Sympathetic activity is not a main cause of blood pressure reduction with exercise training in un-medicated middle-aged/older men

Ehlers, Thomas Svare; Møller, Sophie; Hansen, Camilla Collin; Tamariz-Ellemann, Andrea Sofia; Vermeulen, T D; Shoemaker, J K; Gliemann, Lasse; Hellsten, Ylva

Published in:
Scandinavian Journal of Medicine & Science in Sports

DOI:
10.1111/sms.14300

Publication date:
2023

Document version
Publisher's PDF, also known as Version of record

Document license:
CC BY-NC-ND

Citation for published version (APA):
ORIGINAL ARTICLE

Sympathetic activity is not a main cause of blood pressure reduction with exercise training in un-medicated middle-aged/older men

Thomas S. Ehlers1 | Sophie Møller1 | Camilla C. Hansen1 | Andrea S. Tamariz-Ellemann1 | Tyler D. Vermeulen2 | J. Kevin Shoemaker2 | Lasse Gliemann1 | Ylva Hellsten1

1Department for Nutrition, Exercise and Sports, University of Copenhagen, Copenhagen, Denmark
2School of Kinesiology, Western University, London, Ontario, Canada

Correspondence
Ylva Hellsten, The August Krogh Section for Human Physiology, The Department of Nutrition, Exercise and Sports, University of Copenhagen, Universitetsparken 13, Copenhagen Dk-2100, Denmark.
Email: yhellsten@nexs.ku.dk

Funding information
Lundbeckfonden, Grant/Award Number: R289-2018-116; Sundhed og Sygdom, Det Frie Forskningsråd, Grant/Award Number: 8020-000167A and 6110-00632

Background: This study tested the hypothesis that training reduces resting sympathetic activity and improves baroreflex control in both hypertensive and normotensive men but reduces blood pressure only in hypertensive men.

Methods: Middle-aged/older un-medicated stage-1 hypertensive males (mean age 55 ± 3 years; n = 13) and normotensive controls (mean age 60 ± 5 years; n = 12) participated in 8 weeks of supervised high-intensity interval spinning training. Before and after training, muscle sympathetic nerve activity (MSNA) and blood pressure were measured at rest and during a sympatho-excitatory cold pressor test (CPT). Based on the measurements, baroreceptor sensitivity and baroreceptor threshold were calculated.

Results: Resting MSNA and baroreceptor sensitivity were similar for the hypertensive and the normotensive groups. Training lowered MSNA (p < 0.05), expressed as burst frequency (burst/min), overall, and to a similar extent, in both groups (17% and 27%, respectively, in hypertensive and normotensive group), whereas blood pressure was only significantly (p < 0.05) lowered (by 4 mmHg in both systolic and diastolic pressure) in the hypertensive group. Training did not (p > 0.05) alter the MSNA or blood pressure response to CPT or increase baroreceptor sensitivity but reduced (p < 0.05) the baroreceptor threshold with a main effect for both groups. Training adherence and intensity were similar in both groups yet absolute maximal oxygen uptake increased by 15% in the normotensive group only.

Conclusion: The dissociation between the training induced changes in resting MSNA, lack of change in baroreflex sensitivity and the change in blood pressure, suggests that MSNA is not a main cause of the blood pressure reduction with exercise training in un-medicated middle-aged/older men.

KEYWORDS
baroreflex, exercise training, hypertension, microneurography, MSNA, sympathetic activity
1 | INTRODUCTION

