Hemodynamic and Neurohormonal Effects of Clonidine in Patients With Preganglionic and Postganglionic Sympathetic Lesions
Evidence for a Central Sympatholytic Action

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Background. Clonidine, a partial presynaptic and postsynaptic \( \alpha \)-adrenoceptor agonist, has been shown to lower blood pressure in normal subjects but not in tetraplegics; however, the mechanisms of this action have not been elucidated.

Methods and Results. The hemodynamic and hormonal basis of the hypotensive action of clonidine was investigated in tetraplegics with complete cervical spinal cord transection and preganglionic sympathetic denervation, in patients with unilateral brachial plexus injury and postganglionic sympathetic denervation, and in normal subjects. In normal subjects, the fall in blood pressure after clonidine infusion was accompanied by a reduction in cardiac output that was predominantly due to a fall in stroke volume and in heart rate. The lack of fall in blood pressure, cardiac output, and stroke volume in tetraplegics indicates that these effects are exerted at a supraspinal level and require intact descending sympathetic pathways. After clonidine infusion, digital skin vasodilatation occurred in normal subjects, in the innervated but not the denervated limb of patients with unilateral brachial plexus injury, and in tetraplegics, indicating that this response is due to the central sympatholytic effect of clonidine. Plasma norepinephrine was much lower in tetraplegics compared with normal subjects, and after clonidine infusion, it fell substantially in normal subjects alone. Plasma renin activity did not change. Bladder stimulation in tetraplegics resulted in a rise in blood pressure and vasoconstriction in digital skin vessels. The inability of clonidine to significantly reduce or abolish the pressor and digital vasoconstrictor responses after bladder stimulation in tetraplegics indicates that clonidine does not exert a major effect on spinal preganglionic neurons or peripheral presynaptic \( \alpha \) -adrenoceptors.

Conclusions. Therefore, clonidine is a suitable drug for use in analyzing the central supraspinal levels of control in varying circulatory disorders, such as hypertension and postural hypotension. (Circulation 1991;84:75–83)

The mechanisms by which clonidine, a partial presynaptic and postsynaptic \( \alpha \)-adrenoceptor agonist, lowers blood pressure in humans are not fully understood. Therefore, its continuing use as a neuropharmacological tool necessitates further understanding of the hemodynamic and hormonal basis of its depressor action and exclusion of peripherally induced vasodilatation.

Evidence from studies in animals indicates that clonidine lowers blood pressure predominantly by stimulation of \( \alpha \) -adrenoceptors in the brainstem, resulting in suppression of sympathetic outflow.\(^1\,^2\) However, an action of clonidine on central pathways of the baroreceptor reflex\(^3\) and peripheral presynaptic receptors\(^4\,^5\) has also been reported. Evidence for a central action in humans was provided by the demonstration that blood pressure fell after clonidine infusion in normal subjects but not in tetraplegics with complete cervical spinal cord transection, in whom there is a separation of cerebral from spinal and peripheral sympathetic pathways.\(^6\,^7\) These earlier studies included only tetraplegics with preganglionic sympathetic denervation, and measurements of cardiac output, regional blood flow, cutaneous tem-
peratures, plasma renin activity, and regional blood flow responses to bladder stimulation were not made. The hemodynamic and hormonal basis of hypotension induced by clonidine and a possible vasodilatory action mediated at peripheral presynaptic \( \alpha \)-adrenoceptors could therefore not be assessed. We have investigated the central and peripheral mechanisms of action of clonidine by studying its effects in normal subjects and tetraplegics with measurements of stroke volume, cardiac output, regional blood flow, cutaneous temperatures, plasma norepinephrine, epinephrine, and plasma renin activity.

To investigate whether clonidine lowers blood pressure by an action on spinal preganglionic neurons or on peripheral presynaptic \( \alpha \)-adrenoceptors, we have studied its effects on the pressor and vasoconstrictor responses to bladder stimulation in tetraplegics. To further determine its peripheral actions, we have made simultaneous comparisons of vascular responses to clonidine in the innervated and denervated limbs of patients with unilateral brachial plexus injury who have postganglionic sympathetic denervation.

