The Effects of Moxonidine, a Novel Imidazoline, on Plasma Norepinephrine in Patients With Congestive Heart Failure

Karl Swedberg, MD, PhD, FACC,* Claes-Håkan Bergh, MD, PhD,† Kenneth Dickstein, MD,‡ John McNay, MD,§ Mitchell Steinberg, MD, PhD,§ for the Moxonidine Investigators

Göteborg, Sweden; Stavanger, Norway; and Indianapolis, Indiana

OBJECTIVE To evaluate the dose response relationship of moxonidine on plasma concentration of norepinephrine during acute and chronic administration in patients with congestive heart failure (CHF).

BACKGROUND Sympathetic activation is increased in heart failure. Moxonidine is an imidazoline ligand acting on the central nervous system (CNS) receptors to decrease sympathetic activation.

METHODS Ninety-seven patients with heart failure and New York Heart Association class II–III symptoms and ejection fraction <40% were randomized to placebo or one of three target doses of moxonidine, 0.1, 0.2 or 0.3 mg administered twice daily. An initial dose of moxonidine 0.1 mg twice a day (b.i.d.) was followed by weekly increments of 0.1 mg b.i.d. until target dose. The second and third study days occurred after four weeks (at target dose) and after 12 weeks, respectively. At each study day, repeated blood samples were drawn.

RESULTS There was a significant dose-related decrease of systolic blood pressure across all three study days. Heart rate decreased significantly on study day 3 in a dose-related manner. The acute 2 h decrease in plasma norepinephrine in response to all three doses of moxonidine was significantly different compared with placebo after four and 12 weeks. There was a significant linear relation between dose and plasma norepinephrine after four and 12 weeks in both 2 h peak and the time averaged effect (8 h). The number of adverse events was similar in the moxonidine and placebo groups.

CONCLUSIONS The increased sympathetic activation in CHF can be reduced by moxonidine through CNS inhibition. (J Am Coll Cardiol 2000;35:398–404) © 2000 by the American College of Cardiology

Congestive heart failure (CHF) is associated with high morbidity and mortality (1–3). The sympathetic nervous system is activated (4) and related to both the degree of heart failure and to the prognosis (4–6). Pharmacological therapy has been shown to decrease morbidity and mortality mainly through inhibition of angiotensin converting enzyme (ACE) activity (1,2) or beta-adrenoreceptor antagonism (7–10). These therapies are both directed towards counteracting neuroendocrine activation and the sympathetic activation in particular. The efficacy of enalapril in severe CHF is associated with a reduction of plasma norepinephrine levels (5). Accordingly, the reduction of sympathetic nervous system activity remains a primary pathophysiological target both in patients with overt CHF as well as those with asymptomatic left ventricular dysfunction (11).

As an alternative to blocking the peripheral effects of norepinephrine, inhibiting central sympathetic outflow may represent a useful means to interfere generally with the adverse effects of elevated catecholamines on cardiac function (12). Agents acting on central sympathetic outflow, such as the α2-agonist clonidine, have been studied in short term intravenous and oral studies (13,14). Moxonidine is a novel imidazoline ligand that acts specifically on central nervous system (CNS) receptors to decrease sympathetic nervous system tone (15). In preclinical studies, antihypertensive effects appear to correlate with its potency at putative brainstem imidazoline sites rather than to α2 receptors (16). In clinical studies, moxonidine is an effective treatment for hypertension and is equipotent to clonidine with fewer α2-mediated side effects (17). The gastrointestinal absorption of moxonidine is rapid (t-max. 1 h after dosing)
with elimination primarily via the urine. In postmarket surveillance studies, moxonidine has been shown to be well-tolerated; the most frequent side effects have included dry mouth, dizziness and headache, all reported in <3% in hypertensive patients (18).

The pharmacodynamic effects of moxonidine in patients with CHF are limited and, prior to this study, have only been evaluated in an acute hemodynamic study including 10 patients (19). The aim of this study was to determine the dose response relationship of oral moxonidine on plasma concentration of norepinephrine during acute and chronic administration in patients with symptomatic CHF. Additionally, tolerability was assessed with particular attention to the incidence of symptomatic hypotension and effects on vital signs.

