Dynamic sympathetic regulation of left ventricular contractility studied in the isolated canine heart

HIROSHI MIYANO,1 YASUNORI NAKAYAMA,1 TOSHIKI SHISHIDO,1 MASASHI INAGAKI,1 TORU KAWADA,1 TAKAYUKI SATO,1 HIROSHI MIYASHITA,1 MASARU SUGIMACHI,1 JOE ALEXANDER, Jr.,2 AND KENJI SUNAGAWA1

1Department of Cardiovascular Dynamics, National Cardiovascular Center Research Institute, Osaka 565, Japan; and 2Department of Biomedical Engineering, Vanderbilt University, Nashville, Tennessee 37235

Miyano, Hiroshi, Yasunori Nakayama, Toshiaki Shishido, Masashi Inagaki, Toru Kawada, Takayuki Sato, Hiroshi Miyashita, Masaru Sugimachi, Joe Alexander, Jr., and Kenji Sunagawa. Dynamic sympathetic regulation of left ventricular contractility studied in the isolated canine heart. Am. J. Physiol. 275 (Heart Circ. Physiol. 44): H400–H408, 1998.—We investigated the dynamic sympathetic regulation of left ventricular end-systolic elastance (E₂ₙ) using an isolated canine ventricular preparation with functioning sympathetic nerves intact. We estimated the transfer function from both stellate ganglion stimulation to E₂ₙ and ganglion stimulation to heart rate (HR) for both left and right ganglia by means of the white noise approach and transformed those transfer functions into corresponding step responses. The HR response was much larger with right sympathetic stimulation than with left sympathetic stimulation (4.3 ± 1.4 vs. 0.7 ± 0.6 beats·min⁻¹·Hz⁻¹, P < 0.01). In contrast, the E₂ₙ responses without pacing were not significantly different between left and right sympathetic stimulation (0.72 ± 0.34 vs. 0.76 ± 0.42 mmHg·ml⁻¹·Hz⁻¹). Fixed-rate pacing significantly decreased the E₂ₙ response to right sympathetic stimulation (0.53 ± 0.43 mmHg·ml⁻¹·Hz⁻¹, P < 0.01), but not to left sympathetic stimulation (0.67 ± 0.32 mmHg·ml⁻¹·Hz⁻¹, not significant). Although the mechanism by which the sympathetic nervous system regulates cardiac contractility is different depending on whether the left or right sympathetic nerves are activated, this difference does not affect the apparent response of E₂ₙ to dynamic sympathetic stimulation.

left ventricular end-systolic elastance; transfer function; sympathetic nervous system; inotropic action; force-frequency mechanism

IT HAS BEEN WELL ESTABLISHED that the sympathetic nervous system regulates contractility (10, 11, 21–23, 32, 38, 39). Previous investigations have shown that tonic electrical stimulation of the stellate ganglia (16, 22), middle cervical ganglia (16), or left inferior cardiac nerves (10) increased both heart rate (HR) and contractility. It has been shown that, because of the spatial inhomogeneity of sympathetic innervation of the heart (1, 2, 27, 28, 30), the chronotropic effect is stronger with right than with left sympathetic nerve stimulation, whereas the inotropic effect is stronger with left sympathetic nerve stimulation (10, 22, 29, 30). Hence, it appears that the left sympathetic nerves regulate cardiac contractility primarily by means of a direct inotropic mechanism, whereas the right sympathetic nerves regulate contractility by taking advantage of a force-frequency mechanism.

In those investigations, however, ventricular contractility was assessed with the use of indexes known to depend on loading conditions, such as maximum rate of rise in pressure (10, 11), left ventricular pressure (29), local isometric force of the left ventricular surface (2, 38), or intramyocardial pressure (16). Thus any changes in loading conditions that might result from sympathetic stimulation could alter the apparent contractility in those experiments even though true contractility might remain unchanged. Those studies, furthermore, have focused on the cardiac responses to tonic sympathetic stimulation. Because sympathetic nerve activity is dynamically regulated under physiological conditions (7, 14, 15, 26), a clarification of the dynamic characteristics of the sympathetic regulation of cardiac contractility is critical in understanding how the sympathetic nervous system regulates contractility.

