Antiadrenergic Effect of Chronic Amiodarone Therapy in Human Heart Failure

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OBJECTIVES
The aim of the present study was to evaluate the influence of amiodarone on neurochemical parameters of sympathetic nervous activity in patients with congestive heart failure.

BACKGROUND
Unlike most antiarrhythmic agents, amiodarone has been shown to exert a beneficial effect on survival in some studies of patients with congestive heart failure. The pharmacology of this agent is complex, and as such, the mode of its action is unclear in humans. Some experimental studies suggest that amiodarone exerts a sympatholytic effect.

METHODS
To evaluate the effect of amiodarone on sympathetic nervous activity, we measured the total systemic and cardiac norepinephrine (NE) spillover rate by isotope dilution in 58 patients with severe heart failure (left ventricular ejection fraction \( \geq 20\% \)), 22 of whom were receiving chronic amiodarone treatment. Release rates for dihydroxyphenylalanine (DOPA, a precursor of NE), and endogenous and radiolabeled dihydroxyphenylglycol (DHPG and \(^3\)H-DHPG, intraneuronal metabolites of NE and \(^3\)H-NE, respectively) were also determined to assess sympathetic neuronal integrity.

RESULTS
Amiodarone-treated patients had significantly lower cardiac spillover rates for NE (42%, \( p < 0.001 \)), DOPA (74%, \( p < 0.001 \)), DHPG (44%, \( p < 0.01 \)) and \(^3\)H-DHPG (51%, \( p < 0.01 \)) than those patients not treated with amiodarone. Hemodynamic assessment of amiodarone-treated patients revealed higher cardiac output (4.4 ± 0.2 vs. 3.7 ± 0.2 liters/min, \( p < 0.01 \)), and slightly lower pulmonary capillary wedge pressure (18 ± 2 vs. 22 ± 1, \( p = \text{NS} \)) than in untreated patients. After correction for the potential confounding effect of hemodynamic differences, amiodarone-treated patients continued to demonstrate significantly lower spillover rates of NE, DOPA and DHPG from the heart.

CONCLUSIONS
These data indicate that amiodarone may exert beneficial effects on the failing human heart through a sympatholytic process, and this action appears to be relatively cardioselective. (J Am Coll Cardiol 1999;33:1553–9) © 1999 by the American College of Cardiology

Although the use of angiotensin-converting enzyme inhibitors (1,2) has significantly reduced total heart failure (HF) mortality and recent studies of third-generation beta-adrenergic blocking agents show similar promise (3), sudden death due to ventricular tachyarrhythmia remains a major clinical issue in the management of HF patients. Accordingly, numerous studies have been performed to identify those patients at greatest risk of arrhythmic death, with the aim of instituting preventative therapy. Unfortunately, the vast majority of antiarrhythmic agents have either been ineffective or proarrhythmic in HF patients (4).

To date, amiodarone is the only antiarrhythmic agent that has been shown to exert a beneficial effect on survival in HF patients (5), although not all studies have supported this observation (6). In conjunction, amiodarone has been shown to be particularly effective in suppressing ventricular ectopy and ventricular arrhythmias in a variety of clinical circumstances (7). Despite the increasing use of amiodarone, the precise means by which it exerts its antiarrhythmic actions remains uncertain. Although classified as a class III antiarrhythmic agent by virtue of its effects on the delayed rectifier current and consequently action potential duration, amiodarone exerts a wide range of actions including blockade of inward sodium and calcium currents (8,9) and alpha- and beta-adrenoceptor antagonism (10). In recent studies from our group (11), the acute intravenous administration of amiodarone in rats reduced the rate of norepinephrine release from the heart dose-dependently during nerve stimulation.

The demonstration of a potential sympatholytic action of amiodarone therefore could have particular significance, given that: i) the cardiac norepinephrine spillover rate is markedly increased in the failing human heart (12–14), and is strongly associated with an adverse prognosis (15); and ii) beta-blocking drugs exert beneficial effects on both
symptoms and outcome in patients with heart failure (3,16). Within this context, the aim of this study was to evaluate the effects of long-term amiodarone therapy on total systemic and cardiac sympathetic function in human heart failure.

