A TECHNIQUE COMMONLY USED for the measurement of carotid diameter in humans.

Effect of vasoactive drugs on carotid diameter in humans.

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A TECHNIQUE COMMONLY USED for the measurement of baroreflex sensitivity in physiological and clinical studies involves the use of vasoactive drugs. Blood pressure is either elevated by phenylephrine or lowered by nitroglycerin (or related nitro compounds), and the resulting changes in R-R interval are related to corresponding systolic pressure values. The slope of the linear regression line for the R-R interval-systolic pressure relationship is taken as an index of cardiac vagal baroreflex sensitivity (34).

The linearity of the relationship between systolic pressure and R-R interval may imply that, within the arterial pressure range studied, drug-induced changes in arterial pressure result in proportional changes in carotid sinus diameter; changes in vessel wall strain lead to proportional changes in baroreceptor firing frequency; baroreceptor firing rate is translated to proportional changes in cardiac vagal nerve discharge; and the level of efferent vagal discharge is linearly related to R-R interval. The linear relationships between myelinated baroreceptor afferent discharge and cardiac vagal activity and between vagal activity and R-R interval have been established (13, 20, 24). On the other hand, the quantitative aspects of the process of how drug-induced changes in blood pressure are translated into baroreceptor firing are less clear. The relationship between pressure and diameter was found to be nonlinear for many types of vessels, with the change in diameter produced by a unit change in pressure diminishing as pressure increased (8). In a recent study in humans, it was shown that the carotid pressure-diameter relationship approached saturation at normal systolic pressure values (16). A similar pressure-diameter characteristic was reported for the aorta as well (26). How, then, increases in systolic pressure produce linear increases in R-R interval is an open question.

α-Adrenergic agonists have been reported to activate smooth muscle fibers within the wall of the carotid sinus. Peveler et al. (31) found that the carotid sinus diameter was reduced during phenylephrine-induced blood pressure elevations in the conscious dog. They suggested that smooth muscle in the sinus wall was activated and smooth muscle contraction influenced baroreceptor firing. This line of reasoning assumes that barosensory elements are coupled in series to vessel wall smooth muscle. Others (5, 15, 28), working on the isolated carotid sinus and aortic arch, also reported smooth muscle activation and vessel constriction in response to catecholamine administration. Similar data are not available in humans, and it is uncertain to what extent animal data can be extrapolated to humans, considering the species differences in carotid wall structure. In the dog and other laboratory animals, the carotid artery is of the muscular type, whereas in humans, it is of the elastic type (3). When blood pressure is elevated by vasoactive drugs, the actual change in diameter reflects the net effect of passive dilatory forces and active smooth muscle contraction. How the balance is set in humans is not known.

In view of the above uncertainties, we studied the changes in carotid diameter during blood pressure elevations and reductions induced by vasoactive drugs commonly used for the assessment of baroreflex sensitivity in humans.

METHODS

Subjects. This study was carried out on eight young, healthy volunteers, 20–24 yr of age, who were nonsmokers, normotensive, and free of medications. All gave written informed consent to participate in the study, which was

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approved by the Ethical Committee of Semmelweis University of Medicine (Budapest, Hungary).

Two subjects were excluded from data analysis: in one subject, blood pressure and carotid diameter fluctuated to such an extent that baseline values could not be established; in another subject, carotid diameter increased during the phenylephrine-induced rise in pressure and continued to be enlarged even when blood pressure returned to the control level. Data reported here are from the remaining six subjects, two women and four men.

Measurement of carotid artery diameter. The diameter of the carotid artery and its changes with arterial pulse were measured with ultrasonography. 1.5 cm proximal to the bifurcation. The ultrasonic device consisted of a vessel wall-tracking system (WTS) combined with a conventional ultrasonic scanner (7.5-MHz linear array, Scanner 200, Pie Medical, Maastricht, The Netherlands). The ultrasound probe was placed on the neck, and the carotid artery and sinus region were visualized in two-dimensional mode. The ultrasound system was then switched to M mode, and ultrasound was emitted and received along a selected M line of sight.

