Dynamic counterbalance between direct and indirect vagal controls of atrioventricular conduction in cats

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The vagal system exerts negative effects not only on the sinus node but also on the atrioventricular (AV) node. Vagal stimulation prolongs the AV conduction time (A-V interval) even when its negative chronotropic effect on the sinus node is prevented through constant atrial pacing. On the other hand, prolongation of the heart period (A-A interval) shortens the A-V interval through electrophysiological mechanisms. Thus, during normal sinus rhythm, vagal stimulation affects the A-V interval via two opposing mechanisms (Fig. 1): prolonging the A-V interval by directly affecting the AV node and indirectly shortening the A-V interval by prolonging the A-A interval.

Although numerous investigations on the vagal control of the A-V interval have been conducted, including investigation of the interactions between the direct and indirect mechanisms (15, 16, 22), the way in which dynamic vagal activation affects the A-V interval remains to be elucidated. Because vagal nerve activity changes dynamically in response to environmental stresses, quantification of the A-V interval response to dynamic vagal stimulation is essential for understanding dynamic A-V interval regulation by the vagal system. Leffler et al. (9) investigated dynamic characteristics of autonomic and heart rate effects on P-R interval in humans using spectral analysis and transfer function analysis. However, the transfer function from vagal nerve activity to P-R interval was not measured, because recording of vagal nerve activity was unavailable in the human study. An animal experiment is mandatory to complement the human study and to characterize the direct and indirect effects of dynamic vagal stimulation on the A-V interval. To this end, we applied transfer function analysis using frequency-modulated band-limited Gaussian white noise stimulation (1, 6, 7, 14, 18) in anesthetized cats. The results indicated that the direct and indirect effects were dynamically counterbalanced and exerted stable transient A-V interval response during vagal stimulation.

MATERIALS AND METHODS

Animal preparation. Animals were cared for in accordance with the guidelines set by the Physiological Society of Japan. Seven adult cats of either sex weighing 2.0–3.5 kg were anesthetized with pentobarbital sodium (30–35 mg/kg ip). Supplemental doses of pentobarbital sodium were injected (2 mg/kg iv) as necessary to maintain an appropriate level of anesthesia. The animals were intubated and mechanically ventilated with room air mixed with oxygen. Body temperature was maintained at ~37°C with a heating pad and a heat lamp.

The bilateral vagal nerves were sectioned through a midline cervical incision. We attached a pair of bipolar platinum electrodes to the cardiac end of each vagal nerve for electrical stimulation. To prevent drying and to provide insulation, the stimulation electrodes and nerves were soaked in a mixture of white petrolatum (Vaseline) and liquid paraffin. The chest was opened transversely at the second intercostal space. The bilateral stellate ganglia were sectioned to eliminate sympathetic nerve activity to the heart. We sutured a pair of bipolar stainless electrodes to the right atrium through the right fifth intercostal space to permit pacing. The femoral artery and the femoral vein were cannulated for monitoring of arterial pressure, administering anesthetics, and maintaining fluid balance. A 5-Fr bipolar electrode catheter was introduced in a retrograde manner via the right common carotid artery to the noncoronary cusp of the aortic valve to record activity from the His bundle (12). The His bundle electrogram was band-pass filtered in the frequency range of 50–1,000 Hz.
Stimulation protocols. The study consisted of the following protocols. In protocol 1, to estimate the transfer function from vagal stimulation to the A-V and A-A intervals, we dynamically stimulated the vagal nerves for 10 min. The stimulation frequency was switched every second according to Gaussian white noise, with a central frequency of 5 Hz and a standard deviation of 2 Hz. The pulse duration was set at 2 ms. The baseline heart rate was 155 ± 16 beats/min, and the amplitude of vagal stimulation (4–8 V) was adjusted in each animal to decrease heart rate to ~100 beats/min under 10-Hz tonic vagal stimulation. The efficacy of vagal stimulation on the heart rate did not change >10% throughout the experiment. Dynamic vagal stimulation was repeated under conditions of constant atrial pacing to abolish the influence of the A-A interval changes on the A-V interval. The pacing rate (158 ± 17 beats/min) was set to a level slightly higher than the baseline heart rate. In protocol 2, to identify the transfer function from the A-A interval to the A-V interval, we randomly paced the heart for 10 min according to Gaussian white noise with a pacing interval distribution of 300 ± 50 (SD) ms in the absence of vagal stimulation. The pacing interval was bounded in the range of 200–400 ms to allow the heart to capture every pacing stimulus.

