Myocardial Catecholamine and Neuropeptide Y Depletion in Failing Ventricles of Patients With Idiopathic Dilated Cardiomyopathy Correlation With β-Adrenergic Receptor Downregulation

Fred L. Anderson, MD; J. David Port, PhD; Bruce B. Reid; Patti Larrabee; Glen Hanson, DDS, PhD; and Michael R. Bristow, MD, PhD

Background. Myocardial adrenergic neurotransmitters and β-adrenergic receptor levels were measured in left and right ventricular myocardial specimens obtained from 30 patients with biventricular failure resulting from idiopathic dilated cardiomyopathy.

Methods and Results. Nonfailing myocardium obtained from 12 organ donors provided control data. Norepinephrine, dopamine, and neuropeptide Y concentrations were significantly decreased in failing compared with nonfailing control hearts. The mean ratio of dopamine to norepinephrine and of dopamine to neuropeptide Y in failing hearts was also significantly decreased compared with nonfailing control hearts. Compared with nonfailing control hearts, B_max and β_1-receptor density were significantly decreased in failing hearts and there were positive correlations of B_max and β_1-adrenergic receptors with norepinephrine, dopamine, and neuropeptide Y.

Conclusions. Norepinephrine and its cotransmitter neuropeptide Y are depleted in failing human ventricular myocardium. Decreased norepinephrine stores correlate weakly with β_1-adrenergic receptor downregulation consistent with the hypothesis that norepinephrine depletion occurs in response to increased adrenergic drive. Decreased dopamine relative to norepinephrine implies that an abnormality of dopamine conversion to norepinephrine is not present in failing human heart. (Circulation 1992;85:46–53)

Activation of the sympathetic nervous system in patients with congestive heart failure is one of several important compensatory mechanisms for the preservation of blood flow to critical tissues. In failing myocardium of patients with congestive heart failure from systolic dysfunction, down-regulation of myocardial β_1-adrenergic receptors,1 uncoupling of β_2-adrenergic receptors,2 and a corresponding loss of β-adrenergic responsiveness3 is consistent with chronic exposure to excess catecholamines.4 In failing human heart, the origin of the increased adrenergic drive is norepinephrine derived from myocardial adrenergic neurons.4 Paradoxically, myocardial norepinephrine is depleted in failing heart,5–7 apparently due to a profound decrease in norepinephrine reuptake.8–11 The combination of a marked decrease in neuronal uptake and to a lesser degree a decrease in norepinephrine release11 leads to both an increase in interstitial/synaptic cleft norepinephrine and a depletion of neuronal norepinephrine because reuptake of released norepinephrine is the major determinant of synaptic cleft concentrations and is a major contributor to neuronal stores.4 It is probable, therefore, that myocardial norepinephrine depletion relates to the increase in adrenergic drive that characterizes failing human heart. This increased drive, defined as a coronary sinus norepinephrine level higher than arterial,12,13 is useful for short-term support of failing heart but produces β-receptor desensitization when present chronically.4

The purpose of this study was to measure myocardial adrenergic neurotransmitters and β-adrenergic receptor levels in nonfailing and failing human ventricular myocardium to test the hypothesis that in failing heart, norepinephrine depletion occurs in response to increased adrenergic drive. If this hypothesis is true, then both norepinephrine and its
cotransmitter neuropeptide Y (NPY) should be decreased in failing myocardium and β₁-adrenergic receptor (the “norepinephrine receptor”) but not β₂-receptor density should be directly related to norepinephrine depletion.

Methods

Tissue Acquisition

Hearts were obtained in collaboration with the Utah Cardiac Transplantation Program and the Intermountain Organ Recovery System. All patients or family members signed informed consent documents before participation in this study. Failing myocardium consisting of both right and left ventricles was obtained from 30 patients (average age, 39 years) who had end-stage biventricular heart failure caused by idiopathic dilated cardiomyopathy (IDC) and were undergoing cardiac transplantation. There were 25 men and five women. Before transplantation, these subjects were treated with digoxin, diuretics, and angiotensin converting enzyme inhibitors. None received intravenous β-agonist inotropes, β-blocking agents, or phosphodiesterase inhibitors. Nonfailing myocardium was obtained from seven on-site organ donors whose hearts could not be placed by the Universal Network for Organ Sharing. Normal controls had echocardiographically proven normal left ventricular function defined as fractional shortening ≥25%. There were six men and six women, and the average age of these patients was 32 years. These patients had only a trace exposure to dopamine, averaging 0.8 μg/min for an average of 30 minutes before explantation. Included as additional normal controls were the nonfailing left ventricles of five heart-lung transplantation recipients with primary pulmonary hypertension. On explantation, all hearts were immediately immersed in iced Tyrode’s solution and processed for biochemical assays within 30 minutes.