**Methods**

**Subjects**

Three groups were studied: 1) The first group consisted of seven normal subjects, six men and one woman, aged 26 to 49 years. 2) Another group consisted of seven tetraplegics, all men, aged 18–34 years, who had chronic and physiologically complete cervical spinal cord transection (C3–C7) with separation of central from spinal and peripheral sympathetic pathways. Clinical examination confirmed motor and sensory loss below the segmental level of the cord lesion. Other than the spinal cord lesion there were no systemic complications. 3) The last group consisted of five patients with unilateral brachial plexus injury, all men, aged 19–36 years. All had complete postganglionic lesions that were determined at operation and by nerve stimulation studies. Clinical examination before the study confirmed segmental motor and sensory loss in the affected limb; perfusion to the limb was not reduced. All were otherwise healthy.

All subjects were investigated in a temperature-controlled room (23±1°C) while supine and off medication for at least 3 days; previous medication had no known lasting effects on the autonomic nervous system or the circulation. Care was taken to prevent muscle spasms and bladder distension in tetraplegics, since this can induce sympathetic activity via the isolated spinal cord.\(^8\)

Informed and written consent to the study was obtained from each subject. The study was approved by the ethical committees of St. Mary’s and Stoke Mandeville Hospitals.

**Blood Pressure and Heart Rate**

Noninvasive measurements of blood pressure and heart rate were made at 5-minute intervals using an automated sphygmomanometer (Sentron).

**Aortic Blood Velocity**

Ascending aortic blood velocity was measured using a continuous-wave Doppler transmitter and receiver operating at 3.0 MHz (Exerdop, Quinton Instrument Co., a division of A. H. Robins Inc., Seattle, Wash.). This is a bidirectional, continuous-wave Doppler unit with an ultrasonic beam designed to receive scattered signals from a distance of 6–14 cm from the transducer. The transducer was placed lightly against the suprasternal notch to enable the ultrasonic beam emitted from the transducer to be directed toward the aortic root. Criteria for acceptance of adequate signals were 1) characteristic high-pitched crisp and clear sounds during systole, falling to a minimum or nearly vanishing during diastole and 2) visual signals analyzed on the oscilloscope (model D61, telequipment), rising sharply to a maximum velocity during the early phase of systole, falling to minimum levels before diastole, and remaining there until the beginning of the next systole.

The analog signals were processed by the system so that only the signals representing the flow toward the transducer were detected. The largest Doppler frequency shift in the signal, which corresponds to the maximum velocity of the blood from the ascending aorta occurring at any moment, was recorded during 30 consecutive and complete cardiac cycles. Stroke distance (a measure of stroke volume) was derived by continuous integration of each systolic velocity signal. Relative cardiac output was calculated from the produce of stroke distance and heart rate, and a mean value of 30 complete and consecutive cycles was taken. Peak acceleration (an index of global left ventricular performance) was derived by continuous differentiation of the velocity signals by the microprocessor. Validation of this technique for measuring cardiac output has been performed against invasive techniques.\(^9\)–\(^11\)

**Forearm Blood Flow and Vascular Resistance**

Forearm blood flow and vascular resistance were measured by venous occlusion plethysmography using the method described by Whitney.\(^12\) The changes in the circumference of the forearm were measured using the double-stranded gauge (model 2582, Ormed Ltd., Welwyn Garden City, Hertfordshire, UK). The signal from the gauge was transferred to the coupling unit (model 2583, Lectromed) for temperature compensation and to the preamplifier (type MX2P, Lectromed) and recorded on a chart recorder (type MX216, Lectromed). Readings were made at rest on a 15-second cycle (12-second inflation and 3-second deflation), and the average of 12 successive readings was taken. Forearm blood flow was calculated using a nomogram.\(^12\) Forearm vascular resistance was derived from the ratio of mean arterial blood pressure and forearm blood flow, assuming zero venous pressure.
Digital Skin Blood Flow and Vascular Resistance

