Isolated Presynaptic Inotropic \( \beta \)-Adrenergic Supersensitivity of the Transplanted Denervated Human Heart In Vivo

Wolfgang von Scheidt, MD; Michael Böhm, MD; Brigitte Schneider, MD; Bruno Reichart, MD; Erland Erdmann, MD; and Gernot Autenrieth, MD

**Background.** The regulation of contractility of the transplanted heart depends on circulating catecholamines resulting from cardiac denervation. Supersensitivity to circulating catecholamines may result from loss of presynaptic neuronal uptake or upregulation of postsynaptic \( \beta \)-adrenergic receptors.

**Methods and Results.** Dose–response curves using the \( \beta \)-adrenergic receptor agonists isoproterenol (no neuronal uptake) and epinephrine (neuronal uptake) were performed in vivo. The inotropic response was measured echocardiographically as the increase of fractional shortening (ΔFS) and the increase of the systolic pressure/dimension ratio (ΔP/D). The inotropic response to increasing doses of isoproterenol (5–20 ng/kg·min) was identical in 36 heart transplant recipients compared with 13 control subjects: ΔFS during 20 ng/kg·min isoproterenol amounted to 18.2±6.2% versus 17.4±4.0% (NS) and ΔP/D to 2.3±1.2 mm Hg/mm versus 2.2±0.5 mm Hg/mm (NS), respectively. A vaguely mediated indirect negative inotropic effect in the innervated hearts was excluded by identical inotropic responses to isoproterenol in control subjects without and after atropine pretreatment. The inotropic response to increasing doses of epinephrine (10–40 ng/kg·min) was significantly augmented in 13 heart transplant recipients compared with 11 control subjects: ΔFS during 40 ng/kg·min epinephrine amounted to 19.9±2.6% versus 8.6±2.0% (\( p < 0.001 \)) and ΔP/D to 2.3±0.9 mm Hg/mm versus 0.6±0.3 mm Hg/mm (\( p < 0.001 \)), respectively. Pretreatment with desipramine (blockade of neuronal uptake) in control subjects resulted in a significantly increased inotropic response: ΔFS during 40 ng/kg·min epinephrine amounted to 17.9±3.6% (\( p < 0.001 \)) versus untreated controls, NS versus heart transplant recipients) and ΔP/D to 1.7±0.8 mm Hg/mm (\( p < 0.001 \)) versus untreated controls, NS versus heart transplant recipients).

**Conclusions.** These findings provide evidence against a postsynaptic inotropic supersensitivity or subsensitivity of the \( \beta \)-adrenergic receptor–effector system of the transplanted denervated human heart in vivo. However, a marked presynaptic inotropic supersensitivity is present because of denervation-associated loss of neuronal catecholamine uptake. (Circulation 1992;85:1056–1063)

**Key Words** • heart transplantation • denervation • \( \beta \)-adrenergic sensitivity • neuronal uptake • contractility

Heart transplantation–associated cardiac denervation results in persistent degeneration of the postganglionic ventricular adrenergic nerve terminals, as evidenced by histological\(^1\) and immunohistochemical investigations.\(^2\) Consistently, a persistent noradrenaline depletion of the human ventricular myocardium has been observed.\(^3\)–\(^5\) The loss of the local neurotransmitter release suggests that circulating catecholamines are crucial to increase the contractile function of the transplanted heart. The inotropic response of the denervated heart to circulating catecholamines may be modulated in several ways. It has been postulated that a denervated organ becomes more sensitive to its physiological neurotransmitter.\(^6\)–\(^8\) This supersensitivity may be due to presynaptic loss of neuronal catecholamine uptake (uptake\(_2\)) or due to postsynaptic changes in the \( \beta \)-adrenergic receptor/G protein/adenylate cyclase pathway.\(^9\)–\(^14\) On the other hand, the possibility must be taken into account of an impairment of the inotropic response of the transplanted heart to \( \beta \)-adrenergic receptor agonists, which may result from either denervation itself\(^5,12\) or other transplantation-associated impediments such as graft preservation, repeated rejection episodes, or myocardial side effects of cyclosporine A.\(^15\)–\(^20\) Studies in transplanted experimental animals and humans yielded conflicting results concerning the density of \( \beta \)-adrenergic receptors\(^5,12,13\) and the activity of basal or stimulated adenylye cyclase\(^6,12,21\) in vitro as well as the chronotropic sensitivity to \( \beta \)-adrenergic agonists in vivo.\(^9,10,22\) Evaluation of the inotropic \( \beta \)-adrenergic sensitivity of the transplanted human heart, taking into consideration both presynaptic and postsynaptic changes, has not yet been performed. To investigate each component of the contractile neuroreceptor–effector system, an echocardiographic in vivo study of transplanted compared with control hearts was performed. Dose–response curves were obtained using isoproterenol and epinephrine. Isoproterenol is not removed.