METHODS

This was a double blind, placebo-controlled, multicenter trial with a 12 week duration in patients with symptomatic CHF in New York Heart Association (NYHA) functional class II–III between 21 to 79 years of age. Thirteen centers in Sweden and Norway participated (see Appendix). Patients with an ejection fraction <40% assessed by radionuclide angiography, echocardiography or angiography were eligible. An ACE-inhibitor was required if not contraindicated. The dosage of all medication was stable for at least two weeks before screening. Exclusion criteria included myocardial infarction within the previous 90 days, significant valvular obstruction or advanced pulmonary disease. Systolic blood pressure was >90 mm Hg, and beta-adrenergic blocking agent use within the previous three months was not allowed. The protocol was approved by the ethics committee at each participating center and each subject provided written informed consent.

Protocol. After screening and baseline visits, patients were randomly allocated to one of four treatment arms: tablets for placebo or to target doses of moxonidine of 0.1, 0.2 or 0.3 mg administered b.i.d. All active medication started with a dose of moxonidine of 0.1 mg twice daily followed by weekly dose increments of 0.1 mg b.i.d. (or placebo if needed) to the target dose. If side effects occurred, the dose could be maintained, reduced or withdrawn. The first study day was defined as the first of three separate days when patients were observed for 8 h in the clinic for safety and laboratory assessment. The second study day occurred after four weeks of dosing at which time patients had reached the target dose, if tolerated, and had maintained that dose for two weeks. The third day was at the end of study after 12 weeks. At each study day, repeated blood samples were drawn for assessment of plasma levels of norepinephrine following 30 min of supine rest. Blood samples were drawn before and 1, 2, 4 and 8 h after drug administration. Blood was collected in vials containing glutathione. The plasmas were placed on ice promptly and centrifuged for 20 min. The plasmas were frozen, and they were shipped on dry ice to a central laboratory where assay was performed by high performance liquid chromatography (HPLC).

Possible effects of moxonidine on CNS function were assessed by a questionnaire with specific questions aimed at sedation (Solicited Sedation Events Questionnaire) (20,21). Worsening heart failure and symptomatic hypotension were evaluated by the clinical judgment of the investigators in the absence of predefined criteria.

Statistics. The analyses included efficacy as well as safety evaluations. The primary efficacy end point was the effect of moxonidine on plasma norepinephrine. It was assessed by linear regression of the change of plasma norepinephrine from baseline to day 3 versus administered dose of moxonidine. The general linear model (GLM) compared dosage groups versus placebo with dose as the independent variable having a single degree of freedom, i.e., as a linear effect, and the response variables as the dependent variables. The models were fitted using the type III sums of squares option in the GLM procedure (22). Least squares means were used to summarize the results for each parameter.

Since the daily dosage of moxonidine was, in some cases, lower than the dose to which a given patient was randomized, the dose used for the analyses described below was the morning portion of the actual dose the patient received. The baseline value of a variable was defined as the last measurement obtained prior to the first administration of study drug on Study Day 1 (placebo in 23 cases and 0.1 mg moxonidine in the remaining cases). The predose values for Study Days 2 and 3 were defined as “0 h” values. The linear regression model included fixed effects for dose, study site and the interaction between dose and site. Each dose was also compared with placebo. All tests of significance were conducted at a two-sided alpha level of 0.05, except for overall main effect on plasma norepinephrine level (one-sided alpha level of 0.1).

The change from predose plasma norepinephrine concentration to concentrations at 1, 2, 4 and 8 h after dosing was analyzed in two ways: first, the acute effect of moxonidine compared with placebo was evaluated as the change at 2 h compared with predose values on Study Days 1, 2 and 3. Second, the time-averaged values of plasma norepinephrine over the 8 h interval after dosing were evaluated on Study...
Days 1, 2 and 3. The time-averaged effect was defined as the area between the effect-time curve and the abscissa from predose to the last measurement on the study day, divided by the number of hours between the time of the predose measurement and the last measurement.

Sample size was based on the following assumptions: the average baseline level of plasma norepinephrine is 500 pg/ml ± 250 pg/ml [standard deviation (SD)]; a 25% decrease is clinically significant; a one-sided significance value of 0.1 and a power of 70%. Categorical variables were compared for significance of association by chi-square analysis or Fisher’s exact test as indicated in Tables.