**METHODS**

**Study patients.** Fifty-eight consecutive patients with moderate to severe heart failure who presented to our institution for heart failure management and/or transplant evaluation participated in this study. The mean left ventricular ejection fraction for this patient group was 20 ± 1%. At the time of inclusion in this study, 22 patients were receiving chronic (>1 month) amiodarone therapy, initiated at the discretion of their treating physicians. In 16 of these patients heart failure was the presenting symptom and amiodarone was initiated on the basis of Holter monitor findings. In the remaining six patients, symptomatic ventricular arrhythmias were either the presenting symptom (with subsequent demonstration of left ventricular dysfunction) or were coexistent with symptomatic heart failure. Specific characteristics of the patient population grouped according to treatment with amiodarone are presented in Table 1. All patients gave written informed consent, and the study was performed with the approval of the Alfred Hospital Ethics Review Committee.

**Catheterization protocol.** All patients underwent invasive hemodynamic testing and neurochemical evaluation of total systemic and cardiac sympathetic function. All studies were performed in the morning, and medications were continued in all patients to avoid hemodynamic instability and potential exaggeration of sympathectomization. A thermodilution catheter (7-F Arrow, Arrow International) was inserted percutaneously under local anesthesia via the right internal jugular vein, for the determination of pulmonary arterial pressures, pulmonary capillary wedge pressure and cardiac output. The cardiac output was determined from the average of three cardiac output measurements that varied by less than 10%. Arterial blood pressure was determined invasively via a radial arterial cannula.

At the completion of the hemodynamic assessment a coronary sinus thermodilution catheter (Webster Laboratories, California) was positioned in the coronary sinus under fluoroscopic control. The tip of the thermodilution catheter was confirmed to lie at least 2 cm proximal to the coronary sinus orifice in all cases by injection of radiographic contrast. The coronary sinus blood flow was subsequently determined as previously described (17), and simultaneous arterial and coronary sinus blood sampling was performed. Coronary sinus plasma flow was calculated after determination of each patient’s hematocrit.

**Radiotracer assessment of sympathetic function.** A neurochemical approach to measuring total systemic and cardiac sympathetic activity and neuronal biochemical integrity was employed as previously described by our group. In brief, radiolabeled L-[7-3H]-norepinephrine was continuously infused (0.5 to 1 μCi/min) through a peripheral vein, to achieve a steady-state plasma concentration.

The rate of appearance rate of norepinephrine in plasma was measured as an indirect index of “global” sympathetic nervous activity, and calculated as the ratio of the infusion rate for 3H-labeled norepinephrine to the plasma-specific activity of norepinephrine in plasma, as previously described (18,19).

A more extensive assessment of cardiac sympathetic nervous activity and neuronal function was performed by measuring the transcardiac spillover of norepinephrine, its precursor dihydroxyphenylalanine (DOPA) and dihydroxyphenylglycol (DHPG), the intraneuronal metabolite of norepinephrine. The regional spillover rate for norepinephrine was computed using a modified Fick equation, which includes a correction for the extraction of norepinephrine across the heart (19,20). The cardiac spillover rates for DOPA and DHPG were calculated as previously described (13).

**Biochemical assays.** Upon collection, blood samples were immediately transferred to ice-chilled tubes containing ethylene glycol tetraacetic acid and reduced glutathione. Samples were stored on ice and subsequently separated by centrifugation at 4°C. Plasma samples were stored at −70°C until assay. Norepinephrine, DOPA and DHPG concentrations were determined by high performance liquid chromatography with electrochemical detection (21).
plasma-specific activity of tritiated norepinephrine and dihydroxyphenylglycol was determined by performing timed collections of the detector cell eluant. Radioactivity was measured by liquid scintillation spectroscopy.

**Statistical methods.** Data are presented as the mean ± standard error of the mean. Where normally distributed, between-group comparisons were performed by an unpaired Student t test. Data that were not normally distributed were compared using the Wilcoxon rank-sum test. Between-groups comparison of the frequency of categorical variables was performed using the chi-square test. Relations between continuous variables were examined using the least squares method of linear regression. Analysis of the entire patient population revealed significantly milder hemodynamic impairment in the amiodarone-treated group. To avoid this observation as a confounding factor, a secondary comparison between amiodarone-treated and -untreated individuals was performed using a case-matching approach, where individuals were matched according to mean pulmonary artery pressure, which we have previously reported as being the hemodynamic parameter that correlates most significantly with cardiac norepinephrine spillover (13). The null hypothesis was rejected when the p value was <0.05.

