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±0.0065 (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 Ea 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.
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 $E_a$ and to $E_v$. 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 $E_a$ and $E_v$ 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, Shinano, 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. 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 method\(^{18-20}\) to identify open-loop transfer functions from carotid sinus pressure to $E_a$ and $E_v$, 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 $E_a$ without altering the loading conditions of the left ventricle. Details of the single-beat estimation of $E_a$ 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 $E_v$ by dividing the end-systolic pressure by stroke volume according to its definition.
Estimation of Transfer Functions

The transfer function is an expression of the linear input-output relation in the frequency domain.\(^\text{19}\) Dividing the output-input cross-power spectrum \(\{P_{\text{out} \cdot \text{in}}(f)\}\) by the input power spectrum \(\{P_{\text{in} \cdot \text{in}}(f)\}\) yields the transfer function; i.e.,

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

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\(^\text{24-26}\) 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,\(^\text{24,27}\) varied between three and eight. According to Equation 1, we estimated transfer functions from carotid sinus pressure to \(E_a\) (\(H_{\text{Ea}}\)) and from carotid sinus pressure to \(E_s\) (\(H_{\text{Es}}\)) 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\(^\text{19}\); i.e.,

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

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\(^\text{28}\) of the transfer functions to obtain their respective impulse responses, which are representations of the transfer functions in the time domain.\(^\text{19}\)

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 (\(P_{\text{es}}\)) can be expressed as

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

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

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

and

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

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

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

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

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

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 \(E_a\) to \(E_{es}\), we can evaluate the optimality of energy transmission from the left ventricle to the arterial system. When \(E_a\) equals \(E_{es}\), \(Q_{\text{load}}\) becomes unity and the arterial system extracts maximal energy from a given \(E_{es}\) and \(V_{\text{ed}} - V_o\).
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>Ees (mm Hg/ml)</th>
<th>Ea (mm Hg/ml)</th>
<th>Vvo - Ve (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 16.9  115   123  9.6  165  11.0  12.2  21.4
SD  2.1  25   22  1.3  1.3  20   1.6  2.2  2.0

Values are mean±SD. BW, body weight; CSP, carotid sinus pressure; AoP, aortic pressure; SV, stroke volume; HR, heart rate; bpm, beats per minute; Ees, end-systolic elastance; Ea, effective arterial elastance; Vvo, end-diastolic volume; Ve, end-systolic unstressed volume.

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 Ees, Ea, and Qload change when preload (i.e., Vvo - Ve) abruptly increases or decreases by 20%. Mean values of measured data were used to determine Pes, Ees, Ea, and Vvo - Ve 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 Pes for every beat. After the abrupt changes of Vvo - Ve, we estimated dynamic changes of Ees and Ea every 2 seconds by convolving impulse responses of H_Ees and H_Ea with the previous values of carotid sinus pressure. The next value of the carotid sinus pressure was obtained by Equation 6 with the predicted Ees and Ea at that moment. From these Ees and Ea, we estimated Qload 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_Ees and H_Ea and other paired data. The repeated-measures analysis of variance and Dunnett’s test were used to evaluate effects of the Vvo - Ve changes on Qload. 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 Ees was not significantly different from that of Ea (p>0.05). Using these data, we estimated the following transfer functions.

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 (H_AoP) 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.\textsuperscript{19}

In its general frequency characteristics, $H_{\text{Aop}}$ 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 $H_{\text{Aop}}$, 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 $H_{\text{Aop}}$ 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 0.030±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 $H_{\text{Aop}}$ 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.

\begin{figure}
\centering
\includegraphics[width=0.5\textwidth]{figure4.png}
\caption{Step response of open-loop transfer function from carotid sinus pressure to aortic pressure, which represents how the step change (1 mm Hg) in carotid sinus pressure affects aortic pressure (AoP) in the time domain.}
\end{figure}

