Bilateral Carotid Sinus Control of Ventricular Performance in the Dog

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ABSTRACT

Left and right carotid sinus pressures were independently varied while the left ventricular systolic pressure was recorded in an anesthetized canine preparation with an isolated, isovolumetric left heart. Intrasinus pressures were changed in steps of 50 mm Hg to produce either an increase or decrease in pressure from a mean level of 150 mm Hg. The response to eight combinations of increases and decreases in left- and right-sided pressures was examined. Blockade of the sympathetic impulses to the heart produced a loss of response of left ventricular systolic pressure when the intrasinus pressure was decreased from 150 to 100 mm Hg. Parasympathetic blockade produced a loss of response to an increase in pressure from 150 to 200 mm Hg. Left ventricular systolic pressure was more sensitive to a decrease in pressure from 150 to 100 mm Hg in the right sinus than in the left, but there was no difference in sensitivity between left and right sides when intrasinus pressure was raised from 150 to 200 mm Hg. The summation pattern of the response to simultaneous steps in left and right pressure was mutually facilitative for steps from 150 to 100 mm Hg and mutually inhibitory for steps from 150 to 200 mm Hg. The entire system was simulated with a hybrid computer model consisting of separate functional relations used to represent the baroreceptors, central nervous system, and left ventricle. Due to the baroreceptor characteristics and other nonlinearities, the simulation results suggest that a careful distinction should be drawn between transient and steady-state responses when assessing the relative role of each autonomic division in any baroreceptor reflex.

ADDITIONAL KEY WORDS

baroreceptor reflex computed simulation myocardial contractility autonomic nervous system isovolumetric preparation

Several quantitative analyses, with various levels of sophistication, have been reported for the dynamic baroreceptor control of systemic blood pressure (1-5). Because of the complexity of this system, however, the analyses developed have not included a representation of all the known functional components and their interconnections. Katona et al. (6) were able to take a step closer to this ideal goal by concentrating on a system which is reduced in overall complexity. They presented a model of the baroreceptor control of the heart period (R-R interval) in which the transfer of information (extracted from the arterial mean and pulse pressure) from the baroreceptors to efferent nervous system was considered as one block, and the heart as another block.

The present work is an attempt to carry the process one step further by utilizing functional relationships which separately represent: (1) the left and right carotid sinus baroreceptors, (2) the summation and efferent autonomic distribution effected by the central nervous system, and (3) the ef-
fect of changing levels of nervous activity of both autonomic divisions upon ventricular function. The design of the present work is based upon the earlier observation that both autonomic divisions play a role in the carotid sinus control of ventricular function (7). In this respect, the present work supplies new, physiologically significant, quantitative information that may be of value for incorporation into overall models of the cardiovascular system, such as that of Topham and Warner (8) or the comprehensive work of Beneken and DeWitt (9).

Methods

The isolated, paced, isovolumetric, canine left ventricle preparation used in this study has been extensively described elsewhere (10). Briefly, it is prepared by: (1) ligating the hilus of both lungs, (2) draining the venous return from the superior vena cava and right ventricle, and the thebesian drainage from the left ventricle, (3) perfusing the heart and upper portion of the animal through the left subclavian artery at a constant pressure by means of an elevated constant-height reservoir fed by a roller pump in series with a rotating disc oxygenator using 95% O₂-5% CO₂, into which is drained the blood returning to the heart, and (4) inserting a balloon into the left ventricle through the left auricular appendage, filling the balloon with saline, and connecting it to a strain gauge. An index of ventricular performance is then taken to be the left ventricular systolic pressure generated on the balloon.

The external and common carotid arteries of both sides were carefully isolated. Independent pressure sources were connected to each common carotid artery, and a Statham P23AA pressure transducer was connected to each external carotid artery to measure pressure in the carotid sinus. As shown in Figure 1, the external pressure sources for the common carotid arteries each originated at the arterial end of the coronary-cephalic perfusion circuit oxygenator. The pressure sources consisted of a roller pump, preceded by a heater, and followed by an air capacity chamber and screw clamp resistance. The

![Figure 1](http://circres.ahajournals.org/)

**Figure 1**

Schema of hydraulic circuit used to generate increasing or decreasing steps in intrasinus pressure from an arbitrary mean level. The abbreviations in the figure are as follows: AVD = animal venous drainage; Oxy = oxygenator; RPS = reservoir perfusion system, i.e., that used for the coronary and cephalic circulations in this preparation; SSOS = same (hydraulic) system for the opposite sinus; H = heater; RP = roller pump; CC = capacitance chamber; SCR = screw clamp resistance; CCA, ICA, and ECA = common, internal, and external carotid arteries, respectively; SG = strain gauge; S = solenoid valve; HPA = high pressure air; Atm = atmospheric pressure; F = piston assembly; P = collecting funnel, open to atmospheric pressure; ISS = identical solenoid system, connected to the other piston. See text for description of operation of the system.
CAROTID SINUS CONTROL OF THE VENTRICLE

produce any amplitude step about an arbitrary point to a high-pressure air source (piston up, flow established) by means of solenoid valves. These two branches, plus the other branch with a screw clamp resistance, were then connected to the venous end of the oxygenator via a collecting funnel. The fourth branch was then connected to the common carotid artery. By varying the branch load-resistances by means of the two branches and the three screw clamps, it was possible to produce any amplitude step about an arbitrary mean pressure in the fourth branch which was connected to the carotid sinus. The rise and fall times of the input pressure step functions were usually an order of magnitude less than the time constants of the response of left ventricular systolic pressure. The fourth parallel branch, led directly to the funnel, is not theoretically essential for the generation of the desired waveforms. It was included, however, so that a substantial baseline flow would be continuously established through the system. This helped to insure that variations in the smaller flow through the carotid arteries would induce a considerably lessened effect upon the pressure amplitudes.