Hemodynamic Data

All patients from whom failing hearts were obtained underwent right and left heart catheterization with coronary angiography before cardiac transplantation. Ejection fraction was determined by echocardiography and/or multiple gated acquisition scan.

Receptor Radiolabeling

β₁-Adrenergic receptor density was assessed by 125I]iodocyanopindolol (ICYP) binding as previously described using displacement by 1 μmol/l (−)-propranolol as specific binding.3 Crude membranes were prepared from a 5-g aliquot of left ventricle free wall by contractile protein extraction and washing of a 50,000g pellet. The binding parameters Bmax and Kd were determined by nonlinear least-squares methodology. Additionally, the proportion of β₁-versus β₂-receptors was assessed by betaxolol-ICYP or CGP 20712A-ICYP competition curves, with the proportion of β₁- and β₂-receptors and their Kd values determined by computer modeling as previously described.3 β₁- and β₂-receptor density were measured by ICYP saturation curves. In competition curve measurements, the concentration of ICYP was 50 pmol/l for ICYP Kd values <20 pmol/l, and 100 pmol/l of the ICYP Kd from saturation curves was >20 pmol/l; receptor concentration was 2–5 pmol/l. Additional equilibrium assay conditions for ICYP binding were as described previously.3

Source of Compounds and Reagents

ICYP was purchased from Amersham (Arlington Heights, Ill.). Betaxolol was a gift from Synthelabs (L.E.R.S.), Paris; CGP 20712A was a gift from CIBA-GEIGY (Summit, N.J.), and (−)propranolol was a gift from Ayerst Laboratories (New York, N.Y.). All other chemicals were purchased from standard commercial supplies.

Catecholamine Assay

Tissue concentrations of norepinephrine, epinephrine, and dopamine were determined using the radioenzymatic method of Peuler and Johnson.14 Commercial kits were obtained from Amersham.

Neuropeptide Y Assay

Levels of NPY were determined as described by Hanson and Loonenberg,15 with some modifications. Tissue samples (average weight, 50 mg) were thawed, minced, and boiled in 0.01 normal HCl for 10 minutes. The tissue was then homogenized and separated into two aliquots, one for protein assay and the other for NPY radioimmunoassay. The latter was centrifuged for 30 minutes and the supernatant was removed, frozen, and lyophilized. The lyophilized tissue samples were reconstituted in 250 μl of phosphate-buffered solution plus Triton buffer solution and centrifuged for 30 minutes at 3,500g at 4°C. The supernatant (200 μl) was separated into plastic tubes to which specific antisera (100 μl at 1:160,000 dilution) were added. The assay tubes, together with a series of standard NPY dilutions (5–500 pg per tube, four tubes per dilution), were then incubated for 96 hours at 4°C. 125I NPY labeled with Bolton-Hunter reagent at lysine⁴ (New England Nuclear), average counts 5,000–6,000/min/100 μl, was then added to each tube and incubated for an additional 48 hours at 4°C. After incubation, dextran-coated charcoal was added to each tube and the resultant mixture was centrifuged for 30 minutes at 4°C. The supernatant was separated and counted in a gamma counter. The amount of NPY in each tube, expressed as picograms per tube, was calculated from the bound-to-reference ratio. The antibody for the assay was developed in the laboratory of one of the authors (G.H.). The antibody was derived from rabbit antisera previously immunized with NPY according to the procedure of Hurn and Chantler16 and Suess et al17 as described by Letter et al.18 The NPY antisera had less than 1% crossreactivity with all peptides currently recognized
TABLE 1. Myocardial Catecholamine and Neuropeptide Y Data From Left and Right Ventricles of Two Groups of Patients

