The Antihypertensive Mechanism of Clonidine in Man
Evidence Against a Generalized Reduction of Sympathetic Activity

B. GUNNAR WALLIN, M.D., AND MARIANNE FRISK-HOLMBERG, M.D.

SUMMARY Recordings of multi-unit sympathetic activity were made from muscle branches of the peroneal nerve during i.v. bolus injection of 100 to 275 µg clonidine in seven hypertensive patients. Blood pressure was reduced in all patients, but sympathetic activity and heart rate could either increase or decrease. When plasma levels of clonidine were low, sympathetic activity tended to increase, and when plasma levels were high, activity tended to decrease. Irrespective of whether mean level of sympathetic activity increased or decreased with the fall in blood pressure level, transient fluctuations of blood pressure continued to cause dynamic baroreflex modulation of the sympathetic outflow. It is suggested that the drug influences sympathetic outflow by a combination of central and peripheral effects. (Hypertension 3: 340-346, 1981)

KEY WORDS • muscle nerve sympathetic activity • microneurography • baroreflex mechanisms • blood pressure • clonidine • antihypertensive mechanism

A CUTE and chronic administration of clonidine lowers blood pressure (BP) in humans and is used in the treatment of hypertension. The effect is concentration-dependent, and after intravenous bolus injections, the BP reduction is linearly related to the logarithm of the plasma concentration of clonidine. The mechanism for the BP reduction is only incompletely understood. Clonidine is a partial pre- and postsynaptic α-adrenoreceptor agonist. From animal experiments, it has been postulated that the hypotensive effect is elicited centrally, since the drug is active after intracisternal administration and induces a BP reduction in baroreceptor-denervated animals. The mechanism has been suggested to be a stimulation of central α-adrenoreceptors, causing a reduction in peripheral sympathetic outflow. The arterial baroreflex may be potentiated by clonidine, but since the BP reduction remains after baroreceptor denervation, this cannot be the main hypotensive mechanism of the drug.

In patients, no direct information is available on the effect of clonidine on sympathetic activity, but renal excretion of catecholamines is reduced during "chronic" treatment with clonidine and this has been taken as an indication of reduced sympathetic activity. However, cardiac output and renal blood flow are reported to be reduced after bolus injections of clonidine in doses of 0.2-1 µg/kg. The reduction in catecholamine excretion could therefore partly be explained by these circumstances. Results from previous studies of muscle blood flow in man after clonidine administration are variable, and it is difficult to draw conclusions about sympathetic outflow from such data.

With the introduction of the microneurographic recording technique it has become possible to obtain direct information about sympathetic outflow in humans. Such recordings have shown that sympathetic activity destined for the muscles (SA) consists of vasoconstrictor impulses grouped in the pulse rhythm and occurring preferentially during temporary reductions of diastolic BP. The pulse synchrony and the inverse relationship to spontaneous BP fluctuations are taken as evidence of dynamic baroreflex modulation of the activity. It has also been shown that in a given individual the average amount of MSA is reproducible from day to day, but there are wide interindividual differences in MSA that are unrelated to interindividual differences in arterial BP levels.

In the present investigation, MSA was recorded during intravenous injections of clonidine in man, the aim being to study the relationship between the plasma concentration of the drug and resulting changes of sympathetic activity and BP. Part of the results have been published in preliminary form.

From the Department of Clinical Neurophysiology, and the Section of Clinical Pharmacology and Department of Internal Medicine, Medical Faculty, University Hospital, Uppsala, Sweden. Supported by Swedish Medical Research Council Grants 79-14X-03546-08A and 879-04X-05414-01 and Boehringer Ingelheim A.B. Sweden. Address for reprints: Marianne Frisk-Holmberg, M.D., Section of Clinical Pharmacology, Uppsala University, Box 573 BMC, S-751-23 Uppsala, Sweden. Received January 22, 1980; revision accepted October 21, 1980.
CLONIDINE AND SYMPATHETIC ACTIVITY IN MAN/Wallin and Frisk-Holmberg

