

## Acute Cardiovascular and Sympathetic Effects of Nicotine Replacement Therapy

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**Abstract**—Sympathetic overactivity is implicated in the increased cardiovascular risk of cigarette smokers. Excitatory nicotinic receptors are present on peripheral chemoreceptor cells. Chemoreceptors located in the carotid and aortic bodies increase ventilation (Ve), blood pressure (BP), heart rate (HR), and sympathetic nerve activity to muscle circulation (MSNA) in response to hypoxia. We tested the hypothesis that nicotine replacement therapy (NRT) increases MSNA and chemoreceptor sensitivity to hypoxia. Sixteen young healthy smokers were included in the study (8 women). After a randomized and blinded sublingual administration of a 4-mg tablet of nicotine or placebo, we measured minute Ve, HR, mean BP, and MSNA during normoxia and 5 minutes of isocapnic hypoxia. Maximal voluntary end-expiratory apneas were performed at baseline and at the end of the fifth minute of hypoxia. Nicotine increased HR by  $7 \pm 3$  bpm, mean BP by  $5 \pm 2$  mm Hg, and MSNA by  $4 \pm 1$  bursts/min, whereas subjects breathed room air (all  $P < 0.05$ ). During hypoxia, nicotine also raised HR by  $8 \pm 2$  bpm, mean BP by  $2 \pm 1$  mm Hg, and MSNA by  $7 \pm 2$  bursts/min (all  $P < 0.05$ ). Nicotine increased MSNA during the apneas performed in normoxia and hypoxia ( $P < 0.05$ ). Nicotine also raised the product of systolic BP and HR, a marker of cardiac oxygen consumption, during normoxia, hypoxia, and the apneas ( $P < 0.05$ ). Ve, apnea duration, and O<sub>2</sub> saturation during hypoxia and the apneas remained unaffected. In conclusion, sympathoexcitatory effects of NRT are not because of an increased chemoreflex sensitivity to hypoxia. NRT increases myocardial oxygen consumption in periods of reduced oxygen availability. (*Hypertension*. 2006;47:1162-1167.)

**Key Words:** sympathetic nervous system ■ chemoreceptors ■ smoking

Tobacco smoking is a well-established cardiovascular risk factor worldwide.<sup>1,2</sup> Sympathetic overactivity seems to be a key factor implicated in the excess risk of cardiovascular events with cigarette smoking.<sup>3</sup> Cigarette smoking increases efferent sympathetic nerve traffic acutely,<sup>4,5</sup> as well as norepinephrine and epinephrine release.<sup>6</sup> This catecholamine release increases myocardial work and oxygen consumption through an increase in blood pressure (BP), heart rate (HR), and myocardial contractility.<sup>3</sup> In addition, tobacco induces coronary vasoconstriction and increases the risk of tachyarrhythmias.<sup>1,7</sup>

The adverse effects of cigarette smoking are related to the mixture of chemicals, including nicotine.<sup>8,9</sup> The role of nicotine itself on peripheral sympathetic activity, in the absence of the other components contained in tobacco smoke, is not clear. Characterization of the sympathetic effects of nicotine, per se, is important because it is estimated that millions of smokers use nicotine replacement therapy (NRT) each year to aid tobacco cessation.<sup>10–12</sup>

In this study, we sought to determine whether nicotine increases peripheral chemoreceptor sensitivity. The peripheral chemoreceptors are located near the carotid arteries and the aorta. They are the dominant reflex control mechanism regulat-

ing the ventilatory and neural circulatory control response to hypoxia.<sup>13,14</sup> These receptors have powerful stimulatory effects on ventilation (Ve) and on sympathetic activity.<sup>13–15</sup> Nicotine-induced catecholamine release is probably mediated through nicotinic receptor stimulation in neural tissues.<sup>16,17</sup> Nicotine could increase chemoreceptor activity through excitatory nicotinic receptors present on the glomus cells.<sup>18–20</sup> This is of potential importance, because smoking is frequently accompanied by hypoxemia as a result of carboxyhemoglobinemia and lung disease. The effects of nicotine on chemoreflex sensitivity in humans are unknown. Some, but not all,<sup>21–23</sup> animal studies have been able to show that nicotine increases peripheral chemoreceptor sensitivity to hypoxia.<sup>24–26</sup> This is likely because of the fact that the effects of exogenous nicotine on chemoreceptors depend on the predominance of nicotinic and muscarinic receptors on the carotid bodies.<sup>27</sup> This ratio differs among species, and animal studies on the effects of nicotine on chemoreceptor control are, therefore, difficult to extrapolate to humans. We decided to test the hypothesis that nicotine increases peripheral sympathetic nerve activity to muscle circulation [muscle sympathetic nerve activity (MSNA)] in humans and that it enhances peripheral chemoreflex sensitivity to hypoxia.

