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Effect of Age and High Blood Pressure on Baroreflex Sensitivity in Man

By Brian Gribbin, Thomas G. Pickering, Peter Sleight, and Richard Peto

ABSTRACT

The purpose of this study was to relate baroreflex sensitivity to age and arterial pressure in 61 male and 20 female untreated subjects, aged 19–66 years, whose mean arterial pressures ranged from 70 to 150 mm Hg. In this selected group of subjects there was no correlation between age and arterial pressure. The index of sensitivity used was the increase in pulse interval which occurs reflexly in response to a rise in systolic pressure induced by the intravenous injection of phenylephrine and is measured as the increase in pulse interval in milliseconds per mm Hg rise in systolic blood pressure. It ranged from 1.9 to 48.9 msec/mm Hg. Increasing age and arterial pressure act independently to reduce baroreflex sensitivity. Eight subjects who had normal blood pressure at the time of testing but whose pressure had been elevated in the past, had reflex sensitivities significantly less than expected in persons of the same age and mean arterial pressure. The heart rate in these subjects was not significantly different from that in the controls; the heart rate of the 12 hypertensive subjects aged under 40 years was significantly faster than that of age-matched normotensive subjects but not that of older hypertensive subjects.

KEY WORDS baroreceptors baroreflex predictors phenylephrine
autonomic nervous system pulse interval borderline hypertension
essential hypertension

■ A previous paper from this group showed that arterial hypertension is associated with reduced sensitivity of the baroreflex arc controlling pulse interval (1). Early results also indicated an apparent inverse relationship between age and reflex sensitivity, but because the series was weighted with elderly hypertensives, the significance of this was doubtful. The original method can be criticized, however, because angiotensin was used as a pressor agent and the cardiac response to this drug may not be entirely reflex in nature.

The purpose of this study was to investigate in greater depth the effects of aging and high blood pressure on the reflex arc, and the results indicate a significant and independent

effect of aging and high blood pressure on the sensitivity of the baroreflex control of pulse interval.

Methods

We have modified the method of measuring baroreflex sensitivity described by Smyth et al. in 1969 (2). A quantitative analysis of the reflex can be performed by inducing a rise of arterial pressure and measuring the subsequent slowing of the heart. In the original method, angiotensin was used as the pressor agent, but because of the direct cardiac actions of this drug (3) and the late tachycardia, which probably results from central stimulation of sympathetic pathways (4), it was decided to substitute the α -receptor-stimulating drug phenylephrine. The baroreflex sensitivity is calculated by relating the increase in pulse interval in milliseconds to the transient rise in systolic blood pressure in mm Hg induced by the injection of the phenylephrine (50–200 μ g iv). Plotting pulse interval against systolic blood pressure for such a rise results in a linear relationship, the slope of which is a measure of baroreflex sensitivity. The steeper the slope—that is, the greater the increase in pulse interval per mm Hg rise in systolic pressure—the greater the sensitivity of the reflex. In the earlier study, the

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TABLE 1

Values of Reflex Sensitivity on Two Occasions in the Same Subject

Subject	Interval (months)	I ₀	P ₀	Slope	N
1	12	593 ± 11	115 ± 6	10.8 ± 1.8	6
		831 ± 35	114 ± 11	9.9 ± 2.4	8
P		<0.001	NS	NS	
2	1	1220 ± 132	103 ± 6	20.5 ± 2.5	4
		1050 ± 78	130 ± 9	20.0 ± 2.1	4
P		NS	<0.01	NS	
3	6	767 ± 70	130 ± 12	19.2 ± 3.3	8
		856 ± 43	134 ± 7	17.1 ± 3.4	5
P		<0.05	NS	NS	
4	8	695 ± 53	103 ± 8	13.3 ± 4.0	6
		650 ± 30	101 ± 6	16.2 ± 1.7	3
P		NS	NS	NS	
5	15	748 ± 24	132 ± 3	14.6 ± 4.5	5
		660 ± 31	116 ± 1	18.6 ± 2.8	3
		<0.01	<0.001	NS	

Abbreviations: Interval = time between first and second experiment; I₀ = pre-injection pulse interval (msec); P₀ = pre-injection systolic pressure (mm Hg); Slope = baroreflex sensitivity (msec/mm Hg); N = number of injections.

