Scand J Med Sci Sports 2011: 21: 526–534
doi: 10.1111/j.1600-0838.2010.01094.x

SCANDINAVIAN JOURNAL OF
MEDICINE & SCIENCE
IN SPORTS

Effect of endurance training on blood pressure regulation, biomarkers and the heart in subjects at a higher age

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Accepted for publication 28 December 2009

We reported previously that two otherwise identical training programs at lower (LI) and higher intensity (HI) similarly reduced resting systolic blood pressure (BP) by approximately 4–6 mmHg. Here, we determined the effects of both programs on BP-regulating mechanisms, on biomarkers of systemic inflammation and prothrombotic state and on the heart. In this cross-over study (3 × 10 weeks), healthy participants exercised three times 1 h/week at, respectively, 33% and 66% of the heart rate (HR) reserve, in a random order, with a sedentary period in between. Measurements, performed at baseline and at the end of each period, involved blood sampling, HR variability, systolic BP variability (SBPV) and cardiac magnetic resonance imaging. Thirty-nine participants (18 men; mean age 59 years) completed the study. Responses were not different between both programs ($P > 0.05$). Pooled data from LI and HI showed a reduction in HR ($-4.3 \pm 8.1\%$) and an increase in stroke volume ($+11 \pm 23.1\%$). No significant effect was seen on SBPV, plasma renin activity, basal nitric oxide and left ventricular mass. Our results suggest that the BP reduction observed appears to be due to a decrease in systemic vascular resistance; training intensity does not significantly affect the results on mechanisms, biomarkers and the heart.

Elevated blood pressure (BP) is an increasingly important medical and public health issue (Ezzati et al., 2002). The adoption of healthy lifestyles, exercise being an integral component, is critical for the prevention of high BP (Guidelines Committee, 2003; Pescatello et al., 2004; Physical Activity Guidelines Advisory Committee, 2008; Cornelissen, 2009c). Guidelines recommend at least 30 min of continuous or accumulated physical activity at moderate intensity preferably every day of the week. However, data at intensities below 40% of the heart rate reserve (HRR) are lacking, although this could be of particular interest because it is easier to achieve and implement in daily life, especially at a higher age.

The current report was performed in the context of the overall study protocol of a more comprehensive research trial in which we used a randomized cross-over study design to investigate whether training at a lower intensity (LI) (33% of HRR) has an effect on BP, BP-regulating mechanisms and cardiovascular risk factors, and whether the effect is comparable with an identical training program (i.e., same duration, frequency and type of exercise) at a higher intensity (HI) (66% of HRR), in at least 55-year-old healthy sedentary men and women (Cornelissen et al., 2009a, b; Cornelissen, 2009c). We reported that both training intensities reduced systolic BP (SBP) at rest and during submaximal exercise by approximately 4–6 mmHg, whereas only HI training significantly reduced diastolic BP (DBP) (Cornelissen et al., 2009a). At this time, questions remain on the responsible BP-lowering mechanisms (Pescatello et al., 2004; Cornelissen & Fagard, 2005; Cornelissen, 2009c). So far, the antihypertensive mechanisms of training appear to be multifactorial and probably may depend on the training characteristics. Furthermore, as indicated by the evidence rating of "C" given by the American College of Sports Medicine to this topic, the available evidence is scarce and comes only from uncontrolled, nonrandomized and/or

observational studies (Pescatello et al., 2004). In this report, we primarily aimed to investigate the effect of both training programs on some potential BP-lowering mechanisms, that is (1) the hemodynamic mechanisms of the BP response assessed by the use of magnetic resonance imaging (MRI); (2) the activity of the sympathetic nervous system (SNS) assessed by means of power spectral analysis (PSA) of heart rate variability (HRV) and SBP variability (SBPV); (3) the involvement of the renin–angiotensin system by measuring plasma renin activity (PRA); and (4) endothelial function by investigating biochemical markers. Further, changes in markers of systemic inflammation and those associated with a prothrombotic state may be indicative for an amelioration of endothelial function. Given the close association among systemic inflammation, endothelium dysfunction and high BP, we also assessed the effects of training intensity on soluble E-selectin (sE-selectin), fibrinogen and von Willebrand factor (vWF).

Finally, because the use of MRI in a longitudinal protocol could allow detection of small changes in cardiac morphology, we evaluated, in addition to cardiac function, cardiac structure that may be influenced by training (Fagard, 2003).

