Cardiac and Systemic Sympathetic Activity in Response to Clonidine in Human Heart Failure

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Objectives. We studied the effects of clonidine on cardiac sympathetic activity and left ventricular function in patients with congestive heart failure (CHF).

Background. Sympathetic activation has major prognostic implications in patients with heart failure. Clonidine, an imidazoline and alpha2-receptor agonist, has been shown to cause a reduction in generalized sympathetic activity.

Methods. Nine patients with CHF (left ventricular ejection fraction 22 ± 4% [mean ± SEM]) received a 50 μg and 100 μg bolus of clonidine intravenously. Study measurements included right and left heart hemodynamics, cardiac output, rate of rise in left ventricular peak positive pressure (LV +dP/dt) and tau, along with cardiac and total body norepinephrine spillover. The radiotracer method was used for calculation of norepinephrine spillover.

Results. Right and left heart filling pressures did not change in response to either dose of clonidine. Mean arterial pressure fell after the second dose of clonidine, from 94 ± 8 to 82 ± 6 mm Hg (p < 0.05). The LV +dP/dt was reduced from 737 ± 53 to 629 ± 43 mm Hg/s (p < 0.05). Clonidine also caused a significant increase in tau, as measured by the method of Weiss (65 ± 3 vs. 74 ± 4 ms, p < 0.01) and the direct pressure half-time technique (48 ± 2 vs. 54 ± 3 ms, p < 0.01). Cardiac norepinephrine spillover fell from 121 ± 29 to 52 ± 20 pmol/min in response to 100 μg of clonidine (p < 0.01 vs. control).

Conclusions. Despite a significant fall in arterial pressure, clonidine caused a marked reduction in sympathetic activity directed at the heart. The negative inotropic and lusitropic effects appear to be secondary to this reduction in sympathetic drive. Because increased cardiac and generalized sympathetic activity are strong predictors of an adverse outcome in patients with CHF, the role of centrally active sympathoinhibitory agents in the therapy of CHF deserves further exploration.

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Sympathetic activation is a hallmark neurohormonal abnormality in patients with congestive heart failure (CHF), which has major prognostic implications (1,2). Importantly, this increase in sympathetic outflow is not uniform, with the greatest increase directed at the heart (3). In the setting of CHF this increase in cardiac sympathetic activity has been shown to be a strong predictor of clinical outcome (2). Some adverse effects of increased sympathetic outflow directed at the heart include desensitization and downregulation of cardiac beta-adrenergic receptors (4), impairment of myocardial function and viability (5) and a predisposition to ventricular arrhythmias (6).

Therapy of patients with CHF with beta-adrenergic receptor blockade provides evidence that the inhibition of the effects of sympathetic activation is beneficial in this disease (7,8). Indeed, therapy with a beta-blocker is increasingly common as part of the standard medical regimen of patients with CHF.

Importantly, beta-blockers, while inhibiting beta-adrenergic receptors in the neuroeffector junction, may not reduce efferent sympathetic outflow (9). Furthermore, they do not antagonize other compounds released at adrenergic nerve terminals, such as dopamine and neuropeptide Y (10). Therefore, some investigators have suggested that direct inhibition of central sympathetic outflow might be an effective therapeutic approach in the therapy of heart failure (11,12).

Clonidine is a potent sympatholytic drug with central and peripheral effects. Its mechanisms of action are not completely understood, although it does involve stimulation of alpha2-adrenergic and/or imidazoline receptors in the central nervous system, causing inhibition of sympathetic outflow (13,14). Clonidine also has peripheral effects, including both prejunctional and postjunctional alpha2-adrenergic stimulation, although there is considerable controversy regarding the relative importance of these actions (15,16).

We hypothesized that clonidine would reduce sympathetic activity directed at the heart in patients with CHF. Using the radiotracer method of Esler et al. (3), we measured cardiac and total body norepinephrine spillover in response to the acute administration of clonidine in patients with heart failure. To document the effects of sympathetic withdrawal on left ventricular (LV) performance, direct measurements of LV...
pressure were obtained using a micromanometer-tipped catheter.

