Heterogeneous Transmural Distribution of \( \beta \)-Adrenergic Receptor Subtypes in Failing Human Hearts

Scott L. Beau, MD; Timothy K. Tolley, BS; Jeffrey E. Saffitz, MD, PhD

Background. Downregulation of myocardial \( \beta \)-adrenergic receptor density does not occur in a spatially uniform distribution in patients with congestive heart failure. Rather, it results primarily from loss of receptors in the subendocardium. In patients with dilated cardiomyopathy, \( \beta \)-receptors have been found to be downregulated selectively. These observations suggest that considerable transmural heterogeneity in the distribution of \( \beta \)-adrenergic receptor subtypes exists in the failing human heart. The present study was designed to test this hypothesis.

Methods and Results. We used quantitative autoradiography of radioligand binding sites to measure the distribution of \( \beta \)-adrenergic receptor subtypes in transmural sections of left ventricular myocardium obtained from cardiac transplant patients with ischemic \((n=13)\) and idiopathic dilated \((n=12)\) cardiomyopathy and from 4 subjects with no history of congestive heart failure. Analysis of radioligand binding isotherms revealed a significant reduction in total \( \beta \)-adrenergic receptor density in hearts of patients with ischemic and idiopathic cardiomyopathy \((20.3\pm 1.9\) and \(18.2\pm 2.0\) fmol/mg protein, respectively, versus \(40.0\pm 11.4\) in control subjects; \(P<.01\) for both). Loss of the \( \beta_1 \)-subtype accounted for \(86\%\) of the total reduction in \( \beta \)-receptor density in failing hearts. Despite the significant decreases in overall tissue receptor content, the densities of total \( \beta \)-receptors and \( \beta \)-receptor subtypes in subepicardial myocytes were equivalent in failing and control hearts. However, in contrast to control hearts, in which the transmural distribution of total and \( \beta \)-receptors was uniform \((\text{endocardial}:	ext{epicardial receptor density ratios, } 0.97\pm 0.14\) and \(1.0\pm 0.2\), respectively), hearts of patients with ischemic and idiopathic dilated cardiomyopathy had significantly lower total \( \beta \)-receptor and \( \beta_1 \)-receptor densities in the subendocardium \((\text{ratios, } 0.66\pm 0.06\) and \(0.46\pm 0.09\) for total and \( \beta_1 \)-receptors, respectively, in ischemic cardiomyopathy and \(0.60\pm 0.08\) and \(0.52\pm 0.11\) in diluted cardiomyopathy; \(P<.001\) for all values compared with a ratio of \(1\). Thus, \( \beta_1:eta_2 \) receptor density ratios were markedly decreased in the subendocardium of ischemic and idiopathic dilated left ventricles compared with control hearts.

Conclusions. A significant transmural gradient in the density of myocardial \( \beta_1 \)-adrenergic receptors exists in the hearts of patients with ischemic and diluted cardiomyopathy, resulting in a markedly altered \( \beta_1:eta_2 \) receptor density ratio in the subendocardium. \((\text{Circulation.} 1993;88:2501-2509.\)

Key Words • cardiomyopathy • radiography • radioligand binding

Myocardial \( \beta \)-adrenergic receptor density and responsiveness are known to be diminished in patients with congestive heart failure, but the mechanisms underlying receptor downregulation are incompletely understood. Local factors, rather than systemic conditions, appear to play a principal role. Considerable spatial heterogeneity in \( \beta \)-adrenergic receptor subtype downregulation may occur and could contribute to electrophysiological heterogeneity, leading to malignant ventricular tachyarrhythmias.