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## Methods

The study was approved by the Ethical Committee of Erasme Hospital, Brussels. Each subject signed an informed consent before inclusion in the study.

### Subjects

Sixteen healthy smokers were included in the study (8 women;  $26 \pm 7$  years of age; body mass index,  $21 \pm 3$  kg/m<sup>2</sup>). All of the subjects were regular cigarette smokers ( $18 \pm 8$  cigarettes per day for  $10 \pm 7$  years). None of the subjects were taking any medication.

### Measurements

Breathing was performed via a low-resistance mouthpiece with the use of a nose clip to ensure exclusive mouth breathing. Minute Ve (pneumotachometer, Medical Electronic Equipment) and end-tidal CO<sub>2</sub> (Normcap 200 Capnometer, Datex-Ohmeda) were measured every minute in all of the subjects. Respiratory frequency was monitored with a respiratory monitoring band placed around the subject's thorax (Pletysmograph, Study Data Systems).

Multiunit recordings of postganglionic MSNA were obtained in 11 subjects. In 5 of the subjects, we could not find an adequate MSNA recording site during both experimental sessions (placebo and nicotine). MSNA recording was obtained with a unipolar tungsten electrode inserted selectively into a nerve fascicle of the right or left peroneal nerve, posterior to the fibular head, and a reference electrode was placed subcutaneously 2 to 3 cm from the recording electrode.<sup>4,15</sup> Neural activity was fed to a band pass filter (band width, 0.7 to 2.0 Hz) and a resistance-capacitance integrating network (time constant, 0.1 s) to obtain a mean voltage neurogram. Bursts were identified by a single trained observer blinded to the recording session (B.N.). MSNA was calculated as bursts per minute after careful inspection of the mean voltage neurogram. Acceptable recordings met the following 4 criteria: (1) spontaneous bursts of neural discharge synchronous with HR, (2) no response to arousal stimuli or skin stroking, (3) an increase in nerve burst frequency with apnea, and (4) a signal:noise ratio of 3:1. MSNA recordings were acquired and analyzed on a MacLab 8/s data acquisition system (AD Instruments). The amplitude of each burst was determined, and sympathetic activity was calculated as bursts per minute multiplied by mean burst amplitude expressed in arbitrary units. The absolute amplitude of MSNA depends on voltage amplification, which varies from 1 subject to another but is kept constant during every experiment. Modifications in MSNA during hypoxia and apnea were, therefore, calculated as percentages of changes from values recorded during normal Ve.

All of the subjects also underwent continuous recording of HR (Siemens Medical, ECG Monitoring) and oxygen saturation determinations (Nellcor N-100 C pulse oximeter). Systolic, mean, and diastolic oscillometric BP measurements were performed every 2 minutes with a Physiocontrol Colin BP-880 sphygmomanometer (Colin press Mate, Colin Corp). We also recorded finger BP (Portapres, Finapres Medical System) continuously in 7 subjects to determine whether nicotine increased BP during apneas. It was decided not to record finger BP in 9 of the subjects to avoid the modest discomfort of prolonged finger cuff inflation.

### Protocol and Interventions

All of the subjects were asked to stop smoking 14 hours before the procedure. Each subject was studied twice in random order: once after sublingual administration of a 4-mg tablet of nicotine (Nicorette microtab, nicotine betadex, Pfizer) and once after administration of a placebo tablet. Smoking abstinence was carefully assessed in each subject before every study. Subjects and investigators were unaware of the composition of the tablets.

