Dynamic sympathetic control of atrioventricular conduction time and heart period

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Kawada, Toru, Shi-Liang Chen, Masashi Inagaki, Toshiaki Shishido, Takayuki Sato, Teiji Tatewaki, Masaru Sugimachi, and Kenji Sunagawa. Dynamic sympathetic control of atrioventricular conduction time and heart period. Am J Physiol Heart Circ Physiol 280: H1602–H1607, 2001.—Although power spectra of R-R and P-R intervals in response to random respiration show similar frequency distributions, the way in which dynamic sympathetic regulation contributes to such similarity remains unknown. We estimated the transfer function from sympathetic stimulation to the atrioventricular interval (AV conduction time; \( T_{AV} \)) with and without constant atrial pacing in seven anesthetized cats. The transfer function from sympathetic stimulation to \( T_{AV} \), except for absolute gain values, approximated a low-pass filter similar to that from sympathetic stimulation to the A-A interval (heart period; \( T_{AA} \)). The 90%-rise times did not differ between the \( T_{AA} \) and \( T_{AV} \) step responses (32.3 ± 1.8 vs. 29.6 ± 3.2 ms). Constant pacing augmented the \( T_{AV} \) step response (~0.58 ± 0.10 vs. ~0.86 ± 0.12 ms/Hz, \( P < 0.05 \)) without affecting the 90%-rise time. These findings suggest that the dynamic characteristics of sympathetic control are similar between \( T_{AA} \) and \( T_{AV} \) despite the different electrophysiological mechanisms determining \( T_{AA} \) and \( T_{AV} \). A numerical simulation indicated that if the dynamic characteristics of the sympathetic control do not match between \( T_{AA} \) and \( T_{AV} \), a critical condition for initiation of reentrant tachycardia would be encountered.

The heart period (A-A interval) reflects a rhythmicity or an automaticity of the sinus nodal cells (5), whereas the atrioventricular conduction time (A-V interval) reflects a conduction delay through the atrioventricular nodal cells (14). The different electrophysiological mechanisms responsible for the generation of the A-A and A-V intervals result in the significant difference in absolute length between the A-A and A-V intervals, i.e., the former is much longer than the latter. However, Leffler et al. (9) demonstrated similar distributions of R-R and P-R interval power spectra in response to random respiration, suggesting similar frequency responses of R-R and P-R intervals to autonomic perturbation. To elucidate the physiological mechanisms underlying such similar frequency responses to autonomic perturbation between R-R and P-R intervals, identification of the dynamic transfer characteristics from autonomic nerve stimulation to the A-A and A-V intervals is essential. As for the vagal system, we have shown that dynamic transfer characteristics from vagal stimulation to the A-V interval are similar to those from vagal stimulation to the A-A interval (3). In the present study, we aimed to identify the dynamic transfer characteristics from sympathetic stimulation to the A-A and A-V intervals. Our previous study (Nakahara et al., Ref. 18) indicated that dynamic transfer characteristics from sympathetic stimulation to heart rate approximate low-pass filter and that norepinephrine removal from the neuroeffector junction is one of the determinants responsible for the low-pass characteristics. If this paradigm is also true for the A-V interval response to sympathetic stimulation, dynamic transfer characteristics from sympathetic stimulation to the A-A and A-V intervals would reveal similar low-pass characteristics, regardless of the difference in electrophysiological mechanisms governing the A-A and A-V intervals. We tested this hypothesis in anesthetized cats by use of a white noise technique (1, 3, 6–8, 13, 16–19).

MATERIALS AND METHODS

Animal preparation. Animals were cared for in strict accordance with the Guiding Principles for the Care and Use of Animals in the Field of Physiological Sciences approved by the Physiological Society of Japan. Seven adult cats of either sex weighing 2.4–3.5 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 depth 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 to eliminate vagal innervation to the heart. The chest was opened transversely at the second intercostal space. The bilateral stellate ganglia were exposed.

