

Clonidine and Carotid Baroreflex in Essential Hypertension

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SUMMARY Clonidine is believed to reduce blood pressure by a neural action and animal experiments suggest that this consists in potentiation of baroreflexes. In 16 patients with essential hypertension we studied the effects of alterations in carotid sinus baroreceptor activity (neck chamber technique) on arterial blood pressure (catheter measurements) and heart rate, before and after intravenous administration of 150 μ g and 300 μ g of clonidine. The magnitude of the reflex responses was assessed by the slope of the linear regressions relating applied increase and decrease in tissue pressure at the carotid sinus (and therefore applied decrease and increase in carotid sinus transmural pressure) and resulting changes in mean arterial pressure and R-R interval. Clonidine caused a marked reduction in mean arterial pressure (-26 ± 3 mm Hg) and a slight but significant reduction in heart rate (-5 ± 1 b/min). There was no evidence for a potentiation of the baroreceptor influence on blood pressure, although a slight potentiation of the baroreceptor influence on heart rate was observed in few instances. We conclude that in man clonidine can exert a pronounced hypotensive effect without potentiating baroreceptor influence on blood pressure. Therefore this mechanism does not play a prominent role in the clinical antihypertensive action of the drug. (Hypertension 1: 362-370, 1979)

KEY WORDS • essential hypertension • antihypertensive drug • blood pressure • arterial baroreflexes • clonidine • isometric exercise • cold pressure test • sympathetic activity • carotid baroreceptors

C LONIDINE is believed to induce depression of sympathetic activity and enhancement of vagal influences on the circulation¹ and evidence in animals suggests that this may occur via a potentiation of the arterial baroreflexes. Kobinger et al.²⁻⁴ and Haeusler⁵ have observed that the bradycardia, the hypotension and the reduction in sympathetic nerve traffic that follow electrical stimulation of the carotid sinus nerves become greater after administration of clonidine. Aars⁶ and others⁷ have found that clonidine reduces the threshold of activation of the aortic baroreceptors and increases their firing rate at any given level of arterial blood pressure. Korner and his group^{8, 9} have suggested that the potentiation of the baroreceptor-heart rate reflex induced by clonidine may not only be due to peripheral sensitization of the receptors, but also to an action at a central level.

It has to be emphasized, however, that there is evidence also against a potentiation of the baroreflexes by clonidine. Korner et al.⁹ have reported that, in contrast to heart rate, reflex changes in peripheral

resistance induced by Valsalva maneuver are reduced rather than enhanced after administration of this drug. Hepburn et al.¹⁰ have observed reduction in the reflex renal vasodilatation to stimulation of the arterial baroreceptors after administration of clonidine. Finally the pressure response to carotid occlusion has been found to be depressed by clonidine¹¹⁻¹³ an observation which is not easily reconcilable with the hypothesis of a potentiation of the baroreceptor reflex.

More importantly, all the available evidence regarding the action of clonidine on the baroreflexes derives from animal experiments in which doses of the drug were frequently used that were greater than those employed in clinical practice. There is, therefore, no proof that the hypotension induced by clonidine in man involves a baroreflex mechanism.

The present investigation was performed in human subjects to examine this point. The circulatory responses to an increase and a decrease in the carotid sinus baroreceptor activity were studied in a population of patients with essential hypertension, both before and after administration of therapeutic doses of clonidine. We also investigated the responses of subjects administered clonidine to exercise and cold in order to determine if the excitatory influences on circulation are affected by clonidine.

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Methods

Our study was performed in 16 hospitalized patients with essential hypertension, whose ages ranged from 26 to 64 years (mean 44.6 ± 2.5 years). The patients (nine males, seven females), had diastolic blood pressure values between 100 and 130 mm Hg, and were included in the study if: 1) no cardiac or renal failure was present; 2) no signs or symptoms of coronary or cerebral vascular insufficiency had ever occurred; 3) no major diseases other than the hypertension had been diagnosed; and 4) there had been no treatment with antihypertensive drugs in the 3 weeks preceding the study. All subjects gave free consent to the procedure after having had the nature and the purpose of the investigation explained.

Measurements

In each patient pulsatile arterial blood pressure was measured by a catheter introduced percutaneously into a femoral artery and connected to a strain-gauge transducer (Statham P23DC). Mean arterial pressure was obtained from the pulsatile signal both by electronic damping and by continuous integration of the blood pressure tracing over consecutive 10-second periods. A cardiometer was triggered by the R wave of an electrocardiographic lead and from this record heart rate was calculated in beats/min and heart intervals (R-R interval) in msec.