We used different sequences of Gaussian white noise for different animals. The order of the experimental runs was randomized to reduce the likelihood of bias or of systematic error in our identification approach. The stimulation (or pacing) signal and the His bundle electrogram were digitized at 2,000 Hz through a 12-bit analog-to-digital converter and stored on the hard disk of a dedicated laboratory computer system (NEC PC-9801FA).

Data analysis. AV conduction time was assessed from the His bundle electrogram. The A-H interval was defined as the time from the earliest deflection of the atrial wave to the peak of the His potential. We used a maximum negative point of first derivative of the signal (dV/dt) in the earliest deflection as the A wave position. The H-V interval was defined as the time from the His potential to the earliest deflection of the ventricular wave. We used a time point of maximum negative dV/dt of the earliest deflection as the V wave position. We manually selected the templates for A, H, and V waves and subsequently detected matched signals through an adaptive time-matching algorithm. Discrete time series data were then obtained from the measured A-A, A-V, A-H, and H-V intervals so as to follow the principle of causality, e.g., the A-A interval values were positioned at the time points of each corresponding second A wave and the A-V interval values were positioned at the time points of each corresponding V wave. Finally, we linearly interpolated the respective discrete time series data to a frequency of 8 Hz. In two of seven animals, we could not record the His potential. However, because the other five animals did not show significant H-V interval changes under any of the protocols in the present study, we represented AV conduction time by the A-V interval rather than the A-H interval and pooled the results from all seven animals.

The transfer functions representing the dynamic system characteristics were calculated as follows. We segmented the 8-Hz resampled input-output data pairs into six 50% overlapping bins of 1,024 points each (20). For each bin, a linear trend was removed and a Hanning window was applied. We then performed fast Fourier transformation (2) to obtain the frequency spectra of the input X(f) and output Y(f). Next, we ensemble averaged, over the six bins, the power of the input, Sxx(f), the power of the output, Syy(f), and the cross power between the two, Sxy(f). Finally, we estimated the transfer function, H(f), using the following equation (14)

\[
H(f) = \frac{S_{xy}(f)}{S_{xx}(f)}
\]

We also calculated a magnitude-squared coherence function. The coherence function, Coh(f), is a frequency-domain measure of linear dependence between the input and output signals. It was calculated according to the following equation (14)

\[
\text{Coh}(f) = \frac{|S_{xy}(f)|^2}{S_{xx}(f) \cdot S_{yy}(f)}
\]

In protocol 1, to estimate the transfer function from vagal stimulation to the A-A interval (H\text{VA}_A), we treated the vagal stimulation frequency as the input and the A-A interval as the output of the system. When estimating the transfer function from vagal stimulation to the A-V interval (H\text{VA}_V), we treated the A-V interval as the output. Because we switched the vagal stimulation frequency every second, the input power spectrum was fairly constant up to 0.5 Hz, decreased to 1/10 by ~0.8 Hz, and dropped to noise levels at 1 Hz. We displayed H\text{VA}_A and H\text{VA}_V only in the frequencies <0.8 Hz, because the estimation of the transfer functions was unreliable in the higher frequency range because of a lack of input power. We estimated H\text{VA}_V during normal sinus rhythm (H\text{VA}_V) and constant atrial pacing (H\text{VA}_V), H\text{VA}_V represents the vagally mediated chronotropic effect on the sinus node. H\text{VA}_V represents the direct effect of dynamic vagal stimulation on the A-V interval. H\text{VA}_V represents the total effect (i.e., the combined direct and indirect effects) of dynamic vagal stimulation on the A-V interval.

