Dynamic Effects of Carotid Sinus Baroreflex on Ventriculoarterial Coupling Studied in Anesthetized Dogs

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We evaluated dynamic effects of the carotid sinus baroreflex on ventriculoarterial coupling. In seven anesthetized, vagotomized dogs, we bilaterally isolated carotid sinuses and randomly changed carotid sinus pressure while measuring aortic pressure, aortic flow, and left ventricular pressure. Estimating left ventricular end-systolic elastance (Ees) and effective arterial elastance (Ea) on a beat-to-beat basis, we determined transfer functions from the carotid sinus pressure to Ees (Hes) and from the carotid sinus pressure to Ea (Hea) over the frequency range spanning 0.002–0.25 Hz. Both Hes and Hea exhibited characteristics of a second-order low-pass filter. The gains of Hes and Hea were 0.085±0.065 (mean±SD) and 0.081±0.049 mm Hg/ml/mm Hg, respectively. There were no significant differences in natural frequencies (0.039±0.013 versus 0.039±0.007 Hz) or damping ratios (0.65±0.11 versus 0.64±0.24). The results indicated that the carotid sinus baroreflex dynamically altered Ees and Ea to the same extent in the process of stabilizing arterial pressure. Because the arterial system extracts maximal external work from a given heart when Ea equals Ees, the carotid sinus baroreflex appeared to be designed to regulate the ventricular and arterial properties to optimize the energy transmission from the left ventricle to the arterial system in anesthetized, vagotomized dogs. (Circulation Research 1992;70:1044–1053)

KEY WORDS • carotid sinus baroreflex • ventriculoarterial coupling • end-systolic elastance • effective arterial elastance • transfer function

The left ventricle is a hydraulic energy source and incessantly transmits mechanical energy to the arterial system. Various studies have indicated that the energy transferred from the left ventricle to the arterial system is maximum when the left ventricle is coupled with the physiological arterial system.1-4 To quantify ventriculoarterial coupling, we treated both the left ventricle and the arterial system as elastic chambers.5-8 Figure 1 illustrates the basic framework of the ventriculoarterial coupling in the pressure–volume plane. End-systolic elastance (Ees), which represents contractility of the left ventricle, is the slope of the end-systolic pressure–volume relation (line A in Figure 1). Effective arterial elastance (Ea), which in the steady state approximates arterial resistance divided by the cardiac cycle length, is the slope of the end-systolic pressure–stroke volume relation (line B in Figure 1). Increases in Ee reflect increases in arterial resistance or heart rate. The end-systolic equilibrium point that results when the left ventricle is coupled with the arterial system is obtained as the intersection between lines A and B in Figure 1. Stroke volume is determined as the volume transferred from the left ventricular elastic chamber to the arterial elastic chamber. The shaded area is external work, which represents the energy transferred from the left ventricle to the arterial system. In this framework, the energy transferred from the left ventricle to the arterial system is maximum when Ea equals Ees.7

The carotid sinus baroreflex is a negative-feedback system acting to restore systemic arterial pressure when a disturbance such as a decrease in preload occurs.9 Although many investigators have studied effects of the carotid sinus baroreflex on the cardiac contractility10-14 and arterial resistance,15-17 no one has ever studied its effects on the ventriculoarterial coupling itself. Under the framework of ventriculoarterial coupling, restoration of arterial pressure by the baroreflex may well be achieved through an increase in Ees an increase in Ea, or both. So far, the question of which among these three mechanisms is actually operating remains unanswered. This situation notwithstanding, what does appear fairly certain is that to optimize the energy transmission from the left ventricle to the arterial system, the baroreflex needs to alter both Ees and Ea to the same extent.

The purpose of this study is to evaluate the effects of the carotid sinus baroreflex on the ventriculoarterial coupling with special reference to the energy transmission from the left ventricle to the arterial system.

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Because the disturbances to the cardiovascular system are not only static but also dynamic, we designed the experimental protocol to evaluate dynamic effects of the carotid sinus baroreflex. We first estimated open-loop transfer functions from carotid sinus pressure to $E_{es}$ and to $E_{ae}$. Then dynamic effects of the baroreflex on the ventriculoarterial coupling were evaluated based on these transfer functions. The results indicate that in anesthetized dogs the carotid sinus baroreflex dynamically changes $E_{es}$ and $E_{ae}$ to the same extent, which in turn maximizes the energy transmission from the left ventricle to the arterial system.

Materials and Methods

Preparations

Seven mongrel dogs weighing $16.9 \pm 2.1$ kg (mean $\pm$ SD) were anesthetized with pentobarbital sodium (25 mg/kg i.v.), and supplementary doses (25 mg i.v.) of the anesthetic were administered when necessary. The dogs were intubated and artificially ventilated with room air by using a volume-cycled respirator (SN-480-4, Shimano, Tokyo). Arterial blood gases and pH were monitored and maintained within normal limits by adjustments of respiratory rate and volume, supplementing oxygen gas, or administration of sodium bicarbonate. Heparin sodium (5,000 units) was administered systematically to prevent blood coagulation.