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and their upper and lower poles as well as their spinal cord branches were cut. A pair of bipolar platinum electrodes was attached to the cardiac sympathetic nerves arising from each stellate ganglion 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. A pair of bipolar stainless steel wire electrodes was sutured to the right atrial appendage through the right fifth intercostal space to allow pacing. The right femoral artery was cannulated for the monitoring of arterial pressure. The right femoral vein was cannulated for administration of anesthetics and for maintenance of 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 (3, 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 two protocols. In protocol 1, we dynamically stimulated the cardiac sympathetic nerves for 10 min according to a Gaussian white noise signal (f = 3 ± 1.5 Hz, mean ± SD). The stimulation frequency was switched every 2 s. The pulse duration was set at 2 ms. The baseline heart rate was 165 ± 13 beats/min (mean ± SD). The stimulation amplitude was adjusted in each animal to produce a heart rate increase of ~30 beats/min at a 5-Hz tonic sympathetic stimulation. After the adjustments, the stimulation amplitude ranged from 2.5 to 5.0 V. The efficacy of sympathetic stimulation on the heart rate response did not change more than 10% throughout the experiment. In protocol 2, dynamic sympathetic stimulation was performed under conditions of constant atrial pacing to abolish the influence of changes in the A-A interval on the AV interval. The pacing rate (200 ± 18 beats/min) was set just above the maximal heart rate achieved by the 5-Hz tonic sympathetic stimulation.

We used different sequences of Gaussian white noise for different animals. The order of the experimental protocols was randomized to reduce the likelihood of bias or of systematic error in our identification approach. The stimulation command 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, Tokyo, Japan).

Data analysis. Atrioventricular conduction time was assessed from the His bundle electrogram as follows. The A-H interval was defined as the time from the earliest deflection of the atrial wave to the peak of the His potential. The H-V interval was defined as the time from the His potential to the earliest deflection of the ventricular wave. We manually selected the templates for A, H, and V waves and subsequently matched the templates through an adaptive template-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. Finally, we linearly interpolated the respective discrete time series data to a frequency of 8 Hz. We represented the atrioventricular conduction time in the A-V interval rather than the A-H interval in the present study because the H-V interval did not change perceptibly in either protocol.

The transfer functions representing 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. For each bin, a linear trend was removed and a Hanning window was applied. We then performed fast Fourier transformation to obtain frequency spectra of the input, X(f), and output, Y(f) (2). We then ensemble averaged, over the six bins, the power of the input, $S_{XX}(f)$, the power of the output, $S_{YY}(f)$, and crosspower between the input and output, $S_{XY}(f)$. Finally, we estimated the transfer function, $H(f)$, with the use of the following equation (13)

$$H(f) = \frac{S_{XY}(f)}{S_{XX}(f)}$$

To quantify the linear dependence between the input and output signals in the frequency domain, we calculated a magnitude-squared coherence function, $\text{Coh}(f)$, with the use of the following equation (13)

$$\text{Coh}(f) = \frac{|S_{XY}(f)|^2}{S_{XX}(f)S_{YY}(f)}$$

The coherence value ranges from zero to unity. A unity coherence indicates a perfect linear dependence between the input and output signals, whereas zero coherence indicates total independence between the two signals.

In protocol 1, we obtained the transfer function for sympathetic stimulation to the A-A interval ($H_{S,AA}$) and that of sympathetic stimulation to the A-V interval under no pacing conditions ($H_{S,AV,N}$). Because changes in the A-A interval affect the A-V interval through an electrophysiological mechanism, $H_{S,AV,N}$ includes both a direct sympathetic effect on the A-V interval and an indirect sympathetic effect through changes in the A-A interval. In protocol 2, we estimated the transfer function from sympathetic stimulation to the A-V interval under constant pacing conditions ($H_{S,AV,P}$). $H_{S,AV,P}$ represents the direct sympathetic effect on the A-V interval without including the indirect effect. As the sympathetic stimulation frequency was changed every 2 s, the input power spectrum was fairly constant up to 0.25 Hz. Therefore, we presented transfer functions in the frequencies below 0.25 Hz.

To facilitate intuitive understanding of $H_{S,AA}$, $H_{S,AV,N}$, and $H_{S,AV,P}$, we calculated a step response corresponding to each transfer function. To derive the step response, we obtained the impulse response from the inverse Fourier transformation of the transfer function. We then calculated a time integral of the impulse response up to 60 s. To quantify the step response, the maximum negative response was obtained by averaging the last 10-s data of the calculated step response. The 50- and 90%-rise times, at which times 50 and 90% of the maximum negative response were attained, respectively, were also calculated. We tested the differences in the parameters of the step responses by the Friedman’s test for repeated measures nonparametric multiple comparisons. If there was a significant difference ($P < 0.05$) among three groups, we applied the Student-Newman-Keuls test on the basis of ranks to identify the difference between any two of the three groups (4).

