Feedback effects of circulating norepinephrine on sympathetic outflow in healthy subjects

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Tulppo, Mikko P., Heikki V. Huikuri, Elli Tutungi, Derek S. Kimmerly, Adrian W. Gelb, Richard L. Hughson, Timo H. Mäkkiallo, and J. Kevin Shoemaker. Feedback effects of circulating norepinephrine on sympathetic outflow in healthy subjects. Am J Physiol Heart Circ Physiol 288:H710–H715, 2005. First published October 7, 2004; doi:10.1152/ajpheart.00540.2004.—The amplitude of low-frequency (LF) oscillations of heart rate (HR) usually reflects the magnitude of sympathetic activity, but during some conditions, e.g., physical exercise, high sympathetic activity results in a paradoxical decrease of LF oscillations of HR. We tested the hypothesis that this phenomenon may result from a feedback inhibition of sympathetic outflow caused by circulating norepinephrine (NE). A physiological dose of NE (100 ng·kg−1·min−1) was infused into eight healthy subjects, and infusion was continued after α-adrenergic blockade [with phenotolamine (Phe)]. Muscle sympathetic nervous activity (MSNA) from the peroneal nerve, LF (0.04–0.15 Hz) and high frequency (HF; 0.15–0.40 Hz) spectral components of HR variability, and systolic blood pressure variability were analyzed at baseline, during NE infusion, and during NE infusion after Phe administration. The NE infusion increased the mean blood pressure and decreased the average HR (P < 0.01 for both). MSNA (10 ± 2 vs. 2 ± 1 bursts/min, P < 0.01), LF oscillations of HR (43 ± 13 vs. 35 ± 13 normalized units, P < 0.05), and systolic blood pressure (3.1 ± 2.3 vs. 2.0 ± 1.1 mmHg2, P < 0.05) decreased significantly during the NE infusion. During the NE infusion after PHE, average HR and mean blood pressure returned to baseline levels. However, MSNA (4 ± 2 bursts/min), LF power of HR (33 ± 9 normalized units), and systolic blood pressure variability (1.7 ± 1.1 mmHg2) remained significantly (P < 0.05 for all) below baseline values. Baroreflex gain did not change significantly during the interventions. Elevated levels of circulating NE cause a feedback inhibition on sympathetic outflow in healthy subjects. These inhibitory effects do not seem to be mediated by pressor effects on the baroreflex loop but perhaps by a presynaptic autoregulatory feedback mechanism or some other mechanism that is not prevented by a nonselective α-adrenergic blockade.

METHODS

Subjects and study protocol. An intravenous catheter was placed into the right antecubital vein for drug administration. Physiological doses of NE (50 and 100 ng·kg−1·min−1, each dose 15 min) were infused (Perfusor Ed2, Braun Melsungen) into healthy volunteers (9 men and 2 women, mean age 26 ± 11 yr, all nonsmokers). The doses of NE were based on previous studies, which have shown these doses to result in plasma concentrations of NE equivalent to those under various physiological conditions in healthy subjects and in patients after acute myocardial infarction (2–4). The NE infusion (100 ng·kg−1·min−1) was continued after titrated doses of α-adrenergic blockade [by phenotolamine (Phe)]. Phe injections began with a 200-μg dose (maximum of 3 doses), which was increased to 400-, 600-, and 1,000-μg bolus injections (maximum load of 5 mg) until the baseline blood pressure had been reestablished. Muscle sympathetic nervous activity (MSNA) from the peroneal nerve and HR variability were analyzed at baseline (10 min), during NE infusion (last 10 min), and during NE infusion with Phe administration (10 min, starting when HR and blood pressure had returned to baseline). To determine whether Phe itself had some direct effects on measured variables, data collection was continued for 15 min after NE infusion had been terminated. Because of the differences in the half-lives of NE (~2 min) and Phe (~20 min), it was possible to analyze the possible effects of Phe only (from 5 to 10 min after NE termination) (10).

The subjects were not allowed to eat or drink coffee for 3 h before the tests. Vigorous exercise and alcohol were also forbidden for 48 h before the testing day. The subjects lay in the supine position in a quiet room for at least 15 min before data collection and became accustomed to breathing at a constant metronome-guided rate of 0.25 Hz during the tests. However, none subjects were adapted to breathing at a constant metronome-guided rate of 0.25 Hz during the tests.