The carotid sinus preparation used in this study does not exclude the carotid bodies from the input pressure perfusion system; the chemical composition of the blood perfusing the carotid system can be assumed to be the same as that perfusing the other circuits since they are derived from a common pool (the oxygenator). For the results to be valid, it is thus necessary to assume in this work that the carotid bodies were not stimulated by the experimental maneuvers. The validity of this assumption can be examined from many aspects. First, since only the cephalic, upper trunk, and coronary circulations of the experimental animal were perfused, there was a relatively small volume in the external perfusion circuit (approximately 1.5 to 2 liters). The rotating disc oxygenator used in these experiments had sufficient capacity (600 ml) to effectively buffer short-term (on the order of a minute or less) changes in effluent venous Po2 and PCO2 which may have occurred. This has been confirmed by previous reports using this same isovolumetric left ventricular preparation in which pH and PaCO2 were found to remain constant in control experiments (11). It can likewise be stated with confidence that Po2 remains constant for the duration of the experiment. For example, see Figures 2, 3, 6, 7, and 9 of ref. 12 where it will be noted that the oxygen saturation after each experimental maneuver returns almost exactly to the control value, and the slope of this saturation during control periods does not seem to be significantly different from zero. Since the chemoreceptors are thought to be primarily responsive to decreased Po2 and PCO2 is thus well maintained at a constant value along with PCO2 and pH, it does not seem likely that an abnormal chemical content of the perfusing blood made any significant contribution through the carotid bodies to the reflex effects studied in this work on either a short term, i.e., on the order of the stimulus durations (minutes), or longer term, i.e., on the order of the duration of the experiment. This conclusion is further reinforced by the finding that in this preparation, a large Po2 stimulus, e.g., a change from 100% to nearly 0%, gave on the average only about a 10% change in left ventricular systolic pressure, and this change is mediated primarily by the parasympathetic nervous system (13).

Secondly, the blood flow through the carotid bodies does, no doubt, change as carotid pressure is stepwise changed in increments of 50 mm Hg; however, in most experiments, the steps were taken from and returned to 150 mm Hg, with carotid pressures only rarely being dropped below 100 mm Hg. It has been shown from carotid body electroneurograms in the cat that at a carotid blood pressure of 105 mm Hg the impulse traffic density is very low and almost negligible, this density becoming quite heavy when pressure was dropped to 55 mm Hg by hemorrhage (ref. 14, Fig. 2). In the present experiments, there was always a nominal, and most likely adequate, blood flow through the carotid bodies in terms of keeping all variables within the physiological range sensed as normal by the chemoreceptors. This flow, combined with the normal flow of the cerebral arteries, probably also precluded the presentation of any significant stimulus to the vasomotor and respiratory centers associated with carotid sinus pressure changes, although the altered total cerebral flow undoubtedly changed the chemical composition of cerebral tissues to some extent. This was checked in two animals in which no difference was noted in either the statics or the dynamics of the response of left ventricular systolic pressure to bilateral intrasinus pressure changes before and immediately after ligation of the internal carotid arteries.

Data were successfully obtained in this study from 17 mongrel dogs, weighing 15 to 20 kg, sedated with morphine sulfate, 2 mg/kg iv, and anesthetized with urethane, 400 mg/kg iv, and
chloralose, 40 mg/kg iv. In experiments from ten of these dogs, additional information about the distribution of efferent nervous activity between the two autonomic divisions was gained by blocking conduction of either division after responses with intact nerves had been obtained. The conduction blockade was accomplished either: (1) irreversibly, by cutting both cervical vagosympathetic trunks or all connections to both stellate ganglia, or (2) reversibly, by cooling the vagi or stellate ganglia to 4°C or less. The cooling was accomplished either by the direct topical application of ethyl fluoride or by placing the nerve in a metal trough connected to tubing through which a chilled brine solution was circulated. Conduction blockade was confirmed by the abolition of the responses of left ventricular systolic pressure to direct nervous stimulation central to the cooled site. Conduction blockade of the cervical vagosympathetic trunk will interrupt some sympathetic as well as the parasympathetic pathways, and some of these sympathetic fibers may innervate the heart. However, decentralization of both stellate ganglia in the dog abolished the reflex left ventricular response to stimulation of the carotid baroreceptors and cephalic ischemia (15). Therefore, the effect of sectioning the sympathetic fibers in this trunk probably has no consequent bearing on the conclusions drawn about the response of the studied reflex when parasympathetic influences have been eliminated. Also, section of the cervical vagosympathetic trunk will interrupt the afferent impulses from the aortic receptors. However, it was recently found that the threshold for reflex changes in heart rate, left ventricular systolic pressure, and respiratory movements of the rib cage is at an aortic arch pressure of approximately 100 mm Hg. The maximum rate of change of these reflex-controlled variables occurred at about 175 mm Hg, and 300 mm Hg or more of aortic pressure was required to reach maximal effects (16). Therefore, it is likely that the level of perfusion pressure used in this work was such that the aortic baroreceptor reflex would probably contribute no significant static component to the carotid sinus-left ventricular systolic pressure reflex; consequently, aortic baroreceptor deafferentation probably does not affect the results obtained with this preparation to any substantial degree. With respect to aortic chemoeceptive reflex effects, chemoreceptor electroneurographic recordings show that impulse traffic density is directly proportional to stimulus intensity, there being few impulses when stimulus variables are almost physiologically normal (14). Since, with the perfusion system used, these variables are presumably near normal, aortic chemoreceptor deafferentation also will probably have minimal central effects on the carotid sinus-left ventricular systolic pressure reflex studied here.

