Electrophysiological Effects of Adenosine in the Transplanted Human Heart
Evidence of Supersensitivity

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After cardiac transplantation, the denervated donor atria and ventricles demonstrate increased
sensitivity to infusions of sympathomimetic amines. Recently, supersensitivity of the canine
sinus and atrioventricular (AV) nodes to acetylcholine has also been demonstrated after
cardiac transplantation. Acetylcholine and the endogenous nucleoside adenosine exert
similar electrophysiological effects in both the sinus and AV nodes, and share a common
transduction process. We, therefore, hypothesized that after orthotopic cardiac transplanta-
tion, the donor (denervated) sinus node would demonstrate greater sensitivity to exogenous
adenosine than the recipient (innervated) sinus node. The effects of incremental doses of
intravenous adenosine (37–112 μg/kg) on changes in sinus cycle length (SCL) (ΔSCLmax %),
changes in PR interval (ΔPRmax %), time to peak effect (sec), and duration of electrophysio-
logical effects (sec) were prospectively measured in 28 orthotopic cardiac transplant patients
and nine control subjects. The baseline SCL was 795±71 msec for the control subjects, 891±43
msec for the recipient atria, and 700±18 msec for the donor atria (p<0.05, donor vs. recipient).
The ΔSCLmax % for each dose of adenosine was similar in the innervated control and recipient
atria. In contrast, the donor sinus node demonstrated a threfold to fourfold increased
response to adenosine as compared with the recipient sinus node and a threfold to sixfold
increased response as compared with control subjects. Similarly, the donor AV node dem-
onstrated a threefold to fivefold increase in PR interval as compared with control subjects.
The duration of sinus node slowing in the denervated atria was threfold to fivefold longer than in
the recipient and control atria (p<0.001). The duration of AV node slowing in the denervated
atria was threfold to fivefold longer than in the control AV node (p<0.0001). Therefore, the
responses to adenosine of the donor (denervated) sinus and AV nodes were of greater
magnitude and duration than those observed in innervated recipient and normal control
hearts, findings consistent with adenosine supersensitivity in the denervated human heart.
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Denervation supersensitivity refers to the
exaggerated response of tissue to a neuro-
transmitter when its nerve supply is
interrupted. After cardiac transplantation in ani-
mals and humans, the denervated sinus and atrio-
ventricular (AV) nodes demonstrate supersensitive
responses to sympathomimetic amines. Recently,
supersensitivity to acetylcholine (ACh) has also been
demonstrated in denervated canine sinus and AV

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Because the endogenous metabolite adeno-
sine and the neurotransmitter ACh have similar
electrophysiological effects on the sinus and AV
nodes, which are mediated by a common transduc-
tion process, we hypothesized that the donor (den-
vated) sinus and AV nodes would demonstrate
increased responsiveness to intravenous bolus injec-
tions of adenosine after cardiac transplantation.

The technique of orthotopic cardiac transplanta-
tion leaves in situ portions of both atria along with
their respective venoatrial junctions. The recipient

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atrial remnant, which retains the sinus node, is thought to remain normally innervated. Therefore, to test this hypothesis, we prospectively studied the chronotropic and dromotropic effects of adenosine in donor and recipient atria in patients after orthotopic cardiac transplantation.

Methods

Patient Population

Two groups of male patients, all of whom were younger than 60 years of age, were studied in a protocol approved by a committee on the conduct of human research at the medical college of Virginia, the University of Virginia School of Medicine, and the McGuire Veterans Administration Medical Center. All patients gave written informed consent before participation in the study. All cardiac medications that affect sinus or AV node function (e.g., digoxin, β-blockers, calcium channel blockers, and type Ia antiarrhythmic drugs) were discontinued at least four half-lives before study, except in one transplant patient taking digoxin (0.125 mg) and in another taking metoprolol (25 mg b.i.d.). Patients receiving theophylline or dipyridamole were excluded from this study because of the effects of these drugs on adenosine metabolism. Additionally, patients with symptomatic New York Heart Association (NYHA) functional class III/IV congestive heart failure were excluded from the study.

