Effects of Chronic Clonidine Administration on Sympathetic Nerve Traffic and Baroreflex Function in Heart Failure

Guido Grassi, Carlo Turri, Gino Seravalle, Giovanni Bertinieri, Alberto Pierini, Giuseppe Mancia

Abstract—Congestive heart failure is characterized by a sympathetic activation that is coupled with a baroreflex impairment. Whether these alterations are affected by clonidine is unknown. In 26 normotensive patients age 58.0 ± 1.1 years (mean ± SEM) affected by congestive heart failure (New York Heart Association functional class II or III) and treated with furosemide and enalapril, we measured mean arterial pressure, heart rate, venous plasma norepinephrine, and muscle sympathetic nerve traffic (microneurography) at rest and during baroreceptor stimulation and deactivation caused by stepwise intravenous infusions of phenylephrine and nitroprusside, respectively. Measurements were repeated after a 2-month administration of transdermal clonidine patch (14 patients) or placebo (12 patients) according to a double-blind, randomized sequence. Clonidine caused a slight, nonsignificant reduction in mean arterial pressure and heart rate without affecting exercise capacity and echocardiographically determined left ventricular ejection fraction. In contrast, both plasma norepinephrine and sympathetic nerve traffic were significantly reduced (−46.8% and −26.7%, respectively; P<0.01 for both). This reduction was coupled with no change in cardiac and sympathetic baroreflex responses. Transdermal placebo administration for a 2-month period did not affect any of the above-mentioned variables. Thus, in congestive heart failure patients who are undergoing conventional drug treatment, chronic clonidine administration exerts marked sympathoinhibitory effects without adversely affecting cardiac functions and clinical state. Whether this leads to further therapeutic benefits remains to be tested. (Hypertension. 2001;38:286-291.)

Key Words: nervous system, sympathetic □ nervous system, autonomic □ baroreceptors □ clonidine □ heart failure

Several studies have shown that in congestive heart failure (CHF), survival is inversely related to the degree of sympathetic activation that characterizes this clinical condition.1–4 They have also shown that the reduction in mortality observed with the administration of a number of drugs may be related to sympathetic deactivation, which is thus regarded as a desirable therapeutic goal in all patients in whom cardiac function is impaired.5,6

Sympathetic deactivation in CHF has been documented for ACE inhibitors, digitalis, and β-blockers.3,7–11 Recent observations have shown that in CHF patients, acute administration of clonidine is accompanied by a reduction in norepinephrine (NE) spillover from sympathetic nerve terminals, 12 and plasma NE is markedly reduced after repeated intravenous doses of the drug over a 1-week period.13 The aim of the present study has been to determine the sympathoinhibitory effects of clonidine in CHF under chronic therapeutic conditions and in the context of a controlled experimental design. Sympathetic activity was assessed not only by plasma NE but also by microneurography from a peroneal nerve, which allows direct quantification of sympathetic nerve traffic to the skeletal muscle districts (MSNA).8,9 Baroreflex modulation of MSNA was also studied before and after chronic administration of the drug to investigate whether any drug-induced sympathoinhibition might depend on an enhancement of the reflex inhibitory control, as has been reported for the sympathoinhibition induced by several drugs in CHF8,9,14 and by clonidine in hypertension.15

Methods

Study Population

Our study was performed in 30 patients (22 men, 8 women) with CHF who were undergoing chronic oral treatment with furosemide (25 to 50 mg/d) and an ACE inhibitor (enalapril, 10 mg/d [n=18], quinapril, 10 mg/d [n=4], or captopril, 12.5 mg TID [n=8]). Recruitment criteria were as follows: (1) clinically stable CHF classified as New York Heart Association (NYHA) functional class II or III; (2) no clinical or laboratory evidence of valvular heart disease, renal insufficiency, diabetes mellitus, or other conditions known to impair autonomic function; (3) no history or objective evidence of hypertension; (4) body mass index <27 kg/m²; (5) presence of sinus rhythm; (6) no myocardial infarction or stroke in the preceding 6 months; and (7) no history of excessive alcohol consumption. The CHF condition was ascribed to ischemic heart disease in 21 patients and to nonischemic heart disease in 9 patients.