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LOW-FREQUENCY (LF) oscillations of heart rate (HR) have been proposed to be under the control of sympathetic and vagal outflow. The normalized LF component of HR variability increases during most laboratory interventions that result in increased sympathetic outflow, including passive head-up tilt, moderate exercise, and nitroprusside infusion (15–18). Paradoxically, some physiological and pathological conditions known to increase sympathetic outflow have involved a marked reduction in the LF power spectral component and the LF-to high frequency (HF) ratio, for example, heavy physical exercise, passive head-up tilting preceding syncope, and severe heart failure (9, 31, 33).

The physiological background of the decreased LF spectra of R-R intervals during increased sympathetic outflow has not been fully elucidated. Resetting of baroreflex circulatory regulation has been proposed as one possible reason. Other speculated reasons are saturation of the LF oscillatory system during high sympathetic activity or a central effect of neurohumoral excitation, such as high levels of circulating catecholamines (33). The purpose of the present study was to test the latter hypothesis by examining the effects of circulating norepinephrine (NE) on autonomic regulation using physiological doses of intravenous NE infusion with and without α-adrenergic receptor blockade. We hypothesized that some other mechanism than that mediated by the baroreflex loop might be involved in the inhibitory effect of circulating NE on sympathetic outflow.
Hz for the duration of the experiments. Blood pressure was measured with an automatic oscillometric blood pressure recorder at every 3 min throughout the protocols (Dinamap, Criticon) and on a beat-to-beat basis by tonometry (Pilot, Colin Medical Instruments; San Antonio, TX).

The subjects with atrial or ventricular ectopic beats and those with any episodes of rhythm originating outside the sinus node (e.g., atrioventricular nodal rhythm) during the experiment were excluded (3 subjects). The protocol was approved by the ethics committee of the University of Western Ontario (London, Ontario, Canada), and all subjects gave written informed consent.

R-R interval and MSNA recordings. The R-R intervals were recorded with a Polar R-R recorder having a sampling frequency of 1,000 Hz (Polar Electro) (22). A continuous surface electrocardiogram was also monitored (model TEC-7100, Nihon Kohden) and recorded (Oxford Medilog 4500, Oxford Instruments) during the experiments to confirm the sinus origin of the beats. All R-R intervals were edited manually to exclude all premature beats and noise. The mean HR and the standard deviation of all R-R intervals (SDNN) were used as time-domain measures of HR variability. An autoregressive model was used to estimate the power spectrum densities of HR variability and quantified by measuring the area under two frequency bands: LF, from 0.04 to 0.15 Hz; and HF, from 0.15 to 0.4 Hz. The spectral component values are presented in absolute (ms²) and normalized units (nu), which were obtained by dividing the power of each component by total variance, from which the very LF component had been subtracted, and multiplying this value by 100 (16). MSNA was recorded from the peroneal nerve and analyzed as described previously (24).

Cross-spectral method. An index of baroreflex sensitivity (BRS), αLF, was calculated as the square root of the ratio between LF R-R interval and LF systolic pressure spectral powers when coherence between the signals was >0.5 (6, 19, 21). We similarly calculated the baroreflex transfer function in the HF band as αHF. NE infusion results in decreased coherence between systolic pressures and R-R intervals below 0.5, as described earlier (1). Therefore, BRS was calculated for only five subjects during the first NE dose and for three subjects during the second NE dose. BRS was calculated for seven subjects at baseline, during NE infusion with Phe, and during Phe only. A Valsalva test was also performed in four subjects to evaluate sympathetic reflex function at baseline, during NE infusion (100 ng·kg⁻¹·min⁻¹), and under Phe-only conditions.

Statistics. Standard statistical methods were used for the calculation of means and standard deviations. Normal Gaussian distribution of the data was verified by the Kolmogorov-Smirnov goodness-of-fit test (z value > 1.0). ANOVA for repeated measurements was used to compare the changes in HR, blood pressure, HR variability, and MSNA parameters during the different protocols, followed by post hoc analysis (tests of within-subjects contrasts with SPSS 12.0.1 for Windows).