A three-level factorial experimental design (17) was used with all nerves intact, since this technique affords an efficient means of obtaining data about the central summation and interaction of the left and right carotid sinus responses. The nominal increasing and decreasing step amplitudes used were 50 mm Hg, about nominal mean levels of 150 mm Hg. A wider variety of input pressure waveforms was not used owing to the considerable experimental time required for the completion of a full factorial design plus the nerve-blockade maneuvers.

The total intrasinus pressure-left ventricular systolic pressure reflex system was then simulated on a hybrid computer. For the purposes of simulation, the system was subdivided into three functional blocks, namely, the carotid sinus baroreceptors, the central nervous system, and the heart. A great deal of information about baroreceptor input pressure-nerve firing relationships exists (18-22), but the specific trans-
fer characteristic employed in the present work is that of Poitras et al. (18). The central nervous system characteristic is primarily derived from the present experiments, and the heart is represented by a model previously derived in this laboratory (23).

Results
STEADY-STATE ANALYSIS

Figure 2 illustrates the general shape of the response of left ventricular systolic pressure to a pattern of step changes in right carotid sinus pressure. Note that the relative speed of the response is not only dependent upon whether the intrasinus pressure is increasing or decreasing, but it is also dependent upon the preceding pressure level from which the step was taken. For example, the response of the left ventricular systolic pressure to the first step from 60 to 115 mm Hg has a small overshoot and is significantly faster than the response to the last step from 123 to 60 mm Hg. Also, the response to the second step, from 115 to 164 mm Hg, has no overshoot.

![Diagram of ventricular systolic pressure response to carotid sinus pressure changes](http://circres.ahajournals.org/)

**FIGURE 3**
Illustration of results of autonomic nervous system blockade on responses of left ventricular systolic pressure (LVSP) to changes in intrasinus pressures. The tracings of left ventricular systolic pressure in this and all subsequent figures are recorded simply as the envelope of the maximum systolic amplitude of the total balloon pressure illustrated in Figure 2. The top three channels illustrate the effects of vagal blockade, immediately after the arrow, and it is seen that some degree of parasympathetic tone has been eliminated as well as the response to steady increases in intrasinus pressure above 150 mm Hg. The three lower channels taken from a different experiment illustrate the effects of sympathetic blockade applied several minutes before the arrow, and the consequent elimination of responses of left ventricular systolic pressure to steady decreases in intrasinus pressure from 150 mm Hg.
overshoot and is slower than the first step from 60 to 115 mm Hg, even though both are induced by step increases in intrasinus pressure. The general features of the waveform of the left ventricular systolic pressure illustrated in Figure 2 are characteristic of all animals studied and, as will be illustrated subsequently, are especially significant in view of the waveform characteristics of the response of left ventricular systolic pressure to step changes in efferent autonomic activity (23). The peculiar nature of this complex response is somewhat elucidated by the responses of left ventricular systolic pressure during nerve blockade. The top three channels of Figure 3 illustrate the effect of parasympathetic blockade with the sympathetic division intact. The left panel shows the normal response to a combined increase in left and right carotid sinus pressure. There is an overshoot in the response of left ventricular systolic pressure when input pressure is decreased to 150 mm Hg but no corresponding undershoot when this pressure is elevated from 150 mm Hg. The first part of the right panel in the upper half of this figure is typical of all experiments and illustrates the increase in left ventricular systolic pressure found while the vagi were being cooled (arrow labeled “vagal blockade”). With the preparation used in this study, left ventricular systolic pressure typically remains elevated throughout the duration of vagal blockade except for an occasional slow decrease which is probably due to general deterioration of the preparation. This apparently indicates that, along with all other afferent and efferent impulse traffic present in this nerve trunk, the prevailing cardiac parasympathetic tone has been eliminated by the nerve blockade. This panel also illustrates that the vagal blockade abolishes the depressant response of left ventricular systolic pressure to increases in bilateral carotid sinus pressure above 150 mm Hg. Although not illustrated in the figure, the vagal blockade maneuver does not alter the response of left ventricular systolic pressure to decreases of intrasinus pressure from a control level of 150 mm Hg.

The lower three channels of Figure 3 illustrate the effect of sympathetic blockade with the vgosympathetic trunks intact. The left panel shows the response of left ventricular systolic pressure to decreases of 50 mm Hg in left and right intrasinus pressures from a steady control level of 150 mm Hg. The tracing in the right panel was obtained after blockade of the impulse traffic through the stellate ganglia. The normal increase in left ventricular systolic pressure to a reduction in carotid sinus pressure has been eliminated although there may still be a slight decrease when the input pressure is elevated above 150 mm Hg. The somewhat random oscillation which appears to be superimposed on the response in the left panel has been shown by previous work to be a respiratory disturbance of central origin, probably not due to carotid body ischemia (24). The amplitude of this disturbance is greatly augmented under conditions of decreased intrasinus pressure (100 mm Hg) from its almost insignificant presence at 150 mm Hg. This may merely be indicative of an induced increase in sympathetic activity and a concomitant increase in amplitude of respiratory center modulation of the activity of the cardiac vasomotor centers, each consequent to the decreased intrasinus pressure.