RESULTS

The patient demographics at baseline as originally randomized are presented in Table 1. There were 97 subjects with an average age of 66 years. Angiotensin converting enzyme-inhibitor therapy was used by 60% of the patients. Groups were well-matched for most variables except baseline norepinephrine (highest in the placebo group) and concomitant ACE inhibitor use (lowest in the placebo group). The maximal dose levels achieved are shown in Table 2. Six patients could not reach the allocated dose level because of hypotension. However, all such patients could be maintained on moxonidine at a lower dose level.

The effects of moxonidine on standing systolic blood pressures and heart rate before and 2 h after drug intake on each study day are presented in Figure 1. There was a significant decrease of mean systolic blood pressure after the first dose on Study Day 1 (all patients received 0.1 mg) compared with placebo (p = 0.0046); on Study Days 2 and 3, the effect on blood pressure was dose-related (p = 0.0051 and 0.0001 for Study Days 2 and 3, respectively). Significant falls to a similar extent in diastolic pressures were likewise noted especially at the higher doses. The mean change in standing heart rate 2 h after dose was not significant compared with placebo for any dose on any of the three study days. However, small (about 6 beats/min) but significant (p < 0.05) decreases in supine heart rate were noted for the highest two doses on both Study Days 2 and 3 compared with placebo.

The mean plasma level of norepinephrine of the entire study population at baseline according to randomized assignment for each group is shown in Table 1. The effects of moxonidine on plasma norepinephrine are shown in Figure 2 and in Table 3. In the placebo group, there was a gradual increase of trough plasma norepinephrine before the morning dose over the 12 week study period by approximately 25% (Fig. 2). In each of the moxonidine groups, the plasma trough concentrations tended to be less on Study Days 2 and 3 compared with the placebo group, but these changes did not reach significance. For example, there was a fall in predose norepinephrine levels of 51 ± 38 pg/ml (n = 71) and 78 ± 25 pg/ml (n = 69) in the combined moxonidine groups compared with their respective placebo groups on Study Day 2 (p = 0.256) and Study Day 3 (p = 0.284). On the other hand, there was a clear reduction in plasma norepinephrine levels in each drug group that was maximal

### Table 1. Baseline Demographic Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Placebo (n = 23)</th>
<th>Moxonidine 0.2 mg (n = 24)</th>
<th>Moxonidine 0.4 mg (n = 26)</th>
<th>Moxonidine 0.6 mg (n = 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (%)</td>
<td>14 (61%)</td>
<td>19 (79%)</td>
<td>20 (77%)</td>
<td>20 (83%)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>67</td>
<td>66</td>
<td>65</td>
<td>65</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>78 ± 3</td>
<td>77 ± 3</td>
<td>82 ± 4</td>
<td>77 ± 3</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>28 ± 5</td>
<td>27 ± 2</td>
<td>29 ± 1</td>
<td>28 ± 1</td>
</tr>
<tr>
<td>NYHA class</td>
<td>2.5 ± 0.1</td>
<td>2.7 ± 0.1</td>
<td>2.6 ± 0.1</td>
<td>2.4 ± 0.1</td>
</tr>
<tr>
<td>Norepinephrine (pg/mL)</td>
<td>498 ± 58</td>
<td>432 ± 49</td>
<td>449 ± 37</td>
<td>404 ± 34</td>
</tr>
<tr>
<td>Median</td>
<td>410</td>
<td>347</td>
<td>400</td>
<td>361</td>
</tr>
<tr>
<td>Systolic pressure (mm Hg)*</td>
<td>119 ± 5</td>
<td>121 ± 4</td>
<td>115 ± 4</td>
<td>121 ± 5</td>
</tr>
<tr>
<td>Heart rate (beats/min)*</td>
<td>75 ± 2</td>
<td>74 ± 3</td>
<td>77 ± 2</td>
<td>80 ± 3</td>
</tr>
<tr>
<td>Patients on ACE inhibitors (%)</td>
<td>48</td>
<td>63</td>
<td>54</td>
<td>75</td>
</tr>
</tbody>
</table>

Unless otherwise specified, all continuous variables are expressed as mean (SEM).
ACE = angiotensin converting enzyme; NYHA = New York Heart Association.
*Standing values.