Although Bristow et al have analyzed the distribution of \( \beta \)-adrenergic receptors in multiple membrane fractions of myocardium from patients with pulmonary hypertension, most previous studies of altered \( \beta \)-adrenergic receptor density and function in diseased myocardium have used conventional membrane fractions \((30000\) to \(50000\)g pellets) prepared from homogenates of whole tissue, an approach with limited anatomic resolution that also entails other unavoidable shortcomings. Crude membrane preparations comprise mixtures of cell surface and intracellular membranes of multiple cell types. In addition, conventional membrane preparations \((30000\) to \(50000\)g pellets) are typically depleted of the putative intracellular compartment \((\text{light vesicle fraction})\) in which \( \beta \)-receptors are thought to be sequestered in response to prolonged agonist stimulation. To overcome these limitations, we have developed quantitative autoradiographic techniques to characterize the total tissue content of \( \beta \)-receptors in transmural sections of the heart. Using this approach, we observed that downregulation of \( \beta \)-adrenergic receptors in failing human myocardium did not occur uniformly in the transmural distribution. Rather, decreased \( \beta \)-receptor density was found to be a result of a selective reduction of \( \beta \)-receptors on subendocardial myocytes.
TABLE 1. Clinical Features of Cardiac Transplant Recipients

<table>
<thead>
<tr>
<th>Age, y</th>
<th>47.8±2.6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>22</td>
</tr>
<tr>
<td>Black</td>
<td>3</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
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<tr>
<td>Male</td>
<td>23</td>
</tr>
<tr>
<td>Female</td>
<td>2</td>
</tr>
<tr>
<td>NYHA functional class</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>2</td>
</tr>
<tr>
<td>III</td>
<td>8</td>
</tr>
<tr>
<td>IV</td>
<td>15</td>
</tr>
<tr>
<td>Hemodynamic Index</td>
<td></td>
</tr>
<tr>
<td>Cardiac output, L/min</td>
<td>4.7±0.3</td>
</tr>
<tr>
<td>Cardiac index, L·min⁻¹·m⁻²</td>
<td>2.4±0.1</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>22.3±1.6</td>
</tr>
<tr>
<td>PCWP, mm Hg</td>
<td>19.3±1.4</td>
</tr>
</tbody>
</table>

NYHA indicates New York Heart Association; LVEF, left ventricular ejection fraction; and PCWP, pulmonary capillary wedge pressure.

Bristow et al² have shown that β-adrenergic receptor downregulation in patients with idiopathic dilated cardiomyopathy is attributable mainly to reduction of the β₁-adrenergic receptor subtype. This important observation, coupled with our findings of a nonuniform distribution of β-receptors in the failing heart, suggests that a substantial transmural gradient might exist in the distribution of β₁-adrenergic receptor subtypes in failing human myocardium. Accordingly, the goal of the present study was to quantitatively delineate the transmural distribution of myocardial β₁-adrenergic receptor subtypes and determine whether regional heterogeneity occurs in the distribution of myocardial β-receptor subtypes in patients with chronic congestive heart failure.

Methods

Tissue Procurement

Transmural samples of left ventricular myocardium were obtained from hearts of 13 patients with ischemic cardiomyopathy and 12 patients with idiopathic dilated cardiomyopathy who underwent cardiac transplantation at Barnes Hospital from March 1991 to October 1992. Selected clinical features of these transplant recipients are shown in Table 1. Eleven patients were being treated with intravenous dobutamine (mean dose, 7.0±1.2 μg·kg⁻¹·min⁻¹) at the time of transplantation, and all patients were taking other medications, including diuretics, digoxin, and angiotensin-converting enzyme inhibitors or other vasodilators.

Transmural samples of left ventricular myocardium were also obtained from four nonfailing control hearts. These samples came from three vital organ donors and one valve homograft donor whose hearts were not used for transplantation. These donors included two motor vehicle accident victims (a 38-year-old man and 3-year-old boy) with massive closed-head injury, a 43-year-old woman with brainstem herniation following cerebrovascular accident, and a 27-year-old man who died of a gunshot wound to the head. All four subjects had been treated with intravenous dopamine (mean dose, 8.4±2.6 μg·kg⁻¹·min⁻¹), and one patient had received intravenous dobutamine (3.6 μg·kg⁻¹·min⁻¹) within 24 hours of tissue harvest, but none had a clinical history of congestive heart failure. Informed consent was obtained for use of organs in research in all cases. The study protocol was approved by the Washington University Human Studies Committee.