Hypertension is a multifactorial and heterogeneous condition. One potential contributing factor is sympathetic nerve activity, in that an increase in sympathetic activity can lead to an increase in total peripheral resistance, resulting in elevated blood pressure.\(^1\) It is known that regular aerobic exercise training effectively reduces blood pressure in individuals with essential hypertension\(^2\,3\) and one of the proposed mechanisms underlying the effect is a reduction in sympathetic activity.\(^4\,6\) This proposition is largely based on evidence of increased sympathetic activity measured as muscle sympathetic nerve activity (MSNA), in hypertensive individuals compared to normotensive individuals.\(^7\,11\) However, direct evidence for a role of sympathetic activity in the blood pressure reducing effect of training is scarce in part due to the delicate nature of MSNA measurements which are technically difficult and very time consuming to obtain. To date, only two studies have examined the influence of exercise training by use of microneurography to directly determine muscle sympathetic nervous activity (MSNA) in hypertensive subjects and the results have been diverging. Laterza et al.\(^12\) reported that exercise training lowered blood pressure concomitantly with a lowering of MSNA and complete resetting of the baroreceptor reflex in younger untreated hypertensive individuals and proposed that the lowering of arterial pressure was due to a lowering of sympathetic activity. In contrast, a subsequent study involving middle-aged to older, medically treated, hypertensive men was unable to provide evidence for reduced sympathetic activity measured as muscle sympathetic nerve activity, baroreflex sensitivity, and arterial blood pressure in a group of medically untreated hypertensive sedentary males and matched normotensive males. We hypothesized that training would reduce resting sympathetic activity and increase baroreflex control in both groups but reduce blood pressure in the hypertensive group only, thereby suggesting a dissociation between lowering of MSNA and blood pressure. A secondary hypothesis was that there would be a lowering of the MSNA response to a cold pressor test in both groups after the training period.

For assessing sympathetic reactivity, a maneuver causing sympatho-excitation is commonly used, for example, dynamic or static handgrip exercise or a cold pressor test.\(^16\) though only few studies have investigated the response to training in at-risk populations in these parameters and only one in hypertensive individuals.\(^12,17\) In the present study, the cold pressor test was included to assess the influence of an exercise training period on the MSNA and blood pressure response.

The purpose of the present study was to evaluate the effect of 8 weeks of intense aerobic interval training on muscle sympathetic nerve activity, baroreflex sensitivity, and arterial blood pressure in a group of medically untreated hypertensive sedentary males and matched normotensive males. We hypothesized that training would reduce resting sympathetic activity and increase baroreflex control in both groups but reduce blood pressure in the hypertensive group only, thereby suggesting a dissociation between lowering of MSNA and blood pressure. A secondary hypothesis was that there would be a lowering of the MSNA response to a cold pressor test in both groups after the training period.

2 | METHODS

The study was approved by the Ethics Committee of the Capital Region of Copenhagen (H-18057185) and conducted in accordance with the guidelines of the Declaration of Helsinki; ClinicalTrials.gov identifier: NCT03778489. Written informed consent was obtained from all subjects before enrollment into the study.

2.1 | Study participants

Twenty-five middle-aged/older sedentary males were included in the study: 13 males with untreated stage 1 essential hypertension and 12 normotensive males. Inclusion criteria included an age between 40 and 70 years with a body mass index (BMI) of 20–35 kg/m\(^2\), ambulatory BP of >125/80 (hypertensive; HYP) or...
Absorption (DXA)-scan (Lunar Prodigy Advance; General Electric) was completed. One hour after a standardized breakfast consisting of a yoghurt drink and a piece of fruit, subjects completed two sub-maximal cycling bouts separated by 2 min of rest followed by a graded exercise test to exhaustion to determine maximal oxygen uptake (VO2-max). Maximal oxygen uptake (VO2-max) was confirmed by a plateau of VO2, HR and a RER > 1.1. After 10 min of rest, the participants conducted a verification test by cycling at a resistance corresponding to 110% of the maximal resistance achieved at exhaustion. Following >24 h after the experimental day, measurements of blood pressure were conducted by the participants in their homes with an automatic upper-arm blood pressure monitor (M7; OMRON). Six consecutive measurements were performed after at least 15 min of rest on three different mornings and three different evenings. All blood pressure measurements were completed on a regular work day.

