

# Sympathetic reserve, serum potassium, and orthostatic intolerance after endurance exercise and implications for neurocardiogenic syncope

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## Aims

To elucidate the mechanisms of orthostatic intolerance (OI) after endurance exercise which are incompletely understood.

## Methods and results

We investigated beat-to-beat haemodynamic and autonomic parameters in 51 male athletes during supine rest and after active standing the day before and 2 h after a marathon run. None of the subjects before the marathon [non-orthostatic intolerance (Non-OI)], but 14 after the marathon [orthostatic intolerance (OI)] exhibited with pre-syncope. There were no differences between OI and Non-OI before the marathon. After the marathon, only Non-OI was able to increase sympathetic modulation to resistance vessels from already increased basal levels in response to standing; OI could not. OI instead exhibited a decrease in total peripheral resistance and a paradoxical increase in parasympathetic sinus node modulation. We observed a significant correlation between serum potassium before the race and the maximally achieved sympathetic drive after the marathon ( $r = 0.55$ ,  $P = 0.001$ ).

## Conclusion

Post-exercise OI is associated with a 'high basal sympathetic modulation of vasomotor tone in combination with a diminished orthostatic sympathetic response' to resistance vessels. This situation may mimic the OI in some clinical conditions, which are also known to be associated with increased 'basal' sympathetic tone. The role of serum potassium deserves further study.

## Keywords

Marathon • Haemodynamics • Autonomic nervous system • Syncope • Spectral analysis • Continuous blood pressure

## Introduction

A high incidence of orthostatic intolerance (OI) is observed after endurance exercise. Recurrent syncope has been described during or after exercise.<sup>1,2</sup> The pathophysiological mechanisms of this phenomenon are incompletely understood. Earlier investigations suggested that blood pressure control is impaired as a result of a diminished baroreflex control in trained individuals.<sup>3</sup> Other investigators showed that trained individuals have more compliant, distensible ventricles and therefore a steeper slope of the Frank–Starling curve, which could be beneficial to the performing athlete.<sup>4</sup> However, such a state-of-affairs might be a disadvantage during orthostasis. More recent works demonstrate that abnormal autonomic vascular or cardiac regulation could be the

cause of unexplained syncopal episodes.<sup>1,2,5,6</sup> However, heart rate (HR) or blood pressure variability was not measured in these studies. Moreover, the results were obtained retrospectively on the tilt table in athletes with a history of exertional or post-exertional syncope. In some instances, pharmacological interventions with isoproterenol or isosorbide dinitrate were carried out.<sup>2,5</sup> To the best of our knowledge, a prospective 'real life' study elucidating the mechanism of OI after long endurance exercise such as a marathon has not been done. We prospectively studied haemodynamic and autonomic responses in a large number of marathon runners before and after a marathon run to identify subjects with post-exertional OI during active standing. We conducted measurements to elucidate the cause of OI in affected individuals.

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## Methods

### Ethical approval

All subjects gave their written voluntary informed consent and the local ethics committee (KH Barmherzige Brüder) approved the study. The studies conformed to the standards set by the latest revision of the 'Declaration of Helsinki'.

### Study population

We studied 51 men. Men were chosen in order to avoid interference by different phases of the menstrual cycle unavoidable in female participants. All men were healthy and all had been previously screened for cardiovascular and metabolic diseases. None of the subjects had any medication or were taking any drug. None of the participants had a history of syncope, nor had they ever experienced OI in the past. Subjects were recruited from running sports clubs ensuring a brought spectrum of performance as judged from weekly training time and/or the results of previous marathons. All runners were amateurs but the training work load of up to 12 h per week ensured excellent performance in some of them. All subjects who agreed initially to participate took part in pre- and post-marathon measurements. All subjects finished the competition. So, there were no subjects lost from recruitment to follow-up. However, only a subset of 37 subjects volunteered for blood sampling the day before and 2 h after the marathon.

Each participant had recorded his training time schedule over years. From these detailed records, we extracted the weekly net exercise time (WNET) in minutes averaged from the respective periods (last year, last month, and last week).

### Study protocol

The subjects were studied on the day before (Day 1) and immediately following recovery, 2 h (hours + 2) after the Graz, Austria marathon. This marathon has a difference in elevation of 37.2 m. The average temperature during the run was 20°C, the average humidity was 78%. The simultaneous use of five haemodynamic and autonomic monitors (see recorded variables) allowed that all subjects were investigated at 120 ± 15 min after the competition. After running, the subjects were classified as OI ( $n = 14$ ) when clear-cut pre-syncope symptoms such as lightheadedness, nausea, dizziness or visual blurring occurred during active standing that were severe enough to necessitate termination. 'Non-OI' ( $n = 37$ ) was those in whom no symptoms occurred. The runners drank non-alcoholic liquids *ad libitum* throughout the competition and after the race. Athletes were instructed prior to the race to keep a careful mental note of how much fluid they consumed during and after the race. Fluid intakes during and 2 h after the competition were obtained from personal recall. Body weight was measured at Day 1 and hours + 2 using a calibrated electronic scale (Seca, Vogel and Halke, Hamburg, Germany). All subjects were weighed with emptied bladders in standardized clothing. Height was measured to the nearest centimetre with a calibrated scale before the competition while the subjects standing. During 2 h after the competition, all subjects rested, walking about quietly and sitting alternatively. The 2 h interval was chosen to ensure stable haemodynamics during recumbency. All measurements were performed during 10 min of supine rest and subsequently during 6 min of active standing or until pre-syncope occurred whichever first. Instrumentation was performed immediately after the subjects had lain down. Data collection for the supine measurements was begun 10 min later, when haemodynamic and autonomic parameters were stable. The 6 min

time span of active standing was chosen since haemodynamic adjustments are complete after this period.

