High plasma norepinephrine attenuates the dynamic heart rate response to vagal stimulation

Tadayoshi Miyamoto,1,2 Toru Kawada,1 Hiroshi Takaki,1 Masashi Inagaki,1 Yusuke Yanagiya,1,3 Yintie Jin,1,3 Masaru Sugimachi,1 and Kenji Sunagawa1

1Department of Cardiovascular Dynamics, National Cardiovascular Center Research Institute, Osaka 565-8565; 2Japan Space Forum, Tokyo 105-0013; and 3Organization for Pharmaceutical Safety and Research, Tokyo 100-0013, Japan

Submitted 31 July 2002; accepted in final form 11 February 2003

Miyamoto, Tadayoshi, Toru Kawada, Hiroshi Takaki, Masashi Inagaki, Yusuke Yanagiya, Yintie Jin, Masaru Sugimachi, and Kenji Sunagawa. High plasma norepinephrine attenuates the dynamic heart rate response to vagal stimulation. Am J Physiol Heart Circ Physiol 284: H2412–H2418, 2003. First published February 21, 2003; 10.1152/ajpheart.00660.2002.—To better understand the pathophysiological significance of high plasma norepinephrine (NE) concentration in regulating heart rate (HR), we examined the interactions between high plasma NE and dynamic vagal control of HR. In anesthetized rabbits with sinoaortic denervation and vagotomy, using a binary white noise sequence (0–10 Hz) for 10 min, we simulated the right vagus and estimated the transfer function from vagal stimulation to HR response. The transfer function approximated a first-order low-pass filter with pure delay. Infusion of NE (100 μg·kg−1·h−1 iv) attenuated the dynamic gain from 6.2 ± 0.8 to 3.9 ± 1.2 beats·min−1·Hz−1 (n = 7, P < 0.05) without affecting the corner frequency or pure delay. Simultaneous intravenous administration of phentolamine (1 mg·kg−1·h−1) and NE (100 μg·kg−1·h−1) abolished the inhibitory effect of NE on the dynamic gain (6.3 ± 0.8 vs. 6.4 ± 1.3 beats·min−1·Hz−1, not significant, n = 7). The inhibitory effect of NE at infusion rates of 10, 50, and 100 μg·kg−1·h−1 on dynamic vagal control of HR was dose-dependent (n = 5). In conclusion, high plasma NE attenuated the dynamic HR response to vagal stimulation, probably via activation of α-adrenergic receptors on the preganglionic and/or postganglionic cardiac vagal nerve terminals.

Address for reprint requests and other correspondence: T. Miyamoto, Dept. of Cardiovascular Dynamics, National Cardiovascular Center Research Institute, 5-7-1 Fujishirodai, Suita, Osaka 565-8565, Japan (E-mail: miyamoto@res.ncvc.go.jp).

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

HEART (HR) is mainly regulated by the sympathetic and parasympathetic nervous systems. Sympathetic activation and/or vagal withdrawal increases HR, whereas sympathetic withdrawal and/or vagal activation decreases HR. Accordingly, information on the mean level of HR alone does not allow a separate estimate of efferent activities of the two divisions of the autonomic nervous system. In contrast, information on the dynamic HR response has been considered useful in assessing vagal efferent nerve activity separately from sympathetic efferent nerve activity, because dynamic HR regulation is much faster via the vagal system than via the sympathetic system (3, 12). Accordingly, the high-frequency (HF) component (>0.15 Hz in humans) of HR variability (HRV) might reflect the cardiac vagal efferent nerve activity (2, 23). However, this notion is simplistic, in that it disregards interactions between the sympathetic and vagal systems.