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

The averaged $H_{\text{Ees}}$ and $H_{\text{Ea}}$ are illustrated in Figure 5. Just like $H_{\text{Aop}}$, both $H_{\text{Ees}}$ and $H_{\text{Ea}}$ 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 $H_{\text{Ees}}$ and $H_{\text{Ea}}$ were remarkably similar with a slight difference in phase characteristics. The gains of $H_{\text{Ees}}$ and $H_{\text{Ea}}$ 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 0.65±0.10).

\begin{figure}
\centering
\includegraphics[width=0.8\textwidth]{figure5.png}
\caption{Open-loop transfer functions from carotid sinus pressure to end-systolic elastance ($H_{\text{Ees}}$, panel A) and to effective arterial elastance ($H_{\text{Ea}}$, panel B) with their coherence functions (COH). The bold lines are means, and the accompanying two thin lines indicate ±SD. Note that absolute gains as well as general shapes of $H_{\text{Ees}}$ and $H_{\text{Ea}}$ were quite close, but there was a slight difference in their phases. See text for details.}
\end{figure}
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 $V_{ed}-V_o$ 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 $V_{ed}-V_o$ was increased by 20%.

The effects of the carotid sinus baroreflex on $Q_{load}$ before and after $V_{ed}-V_o$ 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 $V_{ed}-V_o$, 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 $V_{ed}-V_o$. 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.13 and Sherif et al.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 \( V_{el}-V_{es} \) 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 \( V_{el}-V_{es} \) 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.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, \( E_{a} \) 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.31-35 The mechanical efficiency of the left ventricle is defined as the ratio of the external work to myocardial oxygen consumption. Burkhoff and Sagawa34 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
not necessarily give the minimum oxygen consumption per unit time. What is important for the oxygen supply system to the heart is not the amount of oxygen per beat but that of unit time. Therefore, we define the optimal heart as that which requires minimal oxygen per unit time to support required cardiac work for a fixed afterload. Specifically, optimality of the heart (Q_{heart}) is defined as

\[ Q_{heart} = \frac{V_{O2min}}{V_{O2}} \tag{10} \]

where V_{O2min} is the theoretically estimated minimum oxygen consumption per unit time to generate the required cardiac output against a fixed arterial resistance. When V_{a} = V_{o}, arterial resistance, and cardiac output are given, Q_{heart} becomes a function of E_{a}/E_{es} (see "Appendix"). Figure 10 illustrates a representative example of Q_{heart} as a function of E_{a}/E_{es}. When E_{a}/E_{es} 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^44 for a heart with a physiological preload and arterial system.

In this study, the mean E_{a}/E_{es} was slightly higher than unity, and Q_{heart} was 0.88±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_{a}/E_{es} constant while controlling E_{es} 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.

**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 baroreceptors might have offset the mean level of E_{a} and E_{es} to higher levels.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.37 Indeed, in this study, the mean value of heart rate was 165±20 beats per minute, and heart rate changes were relatively small. If the vagal nerves had been preserved, the gain of H_{es}, 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.14

Therefore, the gain of H_{es} can be larger than that of H_{es} 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_{a}/E_{es} varies between 0.5 and 1.0 in chronically instrumented dogs.38 As shown in Figure 10, the E_{a}/E_{es} that varies between 0.5 and 1.0 can optimize both Q_{load} 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_{a} (and E_{es}), and E_{a}/E_{es} will increase to unity. This means that the baroreflex will optimize Q_{load} 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_{a}/E_{es} to 0.5, which means the baroreflex will optimize Q_{heart} at the expense of Q_{load} during the depressor response. Although these features sound plausible, a relatively high basal E_{a} 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.

**Rationale Behind Use of the White-Noise Approach**

Because the carotid sinus baroreflex contains significant nonlinearities,3 we used the white-noise method\(^{18-20}\) to evaluate transfer functions. To minimize the nonlinear effects by thresholds and saturations of the baroreflex, the perturbed carotid sinus pressure was limited within ±25 mm Hg around the mean of aortic pressure. The open-loop transfer function of the carotid sinus baroreflex, H_{an}, thus obtained was comparable to those previously reported.39-42 The gain of the baroreflex is known to be dependent on the amplitude of the carotid sinus perturbation,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.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.