2.2 Experimental design

Prior to enrollment in the study subjects underwent a screening procedure including a medical examination. Before and after the 8-week training-intervention, subjects completed two experimental days to evaluate body composition and cardiovascular fitness (experimental day 1), recordings of peroneal MSNA levels during rest and a 2 min cold pressor test (experimental day 2). Experimental days were separated by at least 5 days. Subjects refrained from caffeine, alcohol and exercise for 24 h prior to experimental days, and recorded their food intake in the morning of the experiment upon arriving at the laboratory between 8 and 9 am to ensure standardized conditions and no influence of food intake. The subjects were part of a larger study and baseline characteristics; blood pressure and training responses are also being reported elsewhere.19,20

2.3 Screening

The screening procedure consisted of 6 consecutive measurements of clinical blood pressure, by an automatic upper-arm blood pressure monitor (M7; OMRON) 20 min of rest in the supine position in a quiet dim room, a 12-lead ECG, blood sampling (in fasted state) (RBC, Hb, HbA1c, Creatinin, CRP, ALAT, ASAT, GGT, APTT, INR, Coagulation factors II + VII + X), a health questionnaire and a physical evaluation by medically trained personnel. Part of the screening procedure included a graded exercise test on a cycle ergometer to determine the maximal oxygen uptake (VO2-max) using a breath-by-breath gas analyzing system (Oxycon Pro; Viasys Healthcare). This test also served as a habituation trial.

2.4 Experimental day 1

Subjects reported to the laboratory in the morning after overnight fasting (>10 h). A whole body Dual X Ray
2.6 | Analysis of sympathetic nerve activity

Recordings of resting MSNA and MSNA during cold pressor test were analyzed in Labchart 8 (ADinstruments). Bursts were validated with a 2:1 burst-to-noise ratio and a fixed delay to the corresponding R-wave. Sympathetic activity was expressed as bursts per minute (burst frequency) or number of bursts per 100 heartbeats (burst incidence). MSNA during cold pressor test was reported as the delta value for the last minute of the 2 min cold pressor test compared to resting conditions.

Calculations of spontaneous baroreflex sensitivity were done by assigning all cardiac cycles of the measured resting period in bins of 2 mmHg from highest to lowest value according to their diastolic value and whether or not the specific cardiac cycle was associated with a sympathetic burst. For each bin, the probability of an association with a sympathetic burst was expressed as a percentage. Baroreflex sensitivity was expressed as the mean slope value for the linear regressions between the probability of a burst (%) for blood pressure values within the 2 mmHg bin, from the lowest to the highest blood pressure value in the recording (see Figure 1). The baroreflex threshold was calculated as the diastolic value for the abovementioned linear slopes corresponding to 50% probability for a heartbeat to be associated with a burst.15

For representative example of MSNA recording see Figure 2.

2.7 | Exercise training intervention

The training-intervention lasted for 8 weeks and consisted of three weekly high-intensity interval training sessions with a duration of approximately 60 min. Training was maintained after the training-intervention with two training sessions every week, until subjects had completed post-testing. All participants completed at least 20 training sessions, HYP completed on average 23.3 sessions and NORM 23.7 sessions. Training was conducted as intervals of 4–5 min duration of cycling at gradually increasing percentages of heart rate_{max} with majority of training time spent between 80% and 90% of heart rate_{max}. Training intensity was increased by addition of shorter intervals 2–4 min at near-all-out effort after the first week and again after week three (For further details on training, see Møller et al.19). All training sessions were supervised, and heart rate was monitored (Polar team 2 system, Polar, Electro Oy).

2.8 | Statistical analysis

Prior to the study, we performed an a priori power calculation calculated from previous MSNA data showing a sample size of 10 participants per group for a statistical power of 0.8 and an \( \alpha \)-value of 0.05. Statistical analyses were performed on paired observations, using ANOVA to determine overall effects of group and training. Analyses within- and between-group differences were performed using linear mixed model with Tukey’s post hoc analysis and fdr adjustment with a significance level of \( p < 0.05 \). Residual and Q-Q plots were used to confirm the homogeneity of covariance and normal distribution of the dataset. Variables that were not normally distributed were corrected for skewness by log transformation and/ or removal of extreme outliers and fitted to a normal distribution. Extreme outliers were categorized as data points that are three times the interquartile range below the first and above the third quartile. Statistical analyses were performed using R (version 4.0.2; The R Foundation) on the RStudio interface (version 1.3.1073; RStudio). Data are presented as mean ± SD. Due to the large inter-individual variability of the MSNA values, we included only paired values for analysis of the change with training.
and included blood pressure data were from the same participants to match with MSNA data.