The preliminary interpretation of the steady-state results of nerve-blockade maneuvers, which were qualitatively similar in all animals studied, can then be stated for reflex intrasinus pressure regulation of ventricular function as follows. When pressure steps are taken from a mean of 150 mm Hg in this preparation, (a) parasympathetic activity is greatest at carotid sinus pressures in excess of 200 mm Hg and decreases as this pressure is lowered toward 150 mm Hg, (b) sympathetic activity is greatest at carotid sinus pressures of less than 100 mm Hg and decreases as this pressure is increased toward 150 mm Hg, and (c) there is some degree of overlap in the midpressure region between the points at which the activity of
each division no longer appears to decrease; i.e., sympathetic activity may continue to decrease until intrasinus pressure has exceeded 160 to 170 mm Hg, and vagal activity may continue to decrease until this pressure is less than 130 to 140 mm Hg.

The steady-state amplitude of the responses of left ventricular systolic pressure to increases or decreases of 50 mm Hg in left or right or both intrasinus pressures are summarized in Table 1. In section A of the table, illustrating the responses to decreasing pressure steps from 150 to 100 mm Hg, (a) a step in right intrasinus pressure elicits a significantly greater response than that in the left, and (b) the response of left ventricular systolic pressure to a step delivered simultaneously to both sinuses elicits a significantly greater response than that which is computed as the simple sum of the individual responses in the first two columns. Note that all three maneuvers were successfully completed in only fifteen animals, but that the right-left comparison only was also made for two additional animals. The same type of comment also applies to the numbers of animals in section B of the table, where for intrasinus pressure steps increasing from 150 to 200 mm Hg, (a) there is no significant difference between the responses of left ventricular systolic pressure to left and right intrasinus pressure changes, and (b) the response to simultaneous left and right pressure steps is significantly less than the summed response computed from the separate left and right responses of the first two columns.

All of the steady-state results, with all nerves intact, can conveniently be described by a multinomial regression equation which was derived for five experiments, as illustrated in Table 2. The form of the regression equation used was:

\[
\Delta LVSP = b_1P_{lcs} + b_2P_{rcs} + b_3P_{lcs}^2 + b_4P_{rcs}^2 + b_5P_{lcs} \cdot P_{rcs}
\]

where LVSP is the left ventricular systolic pressure, \(P_{lcs}\) is the left carotid sinus pressure, and \(P_{rcs}\) is the right carotid sinus pressure. The negative sign of coefficients \((b_1, b_2)\) for the linear terms in the table indicates that the primary response of left ventricular systolic pressure is in the direction opposite to the intrasinus pressure change. For all but the first equation, the right linear term \((b_2)\) is greater than the left \((b_1)\); however, with this same exception plus that of experiment no. 17, the three remaining left quadratic coefficients \((b_3)\) are negative, while all of those for the right \((b_4)\) and for the interaction term \((b_5)\) are positive. If attention is now restricted to a regression equation whose coefficients are the means of all the

### Table 1

Comparison of Responses of Left Ventricular Systolic Pressure to Separate Left and Right, and Combined Versus Left and Right Sum of Separate Step Changes of Carotid Sinus Pressure

<table>
<thead>
<tr>
<th></th>
<th>Right</th>
<th>Left</th>
<th>Right — left</th>
<th>Combined</th>
<th>Sum</th>
<th>Combined — sum</th>
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<tbody>
<tr>
<td>A. Step decreases in pressure from 150 to 100 mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N*</td>
<td>17</td>
<td>17</td>
<td>17</td>
<td>15</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>(\bar{X})</td>
<td>9.45f</td>
<td>4.01</td>
<td>5.44</td>
<td>19.74</td>
<td>13.18</td>
<td>6.55</td>
</tr>
<tr>
<td>se</td>
<td>1.15</td>
<td>0.69</td>
<td>1.13</td>
<td>2.82</td>
<td>1.65</td>
<td>1.51</td>
</tr>
<tr>
<td>(P)</td>
<td>&lt; 0.005</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B. Step increases in pressure from 150 to 200 mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>11</td>
<td>11</td>
<td>11</td>
<td>9</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>(\bar{X})</td>
<td>-6.27</td>
<td>-5.99</td>
<td>-0.28</td>
<td>-9.6</td>
<td>-12.42</td>
<td>-2.82</td>
</tr>
<tr>
<td>se</td>
<td>0.80</td>
<td>0.73</td>
<td>0.83</td>
<td>1.09</td>
<td>1.44</td>
<td>0.76</td>
</tr>
<tr>
<td>(P)</td>
<td>&lt; 0.01</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* N = number of animals, \(\bar{X}\) = mean, se = standard error, \(P\) = significance as determined from paired t-test. † All values are expressed as percent changes from control.