### Recorded variables

We used the Task Force™ monitor (TFM; Task Force Monitor™, www.cnsystems.at) to monitor beat-to-beat HR by ECG, beat-to-beat stroke index (SI) by impedance cardiography<sup>7</sup> and beat-to-beat blood pressure by the vascular unloading technique,<sup>8</sup> which was corrected automatically to the oscillometric blood pressure measured on the contra-lateral arm. The oscillometric device of the TFM was used. This instrument had been previously validated against the Dinamap® Blood Pressure Monitor 1846SX (Critikon, Tampa, FL, USA) and the Spacelabs® Medical Blood Pressure Monitor (Spacelabs, Redmond, WA, USA).<sup>9</sup> Total peripheral resistance index (TPRI) was calculated according to the formula:  $TPRI = \text{mean arterial blood pressure} / \text{cardiac index (CI)}$ ;  $CI = HR \times SI$ .

The TFM allows intervention marks to be set to define periods for automated statistical analysis. Intervention marks were set to define following steady-state periods: (i) the last 2 min of supine rest, (ii) the second and third minute of standing, and (iii) the last 2 min before the end of active standing. The TFM automatically provides the 0.05–0.15 Hz band of R–R interval variability in normalized units (RRI LFnu), the 0.15–0.40 Hz band of R–R interval variability in normalized units (RRI HFnu), as well as the 0.05–0.15 Hz band of systolic blood pressure variability in absolute (SBP LF) and normalized units (SBP LFnu), using power spectral analysis applying an autoregressive methodology.<sup>10</sup> Keeping in mind the limitations of spectral analysis in quantifying autonomic nervous system tone by power spectral densities, these bands are referred to as parasympathetic modulation of the sinoatrial node (RRI HFnu) and sympathetic modulation of vasomotor tone (SBP LF, SBP LFnu).<sup>11,12</sup> Baroreceptor reflex sensitivity (BRS) was automatically assessed using the sequence technique.<sup>13</sup> All functions of the TFM<sup>7,8</sup> have been assessed previously, and the instrument has already been used successfully in a number of clinical studies.<sup>14,15</sup>

### Blood chemistry

Thirty-seven of 51 subjects agreed to blood testing, drawn the day before and 2 h after the marathon by venipuncture without tourniquet in the sitting position. Blood testing was not enforced as necessary part of the study in order not to lose recruited subjects. Blood testing was considered an invasive procedure by some of our individuals. Assays for serum electrolytes, protein, and albumin were carried out with Cobas Integra 400 plus (Roche™), using standard methods and the manufacturer's reagents, on serum that had been collected into silicone gel separator tubes and stored at 4°C after centrifugation within 10 min of collection. Routine haematological assays for haemoglobin and haematocrit were carried out with CD 3200SL system (Abbott™) on EDTA-anticoagulated samples that had also been stored at 4°C. The analyses were performed in the chemistry department of our hospital, which is accredited for medical testing by the Austrian government and regularly and successfully takes part in routine quality control testing performed by the Austrian Society of Laboratory Medicine.

## Statistical analysis

We performed a power calculation of the rates of OI and Non-OI as related to the main outcome variable, namely sympathetic modulation of vasomotor tone (see Results section).

Data are presented as mean  $\pm$  SD. For assessing intra-individual changes in haemodynamic and autonomic parameters at different time points, repeated ANOVA (rANOVA) was performed. For the relation between pre-race serum potassium and the percentage change of SBP LF and SBP LFnu between supine and active standing 2 h after the marathon, single regression analyses and repeated ANCOVA (rANCOVA) were performed. The outcome variable of interest in rANCOVA is SBP LFnu. This variable was measured supine, and during the first and final minute of active standing. The covariates of interest are weight change and pre-race potassium. The common covariance matrix of the within-subject variables must be spherical. This assumption was confirmed by Mauchly's sphericity test.<sup>16</sup> In this model, there are no random effects specified. But we do have fixed effects (between and within subjects effects: weight change, pre-race potassium, and time points of measurement of SBP LFnu). Group differences were compared by the paired and unpaired Student's *t*-test as appropriate (paired *t*-test for comparing the same subjects before and after marathon and unpaired *t*-test for comparing clinical and biochemical data, HR in the first minute of active standing and change in HR in the final minutes of active standing in Non-OI and OI). We have tested only those variables necessary to disprove our hypothesis, namely (i) differences in HR and in activation of sympathetic modulation of vasomotor tone, (ii) differences in withdrawal of parasympathetic modulation of sinus node function, and (iii) differences in total peripheral resistance after the marathon in Non-OI and OI. Furthermore, we tested differences in blood pressure after the marathon between Non-OI and OI to confirm that the subjective symptoms of fainting were indeed related to a fall in blood pressure. We have previously shown that a high potassium intake improves BRS.<sup>17</sup> Therefore, only the relation of serum potassium to BRS and to sympathetic modulation of vasomotor tone was tested. All reported *P*-values are two-sided. Adjusted *P*-values  $<0.05$  were considered to indicate statistical significance. Mauchly's sphericity test was performed with the use of SAS (version 9.1.3), all other analyses were performed with the use of the Systat 8.0 statistical software.

## Results

### Original tracings

Figure 1A and B shows a typical example of original tracings of haemodynamic and autonomic variables with the TFM in an OI subject before and after the race. As can be seen, artefact-free recordings with consistent trends including the power spectra were obtained.

### Clinical and biochemical variables before and after the race

Demographic data at baseline, training history, the weight change between Day 1 and hours + 2, the fluid intake during the race

and during the 2 h after the competition, competition time, and biochemical parameters of the subjects are shown in Tables 1 and 2. As can be seen, there were no significant differences in competition time (or WNET) between subjects with and without OI. There were also no significant differences with regard to variables presented in Table 1 between those subjects who allowed blood testing and those who did not. Of the 37 subjects who allowed blood samples, there were 31 Non-OI and six OI. Pre-race serum potassium was lower in OI compared with Non-OI ( $P = 0.030$ ). Post-race total serum protein concentration was lower in OI than in Non-OI ( $P = 0.042$ ). There were no significant differences in any of the other measured variables.