Complex sympathovagal interactions are known to occur in regulation of HR. An increase in the background sympathetic tone augmented the HR response to vagal nerve activity (16, 17). Levy (17) termed this phenomenon an accentuated antagonism of the vagal control of HR. Accumulation of cAMP in the sinus nodal cells via activation of the postjunctional β-adrenergic receptors contributed to the accentuated antagonism (20). On the other hand, activation of the prejunctional α-adrenergic receptors influenced acetylcholine (ACh) release from the cardiac vagal nerve terminals (25). Local norepinephrine (NE) administration in the in vivo feline heart attenuated the myocardial interstitial ACh release during electrical stimulation of the vagi via the α-adrenergic mechanism (1). Cholinergic transmission in the parasympathetic ganglia was also attenuated by NE via the α-adrenergic mechanism (24). Taken together, the HR response to vagal stimulation can be enhanced or attenuated by the concomitant sympathetic activity, depending on which of these adrenergic receptors relating to cardiac regulation is the most selectively activated.

Physiological and pathophysiological activation of the systemic sympathetic nerves accompanies an increase in plasma NE concentration (7). Although previous studies from our laboratory demonstrated that concomitant electrical stimulation of the cardiac sympathetic nerve augmented the dynamic HR response to electrical stimulation of the vagus (12–14), plasma NE concentration did not increase perceivably, because sympathetic nerves other than the cardiac sympathetic nerve were not stimulated (15). Accordingly, it remains to be elucidated how changes in plasma NE concentration modulate the dynamic HR response to vagal stim-
ulation. We hypothesized that high plasma NE without direct activation of the cardiac sympathetic nerve affected dynamic vagal control of HR. Inasmuch as plasma NE concentration correlates positively with the severity of cardiovascular diseases such as heart failure (9), elucidating the effects of high plasma NE on dynamic vagal control of HR is essential for a better understanding of the pathophysiological significance of sympathovagal interactions in regulating HR. The purpose of the present study was to examine the effects of high plasma NE on dynamic HR regulation by the vagal system. The results indicated that high plasma NE attenuated the dynamic HR response to electrical stimulation of the vagus.

MATERIALS AND METHODS

Surgical Preparations

Animals were cared for in accordance with guidelines approved by the Physiological Society of Japan. Nineteen Japanese white rabbits weighing 2.4–3.2 kg were anesthetized by intravenous injection (2 ml/kg) of a mixture of urethane (250 mg/ml) and a-chloralose (40 mg/ml) and mechanically ventilated with oxygen-enriched room air. Supplemental doses of these anesthetics were given as necessary via the marginal ear vein. Aortic pressure (AP) was monitored by a micromanometer catheter (Millar Instruments, Houston, TX) inserted via the right femoral artery. A double-lumen catheter was inserted into the right femoral vein for the later administration of pharmacological agents. Sinoaortic denervation was performed bilaterally to minimize changes in sympathetic efferent nerve activity via the arterial baroreflexes. Briefly, the external and internal carotid arteries were identified under a dissecting microscope. The connective tissues between the two arteries were carefully detached from the arterial walls. The connective tissues, including the carotid sinus nerves, were then sectioned between two ligatures placed around the tissues. The aortic depressor nerves, which run separately from the vagi in rabbits, were sectioned at the neck. The vagi were also sectioned at the neck, where a pair of bipolar platinum electrodes were attached to the cardiac end of the sectioned right vagus. To prevent drying and to provide insulation, the stimulation electrodes and the nerve were immersed in a mixture of white petroleum jelly (Vaseline) and liquid paraffin. The right cardiac sympathetic nerve was exposed through a midline thoracotomy and sectioned, resulting in a decrease in HR of 40 beats/min on average. The right cardiac sympathetic nerve is considered more effective than the left cardiac sympathetic nerve in regulating HR (19, 22). Finally, a pair of bipolar stainless steel wire electrodes were attached to the right atrium to record the electrocardiogram for measuring HR. Body temperature was maintained at 38°C with a heating pad throughout the experiment.

