Cardiac Sympathetic Nervous Activity in Congestive Heart Failure

Evidence for Increased Neuronal Norepinephrine Release and Preserved Neuronal Uptake

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Background. Increased concentrations of norepinephrine in coronary sinus plasma reported in congestive heart failure (CHF) could result from increased cardiac sympathetic nerve firing and norepinephrine release or from failure of neuronal uptake mechanisms to recapture released norepinephrine. We have applied neurochemical indexes of cardiac sympathetic nerve function in heart failure patients to delineate the underlying neural pathophysiology.

Methods and Results. Cardiac norepinephrine synthesis, assessed from the cardiac overflow of the norepinephrine precursor dihydroxyphenylalanine (DOPA), intraneuronal metabolism estimated from the overflow of the intraneuronal metabolite dihydroxyphenylglycol (DHPG), neuronal norepinephrine reuptake assessed from the fractional extraction of plasma-tritiated norepinephrine and production of tritiated DHPG across the heart, and norepinephrine spillover to plasma were examined in eight patients with CHF caused by coronary artery disease (left ventricular ejection fraction of 26±5%, mean±SEM) and 14 age-matched healthy subjects. Cardiac norepinephrine spillover was increased eightfold in CHF subjects (127 ng/min versus 14 ng/min in healthy subjects; standard error of the difference [SED], 8 ng/min; P<.002), and cardiac DOPA was increased twofold (P<.02). The fractional extraction of tritiated norepinephrine across the heart was marginally less in CHF subjects (0.63 versus 0.73 in normal subjects; SED, 0.02), but the extent to which pharmacological neuronal uptake blockade with desipramine reduced the cardiac extraction of tritiated norepinephrine (by 71% versus 73% in normal subjects) and reduced the production of tritiated DHPG derived from uptake and intraneuronal metabolism of tritiated norepinephrine was similar in CHF patients and healthy subjects.

Conclusions. The marked increase in norepinephrine spillover from the heart in CHF attributable to coronary artery disease results primarily from an increase in sympathetic nerve firing and neuronal release of norepinephrine, not from faulty neuronal reuptake of norepinephrine. (Circulation 1993;88:136-145)

KEY WORDS • norepinephrine • desipramine • congestive heart failure

Although it is generally accepted that sympathetic nervous activity is increased overall in human congestive heart failure,1-5 biochemical assessment of sympathetic nervous activity to the heart in congestive heart failure has provided many conflicting opinions as the many techniques available to measure it. Although early workers considered that there was a functional denervation of the heart in heart failure, based on findings of reduced myocardial norepinephrine stores,6,7 reduced responsiveness of the myocardium to the indirect actions of tyramine,8 and reduced myocardial norepinephrine synthesis and turnover,9,10 more recent findings, in particular an increased aorto-coronary sinus plasma norepinephrine gradient11,12 and an increase in the rate of norepinephrine spillover to plasma from the heart,4 have suggested that cardiac sympathetic nervous activity is increased in congestive heart failure.

Controversy exists regarding the interpretation of increased cardiac norepinephrine spillover to plasma in heart failure. The rate at which norepinephrine escapes from the neuroeffector junction and appears in coronary sinus plasma is dependent on several factors, including the rate of neuronal release of norepinephrine and the capacity for neuronal reuptake.13-16 An increase in the aorto-coronary sinus plasma norepinephrine gradient could result from either an increase in norepinephrine release or from a reduction in the capacity for neuronal uptake without any concomitant increase in norepinephrine release.

Evidence has now emerged to support both normal4 and reduced17 neuronal uptake of norepinephrine by the cardiac sympathetic nerves, based on observations made with two available methods for assessing neuronal uptake.
TABLE 1  Clinical Characteristics of the Patients With Congestive Heart Failure

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Wt (kg)</th>
<th>Cause</th>
<th>NYHA class</th>
<th>Symptom duration (years)</th>
<th>LVEF (%)</th>
<th>RVEF (%)</th>
<th>Previous therapy</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>64</td>
<td>M</td>
<td>77.0</td>
<td>HT, CAD</td>
<td>II/III</td>
<td>3.5</td>
<td>27</td>
<td>56</td>
<td>D, En, F, I</td>
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<td>71.5</td>
<td>CAD</td>
<td>III</td>
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<td>16</td>
<td>28</td>
<td>D, C, E, W</td>
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<tr>
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<td>74</td>
<td>M</td>
<td>62.5</td>
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<td>M</td>
<td>74.0</td>
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<td>IV</td>
<td>7.5</td>
<td>8</td>
<td>22</td>
<td>D, C, F, W</td>
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<td>5</td>
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<td>M</td>
<td>79.5</td>
<td>CAD</td>
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<tr>
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<td>86.0</td>
<td>CAD</td>
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<td>88.0</td>
<td>CAD</td>
<td>III</td>
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<td>8</td>
<td>62</td>
<td>M</td>
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<td>II</td>
<td>2.5</td>
<td>39</td>
<td>50</td>
<td>C, F, I</td>
</tr>
</tbody>
</table>

NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; RVEF, right ventricular ejection fraction; HT, hypertension; CAD, coronary artery disease. Drugs D, C, E, En, F, I, and W denote digoxin, captopril, ethacrynic acid, enalapril, frusemide, isordil, and warfarin, respectively. No drug therapy was given on the day of the study.

To reconcile these differences, we sought to establish in more detail the biochemical profile of cardiac sympathetic nervous function in patients with congestive heart failure. Biochemical measurements of norepinephrine synthesis, turnover, apparent release, and neuronal uptake were examined in concert to assess the functional integrity of the cardiac sympathetic nerves in congestive heart failure. Cardiac dihydroxyphenylalanine (DOPA) spillover was used as a measure of the rate of cardiac neuronal norepinephrine synthesis. DOPA is formed by the hydroxylation of tyrosine in the rate-limiting step of catecholamine biosynthesis, and its concentration in the plasma pool is thought to reflect, in part, the rate of norepinephrine synthesis by sympathetic nerves.19-21 DOPA appearing in coronary sinus plasma is derived primarily from the cardiac sympathetic nerves.22 Cardiac dihydroxyphenylglycol (DHPG) spillover provides an index of norepinephrine turnover by cardiac sympathetic nerves. DHPG is an exclusively intraneuronal metabolite formed by the deamination of norepinephrine leaking from vesicular stores or from norepinephrine recaptured after release.23,24

The apparent release rate of norepinephrine was measured for the heart and the body as a whole using the steady-state radiotracer technique,25-27 and the integrity of norepinephrine uptake was assessed in the heart from the fractional extraction of radiolabeled norepinephrine in transit27-31 and from the rate of production of tritium-labeled DHPG, formed intraneuronally after capture by neuronal uptake of tritium-labeled norepinephrine in plasma.28 These indexes of neuronal uptake of norepinephrine were assessed both in the presence and absence of the pharmacological inhibitor of neuronal uptake, desipramine.

The findings in heart failure were compared with those of aged-matched normal subjects and patients with pure autonomic failure (idiopathic orthostatic hypotension), the latter group providing a yardstick of cardiac sympathetic denervation.22 The aim of this study was to determine whether the heart is in fact functionally denervated in patients with severe congestive heart failure and to ascertain whether increased levels of norepinephrine in coronary sinus plasma in congestive heart failure result from either increased neuronal release of norepinephrine (and hence, nerve firing) or from impaired cardiac neuronal reuptake of norepinephrine.

Methods

Recruitment of Patients

Eight patients with chronic congestive heart failure (mean age, 64 years; range, 55 to 74 years and 14 healthy aged-matched normal subjects (mean age, 55 years; range, 35 to 78 years) participated in this study, which was performed with written informed consent and the approval of the Alfred Hospital Ethics Review Committee.

All eight patients had a protracted history of symptomatic congestive heart failure (mean, 4.8 years; range, 2.5 to 7.5 years) consequent upon either coronary artery disease and previous myocardial infarction (n=6) or a combination of previous myocardial infarction and hypertension (n=2) (Table 1). All had left ventricular ejection fractions measured by radionucleotide ventriculography of <40% and were receiving standard anti-failure therapies (Table 1). No patient had suffered recent myocardial infarction or unstable angina. There were no cases of uncorrected valvular heart disease. Patients with significant noncardiac medical illnesses such as chronic lung, liver, or renal diseases were not recruited for this study. Normal subjects were recruited...
from the community by advertisement and were screened by medical history, examination, and routine laboratory tests.