**RESULTS**

The demographic and hemodynamic data are detailed in Table 1, classified according to treatment with or without amiodarone.

**Neurochemical indices of total systemic and cardiac sympathetic activity.** The arterial concentration of norepinephrine was elevated in this heart failure patient group, as previously described (15,22), but similar between patients according to amiodarone treatment (treated vs. untreated: 2.6 ± 0.3 vs. 3.3 ± 0.3 nmol/liter, p = NS). Similarly, the total body spillover rate for norepinephrine to plasma was not significantly different between amiodarone-treated patients and their nontreated counterparts (5.6 ± 0.4 vs. 4.6 ± 0.4 nmol/min, p = NS). The arterial concentration of DOPA, the norepinephrine precursor, was similar in treated and untreated patients (10.8 ± 0.9 vs. 9.9 ± 0.6 nmol/liter, p = NS). The arterial concentration of DHPG, the major intraneuronal metabolite of norepinephrine, was also similar among the two patient groups (treated vs. untreated: 6.2 ± 0.4 vs. 7.6 ± 0.4 nmol/L).

Despite the lack of apparent effect of amiodarone on indices of total systemic sympathetic activity, significant differences in the neurochemical markers of cardiac sympathetic neuronal function were evident (Fig. 1). The cardiac norepinephrine spillover rate was 42% lower in those patients treated with amiodarone (248 ± 22 vs. 433 ± 50 pmol/min, p = 0.001). There was also lower cardiac release rate for DOPA in amiodarone-treated patients (55 ± 23 vs. 211 ± 29 pmol/min, p < 0.001). The cardiac release rate for DHPG and tritium-labeled dihydroxyphenylglycol (H-DHPG SR), for patients not treated with amiodarone (A-) and those treated with amiodarone (A+). *p < 0.05, **p < 0.01, ***p < 0.001.

Figure 1. Bar graphs representing the differences in cardiac spill-over rates for norepinephrine (NE SR), dihydroxyphenylalanine (DOPA SR), dihydroxyphenylglycol (DHPG SR) and tritium-labeled dihydroxyphenylglycol (H-DHPG SR), for patients not treated with amiodarone (A-) and those treated with amiodarone (A+). *p < 0.05, **p < 0.01, ***p < 0.001.

**Hemodynamic profiles, and influence on sympathetic activity.** Although the group of patients treated with amiodarone had a similar mean left ventricular ejection fraction to those not receiving amiodarone, they were characterized by a higher cardiac output (Table 1). Amiodarone patients also had a nonsignificant trend toward lower pulmonary arterial and wedge pressures. The heart rate of amiodarone-treated patients was significantly lower than that in their untreated counterparts. The mean arterial pressure was not different between the two groups.

In view of a previous report from our group that demonstrated a strong, positive relationship between pulmonary arterial pressure and cardiac sympathetic activity (13), we compared the cardiac norepinephrine spillover between groups, by matching the mean pulmonary artery pressure of the 22 amiodarone-treated patients with 22 nontreated patients (Table 2). In this analysis, the cardiac spillover rate for norepinephrine, DOPA and DHPG continued to be significantly lower in patients treated with amiodarone. After adjustment in this manner, cardiac output continued to be significantly higher in amiodarone-treated patients. In
patients not treated with amiodarone, a weakly significant correlation between cardiac output and cardiac norepinephrine spillover rate could be demonstrated (r = -0.35, p = 0.04), but no relationship between cardiac output and DOPA or DHPG spillover from the heart was evident. In a separate case-matching analysis, patients in the two study groups were matched according to cardiac output (Table 3). In this analysis, a major influence of amiodarone on sympathetic neuronal biochemical integrity was still evident.

Mechanism of action. To explore the potential mechanism for the effect of amiodarone on cardiac sympathetic neuronal function, we examined the relationship between the cardiac spillover rates for DOPA, norepinephrine and DHPG as an index of sympathetic neuronal biochemical integrity. In amiodarone-treated patients the ratio of cardiac DOPA spillover to cardiac norepinephrine spillover was significantly lower than in nontreated patients (Fig. 2). In contrast, the ratio of the cardiac spillover rates for both DHPG and 3H-DHPG and norepinephrine were not significantly different among patient groups (Fig. 2).