Methods

Patient characteristics. Nine patients with CHF secondary to dilated cardiomyopathy participated in the study. The etiology of the LV dysfunction was ischemic in seven andidiopathic in two patients. Eight patients were men (mean age 58 ± 4 years). All patients were in New York Heart Association functional class II and III and had an ejection fraction by radionuclide angiography of ≤35% (mean 22 ± 4%). Medical therapy included angiotensin-converting enzyme inhibitors and diuretic agents (n = 9), digoxin (n = 8), nitroglycerin (n = 5) and amiodarone (n = 2). None of the patients were taking beta-blockers. All medications were held on the morning of the study. The protocol was approved by the Ethical Review Committee for Human Experimentation of the University of Toronto. Written informed consent was obtained from all patients.

Hemodynamic and coronary flow measurements. A diagnostic right and left heart catheterization was performed, without sedation. A pulmonary artery catheter was left in place after the diagnostic procedure. A 7F coronary sinus thermocatheter (type CCS-7U-90B, Webster Laboratories) was inserted from an antecubital vein and positioned in the coronary sinus for flow measurements and blood sampling. A 7F micromanometer-tipped catheter (Millar Industries) was positioned in the LV for assessment of contractility (rate of rise in LV peak positive pressure [dP/dt]), relaxation (tau) and LV end-diastolic pressure. The time constant of isovolumic relaxation was determined in two different ways using techniques previously described by our group (17). The first method is a modification of that described by Weiss et al. (18), such that tau (T1) is equal to –1/slope of the regression line for the natural logarithm of LV pressure versus time for the period from –dP/dt to 5 mm Hg above LV end-diastolic pressure. The second method is the direct measurement of the pressure half-time (T1/2), as described by Mirsky (19). With this method tau is measured directly, as the time required for LV pressure to fall to one-half of its value at –dP/dtmax. Left ventricular pressure and the electrocardiogram (ECG) were digitally recorded at 300 Hz using a Macintosh personal computer equipped with a multichannel analogue to digital converter. Data files were stored to disc for later analysis. Using customized software developed in Labview (Version 3.0, National Instruments Corporation, Austin, Texas), tau was calculated off-line using identical methods to those described earlier. Femoral artery pressure was monitored from an 8F side-arm sheath (Cordis Laboratories). Cardiac output was measured by the Fick method. The ECG, right atrial pressure, pulmonary artery pressure, femoral artery pressure and LV pressure and its first derivative (continuous electronic differentiation) were recorded on a strip-chart recorder. For each variable, the results were expressed as an average measurement of 10 cardiac cycles in patients with sinus rhythm, and 15 cardiac cycles in patients with atrial fibrillation (n = 2). Coronary sinus blood flow measurements were performed in duplicate at each measurement point according to the method of Ganz et al. (20). All hemodynamic and blood flow analyses were performed by a technician who had no knowledge of the experimental condition.

Norepinephrine spillover measurements. Sympathetic activity was estimated by the measurement of cardiac and total body norepinephrine spillover (3). For these measurements, tritiated norepinephrine (1 to 1.2-μCi/min with a 16-μCi priming bolus of L-[2,5,6-3H] norepinephrine; New England Nuclear) was infused into the femoral vein to steady-state concentration in plasma. Norepinephrine clearance and spillover rates were calculated as follows (21):

\[
\text{Total body norepinephrine clearance (liters/min)} = \frac{[3H\text{NE infusion rate}}{\text{Arterial plasma [3H\text{NE concentration}}}
\]

\[
\text{Total body norepinephrine spillover (nmol/min)} = \frac{[3H\text{NE infusion rate}}{\text{Plasma NE specific activity}}
\]

Cardiac norepinephrine spillover (pmol/min)

\[
= [\text{NE_{cs}} - \text{NE_{art}} + (\text{NE_{ext} \times \text{NE_{art}}})] \times \text{CSPF}
\]

where \([3H\text{NE}\) indicates tritium-labeled norepinephrine; \(\text{NE_{ext}} = \text{transcardiac fractional extraction of tritium-labeled norepinephrine}; \text{NE_{cs}} \text{and } \text{NE_{art}} = \text{coronary sinus and arterial plasma norepinephrine concentrations, respectively; and } \text{CSPF} = \text{coronary sinus plasma flow.}\)