Measurements

Blood pressure (BP) was measured by (1) a mercury sphygmomanometer, with the first and fifth Korotkoff sounds being taken as markers of systolic and diastolic values, respectively, and (2) a finger photoplethysmographic device (Finapres 2300, Ohmeda) capable of

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providing accurate and reproducible beat-to-beat systolic and dia-
stolic values.8 Heart rate (HR) was continuously monitored by a cardio-
ictohometer triggered by the R wave of an ECG lead. Respi-
ration rate was monitored by a strain-gauge pneumograph positioned
at the midchest level. Measurements included an echocardiogram
performed in M-mode and in B-mode. This allowed us to assess left
ventricular end-diastolic and end-systolic diameters and volumes and
to calculate left ventricular ejection fraction (LVEF) and fractional
shortening.8 Echocardiographic data were collected by a single
operator unaware of the experimental design. The within-operator
coefficients of variation of left ventricular diameters and volume
measurements (ie, within-operator reproducibility) were 5.9% and
5.4%, respectively.

Multifrequency recording of efferent postganglionic MSNA was ob-
tained through a tungsten microelectrode inserted into the right or
left peroneal nerve, as previously described, 8,9 and displayed with
BP, HR, and respiratory movements on thermal paper by an ink
pen. The muscle nature of MSNA was assessed
was accepted only if the signal-to-noise ratio was
9.54%, respectively.

Theophylline (PHE) was increasingly infused through the cannula that
was placed in the antecubital vein at a dose of 0.3, 0.6, and 0.9 µg · kg−1 · min−1. Nitroprusside (NTP) was also infused increasingly in an
antecubital vein at a dose of 0.4, 0.8, and 1.2 µg · kg−1 · min−1. Each
infusion was maintained for 5 minutes, and the drug initially infused
was selected randomly. The end of the first infusion was spaced from
the beginning of the second one by a recovery time of 45 minutes.
Mean BP (diastolic BP plus one third of pulse pressure), MSNA, and
HR were averaged for 5 minutes before infusion and for 5 minutes
each step infusion. We estimated baroreceptor modulation of
MSNA and HR by calculating (1) the change in the number of bursts
per minute; (2) the percent change in total integrated activity, ie,
mean burst amplitude times number of bursts over time; and (3) the
absolute change in HR in relation to the change in mean BP induced
by each dose of PHE and NTP.

Protocol and Data Analysis
All patients were followed up on an outpatient basis. After a
screening visit, they were asked to maintain their diuretic regimen
and to standardize their ACE inhibitor treatment by taking enalapril
at a morning oral dose of 10 mg for 2 weeks. They were then asked
to come to the outpatient clinic in the morning, after a 48-hour
abstinence from smoking (in the 7 smokers) and alcohol consump-
tion. After assumption of the supine position, patients were fitted
with intravenous cannulas, the ECG lead, the finger BP recording
device, and microelectrodes for MSNA recording. After a 30-minute
interval, a blood sample was drawn, and BP was then measured 3
times with a mercury sphygmomanometer, the 3 values being
averaged. BP, HR, MSNA, and respiration rate were measured
continuously during an initial 10-minute baseline condition, the
stepwise infusion of one vasoactive drug, a second 10-minute
baseline condition, and the stepwise infusion of the second vasoac-
tive drug. In half of the patients, PHE was infused first, whereas NTP
was infused first in the remaining half. Echocardiography and the
exercise tolerance test (cycloergometer) were performed in the
afternoon. The exercise tolerance test began after a 5-minute rest in
the sitting position and with an initial workload of 25 W and a
subsequent workload increase of 25 W every 3 minutes until exercise-limiting symptoms, ECG abnormalities, or abnormalities of
BP values (taken every minute during each step) appeared. Subjects
were then randomized in a double-blind fashion to add to existing
treatment either a transdermal clonidine patch, which released 0.1
mg of the drug daily, or placebo. In both instances, no dietary or
lifestyle changes were advised. Subjects were asked to replace the
patch every 7 days, to undergo a clinical visit after 4 weeks, and then
to double the patch size to provide a release of clonidine of 0.2 mg
daily for 4 additional weeks. Adherence to treatment was verified by
counting the number of patches used. The 2-month treatment period
ended with a clinical visit, a second experimental session, an
rchocardiographic examination, and an exercise test as done for the
first study. The study protocol was approved by the Ethics Com-
mittee of our institution. All patients gave written consent to the study
after being informed of its nature and purpose.