Hemodynamic Tests

In each patient we studied the circulatory responses to changes in the activity of the carotid sinus baroreceptors, isometric exercise and cold.

Alterations in the activity of the carotid sinus baroreceptors were obtained by means of a variable pressure neck chamber, which has been described previously.¹⁴ In brief, the neck was enclosed in a plastic box extending from the shoulders to a plane just above the chin, the ear lobes and the occiput. The box had double rubber seals at both its inferior and its superior openings, which allowed a vacuum cleaner to induce positive and negative pressure changes in its interior over a range of ± 60 mm Hg. Within this range, changes in pneumatic pressure around the neck are linearly transmitted to the tissues surrounding the carotid sinuses, although only 86% of the positive pressure, and 64% of the negative pressure are normally transmitted.¹⁴ Therefore, positive and negative pressure changes obtained with the neck chamber are accompanied by decrease and increase in carotid sinus transmural pressure, which results in decrease and increase in the activity of the carotid sinus baroreceptors with respect to the level set by the existing arterial blood pressure. In each subject several different changes in negative and positive pressure were applied to the neck, the maximal stimuli being adjusted so that, once correcting for the imperfect pressure transmission through the neck tissues, pressure changes in the tissues outside the carotid sinuses never exceeded ± 40 mm Hg. As in previous studies^{12, 13}

pressure changes were induced very rapidly (90% of the change completed in less than 1 second) and were maintained for 120 seconds.

Isometric exercise consisted in steadily gripping a spring with one hand for 90 seconds. The spring was connected to a dynamometer which allowed the strength of gripping to be measured. This exercise was performed in each subject at 40% of his maximal strength, which was established (by a short-living gripping) at the beginning of the study, and confirmed at the end of it.

Exposure to cold was obtained by the traditional method of immersing one hand of the subject in water at 0°C. This test was maintained for 60 seconds.

Protocol and Data Analysis

Each study was performed with the patient supine and began at least 20 minutes after the positioning of the intra-arterial catheter to allow the patient to recover from whatever stress was involved in the invasive procedure. Initially, a series of four different positive and four different negative changes in neck pressure, one isometric exercise and one immersion of a hand in cold water were performed in a random order, with the stimuli spaced at least 120 seconds from each other. Then, clonidine hydrochloride (Catapres) was administered by rapid intravenous injection. Eight subjects (mean age 46 ± 4 years) received a dose of 150 μg and the remaining eight (mean age 43 ± 3 years) received a dose of 300 μg (these doses corresponded to 2.2 ± 0.1 and 4.3 ± 0.1 $\mu\text{g}/\text{kg}$ of body weight, respectively). Finally, the various hemodynamic tests were performed again, beginning 5 minutes after the injection of clonidine and following the sequence and the intervals described above. The entire study usually lasted about 100 minutes and was always terminated no more than 45 minutes after the administration of clonidine.

The circulatory effects of hand-grip and cold were evaluated by averaging mean arterial pressure and heart rate values measured in the 10 seconds preceding and in the last 10 seconds of the stimulus application. The carotid baroreceptor reflex was evaluated by the method described in previous studies.^{15, 16} Stimuli applied to the carotid sinus baroreceptors were expressed as changes in tissue pressure outside the carotid sinuses, which were in turn derived from changes in box pressure corrected for the imperfect pressure transmission through the neck tissues (see above).¹⁴ For statistical comparison the following arterial blood pressure and heart rate or interval values were considered: 1) control value (the average value during the 30 seconds before the change in neck-tissue pressure); 2) early response (the average value in the 10-second period from 5 to 15 seconds after the change in neck-tissue pressure); and 3) late or steady-state response (the average value occurred in the last 30 seconds of the neck-tissue pressure changes). These values were studied in order to take into account both the initial rapidly-developing and partly-transient response that follows alterations in carotid barorecep-

