Neurotransmitter Depletion Compromises the Ability of Indirect-Acting Amines to Provide Inotropic Support in the Failing Human Heart

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To test the hypothesis that cardiac norepinephrine depletion related to heart failure alters contractile responses to β-adrenergic agonists with a component of "indirect" action (acting by release of neuronal norepinephrine), we examined the inotropic potential of several pharmacologically distinct β-agonists. Contractile responses to the nonselective β-agonist isoproterenol, the β₂-selective agonist zintrol, and the direct- and indirect-acting agonists dopamine and dopexamine were compared in isolated right ventricular trabeculae removed from failing, nonfailing innervated, and previously transplanted and, therefore, denervated nonfailing human hearts. In failing hearts, the contractile response to isoproterenol was significantly lower (41%) than that in nonfailing innervated hearts. The responses to the mixed agonists dopamine and dopexamine were even more attenuated in failing hearts, to a level 76–90% lower than those of nonfailing innervated hearts. In denervated, previously transplanted, nonfailing hearts, the contractile responses to the mixed agonists dopamine and dopexamine were 66–72% lower than those in the nonfailing innervated group, but the response to isoproterenol was not significantly different. The response to zintrol was not significantly different among the three groups. In subjects with severe heart failure, in vivo hemodynamic responses to dopexamine were compared with those of the direct-acting β-agonist dobutamine. Responses to dopexamine and dobutamine were measured before and after prolonged continuous infusions of each drug. The response to dopexamine, but not to dobutamine, diminished over time. We conclude that a large component of the inotropic response to dopamine and dopexamine in human hearts is due to the ability of these agonists to promote the release of neuronal norepinephrine; when neuronal norepinephrine is depleted, indirect-acting agonists are less able to produce an inotropic response. (Circulation 1990;81:929–938)

β-Adrenergic receptor agonists are commonly used for short-term inotropic support in individuals with severe myocardial dysfunction. There are currently a large number of β-agonists available for clinical use, and these agents possess a variety of pharmacologic profiles. These include compounds such as the nonselective full agonist isoproterenol,1 the relatively nonselective β-agonist dobutamine,2,3 compounds with mixed direct- and indirect-acting properties such as dopamine4 and dopexamine,5 and the endogenous catecholamines, epinephrine, and norepinephrine.1

When sympathomimetic agents are used in the treatment of low-output heart failure, their pharmacologic properties and the pathophysiologic state of the failing heart must be considered. In end-stage failing hearts with idiopathic dilated cardiomyopathy, β₁-adrenergic receptors are often down-regulated by as much as 60%.6 In contrast, β₂-receptor density is generally preserved6; however, the coupling efficiency of β₂-receptors to subsequent events in the effector pathway is mildly (about 30%) reduced.6,7 In addition to receptor-related changes, high adrenergic

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drive or other pathophysiologic adjustments to heart failure can cause marked depletion of neuronal norepinephrine in failing ventricular myocardium.8

Based on the above abnormalities, it would be expected that in the failing heart the activity of selective β1-agonists would be markedly reduced, whereas the inotropic effect of selective β2-agonists would be attenuated to a lesser degree, and this in fact is the case.6 It could be further postulated that indirect-acting amines, which are dependent on the availability of releasable neuronal norepinephrine, would exhibit an additional component of attenuation that is secondary to neurotransmitter depletion. However, this latter possibility has not been examined previously in the failing human heart.

Accordingly, we tested the hypothesis that positively inotropic β-agonists that possess indirect or norepinephrine-releasing properties would have diminished inotropic potential in the norepinephrine-depleted failing human heart. To this end, we examined the inotropic effects of two “mixed” or direct- and indirect-acting agonists, dopamine and dopexamine, and compared them with the direct-acting, nonselective, full agonist isoproterenol and the direct-acting β2-selective agonist zintrol.9 Comparisons were made in isolated right ventricular trabeculae from patients undergoing cardiac transplantation for end-stage biventricular failure (failing heart), from patients with globally normal ventricular function undergoing retransplantation because of coronary atherosclerosis (denervated, nonfailing heart), and from organ donors with normal cardiac function whose hearts were not used for cardiac transplantation (innervated nonfailing heart).