Digital skin (index finger) blood flow was measured continuously with a laser Doppler flowmeter (Periflux, model PF2b, Perimed Ltd., Sweden). A red laser light produced by the instrument is led to the skin surface by an optical fiber to the probe held in place by a plastic probe holder. The light penetrates the skin and is repeatedly reflected and refracted and gradually absorbed. The multiple scattering produces a volume of isotopic illumination in front of the probe head (hemisphere with a radius of ~1 mm), and the red blood cells traversing this volume are struck by light partly reflecting it. Some of the light is altered in frequency (Doppler shift) by the red blood cells moving in the microvasculature and is returned to the instrument by efferent optical fibers arranged in parallel with the afferent fibers carrying the light of the instrument. Dual efferent light guides are used to reduce noise resulting from variations in the light signal. The frequency shift of the light is detected by photodetectors, which produce a voltage signal directly proportional to the quantity of blood flow (velocity and number of red blood cells) in the microvasculature of superficial skin. The signal was recorded on a chart recorder (BBC SE120, Coventry, UK). In all patients with unilateral brachial plexus injury, recordings of blood flow from the palmar aspect of both the right and left index finger were made simultaneously using two machines.

Cutaneous Temperatures

Skin temperatures were measured by thermistors (Pan Labs Inc., Bothell, Wash.) at the forehead, chest, abdomen, palmar aspect of the left index finger, and the plantar surface of the first toe.

Bladder Stimulation

In tetraplegics, bladder stimulation was performed for 5 minutes by tapping the finger tips about once per second on the anterior abdominal wall above the pubic crest.

Blood Collection and Analysis

Blood samples were collected from an indwelling venous cannula at the antecubital fossa at -15, 0, 15, 30, 45, and 60 minutes after clonidine infusion. Tubes were stored on ice until centrifugation at 4°C for separation of plasma.

Plasma renin activity: Blood (5 ml) was collected in chilled tubes containing EDTA (potassium salt) and plasma stored at -20°C until assay. Plasma renin activity was measured by radioimmunoassay of angiotensin I generated from its endogenous substrate in the presence of angiotensinase and converting enzyme inhibitors. The intra-assay coefficient of variation was 4%, and the interassay coefficient of variation was 7%.

Plasma norepinephrine and epinephrine: Blood (5 ml) was collected in chilled tubes containing 20 µl EGTA (0.095% wt/vol), and plasma was stored at -70°C until the assay. Catecholamines were extracted from plasma by solvent extraction using the technique of Smeddes et al. Separation was achieved by high-pressure light chromatography using 5-µm-diameter porous silica beads coated with C18 in a 22 × 0.46-cm column (model RP18, Brownlee Laboratories) and 15% (vol/vol) acetonitrile in 0.05 M phosphate acetic buffer, pH 3.0, containing sodium dodecyl sulfate (120 mg/l) as mobile phase. Catecholamines were detected by electrochemical detection (model 5100 A, ESA Coulochem) with the conditioning cell (model 5021) set at +0.40 V. The analytical cell (model 5011) was set at -0.10 V for electrode 1 and -0.35 V for electrode 2. The interassay coefficient of variation for norepinephrine was 6.6% and for epinephrine was 11.0%.

Drugs

Clonidine (2 µg/kg i.v. Catapres, Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, Conn.) was administered slowly for 10 minutes using an infusion pump.

Data Analysis

Results are presented as mean±SEM. Analysis of variance (GLM procedure, SAS Institute, Cary, N.C.) was used in the analysis of data. If the null hypothesis was rejected, Bonferroni t tests were performed on means at times 0, 15, 30, and 60 minutes after clonidine infusion to further characterize significant differences. A value of p<0.05 was considered significant.

Results

Normal Subjects and Tetraplegics

Blood pressure. After clonidine infusion, a small and transient (5-minute) rise in blood pressure in three of the seven normal subjects was followed by the dominant response, which was, in all subjects, a fall in both systolic and diastolic blood pressure (both p<0.05) (Table 1). Resting blood pressure was lower in tetraplegics compared with normal subjects (p<0.05). A small and transient (10-minute) rise occurred in five of the seven patients, but blood pressure did not fall significantly after clonidine infusion.