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by neuronal uptake\textsuperscript{23,24} and therefore provides the possibility to evaluate selectively the postsynaptic \(\beta\)-adrenergic receptor-effector system. The endogenous catecholamine epinephrine, which is removed by neuronal uptake,\textsuperscript{23,26} is a suitable tool to additionally evaluate the presynaptic component of adrenergic sensitivity.

**Methods**

**Patients**

The patient group consisted of 36 heart transplant recipients (34 men and two women) with a mean age of 44.9±8.1 years. Mean age of the transplanted hearts (28 male hearts and eight female hearts) at time of investigation was 29.3±6.3 years. All patients were investigated beyond the first year after transplantation. Mean interval from transplantation was 2.4±1.5 years. All patients were without a history or physical signs of heart failure. Cardiac function at rest, assessed by two-dimensional and M-mode echocardiography, was normal in each patient. Endomyocardial biopsy and coronary angiography were performed in all patients within 24 hours after the investigation. Patients with the presence of acute rejection as evaluated in accordance with the Billingham criteria\textsuperscript{16} and patients with the presence of graft atherosclerosis were excluded. Immunosuppression consisted of 302±98 mg/day cyclosporine A (\(n=36\)), 7.8±2.1 mg/day prednisone (\(n=36\)), and 54±18 mg/day azathioprine (\(n=14\)). Thirty-four patients received an antihypertensive medication: enalapril 11.8±6.9 mg/day (\(n=32\)), verapamil 194±96 mg/day (\(n=15\)), or furosemide 44±25 mg/day (\(n=22\)). Antihypertensive medication was stopped 24 hours before the investigation. Inotropic response to isoprenaline was evaluated in all 36 patients. Inotropic response to epinephrine was evaluated in a subgroup of 13 consecutive patients who did not differ from the whole group regarding age, interval from transplantation, immunosuppression, or antihypertensive medication. The control group consisted of a total of 13 healthy, nonsmoking male subjects without any medication. All control subjects were without a history of cardiac disease, and physical examination gave normal results. ECG and echocardiography were normal in each control subject. Mean age was 31.6±4.1 years and did not differ significantly from donor heart age.

**Measurements**

Two-dimensional guided M-mode echocardiography in a short-axis view was performed using phased-array equipment with a 2.5 MHz transducer (Toshiba, SSH 65 A). All recordings were taken by the same investigator and evaluated blindly by two principal investigators of the echocardiography department. End-diastolic diameter (EDD) and end-systolic left ventricular diameter (ESD) were measured as the mean of five cardiac cycles according to standard guidelines.\textsuperscript{27} Fractional shortening was calculated as 100(EDD−ESD)/EDD. To control for effects of potentially different afterload conditions, the pressure/dimension ratio was calculated as the ratio of systolic blood pressure to ESD.\textsuperscript{28,29} Arterial blood pressure was measured in the right arm by an automated sphygmomanometer (Accutorr, Datascexe, Bremen, FRG). Heart rate was obtained from simultaneous ECG recordings. Mean arterial blood pressure was calculated as diastolic pressure plus one third of pulse pressure.