Excised hearts were rinsed immediately in cold modified Krebs solution (containing in mmol/L: NaCl 118, KCl 4.7, CaCl₂ 2.5, MgCl₂ 0.54, NaHCO₃ 25, NaH₂PO₄ 1, dextrose 11, ascorbic acid 0.001, pargyline 0.102, and EDTA 0.050), and transmural blocks of ventricular myocardium were dissected, frozen, and stored in sealed containers at −70°C until used in experiments. Regions of grossly discernible myocardial necrosis or fibrosis were excluded.

Radioligand Binding Assays

The total tissue content of β₁-adrenergic receptors in transmural sections of left ventricular myocardium was determined with radioligand binding isotherms. Transmural, 12-μm-thick frozen sections of unfixed tissue were cut with a cryostat-microtome and mounted on gelatin-coated slides. Slide-mounted tissue sections were incubated at 37°C in buffer (NaCl 154 mmol/L, MgCl₂ 10 mmol/L, Tris-HCl 10 mmol/L, pH 7.4) containing selected concentrations (1.1 to 107 pmol/L) of (−)[³H]iodocyanopindolol (ICYP) (1900 to 2200 Ci/mm; New England Nuclear, Boston, Mass). Nonspecific binding was defined as binding of radioligand in the presence of 10⁻⁶ mol/L l-propranolol. Sections were incubated with radioligand under conditions found in previous studies to establish steady-state binding. Large volumes of buffer (50 mL) were used so that the concentration of free radioligand did not change measurably during incubation intervals. After selected intervals of radioligand binding, sections were rinsed for 1 hour at 22°C in buffer that did not contain radioligand or unlabeled displacer, conditions previously shown to selectively remove nonspecifically bound radioactivity without removing specifically bound radioactivity. Sections were then dipped briefly in distilled water to remove buffer solutes and air-dried. The amount of radioligand bound in each section was determined by scraping sections from the slides with a razor and quantifying radioactivity in each with gamma scintillation spectrometry. In all experiments, data points were calculated as means of duplicate or triplicate determinations. Specifically bound radioactivity was normalized to account for modest variations in section thickness, section size, or amounts of interstitial fibrosis by measuring the total area and protein content in sets of transmural sections obtained at regular intervals during the preparation of large numbers of serial sections during each individual experiment. Areas were measured by digitizing the outlines of enlarged photographs of the sections with computer-assisted planimetry. Cellular protein was assessed in individual sections scraped from non–gelatin-coated slides by the method of Lowry...
et al\textsuperscript{12} using bovine serum albumin standards. Because this method is insensitive to collagen and other extra-
cellular matrix proteins, effects on apparent receptor
density caused by potential differences in the relative
amounts of interstitial fibrosis that occur among failing
and nonfailing ventricles were minimized.

The relative proportions of $\beta_1$- and $\beta_2$-receptors in
left ventricular myocardium were determined by incu-
bating transmural sections with ICYP in the presence of
CGP-20712A, a highly selective $\beta_1$-antagonist, under
defined conditions in which the unlabeled displacer
inhibited radioligand binding to $\beta_2$-receptors by nearly
100\% without significantly affecting binding to $\beta_2$-recep-
tors. Optimal conditions for this purpose were deter-
mined in preliminary competition binding experiments
in which transmural sections from two nonfailing and
four failing hearts were incubated under equilibrium
binding conditions with 25 pmol/L ICYP and 18 separ-
ate concentrations of CGP-20712A ranging from $1 \times 10^{-6}$
\text{mol/L} to $3 \times 10^{-5}$ \text{mol/L}. Total $\beta_2$-receptor bind-
ing in each experiment was determined in additional
sections incubated with 25 pmol/L ICYP with or without
$L^{-4}$ \text{mol/L} $\alpha_1$-propranolol. After incubation for 1 hour at
37\degree C, sections were rinsed, dried, and scraped, and
radioactivity was quantified as described for binding
isothersms. With analysis of the competition binding
curves (as described below and as shown in the “Re-