In a companion clinical study, we compared the hemodynamic effects of the direct-acting β-agonist dobutamine to the indirect-acting agent dopexamine in patients with severe end-stage heart failure. The results indicate that in the human heart the presence of releasable norepinephrine is an important part of the mechanism of action of dopamine and dopexamine and that this indirect component is compromised by the norepinephrine depletion that occurs as a consequence of either surgical denervation or end-stage heart failure.

Methods

Tissue Acquisition

All hearts were obtained in collaboration with the Utah Cardiac Transplant Program and the Intermountain Organ Recovery System. Nonfailing hearts were obtained from organ donors whose hearts were unable to be used for transplantation after multiple attempts to place the organ for transplantation were exhausted. Failing hearts were obtained at the time of surgery from patients undergoing cardiac transplantation for either ischemic cardiomyopathy or idiopathic dilated cardiomyopathy, except in one patient in whom heart failure was secondary to adriamycin cardiotoxicity. Previously transplanted hearts were obtained from individuals with normal cardiac function undergoing retransplantation because of graft atherosclerosis. The nonfailing hearts were designated as being “innervated” to distinguish them from the nonfailing previously transplanted hearts that were chronically denervated; the average time of implantation was 694 ± 168 days (range, 229–1,182 days). Although any isolated tissue in the strictest sense is denervated, functional denervation of isolated heart muscle does not take place during the first 24–48 hours.10 Therefore, for the purpose of this study, the terms “innervated” and “denervated” are applied in a functional sense; nonfailing donor hearts were considered innervated, and previously transplanted hearts were considered denervated. All patients or family members of donors signed informed consent documents before participation in the study.

Tissue Contractile Responses

The contractile response of isolated ventricular tissue was determined as previously described.6,11,12 Briefly, hearts were placed into ice-cold Tyrode’s buffer immediately after cardectomy. Eight individual trabeculae were isolated from the free wall of the right ventricle and placed in an 80-ml muscle bath chamber containing Tyrode’s buffer equilibrated with 95% O2, 5% CO2, and kept at 37°C. Trabeculae were suspended between plastic mounting clips and allowed to equilibrate for 2 hours, and bath volumes were exchanged with fresh buffer every 30 minutes. After the first 30 minutes of equilibration, 0.8–1.2 g of tension was added to each muscle strip to obtain the maximum tension response, and a field current (square-wave pulse) was passed through the bath at a frequency of 1 Hz and a pulse duration of 5 msec at a voltage just above threshold (usually 10–15 V). Bovine serum albumin (0.1%) was added to the muscle bath chambers to reduce nonspecific binding of the drugs. Serial dilutions of the drugs were made up in distilled water containing 1 mM ascorbate. In a typical experiment, four drugs were added to two chambers each. Drugs were delivered throughout several log doses, at half log dose intervals (1 × 10^-9 to 1 × 10^-4 M for isoproterenol, 1 × 10^-8 to 1 × 10^-4 M for dopamine and dopexamine, and 1 × 10^-10 to 1 × 10^-5 M for zintrol). The time between consecutive dose intervals was 2 minutes for isoproterenol and 4 minutes for all other compounds, reflecting differences in the time necessary to reach maximum tension for each drug. Contractility was measured by individual Kistler-Morse deflection sensor cartridges with signal amplification by Accudata 105 DC amplifiers (Honeywell) and recorded on an eight-channel Visicorder (model 1508A, Honeywell). Contractile responses were measured as net gain in amplitude from baseline (mg tension).

β-Adrenergic Receptor Labeling

Crude membrane tissue preparations were made as previously described.6,13 Briefly, 5–6-g aliquots of
right ventricular free wall were dissected free of epicardium and endocardium, finely minced, treated with 0.5 M KCl to remove contractile proteins, homogenized with a Polytron (Brinkmann Instruments, Westbury, New York), and washed and spun to recover a 50,000g pellet. Washed membranes were resuspended in a sucrose and Tris buffer and stored at −80°C until used in individual assays. β-Adrenergic receptor density was determined with [125I]iodocyanopindolol with and without 1 μM (−)-propranolol as previously described.8 Receptor density (Bmax) and affinity (Kd) were determined by a nonlinear least-squares fit of the specific binding curve as previously described.6 All protein concentrations were measured by the Lowry technique14 as modified by Peterson.15

Tissue Catecholamine Levels

Tissue and plasma norepinephrine levels were determined by radioimmunoassay with commercially available kits from Amersham (Arlington Heights, Illinois).