The control group consisted of nine male patients referred for either electrophysiological evaluation of cardiac arrhythmias or for cardiac catheterization to evaluate chest pain. All patients were in normal sinus rhythm and had no evidence of sinus or AV node disease. Five patients had no structural heart disease, two patients had coronary artery disease, one had mitral regurgitation, and one had an idiopathic dilated cardiomyopathy.

The second group consisted of 30 patients who were studied 3 weeks to 4 years (56±13 weeks) after orthotopic cardiac transplantation. Twenty-nine patients were taking cyclosporin A, 28 were taking azathioprine, and 10 were taking prednisone. Eleven patients were taking furosemide, and most were treated with angiotensin converting enzyme inhibitors.

All patients had a normal 12-lead electrocardiogram (ECG) with normal PR, QRS, and QT intervals before study. Additionally, all patients had a 24-hour Holter recording (Marquette, Milwaukee, Wisconsin) within 2 weeks of their study. Patients were excluded if the Holter demonstrated the presence of sinus or junctional bradycardia with less than 60 beats/min (in the donor heart).

Cardiac transplant patients were studied after routine endomyocardial biopsy. Data from two patients with histological evidence of acute moderate-severe rejection were not included in the analysis. Four patients had either frequent premature atrial contractions (one patient) or atrial flutter or fibrillation (three patients) in the recipient (remnant) atrium. In these four patients, only data from the donor sinus and AV nodes were included in the analysis.

Electrophysiology Study

Studies were performed with patients in the non-sedated, fasting state. All transplant patients had a 6 or 7F hexapolar catheter (USCI, Inc., Billerica, Massachusetts) introduced through an internal jugular vein. The catheter was used to map the right atrium until a stable site was found where bipolar donor and recipient atrial electrograms could be recorded (Figure 1). In five control subjects, quadripolar catheters were positioned in the high right atrium and across the tricuspid valve to record His bundle activity. Intracardiac recordings were filtered at 30–500 Hz and simultaneously displayed along with three surface ECG leads on a multichannel recorder (VR-16, Electronics for Medicine, Pleasantville, New York). In 12 consecutive transplant patients, phasic arterial pressure was monitored during and after intravenous injections of adenosine.

Drug Administration

Crystalline adenosine (Sigma Chemical Co., St. Louis, Missouri) was dissolved in normal saline at a concentration of 5 mg/ml. Adenosine concentration
was confirmed by high-performance liquid chromatography. Incremental doses of adenosine (37, 75, and 112 μg/kg) were injected during 3–5 seconds through an 8.5 F sheath in the right internal jugular vein and immediately flushed with 10 ml saline. The intravascular half-life of adenosine is less than 5 seconds.

Intracardiac electrograms, surface ECG, and arterial pressure were monitored before and for several minutes after the initial injection of adenosine. Incremental doses of adenosine then were injected after a 1–2-minute reequilibration period, during which the baseline sinus rate was reestablished. Testing was terminated when a sinus pause or AV block of at least 4 seconds was observed. In the transplanted patients, intra-atrial potentials from near the donor sinus node (A) and recipient sinus node (A') were recorded, as was the AR interval from the surface ECG (donor heart, Figure 1). In control subjects, measurement of the PR or AR interval was made. Therefore, indirect measurements of sinus cycle length (SCL) (A-A and A'-A') and AV nodal conduction (AR or PR) were made before and after each adenosine dose.

In an additional eight transplant patients, the effects of adenosine on the donor and recipient sinus node were evaluated before and after autonomic blockade with propranolol (0.2 mg/kg i.v.) and atropine (0.04 mg/kg i.v.). An additional five control subjects were also studied before and after autonomic blockade.

Data Analysis

The response of the sinus node to adenosine was evaluated by measuring the following three parameters: maximal change in SCL (ΔSCL_max%), time to peak effect (seconds), and duration of effect (total time for which SCL was 20 msec longer than baseline value) in the donor and recipient atria. The ΔSCL_max% was determined by comparing the mean SCL of five beats immediately preceding the adenosine injection with the longest SCL measured after adenosine injection. If no response of the sinus or AV node was detected at a given dose of adenosine, then, for purposes of analysis, data from these patients were excluded at that dose.

