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ORIGINAL ARTICLE

Tonic activity of carotid body chemoreceptors contributes to the increased sympathetic drive in essential hypertension

Maciej Siński[1], Jacek Lewandowski[1], Jacek Przybylski[2], Joanna Bidiuk[1], Piotr Abramczyk[1], Agnieszka Ciarka[3] and Zbigniew Gaciong[1]

Carotid chemoreceptors provoke an increase in muscle sympathetic nerve activation (MSNA) in response to hypoxia; they are also tonically active during normoxic breathing. The contribution of peripheral chemoreceptors to sympathetic activation in hypertension is incompletely understood. The aim of our study was to investigate the effect of chemoreceptor deactivation on sympathetic activity in untreated patients with hypertension. A total of 12 untreated hypertensive males and 11 male controls participated in this randomized, crossover, placebo-controlled study. MSNA, systolic blood pressure(BP), diastolic BP, heart rate (HR), electrocardiogram, hemoglobin oxygen saturation (Sat%) and respiratory movements were measured during repeated 10-min periods of respiration with 100% oxygen or 21% oxygen in a blinded fashion. Compared with controls, hypertensives had higher resting MSNA (38 ± 10 *vs.* 29 ± 0.9 burst per min, $P<0.05$), systolic BP (150 ± 12 *vs.* 124 ± 10 mm Hg, $P< 0.001$) and diastolic BP (92 ± 10 *vs.* 77 ± 9 mm Hg, $P<0.005$). Breathing 100% oxygen caused significant decrease in MSNA in hypertensive patients (38 ± 10 *vs.* 26 ± 8 burst per min and 100 ± 0 *vs.* 90 ± 10 arbitrary units, $P<0.05$) and no change in controls (29 ± 9 *vs.* 27 ± 7 burst per min and 100 ± 0 *vs.* 96 ± 11 arbitrary units). BP, respiratory frequency and end tidal CO_2 did not change during chemoreceptor deactivation with hyperoxia. HR decreased and Sat% increased in both the study groups. These results confirm the role of tonic chemoreceptor drive in the development of sympathetic overactivity in hypertension.
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INTRODUCTION

Increased sympathetic activity is an important factor contributing to the development of essential hypertension.[1–5] The cause of autonomic dysregulation in essential hypertension has been extensively investigated, but remains incompletely understood. Animal and human studies report evidence of increased sympathetic activity secondary to chemoreceptor activation in systemic hypertension.[6–9] In an animal model of essential hypertension, chemoreflex activation in response to physiological stimuli was increased;[6] this was also observed in patients with borderline systemic hypertension.[7] In addition, patients with systemic hypertension have carotid body chemoreceptors enlargement,[8] and greater increases in blood pressure (BP) and ventilation in response to hypoxia.[9] Even subjects with a family history of hypertension have augmented chemoreceptor activation during normoxia.[10]

Peripheral arterial chemoreceptors have a significant physiological tonic activity in normoxia.[11] In healthy subjects, chemoreflex deactivation with 100% oxygen can cause a reduction in sympathetic activity measured by microneurographic methods.[12] Various studies document tonic chemoreflex activation contributing to resting muscle sympathetic nerve activation (MSNA) in pathological conditions where patients are either normoxic, such patients presenting sleep apnea investigated during wakefulness,[13] or hypoxemic as a result of chronic obstructive lung disease[14] or pulmonary arterial hypertension.[15] In hypertensive patients, studies show that tonic chemoreceptor activity is augmented and that deactivation of carotid body chemoreceptors may elicit reductions in BP, peripheral resistance and ventilation as compared with normotensive patients.[10,16]

Despite the prevailing evidence of chemoreceptor dysfunction in systemic arterial hypertension, the contribution of peripheral chemoreceptors to sympathetic activation in untreated patients with systemic hypertension has not been fully determined. We hypothesized that tonic chemoreflex activation might contribute to the increased sympathetic outflow in patients with untreated primary hypertension, and that chemoreflex deactivation with 100% oxygen would, therefore, cause a reduction in sympathetic nerve activity. We tested this

[1]Department of Internal Medicine, Hypertension and Vascular Diseases, Medical University of Warsaw, Warsaw, Poland; [2]Department of Biophysics and Physiology Medical University of Warsaw, Warsaw, Poland and [3]Department of Cardiovascular Diseases, Catholic University of Leuven, Leuven, Belgium
Correspondence: Dr M Siński, Department of Internal Medicine, Hypertension and Vascular Diseases, Medical University of Warsaw. Banacha 1a, 02-097 Warsaw, Poland.
E-mail: msinski@wum.edu.pl
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hypothesis in a randomized, double-blinded, placebo-controlled, crossover study.

