The Effect of Clonidine on Cerebral Blood Flow Velocity, Carbon Dioxide Cerebral Vasoreactivity, and Response to Increased Arterial Pressure in Human Volunteers

Hye-Won Lee, M.D.,* James E Caldwell, M.B.Ch.B., Barbara Dodson, M.D.,† Pekka Talke, M.D.,‡ Joan Howley, M.D.†

Background: Because patients may be taking clonidine chronically or may be receiving it as a premedication before surgery, the authors investigated its effect on cerebral hemodynamics.

Methods: In nine volunteers, middle cerebral artery mean blood flow velocity (Vm) was measured using transcranial Doppler ultrasonography (TCD). CO₂ vasoreactivity was measured before clonidine administration (preclonidine), 90 min after clonidine, 5 µg/kg orally, then following restoration of mean arterial pressure (MAP) to the preclonidine level. In addition, Vm was measured after a phenylephrine-induced 30-mmHg increase in MAP.

Results: After clonidine administration, Vm decreased from 62 ± 9 to 48 ± 8 cm/s (P < 0.01), and MAP decreased from 86 ± 10 to 63 ± 5 mmHg (P < 0.01; mean ± SD). Clonidine decreased the CO₂ vasoreactivity slope from 2.2 ± 0.4 to 1.2 ± 0.5 cm s⁻¹ mmHg⁻¹ (P < 0.05); restoring MAP to the preclonidine level increased the slope to 1.60 ± 0.5 cm s⁻¹ mmHg⁻¹, still less than the preclonidine slope (P < 0.05). CO₂ vasoreactivity expressed as a percentage change in Vm, decreased after clonidine, 3.5 ± 0.8 versus 2.4 ± 0.8 %/mmHg (P < 0.05); this difference disappeared after restoration of MAP, 5.1 ± 1.2 %/mmHg. With a 30-mmHg increase in MAP, Vm increased by 13% before and after clonidine (P < 0.05).

Conclusions: Clonidine, 5 µg/kg orally, decreases Vm and slightly attenuates cerebral CO₂ vasoreactivity, therefore decreased cerebral blood flow and mildly attenuated CO₂ vasoreactivity should be anticipated. (Key words: Administration; oral, α₂ agonist: clonidine. Cerebral: blood flow velocity; CO₂ vasoreactivity; autoregulation. Monitoring, cerebral: transcranial Doppler ultrasonography, Pa₅0.)

The α₂ agonist clonidine is a commonly used centrally acting antihypertensive drug. There is interest in the potential role of clonidine and other more selective α₂ agonists in anesthesia because they reduce opioid and volatile anesthetic requirements during surgery, reduce plasma catecholamine concentrations, improve hemodynamic stability, and have potent analgesic properties.³

Central α₂ receptors have a role in the regulation of the cerebral circulation,⁴ and α₂ agonists, including clonidine, decrease cerebral blood flow (CBF), ⁵-⁶ and produce constriction of cerebral arteries.⁶-⁹ Data from animal studies give conflicting results on the effect of clonidine on cerebrovascular reactivity to CO₂. Clonidine has been reported to decrease cerebral blood flow and reduce cerebral CO₂ vasoreactivity¹⁰ and to enhance cerebrovascular reactivity to CO₂.¹⁰ Despite considerable interest regarding the effect of clonidine on CBF, there are no human studies that examine the effect of α₂ agonists on cerebral CO₂ vasoreactivity.

Transcranial Doppler ultrasonography (TCD) is a noninvasive technique that offers reliable measurement of CBF velocity,¹¹,¹² CO₂ vasoreactivity,¹³ and autoregulation.¹⁴,¹⁵ We used TCD to measure the influence of clonidine on CBF velocity, CO₂ vasoreactivity, and the response of the cerebral circulation to increased arterial pressure.