The effect of adenosine on AV nodal conduction was assessed by measurement of the PR interval in control hearts and the AR interval in donor hearts. The AR interval was measured from the rapid deflection of the atrial electrogram to the earliest onset of either the surface QRS or the far-field ventricular electrogram. Accuracy of all measurements was ±5 msec at a paper speed of 100 mm/sec (all transplants, five controls) and ±10 msec at a paper speed of 50 mm/sec (four controls). The maximal change in AV nodal conduction (ΔPR_max%), time to peak effect, and duration of effect in response to adenosine were compared in the donor and control atria, and donor and control AV nodes.

Nonparametric statistics were used to analyze the data because of differences in sample sizes receiving different adenosine doses. The differences among groups for SCL, ΔSCL_max%, ΔPR_max%, duration of effect, and peak effect were tested using the Kruskal-Wallis test. When a significant difference (p<0.05) was found, the Wilcoxon rank sum test was used to test for differences in the variables between all combinations of any two groups (e.g., donor vs. recipient, recipient vs. control, and donor vs. control). The p value was corrected to take into consideration multiple comparisons with the Bonferroni adjustment. Analysis of the effects of incremental doses of adenosine within a single group was performed using the Wilcoxon signed rank test. Linear regression analysis was performed to correlate changes in SCL with posttransplant time and ischemic donor time for the donor heart. All values are expressed as mean±SEM.

Results

The baseline clinical characteristics of the control and transplant patients were similar. The mean age and ejection fraction for the control population were 53±4 years and 47±4%, respectively. For the cardiac transplant patients, the mean age was 48±2 years, and the ejection fraction was 56±2%. The donor heart was explanted from patients whose mean age was 24±1 years (p<0.01 vs. recipients and controls). The baseline SCL was 795±71 msec for control subjects, 891±43 msec for the recipient sinus node, and 700±18 msec for the donor sinus node (p<0.05, donor vs. recipient).

Effects of Adenosine on the Sinus Node

All control subjects received three incremental doses of adenosine (37, 75, and 112 μg/kg). At each dose of adenosine, the resulting maximal SCL showed a significant increase as compared with baseline and that observed with the immediately preceding dose. Similar to the sinus node from control subjects, the recipient sinus node showed significant increases in SCL to incremental adenosine doses.

The donor sinus node showed pronounced sensitivity to adenosine. All 28 donor sinus nodes responded to 37 μg/kg of adenosine, whereas only 10 of 24 recipient sinus nodes and five of nine control sinus nodes demonstrated a response.

The ΔSCL_max% for the donor heart was significantly greater than that seen in the recipient and control patients at each of the adenosine doses given (Table 1, Figure 2). There were no significant differences in SCL between recipient and control sinus nodes at any dose. There was no significant linear correlation between ΔSCL_max% in the donor heart and the time after cardiac transplantation (r=0.23 and p=0.3 at 37 μg/kg; r=0.11 and p=0.6 at 75 μg/kg; and r=0.1 and p=0.9 at 112 μg/kg), or the ischemic time of the donor heart (r=0.2 and p=0.3 at 37 μg/kg; r=0.4 and p=0.10 at 75 μg/kg; and r=0.41 and p=0.2 at 112 μg/kg).

The time to peak effect for donor, recipient, and control patients is shown in Table 1. There were no
significant differences among each of the three groups for any dose.

There were pronounced differences in the duration of chronotropic effects. The donor sinus node demonstrated responses that were threefold to 4.5-fold greater than those of the recipient and control. Summary data are shown in Table 1.

AV Nodal Effects

For each adenosine dose, the resulting maximal PR interval showed a significant increase as compared with baseline and the immediately preceding adenosine dose.

The donor AR interval was prolonged at doses of 37, 75, and 112 μg/kg in all transplant patients but in only five of nine control subjects at doses of 37 and 75 μg/kg. The donor AR interval was significantly more prolonged (threelfold to fivefold) than the control PR interval for each adenosine dose except at 112 μg/kg when the difference did not reach statistical significance because of the small sample size. The duration of dromotropic effect was also significantly longer in the donor heart (Table 1). In virtually all patients, the AV node was more sensitive to adenosine than the sinus node.