Methods

Patients

Eight experiments were performed on seven previously untreated hypertensive patients (one woman and six men; age range, 34 to 60 years), who had given their informed consent to the study, which was approved by the Ethical Committee of the Medical Faculty of the University of Uppsala. One patient was investigated twice at an interval of 4 months. The diagnosis of hypertension was based on three separate BP determinations on the right upper arm after 5 minutes' rest in supine position. The hypertension was categorized after checking the medical history, physical examination, laboratory screening including blood cell counts, fasting blood sugar, serum electrolytes, blood urea, serum creatinine, creatinine clearance, plasma renin activity (PRA)/urinary sodium excretion index, chest x-ray, ECG, and intravenous pyelogram. A bilateral renal angiogram was performed on one patient (No 1). Individual data for the patients are given in table 1. On the basis of these tests one patient was considered to have renal (No 4) and the other six essential hypertension. Three patients corresponded to World Health Organization (WHO) hypertension Stage I; the others were regarded as WHO Stages II and III respectively. Of the patients with essential hypertension, one (No 6) had high PRA and two (No 1 and 3) low PRA. One patient (No 1) got an urge to void in connection with the injection of clonidine. The urge declined and disappeared after 30 minutes, which were excluded from the quantitative analysis. Apart from the hypertension, the patients were healthy and took no medications. They reported no untoward effects of the experiment.

Recording Equipment

Muscle nerve sympathetic activity was recorded with tungsten microelectrodes from muscle branches of the peroneal nerve at the fibular head. The technique has been described in detail and evidence for the recorded activity being composed of sympathetic vasoconstrictor impulses has been summarized.17, 18 Both the filtered original neurogram and a mean voltage neurogram (obtained by passing the filtered neurogram through an RC-integrating unit with a time constant of 0.1 s) were stored together with other variables on an 8-channel FM tape recorder.

Blood pressure was measured noninvasively in five experiments, with a mercury sphygmomanometer on the right upper arm. In three experiments, BP was monitored intraarterially through a catheter in the radial brachial artery connected to an EMT 35 pressure transducer and an EMT 31 electromanometer (Siemens-Elema). Electrocardiogram (ECG) was recorded by surface chest electrodes. Respiratory movements were monitored by a strain gauge attached to a rubber band strapped around the chest. Clonidine hydrochloride (Catapresan) was given as a bolus injection in doses from 100 to 275 µg in 4 ml saline over 3 minutes. Plasma concentrations of clonidine were analyzed by a gas liquid chromatographic method.1 Venous samples for clonidine determinations were drawn at fixed intervals. Plasma renin activity was determined in venous samples drawn after 45 minutes of supine rest prior to the experiment. A standard radioimmunoassay kit (NEN) was used.

Experimental Procedure

After the hypertension had been diagnosed, the patients were invited to participate in the study. For the investigation, they came to the laboratory after a light breakfast. Smoking was prohibited for 24 hours before the study, which was performed with the patients in the supine position. Nerve electrodes were inserted and when a recording site was found with good signal-to-noise ratio for sympathetic impulses, the activity at rest was recorded during a control period of 15 to 20 minutes. Clonidine was then injected and the BP and MSA recorded for a further 30 to 45 minutes.

Data Analysis

After the experiment, experimental records were displayed on an inwriter with a paper speed of 3 to 5 mm/sec (Minograph 800, Siemens-Elema). For analysis, records were divided into 3-minute periods, sympathetic bursts were marked on the mean voltage neurogram, and for each 3-minute period, burst incidence (in bursts/100 heart beats or bursts/min) and heart rate were determined. In experiments with intraarterial BP recordings, the mean voltage neurogram and the BP signal were AD-converted and fed into a computer (PDP 11/40), and for each 3-minute period, quantitative determination of various BP parameters were made. In figures 1 and 2, diastolic BP decrease had occurred about 10 minutes after the end of injection. Clonidine was then injected and the BP and MSA recorded for a further 30 to 45 minutes.