RESULTS

Figure 1A shows representative time series data obtained from protocol 1. The top panel shows the stimulation frequency of the cardiac sympathetic nerves according to a Gaussian white noise signal. The middle panel shows the associated A-A interval response. Increasing sympathetic stimulation frequency shortened the A-A interval, whereas decreasing it prolonged the A-A interval. The A-A interval did not respond to rapid changes in the sympathetic stimulation frequency. The bottom panel shows the A-V interval response. Although the A-V interval showed pro-
portional changes to the A-A interval response, the magnitude of the A-V interval response was much smaller than the A-A interval response.

Figure 1B shows time series data obtained from protocol 2 in the same animal. The sympathetic stimulation frequency (top), the A-A interval (middle), and the A-V interval response (bottom) are shown. The A-A interval was fixed at a constant pacing interval. The constant pacing increased the mean level of the A-V interval and enhanced the dynamic A-V interval response to sympathetic stimulation when compared with Fig. 1A. Because we used the same command signal for sympathetic stimulation between protocols 1 and 2, the A-V interval response under constant pacing conditions was similar to the A-A interval response under no pacing conditions except for the difference in the magnitude of response.

Figure 2A shows the averaged $H_{S,AA}$ (left), $H_{S,AV,N}$ (center), and $H_{S,AV,P}$ (right). The top and middle panels are the gain and phase plots of the transfer functions, respectively. The gain decreases as the frequency increases in all three transfer functions. The decreasing slopes in the higher frequency range (0.04–0.08 Hz) were $-11.5 \pm 0.6$, $-10.8 \pm 0.4$, and $-12.3 \pm 1.0$ dB/octave in $H_{S,AA}$, $H_{S,AV,N}$, and $H_{S,AV,P}$, respectively. These values approximated the decreasing slope of a second-order low-pass filter ($-12$ dB/octave). There were no significant differences in the decreasing slope
among the three transfer functions. The phase difference approaches $-\pi$ radians in the lowest frequency in all three transfer functions, reflecting the fact that sympathetic stimulation shortens both the A-A and the A-V intervals. The phase difference increases as the frequency increases. The phase difference is dispersed in the frequencies above 0.1 Hz in $H_{S,AV,N}$ and $H_{S,AV,P}$, possibly because of a low signal-to-noise ratio in these frequencies. The coherence shows a moderate linearity in the frequencies below 0.1 Hz in $H_{S,AV,P}$. The coherence seems to be lower in $H_{S,AA}$ and $H_{S,AV,P}$. A-V interval.

**Simulation study.** Once the dynamic characteristics of $H_{S,AA}$ and $H_{S,AV,P}$ are identified, we can manipulate the parameters of the transfer function to examine what would happen if the parameters were deviated from their normal physiological values. We examined, with the use of a mathematical model (see APPENDIX), the influences of the frequency bandwidth and dynamic gain of $H_{S,AV,P}$ on the A-V interval step response to sympathetic stimulation (Fig. 3, A and B). The simulation results indicate that if the parameters of $H_{S,AV,P}$ vary, the A-V interval response would play an important role in determining the low-pass filter characteristics of sympathetic regulation.

The constant pacing significantly increased the gain of the transfer function and augmented the A-V interval step response without affecting the 50- or 90%-rise time (Table 1). Shortening of the A-A interval prolongs the A-V interval through the electrophysiological mechanism, and vice versa, in the absence of autonomic innervation (10). The electrophysiological effect of changes in the A-A interval on the A-V interval is almost instantaneous in the frequency range of 0.01–0.1 Hz (3). As a result, changes in the A-A interval during sympathetic stimulation dynamically attenuated the direct effect of sympathetic stimulation on the A-V interval.