Accordingly, the aims of the present report were to determine the effects of endurance training at LI and HI on (1) the potential BP-regulating mechanism associated with the observed exercise-induced BP reduction; (2) biomarkers of systemic inflammation and prothrombotic state; and (3) cardiac structure and function.

Material and methods

Study design and participants

A detailed description of the study design, eligibility criteria, screening and main results are presented elsewhere (Cornelissen et al., 2009a, b; Cornelissen, 2009c). We used a randomized cross-over design including three 10-week periods. In the first and third period, participants exercised at, respectively, LI and HI in random order, with a sedentary period in-between.

Participants were recruited from the general population. They had to be at least 55 years old, sedentary, non-smoking healthy men or women (SBP $\geq$ 120 mmHg and/or DBP $\geq$ 80 mmHg), who did not receive pharmacological treatment known to affect BP, BP-regulating mechanisms or cardiovascular risk factors and without high or very high cardiovascular risk according to prevailing guidelines (Guidelines Committee, 2003).

Training intervention

Training programs involved supervized aerobic sessions, at the fitness centre at the Faculty of Kinesiology and Rehabilitation Sciences of the University of Leuven, with participants exercising 3 days/week during 50 min per session at, respectively, 33% or 66% of HRR, excluding warming up and cool-down. Training heart rate (HR_{ex}) was calculated using the formula of Karvonen, which is as follows: $HR_{ex} = HR_{rest} + [(HR_{max} - HR_{rest}) \times 0.33$ or $0.66]$. Maximal HR (HR_{max}) was derived from the baseline maximal graded exercise test. For cycle exercise, HR_{rest} was taken as the heart rate (HR) measured in the sitting position, and, for exercises in the standing position, we took the HR measured in the standing position at baseline. During the sedentary period, subjects were contacted every 3 weeks and were asked to answer/fill in a short questionnaire about their behavior and to keep dietary, drinking and physical activity habits as stable as possible.

Measurements

Measurements were performed at baseline and at the end of each of the three 10-week periods. For logistical reasons, the sequence of the tests and the time after the last exercise bout could differ for each study period. However, the median number of days was always 3 or 4 days (range 2–7). Measurements of HRV and SBPV were performed between 08:00 and 13:00 hours after abstinence from caffeine for at least 12 h. All measurements, except MRI, were performed by the same investigator (V.A.C.) and were performed in a laboratory with a room temperature between 18 °C and 23 °C. Blood samples were taken in the morning after an overnight fast. On a separate day, cardiac MRI measurements were performed in a subset of participants. The analysis of MR images was performed by a blinded investigator (K.G.). The study was approved by the Ethical Committee of the Faculty of Medicine of the University of Leuven and written informed consent was obtained from all participants.

HR and SBPV

A 15 min record was taken while the subjects laid quietly in the supine position. Then, subjects were asked to stand without support for 10 min while the same data were recorded. HR was registered with three suitable ECG leads (ECG monitor 78353A; Hewlett Packard, Philips Medical Systems, Eindhoven, the Netherlands) for HRV analysis and beat-to-beat BP was registered with a non-invasive finger photoplethysmograph for SBPV (Finapres; Ohmeda 2300, Englewood, Colorado, USA). Off-line signal processing was performed to analyze the records using methods published earlier (Aubert et al., 1999; Cornelissen et al., 2009b). PSA, performed by the Fast Fourier Transform algorithm, allowed estimating the power in the low-frequency (LF) and the high-frequency (HF) range (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). Signal powers of each band were calculated as integrals under the respective power spectral density functions. We expressed the LF and HF powers in relative units, that is the absolute power divided by the partial power (= 0.04–0.4 Hz). In addition, the LF to HF ratio was calculated. All software was developed in house by the Laboratory of Experimental Cardiology using Labview 6.1 (National Instruments, Austin, Texas, USA) for Windows.

Blood analysis

PRA was analyzed by the biochemical laboratory of our institution. Fibrinogen was analyzed at the center for Molecular and Vascular Biology (KULeuven, Leuven, Belgium), sE-selectin, vWF and nitric oxide (NOx) (estimated by plasma nitrate and nitrate levels) were analyzed at the Cardiology and Diabetology Units (Cliniques Universitaires Saint Luc, UCL, Brussels, Belgium). An acceptable degree of imprecision was obtained for all biochemical tests (intra- and inter-assay coefficient of variation $<9\%$).