Results

Effects of Clonidine on Arterial Blood Pressure

Usually arterial BP started to decrease during the injection of clonidine, and in most cases the maximal decrease had occurred about 10 minutes after the end of the injection (fig. 1). Both systolic and diastolic BP decreased in all experiments, the decrease of mean BP ranging between 5% and 27%. This BP decrease lasted throughout the whole observation period (fig. 1). At 30 minutes after the injection, plasma concentrations of clonidine ranged between 0.45 and 1.18 ng/ml. In agreement with earlier observations,1 the BP decrease was linearly related to the logarithm of the plasma concentration (r = 0.70, p < 0.05). There was no systematic relationship between the BP reduction and the patient's "renin status."
TABLE 1. Clinical and Experimental Data on All Patients

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age, sex</th>
<th>PRA (ng/ml/hr)</th>
<th>UNa excretion (mM/24 hrs)</th>
<th>BP ambulant (supine mm Hg)</th>
<th>Mean control values during experiment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>BP (mm Hg)</td>
</tr>
<tr>
<td>1</td>
<td>34 F</td>
<td>0.30</td>
<td>168</td>
<td>150/95</td>
<td>142/93</td>
</tr>
<tr>
<td>2</td>
<td>38 M</td>
<td>0.65</td>
<td>179</td>
<td>150/105</td>
<td>148/108</td>
</tr>
<tr>
<td>3</td>
<td>40 M</td>
<td>0.51</td>
<td>208</td>
<td>180/115</td>
<td>154/94†</td>
</tr>
<tr>
<td>4*</td>
<td>44 M</td>
<td>1.00</td>
<td>63</td>
<td>185/110</td>
<td>182/115†</td>
</tr>
<tr>
<td>5</td>
<td>51 M</td>
<td>1.63</td>
<td>179</td>
<td>175/115</td>
<td>181/106†</td>
</tr>
<tr>
<td>6</td>
<td>52 M</td>
<td>3.70</td>
<td>127</td>
<td>170/110</td>
<td>165/115</td>
</tr>
<tr>
<td>7</td>
<td>60 M</td>
<td>1.39</td>
<td>238</td>
<td>180/110</td>
<td>158/103</td>
</tr>
</tbody>
</table>

Abbreviations: PRA = Plasma renin activity; UNa = Urinary sodium; BP = Blood pressure.

*Subject with renal hypertension.
†Intraarterial measurement.
§p < 0.05, significantly different from control value.
||p < 0.01, significantly different from control value.

Effect on Heart Rate

The effect on heart rate was variable. In six experiments, mean heart rate decreased (range 1.4–8.3 beats/min), and in two experiments, it increased (5.7 and 9.4 beats/min). There was no relationship between plasma concentrations of clonidine and the change of heart rate, nor between changes of heart rate and sympathetic activity. In table 1, the individual values for preinjection heart rate, BP, and amount of MSA are given. Figure 2 summarizes individual changes and gives the means of the respective values before and after injection of clonidine.

Effect on Muscle Sympathetic Activity (MSA)

During the control period, MSA showed its usual pulse synchrony, with bursts of impulses occurring intermittently, mainly during spontaneous BP reductions. In a given individual, the incidence of bursts...
CLONIDINE AND SYMPATHETIC ACTIVITY IN MAN/Wallin and Frisk-Holmberg

TABLE 1 (Continued)

