Chemoreflex and Metaboreflex Responses to Static Hypoxic Exercise in Aging Humans

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ABSTRACT

HOUSSIERE, A., B. NAJEM, A. PATHAK, O. XHAËT, R. NAEIJE, and P. VAN DE BORNE. Chemoreflex and Metaboreflex Responses to Static Hypoxic Exercise in Aging Humans. *Med. Sci. Sports Exerc.*, Vol. 38, No. 2, pp. 305–312, 2006. **Purpose:** We tested the hypothesis that aging decreases the contribution of metaboreceptors to sympathetic responses during exercise in hypoxia. **Methods:** We recorded sympathetic nerve traffic to muscle circulation (MSNA), heart rate (HR), blood pressure (BP), minute ventilation (V_E), and blood lactate (BL) in 12 older (55 ± 10 yr) and 12 younger (22 ± 2 yr) normal subjects during three randomized interventions: isocapnic hypoxia (chemoreflex activation), isometric handgrip exercise (HG) in normoxia (metaboreflex activation), and HG during isocapnic hypoxia (concomitant metaboreflex and chemoreflex activation). All interventions were followed by a forearm circulatory arrest period to allow metaboreflex activation in the absence of exercise and chemoreflex activation. **Results:** Older subjects had higher resting MSNA (38 ± 12 vs 23 ± 9 bursts per minute; $P < 0.01$) and BP ($P < 0.001$). Heart rate, minute ventilation, and blood lactate did not differ (all $P > 0.5$). MSNA responses to HG in normoxia ($P < 0.05$) and in hypoxia ($P < 0.05$) were smaller in the older subjects, but were similar during hypoxia alone. The increase in HR was smaller in the older subjects for all interventions (all $P < 0.05$). In contrast, the increase in systolic and diastolic BP, V_E, and BL were similar in both groups ($P > 0.05$). During the local circulatory arrest, MSNA and BP remained elevated in both groups after HG in normoxia ($P < 0.01$) and in hypoxia ($P < 0.01$), but MSNA changes were smaller in the older subjects ($P < 0.05$). **Conclusion:** Aging reduces sympathetic reactivity to isometric handgrip, but does not prevent the metaboreceptors to remain the main determinant of sympathetic activation during exercise in hypoxia. **Key Words:** METABORECEPTORS, CHEMORECEPTORS, ELDERLY, HANDGRIP, HYPOXIA

Exercise and hypoxia are two potent stimuli of the sympathetic system (7,8,11,18,20,21,26,27). Isometric exercise produces ischemic metabolites that activate chemosensitive afferent nerve fibers called "muscle metaboreceptors." These receptors increase sympathetic nerve activity in muscle blood vessels (muscle sympathetic nerve activity (MSNA)) (11). Sympathetic vasoconstriction increases vascular resistance in nonexercising muscles (17) and thereby increases blood pressure (BP) and perfusion pressure (18,23,27). This rise in pressure limits any decrease in blood flow in exercising muscles (17). Metaboreflex regulation could be particularly important during exercise in hypoxia because oxygen delivery to the muscles is reduced. Isometric exercise is also associated with increases in heart rate (HR) and minute ventilation (V_E) (7–9,21,24).

The peripheral chemoreceptors located in the carotid bodies are sensitive mainly to hypoxia and, in response to this stimulus, increase V_E, HR, and MSNA (7,8,20,21,26). Peripheral chemoreflex activation leads to vasoconstriction of muscle vessels, which favors blood flow redistribution to the brain, the heart, and the kidneys (19). Unlike static muscle contraction, however, increases in MSNA, elicited by peripheral chemoreflex activation, are not accompanied by an increase in BP (7,8,20,21).

Metaboreceptors and chemoreceptors exert differential effects on the cardiorespiratory and autonomic responses during handgrip in hypoxia (8). Metaboreceptors play little role in the increase in HR. Both chemoreceptors and metaboreceptors contribute to the increase in V_E, but metaboreceptors are major determinants of the rise in MSNA and BP (8).

