Alpha₂-Adrenergic Receptor–Induced Vascular Constriction in Blacks and Whites

Mordechai Muszkat, Gbenga G. Sofowora, Alastair J.J. Wood, C. Michael Stein

Abstract—Black Americans have a reduced hypotensive response to the α₂-adrenergic receptor agonist clonidine compared with whites, despite similar central sympathoinhibition. This reduced hypotensive response might be explained by greater postsynaptic vascular α₂-adrenergic receptor vasoconstrictive response. However, clonidine has a low α₂/α₁ selectivity ratio. Therefore, to determine the role of altered α₂-adrenergic receptor vascular sensitivity in ethnic differences in vascular response, we compared local vascular responses with the highly selective α₂-adrenergic receptor agonist dexmedetomidine in healthy black (n=18) and white (n=19) subjects. Increasing doses of dexmedetomidine (0.001 to 1000 ng/min) were infused into a dorsal hand vein, and the local response was measured with a linear variable differential transformer. Dexmedetomidine caused pronounced vasoconstriction, with an average (±SD) maximum response of 74.5±17.72% but with no difference between blacks and whites. There was substantial intersubject variability in the sensitivity to dexmedetomidine; the dose resulting in 50% (ED₅₀) of maximum vasoconstriction ranged from 0.08 ng/min to 256 ng/min. The geometric mean ED₅₀ was 2.28 ng/min (95% CI, 0.02 to 271.6 ng/min) in blacks and 1.58 ng/min (95% CI, 0.11 to 24.55 ng/min) in whites (P=0.59). Our data indicate that α₂-adrenergic receptor–induced vasoconstriction is similar in blacks and whites. These findings do not support the hypothesis that altered α₂-adrenergic receptor sensitivity is the explanation for the decreased blood pressure response to systemic administration of clonidine in blacks. The response to dexmedetomidine provides a model that will allow further study of the regulation of α₂-adrenergic receptor–mediated vascular responses.

Key Words: adrenergic receptor agonists ■ ethnicity ■ human ■ receptors, adrenergic, alpha ■ vasoconstriction ■ veins

Hypertension is more prevalent and more severe in black Americans and is associated with greater morbidity and mortality rates. Several environmental and genetic factors have been suggested to contribute. Many investigators have observed that blood pressure responses to stress are higher in normotensive black than white subjects. This finding suggests that ethnic differences exist, either in regulation of sympathetic activity or in vascular response to the same degree of sympathetic activation. In keeping with this possibility is the observation that the decrease in blood pressure in response to antihypertensive drugs acting through adrenergic mechanisms is smaller in blacks.6,7

We and others have previously examined the hypothesis that there are ethnic differences in sympathetic activation and vascular response. On balance, there do not appear to be differences between well-matched black and white subjects in sympathetic activity, either at rest or after stimulation, measured by means of two complementary techniques, norepinephrine spillover and muscle sympathetic nerve activity.8–10 However, several different groups have reported ethnic differences in vascular sensitivity. These include the following findings: attenuated β₂-adrenergic11–13 and endothelium-dependent nitric oxide–mediated vasodilation12,14 and enhanced α₁-adrenergic receptor (AR) vasoconstriction in blacks.5

Presynaptic α₂-ARs mediate inhibition of sympathetic activity centrally by decreasing sympathetic outflow, whereas postsynaptic vascular α₂-ARs mediate vasoconstriction peripherally. Despite the considerable interest in possible ethnic differences in the regulation of adrenergic response, the contribution of the α₂-AR is not clear.