For the purpose of providing a benchmark of cardiac sympathetic denervation, six patients with pure autonomic failure (PAF) were also tested. All six patients with PAF had a long history of symptomatic postural hypotension, and the diagnosis was confirmed using standard noninvasive and invasive tests of autonomic reflex function.22

**General Procedure**

To avoid the confounding influence of multiple drug therapies, all medications were withdrawn before the study. To achieve this safely in patients dependent on antifailure therapy, all patients had their therapy optimized in the 4 weeks preceding the study. Three days before the study, patients were electively admitted to the hospital for stepwise withdrawal of medications under medical supervision. Those receiving long-term oral anticoagulant therapy (with warfarin in patients 2, 4, 5, and 6) had their oral therapy withheld on admission and were converted to intravenous heparin for the prestudy and immediate poststudy periods. Oral anticoagulation was resumed on the evening of the day of study. Medications other than the loop diuretic, furosemide, and short-acting nitrates were ceased 48 hours before the study. Furosemide was withheld for 24 hours, and short-acting nitrates were withheld only on the morning of the study.

All patients were studied at rest in the supine position 2 hours after eating a standardized light breakfast. Tea, coffee, and alcohol were withheld for a minimum of 12 hours before the study. Cardiac output and right heart pressure measurements were made using a Swan-Ganz thermodilution catheter. Total-body and cardiac sympathetic function were assessed according to the methods described below.

**Measurement of Total-Body Norepinephrine Spillover and Clearance**

The total-body norepinephrine spillover rate, a biochemical index of the overall integrated sympathetic nerve firing rate, and plasma norepinephrine clearance were measured using the radiotracer method developed in our laboratory.25-27

In brief, the method involves the continuous intravenous infusion of a tracer dose of norepinephrine (0.70 μCi/min Levo-[2-3H] norepinephrine, specific activity 12 to 20 Ci/mmol, New England Nuclear, Boston) to a steady-state concentration in plasma. The total norepinephrine spillover to plasma and total plasma norepinephrine clearance can then be calculated25 as follows.

\[
\text{Total NE spillover} = \frac{\text{[H]NE infusion rate (dpm/min)}}{\text{plasma NE specific activity (dpm/pg)}}
\]

and

\[
\text{total NE clearance} = \frac{\text{[H]NE infusion rate (dpm/min)}}{\text{plasma [H]NE concentration (dpm/mL)}}
\]

where NE = norepinephrine, dpm = disintegrations per minute of tritium-labeled NE, and [3H]NE = tritium-labeled norepinephrine.

**Cardiac Norepinephrine Spillover**

The rate of norepinephrine spillover from the heart was calculated according to the Fick principle, corrected for fractional extraction of [3H]NE across the heart27,29:

\[
\text{Cardiac NE spillover} = \frac{[(\text{NE}_C - \text{NE}_A) + (\text{NE}_A \times \text{NE}_E)] \times \text{CSFP}}{2}
\]

where \(\text{NE}_C\) = plasma NE concentration in the coronary sinus, \(\text{NE}_A\) = arterial plasma NE concentration, \(\text{NE}_E\) = the fractional extraction of tritiated NE in single passage through the heart, and \(\text{CSFP}\) = coronary sinus plasma flow (mL/min).

Arterial and coronary sinus sampling were performed using our previously published methods.30,31 The coronary sinus was catheterized using a 7F coronary sinus thermodilution catheter (Webster Laboratories, type CCS-7U-90B) introduced via an antecubital venous sheath. Coronary sinus plasma flows were derived from thermodilution-determined blood flows and the hematocrit.32

**Cardiac Spillovers of DOPA and DHPG**

The cardiac spillover of DOPA was calculated according to the formula

\[
\text{cardiac DOPA spillover} = (\text{DOPA}_C - \text{DOPA}_A) \times \text{CSBF}
\]

where \(\text{DOPA}_A\) and \(\text{DOPA}_C\) are the DOPA concentrations in the arterial and coronary sinus effluent plasma, and \(\text{CSBF}\) is the coronary sinus plasma flow. Plasma flow was used to calculate the cardiac spillover of DOPA based on results from our laboratory showing that 86% of exogenous DOPA added to whole blood is recoverable from the plasma compartment (unpublished data).

The cardiac spillovers of DHPG and 3H-DHPG were calculated as follows.

\[
\text{Cardiac DHPG spillover} = (\text{DHPG}_C - \text{DHPG}_A) \times \text{CSBF}
\]

where \(\text{DHPG}_A\) and \(\text{DHPG}_C\) are the DHPG concentrations in the arterial and coronary sinus effluent plasma, and \(\text{CSBF}\) is the coronary sinus blood flow. Blood flow rather than plasma flow was used to calculate the cardiac spillover of endogenous and tritium-labeled DHPG based on results showing that DHPG added to whole blood is equally distributed between the plasma and the red cell compartment.33

**Catechol Assays**

Arterial blood samples were transferred immediately to ice-chilled tubes containing an anticoagulant and antioxidant (EGTA plus glutathione). Plasma was separated by centrifugation at 4°C, and samples were subsequently stored at -70°C until assayed.