RESULTS

Heart rate, blood pressure, and MSNA. The mean value of HR decreased and blood pressure increased progressively during the incremental doses of NE infusion (Fig. 1, A and B), and both returned to baseline levels after titrated Phe administration (table 1). MSNA decreased significantly during NE infusion and remained significantly below the baseline value after NE+Phe administration (Fig. 1C). The mean value of HR and MSNA recovered back to baseline values during PHE-only conditions (Fig. 1, A and C). Therefore, the MSNA site was maintained throughout the protocol and possible technical problems cannot explain the loss of signal during NE infusion (see also Fig. 2). Representative examples of R-R interval spectra, continuous noninvasive blood pressure, and MSNA at baseline, during NE infusion (50 and 100 ng·kg⁻¹·min⁻¹), during NE infusion after α-adrenergic blockade by phentolamine (Phe), and during Phe-only conditions. Values are means ± SD. ANOVA for repeated measurements was used, followed by post hoc analysis (paired t-test); nu, normalized units.

Fig. 1. Heart rate [HR; in beats/min (bpm); A], mean blood pressure (BP; B), muscle sympathetic nerve activity (MSNA) from the peroneal nerve (C), and low-frequency (LF) oscillation of R-R intervals (D) at baseline, during incremental norepinephrine (NE) infusion (50 and 100 ng·kg⁻¹·min⁻¹), during NE infusion after α-adrenergic blockade by phentolamine (Phe), and during Phe-only conditions. Values are means ± SD. ANOVA for repeated measurements was used, followed by post hoc analysis (paired t-test); nu, normalized units.
baseline during NE infusion without and with Phe administration and with PHE-only conditions are shown in Fig. 2.

**HR variability.** SDNN increased significantly during the first NE dose but was not different from baseline with other interventions. HF power in absolute units increased significantly during the NE infusion but was not different from baseline with NE/Phe intervention and decreased below baseline with Phe only (Table 1). The mean value of LF power in absolute units did not change significantly during the intervention (decreased in 5 of 8 subjects). Expressed in nu, HF power increased (in all subjects) and LF power decreased during the NE and NE/Phe interventions (decreased in 7 of 8 subjects), and both recovered back to baseline levels during Phe after the NE effect. Similarly, LF/HF decreased during the initial dose of NE, remained significantly ($P < 0.05$) below the baseline value after NE/Phe administration, and recovered back to the baseline with PHE only. All values are shown in Table 1.

**Blood pressure variability and BRS.** The HF power of systolic blood pressure oscillation did not change during the interventions (Table 2). The mean value of LF power of systolic blood pressure oscillation decreased during the NE infusion ($P < 0.05$) and remained significantly ($P < 0.05$) below the baseline after NE/Phe administration (Table 2). BRS, expressed as $\alpha$LF, did not change during the interventions, and $\alpha$HF decreased below the baseline during Phe only.