To address the possibility that alterations in central or peripheral α₂-AR activity contribute to ethnic differences in blood pressure regulation, we previously infused clonidine, an α₂-AR agonist, in healthy black and white subjects and found that although the decrease in sympathetic activity was similar, the decrease in blood pressure was markedly smaller in blacks.10 This finding—that the decrease in blood pressure after clonidine was attenuated, despite a similar degree of sympathoinhibition in blacks—could occur if increased postsynaptic α₂-AR sensitivity resulted in enhanced vasoconstriction in response to the peripheral effects of clonidine and thus attenuated its central hypotensive response. Therefore, to address this possibility, we examined the hypothesis that the
peripheral vasoconstrictor effects of an \( \alpha_2\)-AR agonist are greater in blacks than in whites. However, since clonidine, in addition to its \( \alpha_2\)-AR agonist properties, is a partial \( \alpha_2\)-AR agonist,15,16 vascular responses to clonidine might represent the sum of its effects on both \( \alpha_1\) and \( \alpha_2\)-ARs. Therefore, we studied local vascular responses to dexmedetomidine, an \( \alpha_2\)-AR, which has an \( \alpha_x/\alpha_2\) selectivity ratio 8 times higher than clonidine.17

To determine if \( \alpha_2\)-AR vascular sensitivity was increased in blacks and to minimize the confounding effect of reflex activation, which would occur after systemic administration, we studied local vascular responses by using the dorsal hand vein model, a technique that allows the infusion of low doses of vasoactive drug directly into the vessel studied. We measured vascular responses to the \( \alpha_2\)-AR agonist dexmedetomidine, which has not been previously studied in this model.

**Methods**

The Institutional Review Board of Vanderbilt University Medical Center approved the study protocol, and subjects gave written informed consent. Thirty-seven subjects (18 blacks, 19 whites) participated. Subjects were healthy, with no clinically significant abnormality detected by history, physical examination, or routine laboratory tests. Ethnicity was determined by self-report and required that all four grandparents and both parents were of the same ethnic group as the subject. A family history of hypertension was determined by self-report and was based on a history of hypertension in parents or siblings.

Subjects took no medications for at least 2 weeks and abstained from alcohol and caffeine for 5 days before the study. Each subject received 4 days of a diet containing 150 mmol/d of sodium, 70 mmol/d of potassium, and 600 mmol/d of calcium. Studies were performed after an overnight fast, on the morning of the fifth day in the same temperature-controlled room.

**Measurement of Vascular Responses**

Venous responses were measured in a dorsal hand vein by use of a linear variable differential transformer (LVDT) (Schaevitz, model 100 MHR), as previously described.18 This instrument, when mounted on the hand, measures and records changes in the diameter of the vein. Subjects rested on a comfortable bed and remained supine throughout the study. The subject’s arm was placed on a support sloping upward. A 23-gauge needle was inserted into a suitable dorsal hand vein, and an infusion of normal saline was administered for 30 minutes. After 3 stable baseline measurements of hand vein diameter, the drug was infused into the vein over which the LVDT was mounted. Dexmedetomidine HCl (Precedex, Abbott Laboratories), diluted in normal saline, was infused into the dorsal hand vein in increasing doses (range, 0.01 ng/min to 1000 ng/min), with each dose infused for 7 minutes by means of a Harvard syringe pump, and responses were recorded during the last 2 minutes of each dose infusion.

Heart rate was monitored continuously with a bedside cardiac monitor (Dinamap MPS, Johnson and Johnson Medical), and blood pressure was measured in the arm on the side opposite the side receiving the hand vein infusion by means of the same semiautomated device (Dinamap MPS).

Blood samples for measurement of norepinephrine concentrations were obtained at baseline (after 30 minutes of rest), after the 100-ng/min dexmedetomidine dose, (cumulative dose, 1.34 \( \mu g \)), and after the final 1000-ng/min dose (cumulative dose, 12.25 \( \mu g \)).

**Analysis of Hand Vein Response to Dexmedetomidine**

Venoconstriction was expressed as the percentage reduction in vein diameter from baseline maximal dilation, defined as the average of 3 stable baseline measurements of hand vein diameter. Data for the dexmedetomidine hand vein responses were plotted as individual semilog dose-response curves and analyzed with the use of a sigmoid dose-response model (Prism 3.0 software). The dose that produced 50% (ED\(_{50}\)) of maximum venoconstriction (E\(_{\text{max}}\)) was determined for each subject, and these values were used to compare sensitivity to dexmedetomidine in the two ethnic groups.

Hand vein data up to the 100-ng/min dose were analyzed for 34 subjects, since maximum effect had been obtained and no systemic effects observed at this dose, confirming the lack of systemic \( \alpha_2\)-AR effects of dexmedetomidine. In 3 subjects, the data analysis included the 250- and 500-ng/min data points.

