Interaction of Canine Carotid Sinus and Aortic Arch Baroreflexes in the Control of Total Peripheral Resistance

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SUMMARY. Interaction of carotid sinus and aortic arch reflex control of total peripheral resistance was studied in eight dogs anesthetized with sodium pentobarbital and placed on constant flow cardiac bypass. Carotid sinus and aortic arch baroreceptor areas were isolated and separately perfused at controlled pressures. Combinations of carotid sinus and aortic arch pressures were delivered at random in steps of 25 mm Hg over the 50–225 mm Hg pressure range, and systemic arterial pressure was measured. Changes in arterial pressure reflected changes in total peripheral resistance. A multiple linear regression showed that both carotid sinus and aortic arch pressures exhibited a sigmoidal relationship with arterial pressure. Independent of carotid and aortic baroreceptor pressures, arterial pressure was found to be a periodic function of time (period = 2 hours) in all dogs. The average carotid sinus reflex open loop gain was found to be 0.231 ± 0.092, while average aortic arch open loop gain was 0.141 ± 0.088. The gain of either the carotid sinus or aortic arch reflex was not influenced by the absolute pressure level of the other receptor area. In a separate series of experiments performed in the same dogs, we tested the hypothesis that a nonlinear temporal summation of the reflex control of total peripheral resistance might exist when the inputs to carotid and aortic baroreceptors are changed simultaneously. With both inputs held at the region of maximum gain, 25 mm Hg step changes were imposed first on carotid sinus pressure, then on aortic arch pressure, and then on both simultaneously. A temporal inhibition of the two reflexes showed that simultaneous excitation of both receptors resulted in a smaller reflex response than the sum of individual responses. (Circ Res 55: 740–750, 1984)

HIGH pressure arterial baroreceptors located in the carotid sinus and aortic arch send information on arterial pressure to the medulla by two different afferent pathways. The central nervous system receives and integrates these signals, and sends efferent signals to the cardiovascular system which influence the arterial blood pressure. How the signals from the carotid sinus and aortic arch interact and are integrated has been the subject of many studies (Glick and Covell, 1968; Angell-James and Daly, 1970a, 1970b; Donald and Edis, 1971; Hosomi and Sagawa, 1979; Kendrick et al., 1979; Guo et al., 1982; Isikawa and Sagawa, 1983). Despite these studies, the degree of interaction of the two reflex systems has not been resolved. The different modalities of stimulation to each receptor area, and the differences in species used, could account for some of the discrepancies in results. Because of the technical difficulty in forcing the aortic arch with a natural stimulus, only a few investigators have simultaneously and independently perturbed both the carotid sinus and aortic arch baroreceptors with changes in pressures in those regions (Angell-James and Daly, 1970a, 1970b; Donald and Edis, 1971).

Two types of interaction can exist between reflex systems. The first type, which we term "gain interaction," defines the ability of one reflex system to change the gain of the other reflex system. In this case, the slope of the arterial pressure-receptor pressure relationship changes when the other receptor pressure varies. The second type of interaction, which we term "temporal interaction," defines the interaction of reflex systems when stimuli are delivered to both receptors at the same time. This definition is based on the summation of the output responses to separate stimulation of each receptor area compared to the output response to simultaneous stimulation of both receptor areas. A response would be considered to be facilitatory, linearly additive, or inhibitory if the response to simultaneous stimulation of the two receptor areas were greater than, equal to, or less than (respectively) the sum of the individual responses (Sagawa and Watanabe, 1965). This temporal interaction depends on several factors, and can easily be misinterpreted. To measure the degree of temporal interaction, it is important to know whether gain interaction is present. In the case in which only gain interaction is present, and the receptors were forced separately as well as simultaneously, one could demonstrate either an inhibitory or facilitatory temporal type of interaction, depending on the direction of the change in receptor pressure (Ishikawa and Sagawa, 1983). This is a particular manifestation of gain interaction, due to...
the different slopes of the receptor response curves. It should be emphasized that this result is distinct from that of true temporal interaction as described above. In the experiments we performed, we first measured the receptor response curves to determine whether gain interaction was present. We then measured the temporal interaction between reflex systems.

The purpose of this present study was to measure steady state changes in systemic arterial pressure at constant flow caused by the stimulation of the carotid sinus and aortic arch baroreceptors at various perfusion pressures over the full working range of the reflex systems. In two independent studies performed in the same dogs, gain interaction was not found to be a significant factor in carotid sinus-aortic arch interaction in the control of total peripheral resistance. We have found evidence for temporal interaction, which was found to be inhibitory.