Simultaneous activation of metaboreceptors and chemoreceptors occurs during high-altitude exercise or when patients experience sudden cardiorespiratory compromise. Aging is accompanied by an increase in resting MSNA (8,12–15), BP, as well as a reduction in β-adrenergic sensitivity (1), which could modify the cardiovascular, ventilatory and sympathetic response to exercise in hypoxia. Aging was associated with an attenuated MSNA and BP response to isometric exercise in one study (12). In addition, because of their higher resting MSNA levels, older subjects disclosed a lower relative rise in MSNA during handgrip in another study (15). Older subjects also

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had lower HR and ventilatory responses to isocapnic hypoxia (10,16,25); however, aging did not affect the MSNA response to hypoxia in another study (2). Effects of aging on the sympathetic response to concomitant metaboreflex and chemoreflex activation are unknown. An altered metaboreflex and chemoreflex regulation could limit physical aptitude by amplifying dyspnea sensation (elevation of the ventilatory equivalent) and by restraining oxygen transport (cardiac output limited by BP elevation). A better understanding of metaboreflex and chemoreflex control and their interactions may enhance our knowledge of exercise limitation with aging and also in patients with cardiopulmonary impairment.

We tested the hypothesis that aging decreases the sympathetic response to exercise in hypoxia. Healthy young and older subjects underwent isocapnic hypoxia without exercise, isometric handgrip during normoxia, and isometric handgrip during isocapnic hypoxia. Hypoxia was achieved by breathing a low oxygen (O_2) content gas mixture, whereas carbon dioxide (CO_2) was titrated to maintain isocapnia in the presence of hyperventilation. These interventions were followed by a period of post handgrip ischemia to study the contribution of metaboreflex activation to the cardiorespiratory and sympathetic responses to exercise in hypoxia.

METHODS

Subjects. The study included 12 sedentary, healthy young subjects with a mean age of 22 yr (range ± 2) and 12 sedentary, healthy older subjects with a mean age of 55 yr (range ± 10). Our hypothesis for sample size calculations was that difference in means between the two groups would be 40%, thus the sample size needed in each group to demonstrate a statistically significant difference at a *P* value from 0.05, with a power of 90%, with an alpha of 0.05 and a beta of 0.05 was 11 subjects.

Subjects were not taking any medication. The ethical committee approved the study protocol, and informed written consent was obtained from each subject.

Measurements. We obtained continuous recordings of the electrocardiogram (Siemens Medical, ECG Monitoring, Erlangen, Germany), V_E pneumotacometer (Medical Electronic Equipment, Brussels, Belgium), oxygen saturation (Nellcor N-100 C Pulse Oxymeter, Pleasanton, CA), and end-tidal CO_2 (Normocap 200 Capnometer, Datex-Ohmeda, Hatfield, UK). BP (Physiocontrol Colin BP-880 sphygmomanometer, Colin press Mate, Colin Corp., Komaki City, Japan) was measured every minute during each intervention. Breathing was performed via a mouthpiece with the use of a nose clip to ensure exclusive mouth breathing. Blood lactate (BL), taken in a vein of the exercising arm, was determined after each intervention for 11 of the 12 young subjects and in 10 of the 12 older subjects.

Muscle sympathetic nerve activity was recorded continuously by obtaining multiunit recordings of postganglionic sympathetic activity, measured from a nerve fascicle in the peroneal nerve posterior to the fibular head (3) in all the subjects. Electrical activity in the nerve fascicle was measured using tungsten microelectrodes (shaft diameter 200 μm, tapering to a noninsulated tip of 1–5 μm; Frederick Haer, ME). A subcutaneous reference electrode was inserted 2–3 cm away from the recording electrode, which was inserted into the nerve fascicle. The neural signals were send to the Nerve Traffic Analysis System of the University of Iowa (Ames, IA). This equipment amplified, filtered, rectified, and integrated the nerve traffic recordings to obtain a mean voltage display of sympathetic nerve activity. Acceptable recordings met the following four criteria: Spontaneous bursts of neural discharge synchronous with HR, no response to arousal stimuli or skin stroking, an increase in nerve burst frequency with apnea, a signal to noise ratio of 3:1. These recordings were displayed on a Power Macintosh Computer (Apple Computer, Cupertino, CA) using the MacLab 8/s data acquisition system (AD Instruments, Castle Hill, Australia).

Protocol and interventions. The subjects were studied in the supine position under carefully standardized conditions. The maximal voluntary contraction (MVC) of their dominant forearm was determined carefully in triplicate with a handgrip dynamometer. Isometric handgrip exercise of the dominant arm was performed at 30% MVC in all subjects.

A 3-min baseline period of stable ventilation, with volunteers breathing room air, was followed by 3 min of three interventions performed in random order, namely (a) isocapnic hypoxia without exercise (10% O_2 in 90% N_2, with CO_2 titrated to maintain isocapnia); (b) isometric handgrip exercise of the dominant arm at 30% MVC in normoxia; and (c) isometric handgrip exercise during isocapnic hypoxia.