<table>
<thead>
<tr>
<th>BP (mm Hg)</th>
<th>Heart rate (beats/min)</th>
<th>Symp. bursts (no./100 heart beats)</th>
<th>Symp. bursts (no./min)</th>
<th>Clonidine dose (µg/kg body wt)</th>
<th>Clonidine plasma conc. at 30 min (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>131/89</td>
<td>79.9</td>
<td>43.0 ± 2.0</td>
<td></td>
<td></td>
<td>34.3 ± 1.6</td>
</tr>
<tr>
<td>128/87</td>
<td>69.2</td>
<td>68.8 ± 3.8</td>
<td></td>
<td></td>
<td>47.6 ± 2.5</td>
</tr>
<tr>
<td>131/78†</td>
<td>62.1</td>
<td>87.0 ± 4.2</td>
<td></td>
<td></td>
<td>54.0 ± 3.2</td>
</tr>
<tr>
<td>165/106†</td>
<td>88.7</td>
<td>26.3 ± 3.2</td>
<td></td>
<td></td>
<td>23.3 ± 2.7</td>
</tr>
<tr>
<td>143/93‡</td>
<td>69.6</td>
<td>63.9 ± 3.9§</td>
<td>44.4 ± 2.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>141/107</td>
<td>51.1</td>
<td>76.8 ± 3.9</td>
<td></td>
<td></td>
<td>39.3 ± 1.7</td>
</tr>
<tr>
<td>109/77</td>
<td>77.2</td>
<td>52.7 ± 4.0</td>
<td></td>
<td></td>
<td>40.7 ± 3.1</td>
</tr>
<tr>
<td>107/79</td>
<td>68.9</td>
<td>84.5 ± 4.5</td>
<td></td>
<td></td>
<td>58.2 ± 2.4</td>
</tr>
</tbody>
</table>

was fairly constant during the entire control period, but there were wide differences among individuals, the range being 19-68 bursts/min (table 1, fig. 2). In the patient (No 2) who underwent two experiments, mean burst incidence during the control periods was reproducible (45 and 39 bursts/min respectively). During and after the clonidine injection, the pulse synchronous character of the MSA remained unchanged (fig. 3). In four experiments mean burst incidence increased, and in four it decreased (fig. 2). The changes in burst incidence occurred shortly after the clonidine administration, coinciding with the reduction of BP; the new level of nerve activity then remained approximately constant (fig. 1). Figure 3 shows examples of original records from experiments in which the number of bursts decreased (A) or increased (B). Regardless of whether bursts increased or decreased, there was still an inverse relationship between spontaneous dynamic BP fluctuations and transient variations of sympathetic activity. After the clonidine injection, however, this dynamic interplay occurred at lower BP values than before. Minor unintentional electrode adjustments sometimes occurred during the long experiments, thereby changing signal-to-noise ratio for sympathetic impulses. Although the detection of bursts was not affected (burst incidences did not change), these adjustments made it difficult to compare mean voltage amplitudes of the bursts between different segments of a recording. Mean values of burst incidence before and after clonidine are summarized for each individual in figure 2.

The change in MSA was related to the initial level of sympathetic activity. As shown in figure 4 left, the tendency was that in subjects with low initial burst in-

**Figure 2.** Individual and mean (heavy line) values of diastolic blood pressure (BP), heart rate, and sympathetic nerve activity before (A) and after (B) injection of clonidine.
FIGURE 3. Sympathetic and blood pressure responses to clonidine in two patients. Note that although blood pressure decreased in both cases, the sympathetic activity decreased in A and increased in B.

circumstance, the level of MSA increased after clonidine, and in subjects with high initial incidence, it decreased. Figure 4 right illustrates that there was also a relationship between the individual plasma concentration of clonidine and the change in MSA ($r = -0.68, p < 0.1$). The level of sympathetic activity is expressed as bursts/min in figure 4, but results were similar if expressed as bursts/100 heart beats.

Discussion

The present study provides the interesting finding that clonidine sometimes increased and sometimes decreased sympathetic outflow to the muscles. To our knowledge, the effect of clonidine on MSA has not been studied previously but in recordings from cervical sympathetic trunk, cardiac, splanchnic, and renal nerves, clonidine always caused a reduction of sympathetic activity.$^5,0,10,21$ The reason for the difference is not clear, but several factors may contribute. Our experiments were conducted on conscious patients who received doses of 1.4 to 3.3 µg/kg body weight, whereas previous studies were carried out on animals subjected to general anesthesia and surgery, and given higher doses (10 to 30 µg/kg body weight). Although this obviously may be one explanation, the fact that different nerves were studied could also be important. In humans, sympathetic outflow to skin is entirely different from that to muscles,$^{21}$ and in animals, the degree of baroreflex control is known to differ between different vascular beds.$^{23}$ Quantitative differences in the effect of clonidine on different sympathetic nerves have also been reported.$^3,10,14$ and therefore, the effect of clonidine on sympathetic outflow to
the muscles may well differ from that to, for instance, visceral regions.