Patterns of Response to Adenosine

All donor sinus nodes showed either no response or a prolongation in SCL. This was followed by a return to baseline SCL or a slight decrease in cycle length (20 msec). Initially, PR prolongation was seen 2–4 beats before prolongation of SCL. Typically, PR intervals returned to baseline before the SCL (Figure 4). In the recipient atria, prolongation of SCL was followed either by a return to baseline SCL or a pronounced shortening of SCL (20–100 msec), especially at higher adenosine doses associated with decreases in arterial pressure.

Reproducibility

Five transplant patients were tested at adenosine doses repeated at least twice. These serial trials showed less than 10% variability for ΔSCL_max% or ΔPR_max%.

Arterial Pressure

In the 12 patients with arterial pressure monitoring, a decrease in systolic pressure was noted 2–4 seconds after peak effect in the recipient sinus node and 1–3 seconds after peak effect in the donor sinus node. In general, the maximal decrease in systolic arterial pressure (5–10 mm Hg) was noted at doses of 75 or 112 μg/kg.

Autonomic Blockade

Eight transplant patients and five additional control patients were studied before and after autonomic blockade. There was no significant change in the donor sinus or AV node response to adenosine after autonomic blockade. The maximal response of the donor, recipient, and control sinus node to adenosine did not change significantly after autonomic blockade (Figure 3, left panel) although the duration of the response of the control and recipient sinus node was slightly increased (1–3 seconds) at each dose (Figure 3, right panel). For example, the magnitude of maximal donor SCL prolongation was 70±20% at 75 μg/kg before autonomic blockade and 67±18% after autonomic blockade (p=NS and n=8). The duration of effect was 16±2 seconds before autonomic blockade and 16±3 seconds after autonomic blockade. For control subjects (n=5), the magnitude of responses was 6±2 seconds before autonomic blockade and 6.4±2 seconds after autonomic blockade, and the duration of responses was 4±1 seconds before blockade and 5±0.4 seconds after blockade (p=NS). Autonomic blockade completely abolished the reflex sinus tachycardia noted in both the recipient and control sinus node after adenosine injections.

Discussion

The major finding in this study is that the denervated transplanted donor human sinus and AV nodes demonstrate an exaggerated response to exogenous adenosine. The duration of adenosine’s effect on the
TABLE 1. Electrophysiological Responses of the Sinus and AV Nodes of Control Subjects and Transplant Patients