To confirm the compliance of subjects to the nonsmoking, we determined plasma cotinine (Immulate/DPC immunoassay system) on blood samples taken at the beginning of the study. As a result, in all of the subjects, cotinine levels before study were  $<500$  ng/mL ( $267 \pm 57$  ng/mL), corresponding with those of an abstinent smoker.<sup>28</sup>

Subjects were studied in the supine position under carefully standardized conditions. Measurements were performed 40 minutes after administration of the tablet and lasted 20 minutes, when the plasma concentration of nicotine remained stable.<sup>9,11</sup>

The protocol used to test peripheral chemoreflex sensitivity was identical to previous studies.<sup>15</sup> Subjects underwent a 5-minute baseline period of room air breathing once stable baseline Ve had been reached, and this was followed by 5 minutes of isocapnic hypoxia (10% O<sub>2</sub> in 90% N<sub>2</sub>, with CO<sub>2</sub> titrated to maintain isocapnia). Maximal voluntary end-expiratory apneas were performed at baseline and at the end of the fifth minute of hypoxia to eliminate the inhibitory influence of Ve on sympathetic nerve traffic.

### Data Analysis

All of the recordings were analyzed in a blinded fashion. Sympathetic bursts were identified by careful inspection of the mean voltage neurogram during 5 minutes of baseline breathing, during the 5 minutes of hypoxia, and during the apneas. Burst frequency allowed comparison of sympathetic activity recorded during the different experimental sessions (placebo versus nicotine); this is because MSNA amplitude depends on signal amplification, which varies from one experimental session to another but is kept constant within an experimental session. The amplitude of each burst was determined, and sympathetic activity was calculated as bursts per minute multiplied by mean burst amplitude and was expressed as a percentage increase from baseline values within a given experimental session. Burst frequency and amplitude per minute during apneas were obtained by dividing the burst count and amplitude during the apnea by the apnea duration in seconds and then by multiplying this value by 60. This allowed determination of the effects of hypoxia and apneas on sympathetic traffic in the presence of placebo or nicotine. The increase in HR, BP, and Ve was expressed in absolute unit changes from baseline values. In addition, changes in the rate-pressure product (systolic BP multiplied by HR) provided an estimate of the effects of nicotine on myocardial oxygen consumption.<sup>29</sup>

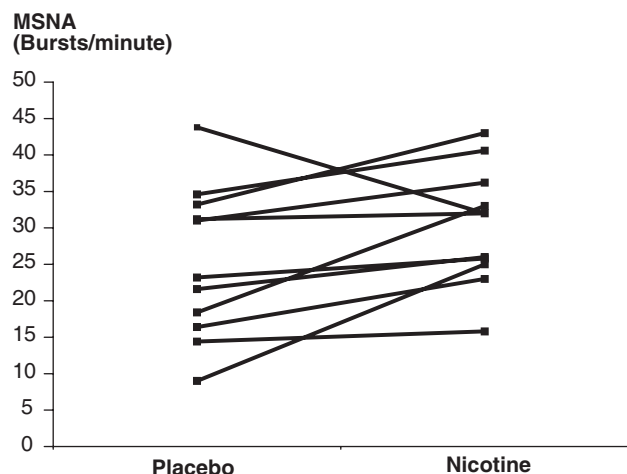
### Statistical Analysis

All of the values were averaged over the entire 5 minutes of baseline and hypoxia. These averaged values were used for the statistical analysis. Results are expressed as mean  $\pm$  SEM. Comparisons were performed using a repeated-measures ANOVA (Statview 5.0, SAS). The ANOVA analysis was followed by post hoc comparisons using