We exposed carotid arteries and vagal nerves through a midline cervical incision. After bilateral ligation of the internal and external carotid arteries, both carotid sinuses were cannulated with elastic tubes and connected with a specially designed servo-pump for perturbation of carotid sinus pressure. We ligated both occipital arteries at their root to eliminate the effects of the chemoreflex.9 The vagal nerves were cut to remove the buffering effects of other baroreflex systems such as the aortic arch baroreflex and the cardiopulmonary baroreflex. A high-fidelity micromanometer (MPC-500, Millar Instruments, Inc., Houston, Tex.) was inserted through the left lingual arteries up to the carotid sinus to measure carotid sinus pressure.

The chest was opened through a median sternotomy, and the heart was suspended in a pericardial cradle. The aortic root was dissected so that an electromagnetic flow probe connected to an electromagnetic flowmeter (MFV-2100, Nihon Koden, Tokyo) could be placed around it. A high-fidelity micromanometer was inserted into the right femoral artery and was advanced retrograde within the ascending aorta to the same level as the aortic flow probe. To measure left ventricular pressure, another high-fidelity micromanometer was inserted through the apex of the left ventricle.

Protocol

We used the white-noise method18-20 to identify open-loop transfer functions from carotid sinus pressure to $E_{es}$ and $E_{ae}$, because the white-noise method enables the estimation of unbiased linear transfer characteristics of a nonlinear system. Perturbing carotid sinus pressure by operating the servo-pump in accordance with a computer-generated pseudorandom binary sequence,19 we measured aortic pressure, left ventricular pressure, and aortic flow simultaneously (Figure 2). Because the pseudorandom binary sequence cycled every 512 seconds and the minimum interval of the perturbation was 1 second, we could sufficiently whiten the power spectrum of the carotid sinus pressure between 0.002 and 0.5 Hz.

The mean level of the carotid sinus pressure was matched to that of aortic pressure. The amplitude of the perturbation was $\pm 25$ mm Hg. Carotid sinus pressure, aortic pressure, left ventricular pressure, and aortic flow were digitized at 200 Hz with a 12-bit resolution and stored on the hard disk of a microcomputer (PC-9801 RAS, NEC, Tokyo) networked to a dedicated laboratory computer system (VAX stations, Digital Equipment Corp., Marlboro, Mass.). To avoid aliasing,19 all data were low-pass filtered before digitization with a corner frequency of 100 Hz.

Estimation of End-Systolic Elastance and Effective Arterial Elastance

We used a single-beat estimation technique to evaluate beat-to-beat $E_{es}$ without altering the loading conditions of the left ventricle. Details of the single-beat estimation of $E_{es}$ are described elsewhere.21-23 Briefly, we first estimated peak isovolumic left ventricular pressure at end-diastolic volume by fitting a sinusoidal function to the isovolumic portion of the measured left ventricular pressure.21 Drawing a tangential line from the estimated peak isovolumic pressure to the right corner of the pressure-ejected volume loop (obtained by the time integration of aortic flow and measured left ventricular pressure) yielded the end-systolic pressure–stroke volume relation line. The slope of this line represents $E_{es}$.

We determined $E_{ae}$ by dividing the end-systolic pressure by stroke volume according to its definition.

\[ E_{ae} = \frac{P_{es}}{V_{syst}} \]

\[ E_{es} = \frac{P_{es}}{V_{esyst}} \]

\[ E_{ae} = \frac{E_{es}}{E_{es} + E_{ae}} \]

\[ E_{es} \approx \frac{P_{es}}{V_{esyst}} \]

\[ E_{ae} \approx \frac{P_{es}}{V_{esyst}} \]

\[ E_{es} \approx \frac{P_{es}}{V_{esyst}} \]

\[ E_{ae} \approx \frac{P_{es}}{V_{esyst}} \]
Estimation of Transfer Functions

The transfer function is an expression of the linear input–output relation in the frequency domain.\(^1\)\(^9\) Dividing the output–input cross-power spectrum \(|P_{\text{out} \rightarrow \text{in}}(f)|\) by the input power spectrum \(|P_{\text{in} \rightarrow \text{in}}(f)|\) yields the transfer function; i.e.,

\[
H(f)=\frac{|P_{\text{out} \rightarrow \text{in}}(f)|}{|P_{\text{in} \rightarrow \text{in}}(f)|} \tag{1}
\]

where \(H(f)\) is the transfer function for a given frequency, \(f\). Considering carotid sinus pressure as the input and \(E_a\) and \(E_s\) as the outputs, we rearranged the data into two channel data sets of 256 elements at a reduced rate of 0.5 Hz (512 seconds). Applying the multichannel autoregressive model\(^24\)-\(^26\) to these data sets, we estimated power and cross-power spectra of carotid sinus pressure and outputs. The order of the autoregressive model, which was determined by Akaike’s information criterion,\(^24\),\(^27\) varied between three and eight. According to Equation 1, we estimated transfer functions from carotid sinus pressure to \(E_a\) (\(H_{Ea}\)) and from carotid sinus pressure to \(E_s\) (\(H_{Es}\)) over the frequency range of 0.002–0.25 Hz.