Data were analyzed by a single investigator unaware of the patients’
status in the active treatment or placebo group. Values from individual
subjects were averaged for the 2 groups and expressed as mean±SEM.
Statistical significance of the difference in mean values was assessed by
2-way ANOVA. The 2-tailed t test for unpaired observations was used
to identify the difference between groups. The 2-tailed t test for paired
observations was used to identify the difference between resting
conditions and baroreceptor stimulation and deactivation and the differ-
ence between baseline and treatment values in either group. The
Bonferroni correction for multiple comparisons was used. A value of
P<0.05 was taken as statistically significant.

Results
In 4 patients (3 with CHF caused by ischemic heart disease and 1 with CHF caused by nonischemic heart disease),
microneurography failed to obtain an initial MSNA recording
of acceptable quality. The data were thus derived from a total
of 26 patients, 14 of whom were randomized to clonidine and
12 to placebo. As shown in the Table, the 2 groups had a
similar age and gender distribution. At baseline, the 2 groups
showed a similar body mass index, BP, LVEF, left ventricular
diastolic diameter, left ventricular fractional shortening,
respiratory rate, and exercise tolerance time with virtually
superimposable values for plasma NE, plasma renin activity,
and MSNA. In both the clonidine and placebo groups, LVEF
and exercise tolerance time were not altered after 2 months.
This was also the case for HR, sphygmomanometric BP, and
plasma renin activity, although in the clonidine group, these
variables showed a slight, nonsignificant decrease. The
number of sympathetic bursts per minute, number of bursts
corrected for HR, and plasma NE were not modified by
placebo, but they were all consistently reduced by clonidine,
the reduction amounting on average to −25.7%, −26.7%,
and −46.8%, respectively (Figure 1).

Figure 2 shows the results obtained during baroreceptor
stimulation and deactivation by infusion of vasoactive drugs.
HR and MSNA (expressed both as bursts/min and as percent
total integrated activity) were progressively reduced by pro-
gressively increasing mean BP via NTP and were progres-
sively increased by progressively reducing mean BP via NTP.
All responses were superimposable before and after clonidine
administration. Baroreflex responses to vasoactive drug infu-
sions also were superimposable between the first and second
studies in the placebo group.

There was no change in NYHA class over the 2 months
of clonidine or placebo administration. In the clonidine-treated

group, the only side effect was xerostomia, which was
 reported by 6 patients.

Discussion
Our study provides the first report on the effects of prolonged
clonidine administration on sympathetic nerve traffic and
baroreceptor cardiovascular control in CHF. The main finding is represented by the evidence that in CHF patients undergoing treatment with furosemide and enalapril, the administration of transdermal clonidine for 2 months was accompanied not only by a consistent and marked decrease in plasma NE but also by a clear-cut and pronounced reduction in MSNA values, which were unaltered in the group that was given placebo. This confirms previous findings that clonidine reduces the elevated plasma NE values that characterize CHF.\textsuperscript{12,13} It adds 3 new pieces of evidence to the previous findings, however. First, the reduction in plasma NE is not due to an increased tissue clearance of this substance secondary to...