3  |  RESULTS

3.1  |  Baseline characteristics

For baseline characteristics, see Table 1. At baseline, HYP was significantly \((p = 0.0002)\) older than NORM whereas there were no differences between groups for weight or BMI. At baseline, there were no differences between groups in fat-percentage \((p = 0.11)\) or \(\text{VO}_2\text{-max} \ (p = 0.92)\). There was a tendency \((p = 0.079)\) toward lower visceral fat-mass in NORM compared to HYP. Training improved \(\text{VO}_2\text{-max} \) in NORM \((p = 0.007)\) and tended \((p = 0.077)\) to improve \(\text{VO}_2\text{-max}\) in HYP with no difference between groups. The basic participant characteristics have previously been reported.\(^{19}\) Some participants failed to complete \(\text{VO}_2\text{-max}\) testing post-training either due to inability to perform the test or to attend. For analysis of \(\text{VO}_2\text{-max}\) \(n = 11\) for HYP and \(n = 12\) for NORM.

<table>
<thead>
<tr>
<th>TABLE 1  Baseline characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Height (cm)</td>
</tr>
<tr>
<td>Weight (kg)</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
</tr>
</tbody>
</table>

Note: Statistical analyses were performed using ANOVA (with the exception of age, where ANCOVA was used) to determine overall effects of group and training. Analyses of within- and between-group differences were performed using linear mixed model with Tukey’s post hoc analysis with fdr adjustment with a significance level of \(p < 0.05\).

\(^a\)Different \((p < 0.001)\) from NORM.
3.2 Resting blood pressure, invasive blood pressure and heart rate

At baseline, HYP had significantly \( (p < 2 \times 10^{-16}) \) higher resting systolic and diastolic home blood pressure measurements compared to NORM. Training significantly lowered both systolic \( (p = 0.0498) \) and diastolic blood pressure \( (p = 0.0019) \) in HYP only by 3% and 5%, respectively. Not all participants completed post-training home blood pressure measurements resulting in \( n = 10 \) for HYP and \( n = 9 \) for NORM for paired analysis.

Mean intra-arterial pressure at rest during the experimental day was significantly higher \( (p = 0.0075) \) in HYP compared to NORM \( (104 \pm 9 \text{ mmHg} \ vs. \ 96 \pm 9 \text{ mmHg}, \) respectively) both before and after training with a significant group effect. Training did not influence mean intra-arterial pressure in either NORM \( (p = 0.082) \) or HYP \( (p = 0.23) \).

At baseline, there were no differences \( (p = 0.82) \) in resting heart rate measured on the experimental day between HYP and NORM. Training did not reduce resting heart rate significantly in either group with no difference within \( (p = 0.52) \) or between groups \( (p = 0.76) \).

3.3 Resting sympathetic activity

At baseline, there were no differences between groups in MSNA burst incidence \( (p = 0.67) \) or burst frequency \( (p = 0.40) \). Training significantly \( (p = 0.049) \) reduced overall burst frequency in both HYP and NORM (by 17% and 27%, respectively, see Figure 3), with no differences between the groups. Training did not reduce burst incidence significantly in either group \( (p = 0.58) \). Due to technical issues, MSNA data were not possible to obtain both pre- and post-training for all participants. Therefore, the number of participants included in the analysis of MSNA were \( n = 11 \) for HYP and \( n = 8 \) for NORM.

3.4 Cold pressor test

Resting mean intra-arterial pressure prior to the cold pressor test was significantly higher in HYP compared to NORM both before \( (p = 0.014) \) and after training \( (p = 0.0061) \). However, the cold pressor-induced response in MSNA variables; MAP \( (p = 0.59) \) or heart rate \( (p = 0.93) \) were not significantly different between the groups (see Table 2). There was a significant group effect for \( \Delta \text{burst frequency} \ (p = 0.031) \) and \( \Delta \text{burst incidence} \ (p = 0.018) \) with no effect within nor between groups showing overall lower \( \Delta \text{burst frequency} \) and \( \Delta \text{burst incidence} \) for HYP compared to NORM.