Because the baroreflex has been known to have sizable nonlinearity, the transfer function was unable to fully represent its input–output relation. As a measure of the linearity of the system, we estimated the squared coherence function \(C(f)\) by dividing the squared magnitude of cross-power spectrum by the power spectra of the input and of the output\(^1\)\(^9\); i.e.,

\[
C(f)=\frac{|P_{\text{out} \rightarrow \text{in}}(f)|^2}{P_{\text{in} \rightarrow \text{in}}(f) \cdot P_{\text{out} \rightarrow \text{out}}(f)} \tag{2}
\]

The coherence function is conceptually analogous to the squared correlation coefficient, \(r^2\), of a linear regression analysis and attains a value ranging between zero and unity. That is, a high value of coherence indicates that changes in output are highly linearly “coherent” with those in input over a given frequency.

We also estimated transfer functions from carotid sinus pressure to aortic pressure in the same way. We used inverse fast Fourier transform\(^28\) of the transfer functions to obtain their respective impulse responses, which are representations of the transfer functions in the time domain.\(^1\)\(^9\)

Optimality of the Afterload

We defined the optimal afterload as that which extracts maximal external work \((E_{W_{\text{max}}})\) from a given left ventricle. We determined the optimality of the afterload \((Q_{\text{load}})\) from the ratio of external work \((E_W)\) to its theoretical maximal value \((E_{W_{\text{max}}})\); i.e.,

\[
Q_{\text{load}}=\frac{E_W}{E_{W_{\text{max}}}} \tag{3}
\]

According to the framework of ventriculoarterial coupling (Figure 1), the end-systolic pressure \((P_{es})\) can be expressed as

\[
P_{es}=SV \cdot E_s=(V_{ed}-V_o-SV) \cdot E_s \tag{4}
\]

where \(SV\) is stroke volume, \(V_{ed}\) is end-diastolic volume, and \(V_o\) is end-systolic unstressed volume. Rearranging Equation 4 yields

\[
SV=(V_{ed}-V_o)/(1+E_a/E_{es}) \tag{5}
\]

and

\[
P_{es}=(V_{ed}-V_o) \cdot E_s/(1+E_a/E_{es}) \tag{6}
\]

Assuming isobaric contraction at a pressure of \(P_{es}\), \(E_{W}\) can be approximated as

\[
E_{W} = P_{es} \cdot SV \\
=(V_{ed}-V_o)^2 \cdot E_s/(1+E_a/E_{es})^2 \tag{7}
\]

By differentiating Equation 7 with respect to \(E_{es}\) one can show that \(E_{W}\) becomes maximal when \(E_{es}\) is equal to \(E_{es}\). Substituting \(E_{es}\) in Equation 7 with \(E_{es}\) yields

\[
E_{W_{\text{max}}}=(V_{ed}-V_o)^2 \cdot E_{es}/4 \tag{8}
\]

Substituting Equations 7 and 8 into Equation 3 yields

\[
Q_{\text{load}}=\frac{4 \cdot E_a/E_{es}}{(1+E_a/E_{es})^2} \tag{9}
\]

Note that \(Q_{\text{load}}\) is independent of preload. Once we know the ratio of \(E_{es}\) to \(E_{es}\), we can evaluate the optimality of energy transmission from the left ventricle to the arterial system. When \(E_{es}\) equals \(E_{es}\), \(Q_{\text{load}}\) becomes unity and the arterial system extracts maximal energy from a given \(E_{es}\) and \(V_{ed}-V_o\).
### Dynamic Effects of Baroreflex on Optimality of the Afterload

Using the identified transfer functions, we examined the dynamic effects of the carotid sinus baroreflex on ventriculoarterial coupling by computer simulation. Because one of the major disturbances to the cardiovascular system is a change in preload, we tested performance of the carotid sinus baroreflex by simulating how \( E_{es} \), \( E_a \), and \( Q_{load} \) change when preload (i.e., \( V_{es} - V_o \)) abruptly increases or decreases by 20%. Mean values of measured data were used to determine \( P_{es} \), \( E_{es} \), \( E_a \), and \( V_{es} - V_o \) in the control conditions. To close the negative feedback loop of the carotid sinus baroreflex, we assumed that the carotid sinus pressure was equal to \( P_{es} \) for every beat. After the abrupt changes of \( V_{es} - V_o \), we estimated dynamic changes of \( E_{es} \) and \( E_a \) every 2 seconds by convolving impulse responses of \( H_{es} \) and \( H_a \) with the previous values of carotid sinus pressure. The next value of the carotid sinus pressure was obtained by Equation 6 with the predicted \( E_{es} \) and \( E_a \) at that moment. From these \( E_{es} \) and \( E_a \), we estimated \( Q_{load} \) to evaluate how the carotid sinus baroreflex affects the energy transmission from the left ventricle to the arterial system in response to the abrupt changes in preload.

### Statistical Analysis

We used the paired t test to compare fitted parameters between \( H_{es} \) and \( H_a \) and other paired data. The repeated-measures analysis of variance and Dunnett's test were used to evaluate effects of the \( V_{es} - V_o \) changes on \( Q_{load} \). Results were reported as mean±SD. A value of \( p<0.05 \) was considered significant.