For each variable, results for the two occasions are given as means ± SD and the significance of the difference; comparisons were by *t*-test for unpaired data.

possible influence of sinus arrhythmia on the analysis was minimized by excluding from the calculation the beats occurring during inspiration. Later comparison showed, however, that there was little benefit in so doing and most of the material presented here is based on computer analysis of all beats up to and including the pressure peak. The reproducibility of the method can be judged from the results for the five subjects we have studied in whom a repeat test was done (Table 1). Although there were some differences between pulse interval and pressure on the two occasions, there is no significant difference in the sensitivities, even when the tests are separated by as much as 15 months.

Sixty-one males and 20 females aged 19–66 years were studied. Control blood pressures were recorded 15–30 minutes after all operative procedures had been completed and before evaluation of baroreflex function. Some subjects were normal, others were patients referred because of high blood pressure. Their mean arterial pressures ranged from 70 to 150 mm Hg (see Fig. 3 for scatter). All those in whom investigations revealed a cause for the hyperten-

sion were excluded from the study. The 31 hypertensive subjects (arbitrarily taken as those with a resting mean arterial pressure of 100 mm Hg or more) were either referred from medical outpatient departments or by general practitioners. The normotensives consisted of ourselves, colleagues, volunteers and eight patients referred because of suspected hypertension but who had normal pressure levels when resting in the laboratory. No subject was taking any drug during the week before investigation and none had been on antihypertensive therapy.

All subjects were studied supine and rested after the percutaneous insertion of a catheter into the brachial artery, with its tip in the axillary artery. Pressures were recorded simultaneously on paper (Grass Instruments Inc.) and magnetic tape (Thermionic 3000). The latter procedure allowed analysis of the data by an IBM 1130 computer system programmed to give a printout of systolic pressure, diastolic pressure, mean arterial pressure (MAP), rate of rise of pressure and pulse interval for each beat, and the regression equations of pressure on pulse interval together with correlation coefficients.

The pressor agent was injected through another catheter placed in an antecubital vein and flushed in by 5–10 ml of saline. The subjects were usually unaware of the injection of phenylephrine which produced rises in systolic pressure of 20–25 mm Hg that lasted approximately 30 seconds. Saline injections not containing phenylephrine were without effect on blood pressure or pulse interval. Analysis of the arterial pressure trace showed that phenylephrine never increased pulse interval before it increased arterial blood pressure.

The sensitivity of the reflex reported for each subject is the average of the values obtained from at least five test injections given more than 3 minutes apart, which allowed a return to control values of pressure and pulse interval.

The relative merits of age, pressure, and pulse interval as predictors of baroreflex sensitivity were assessed by multiple regression analysis. At the same time, the significance of the apparent difference in mean baroreflex sensitivity between the eight normal subjects referred with suspected hypertension and the 73 others was assessed after adjustment for age and pressure.

Results

EFFECT OF AGE ON BAROREFLEX SENSITIVITY

The results indicate that a significant and progressive decrease in baroreflex sensitivity occurs with increasing age of the subjects. Figure 1 demonstrates this finding in both normotensives and hypertensives. The logarithm of the sensitivity has been used because