Heart rate. After clonidine infusion, heart rate fell in tetraplegics and in patients with unilateral brachial injury (both p<0.05) but not significantly in normal subjects (Table 1).

Relative cardiac output. Relative cardiac output fell after clonidine infusion in normal subjects (p<0.05) but not in tetraplegics (Table 1).

Peak velocity and peak acceleration. After clonidine infusion, peak velocity was unchanged in normal subjects and in tetraplegics (Table 1). Peak acceleration fell after clonidine infusion in normal subjects (p<0.05) but not in tetraplegics.

Forearm blood flow and vascular resistance. In normal subjects, clonidine induced a fall in forearm
blood flow, but vascular resistance was unchanged (Table 1). Forearm blood flow was not measured in tetraplegics.

Digital skin blood flow and vascular resistance. A biphasic response in digital skin blood flow occurred in two of the seven normal subjects after clonidine infusion. A small and transient fall in digital skin blood flow lasting up to 5 minutes was followed by the dominant response, an increase in flow (p < 0.05) that was sustained for 2 hours of observation (Figure 1). Digital vascular resistance fell after clonidine infusion (p < 0.05), indicating vasodilatation (Figure 2). Resting digital skin blood flow was higher in tetraplegics compared with normal subjects (p < 0.05). After clonidine infusion, there was a decrease in digital skin blood flow, which was maximal at 2.5 minutes; this was followed by a gradual increase in blood flow but reverted to baseline levels. Digital vascular resistance rose after clonidine infusion (p < 0.05), indicating vasoconstriction.

Skin temperature. In normal subjects, there was a rise in digital and toe skin temperature after clonidine infusion (both p < 0.05) (Figure 2 and Table 1). In tetraplegics, resting digital and toe skin temperatures were higher compared with those of normal subjects (p < 0.05) and were not significantly altered after clonidine infusion (both p = NS). Skin temperatures at the forehead, chest, and abdomen were unchanged after clonidine infusion in normal subjects and in tetraplegics (Table 1).

Bladder stimulation. In tetraplegics, bladder stimulation resulted in a rise in mean blood pressure

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**TABLE 1. Hemodynamic and Hormonal Changes 0, 30, and 60 minutes After Clonidine Infusion in Normal Subjects and Tetraplegics**