### Autonomic and haemodynamic analysis

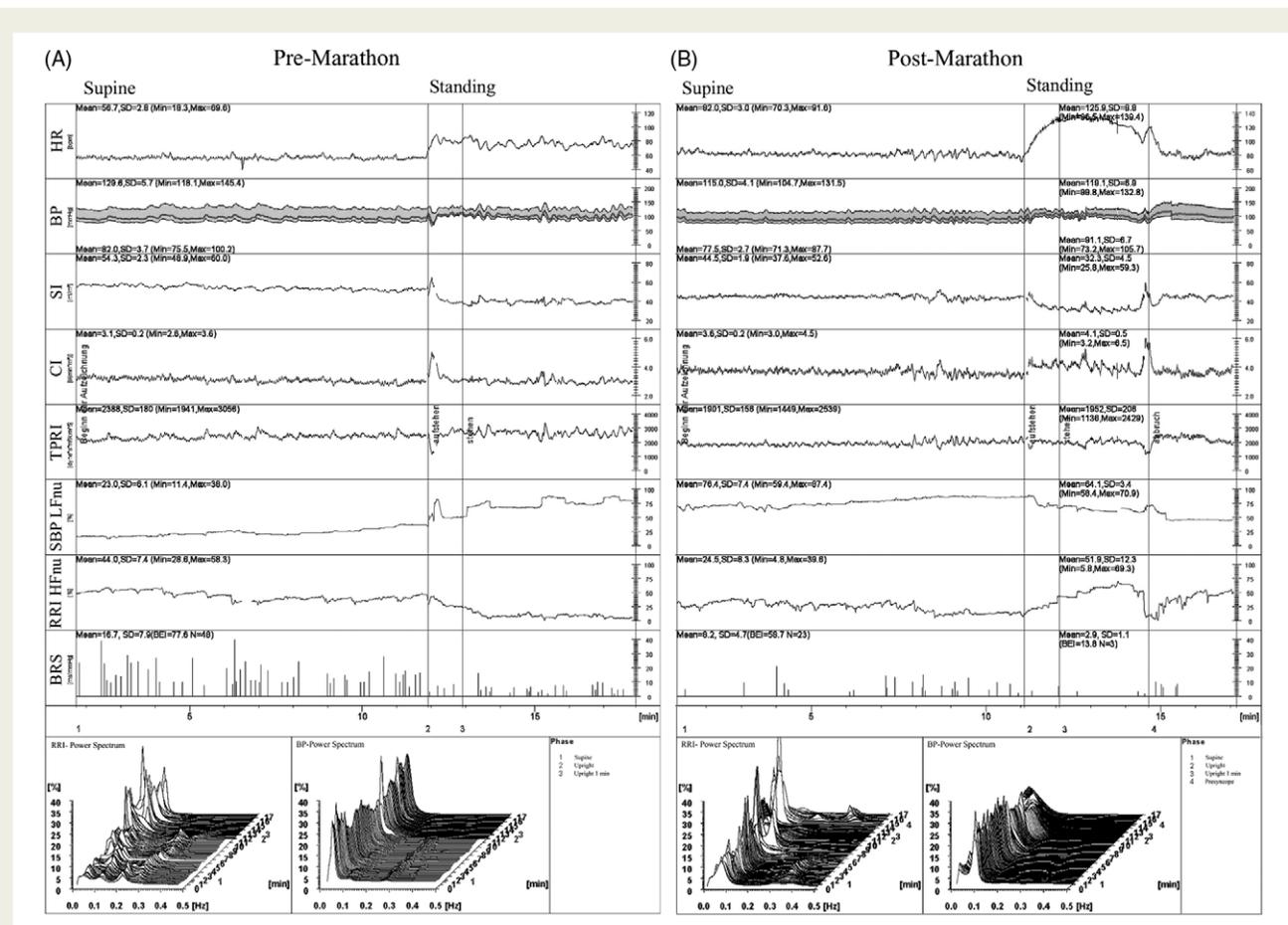
Figure 2A–C shows mean  $\pm$  SD of haemodynamic and autonomic parameters, as well as of thoracic resistance while supine and standing before (left) and 2 h after racing (right). The *P*-values given in Figure 2B and C refer to significant changes in the time course of the variables as obtained by rANOVA. If significant *P*-values are given they refer to the respective observed increase or decrease of the variables in OI and Non-OI.

### Haemodynamic and autonomic changes before the race

As can be seen from the left panels of Figure 2A–C, there were no differences in haemodynamic and autonomic parameters, baroreflex sensitivity, or in thoracic resistance between OI and Non-OI during supine rest and active standing before the race.

### Haemodynamic and autonomic changes after the race

Both OI and Non-OI showed an increased SBP LFnu during supine rest compared with pre-race ( $P = 0.021$  and  $<0.001$ , respectively). Only OI but not Non-OI (rANOVA,  $P < 0.001$ ), showed a failure to increase SBP LFnu after active standing (Figure 2C, bottom right). As shown in Table 1, we observed a rate of 27% of OI (14 out of 51 subjects) and a main outcome variable of sympathetic modulation of vasomotor tone at the time of symptoms of  $58.9 \pm 15.9$  nu in OI vs.  $77.8 \pm 11.8$  nu in Non-OI (mean  $\pm$  SD). Based on this population, we achieved a power of 99% with a type I error (two sided) of 5%. OI also showed a paradoxical increase in RRI HFnu (rANOVA,  $P = 0.001$ ), compared with Non-OI. Only OI (rANOVA,  $P = 0.001$ ) but not Non-OI showed a fall in RRI LFnu after standing. The RRI LF/HF ratio did not change after standing in both groups. Non-OI showed an increase in TPRI during active standing (rANOVA,  $P < 0.001$ ), whereas OI showed a decrease in TPRI (rANOVA,  $P = 0.013$ ) with a marked fall in systolic and diastolic blood pressure (rANOVA,  $P < 0.001$ ). The initial increase in HR after active standing was greater in OI resulting in a higher HR in the first minutes of active standing in OI, compared with Non-OI (unpaired *t*-test,  $P = 0.002$ ). Thereafter OI showed a decrease in HR in the final minutes of active standing, compared with Non-OI ( $\Delta$ HR:  $-8.3 \pm 11.48$  vs.  $+0.5 \pm 3.92\%$ , mean  $\pm$  SD, unpaired *t*-test,  $P < 0.001$ ). SI, CI, thoracic resistance, and baroreflex sensitivity were not different between both groups at any time points.