**Methods**

Eight technically successful experiments were performed using male mongrel dogs weighing 21.6 ± 2.9 (SD) kg. The animals were anesthetized with 30 mg/kg sodium pentobarbital given intravenously. An endotracheal tube was inserted and connected to a respirator (Harvard variable phase dog ventilator, model 613). The dogs were respired with room air supplemented with 95% O₂ and 5% CO₂. The animals were heparinized with 7000 units of sodium heparin, with supplemental doses given as needed throughout the day. A rectal probe was inserted to monitor body temperature, which was maintained at 38 ± 1°C.

The right and left carotid sinuses were isolated (Shoukas and Sagawa, 1973; Brunner et al., 1982) from the rest of the circulatory system. The occipital, internal, and external carotid arteries and any small branches originating from the carotid bifurcation were completely ligated. A four-way connector was attached to the distal segment of each common carotid artery, the proximal end of the right common carotid artery, and a servo-controlled nonpulsatile pressure-generating system. Mean intrasinus pressure was monitored with catheters placed in the right and left lingual arteries and commonly joined to a pressure transducer (Statham P23AC). The limb of the four-way connector which had been inserted in the proximal right common carotid artery allowed exposure of the carotid sinus area to the systemic arterial pressure during the remaining surgery. A catheter was inserted into the right common carotid artery for the measurement of systemic arterial pressure. This catheter was connected to a pressure transducer (Statham P23AC). During the above procedures, care was taken to avoid traumatizing the vagus nerve in the cervical region.

The chest then was opened via a mid-sternal thoracotomy. Figure 1 illustrates the perfusion circuit necessary to isolate the aortic arch baroreceptors from the rest of the circulatory system.

Immediately before the heart bypass was initiated, the carotid sinus pressure was controlled at 125 mm Hg. The limb of the four-way connector which had been inserted into the proximal right common carotid artery was removed, and the perfusion cannula for the right vertebral artery was inserted. A second perfusion cannula was inserted into the left internal thoracic artery for retrograde perfusion into the left vertebral artery.

The right and left hearts were bypassed by means of procedures that have been described previously (Shoukas, 1982). As shown in Figure 1, venous blood was drained from the right atrium into a reservoir and returned to the pulmonary artery by pump no. 1 (Sarns model SM6002). The perfusion system was primed with whole blood from a donor dog. Oxygenated blood from the left ventricle was drained into another reservoir and pumped retrograde into the femoral arteries, left internal thoracic artery, and right common carotid artery. This ensured adequate cerebral and systemic perfusion throughout the experiment. Central venous pressure and left atrial pressure were set at approximately 3 mm Hg by adjusting the levels of the outflow tubes draining the right and left sides of the heart. The pump perfusion rate was set so that the dog’s systemic arterial pressure was approximately equal to that prior to the initiation of the bypass. Fine controls were used to modify the pumps so that systemic and pulmonary flows could be set to exactly the same rate. For all dogs, the average perfusion rate was 78.7 ± 13.7 (SD) ml/min per kg.

After the bypass, the aortic pouch was isolated as follows. The brachiocephalic artery was ligated near its origin at the arch. The descending aorta was ligated just above the first intercostal artery. To exclude coronary blood flow and to prevent mechanical distortion of the aortic pouch, a special procedure was used for ligating the aortic root. A rod with a large diameter plug on its end was inserted through the left ventricle, positioned, and tied at the aortic root as close as possible to the heart. A cannula was inserted into the left subclavian artery and
connected to a second servocontrolled nonpulsatile pressure-generating system. Systemic arterial pressure was measured via a catheter inserted into the left common carotid artery and connected to a pressure transducer (Statham P23AC). Using a side arm catheter on the left subclavian artery cannula, we measured aortic arch pressure by connecting the catheter to a pressure transducer (Statham P23AC). Mean central venous and mean left ventricular pressures were measured with catheters inside the cannulas inserted in the right atrium and left ventricle, respectively, and connected to pressure transducers (Statham P23BB). Zero pressure reference for all pressure measurements was set at the junction of the inferior vena cava and the right heart under direct inspection. Pumps 1 and 2 were equipped with tachometers which produced an electrical signal that was proportional to the speed of each pump. The speeds were recorded and calibrated against flows measured with a stopwatch and graduated cylinder. Carotid sinus, aortic arch, and systemic arterial pressures, and right and left atrial pressures and flows were recorded on an ink recorder (Brush model 2800).