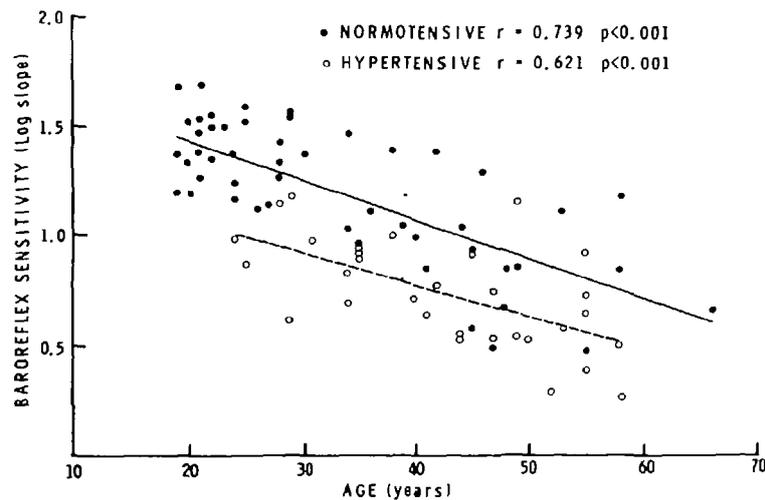


FIGURE 1

Effect of age on baroreflex sensitivity. Each symbol represents one subject's results. The solid and broken lines are regression lines for age on log sensitivity for normotensives and hypertensives respectively.

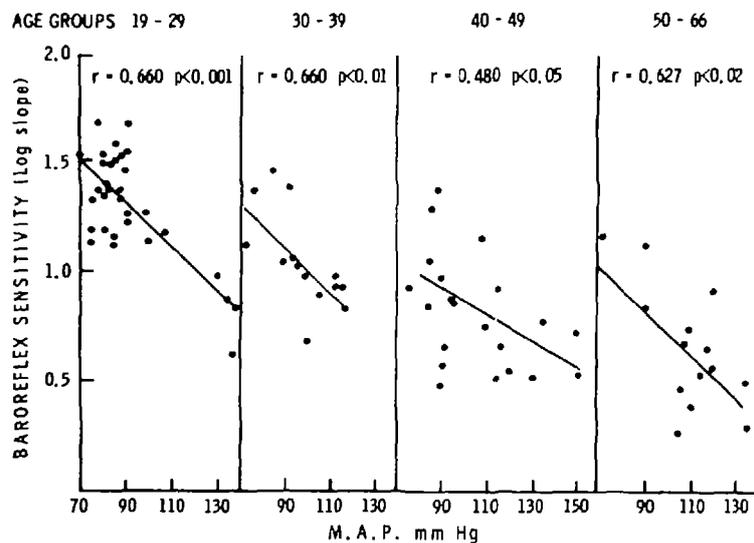


FIGURE 2

Correlation of baroreflex sensitivity and the resting MAP of each subject. The subjects are divided into groups by age and the solid lines are the regression lines of MAP on log sensitivity.

it gives a linear relationship, whereas the plot of slope against age in this study is curvilinear.

EFFECT OF HYPERTENSION ON BAROREFLEX SENSITIVITY

Baroreflex sensitivity is also reduced in subjects with raised blood pressure. The difference in the sensitivity of the reflex

between hypertensives and normotensives of the same age can be observed in Figure 1 but is more clearly displayed in Figure 2, in which the age effect has been minimized by comparing the results from subjects in 10-year age groups. At all ages studied there is a

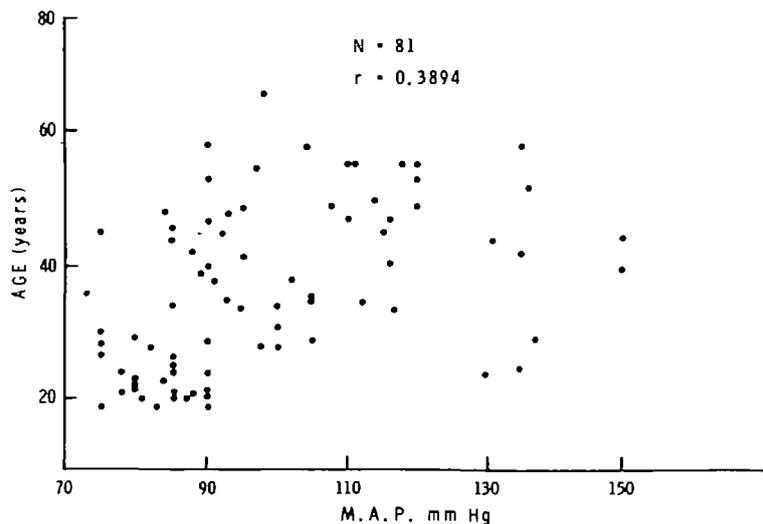


FIGURE 3

Resting MAP of each subject is plotted against age. These two parameters appear unrelated in this study.