**Figure 1** Typical example of an original tracing of haemodynamic and autonomic variables with the Task Force™ monitor in an orthostatic intolerance subject before (A) and after (B) the race. HR, heart rate; BP, blood pressure; SI, stroke index; TPRI, total peripheral resistance index; SBP LFnv, 0.05–0.15 Hz band of systolic blood pressure variability in normalized units; RRI HFnu, 0.15–0.40 Hz band of R–R interval variability in normalized units; BRS, baroreceptor reflex sensitivity.

**Table 1** Clinical data of subjects investigated

Characteristics	Non-postural intolerance (n = 37)		Postural intolerance (n = 14)		P-value
	Mean ± SD	Range	Mean ± SD	Range	
Age (years)	40.2 ± 8.23	26–57	38.9 ± 7.59	29–55	0.635
Height (m)	1.80 ± 6.79	1.63–1.94	1.81 ± 5.08	1.69–1.90	0.499
Weight (kg)	76.2 ± 8.89	60.7–94.8	74.2 ± 9.11	56.7–92.0	0.495
BMI (kg/m <sup>2</sup> )	23.5 ± 1.99	20.4–28.1	23.1 ± 2.17	19.9–26.6	0.672
Duration of training (years)	5.3 ± 4.87	1–22	6.7 ± 4.96	1–16	0.562
WNET last year (min)	357 ± 138.8	120–660	422 ± 142.7	180–720	0.153
WNET last month (min)	405 ± 159.4	120–660	494 ± 118.4	270–720	0.069
WNET least week (min)	187 ± 88.0	0–435	238 ± 93.3	120–480	0.083
Previous marathons (n)	3.0 ± 2.75	0–10	3.00 ± 4.64	0–15	0.983
Δ Weight (%)	–2.0 ± 1.44	–4.72 to 1.13	–2.3 ± 1.74	–5.1 to 0.4	0.578
Fluid intake (mL)	2304 ± 910.0	500–5000	2558 ± 1393.6	600–5000	0.589
Competition time (min)	204.7 ± 32.27	154–287	195.1 ± 30.98	146–244	0.365

P-values have been derived from unpaired Student's *t*-test and denote no significant difference between non-postural and postural intolerance.

BMI, body mass index; WNET, weekly net exercise training; ΔWeight, change in weight from day before to 2 h after competition; Fluid intake, during race and 2 h after competition.

**Table 2** Biochemical parameters of subjects investigated

Characteristics	Non-postural intolerance (n = 31)		Postural intolerance (n = 6)		P
	Mean ± SD	Range	Mean ± SD	Range	
Pre-race serum sodium (mmol/L)	145.3 ± 1.40	143–149	145.2 ± 0.69	144–146	0.838
Post-race serum sodium (mmol/L)	145.7 ± 2.05	140–150	147.0 ± 2.77	143–151	0.217
Pre-race serum potassium (mmol/L)	4.8 ± 0.41	3.9–5.4	4.4 ± 0.13	4.1–4.6	0.030
Post-race serum potassium (mmol/L)	4.7 ± 0.35	4.2–5.7	4.6 ± 0.32	4.1–5.1	0.782
Pre-race serum albumin (g/dL)	5.0 ± 0.20	4.6–5.4	5.2 ± 0.19	4.8–5.3	0.065
Post-race serum albumin (g/dL)	4.9 ± 0.19	4.5–5.3	4.8 ± 0.16	4.4–4.9	0.176
Pre-race serum total protein (g/dL)	7.7 ± 0.50	6.7–9.3	7.9 ± 0.38	7.2–8.4	0.568
Post-race serum total protein (g/dL)	8.0 ± 0.37	7.3–8.8	7.7 ± 0.33	7.1–8.2	0.042
Pre-race haematocrit (%)	43.8 ± 2.94	36.9–49.7	44.8 ± 1.98	43.5–49.2	0.424
Post-race haematocrit (%)	43.9 ± 2.84	34.1–50.5	44.1 ± 1.52	42.4–46.9	0.675
Pre-race haemoglobin (mg/dL)	15.6 ± 1.07	13.4–18.2	15.9 ± 0.64	15.3–17.3	0.444
Post-race haemoglobin (mg/dL)	15.7 ± 1.03	12.8–18.2	15.9 ± 0.49	15.2–16.7	0.639

P-values have been derived from unpaired Student's *t*-test and denote differences between non-postural intolerance and postural intolerance.

We found correlations between pre-race serum potassium with change in SBP LF and SBP LFnu after active standing, respectively (Figure 3). A high pre-race serum potassium was associated with a more pronounced increase in SBP LF and SBP LFnu after active standing ( $r = 0.55$ ,  $P = 0.001$  and  $r = 0.37$ ,  $P = 0.026$ , respectively). This finding was corroborated by rANCOVA taking serum potassium and weight change between the day before and 2 h after the competition as covariates. The results of the rANCOVA are shown in Table 3. In the between-subject analysis, none of the interesting variables showed a significant influence on the outcome (all  $P > 0.05$ ). The within-subject analysis shows that only the interaction between pre-race potassium and time points does significantly influence the outcome ( $P = 0.015$ ).