METHODS

Subjects

A total of 12 hypertensive patients participated in the study (age 37.9 ± 10 years, men, body mass index 28.5 ± 3 kg m^{-2}). All patients underwent routine diagnostic evaluation for hypertension in our department's clinic. Patients with secondary forms of hypertension, including obstructive sleep apnea syndrome, were excluded from the study. None of study subjects were treated with hypertensive agents before the study visit. A total of 11 normotensive subjects (men, aged 36.4 ± 8 years, body mass index 27.0 ± 4 kg m^{-2}) served as controls. Subjects were diagnosed as normotensives based on the values of office BP recordings during routine diagnostic approach.

None of the study participants received any drugs within 2 weeks before measurements, and all participants were otherwise healthy. Three subjects in the hypertensive group and three controls were current smokers. They were asked not to smoke on the morning before the study.

The Ethical Committee of the Medical University of Warsaw accepted the study protocol. All participants provided informed consent.

Protocol and procedures

All measurements were taken in a quiet room after 30 min of supine rest. Arterial BP was measured by a digital photoplethysmograph device capable of providing accurate beat-to-beat systolic and diastolic values (Finapress, Ohmeda 2300, Monitoring Systems, Englewood, CO, USA). Oxygen saturation and end tidal CO_2 ($etCO_2$) were monitored through the study (CapnoCheck Plus, Smith Medical International Ltd., Watford, Herts, UK). Respiratory movements were recorded by PneumoTrace (ADInstruments Pty Ltd., Castel Hill, NSW, Australia). MSNA signals were obtained with the microneurographic technique (Nerve traffic analysis system, University of Iowa, Iowa City, IA, USA). Recording electrode was placed in the peroneal nerve at the popliteal fossa, posterior to the fibular head, and a reference electrode was placed subcutaneously 2–3 cm from the recording electrode. The nerve signals were amplified (gain 70 000–160 000), band-pass filtered (700–2000 Hz), full-wave rectified and integrated with a resistance–capacitance circuit (time constant 0.1 s). Criteria for adequate MSNA recording were: pulse synchrony; facilitation during the hypotensive phase of the Valsalva maneuver; suppression during the hypertensive overshoot after release and increase in the response to breath holding.[17]

All patients underwent baseline recordings at 10 min before the placement of a non-rebreathable mask. After that period they were randomly allocated to breathe either 100% oxygen or air containing 21% oxygen for 10 min through the mask. This was followed by a 10-min recovery period, and then again breathing either 100% oxygen or air containing 21% oxygen for 10 min. Flow rate in the non-rebreathable mask was maintained constant throughout the study. Three patients in control group and one of hypertensive patients had missed $etCO_2$ recordings.

Analyses

Measurements were averaged during the last 3 min of the baseline period before non-rebreathable mask placement and during the last 3 min of the 10-min intervention periods. Sympathetic bursts were carefully identified by voltage neurogram inspection by a single trained observer, blinded to subject and intervention. Sympathetic activity was expressed as burst frequency per minute and integrated MSNA. Integrated MSNA was calculated in the following way: each burst amplitude was determined and sympathetic activity was expressed as burst per minute multiplied by mean burst amplitude (arbitrary units). Burst frequency permits comparison of sympathetic nerve activity between different subjects (hypertensive patients *vs.* normotensive subjects), whereas both burst frequency and amplitude were used to assess the effects of hyperoxia on sympathetic activity in individuals.

Comparison between baseline values in hypertensive patients and normotensive subjects was performed by unpaired *t* tests (two tailed). The effects of 100% oxygen were examined by repeated measurements of analysis of variance with time (before and after) and gas (21 or 100% oxygen) as the within factor and between factor, respectively. The *P* values for analysis within session were obtained *post hoc*. Primary variable was time *vs.* gas interaction. All data are expressed as means ± s.d. Statistical analysis was performed using Statistica 9.0 (Tulsa, Oklahoma, USA).

RESULTS

Table 1 reports the baseline characteristics of the study participants. BP and MSNA were higher in hypertensive patients and heart rate (HR), respiratory rate, and oxygen saturation did not differ between groups during baseline recording.