<table>
<thead>
<tr>
<th></th>
<th>Basal Normals</th>
<th>Basal Tetraplegics</th>
<th>30 Minutes Normals</th>
<th>30 Minutes Tetraplegics</th>
<th>60 Minutes Normals</th>
<th>60 Minutes Tetraplegics</th>
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<tbody>
<tr>
<td>BP (mm Hg)</td>
<td>126±7/74±6</td>
<td>109±5*/66±5*</td>
<td>104±5/59±6†</td>
<td>105±5/59±4</td>
<td>1106±4/61±3†</td>
<td>105±6/61±4</td>
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<tr>
<td>HR (beats/min)</td>
<td>69±3</td>
<td>65±4</td>
<td>58±2†</td>
<td>64±6</td>
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<tr>
<td>PV (m/sec)</td>
<td>0.64±0.04</td>
<td>0.76±0.06</td>
<td>0.62±0.05</td>
<td>0.77±0.05*</td>
<td>0.58±0.05</td>
<td>0.69±0.04*</td>
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<tr>
<td>PA (m/sec/sec)</td>
<td>17.7±1.2</td>
<td>18.0±1.0</td>
<td>14.7±0.9†</td>
<td>18±1.0*</td>
<td>14±1.0†</td>
<td>16±1.0*</td>
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<td>CO (cm/min)</td>
<td>670±80</td>
<td>635±54</td>
<td>571±92</td>
<td>659±82</td>
<td>513±91†</td>
<td>702±52†</td>
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<td>FBF (ml/100 ml/min)</td>
<td>3.3±0.8</td>
<td>...</td>
<td>2.6±0.4</td>
<td>...</td>
<td>2.4±0.6</td>
<td>...</td>
</tr>
<tr>
<td>FVR (mm Hg/ml/100 ml/min)</td>
<td>37±6</td>
<td>...</td>
<td>37±5</td>
<td>...</td>
<td>40±6</td>
<td>...</td>
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<tr>
<td>LDF (V)</td>
<td>0.69±0.2</td>
<td>1.9±0.2*</td>
<td>1.46±0.2†</td>
<td>1.4±0.2†</td>
<td>1.21±0.3†</td>
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<td>LDR (mm Hg/V)</td>
<td>381±129</td>
<td>42±8*</td>
<td>57±6†</td>
<td>57±10</td>
<td>83±16†</td>
<td>54±5</td>
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<td>Epinephrine (pg/ml)</td>
<td>40.4±7</td>
<td>&lt;20</td>
<td>26±7†</td>
<td>&lt;20</td>
<td>28±6†</td>
<td>&lt;20</td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Room</td>
<td>22.6±0.5</td>
<td>22.8±0.5</td>
<td>22.6±0.5</td>
<td>22.9±0.5</td>
<td>22.7±0.5</td>
<td>23.0±0.4</td>
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<td>Forehead</td>
<td>33.2±0.3</td>
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<td>33.7±0.3</td>
<td>32.8±0.4</td>
<td>33.6±0.3</td>
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<tr>
<td>Chest</td>
<td>33.0±0.6</td>
<td>33.6±0.4</td>
<td>32.7±0.7</td>
<td>33.5±0.5</td>
<td>32.6±0.7</td>
<td>33.4±0.5</td>
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<tr>
<td>Abdomen</td>
<td>33.3±0.5</td>
<td>34.8±0.4*</td>
<td>33.8±0.5</td>
<td>34.3±0.3</td>
<td>33.7±0.5</td>
<td>34.0±0.6</td>
</tr>
<tr>
<td>Index finger</td>
<td>27.0±1.3</td>
<td>35.3±0.2*</td>
<td>31.9±1.2†</td>
<td>34.8±0.3*</td>
<td>31.4±1.6†</td>
<td>35.1±0.2*</td>
</tr>
<tr>
<td>Toe</td>
<td>24.2±1.1</td>
<td>32.4±1.6*</td>
<td>26.9±1.4†</td>
<td>33.1±1.6*</td>
<td>27.5±1.4†</td>
<td>33.4±1.2*</td>
</tr>
</tbody>
</table>

Values are mean±SEM; n=7 for normal subjects, and n=7 for tetraplegics. BP, blood pressure; HR, heart rate; PV, peak velocity; PA, peak acceleration; CO, relative cardiac output; FBF, forearm blood flow; FVR, forearm vascular resistance; LDF, laser Doppler flow; LDR, laser Doppler resistance.

*p<0.05 vs. corresponding value in normal subjects; †p<0.05 vs. basal value in corresponding group.

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**FIGURE 1.** Top panel: Plot showing effects of clonidine on digital skin vascular blood flow measured by laser Doppler in normal subjects (n=7) and tetraplegics (n=7). Bottom panel: Plot showing effects of clonidine on digital skin vascular flow measured by laser Doppler in the innervated and the denervated limbs of patients with unilateral brachial plexus injury (n=5). Results are mean±SEM. *Different (p<0.05) for remaining period of observation compared with average of values before clonidine infusion.
Results are mean±SEM. *Different (p<0.05) for remaining period of observation compared with average of values before clonidine infusion.

Figure 2. Plots showing effects of clonidine on percentage change in digital skin vascular resistance assessed by laser Doppler (top panel) and digital skin temperature (bottom panel) in normal subjects (n=7) and tetraplegics (n=7). (p<0.05) with a fall in digital skin blood flow (p<0.05) (Figure 3) and a rise in digital vascular resistance (from 56±8 to 536±199 mm Hg/V, p<0.05). Clonidine induced a small but nonsignificant fall in blood pressure. After clonidine, bladder stimulation again resulted in a significant rise in blood pressure (p<0.05), a fall in digital skin blood flow (p<0.05), and a rise in digital vascular resistance (from 53±6 to 430±151 mm Hg/V, p<0.05).