**Valsalva maneuvers and MSNA response.** For three of four subjects, a clear increase in MSNA was present during the

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**Table 1. HR variability and MSNA data at baseline, during NE infusion without and with Phe administration, and during Phe-only conditions**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>50 ng·kg$^{-1}$·min$^{-1}$</th>
<th>100 ng·kg$^{-1}$·min$^{-1}$</th>
<th>NE + Phe</th>
<th>Phe</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, beats/min</td>
<td>62 ± 8</td>
<td>55 ± 7†</td>
<td>53 ± 7†</td>
<td>63 ± 10</td>
<td>72 ± 18</td>
</tr>
<tr>
<td>SDNN, ms</td>
<td>73 ± 18</td>
<td>101 ± 21*</td>
<td>91 ± 32</td>
<td>93 ± 46</td>
<td>57 ± 19</td>
</tr>
<tr>
<td>HF, ms$^2$</td>
<td>7.3 ± 0.5</td>
<td>8.3 ± 0.6‡</td>
<td>8.0 ± 0.7†</td>
<td>7.8 ± 1.0</td>
<td>6.3 ± 1.4</td>
</tr>
<tr>
<td>HF power, nu</td>
<td>57 ± 13</td>
<td>70 ± 14†</td>
<td>65 ± 13*</td>
<td>68 ± 10*</td>
<td>46 ± 19</td>
</tr>
<tr>
<td>LF, ms$^2$</td>
<td>7.1 ± 0.5</td>
<td>7.3 ± 0.5</td>
<td>7.4 ± 0.9</td>
<td>7.0 ± 1.1</td>
<td>6.5 ± 0.9</td>
</tr>
<tr>
<td>LF power, nu</td>
<td>43 ± 13</td>
<td>29 ± 14†</td>
<td>35 ± 13*</td>
<td>33 ± 9*</td>
<td>54 ± 19</td>
</tr>
<tr>
<td>LF/HF</td>
<td>0.91 ± 0.40</td>
<td>0.48 ± 0.30†</td>
<td>0.65 ± 0.44*</td>
<td>0.47 ± 0.25*</td>
<td>1.93 ± 2.20</td>
</tr>
<tr>
<td>MSNA, bursts/min</td>
<td>10 ± 2</td>
<td>3 ± 1*</td>
<td>2 ± 1†</td>
<td>4 ± 2*</td>
<td>11 ± 2</td>
</tr>
</tbody>
</table>

Values are means ± SD. HR, heart rate; NE, norepinephrine; Phe, phentolamine; SDNN, standard deviation of R-R intervals; HF, high frequency; nu, normalized units; LF, low frequency; MSNA, muscle sympathetic nerve activity. *$P < 0.05$, †$P < 0.01$, and ‡$P < 0.001$, baseline vs. stimulation.
were 5.4

Phe-only conditions. The mean values for the change in MSNA induced a large MSNA response in the baseline phase and under these alterations remained the same after the return of blood pressure to the baseline level after baroreceptor feedback due to elevated blood pressure, because blood pressure among healthy subjects. This attenuation of NE reduced MSNA and LF oscillation of both HR and systolic pressure to the baseline level after

discrepancies (no effects of condition).

DISCUSSION

The results show that the infusion of physiological doses of NE reduced MSNA and LF oscillation of both HR and systolic blood pressure among healthy subjects. This attenuation of sympathetic outflow does not seem to be merely a result of baroreceptor feedback due to elevated blood pressure, because these alterations remained the same after the return of blood pressure to the baseline level after α-adrenergic blockade with Phe. Furthermore, cardiovagal BRS did not change during the NE infusion with Phe, as analyzed by the cross-spectral method (using both LF and HF spectral bands), suggesting that the inhibitory effects of NE on LF oscillation of R-R intervals and MSNA are not explained by altered baroreflex gain but perhaps by a presynaptic autoregulatory feedback mechanism (26) or some other mechanism that is not inhibited by α-adrenergic blockade.

Feedback mechanism of circulating NE. The observation that NE itself results in diminished LF oscillation of R-R intervals and systolic blood pressure, increased HF oscillations of R-R intervals, and reduced MSNA is not surprising, because the elevation of blood pressure caused by NE can be expected to reduce sympathetic outflow and to increase vagal outflow by a baroreceptor feedback mechanism. This effect of NE should be reversible when the baseline blood pressure is restored. This was not the case, however. α-Adrenergic blockade by Phe did result in a decrease of blood pressure and an increase of the average HR to the baseline but had no effect on blunted MSNA, LF oscillation of HR, or systolic blood pressure.

A possible explanation for the lack of effect of Phe on MSNA, LF power of HR, and blood pressure oscillation could be the resetting of the baroreceptor function during the NE infusion. However, BRS, which was analyzed by a cross-spectral method in the present study, did not change during the NE infusion with Phe compared with the baseline level. Second,Valsalva maneuver during the NE infusion and during the condition with the maintained Phe effect resulted in normal MSNA responses. This further demonstrates that baroreflex function is not compromised importantly by NE infusion. In accordance, a study by Undesser et al. (32) showed that α-adrenergic stimulation does not reset the baroreceptor responsiveness caused by infusion of angiotensin. Therefore, it seems more likely that NE has a feedback effect on the sympathetic outflow that is not mediated by the baroreflex loop.