Each intervention was followed by 3 min of local circulatory arrest to the upper arm without handgrip while subjects breathed room air. Local circulatory arrest was produced by inflating a standard blood pressure cuff at 240 mm Hg on the upper arm, 5 s before the end of each intervention. The subjects were instructed to relax their grip after the cuff was inflated.

We decided to use a low grip force that allows muscle chemoreflex activation (21) while minimizing muscle fatigue. Each subject was requested to eliminate or minimize any muscle contraction in resting muscles, especially in the leg muscles, during handgrip. Subjects were not allowed to hold their breath during the handgrip exercise.

Each intervention was followed by a 10-min recovery period and a further 3-min baseline period of stable ventilation, with volunteers breathing room air, before the next intervention was started.

Data analysis. Sympathetic bursts were identified by careful inspection of the mean voltage neurogram during the 3 min of the baseline periods and during the last minute of the intervention periods. Sympathetic bursts were identified by careful inspection of the mean voltage

neurogram by a single trained observer blinded to the interventions. The amplitude of each burst was determined, and sympathetic activity was calculated as bursts per minute, multiplied by mean burst amplitude (arbitrary units (AU)) and expressed as percent increase from baseline values. Burst amplitude depends on neural signal amplification, which varies from one subject to another but is kept constant throughout each experiment. Thus, we used percent increase in amplitude from baseline values to compare changes in sympathetic nerve activity within an experimental session.

The increases in HR, BP, minute ventilation (V_E), and BL were expressed in absolute unit changes from baseline values.

Statistical analysis. Results are expressed as mean ± SD. An ANOVA for repeated measurements determined whether aging affected the overall cardiovascular, respiratory, and sympathetic responses to the interventions (i.e., handgrip, hypoxia and handgrip in hypoxia) and the subsequent local circulatory arrest. The significance of pairwise contrasts, for each parameter during each intervention, was estimated using the Fischer PLSD test (Statview 5.0, SAS Institute, Cary, NC).

To determine whether BMI, grip strength (MVC), and MSNA at rest affect the sympathetic responses to exercise, we performed an ANCOVA for repeated measures with BMI or grip strength or resting MSNA as covariate, MSNA response to exercise as the dependent variable, and age as factor. Other comparisons were performed with paired and unpaired Student's *t*-tests (two-tailed). Significance was assumed at $P < 0.05$.

RESULTS

Subject characteristics. The 12 healthy young subjects (10 men, 2 women) and 12 older subjects (9 men and 3 women) all had normal physical examinations and were receiving no medication. All subjects had a systolic BP <140 mm Hg and a diastolic BP <90 mm Hg. There was a 33-yr age difference between the older and younger subjects (55 ± 10 vs 22 ± 2 yr, $P > 0.05$). Height (older: 170 ± 7 vs young: 175 ± 7 cm; $P = 0.13$) and weight (older: 71 ± 10 vs young: 68 ± 8 kg; $P = 0.43$) did not differ between the groups. BMI, however, was slightly greater in the older (24 ± 2 $kg \cdot m^{-2}$) than in the younger subjects (22 ± 2 $kg \cdot m^{-2}$; $P < 0.05$). Young subjects had a greater maximal voluntary contraction (45 ± 8 kg) than the older (32 ± 10 kg; $P < 0.05$).

Effects of aging on baseline cardiovascular measures, sympathetic activity and ventilation. Older subjects (Table 1) had higher baseline resting MSNA (38 ± 12 vs 23 ± 9 bursts per minute in the younger subjects; $P < 0.01$) and their systolic BP (131 ± 9 mm Hg) and diastolic BP (76 ± 9 mm Hg) were also higher than in the younger subjects (systolic: 121 ± 7 mm Hg and diastolic: 61 ± 7 mm Hg; $P < 0.001$). HR, V_E, and BL did not differ between the two groups (all $P > 0.5$).

Effects of aging on the cardiovascular, respiratory, and sympathetic responses in the three interventions. The responses to the three interventions (hypoxia, handgrip in normoxia, and handgrip in hypoxia) were lower in the older subjects for MSNA burst frequency ($P < 0.01$) and relative amplitude ($P < 0.05$), as well as for HR ($P < 0.01$). The rise in ventilation ($P < 0.001$), MSNA burst frequency ($P < 0.001$), MSNA relative amplitude ($P < 0.001$), HR ($P < 0.0001$), SBP ($P < 0.0001$), and DBP ($P < 0.0001$) differed among the interventions.