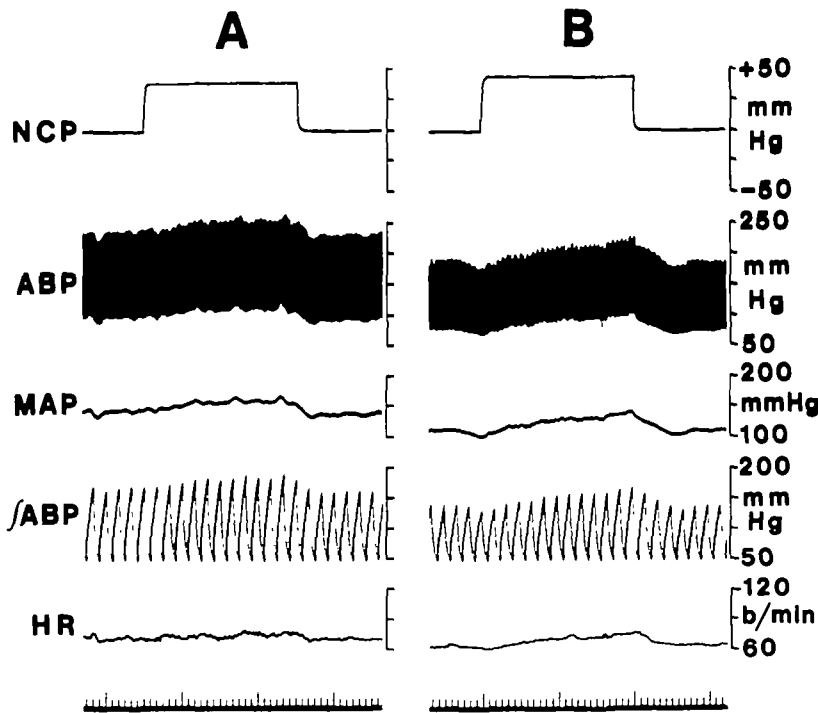


FIGURE 1. Original tracings showing the hemodynamic responses to increase in neck-chamber pressure before (A) and after (B) administration of clonidine at the intravenous dose of 300 μ g. NCP = neck-chamber pressure; HR = heart rate; ABP = pulsatile arterial blood pressure; MAP = mean arterial blood pressure; \int ABP = arterial blood pressure integrated over consecutive 2-second periods. Time is at the bottom in 1 and 5 seconds.

tor activity, and its late stabilized component.^{15, 16}

Data on isometric exercise and cold were calculated as means \pm standard errors for the various groups of subjects. The hemodynamic effects of both maneuvers as well as the effect of clonidine administration were estimated by the *t* test for paired observations. Data on the carotid baroreceptor reflex were calculated in two ways. One, the hemodynamic responses to the greatest increase and decrease in neck-tissue pressure obtained in each subject were considered, with means \pm standard errors and paired *t* test again being used to provide group data and statistical comparisons. Two, linear regressions relating different changes in neck-tissue pressure with different hemodynamic responses were separately calculated for the groups of subjects receiving the lower and the higher dose of clonidine. The statistical comparisons before and after administration of clonidine were obtained by application of covariant analysis to the regressions. Throughout the study a *p* value of at least 0.05 was taken as the level of statistical significance.

Results

Carotid Baroreceptor Reflex

Mean Arterial Pressure

As shown in figures 1 and 2, the greatest increase and decrease in tissue pressure outside the carotid sinuses that we applied in this study caused clear-cut changes in arterial blood pressure, both before and after administration of clonidine. These changes are

shown in figure 3 (left) for all 16 subjects. It is clear that before clonidine, an increase in tissue pressure outside the carotid sinus (pericarotid-tissue pressure) of 34.5 ± 0.7 mm Hg was accompanied by a small but significant early rise in mean arterial pressure and by a more marked rise during the steady-state period. On the other hand, a decrease in pericarotid-tissue pressure of -32.8 ± 0.7 mm Hg was accompanied by a decrease in mean arterial pressure that was already marked in the early phase and was slightly smaller but still highly significant in the later steady-state period of the stimulation. Clonidine caused a significant ($p < 0.001$) and pronounced reduction in basal mean arterial pressure. Under these new circumstances, however, changes in pericarotid-tissue pressure similar to those applied before the drug administration (35.8 ± 0.8 mm Hg and -33.4 ± 0.7 mm Hg, respectively) were accompanied by changes in mean arterial pressure that were not significantly different from those observed before clonidine administration.