Analysis of plasma catecholamines. Catecholamine concentrations were measured with high performance liquid chromatography (HPLC) (9,22,23). Fractions from the HPLC effluent containing tritium-labeled norepinephrine were assayed by liquid scintillation spectroscopy. The detection limit of the method was ±0.1-μmol/liter, and the peak area was linear from 0.1 to 50-μmol/liter. Intra-assay (n = 8) and interassay (n = 14) coefficients of variation were 1.7% and 2.3%, respectively, for the determination of endogenous norepinephrine. The biochemical analyses were performed by personnel who had no knowledge of the experimental conditions.
Figure 1. Hemodynamic responses to 50 and 100 µg of clonidine. The only hemodynamic variable that changed in response to 50 µg of clonidine was femoral artery diastolic pressure, which decreased from 73 ± 6 to 66 ± 6 mm Hg (p < 0.05 vs. control). There was no change in heart rate, filling pressures, femoral artery systolic pressure or cardiac index.

The second 100-µg dose of clonidine (150-µg cumulative dose) caused a more significant hemodynamic response. Femoral artery systolic pressure was reduced from 136 ± 13 to 119 ± 9 mm Hg and femoral artery diastolic pressure fell from 73 ± 6 to 63 ± 5 mm Hg (p < 0.05 vs. control, for both). Mean pulmonary artery pressure was reduced from 29 ± 2 to 26 ± 2 mm Hg (p < 0.05 vs. control); however, no change in LV end-diastolic pressure, right atrial pressure or cardiac index was observed. There was a small but significant reduction in heart rate (from 75 ± 3 to 69 ± 3 beats/min, p = 0.05 vs. control).

Effects of clonidine on left ventricle isovolumic performance indexes (Table 1, Fig. 1). Intravenous clonidine was associated with a negative inotropic and lusitropic response. There was a highly significant decrease in +dP/dt (from 737 ± 36 to 629 ± 43 mm Hg/s, control vs. clonidine 100 µg, p < 0.05). Clonidine also caused a highly significant decrease in the rate of LV isovolumic relaxation as measured by T 1/2 (from 65 ± 3 to 70 ± 4 ms, control vs. clonidine 100 µg, p < 0.01), and by T 1/2 (from 48 ± 2 to 51 ± 2 ms, control vs. clonidine 100 µg, p < 0.01).

Cardiac and generalized sympathetic responses (Table 2, Fig. 2 and 3). Clonidine caused a dose-related reduction in cardiac norepinephrine spillover. In response to the first dose of clonidine (50 µg), cardiac spillover decreased from 121 ± 29

### Table 1. Hemodynamic Responses to Clonidine

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>50 µg</th>
<th>100 µg</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats/min)</td>
<td>75 ± 3</td>
<td>75 ± 3</td>
<td>69 ± 3*</td>
</tr>
<tr>
<td>RA (mm Hg)</td>
<td>10 ± 1</td>
<td>9 ± 1</td>
<td>9 ± 1</td>
</tr>
<tr>
<td>MPAP (mm Hg)</td>
<td>29 ± 2</td>
<td>29 ± 2</td>
<td>26 ± 2*</td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>22 ± 2</td>
<td>22 ± 2</td>
<td>21 ± 3</td>
</tr>
<tr>
<td>FA peak (mm Hg)</td>
<td>136 ± 13</td>
<td>131 ± 12</td>
<td>119 ± 9*</td>
</tr>
<tr>
<td>FA (mm Hg)</td>
<td>73 ± 6</td>
<td>66 ± 6*</td>
<td>63 ± 5*</td>
</tr>
<tr>
<td>FA mean (mm Hg)</td>
<td>94 ± 8</td>
<td>88 ± 7</td>
<td>82 ± 6*</td>
</tr>
<tr>
<td>CI (liters/min per m²)</td>
<td>2.1 ± 0.2</td>
<td>2.0 ± 0.2</td>
<td>2.0 ± 0.2</td>
</tr>
<tr>
<td>LV +dP/dt (mm Hg/s)</td>
<td>737 ± 53</td>
<td>709 ± 48</td>
<td>629 ± 43*</td>
</tr>
<tr>
<td>T1 (ms)</td>
<td>65 ± 3</td>
<td>70 ± 4*</td>
<td>74 ± 4t</td>
</tr>
<tr>
<td>T1/2 (ms)</td>
<td>48 ± 2</td>
<td>51 ± 2*</td>
<td>54 ± 3t</td>
</tr>
</tbody>
</table>

*p < 0.05 versus control. †p < 0.01 versus control. CI = cardiac index; FA peak = femoral artery systolic pressure; FA mean = mean femoral artery pressure; FA = femoral artery diastolic pressure; HR = heart rate; LVEDP = left ventricular end-diastolic pressure; LV +dP/dt = rate of rise in left ventricular peak positive pressure; MPAP = mean pulmonary artery pressure; TL = pressure half-time; T1 = time constant of isovolumic relaxation (tau).