Plasma renin activity. After clonidine infusion, there were no significant changes in plasma renin activity during recumbency in normal subjects or in tetraplegics (Figure 4).

Plasma norepinephrine and epinephrine. In normal subjects, plasma norepinephrine fell after clonidine (from 417±53 to 167±30 pg/ml, p<0.05) (Figure 4). Basal plasma norepinephrine was much lower (21%) that of normal subjects in tetraplegics (p<0.05) and fell after clonidine infusion (from 91±20 to 45±9 pg/ml, p<0.05). Plasma epinephrine fell after clonidine infusion in normal subjects (p<0.05). In tetraplegics, plasma epinephrine levels were below the reproducible detection limit (<20 pg/ml) (Table 1).

Patients With Unilateral Brachial Plexus Injury

Systemic hemodynamics. After clonidine infusion, there was a fall in blood pressure (p<0.05) and heart rate (p<0.05). The reductions in relative cardiac output, peak velocity, and peak acceleration were not significant (Table 2).

Digital skin blood flow. Differential changes occurred after clonidine infusion in digital skin blood flow in the two limbs (Figure 1). In the innervated limbs of patients with unilateral injury, as in the limbs of normal subjects, a biphasic response occurred in two of the five patients, with a small and transient decrease in blood flow (lasting up to 5 minutes), followed by the dominant response of an increase in digital skin blood flow in all patients. Vascular resistance fell (p<0.05), indicating vasodilatation (Figure 5). In the denervated limbs of patients with unilateral injury, as in the limbs of tetraplegics, resting digital skin blood flow was higher compared with the innervated limbs. After clonidine infusion, there was a transient fall in blood flow, which was maximal at 2.5 minutes, followed by the dominant response of increased flow, which was sustained for the observation period of 60 minutes. Vascular resistance rose (p<0.05) after clonidine infusion, indicating vasoconstriction.

Skin temperature. After clonidine infusion, digital skin temperature rose in the innervated limb (p<0.05) and was not altered in the denervated limb (Figure 5 and Table 2).

Discussion

The aim of the present studies was to clearly establish the pharmacological and physiological basis...
for the use of clonidine in the investigation of various circulatory disorders, such as hypertension and postural hypotension.

Resting supine blood pressure in tetraplegics was lower compared with that of normal subjects, presumably because of diminished basal sympathetic nervous activity evidenced by low resting plasma norepinephrine levels and low sympathetic effluent discharge on microneurography.17,18 After clonidine infusion, there was a fall in blood pressure in normal subjects but not in tetraplegics, confirming previous observations.6,7 In these earlier studies, however, measurements of cardiac output, regional blood flow, and cutaneous temperatures were not made, and the hemodynamic basis of hypotension induced by clonidine could not be assessed. In the present study, the depressor response to clonidine in normal subjects was accompanied by a reduction in cardiac output due to a fall in heart rate and stroke volume. The latter effect of clonidine is likely to be due to a reduction in venous return as a consequence of systemic venodilatation,19,20 since studies in animals21,22 have not shown an effect on myocardial contractility and in vitro studies on isolated hearts have not shown a reduction in rate or force of contraction.23 The lack of fall of cardiac output and stroke volume in tetraplegics after clonidine infusion indicates that these effects in humans are exerted at a supraspinal level and probably in the brainstem. A greater fall in heart rate after clonidine infusion in tetraplegics in whom baroreceptor afferents and cardiac parasympathetic efferent fibers are intact is probably due to an action on brainstem centers that increases vagal activity,6 although an action of clonidine on the central pathways of the baroreceptor reflex3 may be contributory. Peak acceleration, an index of global left ventricular performance,10 fell after clonidine infusion in normal subjects but not in tetraplegics and further excludes a direct effect of
this agent on factors reducing cardiac contractility. The depressor response to clonidine in normal subjects occurred independent of suppression of plasma renin (and thus angiotensin II) levels despite a reduction in sympathetic activity. Whether the reduction in plasma renin activity, as may occur in response to reduced sympathetic activity, was counteracted by renin release secondary to hypotension is not certain. The inability of clonidine to lower plasma renin activity in tetraplegics, in whom blood pressure did not change, is not consistent with previous reports that have indicated a direct inhibitory α-adrenergic effect on renin release from the kidney.