The WTS is based on a data-acquisition system capable of capturing the received and amplified radio-frequency (RF) signals synchronously with the emission trigger at a sample frequency of up to 30 MHz. At a 0.4-kHz acquisition trigger rate, the memory holds 2,048 RF lines of 512 data points each, corresponding to 5 s of data. The WTS is also equipped with an acquisition system for reference signals such as blood pressure that are sampled synchronously with the emission trigger (18).

After completion of data acquisition, the data were transferred to a personal computer (PC; 486 DX2/66). The first line acquired was graphically presented on a display, allowing manual identification of the anterior and posterior wall boundaries by placing two markers that represent the sample windows for data processing. Once the walls were identified, the remaining data were transferred and processed on-line. To extract the change in position of either the anterior or posterior wall, averaged over a few RF lines, the approach based on the cross-correlation model for corresponding segments of subsequent RF lines was applied. This method has a low noise sensitivity and is insensitive to the actual RF carrier frequency (17). To ensure that the signals returned by the same structure were always considered, the position of the sample windows was adjusted according to the observed displacements (tracking window). The difference between the displacements of signals of the anterior and posterior walls yielded the change in diameter as a function of time, i.e., the distension waveform. Previous in vitro experiments have shown that this type of ultrasound system can resolve displacements of a few micrometers (18).

Vessel wall strain was defined as the relative change in diameter from end diastole to peak systole and is expressed as percent change. Carotid distensibility was calculated as

$$\frac{2 \Delta D (D \times \Delta P)}{D^2}$$

where $D$ is end-diastolic diameter, $\Delta D$ is the change in diameter from end diastole to peak systole, and $\Delta P$ is the pulse pressure. $\Delta P$ is derived from the Finapres signal. To assess the reproducibility of the carotid dimensions and distensibility, the carotid artery WTS examination was repeated in each subject on a different occasion. At baseline conditions, the coefficients of variation for carotid dimensions and distensibility were $<10\%$ in each of our subjects, which agree well with data published previously (25).

Additional measurements. The subjects were instrumented to record electrocardiogram (ECG), cardiotachogram, respiration, end-tidal $\text{CO}_2$, and arterial blood pressure. R-R intervals were measured from R wave threshold crossings on continuously recorded ECGs. Arterial blood pressure was monitored noninvasively beat by beat in the right middle finger (Finapres, Ohmeda 2300) and was also measured sphygmomanometrically in the brachial artery. Respiration was recorded with an inductive system (Respirtrace Ambulatory Monitoring), and end-tidal $\text{CO}_2$ was monitored with an infrared analyzer (Ohmeda 5200).

Protocol. The subjects reported to the laboratory in the early afternoon, 2–3 h after a light meal. During the day of the study, they refrained from consuming coffee or alcohol. All of our subjects were acquainted with the laboratory environment before they have participated in similar studies before. The subjects were instrumented, and a cannula was inserted into the left cubital vein for drug administration. After a resting period of 15 min in the supine position, phenylephrine (50–150 μg) and nitroglycerin (50–100 μg) were injected alternately in an intravenous bolus to raise and lower blood pressure by ~15–25 mmHg. There were 15 min between injections to allow enough time for blood pressure, heart rate, and carotid dimensions to return to control levels. The injections were repeated at least three times.

