Effects of Long-term Clonidine Administration on the Hemodynamic and Neuroendocrine Postural Responses of Patients with Dysautonomia*

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Patients with mitral valve prolapse syndrome (MVPs), vasoregulatory asthenia, and poor postural adjustment often have orthostatic intolerance characterized by tachycardia and a narrow pulse pressure on standing. Autonomic dysfunction is thought to play an important role. Increased α-adrenergic activity has been shown in MVPs patients with orthostatic intolerance. We measured hemodynamic and neuroendocrine responses to long-term oral clonidine therapy in eight women, aged 36 ± 1.5 years (27 to 44 years). None had responded favorably to β-blockers. Heart rate, blood pressure, oxygen consumption, cardiac output, and plasma norepinephrine levels were measured in both supine and standing positions, before and after one to four weeks of clonidine (0.3 to 0.4 mg daily). Clonidine reduced standing plasma norepinephrine levels, total peripheral resistance, and diastolic blood pressure; a smaller decrease in cardiac output on standing was noted. Plasma volumes increased 12 percent. Mild reductions in plasma catecholamines and total peripheral resistance are associated with fewer, not more, orthostatic symptoms in this group of patients. "Placebo" or mild sedative effects may explain part of the response to clonidine, but the hemodynamic and neuroendocrine data suggest that decreased α-adrenergic hyperactivity may also be important.

Recent work by our group1,4 and work by Coghlan et al5 has demonstrated the presence of autonomic nervous system dysfunction in patients with mitral valve prolapse syndrome (MVPs). Specifically, we documented in women with MVPs and symptoms of orthostatic intolerance the presence of increased α-adrenergic activity both at rest and during orthostatic stress. These MVPs patients also had diminished baroreflex responsiveness when tested with an infusion of phenylephrine. Despite these abnormalities, systemic arterial blood pressures at rest supine tended to be in the lower range of normal, with a reduced pulse pressure.

On standing, MVPs patients often have excessive tachycardia and markedly elevated plasma norepinephrine levels.4,5 This has led some authors to postulate the presence of a hyperkinetic circulatory state and to recommend treatment with propranolol. However, our measurements of standing stroke volume and cardiac output in MVPs patients clearly show that these patients are not hyperkinetic. Stroke volume is diminished, and cardiac output is low or normal. These hemodynamic observations are consistent with the findings of

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Table 1—Characteristics of Patients and Controls*

<table>
<thead>
<tr>
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<th>Patients (n = 8)</th>
<th>Controls (n = 12)</th>
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</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>35 ± 1.7</td>
<td>27 ± 1.2</td>
</tr>
<tr>
<td>(27–44)</td>
<td>(22–37)</td>
<td></td>
</tr>
<tr>
<td>Height, cm</td>
<td>166 ± 2.0</td>
<td>169 ± 2.0</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>58.5 ± 4.0</td>
<td>59.4 ± 2.1</td>
</tr>
</tbody>
</table>

*All were women.

Erbel et al,7 who failed to demonstrate symptomatic improvement of MVP patients when treated with β-blockers. For these reasons, we have measured the neuroendocrine and hemodynamic responses to clonidine of patients with increased α-adrenergic activity and orthostatic intolerance.

**Materials and Methods**

Patients were eight women, aged 27 to 44 years, who had orthostatic intolerance despite substantial increases in heart rate, plasma norepinephrine levels, and total peripheral resistance on standing (Table 1). Five of the eight had classic echocardiographically and phonocardiographically documented MVP. Three others had been referred with a diagnosis of MVP based on physical examination, but did not have diagnostic M-mode or two-dimensional echocardiograms, despite an otherwise identical presentation of a hyperadrenergic orthostatic intolerance. All had failed to respond favorably to treatment with β-blocking agents previously, but had not been taking any medication for at least two weeks prior to study.

Controls were 12 healthy sedentary adult women, aged 22 to 32 years. All were employees or students at the University of Texas Health Science Center, were taking no medications, and were nonsmokers.

Prior to the study, all subjects and controls were familiarized with the laboratory procedures and equipment, and informed written consent was obtained for the protocol previously approved by the Institution's Human Research Review Committee. Initial supine and standing hemodynamic and neuroendocrine measurements were then carried out concurrently in both patients and controls.