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### TABLE 2

Extreme Experimental Responses and Derived Coefficients for Regression Equation Describing Steady-State Amplitude Responses of Left Ventricular Systolic Pressure

<table>
<thead>
<tr>
<th>Expt. no.</th>
<th>Extreme experimental responses (%)</th>
<th>Regression Coefficients</th>
<th>b₁</th>
<th>b₂</th>
<th>b₃</th>
<th>b₄</th>
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</thead>
<tbody>
<tr>
<td>10</td>
<td>(—1, —1) 26.3, —6.7</td>
<td>—9.9</td>
<td>—5.8</td>
<td>+3.7</td>
<td>+3.6</td>
<td>+4.1</td>
</tr>
<tr>
<td>11</td>
<td>(—1, —1) 12.5, —6.5</td>
<td>—4.7</td>
<td>—5.2</td>
<td>—1.1</td>
<td>+1.6</td>
<td>+1.5</td>
</tr>
<tr>
<td>15</td>
<td>(—1, —1) 20.6, —9.7</td>
<td>—4.8</td>
<td>—9.5</td>
<td>—1.6</td>
<td>+3.1</td>
<td>+3.1</td>
</tr>
<tr>
<td>17</td>
<td>(—1, —1) 10.7, —3.7</td>
<td>—0.3</td>
<td>—6.8</td>
<td>+0.9</td>
<td>+3.5</td>
<td>—0.1</td>
</tr>
<tr>
<td>20</td>
<td>(—1, —1) 32.1, —10.0</td>
<td>—9.0</td>
<td>—10.4</td>
<td>—2.5</td>
<td>+6.5</td>
<td>+6.4</td>
</tr>
<tr>
<td><strong>MEAN</strong></td>
<td></td>
<td>—5.74</td>
<td>—7.54</td>
<td>—0.12</td>
<td>+3.66</td>
<td>+3.02</td>
</tr>
</tbody>
</table>

*The (—1, —1) and (+1, +1) response coding indicates the percent changes of the extreme response from control when both intrasinus pressures have been changed from 150 mm Hg to, respectively, the low level (100 mm Hg) and the high level (200 mm Hg).

appropriate table values, it will be seen by substituting the (—1, 0, 1) code values (representing 100, 150, and 200 mm Hg, respectively) into the equation, that for decreasing steps from 150 mm Hg the right carotid sinus has a greater effect than the left, but for increasing steps the response is about the same for left and right sides. Also, the magnitude and positive sign of the interaction coefficient (b₅) are such that the combined left and right responses for decreasing and increasing pressure steps will be respectively greater and less than the simple sum of the individual left- and right-sided responses.

These characteristics are illustrated in Figure 4, a family of curves relating the calculated dependence of left ventricular systolic pressure in the steady state to right intrasinus pressure, when left intrasinus pressure is held constant as a parameter. The curves are plotted from the regression equation whose coefficients are the means given in Table 2, i.e., they represent a composite of five experiments. This figure graphically illustrates the information of Table 1 in that the curves are relatively more spread apart at 100 mm Hg, but converge as input pressure is increased toward 200 mm Hg. The slopes of the curves are considerably steeper in the low-input pressure region than in the high. Although it was not measurable, and it is not statistically proper to extrapolate the computed curves beyond the measured region, it is to be expected that as input pressure is further decreased the curves would level off at a plateau. A minimum of a third-order equation would be needed to additionally describe such a plateau, however, requiring at least a four-level experimental design. This was not attempted. These computed curves are consistent with those based upon cardiac performance measurements taken from a similar preparation (ref. 10, Fig. 8), however, in that all of the curves appear to have a maximum slope in the region of 100 mm Hg of intrasinus pressure.

![Figure 4](attachment:figure4.png)

**FIGURE 4**

Family of curves illustrating a plot of the changes in left ventricular systolic pressure (LVSP), as a percentage of control, expressed as a function of right intrasinus pressure for a series of constant left intrasinus pressures. Each curve is calculated from the regression equation whose coefficients are the means of the values of five experiments as given in Table 2.
DYNAMIC ANALYSIS

Based upon the above derived steady-state amplitude characteristics, a model was derived to represent the dynamic response of left ventricular systolic pressure to changes in intrasinus pressure. The model was derived with the hope that the known nonlinearities of the baroreceptors (18, 20, 22) and the response of left ventricular pressure to efferent autonomic activity (23) combined with a central nervous system characteristic which was assumed to be linear would adequately represent the static and dynamic nonlinearities of the total intrasinus pressure-left ventricular systolic pressure system illustrated above. Figure 5 is a schema of this model which illustrates the relationships used to represent the three functional blocks into which the system was divided. The "analog" or "digital" label below each block designates whether that relationship was implemented on the analog or digital portion of the hybrid computer.

The blocks in the upper left corner of the model depicted in Figure 5 represent the relationships between left and right carotid sinus pressure and their respective nerve-firing patterns (18-22). The relationship derived by Poitras et al. (18) was chosen for incorporation into the present model, since it was based upon multifiber data as well as upon the known nonlinearities of the system. This relationship is illustrated in the block labeled A1, which is the linear part of this relationship in Laplace transform notation. It consists of a proportionality term plus two (primarily) derivative terms. The first of these derivative terms \( \frac{k_1 s}{s + \omega_1} \) has a very fast response (lag time constant of about 5 msec) and is thus almost a pure derivative. The last term \( \frac{k_2 s}{s + \omega_2} \) has a time constant three orders of magnitude greater (about 5 sec) and thus represents the adaptation phenomenon of the baroreceptors.
The static gain function, block D1, following the linear terms, exhibits the required threshold and saturation effects of the carotid sinus receptors. The low and mid range regions of the static characteristics were made linear, but the saturation region was made curvilinear, by Poitras et al. (18). This model was consequently modified here, as illustrated in Figure 5, to make the threshold region also curvilinear (quadratic, for convenience). That a curvilinear threshold region is more physiologically realistic has been noted (22) subsequent to the completion of the present work. The relative concavity of these two curvilinear regions is such that for rapidly changing intrasinus pressures, such as the normal pressure pulse, the positive derivative has a greater effect than the negative derivative at very low intrasinus pressures, and the negative derivative has a greater effect than the positive derivative at high pressures. These characteristics have actually been observed by Christensen et al. (20).