### Results

#### Hemodynamic Parameters

We listed hemodynamic parameters in Table 1. Standard deviation in each animal represents variabilities induced by the white-noise perturbation. The mean level of the carotid sinus pressure was matched to that of aortic pressure (\( p>0.05 \)). Note that the mean value of \( E_{es} \) was not significantly different from that of \( E_a \) (\( p>0.05 \)). Using these data, we estimated the following transfer functions.

### Table 1. Hemodynamic Parameters

<table>
<thead>
<tr>
<th>No.</th>
<th>BW (kg)</th>
<th>CSP (mm Hg)</th>
<th>AoP (mm Hg)</th>
<th>SV (ml)</th>
<th>HR (bpm)</th>
<th>( E_{es} ) (mm Hg/ml)</th>
<th>( E_a ) (mm Hg/ml)</th>
<th>( V_{es} - V_o ) (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>16.0</td>
<td>106±12</td>
<td>124±11</td>
<td>11.2±0.7</td>
<td>174±2</td>
<td>10.4±1.2</td>
<td>10.6±0.7</td>
<td>23.8±1.1</td>
</tr>
<tr>
<td>2</td>
<td>20.5</td>
<td>164±16</td>
<td>153±10</td>
<td>9.4±0.2</td>
<td>187±3</td>
<td>12.0±0.9</td>
<td>14.3±1.0</td>
<td>23.4±0.5</td>
</tr>
<tr>
<td>3</td>
<td>15.0</td>
<td>113±14</td>
<td>148±11</td>
<td>7.7±0.3</td>
<td>189±2</td>
<td>13.6±1.6</td>
<td>16.0±1.2</td>
<td>20.2±0.8</td>
</tr>
<tr>
<td>4</td>
<td>14.0</td>
<td>95±15</td>
<td>110±6</td>
<td>10.2±0.4</td>
<td>143±1</td>
<td>10.3±1.0</td>
<td>10.7±0.6</td>
<td>21.1±0.8</td>
</tr>
<tr>
<td>5</td>
<td>17.0</td>
<td>123±14</td>
<td>129±6</td>
<td>11.2±0.3</td>
<td>137±1</td>
<td>11.3±0.5</td>
<td>11.2±0.3</td>
<td>22.9±0.5</td>
</tr>
<tr>
<td>6</td>
<td>18.0</td>
<td>89±15</td>
<td>96±8</td>
<td>9.1±0.3</td>
<td>159±1</td>
<td>10.4±0.6</td>
<td>10.6±0.9</td>
<td>18.3±0.4</td>
</tr>
<tr>
<td>7</td>
<td>18.0</td>
<td>111±15</td>
<td>101±7</td>
<td>8.6±0.3</td>
<td>164±2</td>
<td>8.6±0.4</td>
<td>12.3±0.7</td>
<td>20.1±0.7</td>
</tr>
</tbody>
</table>

Mean values are mean±SD. BW, body weight; CSP, carotid sinus pressure; AoP, aortic pressure; SV, stroke volume; HR, heart rate; bpm, beats per minute; \( E_{es} \), end-systolic elastance; \( E_a \), effective arterial elastance; \( V_{es} \), end-diastolic volume; \( V_o \), end-systolic unstressed volume.

#### Open-Loop Transfer Function of the Carotid Sinus Baroreflex

Figure 3 illustrates the averaged open-loop transfer functions from carotid sinus pressure to aortic pressure (HAoP) and its coherence function. The bold lines are
means, and the two accompanying thin lines indicate ±SD. Note that both the frequency and modulus axes were logarithmically scaled, i.e., cast as a Bode plot. In its general frequency characteristics, $H_{Aop}$ was a low-pass filter. Its modulus was rather flat up to 0.03 Hz and thereafter decayed at the rate of −40 dB per decade. The phase of $H_{Aop}$, which was perfectly out of phase in lower frequencies, shifted up to slightly more than 180°. These characteristics are consistent with a second-order delay system with a delay element. The coherence function was more than 0.5 up to 0.15 Hz and decreased above that frequency.

We parameterized $H_{Aop}$ by fitting the second-order delay system with a delay element (see “Appendix”). The gain was 0.92±0.41, which was rather low for a feedback system. The natural frequency was 0.03±0.005 Hz, which meant that the carotid sinus baroreflex mainly responded to changes in carotid sinus pressure lower than 0.03 Hz. The damping ratio was 0.59±0.17, which was relatively small and indicated not only that the response of the carotid sinus baroreflex was rather quick, but also that it might have an oscillatory component. There was a short dead time of 1.7±0.6 seconds.

To facilitate interpretation and understanding of the transfer function, we present a step response of $H_{Aop}$ in Figure 4. The step response illustrates how the carotid sinus baroreflex will change aortic pressure in the time domain when the carotid sinus pressure abruptly increases by 1 mm Hg. In response to the step change in carotid sinus pressure, the carotid sinus baroreflex decreased aortic pressure by about 1 mm Hg in the first 20 seconds. The short dead time and slight oscillation of aortic pressure were easily recognizable in the step response.