<table>
<thead>
<tr>
<th></th>
<th>Donor (a)</th>
<th>a vs. b</th>
<th>Recipient (b)</th>
<th>b vs. c</th>
<th>Control (c)</th>
<th>a vs. c</th>
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<tr>
<td>SCL (msec)</td>
<td>700±18</td>
<td>&lt;0.05</td>
<td>891±43</td>
<td>NS</td>
<td>795±71</td>
<td>NS</td>
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<td>ΔSCLmax%</td>
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<td>37 µg/kg ADO</td>
<td>35±12</td>
<td>&lt;0.001</td>
<td>9±3</td>
<td>NS</td>
<td>9±3</td>
<td>&lt;0.001</td>
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<tr>
<td>75 µg/kg ADO</td>
<td>75±18</td>
<td>&lt;0.0001</td>
<td>17±6</td>
<td>NS</td>
<td>12±3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>112 µg/kg ADO</td>
<td>154±48</td>
<td>0.05</td>
<td>40±12</td>
<td>NS</td>
<td>28±4</td>
<td>&lt;0.0001</td>
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<td>Duration (sec)</td>
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<tr>
<td>37 µg/kg ADO</td>
<td>18±2</td>
<td>&lt;0.0001</td>
<td>4±1</td>
<td>NS</td>
<td>4±1</td>
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<td>5±1</td>
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<tr>
<td>112 µg/kg ADO</td>
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<td>&lt;0.0001</td>
<td>9±1</td>
<td>NS</td>
<td>7±1</td>
<td>&lt;0.0001</td>
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<td>Peak (sec)</td>
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<tr>
<td>37 µg/kg ADO</td>
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<td>NS</td>
<td>17±1</td>
<td>NS</td>
<td>15±3</td>
<td>NS</td>
</tr>
<tr>
<td>75 µg/kg ADO</td>
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<td>NS</td>
<td>17±1</td>
<td>NS</td>
<td>15±2</td>
<td>NS</td>
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<tr>
<td>112 µg/kg ADO</td>
<td>16±1</td>
<td>NS</td>
<td>15±1</td>
<td>NS</td>
<td>16±2</td>
<td>NS</td>
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<tr>
<td>PR (msec)</td>
<td>150±4</td>
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<td>...</td>
<td>...</td>
<td>143±6</td>
<td>NS</td>
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<tr>
<td>ΔPRmax%</td>
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<td>37 µg/kg ADO</td>
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<td>10±5</td>
<td>&lt;0.001</td>
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<tr>
<td>75 µg/kg ADO</td>
<td>64±8</td>
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<td>23±12</td>
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<td>37 µg/kg ADO</td>
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<td>3±1</td>
<td>&lt;0.0001</td>
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<tr>
<td>75 µg/kg ADO</td>
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<td>4±1</td>
<td>&lt;0.0001</td>
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<tr>
<td>112 µg/kg ADO</td>
<td>20±2</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>6±1</td>
<td>&lt;0.0001</td>
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SCL, sinus cycle length; ADO, adenosine.

donor sinus and AV nodes is markedly increased as compared with responses in the innervated recipient sinus node and those of control subjects. The increased duration of electrophysiological effect is likely related to absence of baroreceptor reflex modulation of donor SCL, whereas the increased magnitude of response represents a supersensitive response that can be mediated at either the level of the receptor or transduction process, or both.

Cannon was the first to observe enhanced responsiveness of an effector organ to the effects of a neurotransmitter after interruption of its nervous innervation. This principle has since been demonstrated in animal and human studies. For example, in transplanted animal hearts, and in patients after orthotopic and heterotopic cardiac transplants, increased sensitivity to catecholamines has been demonstrated.

There are less data regarding supersensitivity to cholinergic agonists after parasympathetic denervation. The AV nodal conduction time of the denervated canine heart demonstrates a tenfold increase in

FIGURE 3. Left panel: Bar graph showing ΔSCLmax% to adenosine in donor (n=8) and control (n=5) patients before and after autonomic blockade (AB). Right panel: Bar graph showing duration of chronotropic effect on sinus cycle length in donor and control sinus nodes before and after autonomic blockade.
its responses to nicotine,16,17 and recently, enhanced sensitivity of the sinus and AV nodes to ACh was demonstrated in dogs after parasympathetic denervation at the postganglionic level.7

Effects of Adenosine

ACh and adenosine exert parallel electrophysiological effects at multiple levels of the heart.18–23 For example, in supraventricular tissue, the muscarinic cholinergic receptor and the adenosine A2-receptor are coupled to potassium channels by the guanine nucleotide-binding regulatory protein Gq*.23,24 This process results in increased potassium conductance and hyperpolarization of supraventricular tissue toward EK, thereby mediating negative chronotropic and dromotropic effects in the sinus and AV nodes, respectively.25 In contrast to supraventricular tissue, Gq* activated potassium channels are not present in ventricular myocardium. The effects of ACh and adenosine on ventricular tissue are indirect and primarily antiadrenergic, inhibiting adenylate cyclase.26,27 Because the effects of ACh and adenosine are linked at several levels to function in parallel and possibly synergistically, and because parasympathetic denervation results in a supersensitive response to ACh,7 it was hypothesized that the denervated (donor) atrium and AV node would demonstrate an exaggerated (supersensitive) response to adenosine. The data from our study support this hypothesis because the magnitude of response of the donor sinus and AV nodes to adenosine were threefold to fivefold greater than that observed in the recipient and control sinus and AV nodes.