Another potential mechanism for the present findings is the presynaptic autoregulatory feedback inhibition of NE on the sympathetic outflow (14, 26). The exact mechanism of this feedback regulation is not completely defined, but most probably it is mediated by α2-receptors (20). Three different subtypes of α2 receptors (A, B, and C) have been recently identified (20). The inhibitory presynaptic feedback loop requires two receptor subtypes, α2A and α2C (20). It is possible that the regulatory function mediated by these specific receptors is not selectively blocked by the nonselective α-adrenergic blocker Phe, but evidently more research will be needed to prove this.

It is also possible that Phe itself has direct inhibitory effects of LF oscillations of HR and blood pressure. This hypothesis is supported by a previous study (34) where a pure infusion of Phe resulted in decreased LF oscillations of HR and blood pressure. However, the maximal Phe dose was significantly higher (40 mg) in the previous study compared with the present one (5 mg). A larger dose of Phe resulted in a profound increase in MSNA bursts compared with baseline (300%), whereas Phe resulted in only a slightly higher MSNA compared with baseline in the present study (10%). Second, the dose of Phe used here resulted in smaller changes in blood pressure and HR than those observed in the earlier study. Therefore, it is unlikely that the dose of Phe used in the present study could have had profound direct effects on LF oscillation of cardiovascular variability during the NE+Phe condition. More likely, NE itself had the major influence on attenuation of LF oscillations. It is also possible that the large Phe dose used in the previous study resulted in an increased release of NE from nerve terminals as a response to marked hypotension, thereby resulting in increased levels of circulating NE and decreased LF oscillations.

Methodological consideration of LF oscillation calculations. The expression of LF oscillation of R-R intervals in absolute units or nu needs some attention. It is well accepted that LF oscillation of R-R intervals includes more vagal than sympathetic “outflow” at the supine position. This has been documented during vagal blockade by high-dose atropine, which decreases LF power of R-R intervals in absolute units.

Table 2. BP data and cross-spectral analysis of RR intervals and systolic pressure at baseline, during NE infusion without and with Phe administration, and during Phe-only conditions

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>50 ng·kg⁻¹·min⁻¹</th>
<th>100 ng·kg⁻¹·min⁻¹</th>
<th>NE + Phe</th>
<th>Phe</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPsys, mmHg</td>
<td>122±11</td>
<td>130±12‡</td>
<td>148±11†</td>
<td>125±9</td>
<td>123±12</td>
</tr>
<tr>
<td>BPdia, mmHg</td>
<td>65±6</td>
<td>73±5‡</td>
<td>80±10‡</td>
<td>66±6</td>
<td>66±4</td>
</tr>
<tr>
<td>HF, mmHg²</td>
<td>1.5±0.8</td>
<td>1.4±0.8</td>
<td>2.3±1.5</td>
<td>2.2±1.4</td>
<td>1.0±0.2</td>
</tr>
<tr>
<td>LF, mmHg²</td>
<td>3.1±2.3</td>
<td>2.5±2.3</td>
<td>2.0±1.5*</td>
<td>1.7±1.1*</td>
<td>1.8±0.7</td>
</tr>
<tr>
<td>αLF, ms/mmHg</td>
<td>14±7</td>
<td>21±17</td>
<td>13±1</td>
<td>16±11</td>
<td>11±5</td>
</tr>
<tr>
<td>αHF, ms/mmHg</td>
<td>24±12</td>
<td>34±31</td>
<td>15±5</td>
<td>22±15</td>
<td>13±6</td>
</tr>
</tbody>
</table>

Values are means ± SD. BP, blood pressure; BPsys and BPdia, systolic and diastolic BP, respectively; αLF and αHF, baroreflex transfer functions in the LF and HF bands, respectively; *P < 0.05, †P < 0.01, and ‡P < 0.001, baseline vs. stimulation.
>90%. Therefore, LF power of R-R intervals in absolute units is expected to increase during NE infusion (due to enhanced vagal activity), but that was not the case. On the contrary, LF power in absolute bases decreased in five of eight subjects (see Fig. 2). LF power calculated by normalized units decreased in all subjects during NE conditions and in seven of eight subjects during NE+Phe conditions.