**Open-Loop Transfer Functions From Carotid Sinus Pressure to End-Systolic Elastance and From Carotid Sinus Pressure to Effective Arterial Elastance**

The averaged $H_{Ees}$ and $H_{Ea}$ are illustrated in Figure 5. Just like $H_{Aop}$, both $H_{Ees}$ and $H_{Ea}$ could be parameterized as a second-order delay system with a delay element. Note that the absolute gains as well as the general shapes of $H_{Ees}$ and $H_{Ea}$ were remarkably similar with a slight difference in phase characteristics. The gains of $H_{Ees}$ and $H_{Ea}$ were 0.085±0.065 and 0.081±0.049 mm Hg/ml/mm Hg, respectively. There were no significant differences in natural frequencies (0.039±0.013 versus 0.039±0.007 Hz) and damping ratios (0.65±0.11...
versus 0.64±0.24) between \( H_{Ees} \) and \( H_{Ea} \). Dead time of \( H_{Ea} \) (0.51±0.69 seconds) was slightly but significantly shorter than that of \( H_{Ees} \) (2.28±1.27 seconds) \((p<0.05)\).

Figure 6 shows the step responses of \( H_{Ees} \) and \( H_{Ea} \). Except for the small difference in dead time, the step response of \( H_{Ees} \) resembled that of \( H_{Ea} \) both in time course and amplitude. The carotid sinus baroreflex dynamically altered \( E_{es} \) and \( E_a \) almost to the same extent in the process of stabilizing arterial pressure.

Optimality of Ventriculoarterial Coupling

Using these estimated transfer functions, we evaluated how the carotid sinus baroreflex dynamically affects ventriculoarterial coupling. Figure 7 illustrates a representative example of the simulation. In the control condition, \( Q_{load} \) was almost unity. When \( V_{ed-Vo} \) was reduced by 20\%, the systemic arterial pressure abruptly decreased by 25 mm Hg. In response to the change in arterial pressure, the carotid sinus baroreflex increased \( E_{es} \) and \( E_a \) simultaneously to the same extent. The baroreflex restored about half of the decreased pressure within the first 20 seconds. During this dynamic restorative process, \( Q_{load} \) was maintained at its optimal value despite the significant concurrent changes in \( E_{es} \) and \( E_a \). This was also the case when \( V_{ed-Vo} \) was increased by 20\%.

The effects of the carotid sinus baroreflex on \( Q_{load} \) before and after \( V_{ed-Vo} \) changes are summarized in Figure 8. \( Q_{load} \) was 0.99±0.01 in the control condition, which meant that the energy transmission from the left ventricle to the arterial system was almost optimized in anesthetized dogs. In response to the changes in \( V_{ed-Vo} \), although the carotid sinus baroreflex altered \( E_{es} \) and \( E_a \) to restore the arterial pressure, no significant changes were observed in \( Q_{load} \) before (0.99±0.01) and after (0.99±0.01) changes in \( V_{ed-Vo} \). Thus, the carotid sinus baroreflex stabilized arterial pressure in response to changes in preload without compromising energy transmission from the left ventricle to the arterial system.

Discussion

Effects of the Carotid Sinus Baroreflex on End-Systolic Elastance and Effective Arterial Elastance

To evaluate the dynamic effects of the carotid sinus baroreflex on ventriculoarterial coupling, we identified open-loop transfer functions from carotid sinus pressure to \( E_{es} \) and from carotid sinus pressure to \( E_a \). We have shown that the carotid sinus baroreflex changed \( E_{es} \) and \( E_a \) almost to the same extent over the frequency range examined. Both transfer functions were quite similar and showed characteristics of a second-order delay system. The second-order delay system is a kind of low-pass filter. Because the natural frequencies of \( H_{Ees} \) and \( H_{Ea} \) were around 0.03 Hz, the carotid sinus baroreflex mainly responded to changes in carotid sinus pressure lower than 0.03 Hz. The gains below 0.03 Hz were about 0.08 mm Hg/ml/mm Hg, which means that a 25 mm Hg decrease of carotid sinus pressure results in increases in \( E_{es} \) and \( E_a \) by 2 mm Hg/ml. The estimated gain of \( H_{Ees} \) was comparable to those reported by Suga.
et al\textsuperscript{13} and Sheriff et al\textsuperscript{29} (about 15% changes per 25 mm Hg).

There was a small (less than 2 seconds) but significant difference in the dead time between $H_{Ees}$ and $H_{Ea}$. However, because we evaluated transfer functions only up to 0.25 Hz (every 4 seconds), its physiological significance was unclear.

According to the estimated $H_{Ees}$ and $H_{Ea}$, whenever the baroreflex alters $E_{es}$, it is always coupled with a change in $E_{a}$, and vice versa. Because the arterial system will extract maximal external work from a given heart when $E_{a}$ equals $E_{es}$, the carotid sinus baroreflex appears to be preprogrammed to regulate ventricular and arterial properties to optimize the energy transmission from the left ventricle to the arterial system.

**Effects of the Baroreflex on the Optimality of the Energy Transmission**

To quantify the optimality of the energy transmission, we introduced a new index, $Q_{load}$. When $E_{a}$ equals $E_{es}$, $Q_{load}$ becomes unity, which means that the arterial system extracts maximal energy from a given left ventricle. Because the mean value of $E_{a}/E_{es}$ was 1.12±0.15 in this study, $Q_{load}$ was 0.99±0.01 under the control condition. The energy transferred from the left ventricle to the arterial system was almost maximized in anesthetized dogs. In response to the changes in preload, the carotid sinus baroreflex stabilized arterial pressure by adjusting both $E_{es}$ and $E_{a}$ simultaneously. We showed that $Q_{load}$ remained close to unity during this process (Figure 8).