**TABLE 1. Effects of Nicotine on Baseline BP, HR, MSNA, and Ve**

| Parameters                                    | Placebo        | Nicotine       | P     |
|-----------------------------------------------|----------------|----------------|-------|
| Systolic BP, mm Hg                            | 118 $\pm$ 3    | 123 $\pm$ 2    | <0.05 |
| Mean BP, mm Hg                                | 82 $\pm$ 2     | 87 $\pm$ 1     | <0.05 |
| Diastolic BP, mm Hg                           | 63 $\pm$ 1     | 69 $\pm$ 2     | <0.01 |
| HR, bpm                                       | 64 $\pm$ 2     | 71 $\pm$ 3     | <0.05 |
| Rate-pressure product, mm Hg $\times$ bpm     | 7546 $\pm$ 366 | 8686 $\pm$ 308 | <0.05 |
| O <sub>2</sub> saturation, %                  | 97.1 $\pm$ 0.3 | 98.2 $\pm$ 0.3 | <0.01 |
| MSNA, bursts/min                              | 28 $\pm$ 3     | 32 $\pm$ 3     | <0.05 |
| Ve, L/min                                     | 6.4 $\pm$ 0.2  | 6.5 $\pm$ 0.2  | NS    |
| Respiratory frequency, breath/min             | 12.1 $\pm$ 0.7 | 12.0 $\pm$ 0.9 | NS    |
| Apnea duration, s                             | 19 $\pm$ 2     | 23 $\pm$ 4     | NS    |
| Minimal O <sub>2</sub> saturation in apnea, % | 95 $\pm$ 1     | 95 $\pm$ 2     | NS    |
| MSNA during apnea, bursts/min                 | 48 $\pm$ 4     | 56 $\pm$ 5     | <0.05 |
| Amplitude MSNA during apnea, % baseline       | 250 $\pm$ 46   | 231 $\pm$ 25   | NS    |

NS indicates nonsignificant; n=16 except for MSNA where n=11.



**Figure 1.** Individual changes in MSNA burst frequency with nicotine.

Fisher comparisons. Correlations were made with a regression analysis. A  $P$  value  $<0.05$  was considered significant.

## Results

### Effects of Nicotine on Baseline $\dot{V}_E$ , BP, HR, and MSNA

Systolic, mean, and diastolic BP; HR; the rate-pressure product; and MSNA were higher after nicotine than after placebo (Table 1, Figure 1, and Figure 2). Nicotine also increased HR ( $79 \pm 6$  versus  $72 \pm 4$  bpm;  $P < 0.05$ ), the rate-pressure product ( $12\,315 \pm 1139$  versus  $8779 \pm 1052$  mm Hg  $\times$  bpm;  $P < 0.001$ ), and MSNA ( $56 \pm 5$  versus  $48 \pm 4$  bursts/min;  $P < 0.05$ ) during the apnea performed in normoxic conditions. Nicotine had no effect on  $\dot{V}_E$ , on the duration of the apneas, or on the minimal oxygen saturation at the end of apneas. There was no difference in tidal volume with nicotine ( $571 \pm 36$  mL) in comparison with placebo ( $561 \pm 44$  mL;  $P = 0.8$ ). Breathing

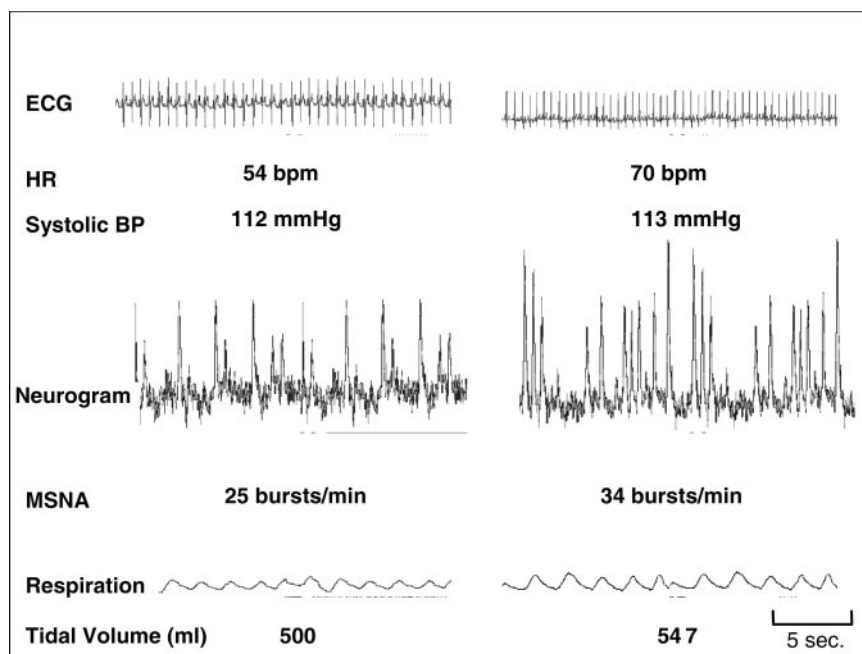
frequency was  $12.0 \pm 0.9$  breaths/min with nicotine and  $12.1 \pm 0.7$  breaths/min with placebo ( $P = 0.8$ ). End-tidal  $\text{CO}_2$  was  $38.0 \pm 0.6$  mm Hg under nicotine and  $38.0 \pm 0.7$  mm Hg under placebo ( $P > 0.9$ ). The duration of tobacco addiction ( $10 \pm 2$  years) and the number of cigarettes per day ( $18 \pm 2$ ) did not correlate with the ventilatory, hemodynamic, and sympathetic responses to nicotine ( $r < 0.3$ ;  $P > 0.3$ ). Changes in MSNA tended to be less marked in subjects with higher baseline burst frequency ( $r = -0.65$ ;  $P = 0.04$ ). There were no differences in sympathetic, ventilatory, or hemodynamic responses to nicotine between men and women ( $P > 0.1$ ).