In protocol 2, to estimate the transfer function from the A-A interval to the A-V interval (H\text{AA}_A), we treated the A-A interval as the input and the A-V interval as the output of the system. We changed every A-A interval randomly, with a mean value of 300 ms. This yielded a relatively flat input power spectrum beyond 1 Hz. We displayed H\text{AA}_A in the frequencies up to 1 Hz. H\text{AA}_A represents the dynamic characteristics of the electrophysiological effect of changes in the A-A interval on the A-V interval.
Statistical analysis. To facilitate interpretation of the determined dynamic characteristics, we calculated a 30-s step response associated with each transfer function. We first applied inverse Fourier transformation to the transfer function and obtained an impulse response. The step response was obtained by a time integral of the impulse response.

To quantitatively examine the differences among $H_{VAA}$, $H_{VNN}$, and $H_{VNP}$, we calculated a maximum response and a time constant in their corresponding step responses by means of nonlinear least-squares fitting. We also calculated a 90%-rise time at which 90% of the maximum response was attained. We tested the differences in parameters by Friedman's test for repeated-measures nonparametric comparison. If there was a significant difference, we applied the Student-Newman-Keuls test based on ranks to identify the difference between any two of the three groups (3).

RESULTS

Figure 2A shows representative time series data obtained from protocol 1 with no pacing. The top panel shows the vagal stimulation frequency according to the Gaussian white noise command signal; the middle panel shows the associated A-A interval response. Increasing vagal stimulation frequency prolonged the A-A interval, whereas decreasing it shortened the A-A interval. The bottom panel of Fig. 2A shows the A-V, A-H, and H-V interval responses. Although changes in the A-V interval were proportional to changes in the A-A interval, the magnitude of those changes was much smaller. Because vagal stimulation did not perceptibly alter the H-V interval, the dynamic response of the A-H interval to vagal stimulation was identical to that of the A-V interval.

Figure 2B illustrates time series data obtained from the same animal under constant atrial pacing. The vagal stimulation frequency, the A-A interval at a constant pacing interval, and the A-V, A-H, and H-V interval responses are shown in Fig. 2B (top, middle, and bottom, respectively). Constant pacing enhanced the A-V interval response to dynamic vagal stimulation. The H-V interval remained unchanged. As a result, the dynamic response of the A-H interval to vagal stimulation was identical to that of the A-V interval.

Figure 3A shows the averaged transfer functions associated with vagal stimulation pooled from all the animals. $H_{VAA}$, $H_{VNN}$, and $H_{VNP}$ are shown in Fig. 3A (left, center, and right, respectively). The top and middle panels are the gain and phase plots of the transfer functions, respectively, and the bottom panels are the coherence functions in Fig. 3A. The gain and phase plots reveal low-pass filter characteristics in all three transfer functions. The phase approaches zero radians in the lowest frequency, reflecting the fact that vagal stimulation prolongs both $T_{AA}$ and $T_{AV}$. The coherence values are $\sim 0.7$ in the frequencies $<0.4$ Hz. The gain was smaller in $H_{VAV}$ than in $H_{VNA}$. The gain of $H_{VAV}$ was smaller with no pacing (Fig. 3A, top center) than with constant pacing (Fig. 3A, top right).

Figure 3B illustrates the calculated step responses associated with $H_{VAA}$, $H_{VNN}$, and $H_{VNP}$. The maximum response was much smaller in the A-V interval (Fig. 3B, right) than in the A-A interval (Fig. 3B, left). The maximum response in the A-V interval was smaller under conditions of no pacing (Fig. 3B, center) than constant pacing (Fig. 3B, right).

Table 1 summarizes the parameters of step responses shown in Fig. 3B. Simultaneous comparison indicated that the maximum step responses were significantly smaller in the A-V interval than in the A-A interval. The maximum step response in the A-V interval was significantly smaller when there was no atrial pacing. Although the time constant associated with $H_{VNN}$ tended to be greater than that associated with $H_{VNP}$ or $H_{VAA}$, there were no statistically significant differences among the responses. The 90%-rise time associated
with $H_{VAV,N}$ was significantly longer than that associated with $H_{VAV}$ but was not significantly different from that associated with $H_{VAV,P}$.

Figure 4 represents the time series data obtained from protocol 2. The top panel in Fig. 4 shows changes in the A-A interval according to the Gaussian white noise command signal, and the bottom panel shows changes in the A-V, A-H, and H-V intervals. Although the A-A and A-V intervals showed a reciprocal relationship, the magnitude of the A-V interval change was about one-tenth of that of the A-A interval change. The H-V interval remained unchanged by the random pacing.