**Statistical Analyses**

Continuous baseline characteristics were analyzed by means of a Student \( t \) test and discrete variables by Fisher exact test. Blood pressure, heart rate, and plasma norepinephrine concentrations at baseline and during the study were analyzed by means of 1-way ANOVA (SPSS, version 11.0) with a post hoc test (Scheffé) for multiple comparisons.

Data for the dexmedetomidine ED\(_{50}\) were log-transformed before analysis and expressed as geometric mean with 95% confidence intervals. Other data are expressed as mean±SD or number.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Blacks ( n=18 )</th>
<th>Whites ( n=19 )</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, M/F, n</td>
<td>10/8</td>
<td>11/8</td>
<td>0.99</td>
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<tr>
<td>Age, y</td>
<td>29.0±9.2</td>
<td>30.6±9.3</td>
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<tr>
<td>Body mass index, kg/m(^2)</td>
<td>26.5±6.4</td>
<td>25.8±4.7</td>
<td>0.69</td>
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<tr>
<td>Family history of hypertension, n</td>
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<td>8</td>
<td>0.99</td>
</tr>
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<td>Systolic blood pressure, mm Hg</td>
<td>113.1±10.7</td>
<td>107.1±9.3</td>
<td>0.09</td>
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<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>64.2±9.7</td>
<td>58.3±5.9</td>
<td>0.04</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>60.9±6.9</td>
<td>60.5±11.7</td>
<td>0.89</td>
</tr>
<tr>
<td>Plasma norepinephrine, pg/mL</td>
<td>167.6±55.0</td>
<td>170.4±70.9</td>
<td>0.9</td>
</tr>
</tbody>
</table>

Data are presented as mean±SD or number.

There was no difference between blacks and whites in dexmedetomidine ED\(_{50}\) (Figure 2). The ED\(_{50}\) was 2.28 ng/min (95% CI, 0.11 to 24.55 ng/min) in white subjects and 1.58 ng/min (95% CI, 0.02 to 271.6 ng/min) in black subjects.

**Results**

**Subject Characteristics**

Demographic data and blood pressure measurements in black (\( n=18 \)) and white (\( n=19 \)) subjects are shown in Table 1. The groups were well matched for gender, age, body mass index, and presence of a family history of hypertension.

**Hand Vein Response to Dexmedetomidine**

Responses to dexmedetomidine with the use of the LVDT model have not previously been defined. A representative dose-response curve of dorsal hand vein response to dexmedetomidine is shown in Figure 1. There was wide interindividual variability in response, with the range of the ED\(_{50}\) spanning several log units, as occurs with other agonists.18 The ED\(_{50}\) ranged from 0.08 ng/min to 256 ng/min, and the geometric mean (95% CI) was 1.91 ng/min (0.042 to 87.1 ng/min), with an E\(_{\text{max}}\) of 74.5±17.72% (\( n=37 \)).

There was no difference between blacks and whites in dexmedetomidine ED\(_{50}\) (Figure 2). The ED\(_{50}\) was 2.28 ng/min (95% CI, 0.02 to 271.6 ng/min) in black subjects and 1.58 ng/min (95% CI, 0.11 to 24.55 ng/min) in white subjects.
(P=0.59). The average $E_{\text{max}}$ (Figure 3) in black subjects was 72.74%±18.21%, and 76.2%±17.57% in whites (P=0.56).

Eight subjects in each group had a family history of hypertension. There was no significant difference in venous $\alpha_2$-AR–mediated responses in subjects with and without a family history of hypertension. For those subjects with a positive family history of hypertension, the $E_{D_{50}}$ was 0.81 ng/min (95% CI, 0.05 to 14.79 ng/min) and those without was 1.9 ng/min (95% CI, 0.05 to 77.6 ng/min) (P=0.17). The $E_{\text{max}}$ in subjects with a positive family history of hypertension was 75.8%±19.69% and in those without was 73.58%±17.05% (P=0.73).