Deactivation of carotid body chemoreceptors with 100% oxygen in hypertensive patients caused the reduction of MSNA measured as burst frequency (38 ± 10 burst per min *vs.* 26 ± 8 burst per min; $P<0.001$) and as percent change of integrated MSNA (Table 2,

Table 2 Effect of chemoreceptor deactivation in hypertensive patients

	100% oxygen		*21% oxygen*		
Variable	*Before*	*During*	*Before*	*During*	P
MSNA, burst per min	38 ± 10	26 ± 8*	38 ± 9	37 ± 10	0.001
MSNA, au	100	90 ± 10*	100	97 ± 9	0.04
Heart rate	69 ± 10	62 ± 7**	68 ± 11	69 ± 10	0.001
Systolic blood pressure, mm Hg	150 ± 12	148 ± 10	148 ± 10	148 ± 13	0.80
Diastolic blood pressure, mm Hg	92 ± 10	91 ± 10	91 ± 11	89 ± 12	0.22
Arterial saturation, %	95 ± 1	99 ± 2*	95 ± 1	96 ± 2	0.01
Respiratory rate, breath per minute	16 ± 2	16 ± 2	15 ± 2	16 ± 3	0.54
$etCO_2$, mm Hg	36 ± 2	38 ± 3	36 ± 2	37 ± 2	0.48

Abbreviations: $etCO_2$, end tidal CO_2; MSNA, muscle sympathetic nerve activation.
*$P<0.01$ and **$P<0.0001$ as compared with baseline.

Table 1 Baseline clinical variables in hypertensive patients and normotensive controls

Variable	*Hypertensive patients* (n=*12*)	*Normotensive controls* (n=*11*)	P
Age, years	37.9 ± 10	36.4 ± 8	0.46
BMI, kg m^{-2}	28.5 ± 3	27.0 ± 4	0.38
Systolic blood pressure, mm Hg	150 ± 12	124 ± 10	<0.001
Diastolic blood pressure, mm Hg	92 ± 10	77 ± 9	0.001
Heart rate, b.p.m.	68 ± 8	67 ± 8	0.9
Arterial saturation, %	95 ± 1	96 ± 2	0.07
Respiratory rate, breath per minute	17 ± 2	15 ± 2	0.16
$etCO_2$, mm Hg	36 ± 2	37 ± 2	0.20
MSNA, burst per min	38 ± 10	29 ± 9	0.03

Abbreviations: BMI, body mass index; $etCO_2$, end tidal CO_2; MSNA, muscle sympathetic nerve activation.

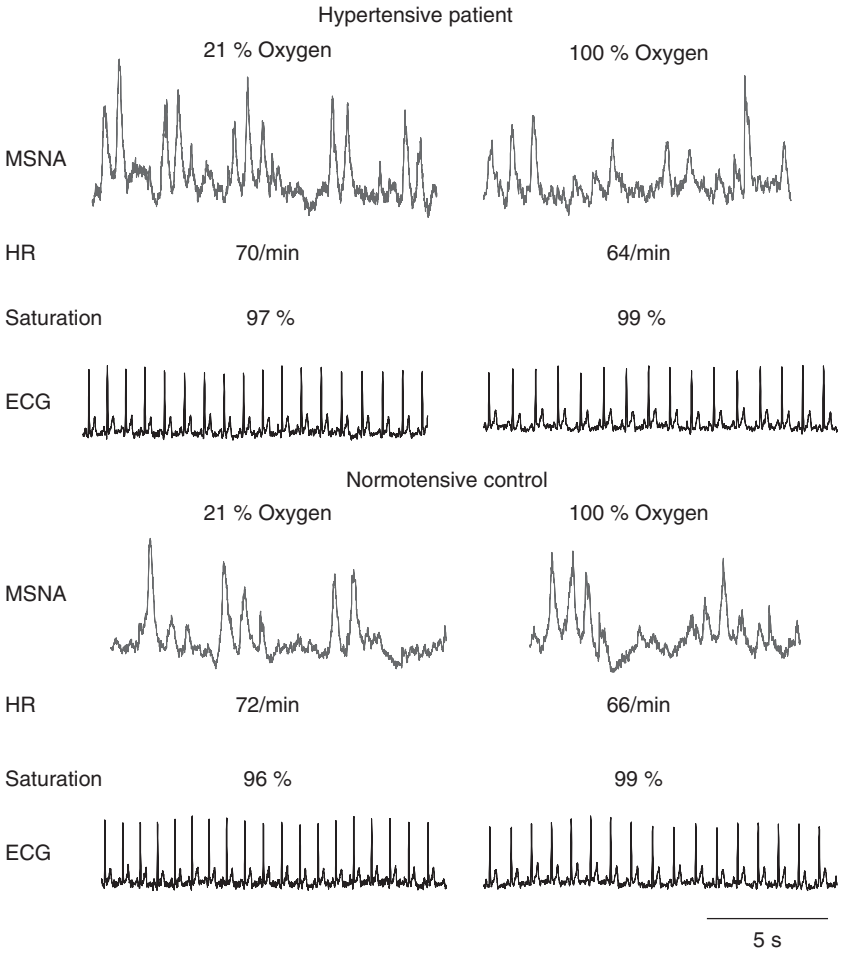

Figure 1 Recordings of MSNA, electrocardiogram (ECG), HR and oxygen saturation in hypertensive patients and normotensive controls before and after chemoreceptor deactivation.