Methods

Subjects

Nine healthy volunteers, aged from 24 to 33 yr, gave informed consent to the study that was approved by
the Committee on Human Research, University of California, San Francisco. Inclusion criteria included normal middle cerebral artery (MCA) blood flow velocities, as determined by TCD evaluation, and a negative history for cardiac or cerebrovascular disease. Volunteers were instructed to abstain from the use of alcohol, caffeine, and tobacco for 24 h before the study.

On arrival in the study room, the subject was placed in the supine position. Monitoring with non-invasive blood pressure (Dinamap 1846 SX, Critikon, Tampa, FL), electrocardiography (ECG), and pulse oximetry was commenced. A 20-gauge intravenous catheter was placed for fluid and drug administration. Lactated Ringer’s solution was administered at a rate of 2–4 ml·kg⁻¹·min⁻¹. A 22-gauge catheter was inserted into the radial artery to measure mean arterial pressure (MAP) continuously and to draw blood samples for measurement of PaCO₂. The volunteer was then placed in a semirecumbent position for the remainder of the study. The transducer that measured blood pressure was zeroed at the level of the right atrium.

Measurement of Mean Blood Flow Velocity

Transcranial Doppler ultrasonography of the right MCA was performed using a Neurogard® monitor (Medasonics, Fremont, CA) with the 2-MHz pulsed Doppler monitoring probe placed at the right transcranial temporal window. Insonation of the MCA was initiated at a depth of 45 mm. Confirmation of MCA identity was achieved by increasing insonation depth to visualization of the bidirectional flow pattern typical of the bifurcation of the internal carotid artery into the middle cerebral and anterior cerebral arteries. Insonation depth was then decreased to the point of maximal signal intensity, and the monitoring probe was locked into position with a Medasonics probe clamp and head strap. Baseline readings were obtained and included mean blood flow velocity in the right MCA (Vm) and pulsatility index (PI).

Pulsatility index was defined as (peak systolic blood flow velocity - peak diastolic blood flow velocity)/Vm.

Ten to 20 min were allowed for the conditions to stabilize after transition to each new experimental state, with continuous TCD monitoring throughout this time. The measured value of Vm was recorded only after it was observed to be stable for at least 1 min at the new steady-state experimental conditions. Measurements of Vm were obtained in triplicate at end-expiration and averaged to obtain a single value.

Measurement of Carbon Dioxide Vasoreactivity

Volunteers were rested in a quiet and dimly illuminated room with their eyes closed until TCD and cardiovascular measurements had been stable for at least 15 min. Then each volunteer breathed normally through a face mask attached to an anesthesia breathing circuit (FiO₂, 0.21) with end-tidal CO₂ measured at the circuit Y-piece (Capnomac, Datex Instrumentarium Inc., Helsinki, Finland). Ten to 15 min were allowed for the volunteer to adapt to the breathing apparatus, before baseline values of Vm, PI, end-tidal CO₂, MAP, heart rate (HR), and PaCO₂ were obtained.

After baseline measurements were attained (i.e., normocapnia), hypocapnia or hypercapnia was induced, the order being alternated with each volunteer. For hypocapnia, volunteers hyperventilated until the end-tidal CO₂ tension decreased by 10 mmHg. When a stable plateau of end-tidal CO₂ tension was achieved, Vm (hypocapnia) was measured. Volunteers then breathed normally for 10 to 15 min. To induce hypercapnia, a rebreathing technique was used. The soda lime was removed from the breathing circuit, and fresh gas flow (oxygen only) was reduced to only that required to maintain an FiO₂ of 0.21–0.30. The end-tidal CO₂ tension was monitored until it increased by 10 mmHg. Air was then added to the fresh gas flow, sufficient to maintain the end-tidal CO₂ tension stable, and Vm (hypercapnia) was measured. Arterial blood samples were taken simultaneously for analysis of PaCO₂ at each measurement of Vm.