<table>
<thead>
<tr>
<th></th>
<th>NE</th>
<th>EPI</th>
<th>DA</th>
<th>NPY</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LV</td>
<td>RV</td>
<td>LV+RV</td>
<td>LV</td>
</tr>
<tr>
<td>Group 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>970±153</td>
<td>1,072±220</td>
<td>1,007±123</td>
<td>44±12</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>7</td>
<td>19</td>
<td>12</td>
</tr>
<tr>
<td>n</td>
<td>30</td>
<td>30</td>
<td>60</td>
<td>30</td>
</tr>
<tr>
<td>p</td>
<td>0.001</td>
<td>NS</td>
<td>0.0021</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>0.001</td>
<td>0.0099</td>
<td>0.0006</td>
<td></td>
</tr>
</tbody>
</table>

Values are mean±SEM.

Results

Hemodynamic Data

Mean values for the 30 patients with heart failure were as follows: right atrial pressure, 8 mm Hg; pulmonary artery pressure, 28 mm Hg; pulmonary artery wedge pressure, 23 mm Hg; cardiac index, 2.0 l/min/m²; and ejection fraction, 16%. Collectively, these data are consistent with severe biventricular failure.

Myocardial Catecholamines

These data are shown in Table 1 (mean±SEM) and Figure 1 (individual data points). Data are given for right and left ventricles separately and combined. An overlap between normal and failing ventricles was noted. Norepinephrine concentrations tended to be higher in right than in left ventricles, but the difference did not reach statistical significance. When analyzed as pooled data for both ventricles, norepinephrine concentrations were significantly decreased in failing hearts. Dopamine concentrations in both ventricles, or when analyzed as pooled data, were significantly lower in failing than in control hearts. Epinephrine concentrations, which were notably

to have significant amino acid sequence homology with NPY; these included peptide YY and peptide PP (avian, rat, and bovine). The antiserum showed less than 1% crossreactivity with NPY fragment 18–36 and 10% crossreactivity with the analogue NPY [Leu⁴¹, Pro⁴²]. In addition, no significant crossreactivity was observed with nonrelated peptides such as neuropeptidin, substance P, or somatostatin. Sensitivity for this assay is 5 pg per sample. Protein concentrations of tissue samples were determined by the Peterson modification of the Lowry method.¹⁹

Statistical Methods

The method of analyzing radioligand-unlabeled ligand competition curves has been previously described,¹ as has the analysis of radioligand saturation curves.¹⁹ Differences between the groups were assessed by Student's t test, with probability of less than 0.05 in a two-tailed distribution being statistically significant. Biochemical data for right versus left ventricles were compared using the Student's t test for paired data. Pooled data for right and left ventricles combined were analyzed using an unpaired t test and analysis of variance.

Figure 1. Graphs show norepinephrine, dopamine, and neuropeptide Y (NPY) concentrations in nonfailing (NF) and failing (F) left (L) and right (R) ventricles. Mean value (--) shown for each ventricle.
lower than norepinephrine concentrations in nonfailing hearts, were not different in nonfailing versus failing ventricles when analyzed as pooled data.

**Neuropeptide Y**

Data are shown in Table 1 and Figure 1. NPY concentrations also tended to be higher in right compared with left ventricles, and the percent differences between nonfailing control and failing hearts were similar to those for norepinephrine. When analyzed as pooled data for both ventricles, NPY concentrations were significantly decreased in failing hearts. Moreover, NPY depletion occurred in proportion to norepinephrine depletion in that the norepinephrine-to-NPY ratio for nonfailing versus failing ventricles was 11.0 and 8.5, respectively ($p=0.869$).

The ratio of myocardial dopamine to norepinephrine and of dopamine to NPY is shown in Figure 2. The mean ratio of dopamine to norepinephrine in failing hearts (0.09) was significantly (0.0001) lower than in nonfailing controls (0.45). Likewise, the mean ratio of dopamine to NPY in failing hearts (0.38) was significantly lower than in nonfailing control hearts (2.54).

**Myocardial β-Adrenergic Receptor Density**

Data (mean±SEM) for β-adrenergic density and ICYP dissociation constant are given in Table 2. Compared with nonfailing control hearts, $B_{\text{max}}$ and β$_\text{1}$-receptor density were significantly decreased, and the proportion of β$_\text{2}$- compared with β$_\text{1}$-adrenergic receptors was increased. These data are consistent with those previously reported from this laboratory.