Protocols

The pulse duration of electrical stimulation of the vagus was set at 2 ms. The amplitude of stimulation (3–6 V) was adjusted in each animal to yield a decrease in HR of ~50 beats/min at 5 Hz. To estimate the transfer function from vagal stimulation to the HR response, we stimulated the vagus using a frequency-modulated pulse train. The stimulation frequency was switched every second at 0 or 10 Hz according to a binary white noise signal. The power spectrum of the stimulation signal was reasonably constant up to 0.5 Hz, decreased gradually to 1/10 at ~0.8 Hz, and was attenuated sharply as the frequency increased to 1 Hz. We estimated the transfer function only up to 0.8 Hz, because the lack of input power above that frequency reduced the reliability of estimation. The frequency range spanned the physiological range of interest sufficiently with respect to the dynamic vagal control of HR in rabbits (12, 13, 20, 21).

Protocol 1 (n = 7). We examined the effects of intravenous infusion of NE on the transfer function from vagal stimulation to the HR response. We first recorded the dynamic HR response to vagal stimulation for 10 min under control conditions. We then initiated intravenous administration of NE at 100 μg·kg⁻¹·h⁻¹ and waited until the new steady states of HR and AP were reached. After 15 min, we repeated the vagal stimulation. The dose of NE was chosen near the maximum dose used in previous studies (6, 11).

Protocol 2 (n = 7). We examined the combined effects of simultaneous intravenous infusion of the α-adrenergic antagonist phenolamine (1 mg·kg⁻¹·h⁻¹) and NE (100 μg·kg⁻¹·h⁻¹) on the transfer function from vagal stimulation to the HR response. Estimation of the transfer function was repeated before and during the pharmacological interventions with an intervening interval of 15 min.

Protocol 3 (n = 5). We examined the dose dependence of the effects of intravenous NE infusion on the transfer function from vagal stimulation to the HR response. The intravenous infusion rate of NE was varied among 0, 10, 50, and 100 μg·kg⁻¹·h⁻¹ in increasing order. Each infusion rate continued for 30 min. Data for the transfer function analysis were recorded from 15 min after the transition of the infusion rate.

Data were digitized at 200 Hz using a 12-bit analog-to-digital converter and stored on the hard disk of a dedicated laboratory computer system. Prestimulation values of HR and AP were calculated by averaging the respective data for the 10 s immediately before vagal stimulation. The mean levels of HR and AP during vagal stimulation were calculated by averaging the respective data over the period of vagal stimulation.

Data Analysis

We resampled the input-output data pairs of the vagal stimulation frequency and HR at 10 Hz and then segmented them into eight 50%-overlapping segments of 1,024 data points each. For each segment, the linear trend was subtracted and a Hanning window was applied. We then performed fast Fourier transformation to obtain the frequency spectrum of vagal stimulation [HR(f)] and that of HR [HR_HR(f)] (5). We ensemble averaged, over the eight segments, the cross power between vagal stimulation and HR [SN_HR(f)] and HR_HR(f)] and the cross power between vagal stimulation and HR [SN_HR(f)]. Finally, we obtained the transfer function [HR_HR(f)] from vagal stimulation to the HR response using the following equation (18)

\[
H(f) = \frac{S_{N-HR}(f)}{S_{N}(f)}
\]

Because the transfer function from vagal stimulation to the HR response approximated a first-order low-pass filter with pure delay in previous studies (12, 13, 20, 21), we parameterized the transfer function by the following equation:

\[
H(f) = \frac{-K}{1 + \frac{f}{f_c}j} e^{-2\pi fl}
\]
where $K$ is the dynamic gain (in beats·min$^{-1}$·Hz$^{-1}$), $f_c$ is the corner frequency (in Hz), $L$ is the pure delay (in s), and $f$ and $j$ represent frequency and imaginary unit, respectively. The negative sign in the numerator indicates the negative HR response to vagal stimulation. The parameters were estimated by means of iterative nonlinear least-squares regression. Errors in the fitting procedure were calculated from the gain and phase differences averaged in the frequencies from 0.01 to 0.8 Hz (see Appendix).