The purpose of this investigation was to examine the dynamic cardiac responses to sympathetic stimulation by means of the white noise approach (7, 15, 20, 34) using an isolated, innervated canine heart model. This preparation enabled us to precisely control the loading conditions of the left ventricle and, hence, allowed us to accurately estimate the dynamic response of contractility to sympathetic stimulation. We assessed left ventricular contractility by means of the end-systolic elastance (E₂ₙ) that is known to be a load-insensitive index of left ventricular contractility (17, 31, 33). The results indicate that, although the mechanism by which the sympathetic nervous system regulates E₂ₙ is different depending on whether the right or left sympathetic nerves are activated, this does not affect the dynamic sympathetic regulation of E₂ₙ under spontaneously beating conditions.

MATERIALS AND METHODS

Surgical preparations. Experiments were performed in the isolated, cross-circulated, blood-perfused canine heart. Animal care was in accordance with institutional guidelines. We used adult mongrel dogs of either sex in this study. In each experiment, two mongrel dogs weighing 15–25 kg were anesthetized with pentobarbital sodium (25 mg/kg iv) after premedication with ketamine hydrochloride (5 mg/kg im) and were artificially ventilated (SNA-480-6, Shinano, Tokyo, Japan). The ventilator was adjusted so as to keep arterial pH, arterial Po2, and arterial PcO2 within their respective normal ranges. Additional doses of pentobarbital sodium (2.0–3.0 mg/kg) were administered as needed to maintain an adequate level of anesthesia. After heparinization (10,000 U/dog iv), arterial and venous cannulas for cross circulation were inserted into the bilateral carotid arteries and the right jugular vein of the support dog, respectively. The chest of the
donor dog was opened midsternally as cannulas connected to cross circulation lines were placed in both the left subclavian artery, at a site distal to the origin of the vertebral artery, and the right ventricle via the right atrial appendage.

Bilaterally, the upper and lower poles of the stellate ganglia as well as their spinal cord branches were cut. The jugular veins, carotid arteries, and vagosympathetic trunks were ligated and cut in the midthoracic region. The right subclavian artery was ligated and cut at a site distal to the origin of the right internal mammary artery. Branches of the right subclavian artery were also cut at their origins. We ligated the descending aorta, inferior vena cava, ayzyous vein, and pulmonary hilus, whereupon we initiated cross circulation. We excised the heart en bloc with the bilateral stellate ganglia. After the chordae tendineae of the mitral valve were cut, a latex balloon was placed in the left ventricle. The balloon was filled with water and connected to a servo-pump to control ventricular volume. Left ventricular pressure was recorded with a 5-F catheter-tip micromanometer (SPC-350, Millar Instruments, Houston, TX) inserted in the balloon. Pairs of bipolar electrodes were applied to each of the stellate ganglia. To prevent desiccation and to provide insulation, the stimulation electrodes and nerves were immersed in a mixture of white petrolatum (Vaseline) and paraffin. A pair of stainless steel electrodes was sutured at the left atrial appendage for constant atrial pacing.

Arterial pressure of the donor dog was continuously monitored through the use of a fluid-filled transducer (Statham, Gould, Oxnard, CA) placed in the side arm of the perfusion circuit. Premedication with indomethacin (1 mg/kg iv) and diphenhydramine hydrochloride (30 mg im) was used to prevent systemic hypotension of the support dog during cross circulation. Hemolymph blood collected from the donor dog and/or 10% dextan solution were used, if necessary, to keep mean arterial pressure of the support dog at or near 100 mmHg.

Experimental protocol. Under stable inotropic conditions, we fixed left ventricular volume at a level that provided a peak left ventricular isovolumic pressure of ~80 mmHg. To estimate the dynamic cardiac response to sympathetic stimulation, we stimulated the right stellate ganglion for 12 min using a frequency-modulated, band-limited binary white noise sequence (15, 20, 34) Hz or from 5 to 0 Hz according to the binary random sequence. The stimulation frequency was altered from 0 to 5 Hz in eight hearts. The stimulation electrodes and nerves were immersed in a mixture of white petrolatum (Vaseline) and paraffin. A pair of stainless steel electrodes was sutured at the left atrial appendage for constant atrial pacing.