**Experimental Protocol**

**Receptor Gain Characterization**

The relationship between arterial pressure and baroreceptor input pressures was determined in the following manner. Arterial pressure was measured at each of 64 combinations of intrasinus and aortic arch pressures (ISP and AAP). Eight levels of input pressures were used ranging from 50 to 225 mm Hg in steps of 25 mm Hg. These 64 ISP-AAP pairs were delivered, using a pseudo-random sequence. Several constraints were placed on the sequence of ISP-AAP input pairs. Neither ISP nor AAP was allowed to remain constant for more than two consecutive data points. During the presentation of the sequence, there were times when only ISP changed, or only AAP changed. Each ISP-AAP pair was held for at least 2–3 minutes so that steady state was reached. Between each point, the size of the step change in either ISP or AAP was variable, ranging from 0 to a maximum of 175 mm Hg. The entire sequence took approximately 2½ hours to complete. After every 10th measurement, arterial pressure was measured with intrasinus and aortic arch pressures set to 125 mm Hg. This provided a control measurement for the effect of time over the entire experiment. We could then evaluate the possibility of degradation of the preparation over the course of the experiment.

**Temporal Interaction**

The inputs to both carotid sinus and aortic arch were set to 125 mm Hg. With the pressure in one receptor area held constant at 125 mm Hg, the region of maximum gain of the other receptor area was determined. For example, when the aortic arch maximum gain region was being determined, carotid sinus pressure was set at 125 mm Hg. Aortic arch pressure was changed in steps of 25 mm Hg from 50 to 225 mm Hg. The region where the maximum response in arterial pressure occurred for a 25 mm Hg step change was defined as the region of maximum gain. The average maximum response to a step change of 25 mm Hg occurred between 100 and 125 mm Hg for carotid sinus, and between 150 and 175 mm Hg for aortic arch. To study temporal interaction, we made step changes of 25 mm Hg only in this region of maximum gain, that is, the most linear portion of the reflex response curves. The change in mean arterial pressure in response to 25 mm Hg step changes in either aortic arch or carotid sinus inputs around the region of maximum gain were determined separately, while the other receptor pressure was held constant. Carotid sinus and aortic arch pressures were then moved simultaneously in the same direction, and the change in mean arterial pressure was determined. This entire procedure was then repeated three more times, randomizing the order of the input. This protocol allowed for separation of the effects of increasing and decreasing receptor pressures.

**Statistical Model and Analysis**

**Gain Interaction.**

One of the simplest models which can accurately describe the arterial pressure response to carotid and aortic arch pressures is given in Equation 1 below:

\[ AP = c_1 + c_2 ISP + c_3 ISP^2 + c_4 ISP^3 + c_5 AAP + c_6 AAP^2 + c_7 AAP^3 \]  

(1)

where \( AP \) = arterial pressure, ISP = intrasinus pressure, AAP = aortic arch pressure.

The model includes linear terms for both carotid sinus and aortic arch pressures. The model also contains higher order carotid sinus and aortic arch terms to account for threshold and saturation behavior of arterial pressure and carotid sinus pressure (Martin et al., 1969; Shoukas and Brunner, 1980), and arterial pressure and aortic arch pressure (Angell-James and Daly, 1970a; Donald and Edis, 1971). A consequence of including these higher order terms is that the shape of the arterial pressure-receptor pressure relationship is sigmoidal.

If there exists an interaction between reflex systems, an additional term, \( cs(ISP*AAP) \), must be included. The simplest model which incorporates these features is given by Equation 2 below:

\[ AP = c_1 + c_2 ISP + c_3 ISP^2 + c_4 ISP^3 + c_5 AAP + c_6 AAP^2 + c_7 AAP^3 + cs(ISP*AAP) \]  

(2)

The interaction term in the model, the ISP*AAP term, allows the level of one receptor input to influence the gain (or receptor sensitivity) measured at the other receptor. The gain or receptor sensitivity for either input is defined as the slope or first derivative of the arterial pressure-receptor pressure relationship. For the model given by Equation 2, receptor gain would be the partial derivative of arterial pressure with respect to receptor pressure. The carotid sinus gain, \( G_{cs} \), is

\[ \frac{\partial AP}{\partial ISP} \bigg|_{AAP} \]

and the aortic arch gain, \( G_{aa} \), is

\[ \frac{\partial AP}{\partial AAP} \bigg|_{ISP} \]

Therefore:

\[ G_{cs} = \frac{\partial AP}{\partial ISP} \bigg|_{AAP} = c_1 + 2c_2 ISP + 3c_3 ISP^2 + c_4 AAP \]  

(3)

\[ G_{aa} = \frac{\partial AP}{\partial AAP} \bigg|_{ISP} = c_4 + 2c_5 AAP + 3c_6 AAP^2 + c_7 ISP \]  

(4)
Equations 3 and 4 show that, for this model, the carotid sinus reflex gain on arterial pressure could be a function of aortic arch pressure, and aortic arch reflex gain could be a function of carotid sinus pressure. The carotid sinus reflex gain not only depends on the level of aortic arch pressure, but also is a function of higher order ISP terms. Of special importance is the fact that the carotid sinus reflex gain is not equal to \( c_i \), the coefficient of the linear term of ISP. Likewise, the aortic arch reflex gain is not equal to \( c_i \). The coefficients \( c_1 \) and \( c_4 \) merely represent the slope of the arterial pressure-receptor pressure relationship when carotid sinus and aortic arch pressures are zero.

