Counteraction of aortic baroreflex to carotid sinus baroreflex in a neck suction model

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Counteraction of aortic baroreflex to carotid sinus baroreflex in a neck suction model. J Appl Physiol 89: 1979–1984, 2000.—Although neck suction has been widely used in the evaluation of carotid sinus baroreflex function in humans, counteraction of the aortic baroreflex tends to complicate any interpretation of observed arterial pressure (AP) response. To determine whether a simple linear model can account for the AP response during neck suction, we developed an animal model of the neck suction procedure in which changes in carotid distension pressure during neck suction were directly imposed on the isolated carotid sinus. In six anesthetized rabbits, a 50-mmHg pressure perturbation on the carotid sinus decreased AP by \(-27.4 \pm 4.8\) mmHg when the aortic baroreflex was disabled. Enabling the aortic baroreflex significantly attenuated the AP response \((-21.5 \pm 3.8\) mmHg, \(P < 0.01\)). The observed closed-loop gain during simulated neck suction was well predicted by the open-loop gains of the carotid sinus and aortic baroreflexes using the linear model \((-0.43 \pm 0.13\) predicted vs. \(-0.41 \pm 0.10\) measured). We conclude that the linear model can be used as the first approximation to interpret AP response during neck suction.

Theoretical Considerations

MATERIALS AND METHODS

NECK SUCTION PROCEDURES have been widely used in the evaluation of carotid sinus baroreflex function in humans (6–9, 17, 18, 24). During neck suction, a negative pressure is applied around the neck to activate the carotid sinus baroreflex, resulting in a decrease in arterial pressure (AP). Because decreased AP deactivates the aortic baroreceptors, negative feedback through the aortic baroreflex operates to increase AP, thereby countering the carotid sinus baroreflex during neck suction. To avoid the countering effect of the aortic baroreflex during neck suction, the initial heart rate response before the beginning of AP response has been used to evaluate the carotid sinus baroreflex function (6–9, 24, 26). However, the initial heart rate response alone cannot account for the total buffering effect of carotid sinus baroreflex against pressure perturbation. A quantitative analysis of the AP response is crucial to extend the interpretation of observed AP response during neck suction. However, to the best of our knowledge, no efforts have been made to quantify the counteraction of the aortic baroreflex to the carotid sinus baroreflex during neck suction. This is possibly because respective evaluations of the carotid sinus and aortic baroreflexes are impossible in human study. Although a simple linear model can be put forward to explain the counteraction of the aortic baroreflex to the carotid sinus baroreflex during neck suction, the presence of interactions between the carotid sinus and aortic baroreflexes (3, 12, 15, 25, 27) may complicate the AP response. To test the hypothesis that the AP response during neck suction can be explained by the linear model, we developed an animal model of the neck suction procedure in which changes in carotid distension pressure during neck suction were directly imposed on the isolated carotid sinus. In the present animal model, we enabled or disabled the aortic baroreflex to measure counteraction of the aortic baroreflex to the carotid sinus baroreflex.

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COUNTERACTION OF AORTIC BAROREFLEX DURING NECK SUCTION

As indicated in Eq. 1, $G_{NS}$ has a negative value and asymptotically approaches $-1$ as $G_{CS}$ increases. Rearranging Eq. 1 for $G_{CS}$ yields

$$G_{CS} = -\frac{G_{NS}}{1 + G_{NS}} \tag{2}$$

Shubrooks (23) adopted Eq. 2 to estimate $G_{CS}$ during neck suction in anesthetized dogs.

When the aortic baroreflex is taken into account, pressure changes during the neck suction procedure can be described by using the block diagram shown in Fig. 1B. $G_{AO}$ indicates the open-loop gain of the aortic baroreflex. We assigned $G_{AO}$ a positive value for convenience and added a negative sign to $G_{AO}$ to describe the negative feedback through the aortic baroreflex. Under these conditions, $G_{NS}$ is

$$G_{NS} = \frac{\Delta P}{\Delta X} = -\frac{G_{CS}}{1 + G_{CS} + G_{AO}} \tag{3}$$

As indicated in Eq. 3, $G_{NS}$ has a negative value and asymptotically approaches $-1$ as $G_{CS}$ increases. In addition, $G_{NS}$ asymptotically approaches zero as $G_{AO}$ increases.