We also estimated the magnitude squared coherence (Coh), which is a frequency-domain measurement of linear correlation between the input and the output, using the following equation

\[
\text{Coh}(f) = \frac{|S_{in-out}(f)|^2}{S_{in-in}(f) \cdot S_{out-out}(f)}
\]

where \(S_{in-out}(f)\) is power of the output.
adopted this model to parameterize the measured transfer functions (See APPENDIX A).

Statistics. Numerical data are presented as means ± SD. The standard deviations of the gains of the transfer functions at each frequency were calculated after logarithmic transformation. We applied a paired \( t \)-test to examine the differences in \( E_{es} \) response between the protocols with and without atrial pacing. An unpaired \( t \)-test was used for assessing the differences in \( E_{es} \) responses between the right and left sympathetic stimulation protocols. Differences in the HR responses to each stimulation of the stellate ganglion were tested using the Mann-Whitney test because of the inhomogeneity of the variance. \( P \) values, \( 0.05 \) were considered significant (6).

RESULTS

Mean values of \( E_{es} \) and HR during random sympathetic stimulation are summarized in Table 1. \( E_{es} \) and HR before nerve stimulation without pacing were not significantly different for left and right sympathetic stimulation protocols. Sympathetic stimulation significantly increased \( E_{es} \) independent of pacing. Random sympathetic stimulation also significantly increased HR.

The rate of left atrial pacing was not significantly different between the two stimulation protocols. As anticipated, the pacing itself significantly increased \( E_{es} \). However, the mean values of \( E_{es} \) during random stimulation were not significantly different between the protocols with and without pacing.

Changes in HR and \( E_{es} \) during random sympathetic stimulation. Figure 1 shows the effects of sympathetic stimulation on HR and \( E_{es} \). As shown in Fig. 1A, random right sympathetic stimulation significantly alters both \( E_{es} \) and HR. In contrast, as shown in Fig. 1B, despite the significant response of \( E_{es} \), left sympathetic stimulation can raise the baseline HR but fails to elicit dynamic alterations in HR.

Dynamic transfer characteristics from sympathetic stimulation to HR. Figure 2 shows the transfer functions from sympathetic stimulation frequency to HR along with their corresponding step responses. As shown in Fig. 2A, the gain of the transfer function from right sympathetic stimulation to HR is relatively constant below 0.02 Hz and decreases above that frequency. The phase was almost in phase in the low frequency range. The natural frequency was 0.030 ± 0.010 Hz. The magnitude squared coherence was over 0.7 up to 0.1 Hz and decreased above that frequency. HR was predominantly linearly dependent on right sympathetic stimulation below 0.1 Hz.

Figure 2B shows the transfer function from left sympathetic stimulation to HR. Although the transfer function is somewhat noisy, its gain in the low frequency range was much smaller than that observed in right sympathetic stimulation. The fact that its coherence was also lower indicates that the linear HR response to sympathetic stimulation was less with left

Table 1. Summary data of mean values of heart rate and left ventricular end-systolic elastance before and during random sympathetic stimulation

<table>
<thead>
<tr>
<th></th>
<th>Pacing (−) control</th>
<th>Pacing (−) during stimulation</th>
<th>Pacing (+) control</th>
<th>Pacing (+) during stimulation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Left sympathetic stimulation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( E_{es} ), mmHg/ml</td>
<td>9.3 ± 1.2</td>
<td>12.3 ± 1.8*</td>
<td>10.3 ± 3.0*</td>
<td>11.8 ± 1.9†</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>127.1 ± 24.3</td>
<td>142.9 ± 17.0*</td>
<td>166.7 ± 18.5</td>
<td></td>
</tr>
<tr>
<td><strong>Right sympathetic stimulation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( E_{es} ), mmHg/ml</td>
<td>8.3 ± 1.7</td>
<td>11.2 ± 3.2*</td>
<td>9.7 ± 3.4*</td>
<td>11.7 ± 4.6†</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>129.1 ± 27.0</td>
<td>162.2 ± 26.3*</td>
<td>164.5 ± 22.4</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as means ± SD. \( E_{es} \), left ventricular end-systolic elastance; pacing (−) and (†), without and with pacing. *\( P < 0.05 \) vs. control without pacing. †\( P < 0.05 \) vs. control with pacing.