progressive decrease in sensitivity with increasing pressure. Although the slope of the regression line in the 40–50 age group is flatter than the others, its correlation coefficient is relatively poor and none of the slopes differ significantly from the overall age-adjusted slope (0.0086). It would therefore appear that even in the sixth and seventh decades, the presence of an elevated arterial pressure is associated with a reduction in the sensitivity of the reflex.

COMBINED EFFECT OF AGE AND PRESSURE ON BAROREFLEX SENSITIVITY

We have shown that increasing age and elevated pressures both influence the sensitivity of the reflex, and we can add that in this study there was no correlation between age and pressure for all our subjects (Fig. 3). The two variables, age and pressure, were therefore considered to act independently, and their effects on the reflex may be expressed by the regression equation: $\text{Log sensitivity} = 2.47 - (0.0164 \times \text{age}) - (0.0086 \times \text{MAP})$ msec mm Hg⁻¹. The standard errors for the partial regression coefficients are ± 0.0019 and ± 0.0012 , respectively.

THE EFFECT OF RESTING HEART RATE ON BAROREFLEX SENSITIVITY

The sensitivity of the blood pressure–heart

rate reflex depends on the interplay of autonomic nervous activity affecting the heart and it falls with a decline in vagal tone (5). In this study comparison of the subjects' resting heart rates was used to detect any gross variation in autonomic tone.

The mean resting heart rate for the 31 subjects with hypertension was 75/min (± 11 sd) and for the 50 normotensives was 68/min (± 9). Corresponding to these figures, the mean pulse intervals were 891 msec for the normals and 820 msec for the hypertensives. The difference is unlikely to be due to chance alone ($P < 0.02$). There is, however, no significant correlation between resting pulse interval and baroreflex sensitivity or age, and the prediction of log sensitivity from a multiple regression using age and MAP is not significantly improved by the additional inclusion of initial pulse interval into the multiple regression.

STUDIES ON YOUNG HYPERTENSIVES AND "BORDERLINE" HYPERTENSIVES

Because of reports of a high output state accompanied by tachycardia in some young patients with hypertension (6, 7), the resting heart rates of the hypertensive subjects aged

TABLE 2

Results on Eight Normals Referred with Suspected Hypertension

Subject	Age	MAP	Observed log sens	Predicted log sens	Difference*
6	35	93	0.954	1.119	+0.165
7	45	92	0.568	0.983	+0.415
8	48	93	0.653	0.930	+0.277
9	24	85	1.155	1.356	+0.201
10	28	82	1.418	1.325	-0.093
11	55	97	0.462	0.790	+0.328
12	49	95	0.845	0.897	+0.052
13	47	90	0.477	0.973	+0.496

The predicted log sensitivity = constant + k_1 age + k_2 pressure was significantly ($P < 0.01$) better if the constant was allowed to have two different values depending on whether the subject was among the eight normotensives or the 73 others than if the constant was constrained to have the same value for all subjects; the difference between the two different values was 0.225.

*Predicted minus observed log sensitivity.

20-39 were compared with those of normotensives of the same age group and with older hypertensives.

The 12 young hypertensives had a mean resting heart rate of 79/min (± 11), and the 34 age-matched normotensives had a mean heart rate of 67/min (± 9). The difference between these is again unlikely to be due to chance alone ($P < 0.01$). There is no significant difference between the young hypertensives and the 19 older hypertensives who had a mean heart rate of 72/min (± 10).