Clinical Study Methods

Before participation in the study, all patients signed informed consent documents approved by the University of Utah Hospital Human Subjects Committee. Hemodynamic responses to dopexamine or dobutamine were determined in patients with severe congestive heart failure (New York Heart Association [NYHA] classes III and IV) due to either coronary artery disease or idiopathic dilated cardiomyopathy. Criteria for inclusion in the study were a cardiac index less than 2.5 l/min/m², pulmonary artery wedge pressure greater than 15 mm Hg, heart rate less than 120 beats/min, and a clinical indication for inotropic therapy. Exclusion criteria were sudden death or a history of uncontrolled symptomatic ventricular tachycardia. Patients were serially assigned to receive either dopexamine or dobutamine, the first seven receiving dopexamine and the next six receiving dobutamine. Hemodynamics were measured with a thermodilution pulmonary artery catheter and a femoral artery catheter. Cardiac output was determined by the thermodilution technique (cardiac output computer, Marquette, Milwaukee, Wisconsin) with the mean of triplicate injections (less than 10% variation) of cold 5% dextrose solution. Heart rate was measured by electrocardiographic telemetry. In addition, a venous blood sample was obtained at baseline, and plasma norepinephrine was measured by radioimmunoassay.

After obtaining baseline hemodynamics that included heart rate, cardiac index, and right atrial, pulmonary artery, pulmonary artery wedge, and systemic artery pressures, we plotted dopexamine or dobutamine dose-response curves with 1, 2, 4, 6, and 8 μg/kg/min doses for dopexamine and 2.5, 5.0, 7.5, and 10.0 μg/kg/min doses for dobutamine. Hemodynamic parameters were redetermined after steady-state pressures were obtained with each dose (≥10 minutes). On completion of the dose-response curves, the dose of each drug that produced an increase in cardiac index of 20–40% over baseline was then administered as a continuous infusion. The goal for the duration of infusion was 72 hours for dopexamine and 48 hours for dobutamine. When loss of efficacy was encountered, the rate of drug infusion was increased incrementally to a predetermined maximum dose of 12 μg/kg/min for either dopexamine or dobutamine. The shorter duration of the continuous infusion period for dobutamine was chosen to more closely match the average duration for dopexamine because of the attrition of dopexamine at rest and individuals from this phase of the study due to adverse side effects. The specific criteria for unacceptable side effects resulting in termination of continuous infusion were a fall in cardiac output greater than 30%, development of pulmonary edema, a heart rate increase of more than 20%, a blood pressure fall of greater than 10 mm Hg, sustained ventricular tachycardia, and severe drug-related side effects.

To measure hemodynamics after infusion, the dopexamine or dobutamine infusion was discontinued for 30 minutes and a new set of baseline values was obtained. Dopexamine or dobutamine dose-response curves were then plotted with the same drug concentrations as used at the beginning of the study.

Drugs and Reagents

Isoproterenol and dopamine were purchased from Sigma Chemical (St. Louis, Missouri); dopexamine was the kind gift of Fisons plc (Leicestershire, England); zinterol was obtained from Bristol-Myers (Evansville, Indiana); dobutamine was purchased from Eli Lilly (Indianapolis, Indiana). [125I]Iodocyanopindolol (2,200 Ci/mmol) was purchased from New England Nuclear (Boston, Massachusetts). All other chemicals and reagents were purchased from standard commercial suppliers.

Statistical Analysis

Methods for the analysis of radioligand-binding data were as previously described.6,11 In the isolated tissues studies, between-group differences were determined with one-way analysis of variance and a multiple comparison test (Fisher’s least significant difference test); a p value less than 0.05 in a two-tailed distribution was considered significant. In the clinical study, between-group differences were determined with unpaired Student’s t test. Differences in dose-response curves were determined by multiple linear regression methods. All data are reported as mean±SEM unless otherwise specified.

Results

Explanted Hearts

In all, tissue from 28 failing, seven nonfailing (nonfailing innervated), and five transplanted (nonfailing denervated) hearts were used (see Table 1). The average ages of the individuals from each group were 41.8±3.1 (failing), 26.1±4.0 (nonfailing), and
47.6±5.7 (transplant) years, and the average age of the nonfailing donors was significantly lower (p<0.05) than the ages of the failing and transplant groups. Statistical analysis of subgroups (younger half vs. older half) of patients with failing hearts in this study showed that there were no age-related decreases in β-receptor density; the β-receptor B\textsubscript{max} in the subgroup 10–42 years of age was 48.5±9.4 fmol/mg, and the B\textsubscript{max} in the subgroup greater than 42 years of age was 57.4±5.1 fmol/mg.