Our goal was to study vascular sensitivity locally while minimizing the contribution of systemic reflex responses. No systemic effects were observed during the dexmedetomidine infusion up to and including the 100-ng/min dose. Systolic blood pressure, diastolic blood pressure, heart rate, and norepinephrine plasma concentrations at the beginning of the study and at the end of the 100-ng/min dexmedetomidine dose were not significantly different (Table 2), confirming the lack of systemic effects. After the 1000 ng/min, heart rate did not change significantly, as compared with baseline (P=0.2); however there was a trend toward a lower systolic blood pressure (105.1±9.7 mm Hg, P=0.087) and diastolic blood pressure (56.8±9.2 mm Hg, P=0.07), and there was a significant decrease in plasma norepinephrine concentration (111.3±51.1 pg/mL compared with 169.0±62.5 pg/mL, P=0.006).

Our study had 90% power to detect 1 log unit difference in $E_{D_{50}}$ and 92% power to detect a difference of 20% in $E_{\text{max}}$, with a 2-tailed probability value of 0.05. Considering the 3 log unit variability in $E_{D_{50}}$ among individuals, this therefore excludes a difference that is likely to be physiologically significant.

### Discussion

The new findings of this study are first, that $\alpha_2$-AR vascular sensitivity is not significantly different in blacks and whites, and, second, that the highly selective $\alpha_2$-AR agonist dexmedetomidine causes pronounced dose-dependent constriction in the human hand vein, thus providing a model that allows the study of vascular $\alpha_2$-AR–mediated responses in vivo in humans.

The predominant hemodynamic effect resulting from the systemic administration of a $\alpha_2$-AR agonist is a decrease in blood pressure and is mediated through the activation of central $\alpha_2$-AR receptors, resulting in inhibition of sympathetic activity. These effects tend to mask the hemodynamic responses such as increased blood pressure that would result from vasoconstriction mediated by peripheral vascular $\alpha_2$-ARs in response to an agonist. Thus, to study $\alpha_2$-AR vascular sensitivity directly, it was necessary to minimize the effects on blood pressure and norepinephrine that occur after the systemic administration of an $\alpha_2$-AR agonist. The hand vein technique we used allows the measurement of vascular response independent of systemic reflexes, since extremely low doses that act mainly on the segment of vessel studied are administered. This technique has been previously used to define the vascular pharmacology of a wide range of drugs.

### Table 2. Systolic and Diastolic BP, Heart Rate, and Plasma NE at Baseline and After Dexmedetomidine Dose

<table>
<thead>
<tr>
<th>Measure</th>
<th>Baseline</th>
<th>Dexmedetomidine, 100 ng/min</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP, mm Hg</td>
<td>110±10.3</td>
<td>110.2±9.1</td>
<td>0.88</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>61.2±8.42</td>
<td>61.6±8.8</td>
<td>0.66</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>60.7±9.5</td>
<td>59.4±8.3</td>
<td>0.20</td>
</tr>
<tr>
<td>Plasma norepinephrine, pg/mL</td>
<td>169±62.5</td>
<td>165.3±66.4</td>
<td>0.69</td>
</tr>
</tbody>
</table>

Data are presented as mean±SD; n=37.
including adrenergic vasodilators and vasoconstrictors, but study of the $\alpha_2$-AR in vivo has been hampered by the lack of an potent and selective agonist.

Several investigators have used clonidine to study human vascular $\alpha_2$-AR responses. However, the relatively low $\alpha_2$-AR/$\alpha_1$-AR selectivity ratio of clonidine results in unwanted $\alpha_1$-AR partial agonist effects that confound the measurement of $\alpha_2$-AR responses. Indeed, perhaps because of its partial $\alpha_1$-AR agonist activity, the coinfusion of clonidine into a hand vein preconstricted with an $\alpha_1$-AR agonist, phenylephrine, reversed the venoconstriction caused by phenylephrine from 81% to 46%, instead of increasing vasoconstriction, as would be expected if it acted as an $\alpha_2$-AR agonist. These partial agonist effects of clonidine also reduced the vasoconstriction induced by norepinephrine by 12%. For these reasons, the role of clonidine as a tool for studying $\alpha_2$-AR regulation of vascular reactivity is limited.