To quantify the linear dependence of HR response on vagal stimulation, we estimated the magnitude-squared coherence function [Coh(f)] by the following equation (18)

$$\text{Coh}(f) = \frac{|S_{N-HR}(f)|^2}{S_N(f) \cdot S_{HR-HR}(f)}$$

**Statistics**

Values are means ± SE. In protocols 1 and 2, differences in mean levels of HR and AP and fitted parameters of the transfer function before and during pharmacological interventions were examined using a paired t-test (10). The differences were considered significant at $P < 0.05$. In protocol 3, the percent change in dynamic gain from control was calculated at each infusion rate of NE. A linear regression analysis was performed on the pooled data of percent gain vs. the common logarithm of the infusion rate as follows

$$\% \text{Gain} = a + b \cdot \log_{10} x$$

where $x$ represents the infusion rate (in µg·kg$^{-1}$·h$^{-1}$) and $a$ and $b$ are the intercept and slope of the linear regression, respectively. The test for the regression slope at $P < 0.05$ was performed to examine the dose dependence in the effects of intravenous NE on dynamic vagal control of HR.

**RESULTS**

Figure 1 shows typical recordings of vagal stimulation and HR response in the presence of the intravenous NE infusion. Random vagal stimulation decreased HR intermittently. Intravenous NE infusion increased the mean level of AP but did not affect the mean level of HR before and during vagal stimulation (Table 1). The amplitude of the HR variation was smaller in the presence than in the absence of intravenous NE. The speed of the HR response to vagal stimulation appeared to be unchanged by intravenous NE.

Figure 2 shows the transfer functions from vagal stimulation to the HR response averaged from all animals in protocol 1. The gain plots, phase plots, and coherence functions are shown. The transfer gain was relatively constant below 0.03 Hz and decreased above the frequency up to 0.8 Hz in the absence and presence of exogenous NE. The phase approached $-\pi$ radians at the lowest frequency and lagged with increasing frequency. Coherence was near unity at frequency <0.3 Hz under control conditions. Coherence was >0.8 at frequency <0.3 Hz in the presence of exogenous NE. The fitted parameters of the transfer functions and errors in the fitting procedure are summarized in Table 2. Intravenous NE infusion decreased the dynamic gain without affecting the corner frequency or pure delay.

Figure 3 shows typical recordings of vagal stimulation and the associated changes in HR in the absence and presence of intravenous phenotolamine and NE infusion. Vagal stimulation randomly decreased HR. Simultaneous administration of phenotolamine and NE decreased the mean levels of AP but did not affect the mean levels of HR (Table 1). The amplitude of the HRV was similar in the presence and absence of pharmacological interventions.

Figure 4 shows the transfer functions from vagal stimulation to the HR response averaged from all animals in protocol 2. The transfer gain was relatively constant at <0.03 Hz and decreased between 0.03 and 0.8 Hz in the absence and presence of pharmacological interventions. The phase approached $-\pi$ radians at the lowest frequency and lagged with increasing frequency. Coherence was near unity at frequency <0.4 Hz in the presence and absence of pharmacological interventions. The fitted parameters of the transfer functions and errors in the fitting procedure are summarized in Table 2. The dynamic gain, corner frequency, and pure delay were not changed by the pharmacological interventions.

Figure 5 depicts the dose dependence in the effects of intravenous NE on the dynamic gain of the transfer function from vagal stimulation to the HR response obtained from protocol 3. NE infusion decreased the dynamic gain to 83.0 ± 8.4, 68.9 ± 13.2, and 62.4 ± 17.9% (means ± SD) at infusion rates of 10, 50, and 100 µg·kg$^{-1}$·h$^{-1}$, respectively. The slope of the regression was significant, indicating that the inhibitory effect of NE on the dynamic gain was dose dependent.
Norepinephrine (NE) attenuates vagal control of heart rate