MRI

MRI was performed on a 1.5 T whole-body scanner(Gyroscan NT; Philips Medical Systems or Siemens Magnetom Symphony, Muenchen, Germany) using a sense-cardiac (Philips Medical Systems) or a body matrix (Siemens Magnetom Symphony) phased-array coil for radio frequency signal reception. Localizing scans were followed by end-expiratory, breathhold, ECG-gated steady-state free precession (SSFP) imaging
acquisitions (for Philips: 2D SSFP/B-TFE, repetition time 3.6 ms, echo time 1.8 ms, flip angle 60°, turbo factor 10, field of view 330 mm, matrix size 160 × 256, slice thickness 7 mm, gap = 0; for Siemens: 2D SSFP, repetition time 46.95 ms, echo time 1.57 ms, flip angle 65°, field of view 400 mm, matrix size 148 × 256, slice thickness 6 mm, gap = 0) for short axis images throughout the left ventricle, horizontal long axis and vertical long axis images.

Using the short axis cine MR images, left ventricular (LV) volumetric measurements such as end-diastolic volume (EDV), end-systolic volume (ESV), stroke volume (SV) and LV mass (LVM) were computed, as well as indices of global ventricular function such as ejection fraction (EF). First, the end-diastolic and end-systolic phase, defined as the phase in which the intra-cardiac lumen is visually the biggest and the smallest with the mitral and the aortic valve closed, respectively, were determined by the analyzer. Secondly, the most basal and the most apical LV slices to be analyzed were determined by the analyzer. The most basal slice was defined as the slice closest to the mitral annulus, containing the myocardial wall for at least 50% of the circumference. The most apical slice was defined as the most distal slice in which a lumen can still be delineated. For each slice in both phases, the endocardial borders were traced manually or semi-automatically with manual corrections by the manufacturer's softwares (Philips Medical Systems and Siemens Magnetom Symphony). Papillary muscles were included in volume, but excluded for mass measurements. For the end-diastolic phase, epicardial borders were traced in each slice.

LV chamber volumes (EDV and ESV) were computed by summing the areas of the endocardial segments for each slice at end-diastolic and end-systolic phase and multiplying these by the slice thickness. SV = EDV − ESV. EF% was defined as (SV/EDV) × 100. Myocardial mass = (the sum of the differences between the plani-metered epicardial area and endocardial area) × the slice thickness × density of myocardial tissue (1.05 g/cm^3).

Statistical analysis

Data analysis was performed using SAS software version 8.2 (SAS Institute Inc., Cary, North Carolina, USA). Sample size calculations were originally performed for office SBP, the primary outcome of our research trial. Power calculations and statistical analyses have been described previously (Cornelissen et al., 2009a). All data, except HRV and SBPV were analyzed using a mixed effects analysis of variance using SAS Proc Mixed. The model used the deltas as response, treatment (LI or HI), period (2 or 4) and sequence (I or II) as fixed effect factors, each baseline value as a covariate and subjects (with sequence of treatment nested) as a random effect. Differences between program baselines were analyzed using the same model but with baseline values as response variables. As several trends could be observed with regard to the effect of training on biochemical markers, post hoc we used a repeated-measures ANOVA in order to the increase statistical power to investigate the effect of training. This model used treatment (LI or HI), time (before or after training) sequence (I or II) and subjects (nested within its sequence) as sources of variance.

For each training program separately, we analyzed the overall effect of training on HRV and BPV in the supine and standing position by using analysis of variance (ANOVA), with phase (before and after training), position (standing or supine) and subjects (nested within its sequence) as sources of variance and tested the interaction between training and position. We further analyzed whether there was a difference in the response between LI and HI training using ANOVA with treatment (LI or HI), position (supine or standing) and subjects (nested within its sequence) as sources of variance. Baseline values were added as covariate in these analyses. Values before and after training are reported as mean (standard deviation) (SD), changes are reported as adjusted least-square means (95%CL). A two-tailed P-value ≤ 0.05 was considered significant.

Results

Thirty-nine (18 men) of 48 originally randomized participants could be included in the final analyses. Age at baseline averaged 59 years (range 55–71), SBP was 126.6 (SD 9.3) mmHg and DBP was 78.7 (SD 7.5) mmHg. As reported previously, LI resulted in a significant increase of VO_2 peak [+2.31 (95% CL+1.06; +3.55 mL/min/kg); $P<0.001$] from a baseline value of 23.1 ± 0.83 mL/min/kg whereas HI induced a significant increase of +3.70 mL/min/kg (+2.47;+4.93) ($P<0.001$) from a baseline value of 21.8 ± 0.83 mL/min/kg. The increase in VO_2 peak was more pronounced ($P<0.05$) with HI than with LI training (Cornelissen et al., 2009a). Similarly, we observed a significantly larger ($P<0.05$) reduction in body weight after training at HI (−1.09 kg; $P<0.001$ from baseline 74.9 ± 2.8 kg) compared with training at LI (−0.27 kg; P = NS from baseline 75.2 ± 2.76 kg) (Cornelissen et al., 2009a). In addition, there were no differences between baseline values and values at the end of the intermediate sedentary period, nor could we observe any period or sequence effect, indicating that there was no significant order or carry-over effect.

