

# Baroreflex Function in Elderly Hypertensives

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**SUMMARY** Baroreflex function was assessed in elderly hypertensive patients and compared with that observed in young hypertensives and young normotensives. Mean arterial pressure was reduced by 20% using intravenous nitroprusside infusion in 10 elderly hypertensive patients (older than 65 years and diastolic pressures over 95 mm Hg), in 10 young hypertensives (under 60 years and diastolic pressures over 95 mm Hg), and in seven young normotensive subjects (under 60 years and diastolic pressures under 95 mm Hg). Elderly subjects demonstrated greater sensitivity ( $p < 0.005$ ) and greater variability of response ( $p < 0.025$ ) to nitroprusside than either young group. There was no significant difference between the slight heart rate increases observed in the supine position in the three groups. However, in the erect position, heart rate increases were significantly less in the elderly hypertensive group than in the young hypertensive group ( $p < 0.01$ ) or the young normotensive group ( $p < 0.005$ ). Furthermore, the slope of the regression line relating change in blood pressure with change in R-R interval was less for the elderly patients than for the young hypertensives ( $p < 0.05$ ) or the young normotensives ( $p < 0.025$ ). We conclude that the heart rate component of the baroreflex is impaired in elderly hypertensives, and anticipate that the clinical response to antihypertensive drugs will be altered. (*Hypertension* 5: 763-766, 1983)

**KEY WORDS** • nitroprusside • heart rate • aging

**A**GING is associated with alteration in many physiological systems that can respond to drugs.<sup>1</sup> Previous workers have shown altered response in the cardiovascular system to various pharmacological agents.<sup>2-5</sup> Baroreflex activity, which is important in cardiovascular homeostasis, has been shown to decline with increasing arterial pressure<sup>6,7</sup> and with increasing age up to 66 years.<sup>8</sup> However, no information is available in older hypertensive patients. Since impaired baroreflex function in such patients would have important therapeutic implications, we assessed some aspects of the baroreflex by studying blood pressure and heart rate response to nitroprusside in a group of such patients, and comparing the results with those observed in young hypertensives and young normotensives.

## Methods and Materials

Three groups of patients were studied — elderly hypertensives, young hypertensives, and young normotensives. The elderly hypertensives were all older than 65 years, with ages ranging from 66 to 80 years.

Diastolic pressures were greater than 95 mm Hg in each case. The supine mean arterial pressure (diastolic pressure +  $\frac{1}{3}$  pulse pressure) ranged from 115 to 154 mm Hg, and the erect mean arterial pressure ranged from 113 to 160 mm Hg. The mean baseline supine heart rate was  $74.9 \pm 2.9$  beats  $\text{min}^{-1}$  and the mean erect heart rate was  $77.3 \pm 2.9$  beats  $\text{min}^{-1}$ .

The young hypertensives were under 60 years of age — ranging from 32 to 56 years. Their diastolic pressures were greater than 95 mm Hg, with supine mean arterial pressures ranging from 114 to 135 mm Hg and erect mean arterial pressure ranging from 117 to 133 mm Hg. The supine mean heart rate was  $78.9 \pm 1.9$  beats  $\text{min}^{-1}$ , and the erect mean heart rate was  $85.8 \pm 1.7$  beats  $\text{min}^{-1}$ .

The young normotensive subjects were under 60 years of age, ranging from 21 to 55 years. Their diastolic blood pressures were less than 95 mm Hg, with supine mean arterial pressure ranging from 89 to 105 mm Hg and erect mean arterial pressures ranging from 87 to 105 mm Hg. The baseline supine heart rate was  $75.6 \pm 2.4$  beats  $\text{min}^{-1}$ , and the erect heart rate was  $81.4 \pm 2.5$  beats  $\text{min}^{-1}$ .

Subjects were free of drugs for at least 4 weeks before the study. They were excluded from the study if the baseline systolic or diastolic pressure fell by more than 10 mm Hg on standing, or if there was any evidence of sinus node or conduction system disease on the electrocardiogram, or if they had a history of angina pectoris, myocardial infarction, or cerebral ischemic episodes. Permission for the study was obtained

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from the Hospital Ethics Committee, and informed consent from the subjects.