Figure 1 summarizes the hemodynamic profile of the patients from whom the failing and transplanted hearts were obtained for the in vitro tissue studies. The preoperative hemodynamic profile of the patients from whom transplanted hearts were obtained was normal by standard criteria (ejection fraction, 0.57±0.06; cardiac index, 2.35±0.26 l/min/m\textsuperscript{2}), and the patients had no evidence of heart failure on physical examination. In contrast, the patients from whom the failing hearts were obtained had ejection fractions (0.17±0.02) and cardiac indexes (1.70±0.10 l/min/m\textsuperscript{2}) that were significantly lower than those of the transplant group. In addition, the mean pulmonary artery (36.4±2.7 mm Hg) and pulmonary artery wedge pressures (23.7±2.0 mm Hg) of the failing group were significantly higher than those of transplanted group (20.2±4.5 and 13.2±5.0 mm Hg, respectively). Right atrial pressures from failing and transplanted groups (11.0±2.1 and 7.8±3.4 mm Hg, respectively) were not different. Hemodynamic parameters from nonfailing hearts harvested from organ donors were unavailable, but in each case, echocardiography revealed normal left ventricular function.

Figure 2 summarizes the β-adrenergic receptor densities for the three groups of hearts used in the in vitro studies. The K\textsubscript{d} for [\textsuperscript{125}I]iodocyanopindolol was not different between groups (8.02±1.71, 8.06±1.07, and 11.30±4.67 pM for nonfailing, failing, and transplant groups, respectively). The B\textsubscript{max} in the failing group was significantly lower (52.7±5.5 fmol/mg protein) than that of the nonfailing group (96.8±13.2 fmol/mg) and the transplant group (83.9±19.2 fmol/mg). Figure 3 depicts the tissue norepinephrine concentrations for these hearts. The concentrations of norepinephrine in failing (470±106 ng/g) and transplanted (37±17 ng/g) hearts were significantly less than those in nonfailing (1,561±295 ng/g) hearts.

Table 1 details the number of hearts and the number of individual right ventricular trabeculae used for each drug in each group of hearts, and Figure 4 is a representation of the net maximal (maximum minus baseline amplitude) inotropic response (mg tension) to each of the agonists in the three groups of hearts. The response to the nonselective, full agonist isoproterenol was significantly lower in failing hearts than that in the nonfailing and transplant groups (1,139±132 vs. 1,814±315 and 2,007±504 mg, respectively). The response to the β\textsubscript{2}-selective partial agonist zinterol tended to be less

<table>
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<tr>
<th>Experimental tissue</th>
<th>Nonfailing</th>
<th>Failing</th>
<th>Transplant</th>
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<td>Isoproterenol</td>
<td>5/15</td>
<td>15/31</td>
<td>5/10</td>
</tr>
<tr>
<td>Zinterol</td>
<td>5/12</td>
<td>19/53</td>
<td>4/8</td>
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<td>Dopamine</td>
<td>2/6</td>
<td>6/12</td>
<td>5/10</td>
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<tr>
<td>Dopexamine</td>
<td>4/8</td>
<td>13/26</td>
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Data are number of hearts/number of trabeculae.
in failing (715±117 mg) and transplanted (773±228 mg) hearts than that in nonfailing (1,008±165 mg) hearts, but their respective 29% and 23% differences were not statistically different. In marked contrast, the responses to the two mixed (direct and indirect) agonists dopamine and dopexamine were considerably less in failing (344±103 and 129±32 mg, respectively) and transplanted (408±139 and 424±89 mg, respectively) hearts compared with nonfailing organ donor control hearts (1,283±329 and 1,260±321 mg, respectively).

**Clinical Investigation**

Table 2 gives the demographic data for all the patients enrolled in the clinical investigation. Patients in the dopexamine and dobutamine groups were not different with respect to age distribution, sex, diagnosis, NYHA functional class, or left ventricular ejection fraction as determined by radionuclide ventriculography. The associated baseline hemodynamics for the above patients are also given in Table 2. At baseline, patients in the two groups were not different with respect to cardiac index, heart rate, and right atrial, pulmonary artery, pulmonary artery wedge, and systemic arterial pressures.