Table 2. Hemodynamic and Neurochemical Profile in Patients Matched by Pulmonary Artery Pressure

<table>
<thead>
<tr>
<th></th>
<th>No Amiodarone (n = 22)</th>
<th>Amiodarone (n = 22)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mm Hg)</td>
<td>80 ± 2</td>
<td>81 ± 2</td>
<td>NS</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>87 ± 4</td>
<td>73 ± 3</td>
<td>0.01</td>
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<tr>
<td>Cardiac output (liters/min)</td>
<td>3.8 ± 0.2</td>
<td>4.4 ± 0.2</td>
<td>&lt; 0.05</td>
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<tr>
<td>Mean PAP (mm Hg)</td>
<td>26 ± 2</td>
<td>26 ± 2</td>
<td>NS</td>
</tr>
<tr>
<td>PCWP (mm Hg)</td>
<td>18 ± 2</td>
<td>18 ± 2</td>
<td>NS</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>21 ± 2</td>
<td>21 ± 2</td>
<td>NS</td>
</tr>
<tr>
<td>Cardiac NE SR (pmol/min)</td>
<td>363 ± 49</td>
<td>248 ± 22</td>
<td>&lt; 0.05</td>
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<tr>
<td>Cardiac DOPA SR (pmol/min)</td>
<td>201 ± 34</td>
<td>59 ± 25</td>
<td>&lt; 0.01</td>
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<tr>
<td>Cardiac DHPG SR (pmol/min)</td>
<td>743 ± 126</td>
<td>413 ± 38</td>
<td>&lt; 0.05</td>
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<tr>
<td>Cardiac 3H-DHPG SR (dpm/min)</td>
<td>7,645 ± 1,208</td>
<td>4,013 ± 614</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

DHPG = dihydroxyphenylglycol; DOPA = dihydroxyphenylalanine; HR = heart rate; LVEF = left ventricular ejection fraction; MAP = mean arterial pressure; NE = norepinephrine; PAP = pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; SR = spillover rate.

Table 3. Hemodynamic and Neurochemical Profile in Patients Matched by Cardiac Output

<table>
<thead>
<tr>
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<th>No Amiodarone (n = 20)</th>
<th>Amiodarone (n = 20)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mm Hg)</td>
<td>80 ± 2</td>
<td>81 ± 2</td>
<td>NS</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>81 ± 3</td>
<td>75 ± 3</td>
<td>NS</td>
</tr>
<tr>
<td>Cardiac output (liters/min)</td>
<td>4.1 ± 0.2</td>
<td>4.2 ± 0.2</td>
<td>NS</td>
</tr>
<tr>
<td>Mean PAP (mm Hg)</td>
<td>27 ± 2</td>
<td>30 ± 3</td>
<td>NS</td>
</tr>
<tr>
<td>PCWP (mm Hg)</td>
<td>18 ± 2</td>
<td>22 ± 2</td>
<td>NS</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>19 ± 1</td>
<td>19 ± 1</td>
<td>NS</td>
</tr>
<tr>
<td>Cardiac NE SR (pmol/min)</td>
<td>408 ± 60</td>
<td>253 ± 24</td>
<td>&lt; 0.05</td>
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<tr>
<td>Cardiac DOPA SR (pmol/min)</td>
<td>199 ± 41</td>
<td>39 ± 21</td>
<td>&lt; 0.01</td>
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<tr>
<td>Cardiac DHPG SR (pmol/min)</td>
<td>779 ± 134</td>
<td>388 ± 37</td>
<td>&lt; 0.05</td>
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<tr>
<td>Cardiac 3H-DHPG SR (dpm/min)</td>
<td>7,485 ± 1,253</td>
<td>3,897 ± 651</td>
<td>&lt; 0.05</td>
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</table>

Abbreviations as in Table 2.

DISCUSSION

In the current study we examined the influence of chronic amiodarone therapy on cardiac and total systemic sympathetic activity using a neurochemical approach established by our group (18,19). The major finding was that amiodarone in clinically relevant doses potently reduced the spillover of norepinephrine to plasma from the heart, in patients with severely depressed left ventricular function.