The similarity of the responses to the carotid baroreceptor manipulation before and after clonidine was substantially confirmed by taking into account the individual responses to changes of different magnitudes in pericarotid-tissue pressure, and by dividing the subjects into the group receiving 150 μ g and the group receiving 300 μ g of the drug (table 1). Confirming our previous observations,¹⁶ both the pressor and the depressor responses were in a significant linear relationship to the respective stimuli, with the exception of the small early response that followed the increase in neck-tissue pressure. Comparison between

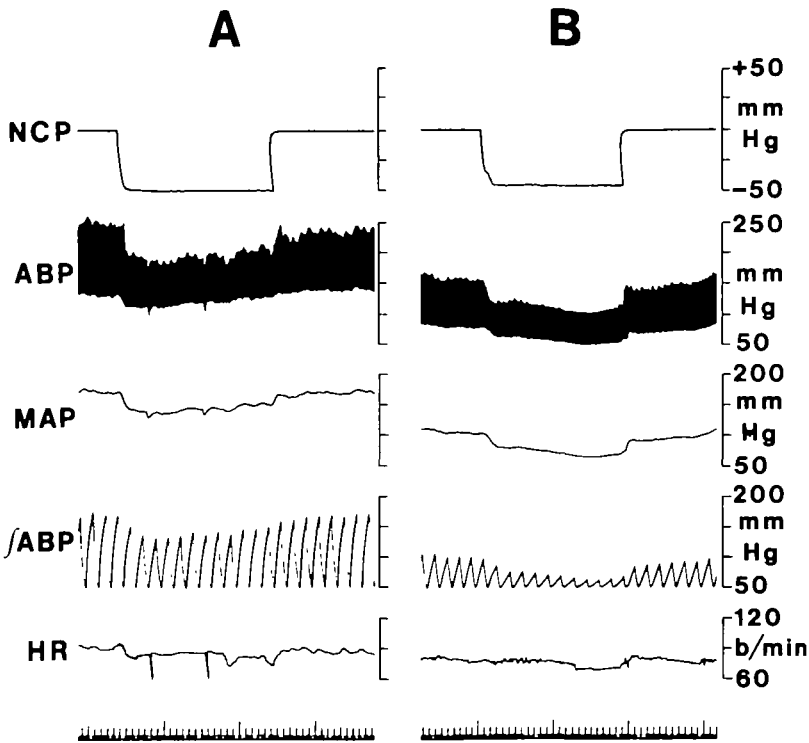


FIGURE 2. Original tracings showing the hemodynamic responses to decrease in neck-chamber pressure before (A) and after (B) administration of clonidine at the intravenous dose of 150 µg. Symbols as in figure 1.