Table 1. HR and AP before and during vagal stimulation

<table>
<thead>
<tr>
<th>Protocol 1</th>
<th>Protocol 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>NE</td>
</tr>
<tr>
<td>HR, beats/min Before</td>
<td>248 ± 9</td>
</tr>
<tr>
<td>During</td>
<td>218 ± 8</td>
</tr>
<tr>
<td>AP, mmHg Before</td>
<td>106 ± 6</td>
</tr>
<tr>
<td>During</td>
<td>100 ± 8</td>
</tr>
</tbody>
</table>

Values are means ± SE. HR, heart rate; AP, aortic pressure; NE, intravenous norepinephrine infusion (100 µg·kg⁻¹·h⁻¹); Phen + NE, intravenous infusion of phentolamine (1 mg·kg⁻¹·h⁻¹) and norepinephrine (100 µg·kg⁻¹·h⁻¹). *P < 0.05; †P < 0.01 vs. corresponding control.

Discussion

We have shown that intravenous NE infusion decreased dynamic gain of the transfer function from vagal stimulation to the HR response. Simultaneous administration of phentolamine with NE prevented the inhibitory effects of intravenous NE on the dynamic gain of the HR response to vagal stimulation, suggesting that the attenuation was attributable to activation of the α-adrenergic receptors on the cardiac vagal nerve terminals.

Effects of Intravenous NE Infusion on Dynamic Vagal Control of HR

Myocardial interstitial NE may be classified into NE of neuronal origin (NE released from the cardiac sympathetic nerve terminals) and NE of plasma origin (NE taken up from the coronary arteries into the myocardial interstitial space). In previous studies, concomitant electrical stimulation of the cardiac sympathetic nerve increased the dynamic gain of the transfer function from vagal stimulation to the HR response (12, 13). Selective stimulation of the cardiac sympathetic nerve alone does not increase plasma NE concentration perceptibly (8, 15, 26). Thus the augmentation of the dynamic vagal control of HR observed in previous studies is mainly attributable to NE of neuronal origin. NE of neuronal origin would activate the postjunctional β-adrenergic receptors on the sinus nodal cells more selectively than the prejunctional α-adrenergic receptors on the cardiac vagal nerve terminals. The preferential activation of the postjunctional β-receptors accumulates cAMP in the sinus nodal cells, leading to augmentation of the dynamic HR response to vagal stimulation (20).

Stimulation of the cardiac sympathetic nerve and intravenous infusion of NE increased left ventricular contractility to a similar extent, providing the resulting myocardial interstitial NE levels are comparable (15). In other words, there appeared to be no qualitative difference between NE of neuronal origin and NE of plasma origin with respect to sympathetic regulation of the heart. However, intravenous NE infusion attenuated the dynamic HR response to vagal stimulation (Figs. 2 and 5, Table 2), in marked contrast to the effects of cardiac sympathetic nerve stimulation (12, 13). Changes in the corner frequency and pure delay of the transfer function from vagal stimulation to the HR response reflect changes in the degradation process of ACh (21). Neither the corner frequency nor pure delay was affected by intravenous NE infusion, suggesting that the degradation process of ACh was not responsible for attenuation of the vagal control of HR. One possible mechanism for attenuation of the vagal control of HR by intravenous NE infusion is activation of α-adrenergic receptors on the cardiac vagal nerve terminals. This interpretation is supported by the fact that simultaneous administration of phentolamine with NE prevented attenuation of the dynamic HR response to vagal stimulation (Fig. 4, Table 2). High plasma NE inhibits cholinergic transmission in parasympathetic ganglia (24) and the neuromuscular termination (1, 25) via activation of the α-adrenergic receptors. The possible augmentation of dynamic vagal control of HR via activation of the β-adrenergic receptors on the sinus nodal cells was not observable during intravenous NE infusion.