**Study Protocol**

A cannula was inserted into a forearm vein. After 15 minutes in the supine position, basal recordings were taken. A continuous intravenous infusion of isoprenaline was started with 5 ng/kg · min and was increased to 10, 15, and 20 ng/kg · min for 5 minutes each in heart transplant recipients and control subjects. Thirty minutes after return to baseline values, the isoprenaline infusion protocol was repeated in control subjects 3 minutes after application of 0.015 mg/kg atropine to exclude potential reflex negative inotropic changes in innervated hearts mediated by the parasympathetic nervous system. Echocardiographic and blood pressure recordings were taken at rest or 3 minutes after application of atropine in control subjects, respectively, and during 5, 10, 15, and 20 ng/kg · min isoprenaline. On a separate day, a continuous infusion of epinephrine was started with 10 ng/kg · min, increasing to 20, 30, and 40 ng/kg · min for 5 minutes each in heart transplant recipients and control subjects. In control subjects, the epinephrine infusion protocol was repeated 3 hours after 1 mg/kg desipramine per os to evaluate the effect of blockade of the neuronal uptake in the control hearts. Echocardiographic and blood pressure recordings were taken at rest or 3 hours after desipramine intake in control subjects, respectively, and during 10, 20, 30, and 40 ng/kg · min epinephrine. This study was in accordance with the declaration of Helsinki. Informed consent was given by each heart transplant recipient and each control individual.

**Statistical Analysis**

Student’s \(t\) test for paired or unpaired data, as appropriate, was performed to compare two means. The response to isoprenaline and epinephrine in controls and heart transplant recipients was compared by analysis of variance for repeated measures. All calculated probability values are two-tailed. All probability values less than 0.05 were considered significant. All group data are given as mean±SD.

**Results**

**Isoprenaline**

Baseline left ventricular function was normal in both groups (i.e., EDD was less than 56 mm and fractional shortening was greater than 30% in each control subject and each transplanted patient) (Table 1). The transplanted hearts performed at significantly smaller EDDs and ESDs and higher heart rates and blood pressure values compared with control hearts. Fractional shortening was identical in both groups. Because of higher blood pressure and smaller ESD, the baseline pressure/dimension ratio was significantly higher in the transplanted group. During isoprenaline, significant increases in fractional shortening, pressure/dimension ratio, and heart rate and a decrease of the ESD were observed in both groups (Table 1). A representative M-mode echocardiography recording is shown in Figure 1. The pulse pressure increased, and changes in EDD as a parameter of preload and mean arterial blood pressure as a parameter of afterload from rest to maximum
TABLE 1. Measurements at Rest or After Atropine and During Isoprenaline in Heart Transplant Recipients and Control Subjects Before and After Atropine

<table>
<thead>
<tr>
<th></th>
<th>Heart rate (bpm)</th>
<th>EDD (mm)</th>
<th>ESD (mm)</th>
<th>FS (%)</th>
<th>SBP (mm Hg)</th>
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<th>MBP (mm Hg)</th>
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<td>Atropine (0.015 mg/kg)</td>
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EDD, end-diastolic diameter; ESD, end-systolic diameter; FS, fractional shortening; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean arterial blood pressure; P/D, pressure/dimension ratio (ratio of SBP to ESD); bpm, beats per minute; HTR, heart transplant recipients; CON-A, controls after atropine.

*p < 0.05, †p < 0.01, ‡p < 0.001: Heart transplant recipients vs. controls or atropine-pretreated controls vs. controls.

§p < 0.05, ||p < 0.01, ¶p < 0.001: Atropine-pretreated controls vs. heart transplant recipients.

**p < 0.05, ††p < 0.01, ‡‡p < 0.001: Isoprenaline vs. rest or atropine, respectively.

Inotropic stimulation did not differ significantly in heart transplant recipients and control subjects (Table 1). The inotropic response, that is, the dose–response curve of the increase of fractional shortening \( \Delta \text{FS} \) and pressure/dimension ratio \( \Delta \text{P/D} \), was identical in heart transplant recipients and control subjects, indicating an unchanged \( \beta \)-adrenergic receptor–effector-mediated (i.e., postsynaptic) inotropic effect (Figure 2). The increase of \( \Delta \text{FS} \) and \( \Delta \text{P/D} \) also did not differ in control subjects before and after atropine pretreatment (Figure 2), thus excluding a potential reflex indirect negative inotropic effect mediated by ventricular parasympathetic nerves during \( \beta \)-adrenergic stimulation. The chronotropic response \( \Delta \text{HR} \) was significantly increased in heart transplant recipients compared with control subjects. However, after inhibition of parasympathetic influences by atropine, the chronotropic response was significantly augmented in control subjects. Compared with atropine-pretreated control subjects, the chronotropic response in heart transplant recipients was smaller (Figure 2).