Endogenous norepinephrine, DHPG, DOPA, and epinephrine plasma concentrations were measured by high-performance liquid chromatography with electrochemical detection according to our previously published method.34 Fractions of the eluant leaving the electrochemical cell were collected into scintillation
vials for measurement of [3H]-labeled catechols by liquid scintillation spectroscopy.

**Pharmacological Neuronal Uptake Block**

The integrity of cardiac neuronal norepinephrine uptake was assessed in six of the eight patients with congestive heart failure and in seven of the 14 normal subjects by studying the extraction and neuronal processing of infused tritiated norepinephrine by the heart before and after the administration of desipramine (CIBA-GEIGY, Sydney, Australia). The removal of tritiated norepinephrine from plasma in transit through the heart and its subsequent intraneuronal processing to tritiated DHPG is largely dependent on an active process of neuronal norepinephrine uptake.28,30,31 The assumption we make, which is not directly testable, is that if neuronal uptake of infused tritiated norepinephrine is normal in the failing heart, then neuronal reuptake of endogenously released norepinephrine similarly is most likely normal. Desipramine was given intravenously over 20 minutes to a total dose of free base of 0.5 mg/kg, a dose that has previously been shown to produce substantial inhibition of neuronal uptake in vivo in humans.28,30,31,35 Comparisons were then drawn among patients with heart failure, the age-matched normal subjects, and the patients with pure autonomic failure.

**Statistical Methods**

Between-group comparisons (eg, heart failure versus normal subjects) were made using one-way ANOVA. Within-subject comparisons of the effects of desipramine were made using a two-way ANOVA. Data are expressed as mean±SEM (standard error of the difference) calculated from the error mean squared of the respective ANOVA table.36 The incremental effects of desipramine for both heart failure patients and normal subjects were also compared using one-way ANOVA. The null hypothesis was rejected at P<.05.

**Results**

**Functional and Hemodynamic Assessment**

Patients with congestive heart failure did not differ significantly in age, weight, or body surface area from their healthy counterparts (63.6 versus 57.2 years; SED, 15 years; 76.5 versus 76.0 kg; SED, 1.5 kg; and 1.92 versus 1.89 m²; SED, 0.02 m², respectively). The heart failure patients exhibited a moderate to severe reduction in functional capacity as reflected in their New York Heart Association (NYHA) class and a moderately severe reduction in biventricular function as indicated by their right and left ventricular ejection fractions (32±6% and 26±5% [mean±SEM], respectively; Table 1). Hemodynamic assessment of the heart failure patients revealed a cardiac index at rest of 2.1±0.1 L · min⁻¹ · m⁻² (Table 2) and a total peripheral resistance index of 43±2 mm Hg · L⁻¹ · min⁻¹ · m⁻². Right atrial and mean pulmonary arterial pressures were elevated, as was the pulmonary capillary wedge pressure (Table 2).

**Total-Body Sympathetic Nervous Function**

Total-body norepinephrine spillover rate to plasma was 61% higher in patients with congestive heart failure than in the normal control subjects (1168 versus 724 ng/min; SED, 60 ng/min; P<.02; Fig 1). The arterial plasma concentration of norepinephrine was, however, 137% higher in the heart failure patients (Table 3) because of the additional influence of a 25% reduction in the rate of norepinephrine clearance from plasma (1.96 versus 2.61 L/min; SED, 0.08 L/min; P<.03). An increase in norepinephrine turnover in heart failure was also reflected in a 74% increase in the concentration of DOPA in arterial plasma (P<.001) and a 37% increase in the arterial plasma DHPG concentration (P<.03, Table 3). Adrenal medullary activation in the heart failure patients was evident in the 92% higher arterial plasma epinephrine concentration (P<.03, Table 3).