HRV and SBPV measures at rest and during orthostatic stress

Both programs caused similar increases in mean RR interval (Table 1). This was associated with an increase of global HRV but unchanged relative LF and HF powers and LF/HF ratio. Irrespective of the training program, we observed significant changes for each variable from supine to standing position, that is (1) a reduction of mean RR, (2) an increase of total HRV, (3) a decrease of HF power; and (4) an increase of LF/HF ratio. We further observed a significant interaction between position and HI training for mean RR; i.e., the orthostatic reduction in mean RR was more pronounced after training and

Table 1. Heart rate variability variables before and after training at lower and higher intensity in 32 participants

	LI training			HI training		
	Before training	After training	*P*	Before training	After training	*P*
Mean RR (ms)			$P_t < 0.01$			$P_t < 0.05$
Supine	872.6 ± 114.3	908.8 ± 126.4	$P_p < 0.001$	867.3 ± 81.0	912.6 ± 103.7	$P_p < 0.001$
Standing	708.0 ± 105.4	727.7 ± 122.0	$Pi = 0.42$	712.7 ± 81.4	712.5 ± 86.4	$P_i < 0.05$
Total power (ln ms^2)			$P_t < 0.01$			$P_t = 0.08$
Supine	6.69 ± 0.87	7.04 ± 0.97	$P_p < 0.001$	6.81 ± 0.79	6.94 ± 0.80	$P_p < 0.001$
Standing	7.20 ± 0.58	7.40 ± 0.59	$P_i = 0.42$	7.21 ± 0.56	7.38 ± 0.48	$P_i = 0.84$
LF power (%)			$P_t = 0.56$			$P_t = 0.43$
Supine	30.2 ± 10.1	31.0 ± 13.5	$P_p = 0.89$	32.2 ± 9.4	30.9 ± 10.4	$P_p < 0.05$
Standing	31.8 ± 10.6	28.9 ± 11.1	$P_i = 0.29$	28.9 ± 11.9	27.9 ± 9.2	$P_i = 0.93$
HF power (%)			$P_t = 0.81$			$P_t = 0.86$
Supine	21.0 ± 9.56	21.3 ± 10.3	$P_p < 0.001$	18.4 ± 9.28	19.0 ± 8.71	$P_p < 0.001$
Standing	11.1 ± 3.66	10.3 ± 4.07	$P_i = 0.65$	11.1 ± 4.04	10.8 ± 4.31	$P_i = 0.61$
LF/HF			$P_t = 0.49$			$P_t = 0.23$
Supine	1.81 ± 1.16	2.02 ± 2.0	$P_p < 0.001$	2.44 ± 1.75	1.87 ± 0.86	$P_p < 0.001$
Standing	3.21 ± 1.69	3.38 ± 2.25	$P_i = 0.96$	2.90 ± 1.61	2.98 ± 1.69	$P_i = 0.11$

Data are presented as means ± SD. No significant differences could be observed between the baseline measurements before the two training periods and between the training responses.

P_t, *P*-value for training effect; P_p, *P*-value for the effect of position; P_i, *P*-value for the interaction between training and position; LI, lower intensity; HI, higher intensity; LF, low frequency; HF, high frequency; LF/HF, low frequency to high frequency ratio.

Table 2. Blood pressure variability variables before and after training at lower and higher intensity in 32 participants

	LI training			HI training		
	Before training	After training	*P*	Before training	After training	*P*
Total power (ln)			$P_t = 0.77$			$P_t = 0.49$
Supine	3.24 ± 0.85	3.18 ± 0.89	$P_p < 0.01$	3.66 ± 0.65	3.44 ± 0.64	$P_p < 0.19$
Standing	3.52 ± 0.53	3.66 ± 0.68	$P_i = 0.46$	3.68 ± 0.70	3.58 ± 0.76	$P_i = 0.60$
Low power (%)			$P_t = 0.62$			$P_t = 0.32$
Supine	32.0 ± 14.6	34.5 ± 15.6	$P_p < 0.001$	33.9 ± 14.7	37.2 ± 12.4	$P_p < 0.001$
Standing	48.4 ± 16.9	48.7 ± 19.2	$P_i = 0.69$	47.4 ± 17.6	50.7 ± 19.6	$P_i = 0.99$
High power (%)			$P_t = 0.33$			$P_t = 0.55$
Supine	7.69 ± 7.06	6.84 ± 5.44	$P_p = 0.06$	5.16 ± 4.07	5.15 ± 2.94	$P_p < 0.01$
Standing	10.4 ± 6.71	8.81 ± 5.66	$P_i = 0.76$	8.10 ± 5.11	9.35 ± 7.65	$P_i = 0.54$