To determine coefficients of the model (\( c_1 \) through \( c_7 \)) and minimize the effects of short-term resetting (Kunze, 1981), a random sequence of inputs must be used. Measuring the arterial pressure responses to random carotid sinus and aortic arch pressures allows for the complete description of the gain interaction of the two reflex systems over the full working ranges of both reflexes. In addition, the effects of time during the experimental protocol can be described if a random sequence of inputs is used.

We wished to quantify the effect of intrasinus and aortic arch input pressures and other potentially relevant factors on arterial pressure. These other factors included the effects of sequence number (which is correlated to time), the magnitude of the step change in either input pressure, and the interaction between intrasinus and aortic arch pressures. The model also included higher order (square and cubic) terms for each of the factors except the interaction term. A general linear model was used containing a total of sixteen elements and was of the form:

\[
AP = a \cdot ISP + b \cdot ISP^2 + c \cdot ISP^3 + d \cdot AAP + e \cdot AAP^2 + f \cdot AAP^3 + g \cdot ISP \cdot AAP + h \cdot SN + i \cdot SN^2 + j \cdot SN^3 + k \cdot DISP + l \cdot DISP^2 + m \cdot DISP^3 + n \cdot DAAP + o \cdot DAAP^2 + p \cdot DAAP^3 + constant
\]

where \( AP \) = arterial pressure, \( ISP \) = intrasinus pressure, \( AAP \) = aortic arch pressure, \( SN \) = sequence number, \( DISP \) = delta intrasinus pressure or the size of the step change in intrasinus pressure, and \( DAAP \) = delta aortic arch pressure or the size of the step change in aortic arch pressure, \( a-p \) are the regression coefficients.

The data for each individual dog were analyzed separately by stepwise multiple linear regression to determine the coefficients in the above model. Separate analyses were performed for each dog since preliminary analyses revealed that the effect of sequence number on arterial pressure was quite different for each dog. Any term that was found to be significant for any of the dogs in the preliminary analysis was retained in the model for all dogs during the final stepwise regression. Only the first 10 variables in Equation 5 were found to be significant in at least one dog, and so were retained. The multiple linear regression was performed on a Data General Eclipse MV 8000 computer using a statistical package from the SAS Statistical Institute. For all of the factors in the model, the significance value was set at \( P < 0.05 \).

**The Effect of the Sequence**

For preliminary evaluation and for the purpose of plotting the results, the data were analyzed as follows. Arterial pressure was plotted as a function of the order in which the data points were obtained.

The resulting plot is shown in the upper left panel of Figure 2. Note that the sequence number on the X-axis represents the order in the 64-point sequence. Sequence number is not exactly equal to time per se, but is closely related to time. Each sequence number is separated from the next point by approximately 2-3 minutes. Notice that there is a large variation in arterial pressure with sequence number. However, much of the variation in arterial pressure in the upper left panel of Figure 2 is due to the fact that intrasinus and aortic arch pressures were also changing. To account for the variation due to random inputs, a multiple linear regression was performed on the raw data with arterial pressure as the dependent variable and intrasinus and aortic arch pressure as independent variables. The residuals from this regression are plotted against sequence number in the upper right panel of Figure 2. A third degree polynomial fit of the residuals against sequence number is shown in the graph. This polynomial fit represents a measure of the effect of sequence number over the course of the experiment adjusted for the linear effect of carotid sinus and aortic arch pressures. As shown in Figure 2, this effect was then subtracted (as shown in the lower right panel) from the arterial pressures in the upper left panel to yield the plot shown in the lower left panel. The result is independent of the effect of sequence order and was used for plotting to demonstrate the effects of intrasinus and aortic arch pressures. The effects of sequencing over the course of the experiment illustrate several points. First, the effect of time, as represented by the sequence number, was large, and the inclusion of time as a factor in the overall model was important to consider. Second, the effect of time was not predictable for all dogs. Figure 3 shows residual-time plots (analogous to the upper right panel of Figure 2) for eight dogs. Note that the variation with time occurred with a period of approximately 2 hours. The control points which were taken after every 10th point in the sequence were subjected to the same adjustment procedure for the effect of time. For the same dog pictured in Figure 2, the control (ISP = 125, AAP = 125) points were 134.8 ± 6.8 mm Hg, and ranged from 128 to 130 mm Hg after the adjustment for time. Control points are shown as solid circles in Figure 2 for dog 4. For all the dogs, mean values ± 50 for control points were 150.3 ± 11.9 before, and 148.8 ± 8.8 mm Hg after, the time adjustment procedure.