Figure 5 shows the hemodynamic dose-response data for dopexamine before and after continuous infusion. Dose-response data after infusion were obtained in five of the seven patients at 36±12 (range, 10.8–72.7) hours after the initiation of inotropic therapy. Responses could not be obtained in the other two patients because of unacceptable sustained tachyarrhythmias. Further, during the continuous infusion period, six of the seven patients receiving dopexamine had their therapy prematurely terminated before the prescribed 72-hour duration of treatment. In three patients, withdrawal was due to intermittent tachyarrhythmias, and in the remaining three patients, dopexamine was discontinued because of loss of efficacy, these patients not responding to titration of dopexamine up to the maximum rate allowed (12 μg/kg/min). After continuous infusion of dopexamine, cardiac index dose-response was significantly reduced (p<0.05) compared with baseline. In addition, right atrial pressure was significantly higher (p<0.05), and pulmonary artery and pulmonary artery wedge pressures tended to be higher (p=NS). Last, five of the seven patients receiving dopexamine infusions experienced nausea.
and/or vomiting (usually when the dose was ≥8 μg/kg/min).

Figure 6 depicts the hemodynamics before and after the continuous infusion of dobutamine. Dose-response curves were obtained after the dobutamine infusion in all six patients at 46±3 (range, 36–48) hours after the beginning of drug infusion. In contrast to the dose-response curves of dopexamine, the dobutamine dose-response curves for cardiac index were not different before and after infusion; that is, there was no detectable loss of efficacy for dobutamine after continuous infusion. In addition, none of the other hemodynamic parameters measured after the dobutamine infusion were different from baseline values. None of the patients receiving dobutamine experienced any clinically significant side effects.

Figure 7 is a representation of central venous plasma norepinephrine concentrations before and after the continuous infusions of dopexamine and dobutamine. Plasma norepinephrine levels tended to increase in patients receiving dopexamine (p=NS) and tended to decrease in patients receiving dobutamine (p=NS).

**Discussion**

Many of the changes in the β-adrenergic receptor/G protein/adenylate cyclase pathway in the failing human heart are now well described.6,7,11,16–19 These include selective down-regulation of the β1-adrenergic receptor,6,17 a preservation of density, but a mild functional uncoupling of the β2-adrenergic receptor,7 and an increase in the measurable pertussis toxin-mediated ADP-ribosylation of G.,18,19 that correlates with an increase in G,-mediated inhibition of adenylate cyclase activity.18

Despite changes in the β-adrenergic receptor pathway that render the failing heart less capable of responding to catecholamines, failing heart muscle is still able to respond vigorously to high-efficacy β-agonists such as isoproterenol6,11,12 or dobutamine.20,21 In isolated tissue removed from failing hearts, these agents produce a contractile response that is similar in magnitude to the response to suprapharmacologic concentrations (10 mM) of calcium.12,21 Thus, the β-adrenergic pathway retains sufficient intrinsic ability to mediate a clinically useful response to β-agonists, and β-agonists remain the treatment of choice for short-term treatment of high filling pressure, low-output states.22 Because of this, β-agonists with potentially useful pharmacologic characteristics continue to undergo development.

One such compound is dopexamine, an N-substituted dopamine derivative, that has several

| Table 2. Demographics and Baseline Hemodynamics in the Clinical Study Groups |
|--------------------------------|-----------------|------------------|
| Age (yr)                     | 47±4            | 50±6             |
| Sex                          | M               | F                |
| M                            | 5               | 2                |
| F                            | 5               | 1                |
| Diagnosis                    | 5 IDC, 2 CAD    | 5 IDC, 1 CAD     |
| NYHA functional class        |                 |                  |
| III                          | 3               | 2                |
| IV                           | 4               | 4                |
| Ejection fraction            | 0.16±0.02       | 0.20±0.03        |
| Cardiac index (l/min/m²)     | 1.6±0.2         | 1.7±0.2          |
| Heart rate (beats/min)       | 97±7            | 100±5            |
| Right atrial pressure (mm Hg)| 14±2            | 14±3             |
| Pulmonary artery pressure (mm Hg)| 36±4         | 42±5             |
| Pulmonary wedge pressure (mm Hg)| 25±4          | 27±2             |
| Systemic arterial pressure (mm Hg)| 76±2         | 74±3             |