Surgical Preparation

Animal care was in accordance with the Guiding Principles for the Care and Use of Animals in the Field of Physiological Sciences approved by the Physiological Society of Japan. Six Japanese white rabbits weighing between 2.4 and 3.1 kg were anesthetized via intravenous injection (2 ml/kg) of a mixture of urethane (250 mg/ml) and $a$-chloralose (40 mg/ml) and mechanically ventilated with oxygen-enriched room air. Supplemental anesthetics were injected as necessary (0.5 ml/kg) to maintain an appropriate depth of anesthesia. AP was recorded through a catheter inserted via the right femoral artery. We vascularly isolated the right carotid sinus from the systemic circulation by ligating the internal and external carotid arteries as well as other small branches originating from the carotid sinus region. The isolated carotid sinus was flushed and then filled with warmed physiological saline. The intracarotid sinus pressure (CSP) was controlled through a catheter inserted from the common carotid artery by a servo-controlled piston pump. We also vascularly isolated the baroreceptor regions of the right aortic depressor nerve near the bifurcation of the right common carotid and subclavian arteries via a midline thoracotomy.

The intracarotid arterial pressure (CAP) was controlled by a second servo-controlled piston pump. The bilateral vagi were cut to eliminate baroreflexes from cardiopulmonary regions. The right vagal nerve was cut intrathoracically to avoid any injury to the right aortic depressor nerve. The remaining carotid sinus and aortic baroreflexes from the left side were interrupted by sinoaortic denervation. Body temperature was maintained at 38°C by using a heating pad.

Protocols

After completion of the surgical preparation, both CSP and CAP were matched to AP, and an equilibrium pressure was obtained. The study consisted of the following three protocols.

Protocol 1. We fixed CAP at the equilibrium pressure throughout the protocol, thereby disabling the aortic baroreflex in response to changes in AP. After AP reached a steady state, we increased CSP above AP by either 30 or 50 mmHg for 60 s to simulate a neck suction procedure. Because the negative pressure is attenuated to 64% from neck to perivascular tissue around the carotid sinus in humans (17), the 30- and 50-mmHg pressure perturbations corresponded to negative pressures of 47 and 78 mmHg around the neck, respectively. The magnitude of pressure perturbation, therefore, should cover the range of the neck suction procedure used in humans.

Protocol 2. To elucidate the counteraction of the aortic baroreflex to the carotid sinus baroreflex, we servo-controlled CAP to follow changes in AP, thereby enabling the aortic baroreflex. After AP reached a steady state, we increased CSP above AP by either 30 or 50 mmHg for 60 s.

Protocol 3. To estimate the aortic baroreflex function alone, we fixed CSP at the equilibrium pressure, thereby disabling the carotid sinus baroreflex in response to changes in AP. After AP reached a steady state, we increased CAP above AP by either 30 or 50 mmHg for 60 s.

The order of protocols was randomized among animals to reduce the likelihood of bias or systematic error in estimating the baroreflex gains. We recorded CSP, CAP, and AP at a sampling rate of 200 Hz using a 12-bit analog-to-digital converter. The data were stored on the hard disk of a dedicated laboratory computer system for subsequent analysis.

Data Analysis

All data are presented as means ± SD. The steady-state AP decrease in each protocol was calculated as the difference between the steady-state and baseline AP values. Baseline AP was obtained by averaging instantaneous AP for 10 s before the pressure perturbation. Steady-state AP was calculated by averaging instantaneous AP for the last 10 s of the 60-s pressure perturbation. We repeated the 60-s pressure perturbation twice in each protocol and represented the steady-state AP decrease as the mean of the two experimental runs.

We examined the differences in steady-state AP decrease between protocols 1 and 2 using a paired t-test (10). The difference was considered statistically significant when $P < 0.05$. All statistical analyses were performed separately on the results associated with the 30- and 50-mmHg pressure perturbations, because the number of samples would be small for a two-way analysis of variance.

To determine whether Eq. 3 can account for the results of protocol 2, we first calculated $G_{CS}$ from the results of protocol 1 using Eq. 2. We also estimated $G_{AO}$ from the results of protocol 3 by substituting $G_{AO}$ for $G_{CS}$ in Eq. 2. After obtaining $G_{CS}$ and $G_{AO}$ values, we predicted $G_{NS}$ according to the right term of Eq. 3. Finally, we compared the predicted $G_{NS}$...
RESULTS

Figure 2A shows typical recordings of CSP, CAP, and AP obtained from protocol 1 with a 50-mmHg pressure perturbation. CSP was matched to mean AP in the first 40 s. We then elevated CSP above mean AP by 50 mmHg in the following 60 s. AP decreased in response to the pressure perturbation. Because the pressure difference between CSP and mean AP was kept at 50 mmHg to simulate the neck suction procedure, the decrease in AP caused an overshoot-like change in the CSP tracing. When the 60-s pressure perturbation was discontinued, CSP was again matched to mean AP. The increase in AP upon cessation of pressure perturbation caused a negative overshoot-like change in the CSP tracing. Throughout the protocol, CAP was maintained at the equilibrium pressure to disable the aortic baroreflex in response to any change in AP.