**Table 1. Parameters of calculated step responses to sympathetic stimulation**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>$H_{S,AA}$</th>
<th>$H_{S,AV,N}$</th>
<th>$H_{S,AV,P}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum Response, ms/Hz</td>
<td>$-3.62 \pm 0.93^{*\dagger}$</td>
<td>$-0.58 \pm 0.10$</td>
<td>$-0.86 \pm 0.12^{\dagger}$</td>
</tr>
<tr>
<td>50%-Rise Time, s</td>
<td>15.1 ± 0.7</td>
<td>11.6 ± 0.9</td>
<td>12.3 ± 1.0</td>
</tr>
<tr>
<td>90%-Rise Time, s</td>
<td>32.3 ± 1.8</td>
<td>23.7 ± 1.6</td>
<td>29.6 ± 3.2</td>
</tr>
</tbody>
</table>

Data are means ± SE. $H_{S,AA}$, transfer function from sympathetic stimulation to the A-A interval; $H_{S,AV,N}$, transfer function from sympathetic stimulation to the A-V interval estimated under no pacing conditions; $H_{S,AV,P}$, transfer function from sympathetic stimulation to the A-V interval estimated under constant pacing conditions. *$P < 0.01$ against $H_{S,AV,N}$; †$P < 0.05$ against $H_{S,AV,P}$, and ‡$P < 0.05$ against $H_{S,AV,N}$.

### DISCUSSION

**Transfer characteristics.** The transfer function representing the sympathetic control of the A-A interval approximated a second-order low-pass filter (Fig. 2, left). Taking into account the reciprocal relationship between the A-A interval and heart rate, these characteristics are comparable with the transfer function from sympathetic stimulation to heart rate estimated in dogs (1, 16) and rabbits (6–8, 18). The 90%-rise time of the A-A interval step response was, however, longer than that estimated in rabbits, suggesting species differences in the positive chronotropic effect of sympathetic stimulation.

The transfer function representing the sympathetic control of the A-V interval also approximated a second-order low-pass filter (Fig. 2, middle and right). These low-pass filter characteristics resemble the frequency responses of vascular resistance (20) and ventricular contractility (16) to sympathetic stimulation. As Berger et al. (1) pointed out, these findings suggest that low-pass filter characteristics of sympathetic regulation reflect the kinetics of the adrenergic receptors or of the intracellular signaling processes coupled to the receptors and are not necessarily intrinsic to effector organs. According to our previous study (18), norepinephrine removal from the neuroeffector junction would play an important role in determining the low-pass filter characteristics of sympathetic regulation.

**Simulation study.** Once the dynamic characteristics of $H_{S,AA}$ and $H_{S,AV,P}$ are identified, we can manipulate the parameters of the transfer function to examine what would happen if the parameters were deviated from their normal physiological values. We examined, with the use of a mathematical model (see APPENDIX), the influences of the frequency bandwidth and dynamic gain of $H_{S,AV,P}$ on the A-V interval step response to sympathetic stimulation (Fig. 3, A and B). The simulation results indicate that if the parameters of $H_{S,AV,P}$ vary, the A-V interval response would play an important role in determining the low-pass filter characteristics of sympathetic regulation.

The constant pacing significantly increased the gain of the transfer function and augmented the A-V interval step response without affecting the 50- or 90%-rise time (Table 1). Shortening of the A-A interval prolongs the A-V interval through the electrophysiological mechanism, and vice versa, in the absence of autonomic innervation (10). The electrophysiological effect of changes in the A-A interval on the A-V interval is almost instantaneous in the frequency range of 0.01–0.1 Hz (3). As a result, changes in the A-A interval during sympathetic stimulation dynamically attenuated the direct effect of sympathetic stimulation on the A-V interval.

**Fig. 3. Simulated A-V interval step response to 1-Hz sympathetic stimulation under sinus rhythm.** A: the natural frequency for the A-V interval response was varied from 4 times ($\times 4$) to one-fourth ($\times 1/4$) of the baseline value (equal to the natural frequency for the A-A interval response). The A-V interval can be transiently prolonged in response to sympathetic stimulation when the natural frequencies for the A-A and A-V intervals do not match. **B:** the dynamic gain of the A-V interval response was reduced to one-half ($\times 1/2$) of the baseline value or set at zero ($\times 0$). When dynamic gain of the A-V interval response is zero, sympathetic stimulation prolongs the A-V interval while shortening the A-A interval. $\Delta AV$: changes in the A-V interval. See APPENDIX for detailed simulation settings.
are deviated from their baseline physiological values, sympathetic stimulation can prolong the A-V interval while shortening the A-A interval. Such imbalance between the A-A and A-V interval controls would occur when the sympathetic innervation on the atrioventricular node, but not on the sinus node, is impaired by regional ischemia and so forth.