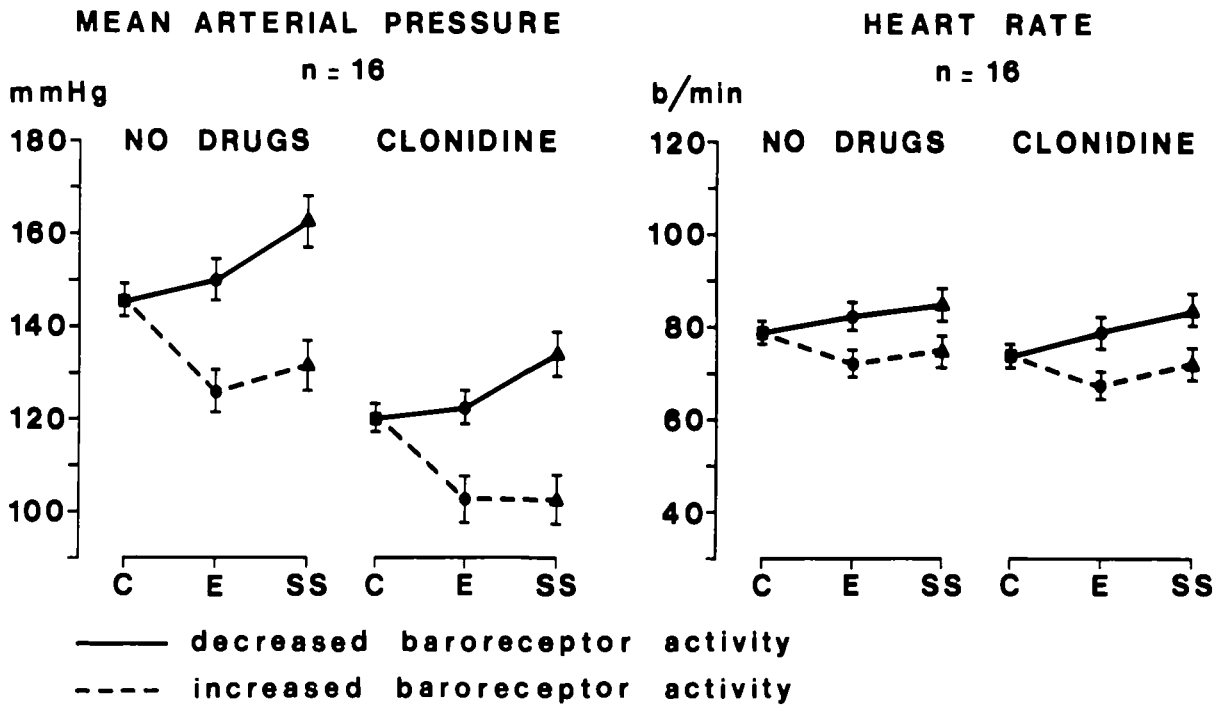


FIGURE 3. Effects of clonidine on the hemodynamic responses to an increase (dashed lines) and a decrease (continuous line) in carotid baroreceptor activity. Data are shown as means \pm SE of the 16 hypertensive subjects in whom clonidine was administered I.V. at a dose of 150 µg (eight subjects) and 300 µg (eight subjects). C = control; E = early responses; SS = steady-state responses. Decrease in carotid baroreceptor activity was obtained by elevating pericarotid-tissue pressure (34.5 ± 0.7 mm Hg before, and 35.8 ± 0.8 mm Hg after clonidine), and increase in carotid baroreceptor activity by reducing pericarotid-tissue pressure (-32.8 ± 0.7 mm Hg before, and -33 ± 0.7 mm Hg after clonidine).

TABLE 1. Changes in Mean Arterial Pressure Compared with Changes in Carotid Baroreceptor Activity Before and After Administration of Clonidine*

	Early			Steady-state		
	B	A	<i>p</i>	B	A	<i>p</i>
Decreased pericarotid-tissue pressure						
clonidine, 150 μ g						
<i>r</i>	0.876	0.906		0.757	0.772	
<i>b</i>	0.576	0.574	NS	0.464	0.466	NS
<i>a</i>	-0.595	-0.526		-0.440	-0.627	
clonidine, 300 μ g						
<i>r</i>	0.853	0.818		0.809	0.775	
<i>b</i>	0.652	0.510	NS	0.433	0.602	< 0.05
<i>a</i>	-0.165	-0.554		-0.120	-0.162	
Increased pericarotid-tissue pressure						
clonidine, 150 μ g						
<i>r</i>	0.356	0.251		0.697	0.732	
<i>b</i>	0.131	0.097	NS	0.541	0.496	NS
<i>a</i>	0.066	-0.183		-0.538	-0.504	
clonidine, 300 μ g						
<i>r</i>	0.236	0.045		0.794	0.512	
<i>b</i>	0.078	0.011	NS	0.297	0.196	NS
<i>a</i>	0.111	-0.345		-0.240	-0.684	

* Data are shown as linear regression of changes in mean arterial pressure (mm Hg) on changes in pericarotid-tissue pressure (mm Hg). Each regression equation was calculated from a pool of 32 measurements taken in eight subjects (four measurements in each subject). *r*, *b* and *a* refer to correlation coefficient, regression coefficient and intercept of each regression line. B refers to the regression equation before and A to the regression equation after the administration of clonidine. *p* was obtained by covariant analysis of the regression lines in these two circumstances. The regression coefficients are positive because a decrease in pericarotid pressure (i.e., an increase in carotid baroreceptor activity) was associated with a decrease in arterial blood pressure and vice versa. Basal values of mean arterial pressure were reduced from 145 ± 4 to 123 ± 4 mm Hg by 150 μ g of clonidine, and from 148 ± 9 to 118 ± 7 mm Hg by 300 μ g of clonidine.

the slopes measured before and after the smaller or the greater dose of clonidine showed no significant difference, with the only exception being the steady-state depressor response, which appeared slightly but significantly increased by the greater dose of the drug.

Heart Rate

As shown in figures 1 and 2, the greatest increase and decrease in pericarotid-tissue pressure caused clear-cut changes in heart rate both before and after clonidine. For the whole group of 16 subjects (fig. 3, right) the changes observed before clonidine consisted in a significant early and steady-state bradycardia and tachycardia, when the pericarotid-tissue pressure was respectively reduced and increased. Clonidine caused a small but significant ($p < 0.001$) reduction in basal heart rate. The bradycardia and tachycardia observed in the early phase of the changes in pericarotid-tissue pressure were unaffected by the administration of clonidine. However, the steady-state bradycardia was slightly but significantly reduced ($p < 0.05$) and the steady-state tachycardia increased ($p < 0.02$) by the clonidine administration. As shown in table 2, a

significant linear relationship was usually present between the shortening and the lengthening of the R-R interval and the increased and reduced pericarotid-tissue pressure, respectively. For the reduced pericarotid-tissue pressure the slopes of the relationship tended to be less after clonidine, although this did not achieve statistical significance. On the other hand, for the increased pericarotid-tissue pressure the slopes tended to be greater after clonidine, the difference being statistically significant in two occasions.

