, ethylenediaminetet-
raacetic acid (EDTA) and serum tubes. EDTA samples (hemo-
gram) were analyzed within 5 h after blood sampling. Lithium
heparin and serum tubes were immediately centrifuged and frozen.
Analysis encompassed measurement of high-sensitivity troponine
T (hsTnT; electrochemiluminescence assay, Roche, Modular
E170; Roche, Basel, Switzerland), hsCRP (immunofluorescence
test, BRAHMS, Kryptor, Henningsdorf, Germany), pro atrial
atriuretic peptide (proANP, enzyme immunoassay, aa 1–98
ELISA kit, Biomedica GmbH & Co KG, Vienna, Austria), leuco-
cytes (Beckman Coulter LH780, Krefeld, Germany), interleukin-6
(IL-6) and tumor necrosis factor alpha (TNF-α). All cytokines
were measured using a chemiluminescence immunoassay
(Immulite 1000, Siemens Healthcare Diagnostics AG, Zürich,
Switzerland).

Echocardiography

Standard transthoracic echocardiography was performed on two
Siemens Acuson Sequoia 512 Systems (Siemens Healthcare Diag-
agnostics AG). The images were stored digitally and analyzed off-
line. Left and right atrial volumes were calculated according to
current recommendations (Lang et al., 2006). Pulsed-wave
Doppler was performed in the apical four-chamber view to obtain
peak early filling (E-wave) and late diastolic filling (A-wave)
velocities. Pulsed-wave tissue Doppler imaging was performed in
the apical four-chamber view to acquire peak septal mitral annular
velocity (e’ and a’) (Nagae et al., 2009).

Cardiopulmonary exercise testing

Cardiopulmonary exercise testing was performed on an ergometer
(ergometrics 800S cycle ergometer; Ergoline GmbH, Bitz,
Germany). Breath-by-breath respiratory data were collected using
a spiroergometry system (Oxycon Alpha, Erich Jäger GmbH,
Würzburg, Germany) and registered as averaged values over 30 s.
Stress ECG parameters were measured with a Schiller AT104
device (Schiller-Reomed AG, Dietikon, Switzerland). We used a
ramp protocol starting at 20 W with a continuously increasing
workload of 30 W/min until exhaustion.
Atrial remodeling and marathon running

SAPWD increased significantly immediately after the marathon and returned to baseline during follow-up (Figs 1 and 2). Table 2 summarizes results of the SAECG. Left atrial (LA) and right atrial (RA) volumes remained unchanged after the race and during follow-up (Fig. 2). There was no correlation between SAPWD and LA or RA volumes at baseline [correlation coefficient $-0.17$, $P = 0.642$ (LA), and $-0.53$, $P = 0.116$ (RA), respectively], immediately post-race [correlation coefficient $-0.3$, $P = 0.398$ (LA), and $-0.42$, $P = 0.23$ (RA), respectively], and at follow-up [correlation coefficient $-0.29$, $P = 0.423$ (LA), and $0.37$, $P = 0.2$ (RA), respectively].

Left ventricular (LV) diastolic function was significantly altered after the race. In particular, peak E and e' decreased, and peak A and a’ increased, resulting in a lower E/A and e'/a’ ratio. All values except peak E returned to baseline during follow-up (Table 3).

Cardiac biomarkers and markers of inflammation

The cardiac biomarkers proANP and hsTnT increased significantly after the marathon and returned to baseline during follow-up (Fig. 3). TNF-$\alpha$ and IL-6 showed a significant increase immediately after the race and returned to baseline within 24 h [Fig. 4(b, c)]. A similar pattern was found in terms of cellular inflammation with a significant increase in total leukocyte and neutrophile granulocyte cell count immediately after the race, and a slight, but still significant elevation 1 day after the marathon. One week after the race hsCRP values had reached baseline levels [Fig. 4(a)].

Hydration status

Hemoglobin and hematocrit as a proxy of hydration status tended to be slightly increased immediately after the race ($43.4 \pm 2.5\%$ versus $45 \pm 2.4\%$ and $148.7 \pm 9\ g/L$ versus $153 \pm 9.2\ g/L$, respectively), but was not significantly different from pre-race values ($P = 0.078$ and $P = 0.17$, respectively). There was a significant decrease in plasma sodium concentration immediately after the race ($139.4 \pm 1.8\ mmol/L$ vs $132.4 \pm 9.8\ mmol/L$; $P = 0.033$).