Figure 5A shows the average $H_{AA-AV}$ obtained from all the animals. The gain plot (top), the phase plot (middle), and the coherence function (bottom) are shown in Fig. 5A. The gain was $0.15 \pm 0.02$ at 0.008 Hz and decreased gradually to $0.09 \pm 0.02$ at 1 Hz. The phase plot indicated an out-of-phase relationship between the A-A and A-V intervals in the frequency range of 0.008 to 1.0 Hz in the absence of vagal stimulation. In this frequency range, the coherence values were $>0.8$.

Figure 5B shows the step response of the A-V interval to the A-A interval derived from $H_{AA-AV}$. The step response reached $>60\%$ of the maximum negative response within a second and then gradually approached the steady-state value of $-0.13 \pm 0.02$ ms.

### DISCUSSION

We have shown that the dynamic characteristics from vagal stimulation to the A-V interval response approximated a low-pass filter. The time constant of the A-V interval step response to vagal stimulation was not significantly different from that of the A-A interval step response. Constant atrial pacing increased the maximum response of the A-V interval step response to vagal stimulation while not affecting the time constant.

### Table 1. Parameters of step responses associated with vagal stimulation in protocol 1

<table>
<thead>
<tr>
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<th>$H_{VAV}$</th>
<th>$H_{VAV,N}$</th>
<th>$H_{VAV,P}$</th>
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</thead>
<tbody>
<tr>
<td>Maximum response, ms/Hz</td>
<td>44.9±14.2</td>
<td>2.4±12.4†</td>
<td>6.3±2.4*</td>
</tr>
<tr>
<td>Time constant, s</td>
<td>2.3±0.5</td>
<td>3.3±1.0</td>
<td>2.9±1.2</td>
</tr>
<tr>
<td>90%-rise time, s</td>
<td>5.6±1.1</td>
<td>7.9±1.6†</td>
<td>6.8±2.3</td>
</tr>
</tbody>
</table>

Data are means ± SD. $H_{VAV}$, transfer function from vagal stimulation to A-A interval; $H_{VAV,N}$, transfer function from vagal stimulation to A-V interval during normal sinus rhythm; $H_{VAV,P}$, transfer function from vagal stimulation to A-V interval during atrial pacing; 90%-rise time, time at which 90% of maximum response was attained.* $P < 0.01$ vs. $H_{VAV}$; †$P < 0.01$ vs. $H_{VAV,P}$; ‡$P < 0.05$ vs. $H_{VAV}$.

Fig. 4. Representative time series data showing random pacing protocol without vagal stimulation in 1 cat. Top, changes in A-A interval according to Gaussian white noise command signal. Bottom, A-V, A-H, and H-V intervals in response to changes in A-A interval. A-H and H-V interval responses are shown by thin lines. A-V and A-H intervals changed reciprocal to A-A interval; H-V interval was unaltered.
Transfer characteristics from vagal stimulation to A-A interval. The transfer function representing the vagally mediated chronotropic effect on the sinus node, $H_{V,AA}$, can be described as a low-pass filter (Fig. 3A, left). Taking the reciprocal relationship between the A-A interval and heart rate into account, these characteristics are comparable to those estimated for the transfer function from vagal stimulation to heart rate in dogs (1) and in rabbits (6, 7). The 90%-rise time of the A-A interval step response (Table 1) was, however, longer than that estimated in rabbits, suggesting species differences in the vagally mediated chronotropic effect on the sinus node. According to our previous investigation on the determinants of the transfer function from vagal stimulation to heart rate (18), one of the possible candidates for such species differences is a level of acetylcholinesterase activity. Difference in the effective vagal stimulation intensity among studies might also affect a corner frequency of the transfer function (1) and thus the 90%-rise time of the corresponding step response.