### Table 2. Number of Patients Randomized to Each Drug Group Compared With Final Dose Achieved

<table>
<thead>
<tr>
<th>Moxonidine Group (mg/day)</th>
<th>Placebo</th>
<th>0.2</th>
<th>0.4</th>
<th>0.6</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total randomized</td>
<td>23</td>
<td>24</td>
<td>26</td>
<td>24</td>
<td>97</td>
</tr>
<tr>
<td>Maximal dose of moxonidine achieved (mg/day)</td>
<td></td>
<td>0.2</td>
<td>24</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>0.4</td>
<td>25</td>
<td>3</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.6</td>
<td>19</td>
<td>19</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values do not reflect deaths and discontinuations (see text).
approximately 2 h following moxonidine administration (Fig. 2 and Table 3). Plasma norepinephrine tended to return progressively toward predose levels after the peak effect. The acute responses to moxonidine (both peak effect at 2 h and the time effect averaged over the 8 h postdosing interval) were dose-related, and the linearized dose-effect trend was significant on both Study Days 2 and 3 (Table 3). The acute 2 h decrease in norepinephrine in response to all three doses was significantly different compared with placebo on Study Day 3, while on Study Day 2, only the response to the highest dose was significantly different from placebo.

The percentage of patients with adverse effects in the moxonidine and placebo groups were similar (74% in placebo vs. 71%, 69% and 75% in moxonidine groups 0.2, 0.4 and 0.6 mg/day, respectively). The number of patients who experienced worsening heart failure or died are displayed in Table 4. Three patients died, 1 patient in the placebo group and 2 in the lowest moxonidine group. Seven patients were judged clinically to have worsening heart failure; 1 patient allocated to the highest moxonidine dosage group (0.6 mg/day), 4 patients in the low dose group (0.2 mg/day) and 2 patients in the placebo group. The combination of worsening heart failure or death was inversely related to dose (p = 0.013, Fisher’s exact test).

Four patients discontinued therapy in the placebo group as well as a total of six patients in the moxonidine groups (3, 1 and 2 in the 0.2, 0.4 and 0.6 mg/day groups, respectively). Other than the three deaths (Table 4), the most common reason for discontinuation was symptomatic hypotension present in two subjects of the placebo group and one patient each in the 0.4 and 0.6 mg/day moxonidine group. The remaining three discontinuations were nonstudy related. Symptomatic hypotension was recorded during the study in a total of 30 patients. This symptom was more frequent in patients receiving moxonidine (3 patients in the placebo group and 6, 11 and 10 patients in the moxonidine 0.2, 0.4 and 0.6 mg/day group, respectively) (p < 0.015, by the Mantel-Haenszel chi-square test). Other symptoms possibly associated with hypotension were dizziness, vertigo and syncope; all were more frequent in the moxonidine-treated groups than in the placebo group, although dose-relatedness was not strong. There were no significant sedative effects in any group as assessed by the Solicited Events Sedation questionnaire.

**DISCUSSION**

This study demonstrates a significant attenuation of plasma norepinephrine concentrations by moxonidine in patients...
with CHF. This was accomplished with relatively few adverse reactions. When symptomatic hypotensive reactions did occur, they could be managed by lowering the dose of moxonidine. Although a trend was evident, we could not demonstrate a sustained reduction in predose plasma norepinephrine over the course of the study in any group compared with placebo. However, it is worth noting that the decreases in plasma norepinephrine seen over the 8 h after dosing observation period on each study day were significant and sustained throughout the 12 weeks of dosing.

**Sympathetic activation and plasma norepinephrine.**

Sympathetic activation can be assessed by measurement of peripheral sympathetic nerve activity (23), myocardial norepinephrine release (24) or plasma norepinephrine by peripheral blood sampling (4). Plasma norepinephrine reflects sympathetic activation in CHF, but the actual contribution of sympathetic cardiac activation is probably underestimated (24). In patients not treated with ACE-inhibitors, plasma norepinephrine concentrations are also related to the degree of CHF (25), and the levels have prognostic implications (4,5). Over time, plasma norepinephrine increases as heart failure progresses (26,27).

The increase of plasma norepinephrine in the placebo group over a 12 week period observed in this study is somewhat more pronounced than previously reported in the V-HeFT II and the SOLVD trial (6,26). There is evidence that plasma norepinephrine concentration in patients with CHF increases over time, presumably reflecting progression of the underlying disease (26,27). For example, the average plasma norepinephrine of both treatment groups in V-HeFT II clearly trended higher at approximately parallel rates of about 40 pg/ml per year over the 48 months of study (26). In the SOLVD trials, the average baseline levels of plasma norepinephrine were significantly higher in the treatment group than they were in the prevention group (6), reflecting the greater severity of failure.