Using an experimental setting similar to the present study, Nakahara et al. (20) demonstrated that intravenous administration of the β-adrenergic agonist isoproterenol increased the dynamic gain of the transfer function from vagal stimulation to the HR response. We had expected that simultaneous administration of phentolamine with NE stimulated the β-adrenergic receptors selectively, resulting in augmentation of the dynamic HR response to vagal stimulation, similar to...
that caused by administration of isoproterenol. However, dynamic gain was not increased by simultaneous administration of phentolamine with NE in the present study (Fig. 4, Table 2). Although the dose of phentolamine was set at 10 times higher than the dose of NE (1), it might have been insufficient to completely block the α-adrenergic action of NE on the vagal nerve terminals. Further increasing the dose of phentolamine relative to NE could result in an increase in dynamic gain. However, because administration of phentolamine decreased AP and the conditions of the animals deteriorated, even in the presence of simultaneous NE infusion (Table 1), we could not increase the dose of phentolamine further.

Impact of Sympathovagal Interactions on Interpretation of the HF Component of HRV

The sympathetic and vagal systems showed low-pass filter characteristics in regulating HR (3). Sympathetic control of HR approximated a second-order low-pass filter; vagal control of HR approximated a first-order low-pass filter (12). Because the natural frequency of the second-order low-pass filter relating to sympathetic control and the corner frequency of the first-order low-pass filter relating to vagal control have similar values, dynamic gain of the HR response in the high-frequency range is much smaller in sympathetic than in vagal control. As a result, the HF component of HRV cannot carry information on sympathetic efferent nerve activity in the corresponding frequency range. In contrast, the HF component can transmit information on vagal efferent nerve activity in the corresponding frequency range. By taking advantage of the differential dynamic characteristics of HR regulation between the sympathetic and vagal systems, the HF component of HRV has served as an index of vagal efferent nerve activity (2, 23). The interpretation regarding the HF component, however, disregards the interactions between the sympathetic and vagal systems.

As demonstrated in previous studies and the present study, concomitant sympathetic activation modulated the dynamic HR response to vagal stimulation (12, 13). Thus the HF component of HRV does not necessarily parallel vagal efferent nerve activity when sympathetic activation coexists. The HF component can be modulated by sympathetic activity, even when the vagal efferent nerve activity that generates the HF component remains unchanged. Making the interpretation of the HF component more complicated is the possibility that sympathetic nerve activation and high plasma NE might exert opposite influences on the dynamic HR response to vagal stimulation. When the dynamic HR response to vagal stimulation is augmented by concomitant sympathetic nerve activity, the HF component might overestimate the vagal efferent nerve activity. When the dynamic HR response to vagal stimulation is attenuated by high plasma NE, the HF component might underestimate vagal efferent nerve activity. Although the significance of high plasma NE relative to sympathetic nerve activity during physiological activation of the sympathetic system was unclear in the present study, high plasma NE associated with exercise or cardiovascular diseases such as heart failure could potentially modulate the dynamic HR response to vagal stimulation. As an example, a decrease in HRV during exercise and during additional infusion of NE demonstrated by Breuer et al. (4) may be in part attributable to the inhibitory effects of high plasma NE on dynamic vagal control of HR.

Table 2. Parameters of the transfer function from vagal stimulation to the HR response

<table>
<thead>
<tr>
<th>Protocol 1</th>
<th>Protocol 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dynamic gain, beats/min/Hz</td>
<td>6.2 ± 0.8</td>
</tr>
<tr>
<td>Corner frequency, Hz</td>
<td>0.12 ± 0.02</td>
</tr>
<tr>
<td>Pure delay, s</td>
<td>0.29 ± 0.03</td>
</tr>
<tr>
<td>G_error, %</td>
<td>9.1 ± 0.9</td>
</tr>
<tr>
<td>θ_error, rad</td>
<td>0.12 ± 0.01</td>
</tr>
</tbody>
</table>

Values are means ± SE. G_error and θ_error, errors in gain and phase values between estimated and fitted transfer functions, respectively. *P < 0.01 vs. corresponding control. Statistical analysis was not performed on G_error and θ_error.
Limitations