The same random sequence was used for dogs 7 and 8. Additionally, in one dog, (dog 8) it was possible to repeat the same 64-point sequence twice. The results obtained at two different times of the day in dog 8 were compared with those obtained in dog 7. Thus, it was possible to evaluate the effects which may have been caused by the random sequence itself. As shown in Figure 3, dogs 7 and 8 exhibited very different variations of arterial pressure with time. From this, we conclude that the variation with time is not dependent upon the random sequence itself. Repeating the same sequence twice in the same dog (8a and 8b) also showed different variations of arterial pressure with time. From this we conclude that the oscillation with time which occurs with a period of approximately 2 hours is an independent process which does not depend upon the choice of animal or of the random sequence used.

**Temporal Interaction**

Data from the temporal interaction protocol were analyzed using a two-way analysis of variance on the changes
in mean arterial pressure caused by changes in carotid sinus input, aortic arch input, both together, and the linear sum of carotid and aortic inputs. Significant differences were investigated using paired t-tests. The significance of the direction of change in input (increasing or decreasing), as well as the order of the inputs, were investigated. No significant differences were found; therefore, the data from all protocols were pooled for subsequent analysis. Significance levels were set at $P < 0.05$ for all analyses.

**Results**

**Gain Interaction**

The last six factors in equation 5 were never found to be significant. The first 10 variables in the general linear model given by Equation 5 all were found to be significant in at least one of the dogs. Therefore, all 10 significant variables were retained in the overall analysis for the entire group. The interaction cross-term was not found to be consistently significant in all dogs. Only two of the dogs (dogs 2 and 4) exhibited a significant gain interaction, and these were both inhibitory. To investigate further the slope change in the "working range," we studied sixteen points, using AAP from 100 to 175 and ISP from 100 to 175, in each dog. The linear slopes of these data were compared, using linear regression and analysis of variance on the slopes. No significant differences in slopes were detected, even for the two dogs in which the interaction terms were significant in the overall analysis. In addition, we performed an overall regression, using data from all the dogs, which was of the form: $AP = c_1 + c_2\text{ISP} + c_3\text{AAP} + c_4\text{ISP}^*\text{AAP}$. P values for ISP, AAP, and ISP*AAP were found to be $<0.00001$, $<0.0008$ and $<0.6884$, respectively. The interaction term in this overall analysis was not significant. Thus, we conclude that there is no significant interaction of this type between carotid and aortic baroreflexes.

As shown in Figure 4, arterial pressure, corrected for the effect of the sequence number, is plotted as a function of intrasinus pressure for eight different levels of aortic arch pressure (dog 5). The curves shown were derived using the coefficients from the 10 variable model multiple regression. Note that the carotid sinus-arterial pressure relationship is sigmoidal in shape at all levels of aortic arch pressure. These sigmoidal curves are "parallel" to each other.
That is, the level of aortic arch pressure does not affect the slope (or gain) of the carotid sinus reflex. However, at the highest level of aortic arch pressure (AAP = 225), the carotid sinus-arterial pressure relationship has the lowest arterial pressures. Similarly, Figure 5 shows arterial pressure, corrected for the effect of the sequence number, as a function of aortic arch pressure at eight different levels of intrasinus pressure.

**FIGURE 3.** Arterial pressure residuals and the best fit polynomials in all the dogs.

**FIGURE 4.** Arterial pressure (corrected for the effect of sequence number) vs. intrasinus pressure at eight levels of aortic arch pressure. Data from dog 5.

**FIGURE 5.** Arterial pressure (corrected for the effect of sequence number) vs. aortic arch pressure at eight levels of intrasinus pressure. Data from dog 5.
Temporal Interaction

For carotid sinus and aortic receptor inputs, these peak gain regions were 100–125 and 150–175 mm Hg, respectively.