Eight subjects were referred to us because of raised arterial pressure, but when rested in our laboratory under investigative conditions, their MAP's were all less than 100 mm Hg. The eight subjects were otherwise healthy; their ages ranged from 24 to 55 years with a mean of 41, and MAP's from 82 to 97 with a mean of 91. Mean resting heart rate was 69/min, and this did not differ significantly from the mean heart rate of the other normotensives.

However, when the observed log baroreflex sensitivities for these eight subjects were contrasted with the values that would be predicted for them on the basis of the data on the other 73 subjects, the eight with suspected

hypertension had lower values than would be expected for their particular ages and MAP's (Table 2).

COMPARISON OF THE USE OF MAP AND SYSTOLIC PRESSURE AS THE STIMULUS TO BAROREFLEX BRADYCARDIA

The site of blood pressure recording in our subjects was distal to the main baroreceptor region of the ascending aorta and carotid artery. The contour of the pulse wave normally becomes modified as it travels distally, with an increase in pulse pressure (8, 9). Amplification of the transient changes in systolic blood pressure induced by the phenylephrine injections could therefore result in falsely low baroreflex sensitivities, and this would be especially the case in the subjects with the greatest amplification of the pressure pulse.

For 20 subjects we therefore calculated the reflex sensitivity as change in pulse interval for a unit change in MAP, in addition to the usual index employing systolic blood pressure. When the sensitivity calculated by the two

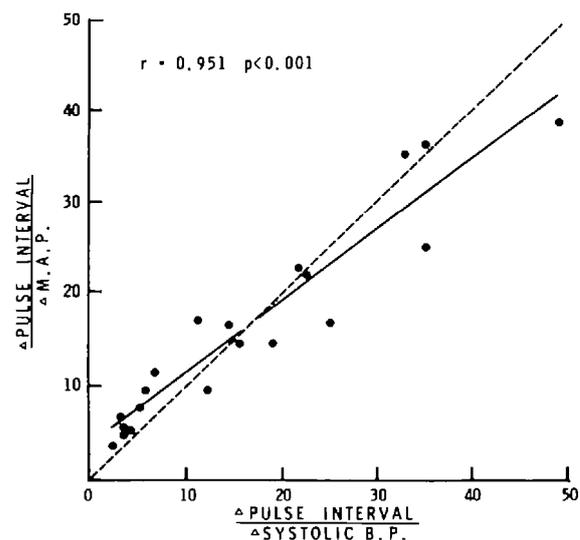


FIGURE 4

Comparison of two ways of expressing baroreflex sensitivity: horizontal axis, as change of pulse interval per change of systolic pressure; vertical axis, as change of pulse interval per change of mean pressure. Each point is the average result for one subject. The solid line is the regression line relating the two methods, and the broken one the line of identity.

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methods is compared (Fig. 4), it can be seen that the agreement is very close, but not identical.

Discussion

The method we have used to demonstrate the changes in baroreflex sensitivity uses systolic arterial pressure as a measure of the stimulus to the baroreceptors and takes no account of changes in the other known influences—pulse pressure, mean pressure, and rate of rise of the arterial pressure pulse (10). However, Figure 4 demonstrates the good correlation between changes in MAP and systolic blood pressure when used as a gauge of baroreflex stimulation. We have also examined the change in pulse pressure and rate of rise of pressure with phenylephrine injection and found that these change very little.

Because we have adopted phenylephrine to raise arterial pressure and stimulate the baroreflex, it is important to establish that the bradycardia produced is reflex in nature and to exclude direct effects of the drug on the heart. Varma et al. (11) showed in dogs given the drug that if the pressure rise was prevented, bradycardia did not occur, and human studies show that the bradycardia can be blocked by atropine (12). However, its action in a patient with a cardiac transplant is to cause a very small increase in heart rate, which should be insufficient to substantially affect our results (13).