Inconsistent with our previous results (6, 7, 18), the phase plot of the present study did not show significant lag time between vagal stimulation and the A-A interval response. Difference in input data processing might have affected the estimation of the lag time. In the present study, we measured the stimulation interval between two consecutive pulses and positioned the stimulation frequency (an inverse of the stimulation interval) at the time point of the second pulse, to provide consistent data processing between stimulation signal and the His bundle electrogram. Thus the stimulation signal used for calculation of the transfer function was, on average, 200 ms (5 Hz) behind the command signal. If the command signal were used for the calculation of the transfer function as in our previous studies, the lag time would be estimated as $\sim 200$ ms.

Transfer characteristics from vagal stimulation to A-V interval. Similar to the transfer function from vagal stimulation to the A-A interval response, the transfer function characterizing the direct effect of dynamic vagal stimulation on the A-V interval, $H_{V,AV,P}$, also approximated characteristics of a low-pass filter (Fig. 3, right). The step responses associated with $H_{V,AA}$ and $H_{V,AV,P}$ revealed similar time constant and 90%-rise time (Fig. 3B, left and right; Table 1). Leffler et al. (9) demonstrated similar distributions of power spectra of R-R and P-R intervals using random respiration, suggesting similar dynamic characteristics of autonomic control of R-R and P-R intervals. The present study confirmed and extended their results in relation to the vagal control of the A-A and A-V intervals. The similarities between the A-A and A-V interval responses suggest that the same kinds of signal transduction sequences are involved in the negative effects of vagal stimulation on the sinus node and on the A-V node.

Constant atrial pacing enhanced the dynamic A-V interval response to vagal stimulation (Fig. 3A, center and right; Table 1). In other words, the dynamic A-V interval response was markedly attenuated when the normal sinus rhythm was maintained. Such dynamic characteristics are consistent with the steady-state A-V interval response in a human study in which baroreflex-induced A-V interval responses were smaller under normal sinus rhythm than under constant pacing (13). The A-V interval response is known to affect ventricular filling (17). A longer A-V interval prematurely terminates left ventricular filling through early mitral valve closure associated with atrial relaxation, whereas a shorter A-V interval reduces the contribution of atrial contraction to ventricular filling. The optimal A-V interval is within the normal A-V interval in dogs (17). However, further experiments are needed to clarify whether the attenuation of A-V interval changes during normal sinus rhythm is more beneficial for overall cardiac function, compared with what is attained by the combination of normal sinus rhythm and the A-V interval changes observed during constant pacing.

Transfer characteristics from A-A interval to A-V interval. The transfer function characterizing the effect of changes in the A-A interval on the A-V interval, $H_{AA-AV}$, indicates a reciprocal relationship between the A-A and A-V intervals in the absence of autonomic nervous activity (Fig. 5A). The frequency-dependent decrease in gain was much less than that observed in $H_{V,AV,P}$. Thus the electrophysiological effect of changes in the A-A interval on the A-V interval is much quicker than the direct effect of vagal stimulation on the A-V interval. The dynamic characteristics of the indirect effect of vagal stimulation on the A-V interval are determined by a serial connection of the chronotropic
effect and the electrophysiological effect (Fig. 1). Because the electrophysiological effect approximates an inverter with an all-pass filter in the frequency range of the present study, the low-pass characteristics of the indirect effect are mainly determined by the chronotropic effect. Therefore, similar time courses in the chronotropic effect ($H_{VAA}$) and the direct effect ($H_{VA-V_A}$) result in similar time courses in the direct and indirect effects of dynamic vagal stimulation on the A-V interval. The indirect effect, however, counterbalances the direct effect via the inverter-like characteristics of the electrophysiological effect.