Data are presented as means ± SD. No significant differences could be observed between the baseline measurements before the two training periods and between the training responses.

P_t, *P*-value for training effect; P_p, *P*-value for the effect of position; P_i, *P*-value for the interaction between training and position; LI, lower intensity; HI, higher intensity; LF, low frequency; HF, high frequency; LF/HF, low frequency to high frequency ratio.

this was associated with a trend to a larger increase of the LF/HF ratio.

Training at LI or HI did not change SBPV variables at rest (Table 2). Standing increased the total power of SBPV and both the relative LF and HF power of SBPV. These orthostatic responses were similar for both interventions and were not affected by training.

PRA and biochemical markers of endothelial function, systemic inflammation and prothrombotic state

For technical reasons, not all biochemical data were available for all subjects. As shown in Table 3, PRA was not significantly altered after training at LI or HI, but in an overall analysis (RMANOVA), we found a tendency for a reduction in PRA ($P = 0.08$). HI, but not LI, caused a slight decrease of sE-selectin whereas markers of endothelial function (NOx) and prothromotic state (fibrinogen and vWF) did not change significantly after training, although fibrinogen tended to decrease after HI ($P = 0.07$). Overall, there were no significant differences between the responses after LI and HI training.

Cardiac structure and function

MRI data were available for 15 participants (seven men) after LI training and 16 participants (nine men) after HI training (Table 4). LVM did not change significantly after training. Further, whereas training

Table 3. Biochemical markers of the renin–angiotensin system and endothelial function at baseline and changes after LI and HI training

	LI training				HI training			
	n	Baseline	Δ Training	*P*	*n*	Before training	Δ Training	*P*
Plasma renin activity (ng/mL/h)	36	1.09 ± 0.89	−0.14 (−0.30; +0.010)	0.07	34	1.06 ± 0.65	−0.10 (−0.26; +0.054)	0.20
sE-selectin (ng/mL)	33	22.3 ± 10.9	−1.26 (−3.17; +0.66)	0.19	34	22.4 ± 11.5	−2.14 (−3.99; −0.30)	0.02
Fibrinogen (μmol/L)	35	9.17 ± 1.18	+0.20 (−0.35; +0.76)	0.50	33	9.46 ± 1.41	−0.53 (−1.12; +0.035)	0.07
Von willebrand Ag (μU/mL)	36	107.6 ± 39.3	−0.11 (−5.19; +4.96)	0.97	37	106.1 ± 39.8	−1.98 (−6.90; +2.94)	0.42
NOx (μmol/L)	36	35.9 ± 20.7	+0.78 (−6.57; +8.15)	0.83	35	37.4 ± 22.6	+5.52 (−1.88; +12.9)	0.14

Baseline data are presented as mean ± SD; changes (Δ) are presented as least square means (95%CL).

P, significance of change during the training period.

LI, lower intensity; HI, higher intensity; *n*, number of subjects.

Table 4. Cardiac structure and function at baseline and changes after lower intensity and higher intensity exercise training

	LI training				HI training			
	n	Baseline	Δ Training	*P*	*n*	Baseline	Δ Training	*P*
LVM(g)	15	97.7 ± 19.6	+5.09 (−1.45; +11.6)	0.12	16	94.9 ± 18.5	+3.9 (−2.4; +10.1)	0.21
SV (mL)	15	74.2 ± 12.7	+6.15 (−1.27; +13.6)	0.10	16	74.3 ± 15.7	+9.0 (+1.87; +16.1)	<0.05
EF (%)	15	62.2 ± 8.7	+2.06 (−1.11; +5.22)	0.19	16	63.4 ± 6.6	+4.2 (+1.18; +7.12)	<0.01
LVEDV (mL)	15	120.1 ± 18.8	+5.76 (−5.29; +16.8)	0.29	16	118.3 ± 20.9	+6.8 (−3.73; +17.3)	0.20
LVESV (mL)	15	46.0 ± 14.9	−1.25 (−7.06; +4.56)	0.66	16	42.8 ± 10.4	−2.97 (−8.43; +2.49)	0.27

Baseline data are presented as mean ± SD; changes (Δ) are presented as least square means (95%CL).