Study protocol. After the diagnostic heart catheterization and insertion of catheters for hemodynamic monitoring, the patient was left undisturbed for a minimum of 20 min and until tritium-labeled norepinephrine reached steady-state concentration in the plasma. Hemodynamic and coronary blood flow measurements were then performed along with measures of total body and cardiac norepinephrine spillover (control measurements). Subsequently, patients were given a 50-µg bolus of clonidine intravenously, and after 20 min, hemodynamic, coronary blood flow and neurochemical measurements were repeated. Patients were then given a second dose of clonidine (100 µg bolus), and hemodynamic and catecholamine measurements were once again repeated after 20 min. The purpose of the initial 50-µg dose was to ensure that the drug was well tolerated and to examine the impact of the drug on sympathetic activity in the absence of major changes in systemic blood pressure. With the second 100-µg bolus, the cumulative dose of clonidine administered was 150 µg. Because clonidine is nearly 100% bioavailable (24), we thought that this dose was representative of the typical starting dose of oral clonidine.

Statistical analysis. Comparisons of the effect of clonidine on hemodynamic variables, catecholamine concentrations and norepinephrine kinetics were made by one-way repeated measures analysis of variance. A Bonferroni correction was applied for multiple comparisons. All data are presented as the mean value ± SEM.

### Results

Baseline hemodynamic variables (Table 1). This study enrolled nine patients with moderately severe CHF. Filling pressures were elevated—mean right atrial pressure 10 ± 1 mm Hg and LV end-diastolic pressure 22 ± 2 mm Hg. The cardiac index was depressed at 2.1 ± 0.2 liters/min per m².
Table 2. Neurochemical and Flow Responses to Clonidine

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Clonidine 50 µg</th>
<th>Clonidine 100 µg</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEart (pmol/ml)</td>
<td>1.5 ± 0.3</td>
<td>1.2 ± 0.3</td>
<td>1.2 ± 0.2*</td>
</tr>
<tr>
<td>NEext (%)</td>
<td>66 ± 4</td>
<td>69 ± 4</td>
<td>69 ± 3</td>
</tr>
<tr>
<td>CSBF (ml/min)</td>
<td>143 ± 35</td>
<td>118 ± 21</td>
<td>109 ± 19</td>
</tr>
<tr>
<td>TBNESCL (l/min)</td>
<td>2.11 ± 0.17</td>
<td>2.04 ± 0.18</td>
<td>1.82 ± 0.17</td>
</tr>
<tr>
<td>TBNESP (nmol/min)</td>
<td>2.98 ± 0.66</td>
<td>2.32 ± 0.56*</td>
<td>1.45 ± 0.36†</td>
</tr>
</tbody>
</table>

* p < 0.05 versus control. †p < 0.01 versus control. CANESP = cardiac norepinephrine spillover; CSBF = coronary sinus blood flow; NEart = arterial plasma norepinephrine; NEext = coronary sinus plasma norepinephrine; NEuni = cardiac extraction of norepinephrine; TBNESCL = total body norepinephrine clearance; TBNESP = total body norepinephrine spillover.

to 79 ± 26 pmol/min (p < 0.05 vs. control). The second dose of clonidine (100 µg) caused an additional fall in cardiac spillover to 52 ± 20 pmol/min (p < 0.01 vs. control).

Similar to the change in cardiac norepinephrine spillover, there was a significant decrease in the plasma norepinephrine concentration gradient measured across the heart (coronary sinus concentration minus arterial concentration). The first dose of clonidine caused a reduction in the transcardiac norepinephrine gradient (p = NS). With the second dose the transcardiac gradient decreased from 1.0 ± 0.3 to 0.4 ± 0.2 pmol/ml (control vs. clonidine 100 µg, p < 0.05).