To explore the physiological meaning of the similarity in the time course between the direct and indirect effects, we simulated the A-V interval response to vagal stimulation while varying the time constant for the direct and indirect effects. Figure 6A shows the simulation of the A-V interval step response to vagal stimulation with fixed time constant (3 s) for the direct effect ($\tau_{direct}$) while the time constant for the indirect effect ($\tau_{indirect}$) changed from one-eighth to eight times $\tau_{direct}$. If $\tau_{indirect}$ is much shorter than $\tau_{direct}$, the A-V interval response becomes oscillatory. Figure 6B shows the A-V interval response with fixed $\tau_{indirect}$ (3 s) while $\tau_{direct}$ changed in the range from one-eighth to eight times $\tau_{indirect}$. If $\tau_{direct}$ is much shorter than $\tau_{indirect}$, the A-V interval step response becomes underdamped. Therefore, if the time constants for the direct and indirect effects do not match, the resultant A-V interval response to vagal stimulation becomes unstable. Under physiological conditions, because the direct and indirect effects have similar time courses, vagal stimulation manifests stable monophasic transient A-V interval response (Fig. 6, A and B, thick lines). Impairment of any one of the direct effects, the chronotropic effect and the electrophysiological effect (Fig. 1), would cause imbalance in the time course between the direct and indirect effects of dynamic vagal stimulation on the A-V interval, thereby leading to unstable A-V interval regulation by the vagal system. Although outcomes of such an imbalance between the direct and indirect vagal effects remain speculative, Fig. 6 indicates that 10-Hz vagal stimulation would prolong the A-V interval by >50 ms if the imbalance exists. Because 50 ms is >50% of the A-V interval under normal conditions, such a prolongation could reduce the effectiveness of AV blood transfer by 20% (17). In addition, the A-V interval could show a variety of step responses if the time courses of direct and indirect vagal effects do not match. If the variation occurs among multiple pathways in the AV node, including fast and slow pathways (8), it might provide substrates for AV nodal reentrant tachycardia.

Limitations. Several variables that can potentially affect the A-V interval have not been considered in the present study. First, we obtained all data from animals under anesthesia. If data had been obtained from conscious animals, the results might have been different. However, because we cut efferent pathways of both vagal and sympathetic systems, the effects of anesthesia on the central nervous system should have had little effect on our conclusions.

Second, there was a difference in the operating range of the A-A interval during the estimation of $H_{AA-AV}$, $H_{VAA}$, and $H_{VA-V_A}$. Because the effect of the A-A interval changes on the A-V interval is known to be greater in shorter A-A interval ranges (19), the difference in the operating range of the A-A interval would have affected the absolute gain values of the estimated transfer functions.

Third, the A-V interval response to changes in the A-A interval depends not only on the operating range of the A-A interval but also on the rate and direction of heart rate change (12). However, if $\dot{\tau}_{direct}$ and $\dot{\tau}_{indirect}$ are considered in protocol 2 through the pacing command of Gaussian white noise. Therefore, $H_{AA-AV}$ might represent average transfer characteristics from the A-A interval to the A-V interval.

Fourth, AV conduction is regulated both by the vagal system and by the sympathetic system. For instance, the sympathetic effects may predominate over the vagal effects during exercise. Although previous studies (11, 21) demonstrated minimal interactions between the vagal and sympathetic systems in regulating AV conduction, further studies are clearly needed to characterize the dynamic interactions between the vagal and sympathetic systems.

Finally, the stimulating pattern of Gaussian white noise is different from the physiological discharge of vagal nerves (5). The asynchronous nature of Gaussian
white noise stimulation relative to each heartbeat would mask a phase-dependent sensitivity of vagal effects on the A-A and A-V intervals (4, 10). According to a study in dogs (10), in which the baseline heart rate was 154 beats/min, steady-state heart rate during vagal stimulation ranged from 79 to 95 beats/min depending on the phase at which the vagal stimulation was applied. Thus the phase-dependent sensitivity (95 – 79 = 16 beats/min) in the steady-state heart rate response to vagal stimulation is ~30% of the phase-independent response (154 – 95 = 59 beats/min). The identified transfer functions in the present study would represent average dynamic characteristics of the phase-independent vagal effects on the A-A and A-V intervals. A somewhat different limitation persists, however: because we stimulated the whole bundle of vagal nerve at once, the response observed cannot account for the possible regional differences in function of individual nerve fibers that make up the nerve bundle.

In conclusion, the transfer function representing the direct effect of dynamic vagal stimulation on the A-V interval approximated a low-pass filter similar to that representing vagally mediated chronotropic effect on the sinus node except for absolute gain values. Under normal sinus rhythm, the direct effect of vagal stimulation on the A-V interval is counterbalanced dynamically by the indirect effect through changes in the A-A interval. The direct and indirect effects of vagal stimulation had similar time constants, leading to a manifestation of stable transient A-V interval response.

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