IDC, idiopathic cardiomyopathy; CAD, coronary artery disease.
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Cardiac Index (L/min/m²)

Heart Rate (beats/min)

Right Atrial Pressure (mm Hg)

Pulmonary Artery Pressure (mm Hg)

Pulmonary Wedge Pressure (mm Hg)

Systemic Arterial Pressure (mm Hg)

Dopexamine Dose (µg/kg/min)

Cardiac Index (L/min/m²)

Heart Rate (beats/min)

Right Atrial Pressure (mm Hg)

Pulmonary Artery Pressure (mm Hg)

Pulmonary Wedge Pressure (mm Hg)

Systemic Arterial Pressure (mm Hg)

Dobutamine Dose (µg/kg/min)

**Figure 5.** Plots of hemodynamic responses to dopexamine at baseline (□) and after continuous infusion (■). The cardiac index after dopexamine infusion was significantly reduced (p<0.05) compared with baseline. Right atrial pressure was significantly increased (p<0.05) after dopexamine infusion compared with baseline. No statistically significant differences between baseline and postdopexamine time points were observed for the other measured hemodynamic parameters.

Theoretical advantages as a therapeutic agent for the treatment of congestive heart failure. Dopexamine is a potent peripheral vasodilator with selective β₂-adrenergic and dopaminergic receptor agonist properties and a very low affinity for either β₁- or α-adrenergic receptors. Dopexamine has also been shown to be a potent inhibitor of sodium-dependent norepinephrine reuptake (uptake). In this context, dopexamine is considerably more potent than the clinically used inotropes dopamine (×10) and dobutamine (×15) and slightly more potent than cocaine (×4). The pharmacologic action of indirect agonists, particularly dopamine, has been extensively described by others.

**Figure 6.** Plots of hemodynamic responses to dobutamine at baseline (□) and after continuous infusion (■). There were no significant differences for any measured hemodynamic parameter between baseline and postdobutamine data.
Most of the inotropic effect of dopexamine appears to be dependent on the presence of neuronal norepinephrine, as previously demonstrated by Mitchell et al. These investigators showed that rabbit atria pretreated with reserpine, which depletes synaptic norepinephrine, were subsequently incapable of an inotropic response to dopexamine. Given the above finding, it was not surprising that in our study both dopexamine and dopamine had limited inotropic efficacy in isolated preparations from failing and transplanted hearts where tissue norepinephrine was considerably lower than that in nonfailing hearts. In addition to the depletion of tissue norepinephrine in both failing and transplanted hearts, the further decrease in the response to dopexamine and dopamine in isolated failing hearts was probably due to subsensitivity phenomena affecting these agonists’ direct action on β-adrenergic receptors. Receptor desensitization would presumably not affect dopexamine or dopamine responsiveness in transplanted hearts where the β-receptor density and the responses to both isoproterenol and zinterol were not different from innervated nonfailing control hearts.

One point to consider is the extent to which agonists such as dopamine and dopexamine are acting as either direct or indirect agonists. In animal experiments, total depletion of synaptic norepinephrine can be accomplished by the administration of reserpine, which allows for direct quantification of either direct or indirect components of agonist stimulation. In lieu of reserpinization, the quantification of either direct or indirect components of agonist action can be assessed in human tissue by using previously transplanted denervated hearts. In this tissue, agonists are limited to acting by direct β-adrenergic receptor stimulation, because synaptic norepinephrine is not present. Thus, in this study, the extent to which dopexamine and dopamine are acting either directly or indirectly in nonfailing and failing innervated hearts is inferred from the results obtained from previously transplanted denervated hearts. Based on these data, in innervated nonfailing and failing human hearts, most of the inotropic response to either dopexamine or dopamine appears to be the result of indirect action.

A potential criticism of the in vitro portion of the study is that the average age of the nonfailing group was significantly lower than that of the failing and transplant groups, and this could have influenced our results. However, statistical analysis of β-adrenergic receptor density in failing hearts showed no age-related differences. Moreover, statistical analysis of a larger group (n=32) of nonfailing hearts studied in our laboratory indicates that age (range, 8–62) has no detectable influence on either β-receptor density or subtype proportions (unpublished data).