Epinephrine

During epinephrine stimulation, significant increases were induced in heart transplant recipients, controls, and controls after desipramine pretreatment for fractional shortening, pressure/dimension ratio, and heart rate, whereas the ESD decreased significantly (Table 2). Systolic and mean arterial blood pressure were constant, and a slight decrease of the diastolic pressure was observed (Table 2). In contrast to the findings using isoprenaline, the inotropic response to epinephrine

![Figure 1](https://circ.ahajournals.org/doi/fig/10.1161/01.CIR.85.3.1058)  
**Figure 1.** Original M-mode echocardiography recording of the left ventricle of a heart transplant recipient at rest (R) and during isoprenaline 5–20 ng/kg · min, respectively. Note increase of fractional shortening during isoprenaline.
(ΔFS, ΔP/D) was significantly augmented in heart transplant recipients compared with control subjects (Figure 3). Increase of fractional shortening and pressure/dimension ratio were about twofold to threefold augmented in heart transplant recipients. After blockade of neuronal uptake with desipramine, the inotropic response in control subjects was significantly increased and became comparable with the inotropic response in heart transplant recipients (Figure 3), indicating an increased inotropic effect after cardiac denervation caused by presynaptic loss of neuronal uptake.

Additional atropine pretreatment was not performed during the epinephrine infusion protocol because the absence of a vagally mediated indirect negative inotropic effect had already been documented during the isoprenaline infusion protocol.

The chronotropic response (ΔHR) was significantly increased in heart transplant recipients and desipramine-pretreated controls compared with control subjects. Because atropine pretreatment was not per-

TABLE 2. Measurements at Rest or After Desipramine and During Epinephrine in Heart Transplant Recipients and Control Subjects Before and After Desipramine

<table>
<thead>
<tr>
<th></th>
<th>Heart rate (bpm)</th>
<th>EDD (mm)</th>
<th>ESD (mm)</th>
<th>FS (%)</th>
<th>SBP (mm Hg)</th>
<th>DBP (mm Hg)</th>
<th>MBP (mm Hg)</th>
<th>P/D (mm Hg/mm)</th>
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<td>HTR (n=13)</td>
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<tr>
<td>Rest</td>
<td>96±13†</td>
<td>45.0±3.8†</td>
<td>28.4±4.2</td>
<td>37.1±5.6</td>
<td>128±19††</td>
<td>78±13†</td>
<td>95±14†</td>
<td>4.6±0.8‡</td>
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<tr>
<td>Epinephrine (40 ng/kg·min)</td>
<td>114±16‡††</td>
<td>44.8±3.6†</td>
<td>19.4±3.1††</td>
<td>56.9±4.9‡† ††</td>
<td>131±23*</td>
<td>69±14*††</td>
<td>91±16*</td>
<td>6.9±1.5‡††</td>
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<td>Controls (n=11)</td>
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<tr>
<td>Rest</td>
<td>64±10</td>
<td>49.7±2.8</td>
<td>31.9±2.7</td>
<td>36.0±4.1</td>
<td>108±12</td>
<td>64±14</td>
<td>79±12</td>
<td>3.4±0.5</td>
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<tr>
<td>Epinephrine (40 ng/kg·min)</td>
<td>72±12††</td>
<td>49.2±2.5</td>
<td>27.3±2.3††</td>
<td>44.5±4.0††</td>
<td>109±11</td>
<td>58±10**</td>
<td>75±10</td>
<td>4.0±0.4††</td>
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<td>CON-D (n=11)</td>
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<tr>
<td>Rest</td>
<td>66±12</td>
<td>50.1±2.9</td>
<td>31.5±2.7</td>
<td>37.0±2.8</td>
<td>122±17</td>
<td>70±8</td>
<td>87±10</td>
<td>3.9±0.5</td>
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<tr>
<td>Desipramine (1 mg/kg p.o.)</td>
<td>69±13</td>
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<td>50.4±2.8</td>
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<td>32.0±2.0</td>
<td>36.7±2.3</td>
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<tr>
<td>Epinephrine (40 ng/kg·min)</td>
<td>87±15‡††</td>
<td>49.9±2.6</td>
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<td>22.8±2.2‡††</td>
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<td>54.3±3.8‡†∥</td>
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EDD, end-diastolic diameter; ESD, end-systolic diameter; FS, fractional shortening; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean arterial blood pressure; P/D, pressure/dimension ratio (ratio of SBP to ESD); bpm, beats per minute; HTR, heart transplant recipients; CON-D, controls 3 hours after desipramine.