Aging affected the responses to the interventions only for the relative changes in MSNA, which were lower in the older subjects ($P < 0.05$).

Effects of aging on the responses to isometric handgrip. Three minutes of isometric (Fig. 1) and (Fig. 2) handgrip increased sympathetic activity in both groups ($P < 0.0002$).

The percent increase in MSNA above baseline levels was lower in the older than in the younger subjects (166 ± 42 vs 248 ± 107%; $P < 0.05$, respectively). Changes in burst frequency did not differ between both groups ($P = 0.60$).

Aging was accompanied by a lower increase in HR in response to isometric handgrip (12 ± 7 vs 19 ± 9 bpm in the older and younger subjects, respectively, $P < 0.05$).

Handgrip increased systolic and diastolic BP, V_E, and BL from baseline values in both groups ($P < 0.01$), but the amplitude of these responses did not differ between the younger and the older subjects (all $P > 0.2$).

Effects of aging on the responses to isocapnic hypoxia. End-tidal CO_2 levels (Figs. 1 and 2) remained at baseline values ($P = 0.8$). The reduction in SaO_2 was similar in the two groups ($P = 0.95$).

Three minutes of hypoxia increased MSNA in both groups ($P < 0.05$ for burst frequency and relative changes in amplitude). Aging did not affect the relative increase in MSNA in response to hypoxia ($P > 0.4$ for burst frequency and relative increase in amplitude). HR increased in both groups ($P < 0.05$), but its rise smaller in the older subjects ($P < 0.002$).

Three minutes of hypoxia did not increase BP and BL in the older and the younger subjects. V_E increased in both groups ($P < 0.05$) and in a comparable manner ($P = 0.5$).

Effects of aging on the responses to simultaneous isometric handgrip and hypoxia. End-tidal CO_2 levels remained (Figs. 1 and 2) at baseline values ($P = 0.8$). The decrease in SaO_2 was similar in the two groups ($P = 0.94$).

TABLE 1. Baseline values ± SD.

	Young	Older
MSNA (bursts per minute)	23 ± 9	38 ± 12
SBP (mm Hg)	121 ± 7	131 ± 9
DBP (mm Hg)	61 ± 7	76 ± 9
HR (bpm)	65 ± 11	65 ± 9
V_E ($L \cdot min^{-1}$)	7 ± 0.9	6.9 ± 1.1
Sat (%)	97 ± 1	97 ± 1

* Significant differences between groups ($P < 0.05$) in muscle sympathetic nerve activity (MSNA), systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), ventilation (V_E), arterial saturation (Sat), and blood lactate (BL).

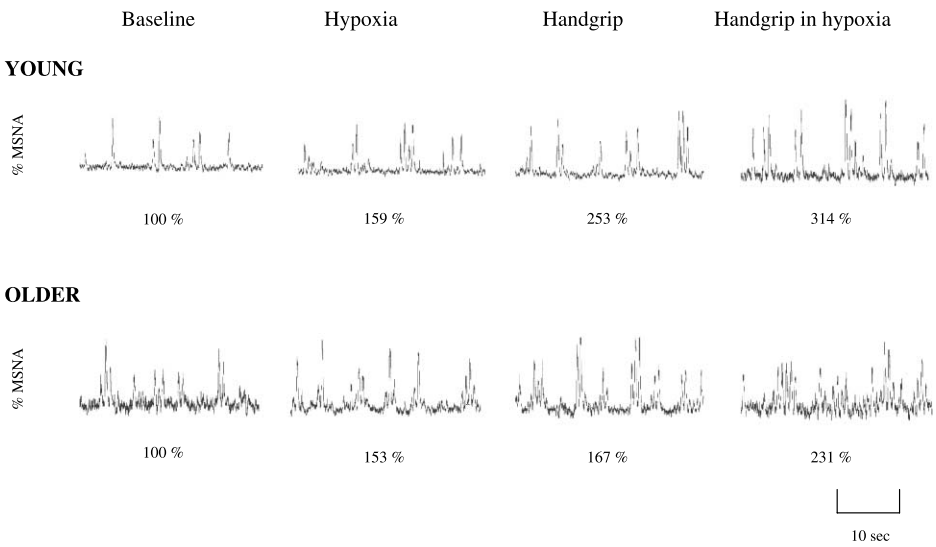

FIGURE 1—Representative recordings of muscle sympathetic nerve activity (MSNA) during baseline, during the third minute of hypoxia, during the third minute of handgrip in normoxia, and during the third minute of handgrip in hypoxia in a young and in an older subject. MSNA responses to handgrip in normoxia and in hypoxia were smaller in the older subjects but were similar during hypoxia alone.