Discussion

The novelty of our study is the demonstration of a transient conduction delay in the atria after a mountain marathon. We interpret the prolongation of the SAPWD as atrial myocardial edema, which is supported by the observation that ventricular myocardial edema in acute myocarditis was associated with a transient prolongation of the QRS duration (Morimoto et al., 2006).

### Results

### Participants’ characteristics

From the 2009 ranking list of the Jungfrau Marathon, 11 male marathon runners matched the inclusion criteria and underwent baseline testing. No athlete had to be excluded because of hypertension, atrial or ventricular arrhythmias during the 24-h Holter monitoring, or an elevated cardiovascular risk profile. One athlete could not participate in the race because of a knee injury. Thus, 10 athletes were included in the final analysis. Mean age was $34.9 \pm 4.2$ years. On average, the athletes trained $10 \pm 2.3$ h per week, and had previously completed $8.5$ (inter-quartile range $5$) marathons. The mean finisher time of the Jungfrau Marathon 2010 did not significantly differ compared to the finisher time of 2009. Table 1 summarizes characteristics of the study participants.

<table>
<thead>
<tr>
<th>Mean/median</th>
<th>Min.</th>
<th>Max.</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>34.9</td>
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</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.2</td>
<td>19.94</td>
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<tr>
<td>BP systolic (mmHg)</td>
<td>119</td>
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<tr>
<td>Heart rate (1/min)</td>
<td>51.5</td>
<td>0.00</td>
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<tr>
<td>BP diastolic (mmHg)</td>
<td>73.5</td>
<td>60.00</td>
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<tr>
<td>VO₂max (ml/kg*min)</td>
<td>66.8</td>
<td>58.9</td>
</tr>
<tr>
<td>Heat rate (1/min)</td>
<td>19.2</td>
<td>7.00</td>
</tr>
<tr>
<td>Endurance training (years)</td>
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<td>0.00</td>
</tr>
<tr>
<td>Training (h/week)</td>
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<td>216.88</td>
</tr>
<tr>
<td>Race time 2009 (min)</td>
<td>238.6</td>
<td>215.42</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± standard deviation, or median (interquartile range).

BMl, body mass index; BP, blood pressure at rest; VO₂max, maximum oxygen uptake; Race time 2009/2010, Jungfrau Marathon finishing time 2009/2010 (*no significant difference between 2009 and 2010, $P = 0.31$).

**Table 1. Baseline characteristics of marathon runners.**

**Twenty-four-hour Holter monitoring**

Prior to the race, 24-h Holter monitoring was performed prior to the race. Three channel ECGs were recorded with a Lifecard CF digital recorder (Spacelabs Healthcare, Nuremberg, Germany) and were manually analyzed and interpreted using the Pathfinder Software. Premature atrial and ventricular contractions and arrhythmias were classified according to onset and QRS morphology.

Data analysis

All analysis was performed using Stata 12.1 (Stata Corporation, College Station, Texas, USA) and GraphPad InStat 3.01 (GraphPad Software, San Diego, California, USA). Values are expressed as mean ± standard deviation or median (interquartile range) as appropriate. Continuous variables were analyzed for normal distribution using Shapiro–Wilk test and qq-plots. Parametric variables were compared by repeated measure analysis of variance applying a Bonferroni correction for multiple comparisons. Non-parametric variables were compared using Friedman’s test and Dunn’s post-estimation procedure applying a Bonferroni correction for multiple comparisons. Correlation-coefficients were calculated to assess potential relation between variables. A two-tailed $P$-value $< 0.05$ was considered statistically significant.
Compatible with our hypothesis of exercise-induced atrial myocardial edema we found a post race increase of proinflammatory markers. In particular, TNF-α has the potential to induce myocardial dysfunction and interstitial myocardial edema (Kubota et al., 1997). Interestingly, post race levels of hsCRP, IL-6 and TNF-α were substantially higher in our study than reported after a flat marathon (Scherr et al., 2011), suggesting an intensity-dependent release.

Inflammation is a crucial initiator of atrial fibrosis because inflammatory stimuli, as well as mechanical stretch, provoke fibroblast proliferation, migration and differentiation into myofibroblasts (Friedrichs et al., 2011). Thus, inflammatory pathways could be regarded as a prerequisite for atrial remodeling and AF (Swanson, 2006; Friedrichs et al., 2011).