An indwelling needle was placed in an antecubital vein, and the subject then rested 30 minutes in the supine position. Plasma volume was determined by Evans blue indicator dilution technique6 and plasma norepinephrine levels by a radioenzymatic method described previously.8 Cardiac output was measured by an acetylene rebreathing technique.9 This method has been validated in our laboratory in normal subjects by comparisons with simultaneous indocyanine green indicator dilution cardiac outputs. A correlation coefficient of 0.94 with a coefficient of variation of 4.7 percent was obtained over the range of 4 to 19 L/min. Oxygen consumption was measured by a modification of the rebreathing technique. Heart rate was obtained by a continuously recorded ECG, and blood pressure was measured with an automated cuff device (Narco Biosystems PE-300).

Following pretreatment studies, patients were given clonidine 0.05 mg orally at bedtime for two to three days, and the dosage was increased every two days until 0.4 mg/day was achieved or side effects occurred. The patients were told they were receiving an antihypertensive drug that may have some beneficial effects on their symptoms. No placebo was given, nor was the drug administered to the normal controls. Hemodynamic and catecholamine measurements were repeated in seven patients after at least one month of therapy. The eighth patient was studied at one week because she was unable to return at the later, planned interval.

**Results**

The patients generally tolerated the clonidine administration, although all complained of dry mouth and sedation. Two

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Patients stopped the medication after the study because of these side effects. The other six requested continuation of the medication because it seemed to decrease their symptoms.

The objective measurements obtained in the study are shown in Figure 1. Pretreatment arterial pressures at rest supine were higher in the patient group, but normalized with clonidine (p<0.02). Supine heart rates tended to decrease with clonidine (0.05<p<0.10), but standing heart rates were identical. Supine peripheral resistance tended to be higher (p=0.06) in the patients before clonidine and was even higher after standing (p<0.01). On standing, the marked rise in peripheral resistance was blunted by clonidine, but still remained somewhat above that of controls. Cardiac output supine was similar for patients and controls pretreatment and fell with treatment (p<0.02). A smaller orthostatic drop was noted after clonidine treatment (p<0.02). The wider AV-O₂ difference in the patients on standing (6.7 ± 0.4 vs 5.3 ± 0.5, vol% p<0.04) was not changed with clonidine. Plasma norepinephrine appeared to decrease after clonidine, although the drop was not statistically significant. Plasma volumes (normalized with respect to height) were significantly lower in the patients pretreatment (16.2 ± 0.8 vs 19.6 ± 0.8 ml/cm, p<0.01) and increased with clonidine to 18.2 ± 1.1 ml/cm.

**DISCUSSION**

Pretreatment, the patients had an increased α-adrenergic responsiveness to orthostatic stress demonstrated by an increased total peripheral resistance and an overshoot in arterial pressure despite significant falls in stroke volume and cardiac output. Their plasma norepinephrine levels tended to be higher and plasma volumes lower.

Clonidine, in small doses, was associated with subjective, symptomatic improvement in six of eight patients. This was accompanied by a decrease in the vasoconstrictor response to standing and with a smaller orthostatically induced fall in cardiac output. Those findings are consistent with previously published work by Onesti et al. who showed that clonidine, administered short-term, produces a fall in resting cardiac output, little or no decrease in supine peripheral resistance, and no orthostatic intolerance. Bonde-Petersen et al. also recently demonstrated that clonidine can prevent the orthostatic intolerance induced by prolonged head-down tilt. The mechanism(s) by which these hemodynamic changes are produced is not known, but there are several possibilities.

A local, central or combined effect of clonidine on baroreflexes has been demonstrated in animals. We have previously demonstrated diminished baroreflex sensitivity in a group of women with MVPs. However, the mechanism whereby clonidine may induce favorable changes in the baroreflex responses is not immediately apparent. Our previous data indicate that the heart rate response to phenylephrine-induced increases in arterial pressure is blunted, whereas the vasoconstrictor response to orthostatic stress is enhanced. This combination of findings does not completely rule out an abnormality of the baroreceptors, but the afferent pathway, but it seems more likely that the dysfunction primarily involves the cardiovascular control centers, efferent pathways, or the effecter organs. Improved cardiac vagal effects may have had a positive role, but vagal function, known to be abnormal in MVPs patients, was not tested in this study. The increase in plasma volume may also be important, since even smaller alterations have been associated with changes in orthostatic tolerance in normal subjects. The cause of the increase in plasma volume is not known, although alterations in sodium excretion or capacitance vessel tone could explain the findings.

In summary, administration of clonidine in low doses to women with hyperadrenergic orthostatic intolerance resulted in both symptomatic and hemodynamic improve-
ACKNOWLEDGMENTS: The authors wish to acknowledge Mr. Willie E. Moore, Jr, for technical assistance, Mr. Kent Dana for statistical advice, and Mrs. Carolyn Donahue for secretarial assistance in preparing this manuscript.

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