No correlations between pre-race serum potassium and baroreflex sensitivity during supine rest and after active standing before and after the competition were found (all  $r < 0.30$  and all  $P > 0.099$ ).

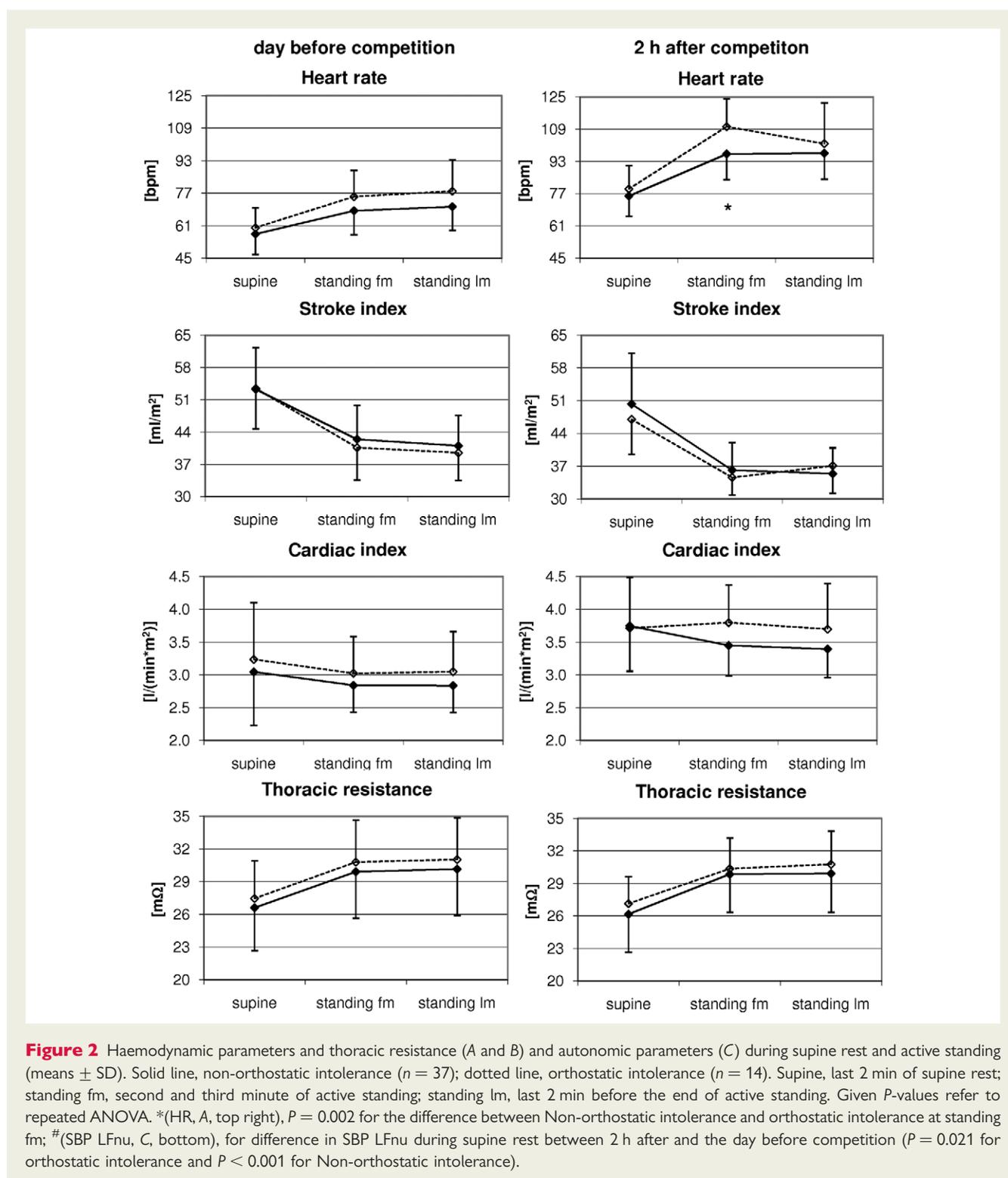
## Discussion

Our study reveals several novel findings: only subjects without OI (Non-OI) were able to significantly increase further sympathetic modulation of vasomotor tone during active standing from an already elevated basal value after the marathon. Furthermore, only Non-OI exhibited a rise in total peripheral resistance after active standing. In addition, subjects with OI showed an inappropriate activation of sinus node parasympathetic modulation before the onset of syncope. Another potentially important finding is the significant positive correlation between serum potassium before the race and the maximally achievable sympathetic drive to resistance vessels, as well as the significantly lower serum potassium in OI compared with Non-OI before the marathon. There were no haemodynamic and autonomic differences between OI and Non-OI before the race.

We are not aware of a prospective 'real life' study of haemodynamic and autonomic mechanisms of post-exercise syncope induced by active standing. The phenomenon was studied earlier in subjects having experienced a post-exercise syncope by re-exposing them later to a tilt table test. Neurocardiogenic syncope was induced in some, but not in all of the fainters,<sup>1,2,5,6</sup> and in part only after pharmacological induction.<sup>2,5</sup> By investigating 51 marathon runners before and after running a marathon, we hoped to find enough subjects with post-exercise pre-syncope to elucidate its mechanisms during the original event. Indeed, after the marathon pre-syncope occurred in 14 out of 51 subjects.

One possible explanation of this finding is that from an elevated baseline sympathetic modulation of vasomotor tone, OI may have exhausted their reserve to increase sympathetic modulation of vasomotor tone and peripheral resistance any further. The diminished increase in TPRI during active standing is in accord with studies by Sneddon *et al.*<sup>18</sup> who demonstrated a fall in forearm vascular resistance immediately after head-up tilt in patients with neurally mediated syncope. We observed an initially greater increase in HR after active standing (Figures 1 and 2A), which may have been caused by circulating levels of epinephrine. Alternatively, this increase in HR may be due to baroreceptor reflex activation in an attempt to counteract the diminished response of resistance vessels (Figures 1 and 2B). However, there were no differences in baroreflex sensitivity between OI and Non-OI (Figure 2B). A reduced parasympathetic drive to the heart cannot be responsible for these findings because RRI HFnu in Non-OI increased rather than decreased.