Training did not alter the cold pressor induced response in \( \Delta \text{MAP} \) or \( \Delta \text{heart rate} \) between or within the groups.

3.5 Baroreflex sensitivity

At baseline, there were no differences between groups in baroreflex sensitivity or baroreflex threshold. Training lowered the baroreflex threshold \( (p = 0.024) \) overall with no difference between groups despite a within group analysis of changes in baroreflex threshold showed a significant reduction \( (p = 0.021) \) in the normotensive group only. Training did not affect the baroreflex sensitivity within or between groups.

3.6 Correlations

At baseline, there was no correlation between burst frequency and diastolic blood pressure for either group (and \( r^2 = 0.34, p = 0.06 \) and \( r^2 = 0.081, p = 0.59 \), HYP and NORM respectively). There was no correlation between burst frequency and systolic blood pressure for either group \( (r^2 = 0.13, p = 0.27 \) and \( r^2 = 0.11, p = 0.35 \), HYP and NORM, respectively).

![Figure 3](image-url)  (A, B) Resting muscle sympathetic nerve activity (MSNA) before and after training. Burst Frequency (BF, A) and burst incidence (BI, B) during rest before and after training. Statistical analyses were performed using linear mixed model to determine overall effects of group and time. \( ^1 \) Overall training effect \( (p = 0.049) \). Data presented as mean ± SD, \( n = 11 \) for HYP and \( n = 8 \) for NORM.
There was no relationship between the change in burst frequency and the change in diastolic blood pressure for either group ($r^2 = 0.008$, $p = 0.83$ and $r^2 = 0.04$, $p = 0.70$, HYP and NORM, respectively). Furthermore, there was no relationship between the change in burst frequency and the change in systolic blood pressure for either group ($r^2 = 0.01$, $p = 0.80$ and $r^2 = 0.002$, $p = 0.93$, HYP and NORM, respectively).

When correlating hemodynamics and burst frequency to age, we found a significant relationship between total peripheral resistance and age in the hypertensive group at baseline ($r^2 = 0.58$, $p = 0.002$) and with the effect of CPT ($r^2 = 0.38$, $p = 0.02$). We found no other relationships, but the remaining correlations to age can be found in Table S1. Furthermore, we found a significant relationship between burst frequency and the baroreceptor threshold at baseline in the normotensive group ($r^2 = 0.48$, $p = 0.038$), indicating that baroreflex threshold goes hand-in-hand with sympathetic activity. Similarly in the hypertensive group, we found a significant relationship between burst frequency and total peripheral resistance ($r^2 = 0.40$, $p = 0.038$), indicating that vascular resistance in the hypertensive group has a hindering effect on sympathetic activity. Remaining correlations can be found in Table S2.

4 | DISCUSSION

The main findings of present study were that there was an overall decrease in resting sympathetic activity with training in the two groups whereas the baroreceptor sensitivity remained unaltered. Blood pressure was lowered with training only in the hypertensive group. There was no effect of training on the cold-pressor response in either group. Prior to training, resting muscle sympathetic activity and baroreflex sensitivity were similar between the normotensive and the hypertensive groups. Lastly, prior to training, the cold pressor test induced a similar blood pressure response but a lower burst frequency response in the hypertensive compared to the normotensive group.