tual Autoradiography

 Autoradiographic methods have been extensively val-
    idated in previous studies.\textsuperscript{4,10,11} Briefly, gelatin-coated
coverslips were coated with Kodak NTB2 nuclear track
emulsion (Eastman Kodak, Rochester, NY), dried at
room temperature for at least 3 hours, and glued at one
end to slides containing radiolabeled sections. After the
emulsion was exposed for approximately 24 hours, the
unglued edge of each coverslip was gently lifted from the
slides, and the emulsion was developed with Kodak
D19 developer (diluted 1:1 with water) for 3 minutes
and fixed with Kodak fixer for 1 minute at 25\degree C. The
tissue sections were then stained with hematoxylin and
eosin, and the coverslips were sealed permanently to the
slides.

The tissue and overlying developed grains in the
emulsion layer were examined by light microscopy. The
densities of total $\beta$-adrenergic receptors and the pro-
portions of $\beta_1$- and $\beta_2$-receptors in cardiac myocytes of
the subepicardium and the subendocardium (defined as
the region of tissue contained within five high-power
fields of the epicardial and endocardial surfaces, respec-
tively, at a magnification of $630 \times$) were determined by
counting grains. Grain densities were compared in corre-
sponding regions of serial sections incubated with
25 pmol/L ICYP with or without $\alpha_1$-propranolol (the sum

\begin{table}
\centering
\caption{Composite Competition Binding Curve Data}
\begin{tabular}{lccc}
\hline
 & $K_{D1}$ & $K_{D2}$ & $K_{D1}/K_{D2}$ \\
 & nmol/L & nmol/L & \\
\hline
Failing (n=4) & 1.92±0.41 & 1408±519 & 0.001 \\
Nonfailing (n=2) & 2.14±0.68 & 4490±2940 & 0.0005 \\
\hline
\end{tabular}
\end{table}

of $\beta_1$- and $\beta_2$-receptors) and those incubated with 25
pmol/L ICYP and $10^{-7}$ \text{mol/L} of CGP-20712A ($\beta_2$
-receptors only). The grain density values were corrected
for the modest amount of ICYP binding to $\beta_1$-receptors
and the modest inhibition of ICYP binding to $\beta_2$-receptors
under the conditions used (see below).

Data from individual sections were determined by cal-
mulating means of grain density measurements from at
least 10 distinct microscopic fields. Composite data
points were derived from the average of at least three
separate sets of transmural sections per patient.

Data Analysis

 Competition binding curves were analyzed with the
iterative curve-fitting program (LIGAND) of Munson and
Rodbard\textsuperscript{13} as modified for microcomputers by McPher-
son.\textsuperscript{14} With this method, initial estimates of selected
binding constants in the defined model are iteratively
refined by nonlinear least-squares curve-fitting tech-
niques based on the Marquardt-Levenberg modification
of the Gauss-Newton method.\textsuperscript{13} When the weighted
sum of the squares was minimized, final parameter
estimates were generated and fitted to the actual data.

The extent to which selected concentrations of CGP-
20712A inhibited binding of ICYP to $\beta_1$- and $\beta_2$-recep-
tors was determined with the following equation of
Neve et al\textsuperscript{15} describing the inhibition of a selective
radioligand by a selective competing ligand:

$$B = \frac{B_{\text{max}1} \cdot L}{L + K_{D1} \cdot (1 + i/K_{i1})} + \frac{B_{\text{max}2} \cdot L}{L + K_{D2} \cdot (1 + i/K_{i2})}$$

where $B$ is the amount of radioligand bound; $B_{\text{max}1}$ and
$B_{\text{max}2}$ are the densities of $\beta_1$- and $\beta_2$-receptors; $L$ is the
concentration of radioligand; $i$ is the concentration of unlabeled displacer; $K_{D1}$ and $K_{D2}$ are dissociation con-
stants of $\beta_1$- and $\beta_2$-receptors, respectively, for the
radioligand; and $K_{i1}$ and $K_{i2}$ are dissociation constants of
the receptors for the unlabeled competing ligands.