Table 3 Effect of chemoreceptor deactivation in normotensive controls

	100% oxygen		*21% oxygen*		
Variable	*Before*	*During*	*Before*	*During*	P
MSNA, burst per min	29±9	27±7	29±8	28±8	0.06
MSNA, au	100	97±10	100	96±10	0.91
Heart rate, b.p.m.	69±7	64±8*	69±8	68±8	0.04
Systolic blood pressure, mm Hg	124±11	124±13	123±11	125±10	0.39
Diastolic blood pressure, mm Hg	77±9	78±9	77±8	79±12	0.72
Arterial saturation, %	96±1	99±1**	96±2	96±1	<0.001
Respiratory rate, breath per minute	15±2	13±2	15±2	14±2	0.08
$etCO_2$, mm Hg	37±2	36±2	37±2	37±2	0.65

Abbreviations: $etCO_2$, end tidal CO_2; MSNA, muscle sympathetic nerve activation.
*$P<0.05$ and **$P<0.0001$ as compared with baseline.

Figure 1). In contrast, 21% oxygen did not significantly affect MSNA values when measured as burst per min or by percent change from baseline (Table 3). In normotensive controls, 100% oxygen administration did not change MSNA values measured as burst frequency (29±9 burst per min *vs.* 27±8 burst per min; NS) or as percent change of integrated MSNA (Table 3, Figure 1).

The application of 100% oxygen did not affect systolic BP (150±12 mm Hg *vs.* 148±10 mm Hg, *P*=NS; 124±11 mm Hg *vs.* 124±12 mm Hg, *P*=NS) or diastolic BP (91±10 mm Hg *vs.* 91±11 mm Hg, *P*=NS; 77±9 mm Hg *vs.* 78±9 mm Hg, *P*=NS) in hypertensive patients or controls, respectively. Deactivation of chemoreflex with 100% oxygen caused significant reduction in HR in both groups; this effect was not observed during room-air breathing (Tables 2 and 3). In hypertensive and normotensive subjects, breathing 100% oxygen increased blood oxygen saturation, but did not affect respiratory rate and $etCO_2$ (Tables 2 and 3).

DISCUSSION

In this study we first demonstrate that in untreated patients with systemic arterial hypertension, activation of peripheral chemoreceptors may contribute to increased sympathetic activity. Second, our study reveals that peripheral chemoreceptor deactivation normalizes sympathetic activity in systemic hypertensive patients. Finally, normalization of MSNA during hyperoxic breathing is accompanied by a decreased HR, but has no effect on arterial BP.

To our knowledge, this is the first study to show that tonic activation of chemoreflexes might be responsible for the sympathetic overdrive in untreated hypertensive patients. Only one study till now has reported that the deactivation of carotid body chemoreceptors may decrease sympathetic activation in systemic hypertension.[18]

However, in this study patients were of an advanced age and on antihypertensive medication, which may influence sympathetic activity. In the recent study by Binggeli *et al.*,[19] the authors used hyperoxic stimuli in hypertensive subjects with and without periodic breathing, and did not find a significant reduction of MSNA in the group without periodic breathing. However, this study was not designed to test our hypothesis, was not placebo-controlled and was not a cross-over design with inclusion of control normotensive patients. Another study[16] found that hyperoxia may influence circulatory parameters in hypertensive subjects, but no direct assessment of sympathetic activation was performed.

Our results confirm that MSNA is significantly higher in hypertensive patients than in normotensive individuals.[3,4,7] One study reported no increase in MSNA in hypertensive patients,[18] but the population included subjects of advanced age being treated with antihypertensive medications, which could affect baseline MSNA levels.[20]

Another important observation of the present study is that acute hyperoxia-normalized sympathetic activity in hypertensive patients reaching the values observed in control subjects. This fact seems to confirm the hypothesis that tonic chemoreflex drive may be responsible, at least in part, for sympathetic overactivity in hypertension. In our study there was no MSNA reduction in normotensive controls after hyperoxic stimuli. Data from previous studies are not consistent across studies. In two studies,[12,13] hyperoxia lowered MSNA in control individuals, but not in the other two.[18,21] The reason for such a discrepancy may be related to control subject selection for the certain study protocol.