P, significance of change during the training period.

No significant differences could be observed between the baselines measurements before the two training periods and between the response to training.

LI, lower intensity; HI, higher intensity; *n*, number of subjects; LVM, left ventricular mass, SV, stroke volume; EF, ejection fraction; LVEDV, left ventricle end diastolic volume; LVESV, left ventricle end systolic volume; Δ, change during the training period.

had only minor effects on LVESV and LVEDV, SV and EF were increased after training, but this was only significant after HI. The overall increase in SV averaged 11 ± 23.1% and was associated with a 4.3 ± 8.1% reduction in HR in the participants in whom MRI measurements were performed.

Discussion

We reported previously that, in this intervention study in at least 55-year-old men and women, LI training induced significant improvements in cardiovascular risk, that is a significant increase in VO_2 peak and significant reductions in resting and exercise SBP. However, HI reduced the cardiovascular risk to a more global extent, that is, only HI favorably affected anthropometric characteristics, DBP, some blood lipids and markers of insulin resistance, in addition to improvements in VO_2 peak, resting and exercise SBP (Cornelissen et al., 2009a). The primary aim of the current report on this intervention study was to focus on the effects of these programs on the BP-regulating mechanism and a number of secondary outcomes such as markers of systemic inflammation, prothrombotic state and cardiac structure.

Hemodynamic mechanisms

So far, the underlying mechanisms responsible for the training-induced BP reductions appear to be unclear and many questions remain about causal relations (Pescatello et al., 2004; Cornelissen & Fagard, 2005; Cornelissen, 2009c). Mean arterial BP equals cardiac output (CO) multiplied by systemic vascular resistance (SVR), so that reductions in BP must be mediated by decreases in one or both of these variables. Based on the decrease of HR and the increase of SV associated with a higher EF observed in the present study, it is likely that CO remained unchanged or even increased (Rowell, 1974) and that the BP observed decreases in our study were due to a reduction in SVR. Whereas results of individual studies have been unclear, a meta-analysis concluded previously that SVR was indeed significantly reduced by endurance training (Cornelissen & Fagard, 2005). Resistance through a vessel equals (blood viscosity × length of the vessel)/vessel radius^4. As can be derived from the formula, only small changes in lumen size are required to make large adjustments to blood flow and pressure. Lumen size can be changed by a number of mechanisms, such as (1) the SNS; (2) the renin–angiotensin system; and (3) paracrine substances released by the endothelial cells (e.g., nitric oxide).

SNS

A reduction in sympathetic nerve activity is one of the most widely investigated BP lowering mechanisms. Our meta-analysis showed a highly significant reduction of plasma norepinephrine (PNE) by 29% after training (Cornelissen & Fagard, 2005). Nevertheless, there remains some controversy whether exercise training lowers sympathetic nerve activity, mainly due to the limitations of the measurement of PNE (Hamer, 2006). PSA of HRV and SBPV provides an alternative and non-invasive method to assess autonomic cardiovascular modulation (Malliani et al., 1991; Parati et al., 1995).

SBPV

Arterial pressure Mayer waves, occurring at ~ 0.1 Hz, are presumed to result from sympathetic vasomotor activity. Therefore, the LF power of SBPV may reflect the magnitude of sympathetic vasomotor variability (Sloan et al., 1997). In agreement with Uusitalo et al. (2002, 2004) and Radaelli et al. (1996) SBPV did not show any significant changes, although BP decreased, most likely due to a reduction in SVR. This apparent discrepancy may be explained by vascular remodelling which occurs through adaptation of the endothelium and/or smooth muscle (Kingwell et al., 1997). Thus, remodeling of peripheral vessels may develop during the time course of training and may modify or counterbalance neural effects on SBPV (Iwasaki et al., 2003).