We measured $K_{D}$ by Scatchard transformation\textsuperscript{16} of
binding isotherm data and, because $\beta_1$-receptors make up
approximately 65\% to 75\% of myocardial $\beta$-recep-
tors, we designated this observed value as $K_{D1}$. Because
ICYP is approximately twofold selective for $\beta_2$-recep-
tors, $K_{D2}$ was assumed to be equal to 50\% of $K_{D1}$. Values
for $K_{i1}$ and $K_{i2}$ were determined by analysis of detailed
competition binding curves as described above and as
shown in Table 2. Using these values and the values for
the concentrations of radioligand ($L$) and displacing
ligand ($i$) and specific binding ($B$), the relative extent
to which CGP-20712A inhibited ICYP binding to $\beta_1$- and
$\beta_2$-receptors was calculated.

All data are expressed as mean±SEM. Statistical
analyses were performed on a MacIntosh IicI computer
using the STATVIEW 4.0 application package. Two-sided
unpaired $t$ tests were used to determine statistically

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\hline
\end{tabular}
\end{table}
significant differences in binding isotherm and grain density measurements. Ratios of total \( \beta \)-receptor and \( \beta \)-receptor subtype densities were analyzed with one-sample \( t \) tests by comparing the observed means to a hypothesized mean of one. Significance was defined as \( P<.05 \) in all cases.

**Results**

**CGP-20712A Competition Binding Studies**

Composite competition binding curves determined in transmural left ventricular sections prepared from two nonfailing and four failing hearts are shown in Fig 1. The data were best fit by biphasic curves indicating the presence of two binding sites. Analysis with the LIGAND program indicated that the affinities of the two binding sites for CGP-20712A differed by approximately three orders of magnitude (see Table 2). Using Equation 1, we determined that at a concentration of \( 10^{-7} \text{ mol/L} \), CGP-20712A inhibited binding of 25 pmol/L ICYP to \( \beta_1 \) sites by 95.5% and 95.1% in control and failing hearts, respectively, whereas binding to \( \beta_2 \) sites was inhibited by only 0.5% and 1.6%, respectively. Thus, all subsequent studies designed to determine the relative densities of \( \beta \)-receptor subtypes were performed by incubating sections with 25 pmol/L ICYP and \( 10^{-7} \text{ mol/L} \) CGP-20712A. All radioactivity and grain density measurements were corrected to account for the 4% to 5% binding of ICYP to \( \beta_1 \)-receptors and the 1% to 2% inhibition of radioligand binding to \( \beta_2 \)-receptors.

**Radioligand Binding Isotherms**

The total content of \( \beta \)-adrenergic receptors in transmural sections was determined by Scatchard analysis of binding isotherms. Representative isotherms and Scatchard plots are shown in Fig 2, and composite results in failing and control left ventricles are shown in Fig 3. The total tissue content of \( \beta \)-receptors (\( B_{max} \)) in the four nonfailing ventricles was 40.0±11.4 fmol/mg protein. Total \( \beta \)-receptor density was reduced significantly in the
combined group of all failing ventricles (B_max = 19.3 ± 1.4 fmol/mg protein, P < .001) and in subgroups of failing ventricles divided according to pathogenesis (B_max = 18.2 ± 2.0, P < .01 and B_max = 20.3 ± 1.9, P = .01 in idiopathic dilated and ischemic hearts, respectively). Treatment with intravenous dobutamine before transplantation had no apparent effect on the total tissue content of β-receptors (B_max = 19.1 ± 2.6 fmol/mg protein in patients treated with dobutamine versus 19.4 ± 1.5 in patients not treated with dobutamine, P = NS).

The reduction in β-receptor density observed in failing ventricles was attributable primarily to a loss of the β_1-receptor subtype (Fig 3). The β_1-receptor density decreased from 30.2 fmol/mg protein in nonfailing ventricles to 12.4 fmol/mg protein in failing ventricles. Thus, 86% of the total reduction in β-receptor density in failing hearts was attributable to this 17.8 fmol/mg protein decrease in β_1-subtype density. The β_1-receptor densities were not significantly different in left ventricles from patients with idiopathic dilated (11.6 fmol/mg protein) and ischemic (13.1 fmol/mg protein) cardiomyopathy. No significant differences were observed in β_2-subtype density (Fig 3) in transmural slices of nonfailing (9.8 fmol/mg protein) and failing (6.9 fmol/mg protein) hearts, nor were any differences in β_2-receptor density noted between heart failure patients with idiopathic (6.6 fmol/mg protein) or ischemic (7.2 fmol/mg protein) cardiomyopathy.