The results of changing the receptor pressures are shown in Figures 8 and 9. Figure 8 shows the average steady state response in mean arterial pressure to 25 mm Hg step changes in carotid alone (19.27 mm Hg ± 1.26), aortic alone (4.66 ± 0.67 mm Hg), carotid and aortic together (19.83 ± 1.26 mm Hg), and the sum of carotid plus aortic (24.00 ± 1.35 mm Hg). Note that the sum of carotid plus aortic is greater than the simultaneous excitation of both inputs (P < 0.05). Figure 9 shows the same results for the peak transient response. The peak transient response is defined as the maximum change in mean arterial pressure produced by a given perturbation of the input. The peak response usually occurred within 10–20 seconds of the perturbation, compared to the steady state response which was measured after 2 minutes. The results for the transient response were: carotid alone (46.08 ± 2.17 mm Hg), aortic alone (15.9 ± 1.29 mm Hg), carotid and aortic together (61.2 ± 2.78 mm Hg), and the sum of carotid alone plus aortic alone (51.6 ± 2.32 mm Hg). The result for the transient response is similar to that for the steady state response. That is, the sum of the carotid plus aortic is greater than the simultaneous excitation of both inputs (P < 0.05). Thus, both the steady state and the transient responses show a similar temporal inhibition (21% steady state and 19% transient), which does not depend on the direction of the change in input or the order of the perturbation.

Discussion

This experiment demonstrates for the first time that there are potentially two types of interaction between carotid and aortic reflexes which may act to control total peripheral resistance. The first type of interaction, which can be described as gain interaction, defines the ability of one reflex to change the gain or sensitivity of the other reflex. The other type of interaction, temporal interaction, is defined when two reflex stimuli are delivered at the same time. The first type of interaction was not found in six of the eight dogs. As shown in Figures 4 and 5, the arterial pressure response to changes in carotid and aortic pressures is shifted in "parallel" when the other receptor pressure is changed. We cannot exclude the possibility that gain interaction may exist between other reflex systems, or for other different...
responses, such as heart rate, or in isolated vascular beds. In contrast, temporal interaction has been clearly demonstrated. The response to changing both carotid and aortic pressures simultaneously was found to be smaller than the sum of the individual responses. The conclusion that there are these two distinct types of interaction is dependent upon the ability to perform a complete study which allows the measurement of both types of interaction in the same dog.

There is much disparity in the literature regarding the interaction of carotid and aortic reflexes. This area has recently been the subject of a thorough review by Sagawa (1983). Perhaps these conflicting results could be explained if the manner in which the interaction was studied is clearly defined. Kendrick et al. (1979) found a strong facilitory summation using carotid and aortic nerve stimulation in the dog. Ishikawa and Sagawa (1983) used isolated carotid sinus perfusion and aortic nerve stimulation in the rabbit to show that interaction of carotid and aortic reflexes could be described as facilitory or inhibitory depending upon the input levels. The results reported here may differ from those found using nerve stimulation due to excitation of both chemoreceptors and baroreceptors in the study by Kendrick. In addition, nerve stimulation vs. isolated perfusion of the receptor area may provide different stimuli in the afferent nerves.

Interaction is often studied by measuring reflex responses after denervation of one or both sets of receptors. Guo et al. (1982) showed that either set of baroreceptors could fully compensate for the absence of the other with respect to inhibition of sympathetic responses. Although their experiments clearly demonstrated differential reflex effects on parasympathetic and sympathetic components of the baroreflex, they were not designed to separate gain from temporal interaction. Ito and Scher (1978) showed that, in the conscious dog, when carotid

FIGURE 7. Three-dimensional representations of the arterial pressure vs. intrasinus and aortic arch pressures for all dogs, corrected for the effect of sequence number. Scales are different and are given for each dog.
TABLE 1

Range and Gain Values for Carotid Sinus and Aortic Arch Reflexes

| Dog | Carotid sinus | | | Aortic arch | | |
|-----|---------------|---------------|---------------|
|     | Range | Peak gain | Ave. gain | Range | Peak gain | Ave. gain |
| 1   | 50-75 | 0.416 | 0.141 | 50-75 | 0.269 | 0.106 |
| 2   | 125-150 | 0.433 | 0.192 | 200-225 | 0.150 | 0.061 |
| 3   | 125-150 | 0.246 | 0.154 | 50-75 | 0.144 | 0.084 |
| 4   | 100-125 | 0.169 | 0.091 | 125-150 | 0.153 | 0.088 |
| 5   | 125-150 | 0.554 | 0.327 | 125-150 | 0.495 | 0.356 |
| 6   | 125-150 | 0.631 | 0.282 | 125-150 | 0.274 | 0.138 |
| 7   | 125-150 | 0.539 | 0.304 | 200-225 | 0.267 | 0.182 |
| 8a  | 125-150 | 0.740 | 0.354 | 175-200 | 0.124 | 0.116 |
| 8b* | 125-150 | 0.774 | 0.383 | 200-225 | 0.070 | 0.056 |