To overcome the multiple limitations of systemic administration of clonidine as a tool for examining $\alpha_2$-AR vascular responses, we explored the use of dexmedetomidine to study the local vascular effects of $\alpha_2$-AR activation. Dexmedetomidine, with an $\alpha_2$-AR/$\alpha_1$-AR selectivity ratio of 1620:1, is approximately 8-fold more selective and therefore provides a novel tool for the study of $\alpha_2$-AR responses in vivo. We found that dexmedetomidine resulted in dose-dependent venoconstriction in the hand vein model, with a maximum of approximately 75%, which is greater than the maximum responses reported with clonidine (27% to 54%). The more specific $\alpha_2$-AR agonist, azepexol (52% to 68%), reduced the vasoconstriction induced by norepinephrine.

The sensitivity to dexmedetomidine among individuals varied considerably, resulting in a $>1000$-fold range in ED$_{50}$. However, venous sensitivity in blacks and whites did not differ, indicating that increased $\alpha_2$-AR sensitivity in blacks is unlikely to explain our previous observation that the reduction in blood pressure after clonidine was attenuated in blacks. Furthermore, the findings of the present study, considered with the results of the previous study that showed a similar decrease in norepinephrine spillover after clonidine in blacks and whites, do not support the hypothesis that presynaptic or postsynaptic $\alpha_2$-ARs are likely to be major contributors to ethnic differences in blood pressure regulation. Therefore, the previous observation that blood pressure responses to clonidine are blunted in blacks may be explained by ethnic differences in other mechanisms of vascular control, such as differences in $\alpha_1$-AR sensitivity, which we have previously shown using phenylephrine, an $\alpha_1$-AR agonist, infused into the brachial artery.

The infusion of incremental doses of dexmedetomidine, 0 to 100 ng/min, resulted in a cumulative dose of 1.34 $\mu$g, 20-fold lower than doses used in studies examining the systemic effects of dexmedetomidine. The cumulative dose of dexmedetomidine administered during the 0 to 100 ng/min part of the hand vein study did not alter blood pressure, heart rate, or plasma norepinephrine concentration, suggesting that there were little or no systemic effects. However, expanding the dose response to include 3 additional doses (250, 500, and 1000 ng/min) resulted in a cumulative dexmedetomidine dose of 12.25 $\mu$g and a significant decrease in plasma norepinephrine concentrations, indicating a systemic effect. Our findings suggest that a dose range of dexmedetomidine spanning 0 to 100 ng/min can be used to define the hand vein response without systemic effects.

We assessed vascular responses by measuring changes in the diameter of a hand vein and thus cannot directly extrapolate our results to other vascular tissues. The constriction of resistance and capacitance vessels is mediated by both $\alpha_1$- and $\alpha_2$-ARs, whereas terminal arterioles and veins may be more affected by postjunctional $\alpha_2$-ARs. Indeed, in young, healthy subjects, $\alpha_2$-ARs were reported to contribute to limb vascular tone more than $\alpha_1$-ARs. The hand vein model, however, is useful in defining agonist-receptor relations in vivo while minimizing the effects of systemic exposure to agonists and the potentially confounding reflex responses. In addition, $\alpha_2$-AR venous response is important in its own right, since as the chief capacitance compartment, the venous bed has profound effects on cardiac filling, which in turn is an important determinant of cardiac output, especially in patients with heart failure.

In summary, we have shown that the infusion of low-dose dexmedetomidine causes pronounced constriction in the human hand vein, confirming the importance of the $\alpha_2$-AR in producing vasoconstriction. Our data indicate that $\alpha_2$-AR vascular responses are similar in blacks and whites and are therefore unlikely to play a role in the previously described ethnic differences in vascular reactivity. Previously described ethnic differences in $\alpha_2$-AR sensitivity may therefore explain the blunted response to clonidine in blacks. The role and regulation of peripheral $\alpha_1$-AR activity in maintaining and altering vascular tone is not clear; the response to the selective $\alpha_2$-AR agonist dexmedetomidine in the human hand vein provides a model that will allow further study of the regulation of $\alpha_2$-AR-mediated vascular responses.

Acknowledgments

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References


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