**Cardiac Sympathetic Function**

Norepinephrine spillover to plasma from the heart was increased 800% in patients with congestive heart failure compared with normal subjects (127 versus 14 ng/min; SED, 8 ng/min; P<.002; Fig 2). The cardiac contribution to the total norepinephrine spillover to plasma was disproportionately increased in heart failure, with cardiac norepinephrine spillover accounting for 10.8% of total-body norepinephrine spillover compared with 1.9% in normal subjects. Among these eight patients with cardiac failure, cardiac norepinephrine spillover values were not related to the NYHA functional class or to the left ventricular ejection fraction. The rise in cardiac norepinephrine spillover was associated with an 83% increase in the cardiac spillover of the norepinephrine precursor DOPA (P<.02, Fig 2) and a 22% increase in the spillover of its intraneuronal metabolite, DHPG. These differences in norepinephrine, DOPA, and DHPG spillover between heart failure patients and normal subjects were not explained by differences in the coronary sinus plasma flow, which was similar in the two groups (111 mL/min in heart failure compared with 104 mL/min in normal subjects; SED, 8 mL/min).

The spillovers of norepinephrine, DOPA, and DHPG observed in congestive heart failure bore no similarities to the pattern observed in PAF (Fig 2). The cardiac spillover of norepinephrine was 420-fold greater (P<.0001), and the cardiac spillovers of DOPA and DHPG were eightfold and 14-fold greater in congestive heart failure (33.6 ng/min compared with 3.9 ng/min in

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**Table 2. Hemodynamic Profiles of the Patients With Congestive Heart Failure**

<table>
<thead>
<tr>
<th></th>
<th>Congestive heart failure (n=8)</th>
<th>Normal subjects (n=14)</th>
<th>SED</th>
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<td>94</td>
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<td>NS</td>
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<td>.03</td>
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<td>.001</td>
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<td>MPAP (mm Hg)</td>
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<td>PCWP (mm Hg)</td>
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<td>10</td>
<td>1.1</td>
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<tr>
<td>CI (L/min)</td>
<td>2.1</td>
<td>3.0</td>
<td>0.04</td>
<td>.001</td>
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<tr>
<td>TPR (mm Hg · L⁻¹ · min⁻¹ · m⁻²)</td>
<td>43.6</td>
<td>32</td>
<td>.7</td>
<td>.001</td>
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</tbody>
</table>

MAP, MRAP, MPAP, and PWCP denote mean arterial, mean right atrial, mean pulmonary artery, and pulmonary capillary wedge pressure, respectively; CI and TPR refer to cardiac index and total peripheral resistance index, respectively. SED, standard error of the difference.

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Norepinephrine uptake: effects of neuronal uptake block with desipramine

The heart. The fractional extraction of tritium-labeled norepinephrine across the heart was 13% less in heart failure (0.63 versus 0.73; SED, 0.02; P < .05). The extent to which desipramine reduced the cardiac extraction of tritium-labeled norepinephrine was similar in heart failure patients and normal subjects. Cardiac extraction of tritium-labeled norepinephrine was reduced 73% by desipramine in heart failure (from 0.63 to 0.17; SED, 0.02; P < .001; n = 6; Fig 2) and by 71% in normal subjects (from 0.70 to 0.20; SED, 0.02; P < .001; n = 7). The residual cardiac extraction after neuronal uptake blockade with desipramine in both normal subjects and heart failure patients was similar to the fractional extraction of tritium-labeled norepinephrine across the heart of patients with PAF (Fig 3).

Before administration of desipramine, the cardiac spillover of tritium-labeled DHPG formed from capture of tritium-labeled norepinephrine was similar in heart failure patients and normal subjects: 11 742 and 10 425 dpm/min, respectively; SED, 2450 dpm/min. Commensurate with the reduction in extraction of tritium-labeled norepinephrine, desipramine resulted in a 32% reduction in the cardiac spillover of tritium-labeled DHPG in heart failure (11 742 dpm/min before versus 7930 dpm/min after desipramine; SED, 1700 dpm/min; P < .03). This was similar in magnitude to the reduction of tritium-labeled DHPG after desipramine administration in the normal subjects (10 425 dpm/min before versus 5629 dpm/min after desipramine; SED, 870 dpm/min; P < .03; Fig 3). The cardiac spillover of endogenous DHPG, although not influenced by desipramine in normal subjects, was reduced 21% after the administration of desipramine in the heart failure patients (157 ng/min before versus 125 ng/min after desipramine; SED, 6.5; P < .05).

Neuronal uptake block with desipramine resulted in a 36% increase in the rate of norepinephrine spillover to plasma from the heart in patients with congestive heart failure (127 ng/min before versus 173 ng/min after desipramine; SED, 2.3; P < .02) but no change in normal subjects (18 ng/min before versus 21 ng/min after desipramine; SED, 1.6).