Orthostatic tolerance is said to correlate with the state of plasma volume; when plasma volume is expanded, OI improves.<sup>19</sup> Our results speak against a reduced plasma volume or a reduced intrathoracic blood volume as being responsible for the occurrence of post-exercise syncope: although plasma volume was not measured in our study, we did measure indirect (albeit not



inaccurate) reflectors of plasma volume changes, such as body weight, haematocrit, plasma protein levels, and albumin. When calculated<sup>20</sup> from the parameters given in Table 2, the change in plasma volume was not different between both groups. Weight change also had no influence on the maximally achievable sympathetic modulation of vasomotor tone as shown by rANCOVA

(Table 3). In addition, thoracic resistance and hence thoracic fluid content was not different in OI and Non-OI during the supine state and after active standing, both before and after the competition (Figure 2A). The Graz marathon takes place in October. As can be seen from the Methods section, the average temperature of 20°C and humidity of 78% were ideal running conditions. Our

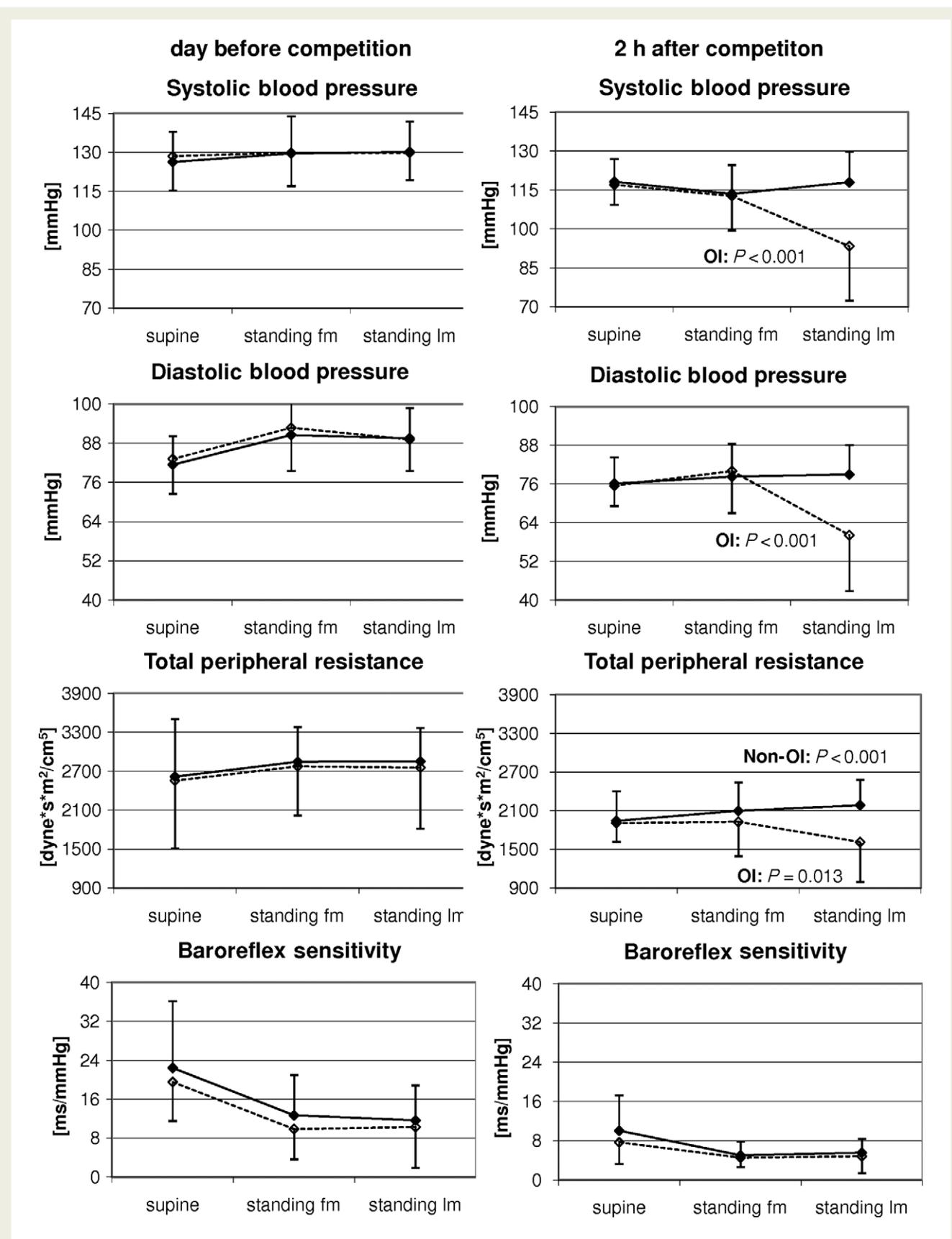


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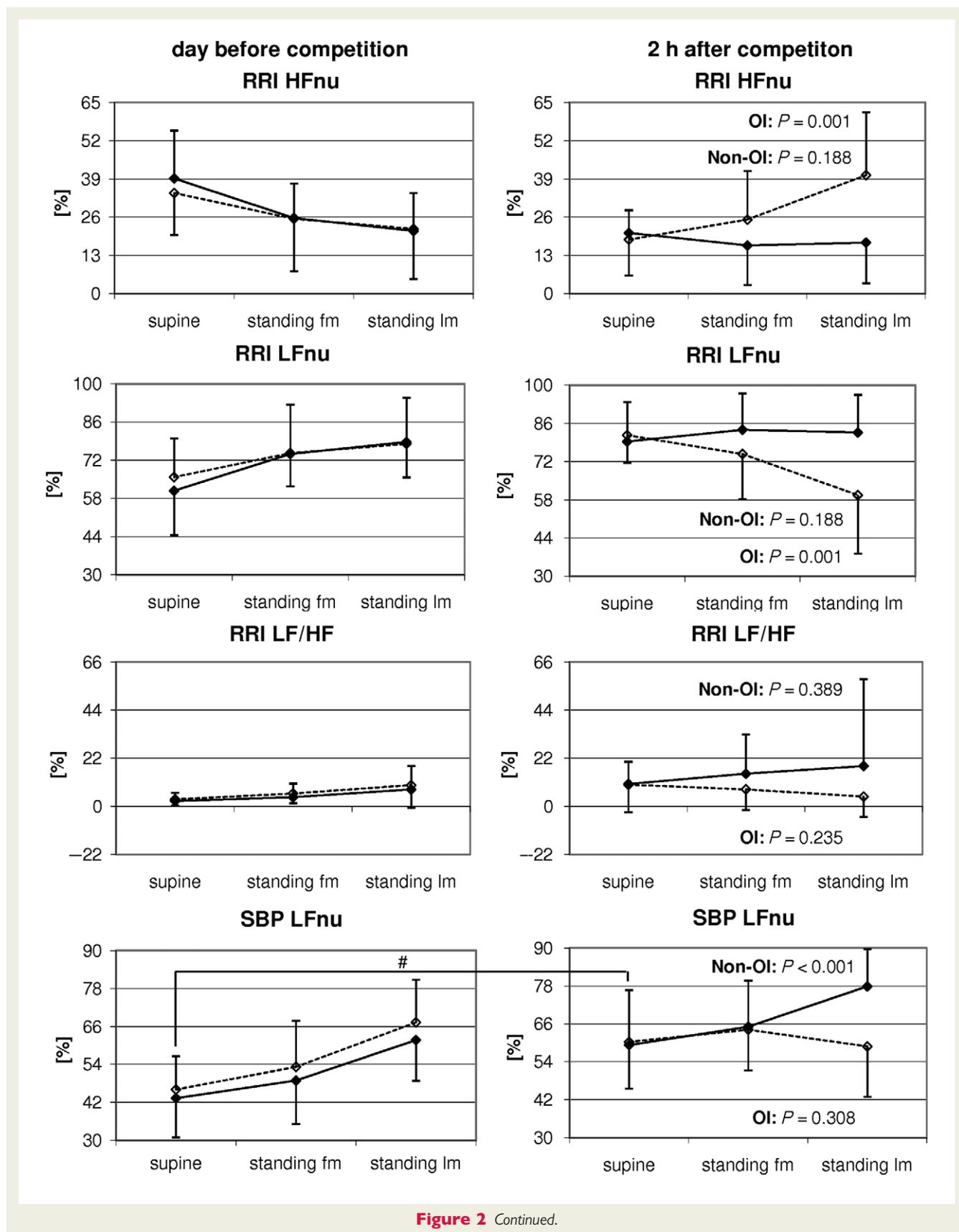
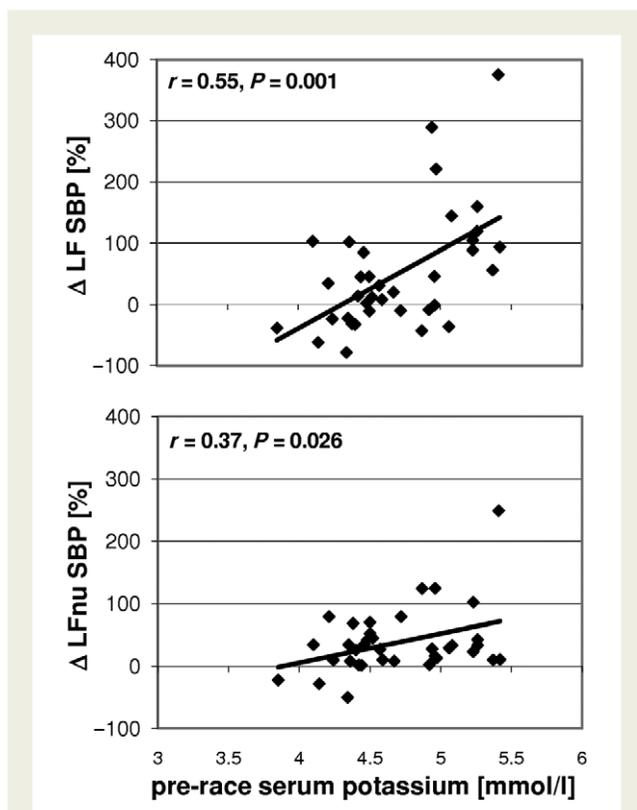


Figure 2 Continued.

findings of lack of plasma volume changes might not apply to extreme conditions as might be seen in the summer and also at warmer venues.

One postulated mechanism in neurocardiogenic syncope is that myocardial mechanoreceptors activated by a volume-depleted ventricle are responsible for the autonomic response observed



**Figure 3** Correlation between pre-race serum potassium and percentage change in sympathetic modulation of vasomotor tone after active standing. SBP LF, 0.05–0.15 Hz band of systolic blood pressure variability in absolute units; SBP LFnu, 0.05–0.15 Hz band of systolic blood pressure variability in normalized units;  $\Delta$  refers to percentage changes between the last 2 min of supine rest and the last 2 min of active standing.