The relation between β-adrenergic density and myocardial catecholamines or NPY using data from nonfailing and failing hearts is shown in Table 3 and Figures 3–5. Using simple regression analysis of receptor density versus log neurotransmitter, there were significant positive correlations of $B_{\text{max}}$ (total β-receptor density) and β$_\text{1}$-adrenergic density with norepinephrine ($r=0.485$ and 0.453, respectively), dopamine (0.282 and 0.276), and NPY (0.322 and 0.368). On the other hand, β$_\text{2}$-receptor density did not correlate with any neurotransmitter and epinephrine did not correlate with β-adrenergic density (Table 3).
Discussion

The major findings of this study are 1) myocardial norepinephrine, dopamine, and NPY levels in patients with heart failure from idiopathic dilated cardiomyopathy (IDC) are decreased compared with nonfailing controls, 2) myocardial norepinephrine and NPY depletion are positively correlated with \( \beta_1 \)-adrenergic receptor downregulation, whereas there is no correlation of adrenergic neurotransmitter level to \( \beta_2 \)-receptor density, and 3) mean ratios of dopamine to norepinephrine and of dopamine to NPY in failing hearts are significantly decreased compared with nonfailing controls.

The mean value for myocardial norepinephrine in nonfailing hearts was consistent with data previously reported for ventricular myocardium of subgroups of patients with normal cardiac function,\(^{21-23}\) A wide range of values in these studies and ours may reflect biological and/or assay variability. In our study, the subgroups from whom nonfailing hearts were obtained were carefully selected to exclude factors that may alter the receptor and/or biochemical characteristics of the myocardial tissue. Thus, hearts procured from organ donors geographically remote from the University of Utah Medical Center, hearts determined to be dysfunctional by virtue of decreased ventricular function by echocardiography, and hearts from patients given intravenous \( \beta \)-agonist inotropes were not used for control data. Justification for the inclusion of tissue from heart-lung recipients with primary pulmonary hypertension is based on the observation that the left ventricles from these patients have normal function and \( \beta_1 \)-adrenergic receptor density compared with their failing right ventricles.\(^{24}\)

Previously reported data pertaining to myocardial dopamine levels in nonfailing human hearts are limited. Maurer\(^ {25}\) reported myocardial catecholamine levels in patients with chronic aortic regurgitation. Right atrial tissue was assayed, and control data were obtained from patients with atrial septal defects. On the basis of this study and data derived from animal experiments, normal myocardial dopamine levels have been considered to be less than 10% of norepinephrine concentrations.\(^{26}\) In our study, mean myocardial dopamine level in nonfailing hearts exposed to trace amounts or no intravenous dopamine was 273 ng/g, and mean ratio of dopamine to norepinephrine in these patients was 0.45.

It is possible that the trace amounts of dopamine received just before explantation (average, 0.8 \( \mu \)g/min \( \times \) 0.5 hr) affected the myocardial dopamine levels in donor heart controls. In this regard, a comparison of myocardial dopamine levels in these patients with a carefully matched subgroup of organ donor patients with nonfailing hearts who received much larger doses of dopamine before explantation (average dose, 18 \( \mu \)g/min \( \times \) 9 hours) revealed a significantly higher level in the latter group (263 ± 69 versus 422 ± 80 ng/g, \( p \) = 0.0008, unpublished data). However, the observation that a 20-fold greater dose of dopamine given for an 18-times longer period produces only a 1.6-fold increase in dopamine concentration suggests that the trace amounts of dopamine administered to the study group did not account for the high dopamine/norepinephrine ratio observed.

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**Table 2. \( \beta \)-Adrenergic Receptor Binding Data in Membranes From Left and Right Ventricles of Two Groups of Patients**

<table>
<thead>
<tr>
<th>Group</th>
<th>( \beta_{max} ) (fmoI/mg)</th>
<th>( K_d ) (pmol/l)</th>
<th>( \beta_1 )</th>
<th>( \beta_2 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV</td>
<td>LV+RV</td>
<td>LV</td>
<td>LV+RV</td>
<td>LV</td>
</tr>
<tr>
<td>1</td>
<td>11.7±6.7</td>
<td>11.1</td>
<td>10.2±1.8</td>
<td>10.5±2.5</td>
</tr>
<tr>
<td>p</td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