Isometric Exercise

In all 16 subjects hand-grip induced a significant and marked increase in mean arterial pressure and heart rate. After clonidine administration basal values of mean arterial pressure and heart rate were significantly lower ($p < 0.001$), but the pressor and tachycardic responses induced by hand-grip were not significantly different from those measured before the drug administration. No significant difference in these two responses were found even when the comparisons were made within the group receiving 150 μ g and the group receiving 300 μ g of clonidine (fig. 4).

TABLE 2. Changes in R-R Intervals Compared with Changes in Carotid Baroreceptor Activity Before and After Administration of Clonidine*

	Early			Steady-state		
	B	A	p	B	A	p
Decreased pericarotid-tissue pressure						
clonidine, 150 µg						
r	0.741	0.640		0.740	0.474	
b	-4.180	-3.898	NS	-2.648	-1.591	NS
a	0.991	1.248		1.492	4.079	
clonidine, 300 µg						
r	0.573	0.602		0.380	0.241	
b	-1.336	-1.467	NS	-0.760	-0.458	NS
a	-0.335	2.355		3.188	2.329	
Increased pericarotid-tissue pressure						
clonidine, 150 µg						
r	0.098	0.664		0.486	0.663	
b	-0.285	-2.446	< 0.05	-1.552	-2.440	NS
a	-1.937	1.784		2.027	1.774	
clonidine, 300 µg						
r	0.376	0.573		0.574	0.805	
b	-0.678	-1.496	NS	-0.915	-3.054	< 0.001
a	-0.631	2.292		1.347	3.490	

*Data are shown as linear regression of changes in the R-R interval (msec) on changes in pericarotid-tissue pressure (mm Hg). Each regression equation was calculated from a pool of 32 measurements taken in the same eight subjects of table 1 (four measurements in each subject). Symbols as in table 1. The regression coefficients are negative because a decrease in pericarotid tissue pressure was accompanied by an increase in the R-R interval and vice versa. Basal values of the R-R interval were increased from 800 ± 64 to 833 ± 56 msec by 150 µg of clonidine, and by 757 ± 34 to 839 ± 41 msec by 300 µg of clonidine.

Cold

Immersion of one hand in iced water caused a marked rise in pressure and a more modest but still highly significant ($p < 0.001$) tachycardia in all subjects. These responses were not significantly different after administration of clonidine. However, when the two subgroups receiving the lower and the greater dose of the drug were separately considered (fig. 5), the pressor response to cold was found to be slightly but significantly ($p < 0.05$) reduced by the higher dose of clonidine.

Discussion

In our patients with essential hypertension, changes in the activity of the carotid sinus baroreceptors above and below the existing level induced alterations in arterial blood pressure that were usually similar in size before and after administration of clonidine in doses that had a pronounced hypotensive effect.

Several considerations can be made with regard to this finding. First, one might argue that it may be difficult to compare blood pressure responses at different baselines, that is, the higher baseline blood

pressure before clonidine, and the lower one after the drug. However this difficulty can be overcome by comparing the slope of the curves relating the blood pressure response to the stimulus, as the different baseline affects both stimulus and response in the same direction. Furthermore, the slope of the stimulus-response curve represents the most meaningful index of baroreflex responsiveness, as it measures the capacity of the reflex to correct a pressure disturbance. As is seen in table 1, this index of baroreflex responsiveness was not usually altered by clonidine.

Second, hypertensive patients have lower pressor and greater depressor responses to carotid baroreceptor manipulation than normotensive subjects.^{15, 16} It is possible, in principle, that the lowering of arterial pressure by clonidine might set back the baroreflex to the normotensive pattern. If this were true, an unchanged depressor response might represent a potentiation of a response which should otherwise be reduced. However, in this case we should have found a markedly potentiated pressor response to carotid sinus deactivation rather than the unchanged pressor response that we have observed.