Test of Response to Increased Arterial Pressure

After the CO₂ reactivity test had been performed, the volunteer was allowed 10 to 15 min to recover. Initial measurements of MAP (MAP) and Vm (Vₐ₀) were made, and then a 30-mmHg increase in MAP was induced slowly with an infusion of phenylephrine (0.5–4.0 µg·kg⁻¹·min⁻¹). The final Vm (Vₕ) was measured when MAP had stabilized at its final increased level (MAP). All measurements during this phase were made with the subject normocapnic and breathing room air. Because Vm is significantly influenced by PaCO₂, arterial blood samples for analysis of PaCO₂ were drawn during all measurements of Vm to document any change in PaCO₂ occurred. All the measurements so far described were made before the administration of chloral hydrate.

Assessment of Clonidine Effect

Each volunteer acted as his or her own control. In the first phase of the study, the measurements described
previously were made before the administration of clonidine (preclonidine measurements). The second phase of the study began 90 min after an oral dose of clonidine, 5 μg/kg. In this phase of the study, the measurements described previously were repeated (postclonidine measurements). In addition, because clonidine decreased the volunteers’ blood pressure, CO\textsubscript{2} vasoreactivity was measured twice, first at the postclonidine MAP and again when MAP had been restored to the preclonidine level (± 5%) by a phenylephrine infusion (MAP-restored measurements).

To assess the effect of clonidine on the response to increased arterial pressure, Vm was measured at three different blood pressures: the original postclonidine MAP, MAP-restored to the preclonidine level (obtained by an infusion of phenylephrine), and finally when MAP was increased 30 mmHg above the MAP-restored level (obtained by increasing the infusion of phenylephrine).

**Analysis of Data**

**CO\textsubscript{2} Vasoreactivity.** Linear regression was used to calculate the slope of the relationship of Pa\textsubscript{CO\textsubscript{2}} and Vm for each volunteer. The Pa\textsubscript{CO\textsubscript{2}} versus Vm relationship derived by linear regression for each volunteer was used to calculate the percent change in Vm/mmHg change in Pa\textsubscript{CO\textsubscript{2}}, over the range of that subject’s Pa\textsubscript{CO\textsubscript{2}} values.

**Response to Increased Arterial Pressure.** Because Vm values are significantly affected by Pa\textsubscript{CO\textsubscript{2}}, we first compared values for Pa\textsubscript{CO\textsubscript{2}} before making comparisons of Vm, e.g. the initial Vm values before and after clonidine.

Comparisons between two treatment groups were by paired t test and between three treatment groups were by repeated measures ANOVA with Student-Newman-Keuls test. All results are presented as mean ± SD, unless otherwise stated. A P value of < 0.05 was considered statistically significant.

**Results**

**General Variables.** After clonidine administration, Vm decreased from 62 ± 9 cm/s to 48 ± 8 cm/s (P < 0.01); PI increased from 0.84 ± 0.06 to 1.15 ± 0.15 (P < 0.01); MAP decreased from 86 ± 10 mmHg to 63 ± 5 mmHg (P < 0.01); neither heart rate, nor Pa\textsubscript{CO\textsubscript{2}} changed (table 1). The decrease in Vm after clonidine was not reversed by increasing MAP to the preclonidine level. Arterial oxygen saturation as measured by pulse oximetry was ≥97% in all subjects.

**Cerebral CO\textsubscript{2} Vasoreactivity.** In all subjects, there was a statistically significant relationship between Pa\textsubscript{CO\textsubscript{2}} and Vm with correlation coefficients all > 0.95. The CO\textsubscript{2} vasoreactivity slope decreased from a control of 2.2 ± 0.4 to 1.2 ± 0.5 cm·s\textsuperscript{-1}·mmHg\textsuperscript{-1} after clonidine administration (P < 0.05). Restoration of MAP to the preclonidine level increased the slope to 1.6 ± 0.5 cm·s\textsuperscript{-1}·mmHg\textsuperscript{-1}(P < 0.05), still less than the preclonidine slope (P < 0.05). CO\textsubscript{2} vasoreactivity, expressed as a percentage change in Vm, decreased after clonidine administration, 3.5 ± 0.8 versus 2.4 ± 0.8 %/mmHg (P < 0.05); this difference disappeared after restoration of MAPs to the preclonidine level, 3.1 ± 1.2 %/mmHg.