**Table 3** Repeated ANCOVA

Source	SS	df	MS	F-ratio	P-value
Between subjects					
$\Delta$ Weight	616.8	1	616.8	1.063	0.310
Pre-race potassium	2115.3	1	2115.3	3.647	0.065
Error	18 560.2	32	580.0		
Within subjects					
a	474.4	2	437.2	2.868	0.064
a $\times$ $\Delta$ Weight	14.8	2	7.4	0.089	0.915
a $\times$ pre-race potassium	739.5	2	369.7	4.471	0.015
Error	5292.8	64	82.7		

SS, sum-of-squares; df, degrees of freedom; MS, mean square; F, F-ratio;  $\Delta$ Weight, weight change from day before to 2 h after competition; a, change over time (repeated measure); outcome variable of interest, SBP LFnu.

and as postulated by others for conventional neurocardiogenic syncope.<sup>21,22</sup> Since there were no differences in SI response between OI and Non-OI, our findings do not support the

concept. Instead we offer a different explanation: a sudden, centrally mediated about-turn to an inappropriate increase in parasympathetic tone could occur 'if the required sympathetic drive cannot be achieved'. This paradoxical activation of parasympathetic tone with a decrease in HR before the onset of syncope would make sense in terms of maintained perfusion of vital organs. Namely, further upright posture without the necessary sympathetic adjustment would be more dangerous even than falling as we know from the detrimental effects from leaving a person in the upright position fixed on the tilting table after a fall in blood pressure. The supine state had been adopted voluntarily following the pre-syncope symptoms as exhibited by our subjects. Warning symptoms protected our subjects and were in any event safer than staying upright under the circumstances. This centrally-mediated about-turn from sympathetic to parasympathetic tone as observed by us fits with the findings of Koizumi and Kollai<sup>23</sup> who showed a reciprocal pattern of discharges after electrical stimulation of the hypothalamus in an animal study. The rationale against the Betzold-Jarisch reflex,<sup>22</sup> as a mechanism of about-turn in autonomic tone, is supported not only by our findings of a maintained stroke volume in OI immediately before syncope (Figure 2A), but also by echocardiographic studies indicating that neurally mediated syncope is not necessarily associated with near-empty nor powerfully contracting ventricles.<sup>24</sup>

Sympathetic nerve recordings in patients with vasovagal syncope mirror our findings with different methods. These studies showed increased muscle sympathetic nerve activity at rest<sup>25</sup> with a sudden cessation of sympathetic outflow at the onset of syncope.<sup>26</sup> Chronic illnesses, such as depression and fibromyalgia, also show evidence for an increased sympathetic outflow and also harbour more patients prone to vasovagal syncope.<sup>27,28</sup> The common link of post-exercise syncope and daily-life vasovagal syncope may be related to a high sympathetic drive at rest with a diminished further sympathetic reserve being available to face additional orthostatic challenges.

A high potassium intake is known to improve baroreflex sensitivity.<sup>17</sup> However, baroreflex sensitivity was not different in OI and Non-OI in our study. A potentially important finding is the significant correlation between serum potassium before the race and the maximally achievable sympathetic drive to resistance vessels, shown by the correlation analysis (Figure 3) and also by rANCOVA taking potassium (and weight change) as covariates (Table 3). This result is more striking since it was observed in the presence of serum potassium values within the 'normal' range. We also found significantly lower serum potassium in OI compared with Non-OI before the marathon. None of our subjects experienced vomiting or diarrhea prior to the race which could have explained this difference. We do not know whether the lower serum potassium concentrations in OI were caused by differences in potassium intake or intra–extra cellular potassium distribution induced by endogenous catecholamines or other mediators. We were not able to obtain reliable dietary information in these subjects. Thus, we can only speculate whether the lower serum potassium levels in association with a limited sympathetic response were due to differences in potassium intake or to an intra–extracellular potassium distribution effect. This latter possibility is not unlikely since cell membrane potential and electrical

discharges are involved in sympathetic responses<sup>23</sup> and both are a matter of intra-extracellular potassium gradient and thus also of extracellular potassium levels. The epinephrine-mediated potassium shifts in relation to sympathetic responses should be investigated in further studies. A high potassium intake may protect from OI, even in the face of minor, if any, effects on serum potassium concentration.<sup>29</sup>

The limitations of our study are obvious: we investigated healthy subjects, not 'fainters' in the usual sense. None of our subjects reported 'neurocardiogenic syncope' as a chronic condition. We could not measure many variables directly, such as plasma volume and muscle sympathetic nerve activity. In addition, we have not controlled for muscle contraction associated with active standing, given the beneficial aspect of the muscle pump in delaying syncope. Furthermore, we have not measured breathing rate which could have affected the power spectra calculation.<sup>30</sup> However, breathing rate during the recovery phase after a marathon is if anything higher than normal (personal observation) which would have led to a decrease in the 0.15–0.4 Hz band of R–R interval variability and not to the observed increase. Furthermore, we are unable to differentiate between sympathetic modulation of vasomotor tone and smooth muscle vascular responses to neurotransmitter release.<sup>31</sup>

Nonetheless, we believe our 'model' of the 'dizzy' athletes may give future directions to syncope research. Since only amateur athletes with a range of poor to excellent performance were investigated, our results are likely to apply to the general population involved in aerobic exercise training. We found that post-exercise OI is characterized by the inability to increase an already very high supine level of sympathetic drive to resistance vessels any further. This state-of-affairs would necessarily lead to diminished peripheral resistance during standing. This phenomenon, coupled with parasympathetic activation, is probably centrally mediated and has the evolutionary advantage of signalling the individual to lie down. Avoiding quiet standing after exercise and this with low muscle tone appears to be the immediate remedy that we can think of. We believe that our observations regarding potassium are interesting, particularly in light of a possible role for potassium channels or dietary interventions. However, these issues will require further studies.

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## Conflict of interest:

The TFM used in the present study was developed in the research laboratory of FS at the Department of Internal Medicine, Krankenhaus Barmherzige Brueder, Graz together with students of the Technical University Graz. F.S. holds patents on the TFM and he is cofounder of the company CNSystems which produces the instrument.

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