Shortening of the A-A interval during sympathetic stimulation increases the tendency of antegrade conduction block in the accessory pathway between the atria and ventricles. If the A-V interval is prolonged at the same time because of the impaired sympathetic innervation on the atrioventricular node, the accessory pathway would recover excitability for the retrograde conduction, thereby initiating atrioventricular reentrant tachycardia (15). This mechanism would contribute to the initiation of some type of reentrant tachycardia that lacks a preceding premature extrasystole.

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.

Second, there was a difference in the operating range of the A-A interval during the estimation of \( H_{S-AV,N} \) and \( H_{S-AV,P} \). Because the effect of sympathetic stimulation on the A-V interval is sensitive to the A-A interval range (22), the difference in the operating range of the A-A interval would have affected the absolute gain values of \( H_{S-AV,N} \) and \( H_{S-AV,P} \).

Third, the A-V conduction is regulated by both the sympathetic and vagal systems. Although previous studies have demonstrated minimal (11, 22) or small interactions (21) between the sympathetic and vagal controls in the steady-state A-V interval response, further studies are clearly needed to characterize the dynamic interactions between the sympathetic and vagal systems.

Finally, sympathetic stimulation according to the Gaussian white noise is different from the physiological discharge pattern in sympathetic nerve activity. Furthermore, because we stimulated the bilateral cardiac sympathetic nerves simultaneously, laterality in the sympathetic innervation on the atroventricular node was not assessed. To elucidate the sympathetic control of the A-V interval by the physiological sympathetic discharge, experiments such as those using sympathetic activation through arterial baroreflex might be required.

In conclusion, the transfer function representing the direct sympathetic effect on the A-V interval approximated a second-order low-pass filter similar to that representing the direct sympathetic effect on the A-A interval despite the different electrophysiological mechanisms governing the A-A and A-V intervals. The similarity in the dynamic sympathetic regulations of the A-A and A-V intervals, together with the similarity in the dynamic vagal regulations of the A-A and A-V intervals (3), yields similar frequency distributions between R-R and P-R interval power spectra observed in a human study (9). A numerical simulation indicates that if the dynamic characteristics of the A-A and A-V interval regulations by the sympathetic system do not match, it would provide a critical condition for initiating reentrant tachycardia.

APPENDIX

Simulation of the A-V Interval Response to Sympathetic Stimulation

On the basis of the estimated transfer functions (Fig. 2), we simulated the A-A and A-V interval responses by a mathematical model of the second-order low-pass filter. The transfer function of the second-order low-pass filter is described as follows

\[
H(f) = \frac{K}{1 + 2\zeta f - f^2}
\]

where \( K \) is the dynamic gain, \( f_n \) is the natural frequency (in Hz), and \( \zeta \) is the damping coefficient; \( f \) and \( j \) denote the frequency (in Hz) and the imaginary unit, respectively. The upper frequency bandwidth of the system is determined by \( f_n \). When \( f_n \) increases, the system response becomes quicker. The coefficient \( \zeta \) determines the damping behavior of the system. Depending on the value of \( \zeta \), the system behaves as underdamped \((0 < \zeta < 1)\), critically damped \((\zeta = 1)\), or overdamped \((\zeta > 1)\).

To mimic the estimated transfer functions, we set dynamic gains for the simulated \( H_{S-AA} \) and \( H_{S-AV,P} \) to \(-3.6\) and \(-0.86\), respectively (Table 1). The damping ratio and the natural frequency were set at 1.1 and 0.03 Hz, respectively, for both the simulated \( H_{S-AA} \) and \( H_{S-AV,P} \). The electrophysiological effect of changes in the A-A interval on the A-V interval was modeled as a simple all-pass filter with a gain of \(-0.1\) (3). Hence the overall transfer function from sympathetic stimulation to the A-V interval, including both the direct and indirect sympathetic effects, was simulated as follows:

\[
[H_{S-AV,P} - 0.1 \times H_{S-AA}] \cdot \text{A-V interval impulse response was then derived from the inverse Fourier transform of the overall transfer function. The A-V interval step response was calculated from a time integral of the impulse response. Figure 3, A and B, illustrates the influences of changes in \( f_n \) and \( K \) on the A-V interval step response, respectively.}

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