Three minutes of handgrip exercise under hypoxic conditions increased MSNA in both groups ($P < 0.01$). The relative increase in MSNA amplitude above baseline values during exercise in hypoxia, however, was smaller in the older subjects than in the younger controls (170 ± 46 vs 266 ± 140%; $P < 0.05$). Changes in burst frequency between older and younger subjects were not significant ($P > 0.36$). Handgrip in hypoxia increased HR in both groups ($P < 0.05$). The absolute increase in HR above resting baseline levels during handgrip in hypoxia was smaller in the older subjects (21 ± 7 bpm) than in the younger volunteers (33 ± 13 bpm; $P < 0.05$). In contrast, the increase in BP, V_E, and BL was not different among the groups during the handgrip in hypoxia ($P > 0.3$).

Effects of aging on the contribution of metaboreflex and chemoreflex activation to the cardiorespiratory and sympathetic responses to handgrip in hypoxia. The effects of aging so far as metaboreflex and chemoreflex activation contributing to the cardiorespiratory and sympathetic responses to handgrip in hypoxia was (Fig. 3) investigated during the third minute of local circulatory arrest following hypoxia, handgrip, and the combination of hypoxia and handgrip, while subjects breathed room air.

SaO_2 returned to baseline values at the second minute of local circulatory arrest ($P = 0.7$), and stabilized at 98 ± 1% during the third minute. SaO_2 during this third minute of circulatory arrest was identical to the baseline SaO_2 ($P = 0.8$). Thus, during this third minute, metaboreflex stimulation was maintained in the absence of chemoreflex activation and this allowed determination of the contribution of metaboreflex activation to the cardiorespiratory and sympathetic response to handgrip in hypoxic conditions.

The only parameter that differed between the younger and older subjects during the local circulatory arrests after the 3 intervention was a lower MSNA relative amplitude in the older subjects ($P < 0.05$). MSNA burst frequency ($P < 0.0001$), MSNA relative amplitude ($P < 0.001$), systolic BP ($P < 0.0001$), diastolic BP ($P < 0.0001$), and BL ($P < 0.0001$) differed between the three local circulatory arrests.

Aging affected the responses to the local circulatory arrests only for the relative changes in MSNA, which were lower in the older subjects ($P < 0.05$). In addition, all parameters returned to baseline values during the third minute of local circulatory arrest after hypoxia.

MSNA and BP fell from end-handgrip values, but remained elevated above baseline values during the post handgrip local circulatory arrest after handgrip in normoxia ($P < 0.01$), as well as after handgrip in hypoxia ($P < 0.01$). This persistent increase in MSNA was smaller in the older subjects after handgrip in normoxia and in hypoxia than in the younger controls ($P < 0.01$ and $P < 0.05$, respectively). Burst frequency was also lower after handgrip in normoxia in the older subjects ($P < 0.05$), but not after exercise in hypoxia ($P = 0.16$). No differences were seen between groups in BP changes from baseline values ($P = 0.87$).

After handgrips, BL remained elevated above baseline values ($P < 0.05$), but no differences were seen between groups (all $P > 0.2$)

V_E, and HR returned similarly to baseline levels during the postexercise local circulatory arrest after handgrip in normoxia and hypoxia in the older and younger subjects (all $P > 0.05$).

Effects of BMI, grip strength (MVC), and MSNA at rest on sympathetic responses to exercise. The difference in BMI between young and older subjects did not affect the increase in MSNA amplitude during exercise ($P = 0.8$).

The difference in absolute MVC between groups did not influence the MSNA amplitude response to exercise ($P = 0.22$).

Greater resting MSNA burst frequency in the older subjects did not blunt the rise in MSNA amplitude during exercise.