Figure 2B shows typical recordings of CSP, CAP, and AP obtained from protocol 2 with a 50-mmHg pressure perturbation. CSP was controlled in the same manner as in protocol 1. The pressure difference between CSP and mean AP was maintained at 50 mmHg during the 60-s simulated neck suction. In contrast to protocol 1, however, CAP was servo-controlled to follow changes in mean AP, thereby enabling the aortic baroreflex. The steady-state AP decrease was attenuated compared with that in Fig. 2A.

Table 1 summarizes the steady-state AP decreases during the simulated neck suction obtained from protocols 1 and 2. The steady-state AP decrease in protocol 2 was significantly attenuated compared with that in protocol 1 under conditions of either 30- or 50-mmHg pressure perturbation.

DISCUSSION

We have shown that the steady-state AP decrease during a simulated neck suction procedure is attenuated by the aortic baroreflex (Table 1). $G_{NS}$ measured in protocol 2 could be predicted from $G_{CS}$ and $G_{AO}$ by using the right term of Eq. 3 (Table 2), suggesting that the AP response during simulated neck suction can be described by the linear model shown in Fig. 1B.

Table 1. Effects of aortic baroreflex on the steady-state arterial pressure response during simulated neck suction

<table>
<thead>
<tr>
<th>Protocol</th>
<th>$\Delta X_{30}$ mmHg</th>
<th>$\Delta X_{50}$ mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protocol 1</td>
<td>$-16.0 \pm 4.4$</td>
<td>$-27.4 \pm 4.8$</td>
</tr>
<tr>
<td>Protocol 2</td>
<td>$-12.4 \pm 2.9^*$</td>
<td>$-21.5 \pm 3.8^*$</td>
</tr>
</tbody>
</table>

Values are means $\pm$ SD. $\Delta X_{30}$ and $\Delta X_{50}$, pressure perturbations of 30 and 50 mmHg, respectively. $^*P < 0.01$ vs. protocol 1.
Counteraction of the Aortic Baroreflex

Although counteraction of the aortic baroreflex to the carotid sinus baroreflex during neck suction has been described (19, 20), a quantitative analysis was required to determine whether the block diagram shown in Fig. 1B can account for AP response during neck suction. As shown in Table 2, GNS measured in protocol 2 was predicted reasonably well from GCS and GAO by using the right term of Eq. 3. These results suggest that the block diagram shown in Fig. 1B is useful as the first approximation to interpret the AP response during neck suction.

Clinical Implications

As indicated in Eq. 3, we must specify GAO to determine GCS from observed GNS. The GAO-to-GCS ratio was −0.6 in the present study. Hosomi et al. (11) reported the GAO-to-GCS ratio of −0.9 using a quick hemorrhage method in anesthetized rabbits. The GAO-to-GCS ratio has been reported as −0.5 in anesthetized dogs (2, 3, 5). On the basis of these findings, we specified the GAO-to-GCS ratio variously at 0 (aortic baroreflex disabled), 0.5, 1, and 2, then calculated the relationship between GCS and GNS (Fig. 4A). We also calculated (GCS + GAO) vs. GNS (Fig. 4B). In the simulation, GCS or (GCS + GAO) monotonously increased as GNS approached −1, regardless of the GAO-to-GCS ratio.

The amplitude of pressure perturbation is known to affect GCS due to the sigmoidal input-output relationship of the arterial baroreflex system (3, 16, 21, 22, 27). Although a 50-mmHg pressure perturbation seems to be sufficiently large to fall within the range of sigmoidal nonlinearity, GNS predicted from GCS and GAO using Eq. 3 conformed to the measured GNS, suggesting a linearity in the steady-state AP response during the simulated neck suction. Attenuation of pressure perturbation through the closed-loop feedback may account for the observed linearity as follows. The steady-state input to CSP during the simulated neck suction was not ΔX itself but ΔX + ΔAP, as in Fig. 1. For instance, the steady-state input to CSP in protocol 1 was 22.6 mmHg, on average, when a 50-mmHg pressure perturbation was applied. Therefore, the steady-state input during the simulated neck suction might have been within the linear operating range of the AP regulation.