The increase in plasma norepinephrine with time appears

<table>
<thead>
<tr>
<th>Study Day/Dose†</th>
<th>2 h Peak Effect</th>
<th>Time Averaged Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Change in Norepinephrine (pg/ml)</td>
<td>p Value</td>
</tr>
<tr>
<td>Study Day 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>−0.4</td>
<td>0.25</td>
</tr>
<tr>
<td>0.1 mg</td>
<td>−43.4</td>
<td></td>
</tr>
<tr>
<td>Study Day 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>−11.7</td>
<td></td>
</tr>
<tr>
<td>0.1 mg</td>
<td>−58.0</td>
<td>0.16</td>
</tr>
<tr>
<td>0.2 mg</td>
<td>−52.9</td>
<td>0.20</td>
</tr>
<tr>
<td>0.3 mg</td>
<td>−125.5</td>
<td>0.001</td>
</tr>
<tr>
<td>Linear Trend∥</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>Study Day 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>92.0</td>
<td></td>
</tr>
<tr>
<td>0.1 mg</td>
<td>−42.2</td>
<td>0.017</td>
</tr>
<tr>
<td>0.2 mg</td>
<td>−43.0</td>
<td>0.008</td>
</tr>
<tr>
<td>0.3 mg</td>
<td>−86.0</td>
<td>0.0008</td>
</tr>
<tr>
<td>Linear Trend∥</td>
<td>0.0015</td>
<td></td>
</tr>
</tbody>
</table>

*Least square mean changes relative to predose plasma norepinephrine concentration on same day. †Dose administered on a twice daily regimen. ‡N differs from number randomized due to dosage adjustments. Variation by study day results from discontinuations and deaths. §For calculation of time averaged effect, refer to Methods section. ||Linear trend of effect vs. dose, refer to Methods section. ¶p values for each dose of moxonidine compared with placebo.

<table>
<thead>
<tr>
<th>Allocation Group</th>
<th>Moxonidine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (N = 23)</td>
</tr>
<tr>
<td>Deaths</td>
<td>1</td>
</tr>
<tr>
<td>Worsening heart failure</td>
<td>3</td>
</tr>
<tr>
<td>Worsening heart failure or death</td>
<td>4</td>
</tr>
</tbody>
</table>

p value calculated by Fisher’s exact test.
patients are probably mediated by actions at both imidazo-
facts and lower plasma norepinephrine in heart failure
published (13,14). The acute beneficial hemodynamic ef-
short-term studies using clonidine in CHF have been
reduced sympathetic activation by central inhibition, and
lowered blood pressure. 
ultimately leading to decreased sympathetic outflow and
or I1 receptors (33) located in this region of the CNS,
Central inhibition of sympathetic activation. A small
study. 

even greater than those in the placebo group seen in this
failure, while the proportional increases in that study were
of both groups are close to the average value of the placebo
in the majority of the patients in this study. Selection of
patients on the basis of prior administration of ACE
inhibitors may have resulted in inclusion of patients later in
the chronological history of heart failure than would have
been true of patients of a similar NYHA class who were
studied before ACE inhibitors became standard therapy for
CHF. However, others have also observed large increases of
plasma norepinephrine over a time interval similar to ours.
In a comparison of low versus high doses of enalapril in
NYHA class III/IV heart failure, the respective increases in
plasma norepinephrine after 12 weeks of observation were
25% and 34% (27). The pretreatment plasma concentration
of both groups are close to the average value of the placebo
group in this study, suggesting similar severity of heart
failure, while the proportional increases in that study were
even greater than those in the placebo group seen in this
study.