The contribution of atrial stretching is reflected by elevated levels of proANP after the marathon, an
Fig. 3. Cardiac biomarkers high-sensitivity troponine T (TroponinT-hs; a), and pro atrial natriuretic peptide (proANP; b), presented at baseline, immediately after the race and during follow-up (1 and 8 days post race). **$P < 0.01$; ***$P < 0.001$.

Fig. 4. High-sensitivity C-reactive protein (hsCRP; a), proinflammatory cytokines (b and c), and cellular markers of inflammation (d), presented at baseline, immediately after the race and during follow-up (1 and 8 days post race). *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$. 
observation that has also been made after races of shorter distances (Toft et al., 1990; Wilhelm et al., 2012a). Although SAPWD and markers of inflammation returned to baseline levels during follow-up, this may not be regarded as “restitutio ad integrum” of the atrial myocardium. Each episode of acute inflammation and atrial stretching may contribute to atrial fibrosis and enlargement with consecutive remodeling over time (O’Keefe et al., 2012).

Consistently, in a study on nonelite runners, the number of completed marathons was an independent predictor of LA and RA size (Wilhelm et al., 2012b). In addition, an animal model showed that long-term intensive exercise training resulted in atrial fibrosis and increased arrhythmia inducibility (Benito et al., 2011).

The prolongation of the SAPWD was not accompanied by a post-race increase in LA or RA volumes. This is in contrast to the study of Trivax et al., who reported acute dilatation of the RA after a marathon race. However, participants in their study were older, less experienced, and had a lower VO2max and a longer race duration, which may have contributed to a greater impact on the right heart (Trivax et al., 2010). In our study, no correlation between parameters of atrial morphology and electrical activation were found, which is consistent with other studies (Ehrlich et al., 2002; Wilhelm et al., 2011), and supports the hypothesis of myocardial edema being responsible for atrial conduction delay.

Several other studies have investigated acute cardiac effects of marathon running, but have focused on ventricular biomarkers and function (Neilan et al., 2006; Knebel et al., 2009; Mousavi et al., 2009; Trivax et al., 2010). In line with these studies, we have demonstrated an increase in cardiac troponin and alterations in LV diastolic function. In contrast to acute myocardial infarction, the increase of hsTnT was only mild and of short duration. Thus, this increase was likely to reflect a reversible membrane leakage of cardiomyocytes with troponin release from the free cytosolic pool, rather than myocardial damage (Scharhag et al., 2008; Scherr et al., 2011).

The transient deterioration of early LV diastolic function was accompanied by an increase of late LV diastolic function. Our results are in line with data from Oxborough et al. who showed that exercise-induced deterioration of LV diastolic relaxation had a direct impact on subsequent LA mechanical function. In particular, LA contractility increased as consequence of reduced LA afterload, secondary to reduced LV filling (Oxborough et al., 2010).

Limitations
Most importantly, our results are limited to a small yet homogeneous group of elite marathon runners. The sample size was limited because of the short time window for post race analysis and the extensive finish line resources required at the “Kleine Scheidegg,” the end point of the Jungfrau Marathon at 2060-m altitude. Altitude may have influenced hemodynamics and atrial conduction at the end of the race. However, given the accordance of alterations of LV parameters with other marathon studies on low altitudes, a potential effect on atrial conduction seems to be negligible. A potential limitation is the indirect method used to assess a possible atrial myocardial edema, since magnetic resonance imaging immediately after the race was impracticable by reason of study design. Although acute myocarditis with ventricular myocardial edema was associated with transient prolongation of the QRS complex, prolongation of the SAPWD may be related to other causes, because electrical conduction in the atria and ventricles is different. We did not review the detailed training diaries in the last weeks prior to the race. Intensive training units with muscular glycogen depletion could have had an impact on the inflammatory response post race (see below).

Perspectives
Our data suggest that the acute inflammatory response after a strenuous marathon may play an important role in the development of atrial remodeling. It has been demonstrated that the increase of proinflammatory cytokines is not attributable to blood mononuclear cells, suggesting a local production in, or release from the exercising tissues (Bernecker et al., 2011). Glycogen depletion of the musculature is a major trigger for IL-6 secretion (Keller et al., 2001). A polarized training for optimizing fat metabolism prior to a marathon race, and carbohydrate alimentation prior to and during the race may help to mitigate the inflammatory response. Whether the levels of circulating proinflammatory cytokines have an impact of atrial conduction should be confirmed in a larger study.

Key words: atrial remodeling, signal-averaged P-wave duration, proinflammatory cytokines, pro atrial natriuretic peptide, marathon running.

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Atrial remodeling and marathon running

References