We did not observe any changes in BP after hyperoxia in either hypertensive patients or normotensive controls. Data from previous investigations on the effects of hyperoxia on circulatory hemodynamics are inconsistent. Although some studies did not find any effects of hyperoxia on BP,[18,12] others found a decrease of BP after hyperoxia in heart transplant recipients,[18] chronic renal failure,[21] sleep apnea[12] and hypertension.[16] The reason for such discrepancy remains unknown. One possible explanation is that brief episodes of hyperoxia may increase central aortic pressure with no effect on brachial pressure, as we demonstrated in a group of young patients with uncomplicated hypertension.[22] It has been demonstrated that hyperoxia may influence systemic vascular resistance, stroke volume and BP.[23,24] Thus, the lack of blood-pressure decrease during chemoreflex deactivation can be explained by local vasoconstricting effect of hyperoxia that could offset the sympathoinhibitory effect of chemoreceptor deactivation. To clarify the influence of carotid body deactivation on the circulatory parameters in hypertensive patients, a more detailed hemodynamic approach including cardiac output measurement would need to be applied.

During the exposure to hyperoxia, HR decreased in both the studied groups. As stimulation of carotid body chemoreceptors leads to an increased HR both in experimental animals and humans,[6,7] their deactivation by hyperoxia is the most plausible mechanism of the observed HR response in the present study. Our results are in agreement with previous observations, which showed a decrease in HR during hyperoxia in healthy individuals and in patients with obstructive sleep apnea.[12,13] However, this effect was not consistently observed in all studies. In subjects with chronic renal failure treated with hemodialysis, there was a decrease in HR observed only in the patient population, but not in healthy controls.[21]

Potential limitations of our study include a limited age range of study participants (from 29 to 52 years old) and the fact that only males were included. We are unable to predict whether we could extrapolate these results to younger or older patients with systemic hypertension. However, it is known that in younger and older healthy individuals, response to carotid body stimulation is similar[25] with a smaller percentage increase in MSNA from elevated baseline levels in older subjects. One study[25] reported no difference in MSNA changes between younger and older subjects after deactivation of chemoreceptors with hyperoxic stimuli.

We know there is a gender difference in sympathetic activation, both in normotensive and hypertensive individuals,[26] with trends towards lower MSNA in females. One can speculate that the response to carotid body deactivation may be different between genders, but to our knowledge there is no data available regarding a different response to hyperoxic stimuli between males and females.

Hyperoxia is a widely used noninvasive procedure to inhibit carotid body activity. However, effects of hyperoxia may not be exclusively the result of the carotid body inhibition. The circulatory effects of hyperoxia were described in healthy subjects and patients with heart failure.[23,24] Long periods of breathing 100% oxygen increased systemic resistance, decreased stroke volume and impaired left ventricular relaxation. It has been shown in the animal model[27] that shorter periods of hyperoxia inhibit ventilatory and circulatory chemoreflex response. This effect was abolished after carotid body denervation. Studies in humans also show that 100% oxygen stimulus inhibits both ventilatory and sympathetic chemoreflex response.[12,13,18,21,28] It is then wise to consider the reduction of MSNA observed in our study as the effect of carotid body inhibition by hyperoxia, but we cannot exclude the role of the local vascular effects. The interpretation of circulatory parameters during hyperoxia in hypertensive subjects need further study.

In the present study etCO2 values were not affected by hyperoxia in hypertensive patients and control subjects, which is in agreement with previous studies.[13,18,28]

The advantage of our study is that it was performed in untreated essential hypertensive subjects, thus reducing the potential effect of medication on MSNA. Furthermore, the study was randomized, subject and observer blinded to gas mixture. The study groups were also matched for age and BMI, and other factors that could impact study results.

CONCLUSIONS

In conclusion, the results of our study show that the tonic chemoreceptor drive may have a role in the development of sympathetic overactivity in untreated hypertension. Our study showed that the deactivation of tonic chemoreceptor activity reduces sympathetic drive. We know that sympathetic overdrive contributes to organ damage in hypertension. Interventions that reduce sympathetic drive may potentially decrease cardiovascular complications. There are no therapeutic interventions that could influence tonic chemoreceptor drive up to now. It is reasonable to speculate that such intervention to reduce sympathetic overactivity could influence end organ damage. Taking into consideration the promising results of catheter-based renal sympathetic denervation in the treatment of resistant hypertension[29] and newly developed strategies affecting the baroreflex,[30] such speculations considering chemoreflex interventions are not unjustified.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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