Central inhibition of sympathetic activation. A small
group of neurons located in the rostroventrolateral reticular
nucleus possess both alpha2 and imidazoline (I1) receptive
sites (29,30). These vasomotor neurons project caudally
within the cord to excite preganglionic sympathetic neurons
probably by release of glutamate. The neurons play an
important role in regulating sympathetic outflow and, thus,
the systematic level of various neurohormones including
norepinephrine, renin and angiotensin (31). Several studies
suggest that moxonidine can specifically activate alpha2 (32)
or I1 receptors (33) located in this region of the CNS,
ultimately leading to decreased sympathetic outflow and
lowered blood pressure. 
Clonidine was the first clinically available drug that
reduced sympathetic activation by central inhibition, and
short-term studies using clonidine in CHF have been
published (13,14). The acute beneficial hemodynamic ef-
effects and lower plasma norepinephrine in heart failure
patients are probably mediated by actions at both imidazo-
line and alpha2 receptive sites. However, clonidine has been
associated with moderate sedation and other nuisance side
effects that have limited its wider use. It has been proposed
that the alpha2 receptor agonist properties of clonidine
might be an important reason for this side effect (16,34).
The equivalent antihypertensive efficacy and lower side
effect profile of moxonidine compared with clonidine
could be explained by a 10-20 fold lower affinity than clonidine
for alpha2 receptors, while having nearly equal affinity for
purported type 1 imidazoline receptors in the rostro-
ventrolateral medulla (15). In support of this, we could not
detect any significant sedative side effects of moxonidine
in this study.

Antiaadrenergic therapies. Treatments that counteract
the increased neuroendocrine activation, and sympathetic
activation in particular, have demonstrated beneficial effects on
morbidity and mortality in heart failure (1,2,8–10). An
intervention that modulates excessive sympathetic activation
by attenuation might, therefore, have important clinical
effects in patients with heart failure. In this regard, it is
worth noting that moxonidine recently has been shown to
reduce transmural norepinephrine gradient as well as
total norepinephrine spillover in patients with moderate
CHF (35). Our findings of fewer events in the higher
moxonidine dose groups might suggest enhanced protection
from adverse cardiovascular events by reduced systemic and
cardiac adrenergic drive. This preliminary observation needs
confirmation in large prospective clinical trials.
The principal adverse effect associated with moxonidine
administration was symptomatic hypotension. This effect,
however, was transient and occurred at the time of peak
drug effect on blood pressure, heart rate and plasma nor-
epinephrine levels. The hypotensive reactions were manage-
able by dose adjustments. The occurrence of symptomatic
hypotension, in combination with the relatively short dura-
tion of the effect on plasma norepinephrine, has subse-
quently been addressed by modifying the dosage formula-
tion to yield enhanced tolerability and sustained plasma
norepinephrine reductions. 

Conclusion. The increased sympathetic activation in CHF
can be reduced by the imidazoline ligand, moxonidine,
probably by acting on a population of adrenergic/im-
idazoline receptive sites within the CNS. While the
findings from this study may be encouraging with regard to
the previously reported prognostic significance of elevated
plasma norepinephrine concentrations in patients with heart
failure, the potential clinical benefit of pharmacologically
targeting elevated plasma norepinephrine must be estab-
lished by controlled clinical trials with morbidity and
mortality as primary end points.

APPENDIX
The following study sites participated in the Moxonidine
Study: Norwegian Center: Rogaland Central Hospital: Ken-
neth Dickstein. Swedish Centers: Boras Hospital, Boras: C.
Wetttervik; Danderyd Hospital, Danderyd: T. Kahan; Falun
Hospital, Falun: H. Saetre; Sahlgrenska University Hospi-
tal/Sahlgrenska, Goteborg: F. Waagstein and C-H. Bergh;
Sahlgrenska University Hospital/Molndal, Molndal: L.
Klintberg; Sahlgrenska University Hospital/Ostra, Gote-
borg: M. Schauffelberger and K. Swedberg; Central Hospi-
tal, Karlstad: R. Karlsson; Linkoping University Hospital,
Linköping: U. Dahlström; Malmö University Hospital, Malmö: L. Erhardt and C. Cline; Norrköping Hospital, Norrköping: O. Nilsson; Uddevalla Hospital, Uddevalla: B. Karlson; Västerås Central Hospital, Västerås: G. Agert.

Acknowledgments
We are grateful for the assistance by Claude Benedict, MD, for reviewing the plasma norepinephrine result. The statistical input of Curtis Wiltse, PhD, and the assistance in data preparation by Karen Zimmerman were most valuable. The input from Gull Andersson, RN, during study conduct and Gunnel Johansson, secretary, for preparing the manuscript is appreciated.

Reprint requests and correspondence: Dr. Karl Swedberg, Department of Medicine, Göteborg University, Sahlgrenska University Hospital/Ostra, S-416 85 Göteborg, Sweden. E-mail: Karl.Swedberg@hjl.gu.se.

REFERENCES