The block D2 represents the central nervous system. Previous work (21, 25) relating to afferent-efferent nervous activity transformations suggests that the dynamics of the central nervous system are at least one order of magnitude faster than either the adaptation of the baroreceptors or the response of left ventricular systolic pressure to efferent activity (23). It was thus decided to model the central nervous system with pure static gains. The form of these static gains was based upon the experimental results of nerve elimination described above. Sympathetic activity from the left and right sides (\(S_l\) and \(S_r\)) was thus made to decrease with increasing intrasinus pressure and finally to reach a constant value in the 150 to 160 mm Hg region. Parasympathetic activity from the left and right sides (\(V_l\) and \(V_r\)) was made to increase with increasing intrasinus pressure, starting from a constant value in the 140 to 150 mm Hg region. These constant values for each autonomic division were set to represent some background tone for each division which was not related to changes in reflex activity induced by the carotid sinus. In the absence of any other information, it was assumed that each of these four characteristics was linear, but the slope of each was made individually adjustable to account for the different sensitivities of each side in any particular animal. The inputs from the left and right sides were combined to form the resultant nervous activity level for each autonomic division, as shown in block D2, by adding the individual components plus their weighted product. The weighted product term is positive for sympathetic activity and negative for vagal activity, to account for the nonlinear combination results described in Table 1.

FIGURE 6

Simulation results for one animal. The labels on each channel correspond with the respective variables of Figure 5, e.g., the top channel is the output of block A1 in Figure 5, the second and third channels are the outputs of blocks A2 and A3, and the sixth channel is the model left ventricular systolic pressure (LVSP) output of block D5 which is to be compared with the real animal responses in the bottom channel. See text for detailed discussion.
The final blocks, D3, D4, A2, A3, and D5, representing the response of the left ventricular myocardium to efferent autonomic activity, are identical with those derived in a previous report (23). Briefly, for sympathetic activity, block D3 is a pure time delay which is shorter for increasing activity than for decreasing activity. The dynamics of the sympathetic response, block A2, are made up of two parallel branches: (1) a very slow (time constant of 25 to 50 seconds) first-order branch and (2) a branch which has a fast underdamped second-order response to increasing ($S > 0$) activity (equivalent time constant of 5 to 10 seconds) and a first-order response to decreasing ($S < 0$) activity (time constant of 10 to 20 seconds). The time delay to increasing sympathetic activity (3 to 6 seconds) is significantly longer than the delay to decreasing activity (1.5 to 3 seconds). The vagal response, block A3, is first order with a time constant of 10 to 15 seconds. The vagal response time delay (3 to 6 seconds), block D4, and the time constant are both symmetrical for increasing and decreasing vagal activity. The final value of left ventricular systolic pressure is given by combining the components of the separate divisions by means of a regression response surface which was derived in the earlier work (23) and which is illustrated in the final block, D5, of the model.

This model was implemented on a hybrid computer which consisted of a General Electric GEPAC/4060 digital machine tied to a Computer Systems Inc. CS1-5800 analog machine. The simulation procedure consisted of first setting the time constants and time delays for the response of left ventricular systolic pressure to separate step changes in activity of the two autonomic divisions. That is, tape-recorded stimuli from the experimental situation, corresponding to the output of block D2 in Figure 5, were applied to the computer model of the left ventricle (bottom row in Fig. 5), and the dynamic computer responses were then matched as closely as possible with the tape-recorded responses of left ventricular systolic pressure of the real animal. Then the tape-recorded intrasinus pressure signals were applied to the entire model of Figure 5, and the parameters of the top row of this figure were varied until a good match with the overall pressure responses was obtained.

Figure 6 is an illustration of the simulation results for two sets of simultaneous changes in left and right carotid sinus pressure in one animal. The fourth and fifth tracing in the figure are, respectively, the left and right intrasinus pressures. The top tracing is the output of block A1 in Figure 5, that is the response of the linear dynamic portion of the carotid sinus transfer for the right side. The overshoot of the adaptation phenomenon of this output variable has a constant height over the entire input range. The second and third tracings in the figure represent the separate sympathetic and vagal components of left ventricular systolic pressure (outputs of blocks A2 and A3, respectively) which result from combined left and right intrasinus pressure changes. The sixth and seventh tracings then illustrate the comparison to be made between, respectively, the simulated left ventricular systolic pressure output (block D5) and that recorded from the animal.

Figure 7 is an illustration taken from a different animal, with the same order of tracings as in Figure 6, except that now the top tracing, $C_r$, is the output of the total carotid sinus transfer, that is after the dynamics and the static gain (block D1 in Fig. 5). By comparing top tracings in Figures 6 and 7, the static gain function can be seen to limit the amplitude of the adaptation overshoot in the high and low pressure ranges, while preserving its amplitude in the mid-pressure input region.

Several characteristics of this response of left ventricular systolic pressure can be analyzed by reference to the internal model variables shown in Figures 6 and 7. The first concerns the relative time constants of the pressure response to a decreasing step from 150 mm Hg and to the return step. Based upon the previous finding that sympathetic
activity predominates in this region, and that it increases in magnitude as pressure is decreased, the previous dynamic analysis would suggest that the response of left ventricular systolic pressure due to a drop in input pressure would rise much faster than it would fall when the pressure was elevated back to control (the response shape of the sympathetic component, S, in Figs. 6 and 7 at arrows A). Rather, it is clearly seen that the actual response is roughly symmetrical, with the falling portion even being slightly faster than its rising portion (arrows B, both figures).