### Effects of Nicotine on $\dot{V}_E$ , BP, HR, and MSNA During Isocapnic Hypoxia

Systolic and mean BP, HR, and the rate-pressure product were higher during hypoxia after nicotine than after placebo (Table 2 and Figure 3). Sympathetic activation induced by nicotine during normoxia persisted during hypoxia and during the apnea in hypoxia. HR was higher during the apnea in hypoxia after nicotine than after placebo ( $99 \pm 6$  versus  $87 \pm 6$  bpm;  $P < 0.01$ ), as was the rate-pressure product ( $14\,709 \pm 1900$  versus  $10\,839 \pm 1173$  mm Hg  $\times$  bpm;  $P < 0.05$ ). Changes in tidal volume after 5 minutes of hypoxia were comparable with nicotine ( $+191 \pm 45$  mL) and placebo ( $+179 \pm 39$  mL;  $P = 0.8$ ). End-tidal  $\text{CO}_2$  did not differ at the fifth minute of hypoxia (nicotine,  $37.6 \pm 0.7$  mm Hg; placebo,  $37.3 \pm 0.6$  mm Hg;  $P = 0.4$ ). There was no effect of nicotine on  $\dot{V}_E$ , respiratory frequency, the duration of the apneas, or the minimal oxygen saturation at the end of apneas.

## Discussion

This study assessed the acute effects of NRT on MSNA and chemoreflex sensitivity to hypoxia in healthy cigarette smokers. The main new findings of our study are that: (1) nicotine, per se, increases peripheral sympathetic nerve traffic; (2) this peripheral sympathetic overactivity persists during marked



**Figure 2.** Recordings of ECG, neurogram, and respiration in a subject after taking a placebo tablet and after a nicotine tablet. HR and MSNA were higher after nicotine than after placebo.

**TABLE 2. Effects of Nicotine on BP, HR, MSNA, and Ve During 5 Minutes of Isocapnic Hypoxia**

| Parameters                                       | Placebo  | Nicotine   | P      |
|--------------------------------------------------|----------|------------|--------|
| Systolic BP, mm Hg                               | 121±2    | 126±2      | <0.05  |
| Mean BP, mm Hg                                   | 87±2     | 89±1       | <0.05  |
| Diastolic BP, mm Hg                              | 67±2     | 69±2       | NS     |
| HR, bpm                                          | 80±3     | 88±3       | <0.01  |
| Rate-pressure product, mm Hg×bpm                 | 9651±361 | 11 011±410 | <0.001 |
| O <sub>2</sub> saturation, %                     | 85.2±0.8 | 85.6±0.7   | NS     |
| MSNA, bursts/min                                 | 25±3     | 32±3       | <0.05  |
| Amplitude MSNA, % baseline                       | 108±8    | 114±13     | NS     |
| Ve, L/min                                        | 8.5±0.4  | 8.5±0.3    | NS     |
| Respiratory frequency, breath/min                | 12.9±0.9 | 13.5±0.9   | NS     |
| Apnea duration, s                                | 12±2     | 12±2       | NS     |
| Minimal O <sub>2</sub> saturation in apnea, %    | 78.0±1.4 | 78.9±2.1   | NS     |
| MSNA during apnea, bursts/min                    | 69±5     | 87±11      | <0.05  |
| Amplitude MSNA during apnea, % fifth min hypoxia | 430±99   | 450±107    | NS     |

NS indicates nonsignificant; n=16 except for MSNA where n=11.

chemoreflex activation and apnea; and (3) these effects are not mediated by increased chemoreceptor sensitivity.