Sympathetic nervous system in heart failure. Congestive cardiac failure has been well characterized as a syndrome marked by neurohumoral activation. Of paramount importance, activation of the sympathetic nervous system has been shown to be associated with an adverse prognosis, based upon measurements of the peripheral plasma norepinephrine concentration and, more recently, the rate of norepinephrine release from the failing heart specifically (15,22). The spatial pattern of sympathoexcitation that occurs in heart failure is not homogeneous, and appears to be most marked in the heart (12,13). Further, increased activity of the cardiac sympathetic efferent fibers may even occur in
isolation in mild heart failure, as reported recently by Rundqvist and colleagues (14). The potential pathophysiologic mechanisms by which increased cardiac sympathetic nervous activity translates into adverse clinical end points are numerous, and include: i) facilitation of ventricular arrhythmia development, ii) exacerbation of underlying myocardial ischemia, and iii) alteration of myocardial structure, including fibrosis and myocyte necrosis (23,24), in addition to the potential effects of down-regulation of beta-adrenoreceptors and their second messenger signaling effector pathways (25,26).

The clinical importance of modulating the sympathoadrenergic neuroeffector pathway in patients with heart failure has been highlighted by the recent multicenter carvedilol study (3). Although this study showed a favorable effect on both morbidity and mortality, the mechanism(s) by which carvedilol exerts this action is not clear. Gilbert and colleagues recently demonstrated that carvedilol reduced the concentration of norepinephrine in the coronary sinus, whereas metoprolol led to an increase, and carvedilol therapy was associated with a somewhat more favorable effect on left ventricular function (27). These data might therefore suggest that the antiadrenergic influence of carvedilol is a key component of its beneficial clinical actions.

**Sympatholytic action of amiodarone in the failing heart.**

In the current study we observed a 42% lower cardiac norepinephrine spillover rate in patients chronically treated with amiodarone. In a recent study from our group, the acute administration of intravenous amiodarone in rats was associated with a significant reduction in the cardiac norepinephrine overflow rate during direct sympathetic nerve stimulation (11). In this study, however, chronic amiodarone dosing had no effect on cardiac norepinephrine release. Our findings are also consistent with previous data which demonstrate that amiodarone attenuates cardiac responses to sympathetic stimulation through mechanism(s) that are not dependent on adrenoceptor blockade (28).

The rate of spillover of norepinephrine to plasma from the sympathetic neuroeffector junction is dependent on a number of factors that include the rate of neurotransmitter release (determined by the synthesis rate, vesicular storage and degranulation and nerve firing rate), the rate of neuronal reuptake and the influence of other factors including the presence of diffusion barriers between the synaptic cleft and plasma (19). In the current study, amiodarone therapy was associated with a marked reduction in the transcardiac release of the norepinephrine precursor DOPA, suggesting that the sympatholytic actions of amiodarone might be mediated by reduced norepinephrine synthesis. In preliminary studies, we examined myocardial tyrosine hydroxylase messenger ribonucleic acid expression in explanted failing tissue, but were unable to demonstrate an effect of amiodarone, albeit in a small number of patients (unpublished observations). This finding, however, does not exclude an effect of amiodarone on tyrosine hydroxylase enzymatic activity, which may be increased under certain conditions by phosphorylation (29). The apparently lower rates of transcardiac DOPA and norepinephrine spillover could, potentially, also be explained by lower rates of sympathetic nerve firing in the amiodarone-treated patients (30), although in this situation a greater reduction in DOPA than norepinephrine spillover would not be expected. In our study, amiodarone-treated patients were somewhat less hemodynamically compromised than nontreated patients, albeit with similar left ventricular ejection fractions. On the basis of previous studies which demonstrated that both cardiac norepinephrine spillover and muscle sympathetic nerve activity were positively correlated with pulmonary arterial pressures (13,31), we attempted to correct for between-group hemodynamic differences as a potential confounding factor. In this analysis, cardiac norepinephrine spillover remained significantly lower, suggesting that the effect of amiodarone was not likely to be mediated by an effect on nerve firing rate per se.