HRV

The HF component of HRV is mediated by variations in vagal activity whereas the LF power reflects both vagal and sympathetic modulations (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). Whereas cross-sectional studies have in general shown that older endurance-trained athletes have significantly higher global HRV and vagal-related HRV indices than their sedentary counterparts (Aubert et al., 2003), results from intervention studies are less conclusive, especially in the older population. An increase (Schuit et al., 1999; Stein et al., 1999; Jurca et al., 2004; Madden et al., 2006) or no change in HRV (Davy et al., 1997; Loimaala et al., 2000; Perini et al., 2002; Uusitalo et al., 2002; Jurca et al., 2004; Uusitalo et al., 2004; Verheyden et al., 2006; Figueroa et al., 2007) have been reported after endurance training in subjects at a higher age. We reported previously that HR recovery following a single exercise session was significantly faster after HI training and to a lesser extent also after LI training. By contrast, training did not affect post-exercise HRV (Cornelissen et al., 2009b). Our present findings show an increase of global HRV together with unchanged relative LF and HF components and LF/HF ratio. Therefore, the reduction in HR, as well as the faster HR recovery (Cornelissen et al., 2009b) observed, may in part be due to other mechanisms than only a change in the sympathovagal balance (Bonaduce et al., 1998), such as a reduction of intrinsic cardiac rhythm (Smith et al., 1989; Loimaala et al., 2000; Scott et al., 2004). Further, the similar increase of global HRV after training at LI and HI adds evidence to the fact that HRV does not appear to respond in a dose-dependent manner (Loimaala et al., 2000; Melanson, 2000).

During orthostatic stress, the reduction in mean RR interval was associated with a decreased vagal activity (lower relative HF values) and a higher LF/HF ratio (Furlan et al., 2000). Autonomic responses to an upright posture change are reduced in the elderly (Laitinen et al., 2004), most likely related to a reduction of the baroreflex control of HR (Robbe et al., 1987) and sympathetic nerve activity and/or a reduced basal tonic vagal control (Laitinen et al., 2004). We reported previously that training increased orthostatic tolerance, i.e., especially HI resulted in a reduced drop of SBP in response to standing (Cornelissen et al., 2009a). In this report, we show that this was associated with a larger increase of the LF/HF ratio, which may reflect an increased baroreceptor function (Moak et al., 2007) or a better maintenance of sympathetic outflow in response to standing (Furlan et al., 1993).

PRA

The renin–angiotensin system is the body's most powerful hormonal system and plays a decisive role in regulating vessel diameter and body fluid volumes. Most of these actions are mediated by angiotensin II, which appears to be determined primarily by the circulating renal renin. Therefore, reductions in renin with training may contribute to the reduction of BP (Pescatello et al., 2004). In the overall analysis, we observed a slight tendency for PRA to be lower after training without any difference between both training programs. Whereas previous individual studies have been inconclusive, a meta-analysis of 10 study groups showed a decrease of 20% in PRA associated with a significant BP reduction after endurance training (Cornelissen & Fagard, 2005).

Endothelial function

The endothelial layer of the vascular wall has endocrine characteristics, producing substances that act locally and remotely in several parts of the organism. Endothelial dysfunction results in a greater vascular tone and less vasodilator function (Pescatello et al.,

2004). Abnormal endothelial function has, therefore, been implicated in the pathophysiology of elevated BP, and as a consequence, improved endothelial health/function has been proposed to explain in part the beneficial effect of exercise on BP (Pescatello et al., 2004). Preservation of normal endothelial function and endothelial-dependent vasodilation primarily depend on the bioavailablility of NOx. In contrast to Maeda et al. (2004) but concordant with Higashi et al. (1999), we found no major effect of training on basal plasma NOx. Nevertheless, the latter authors (Higashi et al., 1999) reported, in agreement with Goto et al. (2003), an increased forearm blood flow in response to acetylcholine after training, demonstrating an improvement in endothelium-dependent vasorelaxation. Therefore, our results together with those of Higashi et al. (1999) could suggest that the measurement of basal levels of plasma NOx may not be a sensitive enough index to detect changes in endothelial function.

Systemic inflammation and prothrombotic state

Endothelial perturbation is also reflected in an elevation of endothelial markers such as sE-selectin and vWF. sE-selectin is an adhesion molecule that appears on the surface of the vascular endothelium in response to lesions, whereas elevated levels of the prothrombotic agents vWF and fibrinogen promote thrombus formation and constitute an important step in systemic inflammation and atherogenesis. Endurance training studies in populations at increased cardiovascular risk support the hypothesized training effect on the inflammatory process, resulting in reduced levels of these markers. So far, little is known about the effects of endurance training in subjects who do not have an overt clinical manifestation of atherosclerosis and have relatively normal levels of these markers. In contrast to Hammett et al. (2006) who found no effect on inflammatory markers of healthy female smokers, we observed significant improvements of sE-selectin and a trend for reduced fibrinogen after HI training. Whereas epidemiological studies suggest a continuous and graded association between exercise and inflammatory markers (Abramson & Vaccarino, 2002), this could not be confirmed here, although a small tendency to better improvements after HI training may be suspected. This, should, however be confirmed by future research.