As emphasized in previous studies, the pulse synchrony of MSA and the inverse relationship between the occurrence of sympathetic bursts and transient variations of diastolic BP provide evidence of dynamic baroreflex modulation of sympathetic outflow to muscles. When a static BP reduction is induced by the vasodilator sodium nitroprusside (which has no direct effects on CNS), evidence of dynamic baroreflex modulation of MSA is still present and at the same time the level of sympathetic activity always increases (Wallin et al., unpublished). Presumably this increase is a static baroreflex effect counteracting the fall in BP. In the present study, dynamic baroreflex modulation of MSA was present after clonidine (fig. 3), but the static BP decrease was sometimes associated with an increased and sometimes a decreased level of sympathetic activity. The findings suggest that, at least in some patients, static baroreflex mechanisms were altered in conjunction with the injection of clonidine. This would agree with data from both animal and human experiments, suggesting that baroreflex mechanisms are affected by clonidine. The results of Mancia et al., namely, that the effect of carotid sinus stimulation (neck chamber technique) on BP in humans remained unchanged after clonidine, need not contradict our results. Both their method of baroreceptor stimulation and their index of effector organ responsiveness are complex, and therefore their results are difficult to compare with both our present findings and the results of Sleight and West on the baroreceptor-heart-rate reflex.

A factor of importance when trying to explain our results is that clonidine has several modes of action that could affect BP differently. On one hand, central sympathetic inhibition and baroreflex resetting will tend to lower BP whereas, on the other hand, peripheral pre- and/or postsynaptic α-adrenoceptor stimulating effects on vascular smooth muscle may exaggerate or diminish the net change of BP. Zaimis has summarized data supporting this model, and Waite used it to explain why successive i.v. administrations of clonidine in cats did not cause a progressive fall of BP despite a continuing decrease of sympathetic activity. It has also been shown that the BP reduction seen after low doses and at low plasma concentrations of clonidine is reverted and that the BP increases again after higher doses. If the relative contribution of these mechanisms differed between subjects it could explain why sympathetic activity sometimes increased and sometimes decreased. For example, in our experiments, MSA decreased at higher plasma concentrations of clonidine (fig. 4 right). This could be explained by assuming that the peripheral postsynaptic α-agonist action of clonidine on the blood vessels (causing vasoconstriction) diminished the BP reduction relative to the degree of baroreflex resetting. We also found that MSA increased at lower plasma concentrations (fig. 4 right). This could be explained by assuming that the peripheral presynaptic α-stimulating action of clonidine (reducing transmitter release) dominated at lower plasma concentrations, thereby exaggerating the BP reduction relative to the baroreflex resetting.

In conclusion, the present results show that the hypotensive effect of clonidine is not always accompanied by a decrease of sympathetic nerve activity and suggest that a central presynaptic α-adrenoceptor effect may not be the unifying mechanism for the hypotension.

Acknowledgments

We thank Marianne Sundblad (R.N.), Lena Fredriksson, and Lis-Karin Wahlen for valuable technical assistance.

References


The antihypertensive mechanism of clonidine in man. Evidence against a generalized reduction of sympathetic activity.
B G Wallin and M Frisk-Holmberg

_Hypertension_. 1981;3:340-346
doi: 10.1161/01.HYP.3.3.340

_Hypertension_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1981 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/3/3/340

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Hypertension_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Hypertension_ is online at:
http://hyper.ahajournals.org//subscriptions/