Fig. 1. Representative records of sympathetic stimulation, heart rate (HR), and left ventricular end-systolic elastance (\( E_{es} \)). A: right sympathetic stimulation changes both \( E_{es} \) and HR. B: left sympathetic stimulation changes \( E_{es} \) without changing HR.
sympathetic stimulation than with right sympathetic stimulation.

The marked differences in the gains of the transfer functions were evidenced as the smaller dynamic gain of the estimated step response to left sympathetic stimulation compared with that to right sympathetic stimulation (left: $0.7 \pm 0.6$ vs. right: $4.3 \pm 1.4$ beats/min, $P < 0.01$) as shown in Fig. 2 (bottom).

Dynamic transfer characteristics from right sympathetic stimulation to $E_{es}$. Figure 3 shows the transfer functions from right sympathetic stimulation to $E_{es}$ with and without constant rate pacing, along with their respective step responses. When the heart was not paced, as shown in Fig. 3A, the gain of the transfer function was relatively constant below 0.03 Hz and decreased at higher frequencies. The phase was in phase in the low frequency range and increasingly delayed with higher frequencies, becoming completely out of phase at 0.05–0.06 Hz. The coherence was $\sim 0.7$ in the low frequency range and increased to 0.8 with frequency up to 0.07 Hz, indicating that most of the response in $E_{es}$ was linear in the low frequency range.

Figure 3B shows the transfer function from right sympathetic stimulation to $E_{es}$ with fixed-rate pacing. As can be seen, general characteristics of gain, phase, and coherence of the transfer function do not change.
with pacing, except that the gain in the low frequency range appears to be decreased.

Comparison of the step responses shown in Fig. 3 (bottom) indicates that pacing significantly decreased the dynamic gain (control: 0.76 ± 0.42 vs. pacing: 0.52 ± 0.43 mmHg/ml, P < 0.01); however, pacing did not significantly alter the natural frequency (control: 0.028 ± 0.006 vs. pacing: 0.029 ± 0.004 Hz).

Dynamic transfer characteristics from left sympathetic stimulation to \( E_{es} \). Figure 4 shows the transfer functions from left sympathetic stimulation frequency to \( E_{es} \) with and without fixed-rate pacing, along with their corresponding step responses. As shown in Fig. 4A, when the heart was not paced, the transfer function from left sympathetic stimulation to \( E_{es} \) and its coherence resembled those from nonpaced right sympathetic stimulation (see Fig. 3A). The natural frequency of the transfer function from left sympathetic stimulation frequency to \( E_{es} \) was 0.030 ± 0.003 Hz. This was not significantly different from that obtained with right sympathetic stimulation.

Figure 4B shows the transfer function from left sympathetic stimulation to \( E_{es} \) with the corresponding step response under fixed-rate left atrial pacing. Pacing did not significantly alter the natural frequency of the transfer function (0.032 ± 0.005 Hz).

As shown in Fig. 4 (bottom), the dynamic gains as assessed by the steady-state gains of the step responses were not significantly different between the conditions with and without pacing (control: 0.72 ± 0.34 vs. pacing: 0.67 ± 0.32 mmHg/ml).

DISCUSSION

Relative contributions of direct and indirect inotropic effects in the sympathetic regulation of ventricular contractility. We have shown in isolated canine left ventricles that the dynamic gain of the inotropic response to right cardiac sympathetic stimulation without pacing was not significantly different from that obtained with left sympathetic stimulation. However, when HR was held constant, the dynamic gain significantly decreased by 30% with right sympathetic stimulation, but not with left sympathetic stimulation. Thus the left sympathetic nerve regulates ventricular contractility primarily by its direct inotropic action, whereas the right sympathetic nerve does so by both its direct inotropic action and indirect action resulting from its positive chronotropic effect.