On the morning of the study, subjects were fasting and rested in a quiet room for 30 minutes where baseline blood pressure and heart rate, erect and supine, were measured by conventional sphygmomanometer and ECG techniques. Then intravenous nitroprusside was administered into an antecubital vein using a constant infusion pump, commencing with  $0.05 \mu\text{g kg}^{-1} \text{min}^{-1}$ . The dose was doubled at 10-minute intervals until a 20% reduction in supine mean arterial pressure was achieved. Supine and erect blood pressure and heart rate were measured at the end of each dose interval, the erect values being measured after the supine and within 30 seconds of standing. Dose response curves for blood pressure were constructed for each patient. One normotensive patient was markedly sensitive to the drug, and smaller doses were given in order to achieve a dose response curve (fig. 1 A).

Results were compared using Student's *t* test for paired and unpaired data, where appropriate. A mean log dose-response curve for blood pressure was determined by linear regression in each group using the data points from each patient. Comparisons between groups of the mean dose response curves were made using covariance analysis.

### Results

The log dose-blood pressure response curves for individuals in each group are shown in figure 1. Increasing doses of nitroprusside resulted in sequential decrements in mean arterial pressure in each group. The slopes of the lines representing the mean dose response curves (% change in mean arterial pressure per unit log change in nitroprusside infusion rate) were similar for the three groups, 14.8 for the young hypertensives, 13.6 for the young normotensives, and 11.6 for the elderly hypertensives. Elderly patients had a more variable response to nitroprusside, however; the degree of scatter about the mean of the dose response curves, estimated by covariance analysis, was greater

than in the young hypertensives ( $F = 2.253, p < 0.05$ ) or the young normotensives ( $F = 2.163, p < 0.025$ ). In addition, the elevation of the line representing the mean dose response of the elderly group was greater than in either young group ( $p < 0.005$ ) indicating greater sensitivity to nitroprusside at all dose levels in the elderly group.

Heart rate responses to nitroprusside are shown in table 1. Despite a 20% reduction in supine mean arterial pressure, the maximum mean ( $\pm$  SEM) increase observed in the supine position was only  $2.6 \pm 1.1$  beats  $\text{min}^{-1}$  in the elderly hypertensives ( $p < 0.025$ ),  $2.9 \pm 1.1$  beats  $\text{min}^{-1}$  in the young hypertensives ( $p < 0.025$ ) and  $5.3 \pm 1.7$  beats  $\text{min}^{-1}$  in the young normotensives ( $p < 0.025$ ).

On standing, there was an increase of  $14.7 \pm 1.7$  beats  $\text{min}^{-1}$  in the young normotensives ( $p < 0.001$ ) and  $12.9 \pm 1.8$  beats  $\text{min}^{-1}$  in the young hypertensives ( $p < 0.001$ ), but in the elderly hypertensives the increase was only  $7.0 \pm 1.6$  beats  $\text{min}^{-1}$  ( $p < 0.005$ ), which was significantly less ( $p < 0.01$ ) than that observed in either young group. In addition, the slopes of the regression lines relating fall in blood pressure to R-R interval change varied in the three groups. This is illustrated in figure 2. When compared by covariance analysis, the slope (2.0) of the line representing the mean value for the elderly hypertensives was significantly less than that for the young hypertensives (slope = 3.9;  $F = 4.6; p < 0.05$ ) or for the young normotensives (slope = 5.3;  $F = 6.2; p < 0.025$ ). The difference between the slopes for the two young groups was not significant. There was no overall relationship between threshold doses of nitroprusside and slopes of the log dose blood pressure curves.