**Autoradiographic Analyses**

The distribution of β-adrenergic receptors in left ventricular subepicardial and subendocardial regions of compact myocytes was determined by autoradiographic analysis of transmural sections prepared from 4 nonfailing and 23 failing left ventricles. Representative autoradiographs are shown in Fig 4.

Despite the significant reduction of total β-receptor density (attributable almost entirely to reduced β_1-receptor density) in whole transmural slices of failing ventricles compared with nonfailing controls, no significant differences were observed in the density of total β-receptors or β-receptor subtypes in subepicardial myocyte regions of control and failing hearts (Fig 5). In marked contrast, however, total β-receptor density and β_1-receptor density were reduced significantly in subendocardial myocytes in the combined group of all failing hearts and in both subgroups of patients with idiopathic dilated and ischemic cardiomyopathies (Fig 5).

The density of total β-receptors was not significantly different in subendocardial and subepicardial myocyte regions of nonfailing ventricles (endocardial:epicardial receptor density ratio, 0.97 ± 0.14) (Fig 6), whereas in failing ventricles, total β-receptor density was significantly lower in subendocardial myocytes than in subepicardial myocytes (ratio, 0.63 ± 0.05, P < .0001). The endocardial:epicardial total β-receptor density ratio was similar in patients with idiopathic and ischemic cardiomyopathy (Fig 6). Moreover, as shown in Fig 7, the distribution of β-receptors was uniform in transmural sections of nonfailing left ventricles (endocardial: epicardial ratio, 1.0 ± 0.2), whereas in the group of all failing ventricles and in the subgroups with idiopathic or ischemic cardiomyopathy, a significant transmural gradient in the density of β-receptors was observed (ratios, 0.49 ± 0.07, P < .0001; 0.52 ± 0.11, P < .001; and 0.46 ± 0.09, P < .001, respectively). With the exception of idiopathic dilated ventricles (ratio, 0.76 ± 0.06, P < .05), significant transmural gradients in β_1-receptor density were not observed.

Fig 8 shows the ratio of β_1:β_2 receptor density in subepicardial and subendocardial myocytes in control ventricles and in patients with heart failure. In the subepicardium of both control and failing left ventricles, the β_1-receptor subtype predominated (β_1:β_2 ratio, 2.33 ± 0.26 and 1.97 ± 0.13, respectively, P = NS). In contrast, β_1:β_2 receptor density ratios were markedly decreased in the subendocardium of failing compared with nonfailing left ventricles (1.04 ± 0.12 versus 2.32 ± 0.45, P < .0001). This decrease was observed in both idiopathic (1.22 ± 0.17, P = .001) and ischemic (0.85 ± 0.14, P < .0001) cardiomyopathy.