This response behavior is easily accounted for in the model by the combination of the carotid sinus overshoot with the distinct but overlapping operational regions of the two autonomic divisions. Thus a decrease of 50 mm Hg in input pressure from 150 mm Hg does not transmit an overshoot (such as at arrow C, Fig. 6) to the central nervous system illustrated at arrow C in Figure 7. The increasing response of left ventricular systolic pressure thus has the normal shape that one would observe with a simple step increase in sympathetic activity (arrow A, both figures). The carotid sinus response to a step increase of 50 mm Hg from a mean level of 100 mm Hg, however, does have an overshoot component (arrow D, Fig. 7), and this component conveyed to the central nervous system primarily falls into the vagal activity region. The addition of a transient vagal component (arrow E, Fig. 7) to the total response of left ventricular systolic pressure then acts to make this total response fall much more rapidly than if the fall were due only to a step decrease in sympathetic activity (arrows B, both figures).

This overshoot also acts to increase the rate of change of the fall in pressure due to sympathetic activity, so that both factors must actually be taken into account. However, in the model, this transient sympathetic effect contributes less to the resultant dynamic time constant than the vagal effect since sympathetic activity did not change above 160 mm Hg in this simulation.

This argument can also be invoked to explain the broad overshoot in left ventricular systolic pressure seen when input pressure

**FIGURE 7**

Simulation results for a different animal for a continuous sequence of combinations of increasing and decreasing left and right intrasinus pressure steps. The top channel is $C_r$, the output of block D1, i.e., the central input from the right carotid baroreceptor, including the nonlinear static gain function. All other channels are as in Figure 6. See text for detailed discussion.
is decreased by 50 mm Hg from 200 mm Hg, but not when the inverse increasing step is taken from 150 mm Hg. Figure 7 most clearly illustrates this phenomenon, where the afferent activity which is transmitted to the central nervous system (top tracing, C_r) has a saturation-limited overshoot for the increasing step (arrow F, Fig. 7) but a non-limited overshoot for the decreasing step (arrow G, Fig. 7). Thus, a transient sympathetic response component (arrow H, both figures) adds to the primarily vagal response for the decreasing step to yield the broad overshoot in the total response of left ventricular systolic pressure (arrows I, both figures). Again, this overshoot also affected the normal symmetry of the vagal response component alone, since vagal activity ceased to change below 140 mm Hg in this simulation. Both effects must thus be accounted for, although the sympathetic transient is the primary factor leading to the broad overshoot of left ventricular systolic pressure.

The second response of Figure 7, i.e., to a step increase of left intrasinus pressure only, is interesting in that here there is no broad overshoot (arrow J). But it was also found that the response of left ventricular systolic pressure to a step decrease of 50 mm Hg from 150 mm Hg in the left carotid sinus had a very small amplitude, as illustrated by the response at arrow K in Figure 7, taken from the same animal. It could be inferred, then, that the gain of the left-sided sympathetic activity was very small. Thus, the transient sympathetic component of the response of left ventricular systolic pressure to a step decrease of 50 mm Hg from 200 mm Hg might be very small. The structure of the model successfully invokes this hypothesis to explain the presence or lack of a broad overshoot, as illustrated by all the tracings of the model and animal responses of Figure 7.

Figure 7 illustrates the model and left ventricular systolic pressure responses to a continuous 15-minute sequence of combinations of changes in left (fourth tracing) and right (fifth tracing) intrasinus input pressures. This figure illustrates that the model predicts the response behavior with reasonable success over a relatively long period, as well as the isolated responses of a different animal of the previous figure. It further illustrates that the model accounts for the nonlinear activity of the separate responses of left ventricular systolic pressure to left and right inputs. Thus, in the animal and model, the response to combined left and right sinus stimulation is greater than the sum of the two individual responses to decreases of pressure from a mean value of 150 mm Hg. Conversely, the response to combined stimulation is less than the sum of the individual responses when intrasinus pressure is increased from a mean value of 150 mm Hg.

**Discussion**

The finding in the present work that the right carotid sinus reflex loop had a significantly higher static gain than that of the left, also found in the systemic pressure control system by Sagawa and Watanabe (26), has three possible bases. The first is simply related to the finding of a greater response of left ventricular systolic pressure to the left sympathetic than to the right sympathetic system for a unit increase in efferent activity of each (15, 19). Thus, if the baroreceptor reflex arcs are predominantly decussated, changes in right intrasinus pressure below 150 mm Hg may have a greater effect on left ventricular systolic pressure than those in the left sinus. Although some evidence exists for a crossed component in the sympathetic pathways of the carotid sinus reflex (27-30), the preponderance of recent evidence suggests that these central pathways are primarily uncrossed (31-36) which would seem to eliminate this hypothesis. The other two bases for the greater right-sided gain are that the sensitivity of the right baroreceptor itself, or the central right sinus gain, may each or both be greater than those of the corresponding left side. Recent evidence that direct electrical stimulation of carotid sinus nerves with equal stimuli var-
ables leads to a greater decrease in blood pressure with the right nerve than with the left (37) would seem to preclude a greater sensitivity of right afferent nerve endings. This does not, of course, simply preclude either a greater innervation of the right sinus than of the left or a greater central gain for the right than the left side.