**Table 3. Regression Analyses for Compiled Data From Nonfailing and Failing Hearts**

<table>
<thead>
<tr>
<th></th>
<th>( \beta_{max} )</th>
<th>( \beta_1 )</th>
<th>( \beta_2 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>NE (log)</td>
<td>0.485(0.212)</td>
<td>0.453(0.205)</td>
<td>0.202(0.041)</td>
</tr>
<tr>
<td>p</td>
<td>0.0001</td>
<td>0.0001</td>
<td>NS</td>
</tr>
<tr>
<td>EPI (log)</td>
<td>0.100(0.010)</td>
<td>0.113(0.017)</td>
<td>0.138(0.019)</td>
</tr>
<tr>
<td>p</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>DA (log)</td>
<td>0.282(0.080)</td>
<td>0.276(0.076)</td>
<td>0.220(0.049)</td>
</tr>
<tr>
<td>p</td>
<td>0.009</td>
<td>0.0137</td>
<td>NS</td>
</tr>
<tr>
<td>NPY (log)</td>
<td>0.322(0.104)</td>
<td>0.368(0.135)</td>
<td>0.041(0.002)</td>
</tr>
<tr>
<td>p</td>
<td>0.05</td>
<td>0.0352</td>
<td>NS</td>
</tr>
</tbody>
</table>

**Figure 3. Scattergram of \( \beta_1 \)-receptor density (\( \beta_1 \)) vs. log tissue norepinephrine (NE).**

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\( \beta_{max} \), \( \beta_1 \), \( \beta_2 \) (fmoI/mg); NE, norepinephrine; EPI, epinephrine; DA, dopamine; NPY, neuropeptide Y; NS, not significant.

Regression analysis, \( R (R^2) \).
Myocardial norepinephrine in failing hearts of patients with IDC was significantly decreased compared with nonfailing control tissue. Patients with IDC from whom these tissues were obtained were clearly distinguished from normal by clinical and hemodynamic criteria, which were consistent with severe biventricular dysfunction. Total $\beta_1$-adrenergic receptor density and the proportion of $\beta_1$- to $\beta_2$-adrenergic receptors were decreased in the ventricles of IDC patients and were similar to data previously reported by us and others.

Norepinephrine concentrations in the failing group were consistent with previous reports that norepinephrine stores are depleted in failing heart. In addition, mean myocardial dopamine concentrations in failing hearts were significantly lower than those in the nonfailing control tissue. Moreover, the ratio of dopamine to norepinephrine was also significantly lower in failing hearts and the variation within the group was minimal. This finding is in variance with data previously reported for patients with severe congestive heart failure in which myocardial dopamine levels were normal or increased and in which there was considerable variation in the dopamine-to-norepinephrine ratio.

The rate-limiting steps involved in regulating norepinephrine synthesis in the myocardial adrenergic neuron include hydroxylation of tyrosine, decarboxylation of DOPA, uptake of cytosolic dopamine into the vesicle, and hydroxylation of dopamine to norepinephrine. These enzymatic steps were not assessed in this study. However, our data provide indirect evidence against the hypothesis that an abnormality of dopamine conversion to norepinephrine or vesicular dopamine uptake leads to dopamine accumulation or that in failing hearts, there is a switch in the rate-limiting step in norepinephrine synthesis from tyrosine hydroxylase to DOPA decarboxylase similar to that reported in the cardiomyopathic Syrian hamster. In that regard, it should be emphasized that our data are derived from patients with IDC and as such may not reflect the ratio of myocardial norepinephrine to dopamine found in patients with congestive heart failure caused by other disorders.

Mean myocardial NPY concentration in nonfailing hearts was 108 ng/g. It has previously been established that norepinephrine and NPY coexist in adrenergic neurons and are distinguished by their separate presence in small and large vesicles, respectively. In the human heart, NPY-containing neurons have been identified in epicardial coronary arteries and myocardium by immunofluorescent staining methods. There are no previous reports of NPY tissue concentrations relative to myocardial catecholamines. Our data indicate that relative to norepinephrine, NPY is present in nonfailing human myocardium in much lower concentrations and is depleted in failing ventricles. Moreover, the ratio of dopamine to NPY for both nonfailing controls and failing hearts is remarkably similar to the ratio of dopamine to norepinephrine. Given the fact that NPY plasma levels are reportedly increased in patients with left ventricular failure, NPY may serve as a useful marker of increased adrenergic drive in patients with this condition.