If the baroreflex were able to affect either $E_{es}$ or $E_{a}$, what would happen to energy transmission from the left ventricle to the arterial system? Because $Q_{load}$ would be higher than 0.90 when $E_{a}/E_{es}$ varies between 0.52 and 1.92, does the carotid sinus baroreflex have to change both $E_{es}$ and $E_{a}$ to maintain optimality of the energy transmission?

The results are illustrated in Figure 9. Conditions were the same as for Figure 8. If the carotid sinus baroreflex affected $E_{es}$ alone, $Q_{load}$ would deteriorate when $V_{od}-V_{es}$ is increased by 20% ($p<0.05$). On the other hand, if the carotid sinus baroreflex affected $E_{a}$ alone, $Q_{load}$ would deteriorate when $V_{od}-V_{es}$ is decreased by 20% ($p<0.01$). Although $Q_{load}$ is relatively insensitive to changes in $E_{a}/E_{es}$ around its optimal point, the carotid sinus baroreflex has to change both $E_{es}$ and $E_{a}$ to maintain optimality of the energy transmission in the process of the baroreflex control of arterial pressure.

In patients with severe heart failure, Asano et al\textsuperscript{30} reported that $E_{a}$ was twice as large as $E_{es}$. They found that in those patients not only was $E_{es}$ low, but also $E_{a}$ was augmented. Those patients maintained arterial pressure at the expense of energy transmission from the left ventricle to the arterial system. What will happen if the preload abruptly decreases in these patients? In patients with severe heart failure, $E_{es}$ may no longer sufficiently respond to the baroreflex. As shown in Figure 9B, the baroreflex that controls arterial pressure by changing $E_{a}$ alone will worsen the energy transmission especially when the preload abruptly decreases. Therefore, the arterial pressure regulation by the baroreflex has deleterious effects on ventriculoarterial coupling in these patients. From these considerations, it is obvious that the baroreflex does not always give beneficial effects on ventriculoarterial coupling.

**Another Index of the Optimal Ventriculoarterial Coupling**

So far we estimated optimality of ventriculoarterial coupling by $Q_{load}$, which is an index of optimal afterload. In our definition, the optimal afterload is the one that extracts maximal external work from a given heart. $Q_{load}$ represents optimality of energy transmission from the left ventricle to the arterial system. On the other hand, some investigators have looked for the condition that maximizes mechanical efficiency of the left ventricle.\textsuperscript{31-35} The mechanical efficiency of the left ventricle is defined as the ratio of the external work to myocardial oxygen consumption. Burkhoff and Sagawa\textsuperscript{34} showed in a theoretical study that the mechanical efficiency per beat is maximized when $E_{a}/E_{es}$ is about 0.5. However, the minimization of oxygen consumption per beat does...
baroreceptors might have offset the mean level of $E_o$ and $E_a$ to higher levels.\textsuperscript{36} Removal of parasympathetic control of the heart must have increased heart rate and might have reduced the gain of the baroreflex to heart rate.\textsuperscript{37} Indeed, in this study, the mean value of heart rate was $165 \pm 20$ beats per minute, and heart rate changes were relatively small. If the vagal nerves had been preserved, the gain of $H_{ao}$ which reflects changes in heart rate, might have been higher.

Furthermore, in the conscious dog, baroreflex control of cardiac contractility has been reported to be weaker than for animals in the anesthetized state.\textsuperscript{14} Therefore, the gain of $H_{ao}$ can be larger than that of $H_{eo}$ in conscious, vagally intact dogs. If that is the case, effects of the baroreflex on ventriculoarterial coupling may differ from those of anesthetized, vagotomized dogs.

Our previous study has shown that $E_o/E_a$ varies between 0.5 and 1.0 in chronically instrumented dogs.\textsuperscript{38} As shown in Figure 10, the $E_o/E_a$ that varies between 0.5 and 1.0 can optimize both $Q_{bad}$ and $Q_{heart}$ simultaneously. If arterial pressure decreases in the conscious, vagally intact dog, the baroreflex will restore the decreased arterial pressure by increasing $E_o$ (and $E_a$), and $E_o/E_a$ will increase to unity. This means that the baroreflex will optimize $Q_{bad}$ while compromising $Q_{heart}$ during the pressor response. On the other hand, if the arterial pressure increases for some reason, the baroreflex will decrease $E_o/E_a$ to 0.5, which means the baroreflex will optimize $Q_{heart}$ at the expense of $Q_{bad}$ during the depressor response. Although these features sound plausible, a relatively high basal $E_o$ must constitute the underlying premise. Detailed analysis of the effects of the baroreflex on ventriculoarterial coupling in conscious and vagally intact animals remains to be investigated.