A plausible explanation for the difference in left and right sensitivities is to be found in the central processing of the information derived from each side. The results of the present work, suggesting that the difference in central processing of the right and left sides would have to be evident only with respect to sympathetic outflow, can be interpreted in the light of other recent evidence to support this concept. In the dog, the vagal cardiomotor centers in the region of the nucleus ambiguus, dorsal motor nucleus, and to a lesser extent in the nucleus solitarius have been found physiologically to exert their influences through both ipsilateral and contralateral vagi (38). However, from the present work there is no significant right and left difference in the response of left ventricular systolic pressure to high input pressures, where vagal activity predominates, nor in the response to direct left and right parasympathetic stimulation (7). These two facts suggest that the right baroreceptor sensitivity is not greater than the left (at least in the high pressure region) and that as a working hypothesis the explanation for the results of the present work, as well as for the blood pressure responses, can be ascribed to a greater central gain for right than for left sinus nerve inputs for sympathetic outflow.

The inhibitory addition of the left and right combined response of left ventricular systolic pressure to combined stimulation of both carotid sinuses in the high input pressure regions of the present work, where changes in vagal activity predominate, probably cannot be ascribed to saturation in the effector mechanism. As shown by an earlier quantitative analysis of the autonomic activity-left ventricular systolic pressure response surface (23), the responses to left and right vagal stimulation do not exhibit saturation either separately or when combined until their amplitude is near maximal (usually in the range of −25 to −40%), a range considerably above the maximal decrease of left ventricular systolic pressure (rarely greater than 15 to 20%) evoked by increases of intrasinus pressure from 150 to 200 mm Hg. One likely source for this inhibitory addition in the steady state may be the saturating characteristic of the baroreceptor. At 200 mm Hg this characteristic is in its nonlinear concave-downwards range (18-20). Such an explanation, of course, does not rule out the possibility of a further saturation effect or a simple inhibitory summation phenomenon (the two are not necessarily the same) in the central nervous system.

The facilitative addition (such that the combined response is greater than the simple sum of the individual responses) of the left and right responses in the low input pressure regions is more easily ascribed to a likely source. The responses of left ventricular systolic pressure to individual left and right sympathetic stimulations combine as a simple sum, at least up to a 100% response amplitude, while the response to decreases of intrasinus pressure from 150 to 100 mm Hg rarely exhibits an increase greater than 40%. Since the upwards concavity of the baroreceptor threshold region at and below 100 mm Hg (19, 20, 22) tends to make the summation inhibitory, the source of the facilitative summation observed is most probably found in the central nervous system.

The findings that sympathetic activity is greatest at very low intrasinus pressures and decreases with increasing intrasinus pressure and that vagal activity is greatest at very high intrasinus pressures and decreases as pressure is reduced are not original to the present work; such phenomena have been described to varying quantitative degrees before (2, 5, 25, 28, 39-41). The results of the present work in the steady state thus tend to support the view of Glick and Braunwald (41).
that there are distinct input pressure regions through which control is exerted by each autonomic division. The present work, in contrast, however, suggests that some degree of overlap between the two divisions exists (Fig. 5). This is opposed to the more classical view of reciprocal activity of the two divisions of the autonomic nervous system. It should be noted here, however, that the results of the present work strongly suggest that a definite distinction must be drawn between the transient and steady-state responses when relative roles are ascribed to the two autonomic divisions in any baroreceptor reflex response. As shown in Figures 6 and 7, because of the broad overshoot or adaptation of the baroreceptor, the afferent input activity may very well transiently activate both autonomic divisions, even though the steady-state response can be attributed almost solely to changes in activity of only one autonomic division. Thus, at least in the baroreceptor reflex, either view of the relative role of each autonomic division may be accepted with equal verity, depending upon whether the transient or the steady-state responses are being described.

The effects of anesthesia on the results of this work must be given consideration. Indeed, it was recently suggested that chloralose anesthesia has a time-varying degradative effect on reflex cardiovascular responses (42). These anesthetic effects will, of course, reflect most heavily on the central nervous block of the model, and it thus seems reasonable to assume that these effects might influence more the static rather than the dynamic characteristic of total reflex response. The degree to which various anesthetic techniques affect the combining of afferent inputs, and the distribution of efferent outputs, however, is unknown such that some word of caution about comparing the results of this work with that of others must be expressed.

The linear, afferent-efferent transformation within the central nervous system which was used in the model derived here is only a convenient approximation. From the simulation experience with the model, it became evident that nonlinear characteristics, with the greatest curvature in the regions corresponding to the input pressure of 150 mm Hg near where the activity of each division is lowest, might give a better fit to the real animal responses. Such a modification was not made, however, since there is no quantitative experimental information on this point, and since there would probably be no significant improvement in the model fit. The assumption that the central nervous system can be represented as a pure static gain is not entirely supported by recent evidence (35); however, the adaptation of the lateral firing pattern observed in some fibers of that work is still approximately an order of magnitude faster than that in the other components of this system, so that the resultant error in the model is not too serious.

One final comment about the overall response of the model deserves mention. The model structure developed here, based upon the known characteristics of each of the corresponding physiologic components, suggests one possible explanation for the variability in the dynamic time constants often cited for the carotid sinus-systemic pressure reflex (2, 3, 37, 43). Thus, this variability in the response is inherent in the present model because of the carotid sinus overshoot, saturation, and threshold, combined with the autonomic activity thresholds; that is, the model successfully accounts for the change in response waveform, and this waveform is a function of the magnitude of the intrasinus pressure step as well as the mean pressure level from which the step was taken.

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