Data recording and analysis. ECG, Finapres, and Respirtrace output signals were recorded on a Grass 7B polygraph and also transferred to a PC after analog-to-digital conversion. Carotid diameter images were recorded continuously on videotape. Marker signals were simultaneously delivered to the PC and the video recorder at regular intervals to synchronize recordings. The WTS cross-correlation algorithm was activated before each drug injection to obtain control data and at the peak of the pressor and at the nadir of the depressor responses induced by phenylephrine and nitroglycerin, respectively. Drug injections were repeated until three successful recordings were obtained. The number of distension (ΔD) pulses available for analysis was limited by the actual heart rate. During each run, five to six distension pulses were recorded in the control condition, three to four pulses at the peak of the pressor response, and six to eight pulses at the nadir of the depressor response. Pressure, diameter, strain (ΔD/D), and distensibility data were pooled for the three runs and averaged. The significance of the differences among data obtained in the different conditions (i.e., control, phenylephrine and nitroglycerin) was tested within each individual by single-factor analysis of variance and Scheffé’s post hoc test. Carotid diameter changes were also evaluated by replaying the videotape and using the two-dimensional analysis program of a commercial echocardiograph (SONOS-1000, Hewlett-Packard). Although the spatial resolution of this cursor-aided on-screen measurement is less (100 μm) than that of the WTS, it allowed us to monitor diameter changes throughout the whole period of pressor and depressor responses (see RESULTS). Using the videotaped data, we were able to determine the relationship between changes in carotid diameter and the reflex responses in R-R interval.

Baroreflex sensitivity (BRS) was determined with the “Oxford method”; i.e., the slope of the linear regression line relating changes in R-R interval to changes in systolic pressure was taken as the measure of BRS. The method has been discussed in detail before (6). In addition, the same R-R interval changes were related to corresponding systolic carotid diameter values using the videotaped data. Cardiac cycles during both inspiration and expiration were involved in the analysis. Our subjects, who regularly participate in similar studies, maintained a fairly steady respiratory pattern. BRS values reported for each subject are the average value of slopes obtained from at least three test injections. BRS values in the individual subjects showed a mean variability of 12.6%.
RESULTS

Baseline data for all subjects are given in Table 1. Carotid diameter and blood pressure tracings obtained by the WTS and Finapres, respectively, during a phenylephrine-induced rise in blood pressure are shown in Fig. 1. Associated with the gradual rise in pressure, carotid diameter increased at both end diastole and peak systole. The early reflection wave became the dominant peak of the distension waveform due to increases in peripheral resistance (29). Carotid distension waveforms in the control situation, at the peak of a pressure response, and at the nadir of a depressor response recorded in one subject are shown in Fig. 2. Carotid dimensions increased during the rise and decreased during the fall in pressure; the magnitude of changes in diastolic diameter exceeded those in systolic diameter during both the pressor and depressor responses. The contour of the distension pulse exhibited characteristic changes: the early reflection wave was accentuated during the rise and was diminished during the fall in pressure. The entire time courses of changes in diameter and pressure induced by phenylephrine and nitroglycerin administration in a representative subject are illustrated in Fig. 3. During the phenylephrine response, pressure and diameter changed in a parallel fashion, but during the nitroglycerin response, the percent reduction in systolic diameter was considerably less than that in systolic pressure. This quantitative difference between systolic pressure and diameter responses during nitroglycerin-induced hypotension was observed in five of the six subjects. In the remaining subject (subject D in Fig. 4), nitroglycerin administration produced only slight hypotension, which was not associated with significant changes in vessel dimensions.

In all subjects, carotid dimension increased during the phenylephrine-induced rise and decreased during the nitroglycerin-induced fall in pressure. Average data describing the changes in pressure, diameter, strain, and distensibility in response to drug administration are given in Table 1. The simultaneous recording of arterial blood pressure and carotid diameter allowed us to determine the corresponding pressure and diameter values and to plot the pressure-diameter relationships. Due to limitations inherent to the Finapres method, data were plotted only for end diastole and peak systole (see Discussion). In Fig. 4, the control pressure-diameter relationship and its changes during drug-induced alterations in pressure are shown for all subjects. Although the response pattern exhibited considerable individual variability, some features common to all responses could be identified. During phenylephrine-induced hypertension, the pressure-diameter relationship “shifted” upward and to the right except for one subject (subject C in Fig. 4) in whom the relationship simply “slid” to the right along the control characteristic. In all subjects, distensibility was significantly reduced. During nitroglycerin-induced hypotension, the pressure-diameter relationship shifted downward and to the left in a nonparallel fashion. The nonparallel shift was associated with a considerable increase in distensibility. Differences among mean values of pressure, diameter, strain, and distensibility obtained in the three conditions were tested by single-factor analysis of variance and Scheffé’s post hoc test. Within individuals, the differences were all significant at the P < 0.05 level. The only exception was subject D in Fig. 4, in whom changes in systolic diameter did not