*p<0.05, †p<0.01, ‡p<0.001: Heart transplant recipients vs. controls, desipramine-pretreated controls vs. controls.

§p<0.05, †p<0.01, ‡p<0.001: Desipramine-pretreated controls vs. heart transplant recipients.

**p<0.05, ††p<0.01, ‡‡p<0.001: Epinephrine 40 ng/kg·min vs. rest or desipramine, respectively.
formed, the vagally mediated negative chronotropic effect during β-adrenergic stimulation was not inhibited in desipramine-pretreated control subjects and untreated control subjects.

Discussion

The results of this in vivo study dealing with the catecholamine-mediated contractile response show that the transplanted denervated human heart exhibits an unchanged inotropic sensitivity of the β-adrenergic receptor–effector system, as evidenced by an identical dose–response curve to isoprenaline in heart transplant recipients and control subjects. This provides evidence against an upregulation of β-adrenergic receptors or an increased activity of the G protein/adenylate cyclase system leading to postsynaptic supersensitivity. Inversely, an impairment of the contractile response resulting from potential denervation-associated or other transplantation-associated alterations (e.g., graft preservation, repeated rejection episodes, or myocardial side effects of cyclosporine A15–20 leading to postsynaptic subsensitivity) is also unlikely to occur. However, because of the loss of neuronal uptake, the inotropic effect mediated by the endogenous catecholamine epinephrine (which is subject to neuronal uptake) is twofold to threefold augmented. This is documented by the leftward shift of the dose–response curve of epinephrine in heart transplant recipients and desipramine-pretreated compared with untreated control subjects. These findings are consistent with an isolated presynaptic inotropic supersensitivity of the transplanted denervated human heart.

Postsynaptic Inotropic Effects

The density of β-adrenergic receptors was found to be increased in myocardial tissue from transplanted13 or denervated5 experimental animals. In contrast, in the transplanted human heart, the density of β-adrenergic receptors was found to be unchanged4,12 or even slightly decreased.10 Basal activity of the adenylate cyclase has been reported to be unchanged12 or increased.23 Stimulated adenylate cyclase activity was found to be unchanged in response to forskolin and increased in response to isoprenaline40 or to be decreased compared with controls in response to isoprenaline, guanine nucleotides, or forskolin.12 The measurement of β-adrenergic receptors and adenylate cyclase activity in transplanted human myocardium is limited by the small tissue specimens harvested by endomyocardial biopsy. This precludes the determination of complete radioligand saturation experiments.10,12,21 In view of these inconsistent findings, evaluation of the β-adrenergic receptor–adenylate cyclase–mediated effect (i.e., the contractile response) is necessary. In denervated dogs, the isoprenaline-induced increase of left ventricular dP/dt was augmented due to an upregulation of β-adrenergic receptors.9 In isolated human right ventricular trabeculae obtained from five patients undergoing retransplantation, the isoprenaline-induced force of contraction was unchanged compared with control ventricular preparations.4