![Figure 10. 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.](image-url)
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 kernels 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. Besides, although we carefully controlled anesthesia and tried to estimate transfer functions from short data (512 seconds) by applying the multichannel autoregressive model, 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 Ees by the single-beat estimation technique to evaluate dynamic changes of Ees without altering preload. Although the predicted peak isovolumic pressure had good correlation with that obtainable by actual aortic occlusion (r=0.951), estimation errors cannot be neglected. These uncertainties of estimated Ees may have lowered the coherence function of Htransfer especially in the relatively high frequency range.

On the other hand, we estimated beat-to-beat Ea 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, Ee is independent of Ees and can be approximated by the ratio of arterial resistance to cardiac cycle length. However, in the transient state, Ee somewhat depends on changes in Ees. According to a preliminary simulation of ours, when Ees abruptly increases twice without changes in arterial resistance and heart rate, Ee decreases slightly in that beat and returns to the previous value in the following beats. Although this apparent beat-to-beat Ee may differ from Ees 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 Ee. Furthermore, this dependence of Ee on Ees will have its effect mainly at frequencies beyond the range of our concern (i.e., above 0.25 Hz) and may not affect estimated Htransfer.

In summary, we evaluated the dynamic effects of the carotid sinus baroreflex on Ees and Ee in anesthetized, vagotomized dogs. The results indicate that the baroreflex dynamically affects both Ees and Ee 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

\[ H(s) = \frac{F_n^2}{s^2 + 2 \cdot Rd \cdot F_n \cdot s + F_n^2} \cdot e^{-T_d \cdot s} \]  

(A1)

where s is the Laplace operator (complex frequency), i.e., j2πf. 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 technique 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. Accuracy of fitting was compared between Htransfer and Hestimated 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_eo – V_o, the left ventricle can change either Ees or heart rate (HR). Ee will reflect changes in HR. If we assume mean arterial pressure equals P_ae, P_ea will be fixed as the product of CO and R. With fixed P_ea, V_eo – V_o, and CO, both Ees and Ee will be functions of HR as follows:

\[ E_{es} = \frac{P_{es}}{V_eo - V_o - CO/HR} \]  

(A2)

and

\[ E_e = \frac{P_{es}}{CO/HR} \]  

(A3)

Dividing Equation A3 by Equation A2, HR will be a function of Ee/Ees as follows:

\[ HR = \frac{CO}{V_{eo} - V_o} \cdot \left(1 + E_{es}/E_{es}\right) \]  

(A4)

We estimate VO2 according to the pressure–volume area (PVA) versus VO2 relation

\[ VO_2 = (A \cdot PVA + B \cdot E_{es} + C) \cdot HR \]  

(A5)

where A=1.8×10^(-5) ml O2/mm Hg/ml, B=0.0018 ml O2/beat/mm Hg · ml, and C=0.010 ml O2/beat. PVA is the sum of potential energy and EW and can be expressed as

\[ PVA = P_{es} \cdot (V_{eo} - V_o - SV)/2 + P_{es} \cdot SV \]

\[ = P_{es} \cdot (V_{eo} - V_o + CO/HR)/2 \]  

(A6)

where the area under the end-diastolic pressure–volume relation line is neglected. By substituting Equations A2, A4, and A6 into Equation A5, VO2 will be the function of Ee/Ees. By differentiating VO2 with respect to Ee/Ees one can show that the Ee/Ees that minimizes VO2 at given CO, R, and V_eo – V_o is as follows:

\[ \frac{2 \cdot B}{A \cdot (V_{eo} - V_o)^2 + 2 \cdot B + 2 \cdot C \cdot (V_{eo} - V_o) \cdot (CO \cdot R)} \]  

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

Acknowledgments

We thank Dr. Yasuhiko Harasawa for his valuable comments and discussions on this investigation and Miss Mayumi Yokomizo for her technical and secretarial assistance.

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_Circ Res._ 1992;70:1044-1053
doi: 10.1161/01.RES.70.5.1044

_Circulation Research_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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