Because there was no significant difference in the stimulation amplitude between right and left sympathetic stimulations (see Experimental protocol), it appears that the dynamic, direct inotropic action of the left sympathetic nerve is stronger than that of the right sympathetic nerve. This does not mean, however, that the left sympathetic nerve is more important than the right sympathetic nerve in regulating contractility under physiological conditions. It is well known that rate-dependent contractility is most manifest in the HR range below 120 beats/min (25). Control HR in the current investigation was significantly larger than 120 beats/min. In such an HR range, it is conceivable that the right sympathetic nerve, through a rate-dependent mechanism, might predominate over the left sympathetic nerve in the regulation of contractility.

The right cardiac sympathetic nerve distributes predominantly to the atria and nodal tissues and minimally to the ventricles. In contrast, the left cardiac sympathetic nerves, to a large extent, innervate the ventricles (2, 27–30), with some distributions to the atrioventricular node (32, 39) and atrium (2, 28, 30). Moreover, the nerves from the left stellate ganglion predominantly affect the electrical activity of the posterior ventricular wall, whereas those from the right stellate ganglion influence electrical activity of the

![Fig. 4. Averaged transfer functions from left sympathetic stimulation frequency to \( E_{es} \) and the calculated step response without (A) and with atrial pacing (B). Solid lines indicate means, and dotted lines represent SE.](http://ajpheart.physiology.org/)
anterior ventricular wall (38). These differences in the innervation of the heart by the right and left sympathetic nerves may explain, at least in part, the left sympathetic dominance in positive inotropic action and the right sympathetic dominance in positive chronotropic action.

Previous investigations have shown that the inotropic effect is stronger with left sympathetic stimulation than with right sympathetic stimulation even under spontaneously beating conditions (16, 22, 29, 30). Although these results appear inconsistent with ours, differences in the methodology used, such as stimulation frequency, amplitude, and pattern, as well as the indexes used for assessing ventricular contractility, might account for these discrepancies.

Linearity of the dynamic sympathetic regulation of $E_a$. As shown in Figs. 3 and 4, the coherence value was 0.6–0.9 in the frequency range below ~0.1 Hz. The corresponding $P$ values were 0.024–0.0003, indicating that changes in $E_a$ are quite linearly coupled with those in sympathetic stimulation. The lower of the coherence values in the low frequency range might be manifestations of slow changes in contractility unrelated to changes in sympathetic stimulation. For instance, because the segment length of analysis in deriving the transfer function was 128 s, even a few extra systoles over 12 min could significantly lower the coherence value in the low frequency range. Other factors, such as the time-dependent deterioration of isolated hearts and the instability of the hemodynamic conditions of the support dogs, both of which could affect ventricular contractility of the isolated heart, might also lower the coherence in the low frequency range. Thus, even though the coherence is a measure of linearity of a system, a relatively low coherence as observed in the low frequency range in this case does not necessarily imply true system nonlinearity. Rather, it could suggest the presence of slow changes in contractility unrelated to sympathetic stimulation.

In the higher frequency range above 0.1 Hz, the coherence values decreased despite the fact that the bandwidth of the input sympathetic stimulation was guaranteed up to 0.5 Hz. Although the exact mechanism by which the coherence value was reduced remains unknown, we speculate that a decreased gain in the high frequency range is responsible for this observation. As shown in the equation for the magnitude squared coherence function (see Data analysis), the coherence quantifies the variability of the output explainable by the input. Hence, if the noise in the output unrelated to the input has a constant level of variability over a wide frequency range, a decreased output variability resulting from a decreased gain in the high frequency range would inevitably lower the coherence value. Thus the low coherence value in the frequency range above 0.1 Hz does not necessarily indicate nonlinearity of the system in this frequency range.