There are several limitations to the present study. First, we obtained data from anesthetized animals. If data had been obtained from conscious animals, the results might have been different. However, we disabled the arterial baroreflexes and cut the autonomic efferent pathways; thus the anesthetics should have had little effect on our results. Second, we could not dissect out the effects of high plasma NE on the preganglionic vagal nerve fibers from the effects on the postganglionic vagal nerve fibers. Although separation of preganglionic and postganglionic mechanisms is of interest, it is beyond the scope of the present study, which focused on interactions between high plasma NE and dynamic vagal control of HR. Finally, high plasma NE may affect autonomic regulation of HR chronically. Further studies focused on the effects of chronic elevation of plasma NE on autonomic regulation of HR are clearly required to elucidate the pathophysiological significance of elevated NE.

In conclusion, high plasma NE without direct activation of the cardiac sympathetic nerve attenuated the dynamic HR response to vagal stimulation. The attenuation was prevented by simultaneous administration of phentolamine with NE. These results indicate that high plasma NE activates the \( \alpha \)-adrenergic receptors on the preganglionic and/or postganglionic cardiac vagal nerve terminals, leading to a reduced ACh release in response to preganglionic vagal stimulation. Owing to the complex interactions between the sympathetic and vagal systems, the HF component of HRV alone may not correctly represent cardiac vagal nerve activity.

APPENDIX

Errors in the fitting procedure of the transfer function. Errors in the fitting procedure were calculated by the gain and phase differences averaged at frequencies of 0.01–0.8 Hz. Gain \( |G(f)| \) and phase \( \theta(f) \) values of the transfer function were calculated from the following equations:

\[
G(f) = \sqrt{H_{re}(f)^2 + H_{im}(f)^2}
\]

\[
\theta(f) = \tan^{-1} \left( \frac{H_{im}(f)}{H_{re}(f)} \right)
\]

Where \( H_{re}(f) \) and \( H_{im}(f) \) are the real and imaginary parts of the transfer function and \( f_0 \) is a fundamental frequency determined from a reciprocal of the segment length of the Fourier transform.

Errors in gain \( G_{error} \) and phase \( \theta_{error} \) were calculated between the estimated \( G_{est} \) and fitted \( G_{fit} \) transfer functions using the following equations:

\[
G_{error} = 100 \times \left[ \sum_{i=1}^{m} \left( \frac{|G_{est}(f_{0,i}) - G_{fit}(f_{0,i})|}{G_{est}(f_{0,i})} \right) \right] \times \frac{1}{m} \times \frac{1}{\text{SE}}
\]

\[
\theta_{error} = \sum_{i=1}^{m} \left( \frac{\theta_{est}(f_{0,i}) - \theta_{fit}(f_{0,i})}{\text{SE}} \right) \times \frac{1}{m} \times \frac{1}{\text{SE}}
\]

Where \( m \) represents the index of frequency corresponding to 0.8 Hz. The error value at each frequency was weighted by the reciprocal of the index of frequency to reflect the logarithmic scaling of the abscissa in the gain and phase plots.

Fig. 4. Transfer functions from vagal stimulation to the HR response averaged from all animals in protocol 2. Transfer functions before (left) and during (right) intravenous phentolamine and NE infusion are shown. Top: gains; middle: phase shifts; bottom: coherence functions. Solid lines, means; dashed lines, means \( \pm \) SE. Transfer functions did not differ markedly before or during pharmacological interventions.

Fig. 5. Dose dependence in effects of intravenous NE infusion on dynamic gain of transfer function from vagal stimulation to HR in protocol 3. Different symbols indicate data from different animals. A regression analysis was performed on pooled data. Solid line, linear regression. Slope was different from zero \( (P < 0.05) \), indicating dose dependence of NE effect.
H2418

NOREPINEPHRINE ATTENUATES VAGAL CONTROL OF HEART RATE


REFERENCES