The average R-R interval itself has major influence on all the time and frequency HR measures, when analyzed in absolute units (2, 31). The normalized units of spectral indexes or LF/HF are less sensitive to the average HR itself, and therefore these indexes are more suitable in this type of research, where the average HR changes during the intervention (like in the present study). Finally, and most importantly, LF power of R-R intervals in normalized units is more correlated to sympathetic activity than the LF power in absolute units studied by MSNA recordings from the peroneal nerve (18). Taken together, decreased LF power in normalized units indicates a decreased sympathetic activity during NE infusion.

The increased average HR from NE interventions to NE+Phe conditions may be confusing because we observed blunted sympathetic activity during these conditions. The decreased blood pressure caused by Phe results in reduced vagal activity via the baroreflex arch, which may well explain the increased HR levels during NE+Phe conditions compared with the pure NE intervention. It is also well documented that the changes in the average HR level mainly reveal the changes in vagal activity at the resting condition, and therefore the vagal outflow covers the effects of sympathetic activity on the average HR (13).

Origin of LF oscillation of HR and blood pressure. LF oscillation of R-R intervals is mediated by sympathetic and vagal outflow. The LF spectral component of R-R intervals is expected to increase during a period of high sympathetic activity. Therefore, it has been surprising, and paradoxical, that certain conditions, such as heart failure (33) and heavy exercise (31), are associated with blunted or even absent LF oscillations and a decreased LF/HF. This has been proposed to result from saturation of the LF oscillatory system at a certain point with high sympathetic activity, but the exact mechanisms for this saturation have not been fully understood (33). Another proposed possibility is that LF oscillations are mainly mediated by vagal outflow (28). In this case, an elevation of blood pressure with NE should be expected to cause an increase rather than no change or a decrease in LF oscillations of HR via baroreceptor-mediated vagal activation, and it cannot explain the observed attenuation of LF oscillation at the time of NE infusion.

NE in physiological and pathological conditions. Increasing levels of circulating NE can be observed in various physiological and pathophysiological conditions, such as passive head-up tilting, vigorous exercise, and various cardiac diseases (2, 4, 5, 12, 16, 17, 23, 25, 27). This is mainly due to excessive sympathetic stimulation resulting in a net outward gradient in NE release versus uptake from the sympathetic nerve endings. During normal short-term physiological interventions, such as passive head-up tilt, reciprocal changes usually occur in the sympathovagal balance, so that sympathetic activation is accompanied by vagal withdrawal (15, 16, 30). On some occasions, however, e.g., immediately after the cessation of exercise or during face immersion (7, 8, 11), vagal activation occurs simultaneously with high levels of circulating catecholamines. Also, in some disease states, such as congestive heart failure, high levels of circulating NE are a typical phenomenon without any evidence of vagal withdrawal (33). The present experimental setting was designed to mimic these conditions, called accentuated sympathovagal interaction (29), and aimed at examining the potential mechanisms of the paradoxical attenuation of the LF oscillation of R-R intervals during specific conditions with preserved vagal outflow accompanied by high circulating NE levels.

The experimental setting of this study differs from physiological or pathological conditions where sympathetic activation occurs. Physical exercise or heart failure causes neural sympathetic activation resulting in increased MSNA and a net increase in circulating NE. In these conditions, increased MSNA reflects the neural sympathoexcitation, which serves as a trigger for elevated NE. The possible feedback effect of circulating NE is not able to reverse the increased MSNA bursts caused by the primary trigger but seems to attenuate the LF cardiovascular oscillations. On the contrary, NE was artificially infused to healthy volunteers in the present study. Therefore, neural sympathetic activation did not occur and MSNA was low rather than high.

Implications. The present results provide indirect evidence of a cardiovascular regulatory mechanism, such as a feedback mechanism of circulating NE to sympathetic outflow, that does not seem to result from altered baroreceptor-mediated regulation. This mechanism may well explain why LF oscillation and the LF/HF of R-R intervals show paradoxical attenuation during the physiological and pathological conditions accompanied by high sympathetic activity and an increased NE outward current from the sympathetic nerve terminals. The present study included only healthy subjects, however, and the results may not be similar in patients with heart diseases. Therefore, generalization of the presumption that circulating NE results in altered autonomic regulation in patients with heart diseases requires more experimental work.

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