Hypocapnia and hypercapnia were associated with minor changes in MAP, all of which deviated < 10% from the normocapnic value (table 1). Hypocapnia and hypercapnia induced statistically significant increases in HR (P < 0.05); these changes were similar in the three phases of the study (table 1). The administration of phenylephrine to restore MAP to control levels produced a decrease in HR (P < 0.05; table 1).

**Response to Arterial Pressure Increase.** Except for the situations wherein Pa\textsubscript{CO\textsubscript{2}} was deliberately manipulated to produce hypo- or hypercapnia, the Pa\textsubscript{CO\textsubscript{2}} values were similar during all phases of the study (table 2). Before clonidine administration, the Vm of 61 ± 9 cm/s increased to 69 ± 9 cm/s after an increase of 30 mmHg in MAP, a median increase of 13% (P < 0.05). After clonidine administration, Vm was 51 ± 7 cm/s, and this value did not change, 54 ± 10 cm/s, with restoration of MAP to the preclonidine level, although it increased by a median of 13% to 62 ± 8 cm/s when MAP was increased a further 30 mmHg (P < 0.05; fig. 1).

**Discussion**

In this study, we found that clonidine decreases Vm. The decrease in Vm was not reversed by restoring MAP to the control level, indicating an effect of clonidine independent of the decrease in MAP. The decrease in Vm was accompanied by an increase in PI, and this observation is consistent with data from animal studies, suggesting that the decrease in Vm is a result of cerebral vasoconstriction.4,9

When α\textsubscript{2}adrenergic receptors on the cerebral arteries of pigs and cats are stimulated, vasoconstriction occurs.7,9 In dogs, α\textsubscript{2} agonists decrease cerebral blood flow, but they do not alter cerebral metabolic rate, sug-
Table 1. PaCO2, Mean Blood Flow Velocity of the Middle Cerebral Artery (Vm), Pulsatility Index, Mean Arterial Pressure (MAP), and Heart Rate (HR) during Cerebral CO2 Vasoreactivity Test

<table>
<thead>
<tr>
<th>Condition</th>
<th>PaCO2 (mmHg)</th>
<th>Vm (cm/s)</th>
<th>Pulsatility Index</th>
<th>MAP (mmHg)</th>
<th>Heart Rate (beats/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preclonidine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normocapnia</td>
<td>39.8 ± 3.4</td>
<td>62 ± 9</td>
<td>0.84 ± 0.06</td>
<td>86 ± 10</td>
<td>58 ± 8†</td>
</tr>
<tr>
<td>Hypocapnia</td>
<td>29.4 ± 4.7</td>
<td>41 ± 7</td>
<td>1.29 ± 0.28</td>
<td>86 ± 8</td>
<td>72 ± 7</td>
</tr>
<tr>
<td>Hypercapnia</td>
<td>48.3 ± 4.1</td>
<td>80 ± 10</td>
<td>0.74 ± 0.06</td>
<td>91 ± 10</td>
<td>66 ± 13</td>
</tr>
<tr>
<td>Postclonidine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normocapnia</td>
<td>42.0 ± 5.2</td>
<td>48 ± 8*</td>
<td>1.13 ± 0.13*</td>
<td>63 ± 5*</td>
<td>54 ± 7†</td>
</tr>
<tr>
<td>Hypocapnia</td>
<td>31.0 ± 4.8</td>
<td>34 ± 5</td>
<td>1.48 ± 0.24</td>
<td>66 ± 7</td>
<td>62 ± 10</td>
</tr>
<tr>
<td>Hypercapnia</td>
<td>51.0 ± 3.5</td>
<td>58 ± 11</td>
<td>0.84 ± 0.30</td>
<td>68 ± 8</td>
<td>59 ± 8</td>
</tr>
<tr>
<td>MAP-restored</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normocapnia</td>
<td>43.9 ± 5.4</td>
<td>51 ± 8*</td>
<td>0.86 ± 0.29</td>
<td>88 ± 10</td>
<td>43 ± 6†</td>
</tr>
<tr>
<td>Hypocapnia</td>
<td>31.3 ± 5.1</td>
<td>37 ± 7</td>
<td>1.19 ± 0.29</td>
<td>90 ± 10</td>
<td>49 ± 9</td>
</tr>
<tr>
<td>Hypercapnia</td>
<td>51.1 ± 4.1</td>
<td>70 ± 4</td>
<td>0.81 ± 0.07</td>
<td>89 ± 13</td>
<td>47 ± 8</td>
</tr>
</tbody>
</table>