### Discussion

Baroreflex function can be studied by examining heart rate responses either to raising<sup>9</sup> or lowering<sup>10</sup> blood pressure. Smyth et al.<sup>9</sup> have related baroreceptor sensitivity to the slope of a line relating elevation of blood pressure, induced by phenylephrine, to the cor-

TABLE 1. Mean Arterial Pressure (MAP) and Heart Rate (HR) Supine and Standing Before and After Nitroprusside Infusion

	Young normotensives	Young hypertensives	Old hypertensives
No.	7	10	10
Age (yrs)	$35 \pm 4.6$	$45.5 \pm 2.9$	$71.2 \pm 1.8$
Supine			
Baseline MAP (mm Hg)	$98.1 \pm 1.9$	$125.8 \pm 3.3$	$132 \pm 6.4$
Baseline HR (bpm)	$75.6 \pm 2.4$	$78.9 \pm 1.9$	$74.9 \pm 2.9$
Nitroprusside MAP (mm Hg)	$76.1 \pm 1.4$	$98.6 \pm 1.9$	$99.9 \pm 5.0$
Nitroprusside HR (bpm)	$80.9 \pm 2.6$	$81.8 \pm 3.4$	$77.5 \pm 3.2$
Standing			
Baseline MAP (mm Hg)	$98.7 \pm 2.4$	$127.5 \pm 2.8$	$130.5 \pm 5.4$
Baseline HR (bpm)	$81.4 \pm 2.5$	$85.8 \pm 1.7$	$77.3 \pm 2.9$
Nitroprusside MAP (mm Hg)	$77.5 \pm 2.1$	$100.5 \pm 2.4$	$99.6 \pm 3.9$
Nitroprusside HR (bpm)	$96.1 \pm 3.3$	$98.7 \pm 3.0$	$84.3 \pm 3.6$

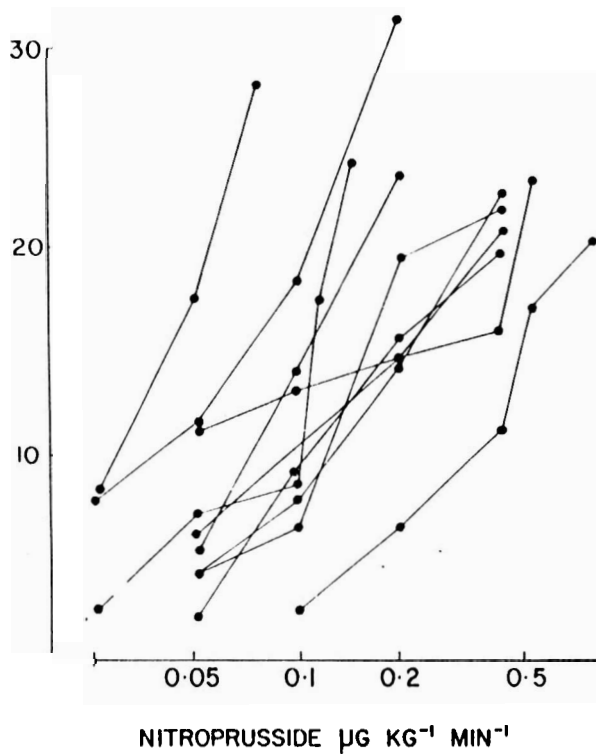
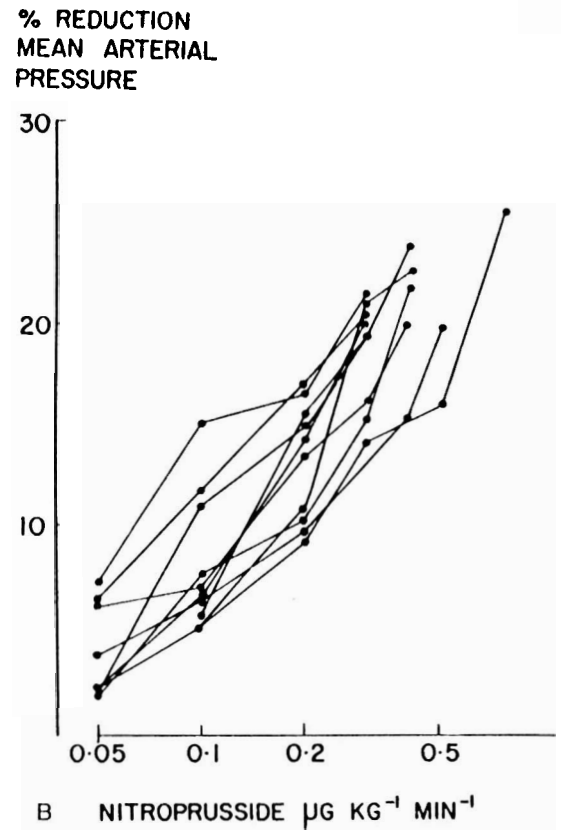
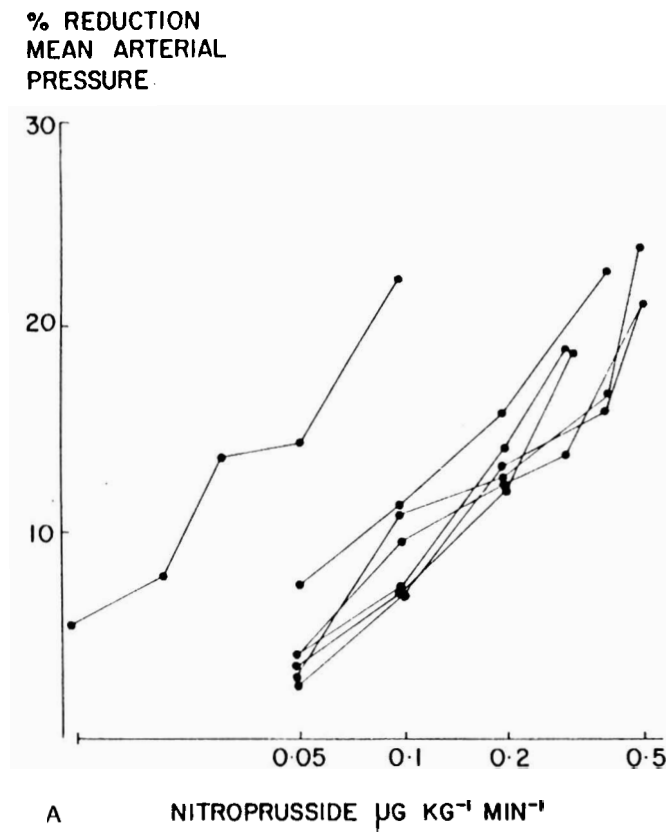