The unchanged inotropic response mediated by the β-adrenergic receptor–adenylate cyclase system found in the present study has two major implications. First, in contrast to experimental animals,10,13 there is in vivo evidence against postsynaptic changes such as upregulation of β-adrenergic receptors or an increased activity of the G protein/adenylate cyclase system as causes of denervation-associated inotropic supersensitivity. This may reflect the fact that the physiological regulation of β-adrenergic receptors in the human myocardium may be maintained by circulating catecholamines,12 the levels of which have been found not to be decreased after cardiac transplantation.32,33 Second, a reduced contractile response after stimulation of the β-adrenergic receptor–effector system is also not observed. Normal baseline contractility of the transplanted human heart has been reported by others34 as well as from our group35; however, an impaired activity of stimulated adenylate cyclase12 or a suspected metabolic inefficiency of the transplanted human heart36 could have resulted in an altered inotropic response during catecholamine stimulation. The present study strongly suggests that this is unlikely to occur. Thus, neither denervation nor other transplantation-associated impediments12,15–20 appear to alter the inotropic response of the transplanted human heart.

Indirect Negative Inotropic Effect?

In experimental animals, sympathetic stimulation results in a vagally mediated attenuation of the increase of the contractile response,36 a phenomenon known as accentuated antagonism or indirect negative inotropic effect.37 In the present study, no difference was found in the inotropic response to isoprenaline in control subjects either before or after the application of atropine. This provides evidence against a vagally mediated indirect negative inotropic effect during β-adrenergic stimulation in humans. This is of importance because postsynaptic supersensitivity of the transplanted human heart has been suggested in a study comparing the heart rate response in heart transplant recipients with controls without muscarinic-cholinoceptor blockade.22 This finding, however, most probably resulted from a reflex vagally mediated negative chronotropic effect in the innervated hearts, attenuating the chronotropic response in controls but not in denervated heart transplant recipients. As the present data show, these influences can be excluded concerning the inotropic response. The indirect negative inotropic effect found in experimental animals is independent of the catecholamine used for β-adrenergic stimulation; that is, it is independent of whether the catecholamine is subject to neuronal uptake (epinephrine, norepinephrine) or not (isoprenaline).36,37 Therefore, in the present study, atropine pretreatment of the control subjects to exclude an indirect negative inotropic effect in humans was performed during the isoprenaline infusion protocol only.

Postsynaptic Chronotropic Effects

In a study of Gilbert et al.,10 the isoprenaline-induced chronotropic response after application of atropine in the innervated recipient atrial cuff and the denervated donor atrium was compared in six heart transplant recipients. This study revealed identical increases in heart rate, a finding consistent with the absence of postsynaptic chronotropic supersensitivity after heart transplantation. In the present study as well as in a study of Quigg et al.,32 the denervated hearts show even
a slightly smaller chronotropic response to isoprenaline compared with atropine-pretreated control subjects. This may indicate a possible postsynaptic chronotropic subsensitivity, probably reflecting a slightly different regulation of the β-adrenergic receptor–adenylate cyclase system in atria as compared with ventricles.12 The contrasting findings of Gilbert et al10 may result from a different experimental protocol: The investigations were performed within 3 months of transplantation, using increasing bolus injections of isoprenaline. Moreover, the patient’s own innervated atrial cuffs served as controls.10 The chronotropic response of these recipient atria briefly after reversal of longstanding heart failure may be different from that of healthy control subjects.

The investigation of the chronotropic response to epinephrine was not an aim of the study protocol. The interpretation of the heart rate response to epinephrine in the present study therefore is limited by the fact that the reflex vagally mediated negative chronotropic effect was not inhibited by atropine.

**Presynaptic Inotropic Effects**

In denervated experimental animals, both presynaptic and postsynaptic inotropic supersensitivity has been found.9,13 The finding of this study that the inotropic response to epinephrine but not to isoprenaline is augmented, is the first experimentally proven evidence for the existence of an isolated presynaptic inotropic supersensitivity of the transplanted denervated human heart. The epinephrine-induced increase of contractility in the present study is in excess of twofold to threefold in the denervated compared with innervated hearts. The fact that blockade of the neuronal uptake with desipramine in the control subjects resulted in a similar leftward shift of the dose–response curve to epinephrine reveals the presynaptic origin of the supersensitivity to epinephrine. Because desipramine does not increase the level of circulating catecholamines,38–40 an enhanced inotropic response to catecholamines by this mechanism is unlikely.