<table>
<thead>
<tr>
<th>Variable</th>
<th>Clonidine Group (n=14)</th>
<th>Placebo Group (n=12)</th>
</tr>
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<tr>
<td></td>
<td>Baseline</td>
<td>2 Months</td>
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<tr>
<td>Age, y</td>
<td>59.6±2.6</td>
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<tr>
<td>Male/female, n</td>
<td>9/5</td>
<td></td>
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<tr>
<td>NYHA functional class II/III, n</td>
<td>9/5</td>
<td></td>
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<tr>
<td>Ischemic/idiopathic etiology, n</td>
<td>6/8</td>
<td></td>
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<tr>
<td>Body mass index, kg/m(^2)</td>
<td>23.2±0.8</td>
<td>23.2±0.8</td>
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<tr>
<td>Sphygmomanometric SBP, mm Hg</td>
<td>128.6±4.0</td>
<td>123.1±3.1</td>
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<tr>
<td>Sphygmomanometric DBP, mm Hg</td>
<td>75.4±2.7</td>
<td>72.1±2.7</td>
</tr>
<tr>
<td>Finger SBP, mm Hg</td>
<td>124.3±3.8</td>
<td>120.2±4.3</td>
</tr>
<tr>
<td>Finger DBP, mm Hg</td>
<td>72.1±1.8</td>
<td>68.7±2.2</td>
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<tr>
<td>Heart rate, bpm</td>
<td>77.9±3.5</td>
<td>73.3±3.6</td>
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<td>LVEF, %</td>
<td>38.9±3.1</td>
<td>40.3±2.6</td>
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<td>Left ventricular end-diastolic diameter, mm</td>
<td>65.9±2.6</td>
<td>65.1±2.7</td>
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<tr>
<td>Left ventricular fractional shortening, %</td>
<td>21.5±1.6</td>
<td>22.0±1.5</td>
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<tr>
<td>Respiration rate, breaths/min</td>
<td>18.1±0.6</td>
<td>17.6±0.5</td>
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<td>Plasma renin activity, (\mu\text{g} \cdot \text{L}^{-1} \cdot \text{h}^{-1})</td>
<td>6.6±1.4</td>
<td>5.5±1.4</td>
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<tr>
<td>Plasma NE, nmol/L</td>
<td>2.88±0.35</td>
<td>1.53±0.15*</td>
</tr>
<tr>
<td>MSNA, bursts/min</td>
<td>51.7±2.3</td>
<td>37.4±3.5*</td>
</tr>
<tr>
<td>MSNA, bursts/100 heart beats</td>
<td>68.1±3.7</td>
<td>49.9±5.0*</td>
</tr>
<tr>
<td>Exercise time, s</td>
<td>378.5±41.5</td>
<td>405.0±55.0</td>
</tr>
</tbody>
</table>

Data are shown as mean±SEM. SBP indicates systolic BP; DBP, diastolic BP.

\*P<0.01, baseline values vs values recorded after 2 months of clonidine or placebo administration.

Figure 1. Scatterplots showing MSNA expressed as bursts/min (left) and bursts/100 heart beats (hb, middle) and plasma norepinephrine (NE) values (right) before (B, ○) and after 2 months of clonidine or placebo treatment (2 mo, ●). Data shown are from individual patients and are mean±SEM; n=14 for clonidine and n=12 for placebo. Asterisks (**P<0.01) refer to level of statistical significance between baseline values and values recorded after 2 months of clonidine or placebo administration.
an increased blood flow but rather to a true reduction in central sympathetic drive. Second, the sympathoinhibition caused by clonidine in CHF also occurs to a major degree when the drug is given on a chronic basis. Finally, this inhibition also takes place to a major degree in patients who are already undergoing treatment with an ACE inhibitor, ie, a drug that exerts clear sympathoinhibitory effects in CHF.7,8