Our group has previously described the decrease in baroreflex control of pulse interval which occurs with increasing hypertension (1). This study now demonstrates that aging is also associated with a decrease in reflex sensitivity and provides an equation relating age and MAP to log baroreflex sensitivity. Both partial regression coefficients are known to within about $\pm 10\%$. They are therefore known with sufficient accuracy for it to be unnecessary to allow for their standard errors when using them for purposes of individual predictions, since the variance of an observed log value about its prediction is 0.038, which is one or two powers of ten greater than the variance of the prediction attributable to

inaccuracies in the partial regression coefficient estimates.

It is not possible at this stage to determine the underlying mechanism of the reduction in reflex sensitivity. That the baroreflex is altered in chronic hypertension has been known for many years, but most information has concerned the resetting of the reflex to the raised arterial pressure level (14, 15). However, Alexander and DeCuir reported on a decreased slowing of the heart in hypertensive rabbits after a pressure rise (16), and Aars showed, in hypertensive rabbits, both a resetting and a reduced sensitivity of baroreceptor afferent nerve traffic over a range of aortic pressures (17). Because the aortic wall was less distensible in the hypertensive animals than in the controls, he postulated, and later attempted to show, that the changes which he observed in baroreflex function were a consequence of the stiffer arterial walls (18). The baroreceptors lie within the arterial wall and they respond to deformation brought about by a change in transmural pressure. If the arterial wall is stiffer than normal, it can then be expected that the receptors will be splinted and protected to some extent from the arterial pressure and will respond to a given pressure rise with a reduced afferent nerve activity. Experiments designed to test the functional ability of the receptors themselves in chronic hypertensive animals show no evidence of impairment (19) and there is no evidence in animals or man of selective baroreceptor degeneration as opposed to degeneration of all arterial wall elements (20, 21). Thus our findings could be explained by the loss of arterial distensibility which occurs both in aging (22-24) and in hypertensive man (25).

Other possibilities should also be considered. Experimental work on animals has shown that central nervous system mechanisms may play a part in altering the heart rate response to elevations in blood pressure. Hypothalamic or rage center stimulation in animals produces elevation in blood pressure and tachycardia and can inhibit the baroreflex (26, 27), and Brod showed similar changes in

blood pressure and heart rate in man during acute emotional stress (28). Although the low resting heart rates of our subjects throughout the investigative period makes it unlikely that alteration in baroreflex function due to emotion was of importance in this study, the hypertensive subjects did have significantly higher heart rates than the normotensives. Despite the direct relationship between preinjection pulse interval and baroreflex sensitivity (5), the introduction of pulse interval into the multiple regression equation along with age and MAP did not improve the prediction of log sensitivity. It is therefore unlikely that this finding can explain the decrease in reflex sensitivity in the hypertensive patients. There is some evidence that vagal tone falls with age (29), but there was no correlation between heart rate and age in our subjects. There have been reports of a changing hemodynamic pattern in the evolution of essential hypertension (6, 7). In young subjects a state of high flow and tachycardia with normal resting peripheral resistance is postulated to evolve into high resistance and low flow in the middle-aged and elderly. Although cardiac outputs were not measured, hypertensives in their 20's and 30's had a mean resting heart rate significantly greater than normotensives in the same age groups.

When considering the relevance of these findings to essential hypertension it is of interest to observe what happens to transient elevations of arterial pressure when the heart rate response is blocked by atropinization. In such a case the blood pressure remains elevated for several minutes until withdrawal of sympathetic tone allows a return to control levels (30). Bevan et al. (31) showed large swings in arterial pressure occurring in normal and hypertensive individuals during their daily activities, and an inadequate buffering of these blood pressure changes could be revealed clinically by both a lability of blood pressure and a state of transient or borderline hypertension. When the eight normotensives who had hypertensive levels over the previous weeks were considered as a group, they showed baroreflex sensitivities significantly

less than would be expected in individuals of the same age and MAP. This suggests that poor baroreflex control could play a part in allowing the elevated pressures which precipitated their referral. We have demonstrated a decrease in baroreflex sensitivity with increasing age and MAP. It is hoped that the formula relating age and MAP to baroreflex sensitivity will aid the discovery of other factors affecting the sensitivity of the reflex.

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