Values are mean ± SD (N = 9). Preclonidine measurements were performed before clonidine administration; postclonidine measurements were performed beginning 90 min after clonidine administration; MAP-restored measurements were performed after the mean arterial pressure postclonidine was restored to the preclonidine level by phenylephrine infusion.

* P < 0.05 versus preclonidine values.
† P < 0.05 versus hypocapnia and hypercapnia values.
‡ P < 0.05 versus preclonidine and postclonidine values.

...suggesting a direct vasoconstrictor effect.68 Our assumption that the decreased Vm after clonidine is a result of cerebral vasoconstriction is supported by the results of Zornow et al., who found a decreased Vm and increased PI with the α2 agonist dexmedetomidine.17

Clonidine-induced vasoconstriction also could explain, at least in part, our observations on CO2 vasoreactivity because CO2 reactivity is influenced by cerebrovascular resistance (CVR).19 The greater the CVR, the lower would be the PaCO2-mediated changes in CBF. Because α2 agonists produce cerebral vasoconstriction,5,6 the CVR would be greater after clonidine administration, and the CO2 vasoreactivity slope would be decreased, which was the effect we found.

In addition, part of the decrease in slope was probably a result of the clonidine-induced decrease in arterial pressure.19,20 With decreasing MAP, CO2 reactivity of the cerebral resistance vessels decreases and eventually is abolished.19,20 We corrected for the influence of decreased arterial pressure by restoring MAP to the preclonidine level, and the CO2 reactivity slope increased somewhat. However, the slope did not return to the

Table 2. Mean Arterial Pressure (MAP), Mean Blood Flow Velocity of the Middle Cerebral Artery (Vm), Heart Rate, and PaCO2 during Phenylephrine-induced Increased of MAP

<table>
<thead>
<tr>
<th>Condition</th>
<th>MAP (mmHg)</th>
<th>Vm (cm/s)</th>
<th>Heart Rate (beats/min)</th>
<th>PaCO2 (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preclonidine phases</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial</td>
<td>88 ± 10</td>
<td>61 ± 9*</td>
<td>61 ± 12*</td>
<td>40.0 ± 2.8</td>
</tr>
<tr>
<td>MAP-increased</td>
<td>118 ± 11</td>
<td>69 ± 9</td>
<td>48 ± 16</td>
<td>40.1 ± 3.2</td>
</tr>
<tr>
<td>Postclonidine phases</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial</td>
<td>67 ± 8</td>
<td>51 ± 7</td>
<td>55 ± 10*</td>
<td>41.6 ± 4.6</td>
</tr>
<tr>
<td>MAP-restored</td>
<td>88 ± 9</td>
<td>54 ± 10</td>
<td>45 ± 13</td>
<td>42.0 ± 3.5</td>
</tr>
<tr>
<td>MAP-increased</td>
<td>117 ± 9</td>
<td>62 ± 8*</td>
<td>43 ± 14</td>
<td>43.2 ± 3.7</td>
</tr>
</tbody>
</table>

Values are mean ± SD (N = 9). Preclonidine measurements of mean blood flow velocity in the middle cerebral artery were performed before clonidine administration; postclonidine measurements were performed beginning 90 min after clonidine administration. Mean arterial pressure was raised in the MAP-increased and MAP-restored (postclonidine MAP restored to the preclonidine level) phases by phenylephrine infusion.