FIGURE 1. Log dose blood pressure response curves to nitroprusside in the erect position. A. Seven young normotensive subjects. B. Ten young hypertensive subjects. C. Ten elderly hypertensive subjects.

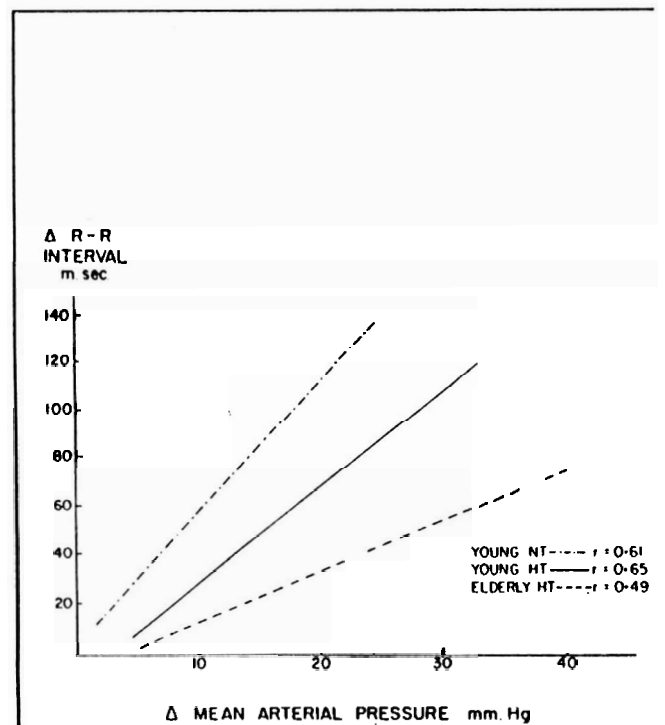


FIGURE 2. Baroreflex sensitivity in young hypertensives and elderly hypertensives.