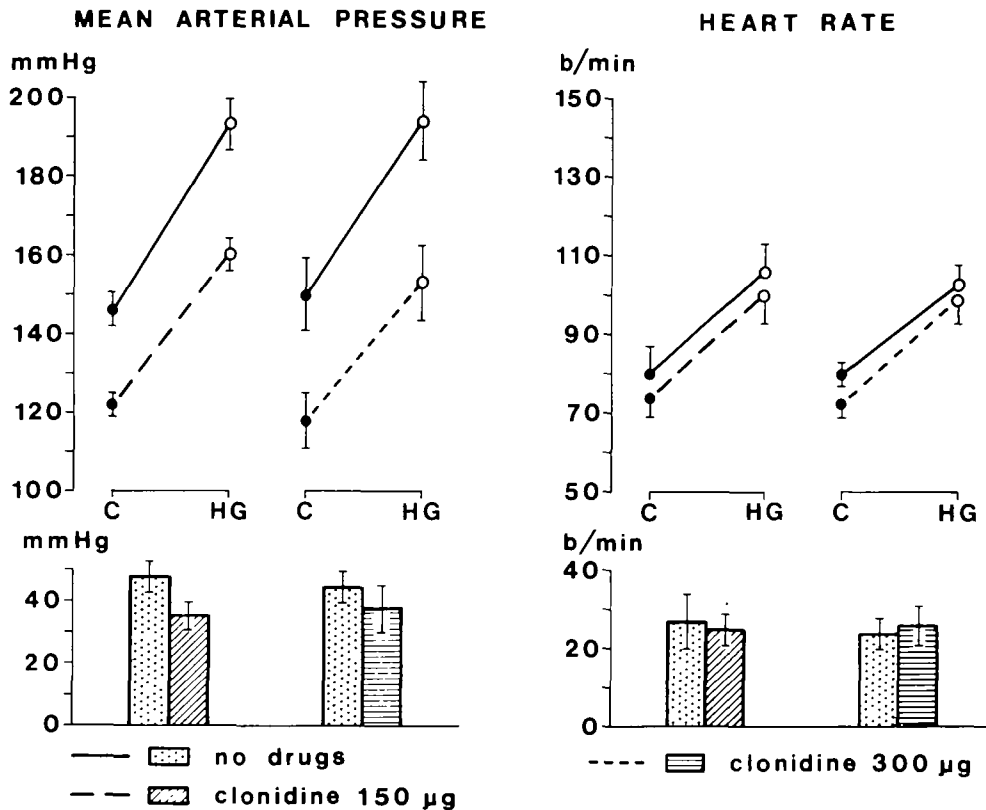


FIGURE 4. Effects of clonidine on the increase in mean arterial pressure and heart rate induced by hand-grip (HG). Data are shown separately for the two groups of subjects receiving 150 μ g (eight subjects) and 300 μ g (eight subjects) of clonidine. Absolute values are shown at the top, changes from control values induced by hand-grip at the bottom. No significant difference exists in the pressor and tachycardic responses to HG before and after administration of the drug.

Third, since our manipulations were limited to the carotid sinus, it might be argued that greater blood pressure responses to the neck chamber were not observed after clonidine because potentiation of the carotid baroreceptor reflex was neutralized by concomitant potentiation of baroreceptors located in the aortic arch. We have approached the problem of the circulatory influence exerted by the carotid and extracarotid baroreceptors in previous studies^{15, 16} in which the reflex changes in heart rate induced by altering the activity of the carotid sinus baroreceptors alone (alterations in carotid transmural pressure by the neck chamber device) were compared with those induced by altering the baroreceptor activity throughout the arterial system (alterations in arterial pressure by means of vasoactive drugs). The results show that although in normotensive subjects the reflex responses to stimulation of the whole baroreceptor population are much greater than the responses to stimulation of the carotid baroreceptors only, in hypertensive subjects they are almost indistinguishable. Thus, baroreflexes other than that of the carotid sinus seem to be largely impaired in human hypertension, a finding which makes our third hypothesis unlikely.

The most likely explanation of our findings is that, in human hypertension, clonidine can exert a pronounced antihypertensive effect without potentiation of the baroreceptor reflex. If there is some potentiation at an earlier or later time after clonidine injection, or if potentiation at the receptor level is balanced by depression at other sites along the reflex arch, both arguments do not deny the conclusion that lowering of blood pressure by clonidine can occur at a time when the baroreflex as a whole is substantially unchanged.