The whole body. In congestive heart failure, desipramine resulted in a 17% reduction in the rate at which norepinephrine was cleared from arterial plasma for the whole body (2.03 L/min before versus 1.68 L/min after desipramine; SED, 0.02 L/min; P < .001; Table 4). This was similar in magnitude (22% reduction) to the influence of desipramine on total norepinephrine clearance in normal subjects. As distinct from the reduction in total norepinephrine spillover rate and plasma norepinephrine concentration observed in normal subjects (Table 4), the administration of desipramine to patients with congestive heart failure resulted in a modest rise in

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**Table 3. Plasma Catechols in Patients With Congestive Heart Failure and in Normal Subjects**

<table>
<thead>
<tr>
<th></th>
<th>CHF (n=8)</th>
<th>Normal subjects (n=14)</th>
<th>SED</th>
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<td>Art plasma (NE) (pg/mL)</td>
<td>650</td>
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<td>32</td>
<td>.002</td>
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<tr>
<td>Art plasma (E) (pg/mL)</td>
<td>117</td>
<td>62</td>
<td>.2</td>
<td>.03</td>
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<tr>
<td>Art plasma (DOPA) (pg/mL)</td>
<td>2234</td>
<td>1279</td>
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<tr>
<td>Art plasma (DHPG) (pg/mL)</td>
<td>1458</td>
<td>1064</td>
<td>50</td>
<td>.03</td>
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</tbody>
</table>

CHF, congestive heart failure; Art, arterial sample; NE, E, DOPA, and DHPG denote norepinephrine, epinephrine, dihydroxyphenylalanine, and dihydroxyphenylglycol, respectively. SED, standard error of the difference.
total-body norepinephrine spillover and the arterial plasma concentration of norepinephrine (1266 ng/min before versus 1382 ng/min after desipramine in congestive heart failure; SED, 30 ng/min; 688 versus 928 pg/mL; SED, 45 pg/mL for total-body spillover and plasma concentration, respectively; \( P < .05 \)). This increase in norepinephrine spillover to plasma in heart failure was accompanied by a reduction in the arterial plasma concentration of the intraneuronal metabolite DHPG (1412 versus 1214 pg/mL; SED, 34 pg/mL; \( P < .05 \)). The comparative effects of desipramine on total-body plasma norepinephrine kinetics and arterial plasma DHPG concentration in congestive heart failure and normal subjects are shown in Table 4.

**Discussion**

In this study we examined cardiac and whole-body sympathetic nervous function in a group of patients with congestive heart failure secondary to coronary artery disease and hypertension. As distinct from previous work\(^{3,37}\), in which the extent of impairment of ventricular function was unclear, the severity of heart failure in the present study was well defined. Our patients had moderately severe congestive heart failure with reduced exercise capacity (as reflected in their functional class), biventricular impairment of systolic function (as indicated by the radionucleotide ejection fractions of the right and left ventricles), reduced resting cardiac output, elevated systemic vascular resistance, and elevation of the right heart, pulmonary, and left ventricular filling pressures.

In the heart failure patients, we observed a 61% increase in total-body norepinephrine spillover to plasma consistent with an overall increase in sympathetic nervous activity. The proportional elevation in the plasma concentration of norepinephrine in heart failure was greater than this because of a 25% reduction in the rate at which norepinephrine was cleared from plasma after its release. Reduced norepinephrine plasma clearance, attributable to lowered cardiac output and regional blood flows, has been described previously in cardiac failure.\(^{4,5}\) The increase in total-body norepinephrine spillover in heart failure was associated with an increase in the arterial plasma concentrations of DOPA and DHPG. Although the plasma concentration of DOPA is not a totally reliable index of sympathetic neuronal failure,\(^{22}\) its elevation in plasma in heart failure probably results from increased norepinephrine synthesis by sympathetic nerves\(^{19-21}\); however, the relative contribution of the activated adrenal medulla remains uncertain. Similarly, although the elevated arterial plasma levels of DHPG in heart failure patients most probably resulted from increased norepinephrine turnover in sympathetic nerves,\(^{20}\) other factors such as reduced plasma clearance of DHPG may have been involved.