responding fall in heart rate. Pickering et al.<sup>10</sup> compared the sensitivity of this method to that using hypotension induced by amyl nitrite as a stimulus to the baroreflex and showed that the amyl nitrite method was 40% less sensitive than that using phenylephrine-induced blood pressure elevation. Despite this, we chose to use the response to blood pressure lowering because this seems more relevant in the clinical setting where hypertensives may receive blood pressure lowering drugs.

The dose response curves to nitroprusside obtained in our two young groups were similar, with the exception of one normotensive subject. In contrast, elderly patients exhibited more variability of blood pressure response to nitroprusside, with more scattered dose response curves. In addition, the elderly were more sensitive to nitroprusside at all dose levels. Thus, the threshold dose calculated by extrapolation of the mean dose response curve was less in the elderly ( $0.009 \mu\text{g kg}^{-1} \text{min}^{-1}$ ) than in young normotensives ( $0.017 \mu\text{g kg}^{-1} \text{min}^{-1}$ ) or young hypertensives ( $0.026 \mu\text{g kg}^{-1} \text{min}^{-1}$ ). Thus, on the average an effect on blood pressure is seen in the elderly at a lower dose, but there is, in addition, greater variability in response to any given dose.

Previous reports of the effects of nitroprusside on heart rate indicate a variable response.<sup>11-13</sup> Schlant et al. (1962)<sup>14</sup> examined the hemodynamic effects of the drug in a group of patients with systolic hypertension and in a group of normotensive patients. In the supine position, they reported an average increase in heart rate of 5.5% following an average decrease in mean arterial pressure of 37.2% in the normotensive group, and an average increase of 25.3% in heart rate following a similar reduction in mean arterial pressure (39.4%) in the hypertensive group. None of these patients was older than 66 years. In no patient, despite a 20% reduction in mean arterial pressure, did we produce this degree of tachycardia.

Elderly patients exhibited diminished heart rate response to hypotension induced by nitroprusside, compared to the young hypertensives and young normotensives in the erect position. In addition, the slope of the line relating R-R interval to fall in arterial pressure was less in elderly hypertensives. We interpreted this as being due to diminished baroreceptor function. Based on the response to phenylephrine-induced hypertension, baroreceptor function has been shown to decline with increasing age up to 66 years<sup>8</sup> and with increasing arterial pressure.<sup>6-8</sup> In the present study, the difference in response between the normotensive and hypertensive young subjects was not statistically significant, but the data differed in the expected direction, i.e., heart rate response in the hypertensives appeared to be less than in the normotensives. The cause of this diminished sensitivity remains unproven. Angell-James<sup>15</sup> has shown that less distensible aortas of atherosclerotic rabbits are associated with less sensitive baroreceptors. It is possible, therefore, that this decrease in baroreceptor sensitivity is due to the increased stiffness in blood vessels, which serves to

splint the baroreceptors and reduce their afferent nerve activity. However, the findings of diminished baroreceptor sensitivity in patients with borderline hypertension<sup>7</sup> who are unlikely to have stiff vessels, and in states of sympathetic overactivity such as exercise, raises the possibility of an alternative cause. Responsiveness of the beta receptors has been shown to be diminished in elderly people,<sup>16</sup> and it is possible that the diminution in heart rate response may represent decreased beta adrenoceptor activity in the elderly. Further study, however, is required to establish the importance of these factors.

Irrespective of the cause, impairment of baroreflex function in hypertensive patients older than 65 years may have important therapeutic implications. Use of vasodilators in the management of hypertension is complicated by the accompanying tachycardia and necessitates the use of concomitant beta-adrenoceptor blocking drugs. However, diminished baroreflex response in elderly hypertensive patients may attenuate this effect and result in greater efficacy of vasodilators with fewer side effects. This raises the possibility of using vasodilator therapy alone in the management of hypertension in the elderly.

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