\textbf{Rationale Behind Use of the White-Noise Approach}

Because the carotid sinus baroreflex contains significant nonlinearities,\textsuperscript{9} we used the white-noise method\textsuperscript{18–20} to evaluate transfer functions. To minimize the nonlinear effects by thresholds and saturations of the baroreflex, the perturbed carotid sinus pressure was limited within $\pm 25$ mm Hg around the mean of aortic pressure. The open-loop transfer function of the carotid sinus baroreflex, $H_{ao}$, thus obtained was comparable to those previously reported.\textsuperscript{39–42} The gain of the baroreflex is known to be dependent on the amplitude of the carotid sinus perturbation,\textsuperscript{42} and the addition of a high-frequency sinusoid to the carotid sinus pressure has been reported to decrease low-frequency gain of the baroreflex.\textsuperscript{40} The relatively small gain estimated by the white-noise method in this study may well be explained by these nonlinearities of the baroreflex. Because there are no sinusoidal perturbations in physiological conditions, a transfer function estimated by a set of single sinusoidal perturbations will be a biased one. Therefore, we used the white-noise method to identify the unbiased linear transfer functions of the nonlinear system.

To quantify the linearity of the baroreflex, we estimated magnitude-squared coherence functions. As shown in Figure 3, the estimated coherence function was more than 0.5 up to 0.15 Hz. This meant that more than half of the variability of aortic pressure was linearly

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure10.png}
\caption{Optimality of the afterload ($Q_{load}$) and optimality of the heart ($Q_{heart}$) (where cardiac output=1.5 l/min=25 ml/sec, fixed arterial resistance=5.0 mm Hg/ml/sec, and preload=20 ml) as a function of the effective arterial elastance divided by end-systolic elastance ($Ea/Ees$). $Q_{load}$ is optimized when $Ea/Ees$ is unity, and $Q_{heart}$ is optimized when $Ea/Ees$ is slightly above 0.5. Both $Q_{load}$ and $Q_{heart}$ are flat around their peaks. Although $Q_{heart}$ will vary with cardiac output, arterial resistance, and preload, its general features, such as the optimal point, are relatively constant.}
\end{figure}

\begin{equation}
Q_{heart} = V_{O2_{min}} / V_{O2}
\end{equation}

where $V_{O2_{min}}$ is the theoretically estimated minimum oxygen consumption per unit time to generate the required cardiac output against a fixed arterial resistance. When $V_{O2} = V_{O2_{min}}$, arterial resistance, and cardiac output are given, $Q_{heart}$ becomes a function of $E_o/E_a$ (see "Appendix"). Figure 10 illustrates a representative example of $Q_{heart}$ as a function of $E_o/E_a$. When $E_o/E_a$ is about 0.5, the heart will be most efficient. Incidentally, the optimal point per unit time is not so different from that per beat\textsuperscript{34} for a heart with a physiological preload and arterial system.

In this study, the mean $E_o/E_a$ was slightly higher than unity, and $Q_{heart}$ was $0.88 \pm 0.03$ in the control condition. Although $Q_{heart}$ was significantly lower than $Q_{load}$ ($p<0.01$), the mechanical efficiency of the heart was fairly well optimized. Because the carotid sinus baroreflex maintains $E_o/E_a$ constant while controlling $E_o$ and $E_a$ in response to changes in arterial pressure, $Q_{heart}$ will not deteriorate further when the baroreflex stabilizes arterial pressure against disturbances to the cardiovascular system. It seems that in anesthetized, vagotomized dogs, the energy transmission was more optimized than was oxygen consumption.

\textbf{Significance of Vagotomy and Anesthesia on Baroreflex Control of Ventriculoarterial Coupling}

We cut the vagal nerves to eliminate the buffering effects of the aortic arch baroreflex and the cardiopulmonary baroreflex. The lack of inputs from aortic arch...
related to that of carotid sinus pressure. This is the equivalent of saying that if we plot measured aortic pressure on the x axis and the linearly predicted one on the y axis in the time domain with the estimated linear transfer function, their correlation coefficient will be more than 0.7. We considered this figure sufficiently high.

Furthermore, since our preliminary study with Wiener kernels9 indicated that the nonlinear response of the baroreflex was minimal, what we characterized as the linear transfer function would represent the major response of the baroreflex.

Several factors besides nonlinearities of the baroreflex can lower the coherence functions. Those are inputs to the baroreflex that are unaccounted for, nonstationarity of the biological system or preparation, and errors in the estimated variables. In this study, we estimated transfer functions considering carotid sinus pressure as the only input to the baroreflex system. However, it has been reported that cardiac or other efferent sympathetic nerve activities are influenced by the higher central nervous system as well as by the baroreflex.43,44 Besides, although we carefully controlled anesthesia and tried to estimate transfer functions from short data (512 seconds) by applying the multichannel autoregressive model,25,26 it was not easy to keep the animal preparation completely stable. These might have lowered the coherence functions besides nonlinearities of the baroreflex.

Limitations

We estimated $E_{as}$ by the single-beat estimation technique21–23 to evaluate dynamic changes of $E_{as}$ without altering preload. Although the predicted peak isovolumic pressure had good correlation with that obtainable by actual aortic occlusion ($r=0.951$),23 estimation errors cannot be neglected. These uncertainties of estimated $E_{as}$ may have lowered the coherence function of $H_{max}$ especially in the relatively high frequency range.