The mechanism for NPY depletion in failing myocardium is not evident from this study but is probably linked to increased myocardial adrenergic drive. In contrast to norepinephrine, a neuronal uptake system for NPY has not been reported, but local peptidase degradation probably occurs. It is therefore likely that in patients with congestive heart failure, a combination of increased myocardial adrenergic drive and an absent uptake system accounts for the depletion of myocardial NPY.

Total $\beta_1$-adrenergic receptor density was decreased in failing ventricles, and there was a weak but statistically significant correlation with decreased myocardial norepinephrine, dopamine, and NPY but not with epinephrine. Marked downregulation of $\beta_1$-receptors and profound sub-sensitivity to catecholamine stimulation characterizes the end-stage failing myocardium of patients with IDC. Evidence supporting a relation between norepinephrine and myocardial $\beta_1$-receptors is derived from model systems in which exposure to $\beta$-agonists can both uncouple and downregulate $\beta$-adrenergic receptors and from patients with heart failure resulting from IDC in which metoprolol can upregulate $\beta$-receptors and restore $\beta$-adrenergic responsiveness.
ceptor downregulation can be inferred from studies in which myocardial β-adrenergic density correlated inversely with coronary sinus norepinephrine in patients with heart failure resulting from IDC. Thus, the data presented in this study establishing a positive correlation between myocardial β-adrenergic receptor density and all potential myocardial adrenergic neurotransmitters is further evidence that exposure to cardiac-derived norepinephrine is the basis for β₁-receptor downregulation.

In failing human ventricle, it is necessary to reconcile the previously reported observations of decreased norepinephrine uptake and release and depleted tissue myocardial norepinephrine with the data derived from the present study, which suggest that an abnormality of one or more of the rate-limiting steps in norepinephrine synthesis is not responsible for norepinephrine depletion. In this regard, it should be emphasized that published data pertaining to norepinephrine release, uptake, activity, and number of uptake, sites reflect cardiac rather than neuronal or synaptic norepinephrine kinetics. The data on decreased release are based on measurements per unit of myocardium, and if attrition of adrenergic neurons is present, it is possible that norepinephrine release per neuron is actually increased. This would be in keeping with data on increased sympathetic fiber discharge in peripheral nerves in heart failure.

There is evidence for progressive dropout or loss of hyperfunctioning adrenergic neurons associated with myocardial failure. Such neuronal loss has been documented in cattle with right heart failure and in the atria and ventricles of failing human heart. The neuronal attrition could be related to the local production of 6-hydroxydopamine, a potentially neurotoxic intermediary product in the biosynthesis of norepinephrine. Presumably, diffusion of synaptic norepinephrine derived from the remaining hyperfunctioning neuronal units would be sufficient to produce and maintain myocardial β₁-adrenergic downregulation, particularly if norepinephrine uptake, activity were depressed independent of the decrease in norepinephrine uptake sites. Under these circumstances, measurements of myocardial norepinephrine, norepinephrine release, and uptake normalized per unit of myocardium would be decreased when in fact, norepinephrine release per unit of neuron and synaptic norepinephrine concentration are increased. However, substantiation of this theory necessitates the identification of potentially toxic norepinephrine metabolites such as 6-hydroxydopamine in failing myocardium.

Conclusions

Our data indicate that 1) norepinephrine stores are depleted in failing human ventricles in the absence of an abnormality of dopamine conversion to norepinephrine, 2) depleted norepinephrine stores correlate weakly with decreased β₁-adrenergic receptor density consistent with the hypothesis that β₁-adrenergic receptor downregulation in the failing human heart is related to increased cardiac-derived norepinephrine, and 3) myocardial NPY depletion may be a helpful marker of increased adrenergic drive in patients with congestive heart failure.

References

11. Sandoval AB, Gilbert EM, Rose CP, Bristow MR: Cardiac norepinephrine uptake and release is decreased in dilated cardiomyopathy (abstract). Circulation 1989;80(suppl II):I-393

KEY WORDS • heart failure • norepinephrine • dopamine • epinephrine • neuropeptide Y • β-adrenergic receptors
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