Cardiac norepinephrine spillover was markedly increased in patients with congestive heart failure. Compared with healthy age-matched subjects, the rate of norepinephrine spillover to plasma from the heart was increased eightfold. This was similar to the findings of Hasking et al\(^{4,37}\) and Swedberg et al\(^{12}\) but contrasts with the findings of Rose et al,\(^{17}\) who found no evidence of increased norepinephrine overflow to plasma or estimated neuronal release of norepinephrine in heart failure. This increase in the rate of norepinephrine appearance in coronary sinus plasma in the present study probably resulted from an increase in cardiac sympathetic nerve firing and neuronal norepinephrine release. This is supported by evidence of an increased rate of norepinephrine synthesis by the cardiac sympathetic nerves in heart failure, as indicated by the elevated rate of spillover of DOPA from the heart and by evidence of normal or near-normal capacity for...
neuronal uptake of norepinephrine by the cardiac sympathetic nerves.

The nature of the relation existing between activation of the sympathetic nervous system and cardiac performance in patients with heart failure and the possible mechanism of such a relation is complex and is a matter of dispute. In the present study involving small numbers of patients with rather homogeneous clinical characteristics, the rate of cardiac norepinephrine spillover was unrelated to NYHA functional class and the left ventricular ejection fraction. Some\textsuperscript{38} but not all\textsuperscript{39} investigators describe a significant inverse correlation between left ventricular ejection fraction and the peripheral plasma concentrations of norepinephrine, and in a larger patient sample we reported an inverse exponential relation between the ejection fraction and cardiac norepinephrine spillover, with patients having the most advanced heart disease having the highest rates of cardiac norepinephrine release.\textsuperscript{40}

We found the capacity for neuronal uptake of norepinephrine in the failing heart to be substantially normal. Evidence supporting this is as follows. (1) The
influence of pharmacological neuronal uptake blockade with desipramine on the fractional extraction of plasma tritium-labeled norepinephrine across the heart and the cardiac spillover of tritium-labeled DHPG was identical in normal subjects and patients with heart failure. Although the fractional extraction of norepinephrine before desipramine was marginally less in heart failure patients than in healthy subjects, the extent to which neuronal uptake block with desipramine reduced neuronal uptake was similar in heart failure patients and normal subjects. That is, the desipramine-sensitive, neuronal uptake−dependent component of norepinephrine uptake from plasma was normal in heart failure. (2) A marked contrast existed in the biochemical indexes of cardiac neuronal norepinephrine uptake between heart failure patients and patients with PAF, who constitute a clinical model of cardiac sympathetic denervation and near-zero neuronal norepinephrine uptake.22 These findings of substantially normal norepinephrine uptake contrast with those of Rose et al.,17 who reported the fractional extraction of norepinephrine by the heart in heart failure to be only marginally above what we observe in the denervated heart of patients with aortic failure, and are similar to what we observe in heart failure after pharmacological neuronal uptake block with desipramine. It is possible (but not formally tested to date) that the sympathetic nerves of the failing heart retain a normal capacity for uptake of norepinephrine when heart failure is attributable to coronary artery disease, as was the case in the present study but not when valvular disease or cardiomyopathy is the cause.

The finding of a normal production and spillover of tritium-labeled DHPG by the heart in heart failure further supports the conclusion of a normal or near-normal capacity for neuronal uptake. As shown by the negligible cardiac production of tritium-labeled DHPG in the denervated heart, tritium-labeled DHPG is formed solely from the intraneuronal metabolism of tritium-labeled norepinephrine captured by neuronal uptake. If the capacity for neuronal removal of tritium-labeled norepinephrine were reduced, the production and subsequent spillover to plasma of tritium-labeled DHPG should be lowered. This was not the case. The fact that desipramine impaired the cardiac production of tritium-labeled DHPG to a similar extent in heart failure patients and normal subjects supports our view that the integrity of neuronal uptake of norepinephrine in the heart was maintained. The uptake of norepinephrine by extracardiac sympathetic nerves similarly is unimpaired in patients with heart failure.41,42

The rate at which norepinephrine spilled over into plasma, both from the heart and for the whole body, increased after desipramine in patients with congestive heart failure. These findings differed from the observed effects of desipramine in normal subjects. Although for a given level of sympathetic nerve firing, proportionally more norepinephrine escapes from the neuroeffector junctions and appears in plasma in the presence of neuronal uptake block, total-body spillover of norepinephrine was in fact decreased by desipramine in normal subjects because of the overriding central sympathoinhibitory influences of desipramine reducing the overall rate of sympathetic nerve firing.30 The presence of heart failure, however, appeared to confer some resistance to this central sympathoinhibitory influence. After the administration of desipramine in heart failure patients, we observed a 10% increase in total-body norepinephrine spillover to plasma and a 36% increase in the rate of norepinephrine spillover to plasma from the heart, consistent with the pharmacological inhibition of neuronal reuptake. Desipramine would not have had this effect in heart failure if impairment of neuronal uptake had been an important determinant of the disposition of the neurotransmitter after its release.