Aerobic exercise training consistently lowers blood pressure in hypertensive individuals and other at-risk populations, and it has been proposed that, at least a part of this decrease, is due to a training-induced reduction in...
sympathetic activity. However, direct evidence for the influence of training on MSNA in humans is somewhat limited and inconsistent and the only two studies that have examined the influence of aerobic training on MSNA in relation to blood pressure in hypertensive individuals, have shown contrasting findings, potentially due to the difference in populations studied. Laterza et al. studied stage 1 un-medicated men, aged 42–45 years on average, and found a relationship between MSNA, baroreceptor sensitivity and blood pressure, and Ehlers et al. studied stage 2 medicated men, which were 60–62 years on average and found a dissociation between MSNA and blood pressure. Apart from age, a major difference between the two studies was that the MSNA levels were markedly lower (22 burst/min) in Laterza et al. versus. (32 bursts/min). Here, we aimed to determine whether this difference between studies could have influenced the discrepancy in findings. Our results in older, stage 1 medically untreated hypertensive men were found to be in accordance with the previous finding in medically treated older men, in that training significantly reduced MSNA to a similar extent in the hypertensive and the normotensive groups, whereas blood pressure was only lowered in the hypertensive group. Thus, regardless of the degree of hypertension and medication, both studies show a dissociation between the training-induced lowering in MSNA and change in blood pressure with training, which in the present study was further supported by a lack of correlation between the training-induced change in sympathetic activity and change in blood pressure at an individual level. In addition, in both the previous and the present study, a dissociation between MSNA and blood pressure was present at baseline as the two groups had similar levels of MSNA despite the difference in blood pressure. In Laterza and co-workers, the lack of effect observed in the normotensive group may primarily be due to the significant difference in age of the participants (~15–20 years) and the difference in baseline MSNA. It may be noted that whereas burst frequency was reduced by training, burst incidence remained unaltered, despite a lack of significant change in heart rate. The reason for this discrepancy is likely the fact that more variation occurs when two measurements, that is, bursts and heart rate, are divided.

Moreover, in contrast to the findings of Laterza et al., in the current study, training was not found to induce a change in the baroreceptor reflex sensitivity in either of the groups. The reason for the discrepancy could again have been due to the difference in age or due to a shorter time of training (8 vs. 16 weeks) in the present study. Another difference between the two studies was that baroreflex sensitivity was determined by infusion of vasoactive compounds in Laterza et al. whereas in the current study it was determined by comparing spontaneous variations in blood pressure and MSNA at rest, thus potentially during more physiologically relevant conditions. Importantly, however, the herein observed lowering of arterial blood pressure with training in the hypertensive group despite the lack of change in baroreceptor sensitivity suggests that baroreceptor sensitivity was not involved in the blood pressure reduction with training.

Since baroreflex sensitivity remained unaltered with training, the training-induced reduction in MSNA remains unexplained. Although it can only be speculated on, one plausible explanation for the lowering of resting MSNA after training would be an increase in peripheral sensitivity to noradrenaline previously reported to occur with training. Another plausible mechanism is an enhanced nitric oxide bioavailability by training, either through increased capacity to form nitric oxide or by a reduction in the amount of reactive oxygen species present. Nitric oxide has been shown to restrain sympathetic activity in studies on both animals and humans, although the precise mechanism of this effect remains unclear.

To further assess the involvement of a neurogenic component, MSNA and blood pressure were monitored in response to a cold pressor test to induce sympathetic excitation. Based on findings in previous studies, we had expected that the blood pressure response and the sympathetic activation would be reduced by the exercise training period. At baseline, the hypertensive group presented a smaller change in burst frequency than the normotensive group, but there were no differences in the change in burst incidence or blood pressure. The difference in change in burst frequency suggests that the hypertensive group had a higher baroreceptor inhibition of sympathetic recruitment. In contrast to our hypothesis, we found no effect of training on the MSNA- or central response to the cold pressor test. The mechanisms underlying the increase in MSNA and blood pressure in response to a cold pressor test are complex and not completely understood; however, it is thought that both central command and the muscle metaboreflex are involved. It should also be noted that the response to the test depends in part on the experience of the participant to the ice-cold water, which influences the neurogenic response and the test consequently induced rather large individual variations in MSNA which may have exceeded limited potential differences.

The training intervention in the current study involved supervised high-intensity aerobic interval training conducted three times per week, where all sessions were heart rate monitored. The intervention, which has been proven to be highly effective for cardiovascular improvements, led to a reduction in both systolic and diastolic pressure of on average 4 mmHg in the hypertensive group. This reduction is clearly clinically relevant and somewhat above expected blood pressure reductions.
based on results from metaanalysis on studies in hypertensive patients.\textsuperscript{2,3,22} Despite the observed blood pressure lowering effect in the hypertensive group, the effect of training on maximal aerobic power was not significant in this group, whereas there was a solid increase of 15% in the normotensive group. The reason for the lack of increase in the hypertensive group is unclear but a plausible explanation is that plasma volume regulating hormones may be affected in the hypertensive state.