Table 2. Gain values obtained from the three protocols

<table>
<thead>
<tr>
<th>ΔX30</th>
<th>GCS</th>
<th>GAO</th>
<th>Predicted GNS</th>
<th>Measured GNS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.37 ± 0.77</td>
<td>0.20</td>
<td>−0.43 ± 0.13</td>
<td>−0.41 ± 0.10</td>
<td></td>
</tr>
<tr>
<td>1.35 ± 0.66</td>
<td>0.19</td>
<td>−0.43 ± 0.09</td>
<td>−0.43 ± 0.08</td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SD. GCS, open-loop gain of the carotid sinus baroreflex (protocol 1); GAO, open-loop gain of the aortic baroreflex (protocol 3); Predicted GNS, closed-loop gain during neck suction predicted from GCS and GAO values (Eq. 3); measured GNS, measured closed-loop gain during neck suction (protocol 2). The predicted and measured GNS values did not differ significantly.

Fig. 4. Relationships between GCS and closed-loop gain during neck suction (GNS; A) and between GCS + GAO and GNS (B) on the basis of Eq. 3. α, Ratio of GAO to GCS. Hatched areas indicate most likely ranges of α according to animal experiments.
tio. Therefore, if we repeat the neck suction procedure in the same subject before and after some environmental stress and observe an increase in the negative value of \( G_{NS} \), we can at least conclude that the arterial baroreflex gain has also increased.

According to the human study in normal subjects by Mancia et al. (18), the regression coefficient of steady-state changes in mean AP on changes in neck tissue pressure is \( \approx 0.41 \). Using this value, we can estimate \( G_{CS} \) to be 2.3 when \( G_{CS} \) equals \( G_{AO} \) on the basis of Fig. 4A. However, these estimations vary depending on the specified ratio of \( G_{AO} \) to \( G_{CS} \). Figure 4 would represent the utility as well as the limitation of the neck suction procedure to estimate the open-loop gain of the arterial baroreflex from the steady-state AP response during neck suction.

**Limitations**

There are several limitations to this study. First, we investigated the carotid sinus and aortic baroreflexes in anesthetized rabbits. Although we chose an anesthetic agent that is minimally suppressive to circulatory regulation, the absolute values of \( G_{CS} \) and \( G_{AO} \) might have been affected by the anesthesia to some degree. However, we compared the predicted \( G_{NS} \) and measured \( G_{NS} \) under the same anesthetic conditions, and we believe that the linear model shown in Fig. 1B would explain the steady-state AP response to neck suction, even in the absence of anesthesia.

Second, CSP and CAP were exposed to nonpulsatile pressure. The absolute gain values might have been different had CSP and CAP been exposed to pulsatile pressure (2, 4). Furthermore, we denervated the left carotid sinus nerve while preserving the left internal carotid artery to maintain the blood flow to the brain. Therefore, the possible interaction between the left and right carotid sinus baroreflexes during neck suction (26) was not assessed in the present study.

Third, we cut the vagi to eliminate the possible baroreflex from the cardiopulmonary regions. Consequently, we were unable to evaluate the vagal control of heart rate during the simulated neck suction procedure. Several investigators suggest the advantage of using the heart rate response over the AP response (6–9, 24) to evaluate carotid sinus baroreflex function by neck suction. Future studies with intact vagi are required to examine the counteracting effects of the aortic baroreflex on the heart rate response during neck suction.

Finally, we filled the isolated baroreceptor regions with warmed physiological saline (13, 14, 21, 22). Because ion content affects the sensitivity of baroreceptors (1), the absolute values of \( G_{CS} \) and \( G_{AO} \) might have been different had we used other solutions, such as Ringers solution. However, because we did not change the intravascular content of the isolated baroreceptor regions among protocols, the sensitivity of baroreceptors to pressure input would have remained unchanged.

In conclusion, the aortic baroreflex counteracted the carotid sinus baroreflex during simulated neck suction and attenuated the steady-state AP response. The linear model shown in Fig. 1B was able to account for the AP response during the simulated neck suction. Therefore, we can estimate the arterial baroreflex gain from the observed AP response during neck suction by assuming the \( G_{AO} \)-to-\( G_{CS} \) ratio. Although the \( G_{AO} \)-to-\( G_{CS} \) ratio in humans is unknown, according to animal experiments, it most likely falls within the range of 0.5–1.0.

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