Blockade of neuronal uptake has been performed using 0.5–1.5 mg/kg desipramine 3 hours before β-adrenergic stimulation.38–41 Because complete inhibition of neuronal uptake may require up to 1.5 mg/kg desipramine,40 the dosage used in the present study (1.0 mg/kg) may have resulted only in an almost complete blockade of neuronal uptake. This may explain the remaining insignificantly smaller inotropic response to epinephrine in control subjects after desipramine pretreatment compared with heart transplant recipients.

In contrast, to neuronally released norepinephrine, which is removed mainly by neuronal uptake (uptake1), circulating norepinephrine and epinephrine are eliminated from the circulation by the nonneuronal uptake mechanism (uptake2) to about 90%.41–43 Nonneuronal uptake is identical for isoprenaline and epinephrine.10,42 and has been found to be unchanged after cardiac transplantation.33 Therefore, it seems surprising that the loss of neuronal uptake is responsible for the increased inotropic sensitivity of the transplanted heart to circulating epinephrine. The explanation is the exceptional dependence of the human heart on the neuronal uptake for removal of both locally neuronally released norepinephrine and circulating endogenous catecholamines (norepinephrine and epinephrine).41 The human heart removes about 69% of circulating endogenous catecholamines by neuronal uptake, and of the total uptake of circulating endogenous catecholamines, about 82% is due to neuronal uptake.41 This is in marked contrast to other vascular beds in which removal of circulating endogenous catecholamines by neuronal uptake amounted to only 4–14%.41

Recently, limited structural sympathetic reinnervation of the transplanted human heart beyond 1 year after transplantation has been reported as assessed by tyramine-induced cardiac norepinephrine release.44 This is in contrast to studies revealing a persistent degeneration of sympathetic nerve terminals1,2 and a persistent norepinephrine depletion3,4 of the transplanted human heart. Although the present study includes only heart transplant recipients beyond the first year after transplantation, there is no evidence for functional ventricular sympathetic reinnervation; a persistent loss of sympathetic neuronal uptake is documented. Moreover, no difference of the epinephrine-induced inotropic response was found in heart transplant recipients less than 2.5 years (n=5) and more than 2.5 years (n=8) after transplantation.

**Clinical Implications**

First, presynaptic supersensitivity leads to a modulated effect of different catecholamines. This has to be taken into account in case of inotropic support of the failing transplanted human heart. Because of local myocardial potentiation, epinephrine and most probably norepinephrine (which was not tested in the present study) will reveal a higher inotrope-to-vasoconstrictor ratio (i.e., a higher β- to α-adrenergic receptor stimulation) resulting in marked increases of myocardial contractility but small effects on vascular resistance. In contrast, dopamine, which predominantly acts indirectly by enhancing the neuronal release of norepinephrine, can be expected to be less effective as an inotropic agent in denervated hearts.1,14

Second, several studies indicate that the transplanted human heart cannot achieve normal peak exercise heart rates, peak exercise cardiac outputs, maximum work loads, or peak oxygen intake.2,45–48 How can these findings be explained in view of the fact that presynaptic adrenergic chronotropic8 and inotropic supersensitivity is present and that baseline and peak exercise levels of circulating norepinephrine and epinephrine are comparable or even higher in heart transplant recipients compared with control subjects?32,33 The most likely explanation is that during peak exercise the local concentration of catecholamines at the synaptic cleft is predominantly dependent on neuronally released norepinephrine, not on circulating norepinephrine or epinephrine.49–51 Thus, degeneration of the ventricular sympathetic nerve terminals after cardiac transplantation has two opposing effects. The loss of neuronal uptake causes profound supersensitivity to circulating endogenous catecholamines. However, the loss of local neuronal release of norepinephrine most probably limits the ability of the transplanted heart to achieve normal maximum exercise heart rates and stroke volumes.
Conclusions

An unchanged inotropic sensitivity of the transplanted human heart to catecholamines that are not taken up by nerve terminals has been documented; this excludes a postsynaptic supersensitivity or subsensitivity to β-adrenergic inotropic stimulation. Inotropic β-adrenergic supersensitivity is exclusively due to presynaptic loss of neuronal catecholamine uptake.

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