Table 1. Cardiovascular parameters and indexes of carotid artery elasticity

<table>
<thead>
<tr>
<th>Measurements</th>
<th>Control</th>
<th>PE</th>
<th>NG</th>
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<tbody>
<tr>
<td>R-R interval, ms</td>
<td>806 ± 305</td>
<td>1,399 ± 166</td>
<td>695 ± 74</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>119 ± 6</td>
<td>135 ± 11</td>
<td>98 ± 16</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>63 ± 5</td>
<td>78 ± 7</td>
<td>51 ± 9</td>
</tr>
<tr>
<td>Carotid diameter at end diastole, µm</td>
<td>5,567 ± 385</td>
<td>5,998 ± 449</td>
<td>5,184 ± 611</td>
</tr>
<tr>
<td>Change in diameter with pulse, µm</td>
<td>922 ± 143</td>
<td>781 ± 106</td>
<td>982 ± 95</td>
</tr>
<tr>
<td>Strain, %</td>
<td>16 ± 2</td>
<td>13.2 ± 2.6</td>
<td>19.7 ± 2.8</td>
</tr>
<tr>
<td>Distensibility coefficient, mmHg⁻¹ × 10⁻³</td>
<td>5.5 ± 0.7</td>
<td>4.4 ± 0.8</td>
<td>8.1 ± 2.4</td>
</tr>
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</table>

Values are means ± SD for 6 subjects during control conditions, at peak of phenylephrine (PE)-induced pressor response, and nadir of nitroglycerin (NG)-induced response.
differ significantly from the control level because nitroglycerin consistently produced only slight hypotension. The magnitude of changes in diameter in response to the actual change in pressure is shown separately for end diastole and peak systole in Fig. 5. As indicated earlier, diastolic diameter changed to a greater extent than systolic diameter during the pressure responses in either direction. Although the relationship between pressure and diameter appeared approximately linear at end diastole, the systolic pressure-diameter relationship exhibited a characteristic nonlinearity (the slope of the relationship was considerably steeper above than below the operational point).

We then compared the R-R interval-systolic pressure and the R-R interval-systolic diameter relationships in the individual subjects using the simultaneously recorded data for R-R interval, systolic pressure, and systolic diameter (Fig. 6, Table 2). The R-R interval-systolic pressure relationships exhibited the expected nonlinearity, i.e., the slope of the relationship was greater for rising than for falling pressures, with a mean ratio of 2.9. The slopes of the R-R interval-systolic diameter relationships for increasing and decreasing diameters were closer, with a mean ratio of only 1.5. In two subjects, the slopes for increasing and decreasing


Table 2. Comparison of slopes and correlation coefficients of baroreflex sensitivity determinations

<table>
<thead>
<tr>
<th></th>
<th>Slope</th>
<th>r</th>
</tr>
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<tr>
<td>RRI-SBP relationship, ms/mmHg</td>
<td>29.1±12.7</td>
<td>0.91±0.03</td>
</tr>
<tr>
<td>Rising pressure</td>
<td>29.1±12.7</td>
<td>0.91±0.03</td>
</tr>
<tr>
<td>Falling pressure</td>
<td>9.9±4.6</td>
<td>0.92±0.04</td>
</tr>
<tr>
<td>RRI-SCD relationship, ms/µm</td>
<td>1,033±399</td>
<td>0.86±0.04</td>
</tr>
<tr>
<td>Increasing diameter</td>
<td>1,033±399</td>
<td>0.86±0.04</td>
</tr>
<tr>
<td>Decreasing diameter</td>
<td>696±173</td>
<td>0.83±0.08</td>
</tr>
</tbody>
</table>

Values are means ± SD for 6 subjects. Changes in R-R interval (RRI) were related to changes in both systolic blood pressure (SBP) and systolic carotid diameter (SCD) as input variables.