Measurements of regional blood flows and temperatures were made to assess their roles in the fall in blood pressure. Forearm blood flow (a resultant of muscle and skin blood flow) fell, but forearm vascular resistance was unchanged after clonidine infusion in normal subjects. Skin temperatures at the forehead, chest, and abdomen were also unchanged, thus excluding an important contribution of these vascular beds to hypotension induced by clonidine. Blood flow to the skin in the hands and feet differs from the forearm, however, since it is mainly controlled by sympathetic vasoconstrictor nerves. The effects of clonidine on digital skin blood flow in normal subjects and patients with preganglionic and postganglionic sympathetic denervation have not been described previously. In two of the seven normal subjects, clonidine caused a transient decrease in digital skin blood flow lasting up to 5 minutes, probably due to its peripheral α-adrenergic agonist effects. The dominant response in all subjects, however, was an increase in digital skin blood flow and temperature, sustained for the 2-hour period of observation. Digital skin vascular resistance fell, indicating active vasodilatation. This effect of clonidine in normal subjects, like its hypotensive action, is likely to be due to a centrally induced reduction in sympathetic outflow and is further supported by a fall in plasma norepinephrine and significant correlations of plasma norepinephrine levels with both the change in digital skin vascular resistance assessed by laser Doppler and mean blood pressure (Figure 6). The substantial fall in plasma norepinephrine after clonidine probably results from reduced sympathetic outflow to various regional vascular beds. The inability of clonidine to reduce vascular resistance in the forearm and cutaneous vascular beds, except in digital vessels, suggests that, in normal subjects, clonidine may influence the splanchnic vasculature.

In tetraplegics, resting skin blood flow and temperature were higher and are in keeping with observations of diminished resting vasoconstrictor tone and much lower plasma norepinephrine levels compared with those of normal subjects. Further vasodilatation did not occur after clonidine infusion, demonstrating that the reduction in digital skin vascular resistance after clonidine infusion in normal subjects is due to a central action of this agent. In tetraplegics, clonidine induced an increase in digital skin vascular resistance, which was maximal at 2.5 minutes and reverted gradually toward basal levels. The mechanisms responsible for the enhanced and sustained vasoconstriction in tetraplegics are unclear but may be related to decentralization supersensitivity to the peripheral α-adrenoceptor agonist effects of clonidine. However, this vasoconstrictor effect of clonidine in tetraplegics is unlikely to account for the lack of fall in blood pressure, since the contribution of digital vascular beds to total systemic vascular resistance remains relatively small.

In tetraplegics, skin irritation or skeletal muscle spasm may induce small changes in plasma norepinephrine through activation of spinal sympathetic reflexes via the isolated spinal cord. A modest fall in plasma norepinephrine occurred in tetraplegics from previously low basal levels after clonidine infusion without an accompanying fall in blood pressure or digital skin vascular resistance and may have been due to its muscle relaxant effects. Whether clonidine additionally lowered plasma norepinephrine by a partial agonistic action on peripheral presynaptic α-adrenoceptors is not certain however.
To investigate whether clonidine exerted an effect on spinal preganglionic neurons or on peripheral presynaptic α-adrenoceptors,4,5 we performed additional studies in tetraplegics and in patients with unilateral brachial plexus injury. In tetraplegics, bladder stimulation resulted in a rise in blood pressure and cutaneous vascular resistance due to a reflex increase in sympathetic activity via the isolated spinal cord.8 The rise in blood pressure and vasoconstriction in digital skin vessels was confirmed in response to bladder stimulation in our patients. After clonidine infusion, bladder stimulation resulted in a significant rise in blood pressure and digital skin vascular resistance. The inability of clonidine to abolish the pressor and vasoconstrictor responses to bladder stimulation indicates that its major hypotensive action is not on spinal preganglionic neurons or on peripheral presynaptic α-adrenoceptors.