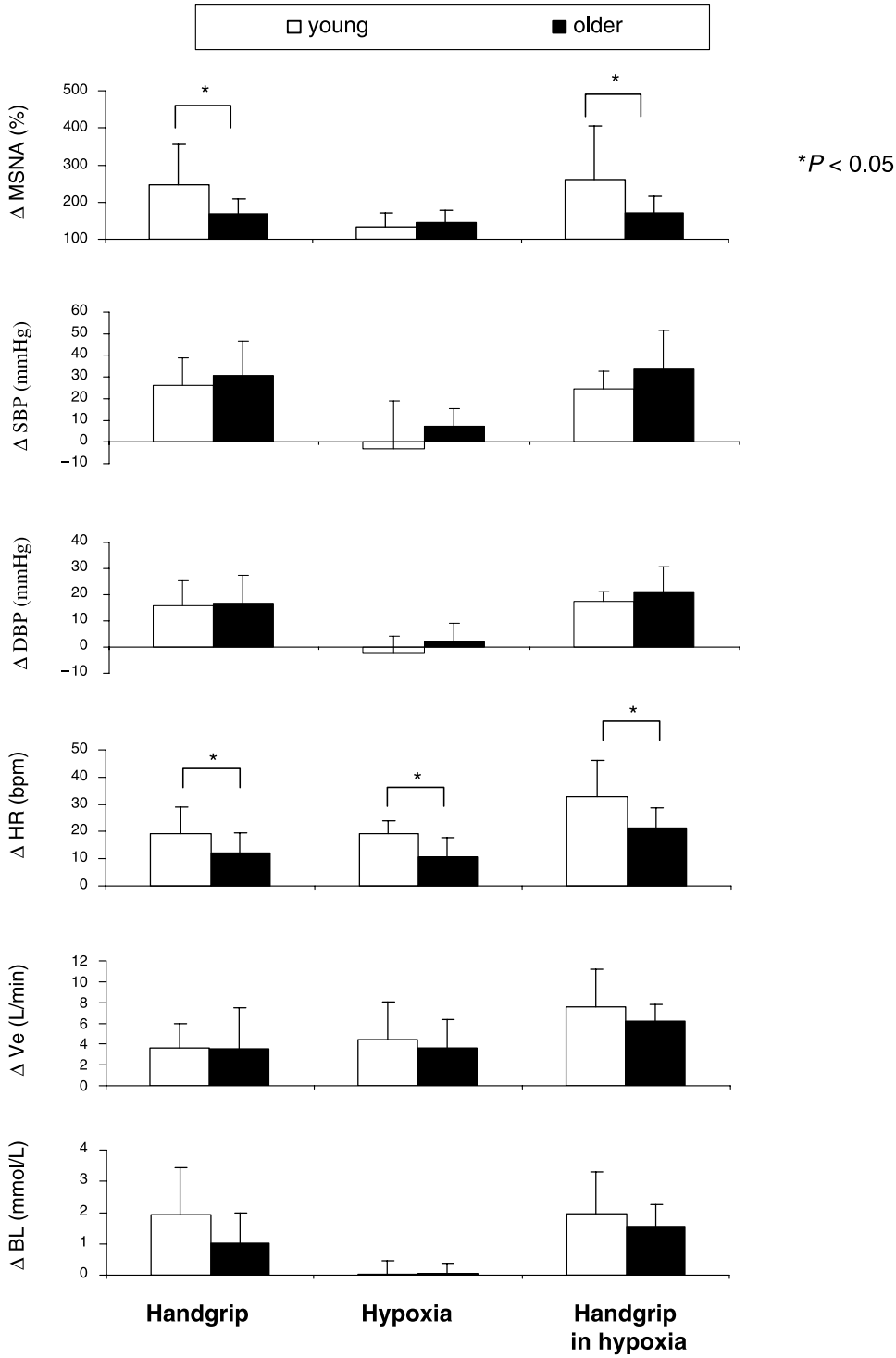

FIGURE 2—Changes in comparison with baseline in muscle sympathetic nerve activity (MSNA), systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), minute ventilation (V_E), and blood lactate (BL) at the third minute of handgrip, hypoxia, and handgrip in hypoxia in young (*white bars*) and in older subjects (*black bars*) Values are shown as mean ± SD. * Significant differences between groups ($P < 0.05$).

Indeed, after normalizing for differences in baseline MSNA burst frequency, the effects of aging on the rise in MSNA amplitude during exercise remained significant between the younger and older subjects ($P = 0.01$).

DISCUSSION

The main new finding of our study is that aging impairs the relative increase in MSNA in response to simultaneous metaboreflex and peripheral chemoreflex activation. Post handgrip ischemia after normoxia, as well as after hypoxia, reveals that this impairment can be attributed to an alteration in MSNA reactivity to metaboreflex activation. Consistent with this hypothesis, handgrip in normoxia was also accompanied by a reduction in MSNA reactivity.