Figure 2. Plots showing changes (Δ) in HR (expressed as bpm [b/min]) and MSNA (expressed as bursts per minute and percent integrated activity [% i.a.]) accompanying stepwise reductions and increases in mean arterial pressure (MAP) induced by intravenous infusions of NTP and PHE, respectively. Solid lines and ● refer to HR and MSNA changes observed under baseline conditions; dashed lines and ○ refer to HR and MSNA changes observed after 2 months of either clonidine or placebo treatment. Data are shown as mean±SEM; n=14 for clonidine and n=12 for placebo.
Previous studies in hypertensive animals and humans have shown that the sympathoinhibitory effects of clonidine may be exerted either through a central mechanism (stimulation of both α₂-adrenergic receptors and imidazoline-1 receptors) or through the arterial baroreflex, which are, through an enhancement of the sympathetic restraint exerted by this reflex. In our CHF patients, however, sudden and short-lasting BP changes induced by vasoactive drugs caused reflex changes in HR and in MSNA that were superimposible before and after chronic administration of clonidine. This allows us to conclude that, at variance from what has been documented for other drugs, clonidine does not potentiate the baroreflex in CHF. It also allows us to speculate that in this condition, the sympathoinhibitory influence of this drug is accounted for mainly by its central effects.

In our CHF patients, the reduction in plasma NE induced by chronic clonidine administration was substantially greater than the reduction in MSNA (−46.8% versus −26.7%). This is unlikely to be explained by an increase in tissue clearance of the adrenergic neurotransmitter, because previous studies have shown systemic clearance of NE to be unaffected by acute administration of clonidine in CHF patients, and because in our patients, administration of clonidine did not lead to an increase in LVEF, and therefore presumably to an impairment in left ventricular function, our conclusions cannot be safely extrapolated to more severe CHF conditions. Because in our patients, administration of clonidine did not lead to an increase in LVEF, and therefore presumably to an increase in tissue blood flow that could have favored disposal of NE secreted from sympathetic nerve terminals. It is more likely to be explained by an additional sympathoinhibitory influence exerted by the drug at the peripheral level, because α₂-adrenergic stimulation inhibits NE release from sympathetic nerve terminals, thus favoring a reduction in plasma NE. A third explanation should be also considered, namely, that the greater reduction in plasma NE compared with MSNA observed during treatment with clonidine might reflect a greater effect of clonidine on sympathetic activity in districts other than that explored in the present study. Because skin sympathetic nerve traffic is not increased in CHF, the most likely candidates are the splanchnic circulation, the kidney, and the heart. A greater sympathoinhibitory effect of clonidine on the heart is not in line with the observation that in our patients, the drug had only a modest bradycardic effect. However, HR is an inaccurate marker of cardiac and overall adrenergic drive. Furthermore, recent observations indicate that in CHF, intravenous clonidine reduces cardiac NE spillover to a greater extent than systemic NE spillover. Thus, the above possibility remains valid.

Our study has a potential limitation and clinical implications. The limitation is that because the patients we examined suffered from mildly symptomatic CHF with a modest impairment in left ventricular function, our conclusions cannot be safely extrapolated to more severe CHF conditions. The clinical implications are that, confirming previous findings obtained in an acute clinical setting, the sympathoinhibitory effects of chronic administration of this drug can be exerted in addition to that exerted by ACE inhibitor treatment, thereby leading to MSNA and plasma NE values virtually indistinguishable from those of healthy age-matched controls. Thus, the addition of clonidine to current treatment of heart failure may more effectively remove a phenomenon that has been shown to have adverse prognostic implications. This may also be obtained by administration of a β-blocker, which has been shown to favorably affect CHF prognosis. Clonidine, however, by inhibiting central sympathetic outflow, may counteract the adverse effects on both the heart and the peripheral circulation induced by the generalized sympathetic activation typical of CHF and may represent an alternative to β-blockers, particularly when these drugs are contraindicated or not tolerated. It should be emphasized, however, that use of this drug in CHF will have to be further tested in clinical studies, because although clonidine did not cause any deterioration in cardiac function and exercise capacity in the present study, inhibition of sympathetic activity by another drug that also exerts central sympathoinhibitory effects, such as moxonidine, has not been shown to provide beneficial effects on clinical outcome (Jay Cohn, MD, unpublished data, 1999). The reasons for this negative result remain to be clarified, although the possibility exists that the dose of the drug used was too high.

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References


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