The possible action of clonidine on peripheral presynaptic α-adrenoceptors was further studied in patients with unilateral brachial plexus injury with postganglionic sympathetic denervation. Although the systemic hemodynamic changes after clonidine infusion (blood pressure, heart rate, stroke distance, relative cardiac output, and peak acceleration) were similar to those observed in normal subjects, differential responses occurred in the upper limbs. In the innervated limbs of patients with unilateral injury, digital skin blood flow and temperature increased and resistance fell, as in the limbs of normal subjects. In the denervated limbs of patients with unilateral injury, as in the limbs of tetraplegics, digital skin blood flow and temperature were higher at rest compared with values in the innervated limb. After clonidine infusion, digital skin blood flow fell and vascular resistance rose. Therefore, digital vasodilatation after clonidine is dependent on the integrity of postganglionic pathways. The lack of vasodilatation in the denervated limb during clonidine infusion is further evidence against a major vasodilatory action on presynaptic α2-adrenoceptors. Although a pharmacological action of clonidine has been reported at this site in animal studies,32,33 the doses of clonidine required were much (seven to 20 times) higher than those used clinically or in our study. An effect of clonidine on peripheral presynaptic receptors was not observed at lower (1–4 μg/kg) doses.33

Therefore, our results make clonidine a suitable drug for use in analyzing the central supraspinal levels of control in varying circulatory disorders, such as hypertension and postural hypotension. The inability of clonidine to lower plasma norepinephrine,34,35 blood pressure, and digital skin vascular resistance35 in patients with pheochromocytoma suggests that central sympathetic nervous activity does not appear to contribute to circulating plasma norepinephrine levels and, in some patients, to vascular tone and blood pressure. In contrast, a role for central neurogenic mechanisms in maintaining raised blood pressure in renovascular hypertension is suggested by the ability of clonidine to lower blood pressure substantially in patients with unilateral renal artery stenosis,36 in whom acutely administered captopril was ineffective. The hemodynamic and hormonal responses to clonidine have additionally served to differentiate, on a functional basis, two subgroups of patients with primary autonomic failure and postural hypotension.37,38 Clonidine lowers blood pressure, digital skin vascular resistance, and plasma norepinephrine levels in patients with multiple system atrophy (Shy-Drager Syndrome), indicating that in the supine position, vascular tone and blood pressure are maintained by sympathetic vasoconstrictor activity.38 This contrasts with patients who have pure autonomic failure (idiopathic orthostatic hypotension), in whom there is no fall in blood pressure, digital skin vascular resistance, or plasma norepinephrine levels after clonidine infusion, indicating a severe reduction in sympathetic nervous activity in the supine position.38

We conclude that, in normal subjects, the fall in blood pressure after clonidine infusion is accompanied by a reduction in cardiac output due predominantly to a fall in stroke volume and in heart rate. The lack of fall in blood pressure, cardiac output, and stroke volume in tetraplegics indicates that these effects are exerted at a supraspinal level and require intact descending sympathetic pathways. Digital skin vasodilatation occurs after clonidine infusion in normal subjects, in the innervated but not the denervated limbs of patients with unilateral brachial plexus injury, and in tetraplegics, indicating that this response is due to the central sympatholytic effect of clonidine. The inability of clonidine to significantly reduce or abolish the pressor and digital vasoconstrictor responses following bladder stimulation in tetraplegics indicates that clonidine does not exert a major effect on spinal preganglionic neurons or peripheral presynaptic α2-adrenoceptors. Therefore, clonidine is a suitable drug for use in analyzing the central supraspinal levels of control in varying circulatory disorders, such as hypertension and postural hypotension.

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References


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