Persistent increases in MSNA during forearm circulatory arrest after handgrip in hypoxia and in normoxia, but not after chemoreflex activation alone, extends to older subjects previous evidence of the importance of metaboreflex activation in the sympathetic response to exercise in

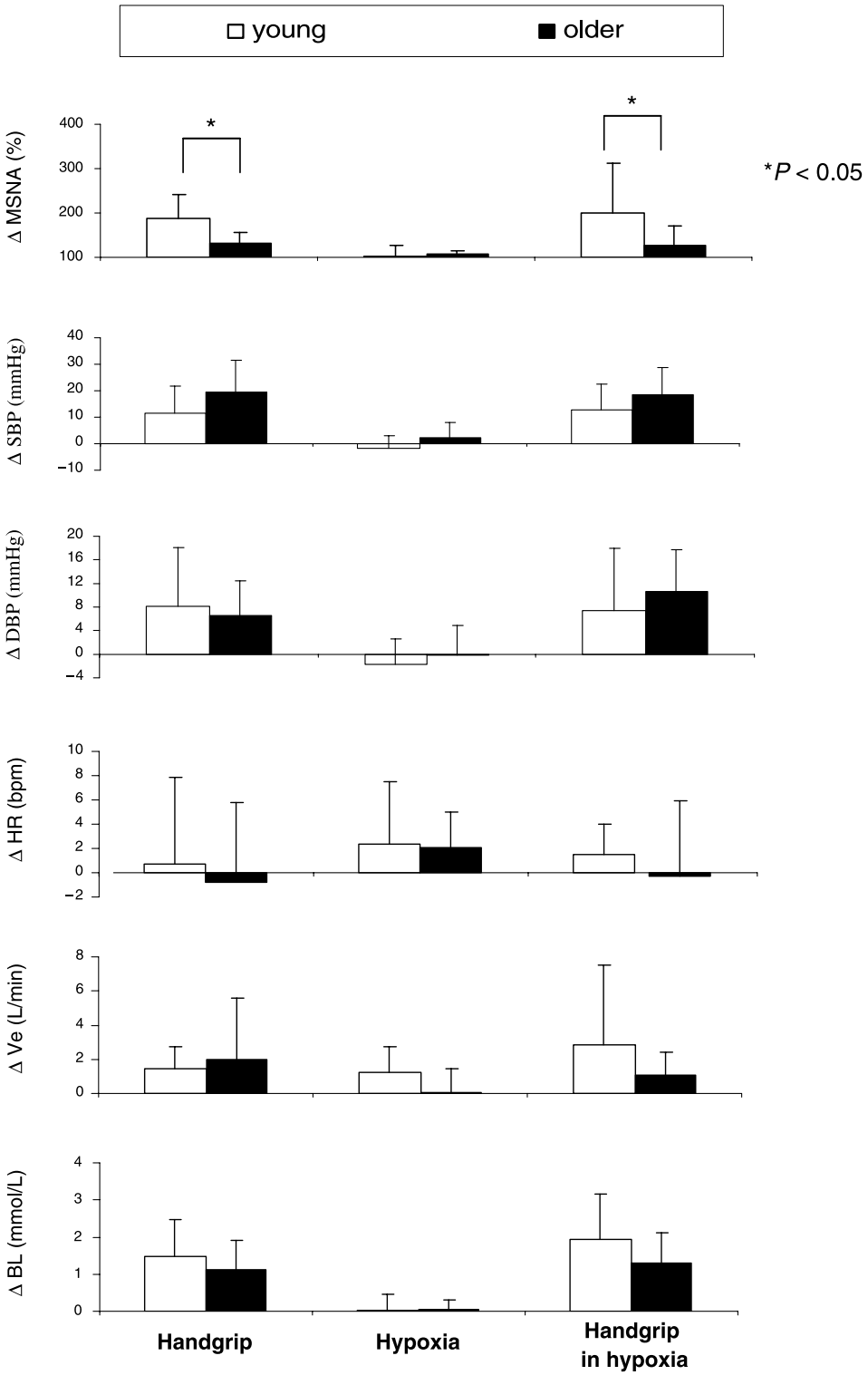

FIGURE 3—Changes in comparison with baseline in muscle sympathetic nerve activity (MSNA), systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), ventilation (V_E), and blood lactate (BL) during the third minute of local circulatory arrest after 3 min of handgrip, after 3 min of hypoxia, and after 3 min of handgrip in hypoxia in younger (*white bars*) and in older subjects (*black bars*). Values are shown as the mean ± SD. * Significant differences between groups ($P < 0.05$).

hypoxia in younger subjects (8). Aging was associated, in a previous study, with attenuated MSNA and BP responses to isometric exercise (12), which was attributed to an attenuated muscle reflex activity. In addition, the sympathetic response to handgrip was smaller in older subjects when MSNA was expressed as percent change of baseline values, because of their higher resting levels of MSNA (15). These authors, however, did not determine MSNA reactivity to hypoxia and exercise in hypoxia.