Our findings show no significant impairment of the baroreceptor control of blood pressure. This is in line with the clinical observations that treatment with clonidine seldom induces orthostatic hypotension.¹⁷

The conclusion that in hypertensive man the hypotensive action of clonidine is not related to potentiation of the baroreceptor reflexes does not deny that such potentiation might also occur in man for components of the baroreflex response other than arterial pressure. In our findings there is some indication that the tachycardic response to carotid sinus inactivation may be enhanced by clonidine. Since in man heart rate responses to baroreceptor manipulation depend almost entirely on the vagus,^{18, 19} this suggests that at the clinical doses we have employed potentiation of

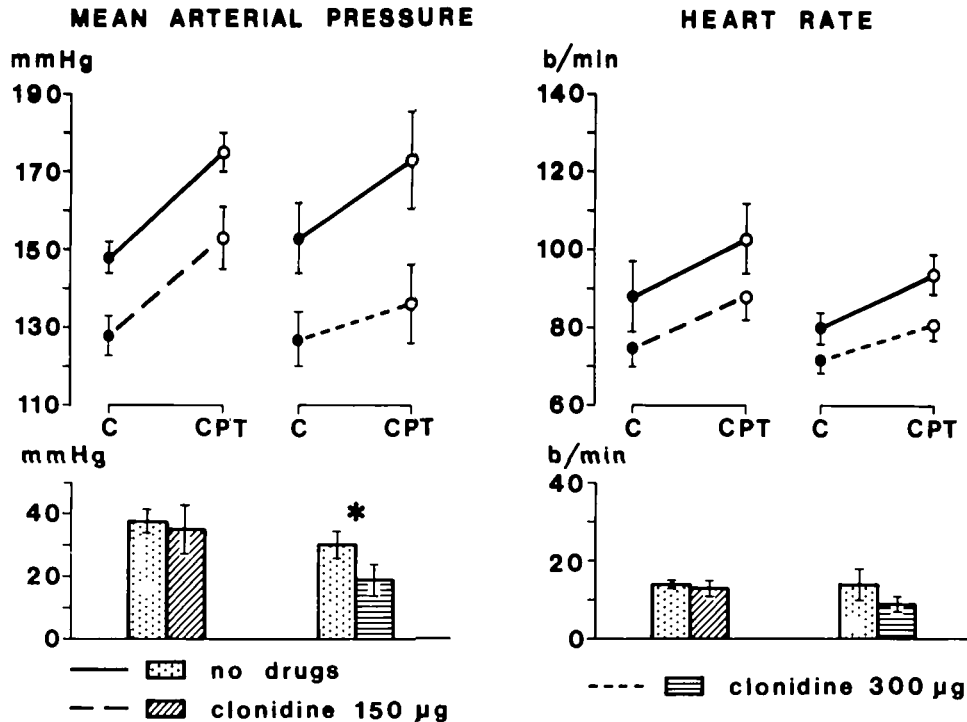


FIGURE 5. Effects of clonidine on the increase in mean arterial pressure and heart rate induced by immersion of one hand in ice water. Data are shown separately for the two groups of subjects receiving 150 µg (eight subjects) and 300 µg (eight subjects) of clonidine. C = control values; CPT = cold pressure test values during ice immersion. Absolute values are shown at the top, changes from control values induced by CPT at the bottom. Hemodynamic responses were similar before and after clonidine, with the only exception of the pressor response, which was slightly but significantly less ($p < 0.05$) after administration of 300 µg of the drug.

carotid sinus reflex might be limited to its vagal component. Also in the rabbit⁸ small doses of clonidine seem to potentiate the vagal efferent component of the reflex with little participation of the sympathetic component. It is possible that potentiation of sympathetic responses regulating blood pressure might also occur in man, but with larger doses of the drug seldom used in the clinical practice.

The predominant opinion is that both in animals²⁰ and man^{21, 22} the lowering of blood pressure induced by clonidine results from a central action of the drug depressing sympathetic activity. An alternative hypothesis suggests peripheral mechanisms, either depressed vascular responsiveness^{23, 24} or stimulation of presynaptic alpha-receptors²⁵ limiting transmitter release. Our present data do not bring direct evidence for or against these interpretations. However, as the depressor response to increased carotid baroreceptor activity is largely due to reduction in sympathetic vasoconstrictor tone,^{26, 27} preservation of this depressor response under clonidine indicates that a noticeable "tonic" sympathetic vasoconstriction persists in hypertensive patients during the therapeutic action of clonidine. Furthermore, our observation of normal cardiovascular responses to stimuli that

reflexly or centrally excite sympathetic vasoconstrictor neurons (isometric exercise and cold,²⁸⁻³⁰) shows that, whatever may be the effect of clonidine on basal sympathetic activity, the drug does not prevent a normal extent of sympathetic activation in response to several phasic stimuli. This may represent an advantage for maintenance of circulatory homeostasis during administration of the drug.

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