5 | PERSPECTIVES

The idea of a neurogenic component in primary hypertension has been longstanding,\textsuperscript{35} and several studies have provided data supporting elevated levels of sympathetic activity in hypertensive individuals.\textsuperscript{36–38} In the present study, there was no difference in burst frequency or burst incidence between the normotensive and the hypertensive group. The finding of similar resting sympathetic activity in normotensive and hypertensive participants is in line with our previous finding on stage 2 medicated hypertensive men\textsuperscript{13} but contrasts findings in other studies.\textsuperscript{38,39} The reason for the discrepancy is unclear but, in the current study, the two groups were purposely selected to be untreated and to have similar body composition, in order to compare groups who primarily differed in terms of baseline blood pressure. Therefore, it is possible that the difference in neurogenic control in previous studies primarily was related to health related differences, other than blood pressure, between groups, for example, such as differences in body composition.\textsuperscript{40} In the present study, further support for similar neurogenic control between the normotensive and hypertensive groups was provided by measurements of baroreflex sensitivity, showing no difference between groups. Given that a lack of difference in baseline MSNA has been observed in both stage 2 medicated,\textsuperscript{13} and stage 1 un-medicated older hypertensive men and that both studies have included direct MSNA measurements as opposed to indirect measurements of, for example, plasma noradrenalin,\textsuperscript{41} it seems reasonable to conclude that increased sympathetic activity is not a singular cause of primary hypertension. Future studies may address the possibility that there is a closer relationship between MSNA and blood pressure in hypertensive than in normotensive individuals, an aspect which could have influenced the outcome of our study. Moreover, future studies may include an assessment of the renin–angiotensin–aldosterone system when evaluating the influence of exercise training on SNA and blood pressure as this system may be altered with training,\textsuperscript{42} an effect which could influence vascular resistance.

5.1 | Study limitations

Microneurography is a difficult method and requires a high level of skill by the assessor, and even so, measurements are not always successful. This is probably the reason as to why there are few laboratories in the world that conduct such measurements. In the present study, data could only be included if successful measurements were achieved on the same individual both before and after the training period and consequently the sample size was somewhat limited. However, based on a priori power calculations of MSNA with results from our previous study and using a statistical power of 0.8 and an \( \alpha \)-value of 0.05, the number of included subjects was sufficient to detect a statistical effect of training.

Blood pressure is known to rise with age,\textsuperscript{40} and the majority of people above 80 years of age have elevated blood pressure. The two groups in the present study differed in age by 5 years. Therefore, an influence of age on the results cannot be excluded; however, we found no relationship between age, blood pressure, or MSNA in the present population. In addition, prevalence of hypertension between 55 and 60 years of age in the general population is not found to be very different.\textsuperscript{43,44}

It is worth noting that the present study, the effect of training on arterial blood pressure was assessed by blood pressure measurements conducted over 3 days at home by the participants, to minimize the influence of white coat syndrome and day-to-day variations.\textsuperscript{25} However, for technical and ethical reasons MSNA was only determined in the laboratory on one occasion pre- and post-training. This appears justified as sympathetic activity seems to have lower day-to-day variation than does blood pressure and is currently the best method to evaluate sympathetic activity at rest. Total peripheral resistance remained unaltered with training despite the lowering of MSNA. This finding probably reflects the fact that resistance is calculated and not directly measured resulting in a variation exceeding the effect of a limited change in MSNA.

Finally, it should be acknowledged that measurements of MSNA do not necessarily represent sympathetic outflow to vascular beds in other organs.

6 | CONCLUSION

It can be concluded that intense aerobic training lowers MSNA in both stage 1 hypertensive men and normotensive middle-aged/older men. However, importantly, there is a dissociation between the level of MSNA and blood pressure, as evidenced by similar baseline levels of MSNA and baroreflex sensitivity in the hypertensive
and normotensive groups and by a reduction in sympa-
thetic activity in both groups despite blood pressure
being lowered in the hypertensive group only. The find-
ing contradicts the intuitive presumption that an in-
crease in sympathetic activity markedly contributes to
hypertension and that a training-induced reduction in
sympathetic activity consequently lowers arterial blood
pressure. The translatability of the current findings to
postmenopausal women is unclear and warrants future
investigation.