The originality of our study resides in that we evaluated the effects of aging on the sympathetic response in two separate conditions known to increase sympathetic activity, but also by combining these two conditions. This allowed us to rule out that larger baseline levels in the older subjects resulted in a nonspecific saturation of MSNA during exercise. This is evidenced by the observation that, despite having higher resting MSNA, older subjects did not raise their MSNA any less during isocapnic hypoxia than

the younger subjects. This speaks against a nonspecific reduction in MSNA responsiveness with aging. This is also further evidenced by our observation that the rise in sympathetic nerve traffic was blunted in the older subjects during local circulatory arrest after handgrip in hypoxia and in normoxia, when MSNA was only modestly elevated (at approximately 120% above baseline values). Last, the ANCOVA also further revealed that elevated resting MSNA could not account for our results.

Aging also did not influence obviously the regulation of MSNA or arterial blood pressure during alterations in systemic O_2 levels in a previous study (2). In addition, evidence indicates that, although aging and gender influenced MSNA at rest, they did not affect MSNA adjustments to acute stress (15).

Although our study reveals a consistent and selective reduction in the relative increase in MSNA during handgrip with aging, it does not provide a clear-cut explanation for this observation. Evidence indicates greater skeletal muscle oxidative potential is found in elderly subjects, which attenuates MSNA responsiveness to exercise (12). Handgrip in hypoxia and normoxia, however, did not result in clear-cut differences in BL in the older subjects in our study. BL, however, is only one of the numerous metabolites that affect metaboreceptor activity during exercise (23) and we cannot exclude that changes in other metabolites (e.g., H+, diprotonated phosphate, K+, adenosine, prostaglandins, and bradykinin) with aging contributed to our observation.

We found that the regulation of BP was similar in the older subjects and in the younger controls, despite that sympathetic reactivity was greater in the young subjects during exercise in normoxia and in hypoxia. Recent studies have shown that aging is accompanied by a reduced responsiveness to norepinephrine (4,28). Thus, it is unlikely that older subjects disclosed a greater vascular responsiveness to a lower sympathetic stimulus and that this can account for similar BP changes in the presence of a lower MSNA reactivity. Our results, instead, could be explained by the fact that MSNA reflects only changes in a single vascular bed. Profound differences are found in the control of sympathetic activity to various tissues and vascular beds. MSNA does not provide an overall index of sympathetic discharge and differential regional sympathetic response during exercise could explain that reduced MSNA reactivity with aging was not paralleled by a lower BP response to exercise in our study.

Effects of aging on the response to handgrip were restricted to those in MSNA, because the ventilatory response to isometric exercise remained unaffected. Modifications in HR during handgrip in hypoxia and normoxia were blunted in the older subjects. This was also observed during chemoreflex activation. Older men also disclosed an attenuated tachycardia in response to acute hypoxemia in a previous study (2). Aging decreases cardiac vagal influence on resting HR, and this mechanism limits reductions in vagal tone during exercise (22). Moreover, β-adrenergic sensitivity decreases with aging (5,22). Previous evidence that metaboreceptors play little role in the rise in HR during ischemic hypoxia (6), together with the rapid and comparable reductions in HR during post handgrip ischemia in the younger and older subjects, argue against altered metaboreflex control mechanisms in the blunted tachycardia during handgrip with aging.

Study limitations. Our study has several limitations. First, we did not perform a local circulatory arrest while subjects where breathing the hypoxic gas mixture, because this would have required longer periods of hypoxia. In mitigation, however, we controlled for the potential confounding effects of central command and mechanoreceptor activation by asking our subjects to perform identical exercises during normoxia and hypoxia. Moreover, a previous study in normal young subjects demonstrated that sympathetic activation during postexercise local circulatory arrest was similar during hypoxia and normoxia (19).

The second limitation is that absolute MVC was less and BMI has slightly greater (6) in the older subjects. Additional studies are needed to determine whether these two factors played a role in the lower MSNA reactivity we observed with aging. Our observations that grip strength, BMI, and MSNA at rest did not affect the MSNA response to exercise suggest, however, that this was not the case.

In conclusion, aging reduces sympathetic reactivity to isometric handgrip but does not prevent the metaboreceptors to remain the main determinant of sympathetic activation during exercise in hypoxia.

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