The first dose of clonidine caused a significant reduction in total body norepinephrine spillover from 2.98 ± 0.66 to 2.32 ± 0.56 nmol/min (p < 0.05 vs. control). There was an additional reduction to 1.45 ± 0.36 nmol/min (p < 0.01 vs. control) in response to the second dose of clonidine. There was no significant change in total body clearance of norepinephrine.

**Discussion**

To our knowledge, this is the first report to examine the effects of clonidine on cardiac sympathetic activity in humans. We have demonstrated that clonidine has potent inhibitory effects on cardiac-specific sympathetic outflow. After a total intravenous dose of 150 µg of clonidine, there was a 59 ± 9% reduction in cardiac norepinephrine spillover. This cardiac sympathoinhibitory effect was much larger than that observed with other agents used in the treatment of CHF, including digoxin and beta-adrenergic blockers (9,22). The results of the present study are consistent with those reported by Lang et al. (12), who found that clonidine significantly reduced total body norepinephrine spillover in patients with heart failure. Similarly, they are consistent with observations that clonidine reduces plasma norepinephrine in patients with heart failure (25,26). Importantly, the decrease in cardiac sympathetic activity that we have documented could not have been inferred from the systemic inhibitory responses, because we (23) and other investigators (21) have shown that cardiac sympathetic responses can be divergent from those observed in the periphery.

A unique feature of this investigation was the simultaneous measurement of cardiac sympathetic activity and LV isovolumic performance. This allowed us to evaluate the effect of sympathetic withdrawal on +dP/dt and tau in patients with CHF. Although previous investigations have demonstrated negative inotropic and lusitropic responses during acute beta-adrenergic receptor blockade (27), these responses may have been modified by a reflex increase in central sympathetic outflow (9).

**Inotropic effects.** The administration of clonidine was associated with important decreases in +dP/dt, a finding which we believe documents the dependency of ventricular contractility on sympathetic outflow in the setting of heart failure. Clonidine did cause a significant reduction in systemic arterial blood pressure, a hemodynamic effect that may also have caused a reduction in +dP/dt (28). Importantly, work from our laboratory (23) and that of others (29) has shown that similar reductions in arterial pressure had no effect on +dP/dt in the setting of heart failure. Although this suggests that clonidine had negative inotropic effects, it is possible that the decrease in

**Figure 2.** Cardiac norepinephrine spillover (CANESP) and total body norepinephrine spillover (TBNESP) at control values and in response to 50 and 100 µg of clonidine. *p < 0.05 versus control. †p < 0.01 versus control. Data are expressed as the mean value ± SEM.

**Figure 3.** Arterial (open bars) and coronary sinus (solid bars) plasma norepinephrine at control values and in response to 50 and 100 µg of clonidine. There is a significant reduction in the transcardiac gradient of plasma norepinephrine in response to 100 µg of clonidine. This results from a significantly greater decrease in the coronary sinus plasma norepinephrine level as compared with the arterial plasma norepinephrine level. *p < 0.05 versus control. †p < 0.01 versus control. ‡p < 0.05 for comparison between the norepinephrine transcardiac gradient (coronary sinus – arterial) with 100 µg of clonidine and control level. Data are expressed as the mean value ± SEM.
heart rate and afterload, along with potential changes in preload, may have contributed to some, or all, of the observed reduction in \( +\text{dP/dt} \).

**Lusitropic effects.** Clonidine was also associated with a negative lusitropic effect. This occurred despite a significant fall in systemic arterial pressure, a hemodynamic effect that would have been expected to cause an acceleration in the rate of isovolumic relaxation (30), particularly in patients with heart failure (31). Tau has been shown to be sensitive to changes in preload, particularly in patients with heart failure and in those with heart failure (23). Further, with the 50-\( \mu \)g dose of clonidine, there was a significant prolongation in tau in the absence of a change in heart rate. Therefore, we believe that the 50 \( \mu \)g dose of clonidine had a direct negative lusitropic effect. With the 100 \( \mu \)g dose, there was a further increase in tau. After this dose, however, there was a significant decrease in heart rate, an effect that may have made some contribution to the observed increase in tau.