Diameters were almost identical; data for one of them is shown in Fig. 6 (top). In all subjects, single linear regression lines could be fitted to data points over the entire range of diameter changes with acceptable accuracy (r = 0.90 ± 0.04). Actually, the relationship between R-R interval and systolic carotid diameter appeared to be closer for the whole diameter range compared with the relationships determined separately for increasing and decreasing diameters (r = 0.86 ± 0.04 and 0.83 ± 0.08, respectively). When the strengths of the R-R interval-systolic pressure and R-R interval-systolic diameter relationships were compared, the former was always closer than the latter. Occasionally, at the peak of the pressor response when systolic diameter did not increase further, the R-R interval kept increasing, causing data points to deviate from linearity, as shown in Fig. 6 (bottom). This additional lengthening of the R-R interval was likely to be the result of concomitant increases in diastolic diameter.

**DISCUSSION**

Using noninvasive methods, we analyzed the pressure-diameter relationships in the human common carotid artery during elevations and reductions in arterial pressure induced by vasoactive drugs. Carotid dimensions increased during the phenylephrine-induced rise and decreased during the nitroglycerin-induced fall in pressure, suggesting that when BRS is determined by pharmacological means, baroreceptor activity is influenced more by pressure-induced passive wall stretch than by drug-induced modulation of local smooth muscle tone. Our data also documented a nonlinear systolic pressure-carotid diameter relationship, with a steeper slope above than below baseline pressure. This nonlinearity appeared to contribute importantly to the difference between the slopes of the R-R interval-systolic pressure relationships for increasing and decreasing pressures.

Increase in carotid diameter during the phenylephrine-induced pressor response. Our finding that in humans carotid dimensions increase during the phenylephrine-induced elevation in arterial blood pressure is at variance with earlier findings (5,31) obtained in experimental animals, where the carotid sinus was reported to constrict in response to catecholamine administration. Our measurements were performed in the common carotid artery 1.5 cm proximal to the bifurcation, whereas in the aforementioned studies in the dog and rat, they were done in the carotid sinus. The different sites of measurement, however, probably do not explain this discrepancy because the wall of the carotid sinus contains less smooth muscle than that of the common carotid artery; consequently, the carotid sinus is not likely to develop more active tension than the common carotid artery in response to a-receptor agonist administration. There are also no data available that would indicate that common carotid artery and carotid sinus diameters could change in opposite directions in response to a-receptor agonist administration. The most reasonable explanation for the discrepancy is the well-documented species differences in carotid wall structure (3). Unlike many other animal species, the carotid wall in humans is elastic, and during the phenylephrine-induced rise in pressure, the passive dilatatory forces are likely to dominate over the active tension developed by smooth muscle contraction within the wall. This means that, in humans during phenylephrine administration, baroreceptor activity is influenced more by passive stretch than by local smooth muscle contraction.

Another difference between this work and the animal studies is that we employed noninvasive methods, whereas the animal studies were invasive. Kober and Arndt (22) emphasized the fact that carotid distensibility is much greater when noninvasive measures are used to gauge distension. Although the study of Peveler et al. (31) was done in conscious dogs, the dogs had prior surgery and placement of ultrasonic crystals on the wall of the carotid artery. The reduction in distensibility caused by surgery may have altered the balance between passive distension and active constriction of the carotid artery during phenylephrine-induced rises in pressure. In humans, exposure of carotid arteries during surgery was also shown to render the vessels more rigid (2).

A related question concerns the role of sympathetic innervation of carotid sinus smooth muscle in baroreceptor activation. In certain species, stimulation of sympathetic efferents to the sinus augments ongoing baroreceptor activity (23). The physiological significance of this observation has never been fully understood. In view of our present finding that a-receptor agonist administration does not constrict the carotid artery, it may be less relevant in humans. It cannot be excluded, however, that catecholamines released from local nerve endings are more effective in producing vascular smooth muscle contraction than when they are administered intravenously. On the other hand, there is no published evidence on sympathetic innervation of the human carotid sinus.