Mean ± se: 100-125 0.466 ± 0.068 0.231 ± 0.035 125-150 0.235 ± 0.044 0.141 ± 0.003

* Dog 8b was excluded from calculations of average gain.

sinus nerves were cut, aortic baroreceptors could maintain the same mean blood pressure level and could reflexly compensate for both increases and decreases in arterial pressure. One might (wrongly) conclude that the reflex which is denervated first has no reflex gain. Note, in Figure 8, that the response to carotid sinus input was not significantly different from the response to both carotid and aortic inputs together. This would imply that the carotid sinus reflex response is not augmented by the addition of aortic arch input (had the order of this experiment been reversed). One might simply conclude that the aortic arch reflex is totally redundant. Although these denervation studies were carefully performed, the basic assumption is that measurement of reflex gain when other receptors are denervated is the same as when other receptors are intact. The resolution of this apparent conflict rests upon the realization that carotid sinus and aortic arch inputs form parallel negative feedback loops. Consider two hypothetical sets of receptors with constant gain which interact by a process of simple addition. When the last set of receptors is denervated, all feedback is lost, and the greatest change in arterial pressure would result. The last set of receptors to be denervated need not necessarily increase its gain after the first set is denervated. This apparent augmentation of reflex gain (or total redundancy of the reflex system) is only due to the nature of the parallel arrangement of feedback pathways. Even though, in this hypothetical system, there was no inhibitory summation of carotid and aortic reflexes, one might have concluded that an inhibitory interaction exists. Therefore, denervation may not be an appropriate method for reaching conclusions regarding interaction of the types described in this paper.

We conclude that gain and temporal interaction can best be described by using methods of isolation and perfusion with physiological ranges of pressures carotid sinus and aortic arch areas. Donald and Edis (1971) described the summation of carotid and aortic reflex effects on hindlimb resistance as simply additive. Angell-James and Daly (1970a) found, in
a preparation similar to ours, an inhibition in the reflex control of resistance which is qualitatively and quantitatively similar to the temporal interaction reported here. In addition to the above considerations, all of the above studies have used dissimilar experimental methods, species, and efferent responses, which might explain the different conclusions regarding interaction of carotid and aortic reflexes.

The results from the multiple linear regression showed that the relationship between arterial pressure and carotid sinus or aortic arch pressure was sigmoidal in shape. This finding is consistent with other reports in the literature (Angell-James and Daly, 1970a; Donald and Edis, 1971) which indicate that these reflexes exhibit a threshold and a saturation as reflected in receptor nerve activity as well as reflex vascular responses. The aortic arch reflex gain curve was found to exhibit its maximum gain at a receptor pressure slightly higher than that of the carotid sinus. This finding is also consistent with previous reports in the literature which indicate that threshold and saturation of the aortic arch reflex is slightly higher than that of the carotid sinus (Angell-James and Daly, 1970a; Donald and Edis, 1971).

The size of the step change in receptor pressure was not found to be significant. Thus, a large change in receptor pressure does not result in a larger or smaller steady state arterial pressure response than the sum of many smaller step changes in receptor pressure. The size of the step change had either a positive or negative sign, thereby indicating the direction of change of the receptor pressure. For this analysis, the direction of change in receptor pressure was included in the factor of step size, and was therefore not found to be significant. Even so, we cannot exclude the possibility that hysteresis exists in the region of maximum gain; in fact, there is evidence in the literature to indicate that this is so (Coleridge et al., 1981).

Sequence number was a highly significant factor in the analysis of the results. The sequence number is closely related to time in this experiment. The preliminary analysis (as shown in Figure 2) showed that the effect of time was even more important than carotid or aortic pressures in determining the arterial pressure. The correction process outlined in Figure 2 shows that it is possible to account for the effects of time, but only because of the randomization of inputs. The efficacy of accounting for time is further emphasized by the removal of most of the variability in the control points. Therefore, the 10 variable statistical models also had to account for the large effects of time. That analysis also showed that the effect of time was not simply a linear factor; arterial pressure was shown to be a function of time. Most interestingly, this effect was different in every dog, emphasizing the importance of analyzing each dog separately. The effect of time does not represent degradation of the preparation with time, nor did it bear any relation to the time when supplemental anesthesia was given. As seen in Figure 3, the variation of arterial pressure due to factors other than time (such as carotid and aortic receptor pressure) persists throughout the experiment. Periodic oscillations in arterial blood pressure in the conscious dog with a period of 2 hours have been previously reported (Shimada and Marsh, 1979). In that study, oscillations in arterial blood pressure were correlated with changes in cardiac output and heart rate. It was also concluded that the renin-angiotensin system was not responsible for the oscillations in blood pressure. Although the state of arousal of the conscious animal may be correlated with the oscillation in blood pressure, the reason for these periodic oscillations with time remains to be elucidated.