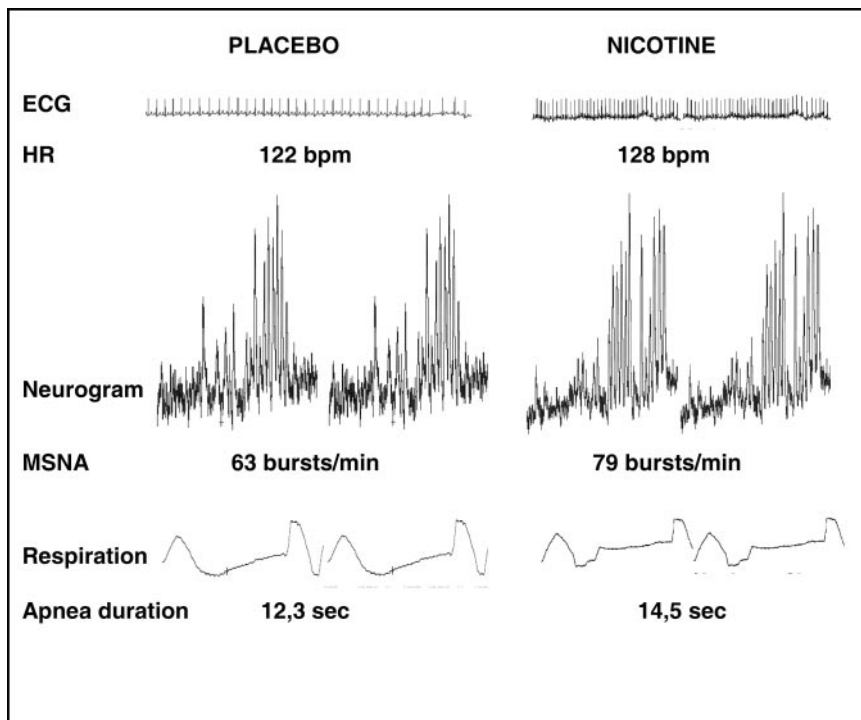
### Nicotine Effects During Normoxia

Sympathetic overactivity is one of the mechanisms implicated in the higher cardiovascular risk in cigarette smokers.<sup>1,4,6,7,9</sup> The adverse effects of sympathetic overactivity are,

mainly, an increase in myocardial work, a decrease in ventricular fibrillation threshold, an acceleration of atrioventricular node conduction, and an induction of coronary vasoconstriction.<sup>30–32</sup> All of these elements contribute to the increased incidence of acute cardiovascular events in cigarette smokers. A considerable decrease in the risk of cardiovascular events occurs immediately after the discontinuation of cigarette smoking.<sup>33</sup> Alterations in BP, HR, and autonomic nervous function are thought to be at least in part responsible for this rapid decrease.<sup>34</sup>

We observed that nicotine induces acute increases in BP, HR, myocardial oxygen consumption, and sympathetic activity while subjects were breathing room air. In a previous study,<sup>4</sup> smoking the first cigarette was also associated with a marked increase in both mean BP and HR but induced a baroreflex-mediated decrease in MSNA. However, smoking increases mean BP ( $\pm 10$  mm Hg)<sup>4</sup> more than nicotine ( $\pm 5$  mm Hg in our study). When the BP increase in response to smoking was blunted by nitroprusside infusion, there was an increase in MSNA. Thus, both cigarette smoking and nicotine increase sympathetic activity when mean BP rises only by 5 mm Hg.