Cardiac structure

Finally, exercise is associated with hemodynamic changes and alters the loading conditions of the heart resulting in specific cardiac adaptations, called athlete's heart (Fagard, 2003). To the best of our knowledge, this is the first study investigating the influence of exercise on cardiac morphology and function, using MRI, in subjects at a higher age. LVM did not change significantly after a training program of 3 h/week for 10 weeks at LI or HI. Whereas there is a general consensus in the literature that LVM, measured by echocardiography (Fagard, 2003) or MRI (Sharhag et al., 2002) is increased in athletic populations, it has been shown that more than 3 h of exercise per week are required to change LVM (Fagard, 2003), which could explain our results.

Limitations

We used PSA of HRV and SBPV to assess autonomic cardiovascular modulation. HRV at HF is a satisfactory, although most likely partly incomplete, measure of vagal cardiac control whereas the LF component reflects both sympathetic and parasympathetic modulation. Moreover, normalization of the LF power by total variance or computation of the LF/HF ratio increases the reliability of spectral parameters in reflecting sympathetic cardiac modulation, particularly when the cardiac sympathetic drive is activated. Further, Sloan et al. (1997) demonstrated the possibility of LF component of SBPV to measure the sympathetic tone to the peripheral vasculature. Nevertheless, the debate continues on the physiological meaning of the LF and HF powers for both HRV and SBPV (Taylor & Studinger, 2006). Thus, it is possible that training had a more pronounced effect on the autonomic nervous system than what we observed, but that this was not adequately captured by HRV and SBPV. Further, for organizational reasons, the sequence of the tests and the time after the last exercise bout could differ for each study period. As the range for measurements was between 2 and 7 days, it may have been that in some participants some of the training-induced changes were attenuated or lost on the day of measurement. In addition, our results suggest a tendency for better effect with HI; however, it may well be that similar effects can be obtained be increasing the duration or the frequency of exercise sessions at LI, i.e., making it isocaloric to HI training. This should, however, be investigated in future trials. Finally, as indicated by Pescatello et al. (2004) and Hamer (2006), the BP-reducing mechanisms are most likely multifactorial and probably there is some inter-individual variability with regard to the effect of training on each of the investigated mechanisms. As our intervention study was powered to observe a training effect on SBP, our sample size may not have been large enough to detect small effect sizes on each of the individual BP-reducing mechanisms in this report.

In conclusion, although several trends were observed with regard to the effect of training on some BP lowering mechanisms, we did not observe major effects on any of them. We showed that the reduction in HR was associated with an increase in SV, so that the BP reduction reported previously is most likely due to a decrease is SVR. This was associated with a similar increase in global HRV and a tendency to a reduction in PRA. Further, only training at HI results in small improvements of some markers of systemic inflammation, especially sE-selectin; whereas, no significant changes were seen in SBPV, basal NOx and LVM. Finally, training intensity did not significantly affect our results. Nevertheless, despite the reported limitations, we believe that our findings may be of interest and could stimulate further larger investigations.

Perspectives

Exercise is a cornerstone therapy in the primary prevention, treatment and control of hypertension. However, the mechanisms responsible for these BP reductions remain unclear. We showed that the BP reduction is most likely due to a reduction in PVR but despite the fact that we observed several trends with regard to the effect of training on the proposed BP lowering mechanisms, we failed to observe a significant effect on any of these mechanisms. As suggested by others (Pescatello et al., 2004; Hamer, 2006), the BP-reducing mechanisms are most likely multifactorial and probably there is some inter-individual variability with regard to the effect of training on each of these mechanism. Therefore, most certainly, more large randomized controlled trials are warranted to investigate the potential BP-lowering mechanisms of different training programs and this in diverse populations while focusing not only on the activity of the SNS, but also paying more attention to other mechanisms such as endothelial function, the renin–angiotensin–aldosterone system and finally also genetic polymorphisms that might influence the BP response to exercise training.

Key words: blood pressure, exercise, hemodynamics, endothelial markers, renin–angiotensin system.

Acknowledgements

We are grateful to Profs. L. Bertrand (Division of Cardiology, UCL) and J.-M. Ketelslegers (Diabetology Unit, UCL) as well as to Mr. Damien Gruson (Diabetology Unit) and Mrs. Stéphanie Mosselmans and Audrey Ginion (Division of Cardiology, UCL) for their contribution to the different biochemical analysis.

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