Mechanisms of Supersensitivity

Although some studies suggest that cardiac transplant patients do not manifest increased β-
adrenergic receptor density or postsynaptic β-adrenergic receptor responsiveness,15,28 other studies indicate that supersensitivity of the denervated heart to catecholamines is primarily because of up-regulation of the β-adrenergic receptor.2,29 Similarly, the mechanism of supersensitivity to ACh after parasympathetic denervation can also be related to up-regulation of the muscarinic cholinergic receptor although not all studies support this view.3,30

The mechanism responsible for adenosine supersensitivity in the donor sinus and AV nodes is not known. Unlike sympathomimetic amines and ACh, adenosine is not a neurotransmitter but, instead, is an endogenous metabolite that is released in increased amounts in response to O2 supply-demand imbalance. Under the conditions of the present study, there is little reason to suggest that possible up-regulation of the adenosine A1-receptor occurred in response to subnormal levels of interstitial adenosine. Recent evidence suggests that sensitivity to adenosine can be altered at either the level of the receptor or transduction process. Incubation of adipocytes with an A1-receptor agonist resulted in down-regulation of not only the A1-receptor but also the receptor-linked G protein.31 Up-regulation associated with supersensitivity of the adenosine A1-receptor has also been demonstrated in ventricular myocytes from guinea pigs under prolonged treatment with the adenosine A1-receptor antagonist theophylline.32

The donor sinus node was noted to have both an increase in magnitude and duration of response to adenosine. The prolonged duration of adenosine response can be related to supersensitivity mediated at the receptor32 or postreceptor level. An absence of baroreceptor reflex modulation of SCL in the donor

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**Figure 4.** Graphic plotting showing time course of electrophysiological effects of adenosine (37 μg/kg) on donor and recipient sinus cycle length and donor AR interval from representative patient. Unfilled squares represent P waves that are not conducted to ventricle.
Potential Limitations

Autonomic innervation and blood supply (through bronchial collaterals) to the recipient sinus node remain intact after orthotopic cardiac transplantation. Because the recipient sinus node, however, can be traumatized secondarily to the surgical procedure or during cardiopulmonary bypass, a separate control population of age-matched subjects with no evidence of sinus or AV node disease during electrophysiological study was evaluated. Importantly, there were no significant differences between baseline SCL in the recipient and control sinus nodes and in the magnitude of response of the recipient and control sinus nodes to adenosine. These data suggest that the differential sensitivities of the recipient and donor sinus nodes were because of donor supersensitivity rather than recipient hyposensitivity.

The donor sinus node might be damaged because of surgical trauma or ischemia during harvesting, preservation, transport, and insertion into the recipient chest. There was, however, no correlation between the magnitude of response of the donor sinus node to adenosine and the duration of preservation (ischemic time) or the time studied after cardiac transplantation. Additionally, all transplant patients had Holter monitor recordings, and only patients with evidence of normal sinus and AV nodal function were included in this study. Finally, in the absence of coexisting disease, the recipient sinus node demonstrates normal heart rate variability and cycle length changes after phenylephrine-induced increases in arterial pressure.

Conclusions

Our findings might have direct clinical relevance because adenosine is a highly effective agent for treatment of supraventricular tachycardia involving the AV node. Because the donor sinus and AV nodes demonstrate adenosine supersensitivity, the dose given to transplant patients to treat supraventricular arrhythmias should be approximately one third to one fifth lower than that given to patients with intact cardiac innervation. It might also be significant that symptomatic sinus bradycardia that develops in patients with episodes of acute severe cardiac rejection is reversed by low-dose theophylline, an agent that antagonizes the effects of adenosine on the sinus and AV nodes.

We have demonstrated increased responsiveness of donor (denervated) sinus and AV nodes to increasing doses of adenosine in man. These observations cannot be attributed to baroreceptor reflex modulation of the recipient sinus and AV nodes alone, and do suggest a direct supersensitive response of the donor sinus and AV nodes to adenosine. These effects can be mediated by up-regulation of the receptor or increased availability of the  G protein that is coupled to the adenosine A1-receptor.

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References


KEY WORDS • adenosine • denervation supersensitivity • cardiac transplantation
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