The exact mechanisms implicated in the increased sympathetic outflow induced by nicotine are unclear. Nicotine binds to nicotinic receptors located in autonomic ganglia, the adrenal medulla, the neuromuscular junction, and the brain.<sup>9,16,17</sup> Sympathetic stimulation could be because of a direct effect of nicotine on the brain and autonomic ganglia. It could also result from catecholamine release from the adrenal glands or from direct release or enhanced release from vascular nerve endings.<sup>16,17,35</sup> The peripheral chemoreceptors regulate resting sympathetic nerve traffic.<sup>13–15</sup> Nicotine did not, however, affect chemoreflex sensitivity, as evidenced by similar minute Ve, apnea duration, and oxygen saturation after nicotine and



**Figure 3.** Recordings of ECG, neurogram, and respiration during apnea in hypoxia in a subject after taking a placebo tablet and after a nicotine tablet. The oxygen saturation shown in the figure is the lowest saturation achieved at the end of the apnea (low O<sub>2</sub> sat.). HR and MSNA were higher after nicotine than after placebo.



placebo in normoxia. Thus, chemoreflex excitation is unlikely to play an important role in the sympathoexcitatory and cardiovascular effects of nicotine.

### Nicotine Effects During Hypoxia

Our study provides the first direct evidence that NRT increases efferent sympathetic nerve traffic in healthy cigarette smokers, and it also reveals that this effect persists during marked chemoreflex activation and apnea. In many circumstances, increased baseline sympathetic activity reduces MSNA reactivity to acute stress, because the saturated system has no further reserve to increase sympathetic nerve firing.<sup>36,37</sup> This contrasts with our observation that the nicotine-induced sympathoexcitation and hypertensive and tachycardic effects persisted even during the intense sympathetic nerve traffic activation elicited by hypoxia and apneas. This highlights the importance of the sympathetic facilitating effects of nicotine in habitual smokers.

Our study reveals that increases in myocardial oxygen consumption with nicotine persist during acute reductions in oxygen availability. This observation has potentially important implications, because cigarette smokers are often hypoxemic as a result of increased carbon monoxide concentrations and lung disease. Smoking is associated with a decrease in nocturnal oxygen saturation.<sup>38</sup> Whether smoking increases the incidence of sleep apnea is debated.<sup>39</sup> However, both conditions are so prevalent that it is likely that many smokers experience repeated episodes of hypoxemia in the presence of elevated nicotine concentrations. This could precipitate cardiac events and sudden death at night.<sup>40</sup>

The sympathetic effects of nicotine are also of primary concern with respect to the clinical risks of NRT. The cardiovascular risk of NRT has not been fully elucidated. There have been anecdotal reports of acute myocardial infarction and stroke in patients taking NRT. However, there is no evidence that NRT increases cardiovascular risk as compared with placebo in smokers with cardiovascular disease.<sup>8–11</sup> NRT encourages smoking cessation. Moreover, it does not increase carbon monoxide concentrations and does not induce a hypercoagulable state, which contribute to the adverse cardiovascular effects of tobacco.<sup>8,9</sup> Nevertheless, whereas NRT is less risky than cigarette smoking, the risk associated with NRT, as compared with other substitution therapies, should not be underestimated in patients with limited coronary reserve and at risk of sudden hypoxic events.

### Nicotine and Chemoreflex Sensitivity to Hypoxia

Nicotine did not affect  $\dot{V}_E$  during hypoxia, the duration of the apneas, or the reductions in oxygen saturation. This suggests that nicotine does not increase peripheral chemoreflex sensitivity. We did not expect these results, because glomus chemoreceptor cells contain excitatory nicotinic receptors.<sup>18–20</sup> However, 2 elements have to be taken into consideration. First, nicotine increased BP in our subjects. This increase in BP, by itself, could decrease peripheral chemoreceptor sensitivity through a baroreflex-mediated mechanism.<sup>41</sup> Further studies are, therefore, needed to determine whether suppression of the BP effects of nicotine may not unmask some increased nicotine-associated chemosensitivity

to hypoxia. Second, chronic exposure to nicotine decreases the sensitivity of, or even completely inactivates, nicotinic receptors.<sup>42</sup> Observations of acute chemoreflex sensitization with nicotine in animal studies may, therefore, not apply to adult chronic cigarette smokers.<sup>21,23–25</sup>

### Perspectives

A study on the dose–response effects of nicotine on sympathetic activity and chemoreflex sensitivity, as well as a study evaluating the effects of nicotine in nonsmokers, are needed to determine whether the effects of nicotine on chemoreflex sensitivity are masked by a relative or complete inactivation of nicotinic receptors in habitual smokers. In conclusion, this study reveals that NRT exerts acute deleterious cardiovascular effects and sympathetic activation. These effects persist during marked chemoreflex activation and apnea.

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