For these reasons, we think that predominantly ventricular contractility is linearly coupled with sympathetic stimulation, at least under the tested conditions.

Effects of sympathetic stimulation on ventricular-arterial coupling. Previous studies have shown that the ratio of $E_a$ to effective arterial elastance ($E_{es}$) dictates the efficiency of mechanical energy transfer from the left ventricle to the arterial system (36, 37). Because $E_a$ depends not only on arterial resistance but also on HR, the fact that the right and left sympathetic nerves have different effects on $E_{es}$ and HR suggests that they have different effects on energy transfer efficiency as well.

To examine the differential contributions of the right and left sympathetic nerves to ventricular-arterial coupling, we used the step responses derived from the relevant transfer functions to simulate the transient changes in the ratio of $E_a$ to $E_{es}$ ($E_a/E_{es}$) that would be observed in response to a 10-Hz step input of right or left sympathetic stimulation. Details of the derivation of the transient responses are provided in APPENDIX B.

Figure 5 shows the transient responses of $E_a/E_{es}$. As can be seen, right sympathetic stimulation, although initially increasing the ratio by 10%, ultimately decreases it by 18%. On the contrary, left sympathetic stimulation decreased the ratio by more than 43%. Thus, under normal conditions in which the ventricle and the arterial system are likely to be matched, that is, when $E_a/E_{es}$ is 0.5–1 (3, 9), right sympathetic stimulation has minimal influence over ventricular-arterial coupling and energy transmission efficiency. However, left sympathetic stimulation would result in considerable mismatch, which would in turn lead to inefficient energy transmission from the heart to the arterial system. However, when ventricular contractility is depressed, that is, when $E_a/E_{es}$ is $>2$ (3), left sympathetic stimulation will improve matching more than will right sympathetic stimulation.

Although it remains unknown whether the left and right sympathetic nerves are selectively regulated un-
under physiological conditions, the differential effects of left and right sympathetic nerves on $E_{es}$ and HR provide the potential for the regulatory system to neurally manipulate ventricular-arterial coupling under various conditions. Further studies are needed to clarify its physiological implication.

Methodological considerations. The isolated, cross-circulated canine heart preparation has been used for examining left ventricular mechanics (4, 12, 13, 25, 33, 35, 37) because this preparation makes it possible to precisely regulate left ventricular loading condition and, hence, to precisely estimate left ventricular contractility. However, because the autonomic innervation is lost during surgical preparation, it has been impossible to use this preparation for examining the autonomic regulation of left ventricular contractility. To overcome this disadvantage, we developed the method to isolate the heart while preserving the autonomic innervation to the heart. Although $E_{es}$ significantly responded to sympathetic stimulation, the surgical preparation for isolating hearts might damage sympathetic nerves and thus make the heart less responsive to sympathetic stimulation. However, the mean increase in $E_{es}$ during sympathetic stimulation in this study was compatible with that observed in conscious dogs during exercise (9). Therefore, we think that the results obtained from this study would be applicable in understanding cardiovascular pathophysiology under more intact conditions.

In this study we kept left ventricular volume constant. However, the end-systolic pressure-volume relationship has been shown to be somewhat different between the isovolumic beat and the ejecting beat. Namely, $E_{es}$ of the small or normal ejection beat exceeds that of the isovolumic beat, i.e., ejecting activation (4, 12, 13, 35). On the other hand, large ejection has a negative effect on end-systolic pressure generation at the same end-systolic volume, i.e., ejecting deactivation (13, 35). Therefore, $E_{es}$ would depend not only on contractility but also on loading conditions. Because the sympathetic activation alters contractility, afterload, and venous return (preload) simultaneously in the in situ heart, the net effect on the $E_{es}$ response to sympathetic stimulation is uncertain from the present results. However, the fact that ejecting activation and ejecting deactivation counteract each other may make $E_{es}$ less sensitive to changes in loading conditions (12, 13, 35). Thus the similar dynamic $E_{es}$ response to sympathetic stimulation would be observed even in the in situ hearts.