* P < 0.05 versus other phases.

Anesthesiology. V 87, No 3, Sep 1997
CLONIDINE AND CEREBRAL BLOOD FLOW VELOCITY

Phase of Study

Fig. 1. Individual values for the effect of increased mean arterial pressure (MAP) on mean blood flow velocities in the middle cerebral artery (Vm). In the preclonidine group, initial MAP was increased 30 mmHg (+30 mmHg) by infusion of phenylephrine. After administration of clonidine, 5 μg/kg orally (postclonidine), MAP decreased; measurements of Vm were made and then repeated when the pressure had been restored to the preclonidine level (MAP restored) and again when it had been increased a further 30 mmHg (+30 mmHg) by infusion of phenylephrine. Clonidine decreased Vm (P < 0.05). There was a statistically significant increase in Vm with a phenylephrine-induced 30 mmHg increase in MAP, before and after clonidine administration (P < 0.05).

![Graph showing pre-clonidine and post-clonidine mean blood flow velocity.]

However, before clonidine administration, we found an increase of approximately 13% in Vm with an increase of 30 mmHg in MAP. We propose two reasons for this observation. First, because we used awake volunteers, a very stable set of study conditions, and a paired study design wherein each subject was his or her own control, we had sufficient statistical power to detect even a small difference in Vm. Second, we increased MAP by 50%, whereas previous studies increased it by a lesser amount, and the effect may either not have occurred or not have been detectable with the smaller increase in MAP. 

A similar effect of MAP increase on Vm also was observed after clonidine administration. For direct comparison with the preclonidine situation, the initial postclonidine MAP was restored to the preclonidine level, and then the Vm change was measured during an additional 30 mmHg increase in MAP. A 13% increase in Vm occurred, i.e., the same magnitude of change as was observed before clonidine administration. When the MAP was increased from the initial postclonidine level to the MAP restored level, no change in Vm was noted. However, in this phase of the study, the increase in MAP averaged only 21 mmHg, and so the results cannot be compared with those obtained before clonidine when the MAP increase was 30 mmHg. The conclusion these data suggest is that the effect of increasing MAP on Vm is essentially the same after clonidine as it was before.

Some aspects of our methodology merit discussion. We used the technique of transcranial Doppler sonation to measure mean blood flow velocity in the MCA. This technique does not allow for measurement of absolute cerebral blood flow, but in any person, there is a good correlation between relative changes in flow velocity and CBF. Because of this good correlation, the validity of using TCD to evaluate CO2 vasoreactivity and Vm response to increased arterial pressure is well established.

The goodness of the relationship of Vm to CBF requires that the diameter of the MCA remains constant. Direct intraoperative observation of the MCA showed that its diameter changed little (2.5%) with moderately increased MAP, and this degree of change would have minimal influence on our results. Similarly, our use of phenylephrine to increase MAP would be expected to have negligible effect on MCA diameter.

Because our subjects were in a semirecumbent position and because the arterial pressure transducer was zeroed at the level of the right atrium, we measured...
MAP and not cerebral perfusion pressure (CPP). Because the subjects remained in the same position throughout the study, the relationship of MAP and CPP would have been constant.

In summary, we conclude that a dose of clonidine, 5 µg/kg, such as might be used for premedication produces significant effects on the cerebral circulation. It decreases MCA blood flow velocity and slightly attenuates the cerebrovascular response to changes in CO₂, via its effects on Vm and MAP and has no effect on the response to moderately increased arterial pressure. We speculate that these effects are consistent with a direct cerebral vasodepressive effect of clonidine. Therefore, decreased CBF and mildly attenuated CO₂ vasoreactivity should be anticipated when oral clonidine is administered as a premedication or as an adjunct to anesthesia or pain management.

References


Anesthesiology, V 87, No 3, Sep 1997