**Sympathoinhibitory effects.** The results of this investigation have potential clinical relevance to the use of sympatholytic agents in CHF. First, we have demonstrated that the potent sympathoinhibitory effects of clonidine were well tolerated. The decrease in blood pressure was moderate, and no patient was symptomatic as a result. Despite the significant fall in \( +\text{dP/dt} \) and increase in tau, LV filling pressure did not rise and the cardiac index was maintained. We believe that this tolerability of clonidine is mainly a result of the reduction in afterload caused by the drug. It is important to recognize that the sympathoinhibitory effect of clonidine was observed despite a significant fall in arterial blood pressure, a hemodynamic response that is classically associated with a reflex increase in sympathetic outflow, both in patients with normal ventricular function and in those with heart failure (23). Second, important sympathoinhibition was obtained with small doses of intravenous clonidine. Because clonidine is nearly 100% bioavailable (24), oral doses of 50 to 100 \( \mu \)g should also be associated with significant inhibitory effects on sympathetic outflow. Such doses of clonidine would likely be associated with a lower incidence of side effects than that observed with traditional antihypertensive regimens in which 200 to 600 \( \mu \)g are administered twice daily (24). Finally, although it has been recognized for many years that sympathetic activation in chronic heart failure is a marker for adverse outcome (1), the hypothesis that a central sympathoinhibitory agent would have beneficial effects on clinical outcome in patients with chronic heart failure has yet to be tested. The tolerability of clonidine, as well as the low dose required to reduce cardiac sympathetic outflow, suggests the feasibility of these agents for potential large-scale clinical trials. It should be noted that the potential role of drugs like clonidine in the therapy of heart failure has been recognized for many years. Indeed, Giles et al. (11) suggested this approach for the treatment of heart failure more than 15 years ago.

**Study limitations.** We do not believe that the sympathoinhibitory responses represent the effect of time, because previous studies from our laboratory have demonstrated that both hemodynamic and neurochemical variables remain stable during periods similar to those involved in the present study (22,23). In a recent study involving patients with severe heart failure, we made hemodynamic and neurochemical measurements at baseline and after a 30-min control period. Hemodynamic variables as well as measures of total body and cardiac norepinephrine spillover remained unchanged during this period (22). In another study examining the same variables in patients with heart failure, we demonstrated that control and recontrol measurements made 40 to 50 min apart were not different (23). Therefore, in patients with chronic heart failure, hemodynamic variables and measures of sympathetic activity are stable and reproducible over an observation period similar to that used in the present report. Therefore, we conclude that the hemodynamic and neurochemical changes observed are secondary to the administration of clonidine and are not an effect of time. Finally, these patients were taking a number of medications that may have had inhibitory effects on both cardiac and systemic sympathetic activity. This may have reduced baseline levels of sympathetic activity, which in turn, may have modified sympathetic responses to clonidine. Nevertheless, clonidine still had potent sympathoinhibitory effects, even in this group with treated CHF.

**Clinical implications.** This report is the first to examine the effects of a direct sympathoinhibitory drug on cardiac sympathetic activity in human heart failure. The results demonstrate that the acute administration of clonidine has potent inhibitory effects on cardiac sympathetic activity in patients with stable functional class II or III CHF, and that this effect is well tolerated. Whether the drug would have similar effects and be well tolerated in patients with more severe disease is a question which our study cannot address. Nevertheless, observations made in this study should lead to further investigations examining the effects of long-term therapy with clonidine or other centrally active sympathoinhibitory compounds on both measures of sympathetic activity and clinical outcome. Because increases in central sympathetic outflow appear to have adverse effects in patients with heart failure (2), the use of central sympathoinhibitory agents in the therapy of this condition has strong appeal. In contrast, it is important to remember that a reduction in central sympathetic outflow, in the absence of adrenergic receptor blockade, may be inadequate to protect the heart from the adverse effects of increased adrenergic drive. Therefore, the efficacy of central sympathoinhibition will have to be compared with the effects of adrenergic receptor blockade. Indeed, it is possible that the most effective approach would be a regimen that included both central sympathoinhibition and peripheral adrenergic receptor blockade. The observation made in this study should lead to further investigations examining the effects of long-term therapy with clonidine or other centrally active sympathoinhibitory compounds on both measures of sympathetic activity and clinical outcome.
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References