Limitations. There are some limitations in this study. We used the white noise approach to identify the dynamic transfer characteristics from sympathetic stimulation to $E_{es}$ (7, 15, 20, 34). Although this approach made it possible to identify the unbiased linear transfer function, input sympathetic stimulation was obviously nonphysiological. However, the fact that coherence values were rather high in the frequency range below 0.1 Hz, where the dynamic sympathetic regulation of $E_{es}$ was by far most effective, indicates that sympathetic inotropic regulation is indeed reasonably linear. Therefore, from a mathematical point of view, similar linear responses would be expected to result even from the natural sympathetic stimulus as long as the amplitude and frequency bandwidth of the natural stimulus were within the tested range. Whether generalizations of our current observations beyond our test conditions are truly valid remains to be investigated.

We only stimulated the sympathetic nerves in this study. However, previous investigations have shown the existence of an interaction between sympathetic and vagal nerves in the regulation of cardiac contractility (11, 21). Kawada et al. (18, 19) also showed a dynamic sympathovagal interaction in the regulation of heart rate. Therefore, simultaneous stimulation of both sympathetic and vagal nerves may induce different dynamic responses in $E_{es}$ through their interaction. Further investigation is necessary to clarify the possible role of dynamic sympathovagal interaction in the modulation of $E_{es}$.

In conclusion, both the right and left sympathetic nerves can induce the same degree of dynamic $E_{es}$ response under spontaneously beating conditions. The right sympathetic nerve dynamically regulated cardiac contractility by both a direct inotropic mechanism and the force-frequency mechanism, whereas the left sympathetic nerve regulated cardiac contractility primarily by a direct inotropic mechanism. However, this difference in mechanisms does not significantly affect the apparent dynamic transfer characteristics from sympathetic stimulation to $E_{es}$.

APPENDIX A

The following algebraic equation describes the transfer function of the second-order model $[H_{m}(f)]$

$$H_m(f) = \frac{K}{1 + 2\hat{\xi} f_n - f_n^2} e^{-2\pi j f L}$$

where $j$ is an imaginary unit and $f$ is frequency. The parameters $K$, $f_n$, $\xi$, and $L$ are the steady-state gain, natural frequency, damping coefficient, and lag time, respectively. We calculated these parameters using an iterative, nonlinear least-squares fitting technique (5).

APPENDIX B

The effective $E_{es}$ is the product of arterial resistance ($R$) and HR ($E_{es}$) (37). Therefore, the ratio of the transient change in $E_{es} / E_{es}$ ($E_{es}/E_{es}(t)$) is calculated as

$$\frac{E_{es}}{E_{es}(t)} = \frac{\Delta HR(t) \cdot \Delta R(t)}{HR \cdot R \cdot \Delta E_{es}(t)}$$

where $HR$, $R$, and $E_{es}$ are the initial values of heart rate, arterial resistance, and end-systolic elastance, respectively. $\Delta HR(t), \Delta R(t)$, and $\Delta E_{es}(t)$ are the transient responses of each
from the initial values to 10-Hz sympathetic stimulation. With the assumption that $R$ does not change during cardiac sympathetic stimulation ($\Delta R(t) = R$), rearrangement of the above equation yields the following equation

$$E_a(t) = \frac{H R}{1 + \Delta H(t)}$$

Therefore, percent changes in $E_a/E_s$ from the initial $E_a/E_s$ are calculated as

$$\% \frac{E_a}{E_s}(t) = \left( \frac{E_a(t)}{E_s} - 1 \right) \times 100$$

We used the averaged step responses of $HR$ and $E_s$ during random sympathetic stimulation (Figs. 2–4, bottom) as $\Delta HR(t)$ and $\Delta E_s(t)$, respectively. The initial values of $E_s$ and $HR$ in this stimulation are 8 mmHg/ml and 80 beats/min, respectively.

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Address for reprint requests: H. Miyano, Dept. of Cardiovascular Dynamics, National Cardiovascular Center Research Institute, 5-7-1 Fujishiriodai, Suita, Osaka 565, Japan.

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REFERENCES