On the other hand, we estimated beat-to-beat $E_a$ by dividing end-systolic pressure by stroke volume, which is somewhat similar to estimating arterial resistance on a beat-to-beat basis. In the steady state, $E_a$ is independent of $E_{as}$ and can be approximated by the ratio of arterial resistance to cardiac cycle length.6 However, in the transient state, $E_a$ somewhat depends on changes in $E_{as}$. According to a preliminary simulation of ours, when $E_{as}$ abruptly increases twice without changes in arterial resistance and heart rate, $E_a$ decreases slightly in that beat and returns to the previous value in the following beats. Although this apparent beat-to-beat $E_a$ may differ from $E_a$ as a system property, when we consider the transmission of energy from the left ventricle to the arterial system, what determines optimality of the ventriculoarterial coupling must be this apparent beat-to-beat $E_a$. Furthermore, this dependence of $E_a$ on $E_{as}$ will have its effect mainly at frequencies beyond the range of our concern (i.e., above 0.25 Hz) and may not affect estimated $H_{max}$.

In summary, we evaluated the dynamic effects of the carotid sinus baroreflex on $E_{as}$ and $E_a$ in anesthetized, vagotomized dogs. The results indicate that the baroreflex dynamically affects both $E_{as}$ and $E_a$ to the same extent and thus does not deteriorate optimality of ventriculoarterial coupling when stabilizing arterial pressure against physiological disturbances.

Appendix

Parameterization of Transfer Functions as a Second-Order Delay System

The second-order delay system with a delay element is expressed as

$$H(s)=\frac{G\cdot\frac{F_n^2}{s^2+2\cdot Rd\cdot F_n\cdot s+F_n^2}}{s^2+2\cdot Td\cdot s} e^{-Td\cdot s}$$

(A1)

where $t$ is the Laplace operator (complex frequency), i.e., $j2\pi f$, $G$ is gain, $F_n$ is natural frequency, $Rd$ is damping ratio, and $Td$ is dead time. We fitted the second-order delay system to the modulus of the estimated transfer function by using the Gauss-Newton nonlinear curve-fitting technique45,46 and determined $G$, $F_n$, and $Rd$. Then we compared the phases of the fitted second-order delay system with those of the estimated transfer functions and determined $Td$.19 Accuracy of fitting was compared between $H_{max}$ and $H_{as}$ by residual errors, and no significant differences were detected.

Derivation of Optimality of the Heart as a Function of Ventricular and Arterial Elastances

We define the optimal heart as one that consumes the minimal oxygen per unit time to meet required cardiac output (CO) at a fixed arterial resistance (R). Because preload is fixed as $V_{ed}-V_o$, the left ventricle can change either $E_{as}$ or heart rate (HR). $E_a$ will reflect changes in HR. If we assume mean arterial pressure equals $P_{va}$, $P_{as}$ will be fixed as the product of CO and R. With fixed $P_{va}$, $V_{ed}-V_o$, and CO, both $E_{as}$ and $E_a$ will be functions of HR as follows:

$$E_{as}=\frac{P_{as}}{V_{ed}-V_o-CO/HR}$$

(A2)

and

$$E_a=\frac{P_{as}}{CO/HR}$$

(A3)

Dividing Equation A3 by Equation A2, HR will be a function of $E_a/E_{as}$ as follows:

$$HR=\frac{CO}{V_{ed}-V_o}\cdot(1+E_a/E_{as})$$

(A4)

We estimate $V_o$ according to the pressure-volume area (PVA) versus $V_o$ relation42–46; i.e.,

$$V_o=(A\cdot PVA+B\cdot E_{as}+C)\cdot HR$$

(A5)

where $A=1.8\times10^{-5}$ ml O$_2$/mm Hg/ml, $B=0.0018$ ml O$_2$/beat/mm Hg · ml, and $C=0.010$ ml O$_2$/beat.8 PVA is the sum of potential energy and EW and can be expressed as

$$PVA=P_{as}\cdot(V_{ed}-V_o-SV)/2+P_{as}\cdot SV$$

$$=P_{as}\cdot(V_{ed}-V_o+CO/HR)/2$$

(A6)

where the area under the end-diastolic pressure–volume relation line is neglected. By substituting Equations A2, A4, A5, and A6 into Equation A5, $V_o$ will be the function of $E_a/E_{as}$. By differentiating $V_o$ with respect to $E_a/E_{as}$, one can show that the $E_a/E_{as}$ that minimizes $V_o$ at given CO, R, and $V_{ed}-V_o$ is as follows:

$$E_a/E_{as}=\frac{2\cdot B}{A\cdot(V_{ed}-V_o)^2+2\cdot B+2\cdot C\cdot(V_{ed}-V_o)(CO\cdot R)}$$

(A7)
In this way, we can estimate the \( V_{\text{O}_{2}}_{\text{max}} \) to meet peripheral demand at given \( V_{\text{E}} \) and \( R \). When \( V_{\text{O}_{2}}_{\text{max}} \) is estimated, one can determine \( Q_{\text{max}} \) according to Equation 10.

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