**Discussion**

In this study, we used radioligand binding techniques and quantitative light microscopic autoradiography to delineate the distribution of β-adrenergic receptor subtypes in transmural slices of left ventricle in nonfailing control subjects and in patients with severe congestive heart failure. The results demonstrated a 52% reduction in total β-receptor density and a 59% reduction in β_1-receptor density in the failing ventricles compared with control hearts. The magnitude of these decreases was similar in patients with idiopathic and ischemic cardiomyopathy. Although similar degrees of β-receptor downregulation have been reported by others,1,2 our results differ from those recently reported by Bristow et
Figure 4. Representative autoradiographs showing relative grain densities in subepicardial and subendocardial myocyte regions in nonfailing and failing left ventricles. Transmural sections were incubated with 25 pmol/L ICYP alone (left panels) or in the presence of 10^-6 mol/L L-propranolol (right panels). A, Control subepicardium; B, control subendocardium; C, failing subepicardium; and D, failing subendocardium. Magnification is the same in all panels. Original magnification ×400. Bar=25 μm.
Bristow et al observed a greater extent of total and β1-receptor downregulation in idiopathic cardiomyopathy than in ischemic cardiomyopathy. This disparity may be related to the smaller sample size of our study or to the fact that a significant number of our patients with idiopathic dilated cardiomyopathy had received intravenous dobutamine before transplantation. An alternative explanation is that in most of their studies, Bristow et al measured receptor densities in conventional membrane preparations that are known to be depleted of light vesicles, the putative intracellular compartment in which sarcolemmal receptors may be sequestered when surface receptors are internalized. A comparison of β-receptor density measured in whole tissue slices and that measured in 30 000g pellets of homogenates of failing human left ventricles suggests that both intracellular sequestration and a net reduction in the total content of receptors may contribute to downregulation. If this is true, then the results of the present study and...
those of Bristow et al, taken together, may indicate that sequestration of $\beta$-receptors is more extensive in hearts of patients with idiopathic compared with ischemic cardiomyopathy.

Autoradiography of radioligand binding sites revealed a significant reduction in total $\beta$-receptor and $\beta_1$-receptor densities in subendocardial myocytes in failing ventricles. The magnitude of these reductions was similar in samples of left ventricles with idiopathic and ischemic cardiomyopathy. Although the mechanisms responsible for the selective reduction of $\beta_1$ receptor density in the subendocardium of failing human hearts are not known, we have previously shown that regional differences in receptor density cannot be attributed solely to regional differences in myocyte size or packing density in failing myocardium. Furthermore, we have recently demonstrated that neuronal uptake of norepinephrine is significantly diminished in subendocardial compared with subepicardial myocyte regions in patients with idiopathic and ischemic cardiomyopathy. Regional differences in sympathetic supply and function in failing hearts may lead to increased concentrations of endogenous agonists in the synaptic cleft surrounding the $\beta$-receptor and thereby contribute to the observed nonuniform downregulation.

In most previous studies of the distribution of myocardial $\beta$-adrenergic receptors in failing human myocardium, cardiac tissue was obtained from transplant recipients who had not received $\beta$-agonist therapy immediately before transplantation, whereas almost half of our patients were being treated with intravenous dobutamine at the time of operation. However, we observed no differences in the density of total $\beta$-receptors and $\beta$-receptor subtypes in patients with or without previous $\beta$-agonist therapy. Furthermore, although the nonfailing control hearts were obtained from subjects who had been treated within 24 hours of tissue procurement with intravenous dopamine at concentrations sufficient to exert $\beta_1$ agonist effects, total $\beta$-receptor density was significantly greater in this group compared with either all failing hearts or the subgroups of idiopathic or ischemic cardiomyopathy. Therefore, the altered $\beta$-receptor densities observed in this study do not appear to be attributable to catecholamine therapy.

Treatment with the $\beta_1$-selective antagonist metoprolol has been shown to increase $\beta$-adrenergic receptor density in some patients with idiopathic dilated cardiomyopathy. Such therapy may potentially restore the transmural distribution of receptor subtypes toward normal. However, the mechanism of action underlying the salutary effects of $\beta_1$-blockers in heart failure remains unclear. Although recent results showed benefits in terms of the combined end point of survival and the development of worsening heart failure, there were no obvious survival benefits with this agent.

Acknowledgments

This study was supported by National Heart, Lung, and Blood Institute grant HL-17646, SCOR in Coronary and Vascular Diseases. Dr. Beau was supported by an American College of Cardiology/Merck Adult Cardiology Research Fellowship Award. Dr. Saffitz was supported by an Established Investigator Award from the American Heart Association. We thank Louise Schoelch and Walter Clermont for photographic assistance; Cindy Behrends, RN, Peggy Emer, RN, Carol Cross, RN, and Laurie Schutte for assistance with tissue procurement and Susan Johnson for preparation of the typescript.

References


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Circulation. 1993;88:2501-2509
doi: 10.1161/01.CIR.88.6.2501

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