In the clinical study, the initial cardiac output response to dopexamine in patients with heart failure was substantial (109% increase over baseline at maximum dose) and in fact was greater than the initial response to dobutamine (73% increase over baseline at maximum dose). Dopexamine also lowered systemic vascular resistance more than did dopamine, and thus, the increased cardiac output observed for dopexamine may have been due, in part, to its greater afterload reducing properties. The initial increase in cardiac output produced by dopexamine measured at baseline was in agreement with the findings of others. However, most previous studies measured hemodynamic changes in an acute setting only and did not attempt to administer dopexamine as a long-term infusion. The exception is a report by Gollub et al. that evaluated the effects of a long-term infusion of dopexamine. These investigators found that approximately 50% of the increase in cardiac index was lost after 22–23 hours of infusion; however, they were able to regain the initial inotropic effect by titrating upward the dose of dopexamine. This increased rate of infusion was accompanied by a higher incidence of adverse reactions. A correlation between higher dose and an increased incidence of side effects has been noted by others as well. Thus, the adverse events (arrhythmias, nausea, and vomiting) noted at higher doses of dopexamine in our study appear to be consistent with the previously reported data.

In contrast to Gollub et al., we were unable to sustain the initial cardiac output response by increasing the infusion rate of dopexamine. In our study, heart rate response was unchanged before and after infusion. In addition, right atrial pressures were
significantly elevated, and pulmonary artery and pulmonary artery wedge pressures tended to be higher after infusion. Thus, the decreased postinfusion responsiveness to doxepamine in our study was not due to decreases in filling pressures. One potential explanation for the differences in our findings compared with Gollub et al is that the subjects in our study had a greater degree of myocardial dysfunction as determined by baseline cardiac function parameters (cardiac index, 1.6–1.7 vs. 1.9–2.1 l/min/m², respectively) and NYHA functional class (57% vs. 40% class IV, respectively). Given the above, it is likely that cardiac function and norepinephrine stores were more compromised in our patients than in the patients studied by Gollub et al. Therefore, tachyphylaxis might have occurred more rapidly in our study due to rapid depletion of more compromised norepinephrine stores.

One point that helps to support this conclusion is that of the five patients in our study for whom dose-response data were collected before and after doxepamine continuous infusion, only one could be considered a positive responder. The degree of heart failure in this patient was relatively mild compared with other patients in our study (cardiac index, 2.54 l/min/m²; right atrial pressure, 12 mm Hg; and pulmonary artery wedge pressure, 20 mm Hg). In addition, this individual’s plasma venous norepinephrine concentration (298 pg/ml) was comparatively low, reflective of a lower level of adrenergic drive and perhaps a less compromised tissue norepinephrine stores.

In keeping with previous observations, drug tolerance did not occur with a 48-hour infusion of dobutamine in our clinical study. However, tolerance to doxepamine can occur after longer infusion periods. The different time course for developing tolerance with a continuous dobutamine infusion compared with a doxepamine infusion suggests that different mechanisms are involved, such as β-receptor down-regulation for dobutamine and norepinephrine depletion for doxepamine.

A limitation of our clinical study is that drug administration was assigned serially rather than randomly. However, baseline venous norepinephrine concentrations tended to be higher in the dobutamine-treated patients, suggesting that heart failure was more advanced in these patients. Because the two groups did not differ with respect to sex, age, diagnosis, functional class, left ventricular ejection fraction, or baseline hemodynamic measurements, the study design probably did not bias the results.

In summary, severely failing and transplanted human hearts can be considered analogous in the sense that they are both “denervated.” In transplanted hearts, denervation is an unavoidable consequence of the surgical procedure. In failing hearts, the “denervation” is the result of neuronal dysfunction and presumably related to the marked decrease in neuronal uptake associated with heart failure. This “partial denervation” results in a reduction in adrenergic neuronal stores of norepinephrine as well as a decrease in norepinephrine release. However, because release is reduced to a relatively lesser extent than is uptake, coronary sinus, and synaptic cleft norepinephrine levels increase in the failing heart. Indirect-acting amines such as dopamine and doxepamine may have limited inotropic potential in failing hearts where neuronal norepinephrine has been severely depleted; they encounter diminished releasable norepinephrine stores as well as receptor subsensitivity resulting from the increased concentrations of synaptic cleft and interstitial norepinephrine. Thus, when inotropic support is found to be necessary in patients with advanced heart failure or in heart transplant recipients, the mechanism of action of the prospective inotropic agent should be considered. In these “denervated” states, the use of indirect-acting β-agonists may not provide the desired amount of inotropic effect.

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