It is important to define clearly what is meant by carotid sinus and aortic arch reflex gain in the present experiments. These results pertain only to reflex gain of systemic arterial resistance, and do not include reflex gain of cardiac pumping or vascular capacity. Allison et al. (1969) reported an aortic arch reflex peak gain of 0.3 and an average gain of 0.3 for reflex control of systemic resistance. The carotid sinus was denervated in their experiment. The difference in aortic gains may be due to the different reflexogenic areas studied. The area of aortic arch which was isolated in the present experiments included only the aortic arch, and not any part of the brachiocephalic or subclavian arteries. We calculated average gain values from data reported by Angell-James and Daly (1970a), and found average aortic and carotid gains of 1.0 and 1.23, respectively. These average gain values were derived from data taken at 30 seconds after the change in receptor pressure (Figs. 6 and 7 of their paper). We are reporting gain values taken at a 2-minute steady state; this may explain the apparent discrepancy in results. The results of our temporal interaction protocol (Figs. 9 and 10) indicate that average steady state gains for carotid and aortic reflexes were 0.76 and 0.20, respectively. The transient gains were found to be much larger; the carotid and aortic transient gains were found to be 1.84 and 0.64, respectively. We have previously reported average carotid sinus reflex gains on systemic resistance in vagotomized dogs to be 0.23 (Brunner et al., 1983). This agrees well with the average gain of 0.231 for carotid sinus reflex control of resistance reported here. In other experiments in which cardiac pumping and vascular capacity were also included, we have reported average carotid sinus gains to be 0.67 (Brunner et al., 1982) and 0.5 (Shoukas and Brunner, 1980). Several investigators have reported carotid and aortic reflex gains on resistance of isolated hindlimbs, rather than the resistance of the entire systemic vascular bed. Dampney et al. (1971) measured separate reflex gains when the other receptor area was eliminated, and found reflex gains on resistance to be 2.2 for carotid sinus, and 1.1 for aortic arch reflexes. Donald and Edis (1971) measured simultaneous reflex gains on hindlimb resistance, and found carotid sinus gain to
be 1.9 and aortic arch gain to be 1.0. These reflex gains on hindlimb resistance should not necessarily be assumed to be representative of the gain on total systemic resistance. Hainsworth et al. (1970) found that changing either aortic or carotid perfusion pressures resulted in consistently greater changes in the hindlimb than in the forelimb.

The results of the present study show that there is no interaction of the "gain type" in the arterial pressure response to carotid and aortic pressure changes. From the results presented here, it is impossible for us to speculate about interaction in the heart rate responses. Glick and Covell (1968) have provided evidence that a large degree of interaction exists in the heart rate response to changes in carotid and aortic pressures. In addition, Guo et al. (1982) have recently shown that the interaction between carotid and aortic reflexes may be very different for heart rate and arterial pressure responses. Thus, the ability to see interaction in reflex responses may depend upon the output variable studied.

The results presented here demonstrate that there are two types of interaction which can describe carotid sinus and aortic arch reflex interactions. We could not demonstrate that a significant gain interaction exists between the two reflexes. That is, neither receptor could influence the gain of the other reflex. However, we could demonstrate a temporal inhibition which exists when inputs to both receptors are delivered simultaneously. The distinction between these two types of reflex interaction may explain apparent discrepancies in the literature concerning reflex interactions. During a complex physiological stimulus such as hemorrhage, inputs from the carotid sinus and aortic arch baroreflexes generally change in the same direction simultaneously. Therefore, the temporal interaction demonstrated in this study is likely to be an important phenomenon in an integrated response. This temporal inhibition may be a manifestation of neural occlusion in the reflex pathway. This finding of temporal inhibition implies that neither the study of the carotid sinus nor the aortic arch reflex alone is sufficient to predict the more complex behavior of the combined reflex response.

We wish to acknowledge the expert technical assistance of Linda S. Watermeier. James R. Jacobs is acknowledged for his generation of the random sequences.

Computational assistance was received from Clinfo, sponsored by the National Institutes of Health Grant SM01RR-35-20. This work was supported by U.S. Public Health Service Grant HL-19039.

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Received April 30, 1984; accepted for publication August 17, 1984.

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INDEX TERMS: Reflex gain · Gain interaction · Temporal interaction · Reflex summation · Systemic circulation · Vascular resistance · Dog
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doi: 10.1161/01.RES.55.6.740

*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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