AUTHOR CONTRIBUTIONS
The study was carried out at University of Copenhagen,
Department for Nutrition, Exercise and Sports. TSE, LG, CCH, and YH designed and planned the study. TSE, SM, CCH, and AST were responsible for data acquisition. TSE, SM, CCH, AST, JKS, and TV analyzed, interpreted, and prepared data. TSE and YH drafted the work. SM, CCH, AST, TV, JKS, and LG all did critical revision of the work for important intellectual content. All authors have
approved the final version of the manuscript and agree to be
accountable for all aspects of the work. All listed persons
designated as authors qualify for authorship, and all those
who qualify for authorship are listed.

ACKNOWLEDGEMENTS
The authors would like to thank Sarah á Rògvi Tolborg,
Melanie Emmonds Kurell, Simon Schultz Patrzalek, and
Christine Maulitz for their contributions to the project.

FUNDING INFORMATION
This work was supported by the Danish Independent
Research Council [Y.H. grant number 8020-00167A and
L.G. grant number 6110-00632] and the Lundbeck
Research Council [Y.H. grant number 8020-000167A
and L.G. grant number R289-2018-116].

CONFLICT OF INTEREST
Ylva Hellsten has received a research grant from NOVO
A/S for an entirely different study.

DATA AVAILABILITY STATEMENT
Data can be made available upon request with the limitation
that GDPR rules have to be abided.

ORCID
Thomas S. Ehlers https://orcid.org/0000-0001-9987-248X
Sophie Møller https://orcid.org/0000-0002-3714-2227
Lasse Gliemann https://orcid.org/0000-0002-0382-2523

REFERENCES
1. Grassi G. Sympathetic neural activity in hypertension and re-
2. Borjesson M, Onerup A, Lundqvist S, Dahlöf B. Physical ac-
tivity and exercise lower blood pressure in individuals with
3. Cornelissen VA, Smart NA. Exercise training for blood pres-
2013;2:e004473.
terval training versus moderate-intensity continuous training
on blood pressure in adults with pre- to established hyperten-
sion: a systematic review and meta-analysis of randomized tri-
5. Cioc EG. High-intensity interval training and hypertension:
maximizing the benefits of exercise? Am J Cardiovasc Dis.
6. O’Sullivan SE, Bell C. The effects of exercise and training
7. Schlaich MP, Lambert E, Kaye DM, et al. Sympathetic augmen-
tation in hypertension: role of nerve firing, norepinephrine
reuptake, and angiotensin neuromodulation. Hypertension.
2004;43:169-175.
9. Wallin BG, Sundlöf G. A quantitative study of muscle nerve
sympathetic activity in resting normotensive and hypertensive
10. Morlin C, Gunnar Wallin B, Eriksson BM. Muscle sympathetic
activity and plasma noradrenaline in normotensive and hyper-
11. Lambert EA, Schlaich MP. Reduced sympathoneural re-
sponses to the cold pressor test in individuals with essential
hypertension and in those genetically predisposed to hyper-
amjhyper.2004.05.008
restores baroreflex sensitivity in never-treated hypertensive
13. Ehlers TS, Sverrisdottir Y, Bangsbo J, Gunnarsson TP. High-
intensity interval training decreases muscle sympathetic nerve
activity in men with essential hypertension and in normoten-
sive controls. Front Neurosci. 2020;14:841.
14. Ray CA, Carter JR. Effects of aerobic exercise training on sympa-
thetic and renal responses to mental stress in humans. Am J
15. Salmanpour A, Kevin Shoemaker J. Baroreflex mechanisms
regulating the occurrence of neural spikes in human muscle
16. Hines EA, Brown GE. The cold pressor test for measuring the
reactibility of the blood pressure: data concerning 571 normal
17. Carter JR, Ray CA. Sympathetic neural adaptations to exercise
guideline for the prevention, detection, evaluation, and
Management of High Blood Pressure in adults: a report of the
American College of Cardiology/American Heart Association


SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.