Possible mechanisms for changes in carotid diameter during pressor and depressor responses. The characteristics of changes in carotid diameter during elevated and lowered blood pressure may be partly explained by features of the pressure-diameter relationship. We could not describe the whole pressure-diameter relationship because the Finapres method measures blood pressure at the finger and the contour of the peripheral pressure pulse is likely to be different from that of the
central (carotid) pressure pulse. Therefore, we had to rely on data obtained at end diastole and peak systole. Those blood pressure values can be reliably measured by Finapres (19, 30). Based on the various patterns of diameter changes observed in our subjects, we propose the following: 1) In some individuals the whole amplitude of the distension wave, caused by the arterial pulse, may fall on the middle portion of the linear ascending segment of the pressure-diameter relationship, therefore lowering and elevating blood pressure-induced proportional changes in end-diastolic and peak systolic dimensions. 2) In other individuals, only the end-diastolic value falls on the linear segment; the systolic value is positioned on the curvilinear segment approaching saturation. Thus the rise in pressure produces a less pronounced change in carotid dimensions than the fall in pressure, and in both cases, diastolic diameter changes more than systolic diameter. In a recent study (16) on carotid pressure-diameter relationships, such an asymmetrical arrangement for end-diastolic and peak systolic values was indeed demonstrated. 3) The shift of the whole pressure-diameter relationship during drug-induced changes in pressure, either parallel or nonparallel, may be related to hysteresis of the pressure-diameter relationship. Due to the viscoelastic behavior of the vessel wall, the pressure-diameter relationship forms a loop for each cardiac cycle in such a way that at identical pressures the diameter is greater for falling than for rising pressures (16, 26). We hypothesize that during elevations in pressure the consecutive loops are not only sliding right due to rising pressure but also shifting upward because of the width of the hysteresis loop. The consecutive loops may start from increasingly higher points on the descending limb of the hysteresis loop. In addition, the width of the hysteresis loop may also change during the pressure response if the viscoelastic properties of the wall are altered by the drug. By a similar mechanism, the relationship may shift downward and to the left during depressor responses. Testing this hypothesis would necessitate measurement of pressure and diameter at the same site in the carotid artery during changes in pressure.

The nonlinearity of the systolic pressure-diameter relationship that we observed in this study might be the result of specific drug action, especially that of nitroglycerin administration. When changes in carotid dimensions were produced by changes in pressure in a neck chamber, the pressure-diameter relationship appeared to be linear (22). The carotid artery is an elastic vessel; nonetheless, its wall contains a certain amount of smooth muscle. Vasodilative drugs may influence carotid viscoelastic properties by contracting or relaxing vessel wall smooth muscle. In this way, phenylephrine administration could result in reduced distensibility and nitroglycerin administration could result in increased distensibility. Among the antihypertensive agents, nitrates were shown to be highly effective in increasing large-vessel compliance (21, 36). In comparison, angiotensin-converting enzyme inhibitors improved compliance moderately, whereas hydralazine, β-blockers, and diuretics lowered only blood pressure but did not influence compliance directly (9, 36). Increased compliance is advantageous because it reduces the impedance to ventricular ejection. Our results indicate that administration of nitrates may have another beneficial effect: during nitrate-induced hypertension, systolic carotid dimension and, consequently, baroreceptor discharge are less reduced; therefore, baroreflex-mediated compensatory adjustments will less likely develop to compromise the efficacy of antihypertensive therapy.