Why, then, should the fractional extraction of norepinephrine by the heart be marginally reduced in heart failure patients? One possible explanation may relate to the nature of the myocardial injury leading to heart failure in these patients. The heart of patients with coronary artery disease probably would contain fibrous scar tissue either localized to areas of previous myocardial infarction or occurring more diffusely throughout chronically ischemic areas. Perfusion of these denervated areas, as a result of collateral blood flow, could lead to a small reduction in the net extraction of plasma tritium-labeled norepinephrine during transit through the heart.

Our results differ from some results obtained in vitro and in animal models of heart failure. Petch and Naylor43 first suggested that sympathetic neuronal uptake was decreased in human heart failure. In that study, the in vitro rate of accumulation of radiolabeled norepinephrine by biopsy samples taken from the right atrium at the time of cardiac surgery for coronary bypass grafting or valve replacement was compared between patients with and without heart failure. Patients assigned to the heart failure group had evidence for reduced uptake of tritium-labeled norepinephrine. It is unclear, however, to what extent heart failure actually existed in this group of patients. The diagnosis was based purely on the clinical assessment of the referring physician and whether the patient was receiving digoxin and diuretics at the time of cardiac surgery. A further difficulty lies in the assessment of neuronal uptake in the presence of digitalization, which in itself may have depressed neuronal uptake. Evidence suggests that ouabain inhibits tissue accumulation of tritium-labeled norepinephrine in vitro.44,45

More recently, Liang et al45 suggested that neuronal uptake activity was diminished in the right ventricle in a dog model of heart failure induced by acute tricuspid avulsion and progressive pulmonary banding. Their conclusion was based on evidence of reduced accumulation of tritium-labeled norepinephrine in right ventricular tissue slices in vitro and of reduced binding of tritium-labeled mazindol, an imidazoline derivative structurally resembling tricyclic antidepressants and capable of blocking neuronal uptake of norepinephrine. However, this technique, using nonperfused slices of tissue, is particularly sensitive to factors such as tissue thickness, tissue accessibility, and diffusibility of the tracers. The dependence on tracer diffusibility and factors influencing diffusion with the in vitro methods for studying norepinephrine uptake has been emphasized by Schönig et al,46 who have reported recently that not only is there preferential labeling of sympathetic nerve varicosities close to the surface of the tissue but there is also preferential labeling of storage vesicles close to the surface of the nerve varicosities. The extent
to which tissue edema, hypertrophy, and fibrosis in heart failure may retard tracer diffusion in nonperfused tissue slices is unknown. In short, in vitro tissue slice methodology may not be well suited for quantifying norepinephrine uptake.

In congestive heart failure, overall sympathetic nervous activity is increased. Norepinephrine spillover to plasma from the heart is elevated disproportionately to that from the body as a whole and increases exponentially with deteriorating left ventricular function.40 The results of the present study indicate that the marked increase in norepinephrine spillover from the heart in heart failure caused by ischemic heart disease results largely from an increase in sympathetic nerve firing and neuronal release of norepinephrine and not from a failure to recapture released norepinephrine. The prevailing view that a functional cardiac denervation exists in heart failure appears to be incorrect, stemming from a misconception equating tissue norepinephrine content with function. It is probable that the increased norepinephrine turnover observed in congestive heart failure reduces tissue norepinephrine stores but without discernable diminution in neural function.

The clinical implications of the pathophysiological changes we describe in the sympathetic nerves of the failing human heart are presently somewhat uncertain but are of interest. It is likely that the intense myocardial sympathetic stimulation implied by our results contributes to the myocardial β-adrenoceptor down-regulation that accompanies heart failure.41 It is not known if the rather unpredictable clinical response to β-adrenergic blockade in cardiac failure is dictated by between-subject differences in the prevailing level of cardiac sympathetic tone. It is possible, although not tested to date, that patients with the highest levels of cardiac sympathetic activity do not benefit from β-adrenergic blockade because they are the most dependent on neural drive for inotropic support of the failing ventricles. Whether the activation of the cardiac sympathetic nerves in cardiac failure contributes materially to arrhythmogenesis42 and influences survival43 is a matter under investigation in several laboratories, including our own.

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