Norepinephrine spillover to plasma may also be influenced by factors affecting the neuronal reuptake of norepinephrine from the synaptic cleft (32). In the current study we did not observe any difference in the transcardiac extraction of tracer norepinephrine across the heart. Although we also observed lower rates of transcardiac spillover

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**Figure 2.** Bar graph comparing the ratios of transcardiac spillover rates for dihydroxyphenylalanine to norepinephrine (DOPA:NE SR), dihydroxyphenylglycol to norepinephrine (DHPG:NE SR) and tritium-labeled dihydroxyphenylglycol to norepinephrine (³H DHPG:NE SR) for nontreated (A−) and treated patients (A+). **p < 0.05.
for both unlabeled and radiolabeled DHPG, these were in direct proportion to the prevailing norepinephrine spillover rate, suggesting that the actions of amiodarone were not mediated by an effect on neuronal reuptake or vesicular storage. This finding is in contrast with the findings of Du et al. (11), who observed a reserpine-like action of acute intravenous amiodarone in rats, as reflected by a dose-dependent increase in cardiac DHPG overflow.

In contrast to the apparent influence of amiodarone on cardiac sympathetic neuronal function, we could not detect any effect upon indices of total systemic sympathetic activity. Specifically, the total body spillover rate for norepinephrine was similar for both amiodarone-treated and untreated patients. Similarly, there were no apparent differences in the arterial concentration of DOPA, DHPG or 3H-DHPG. These findings suggest that the sympatholytic action of amiodarone may be relatively cardiac-specific, although we did not specifically measure the norepinephrine spillover rate for other organs, such as the kidney. One potential explanation for the apparently cardiobeneficial nature of amiodarone could relate to the fact that sympathetic nervous activation occurs earliest and is most prominent in the heart in congestive cardiac failure (14), and that a sympatholytic action would be most readily detected in an organ receiving high sympathetic efferent input. This hypothesis may explain, in part, the apparently contradictory results of the GESICA and CHF-STAT studies of the effect of amiodarone on survival in heart failure (5,6). Were the effects of amiodarone to be most apparent in the setting of high cardiac sympathetic tone, then it could be anticipated that the most compromised patients might derive the greatest benefit. Consistent with this notion, a follow-up study of the GESICA trial demonstrated that the beneficial effect of amiodarone was limited to patients with a heart rate >90/min, and also lower left ventricular ejection fraction (33). In addition, the mean heart rate of patients in the GESICA study was higher than that in CHF-STAT (5,6).

Study limitations. A potential limitation of the present study was its cross-sectional design. We have attempted to account for the potential confounding effect of hemodynamics by matching patients according to their pulmonary arterial pressures, which we have previously shown to be an important determinant of cardiac sympathetic tone (13,34). Although the left ventricular ejection fraction was similar between the two patient groups, amiodarone-treated patients displayed a significantly higher cardiac output. In this study, and in a previous study, we found a significant, albeit relatively weak, relationship between cardiac output and cardiac norepinephrine spillover rate. However, cardiac output bore no relationship to either DHPG or DOPA spillover from the heart, making it unlikely that the between-group differences were solely due to hemodynamic differences. Although it is not possible to account for the hemodynamic differences in the present study, a previous study did identify a favorable effect of amiodarone on left ventricular function (6). Based on this observation it is possible that the amiodarone-treated group may have had even greater sympathoexcitation before initiation of amiodarone due to greater hemodynamic compromise. The observations of Singh et al. (6) also raise the possibility that the more favorable hemodynamic profile seen in this patient group could, in part, be a consequence of the antiadrenergic effect of amiodarone therapy itself, in a manner analogous to the beneficial effects of long-term beta-adrenoceptor blocker therapy (27). The magnitude of the differences in cardiac catecholamine spillover between the groups also suggests that this was not merely due to differences in hemodynamic severity. Most notable was the 74% lower spillover rate for DOPA in amiodarone-treated patients. In fact, the spillover rate was even lower than that previously reported in healthy volunteers (13). Our contention that amiodarone exerts a sympatholytic action is also supported by a recent observation from our group that the drug exerts a reserpine-like action in Chinese hamster ovary cells expressing the vesicular monoamine transporter (35).

In conclusion, the present study demonstrates for the first time a sympatholytic action of chronic amiodarone therapy in humans with congestive heart failure. This action appears to be cardiac specific and may be mediated through an action upon the biosynthetic pathway for norepinephrine. The antiarrhythmic effect of amiodarone may therefore be, in part, due to its antiadrenergic properties. On the basis of these studies it might be anticipated that a beneficial effect of amiodarone might be most apparent in patients with high levels of cardiac sympathetic overactivity, although this remains unclear.

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