R-R interval-systolic pressure vs. R-R interval-systolic carotid diameter relationship. Since the introduction of BRS measurement by pharmacological means, it has been recognized that the slope of the R-R interval-systolic blood pressure relationship was steeper for rising than for falling pressures (11, 32). It has been suggested that this nonlinearity existed because the relationship was sigmoidal and the operational point was close to the threshold level. With the use of the neck chamber technique, however, it was shown that in some subjects the operational point fell on the linear segment (12, 14, 35). Moreover, in athletes, it was found to be positioned close to the saturation level (27). In those subjects with the operational point on the linear segment, the slope of the R-R interval-systolic pressure relationship was not different for falling and rising pressures. Another theory tried to explain the nonlinearity on the basis of hysteresis exhibited by the blood pressure-baroreceptor activity relationship. Baroreceptor firing rates at identical pressures were shown to be higher when pressure was rising than when it was falling (7). The contribution of hysteresis to the nonlinearity, however, is difficult to assess when pressure is elevated and lowered separately from the same blood pressure level (operational point); rather, the pressure should be elevated and lowered in one cycle. When this was done by sequential administration of nitroprusside and phenylephrine, the slope of the R-R interval-systolic pressure relationship appeared to be steeper for falling than for rising pressures, at least in the lower half of the relationship (see Fig. 9.5 in Ref. 13).

The baroreceptor discharge frequency was shown to be influenced by the rate of change in stimulus intensity (1, 4, 10, 33). Differences in the rate of change in carotid sinus wall distension might explain the nonlinearity of the R-R interval-systolic pressure relationship. This assumption, however, seems to be unlikely because the effect of pulse frequency changes on the reflex control of cardiovascular variables over the physiological range of heart rate was found to be small (1, 33). In a study on sinus node responses to neck suction in humans, it was shown that although the rate of pressure change was a determinant of the integrated baroreceptor reflex response, this factor was of negligible importance within the normal range of human arterial rate of pressure change (10).

Our data provide an alternative explanation for the nonlinearity. We found that considerable nonlinearity existed in the systolic pressure-systolic carotid diameter relationship, its slope being steeper for rising than...
for falling pressures. It seems reasonable to conclude that this nonlinearity in the systolic pressure-diameter relationship was expressed in the R-R interval-systolic pressure relationship and contributed significantly to its nonlinearity. When the R-R interval was plotted against systolic diameter, the slopes for increasing and decreasing diameters were almost identical in two subjects and data points could be fitted to a single linear regression line in all subjects.

Modulation of baroreceptor firing during the cardiac cycle may explain some of our findings. Baroreceptors fire during systole and remain silent during diastole at baseline blood pressure levels. However, when the pressure is high (mean aortic pressure of 100–120 mmHg), firing persists throughout the cardiac cycle (4).

Therefore, at and below baseline pressure, only systolic diameter (i.e., wall strain) influences baroreceptor activity, whereas at higher pressures, diastolic wall strain may also contribute. When the R-R interval was re- gressed against systolic diameter, R-R interval values deviated upward from the linear regression line at larger diameter (i.e., higher pressure) values in some of our subjects. It seems likely that this extra lengthening of the R-R interval was due to concommitant increases in diastolic diameter, resulting in baroreceptor firing during diastole, which evoked reflexly more cardiac vagal discharge. On the other hand, when pressure was lowered from baseline, the decrease in baroreceptor activity was determined only by the reduction in systolic diameter because in diastole baroreceptor activity was absent anyway. Therefore, during nitroglycerin administration, the substantial reduction in diastolic diameter was without effect on R-R interval; consequently, data points for the R-R interval-systolic diameter relationship did not deviate much from linearity.

The nonlinear character of the systolic carotid pres- sure-diameter relationship did not fully explain the differences between baroreflex slopes for rising and falling pressures. An additional contributing mecha- nism might be the recruitment of baroreceptor C fibers with increasing pressures. The linear relationship between baroreceptor discharge and cardiac vagal activity was established for baroreceptors with myelinated afferents (20), whereas many of the baroreceptor fibers are unmyelinated. Unmyelinated fibers begin to fire at higher pressures and were shown to provoke powerful arterial pressure reductions and bradycardia (for references, see Ref. 13).

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