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SUMMARY To assess the influence of the autonomic nervous system upon the recovery of the normal human sinus node, the responses to overdrive pacing at multiple cycle lengths of the denervated donor heart sinus nodes of 18 human cardiac transplant recipients were compared to the responses of those 18 patients' innervated, remnant atria and of 20 control subjects with normal sinus node function. The mean average spontaneous sinus cycle length of the donor atria (643 ± 78 msec [SD]) was significantly shorter than that for either the innervated recipient (822 ± 171 msec) or the control atria (840 ± 204 msec). The longest sinus node recovery time occurred after overdrive pacing at cycle lengths of 400 msec or less in 94% of the donor atria, but in only 28% of the recipient atria (p < 0.01) and 10% of the control atria (p < 0.0001). Secondary postspacing cycles were longer than the initial postspacing pause after at least one pacing intervention in only 6% of the donor, but in 78% of the recipient (p < 0.01) and 45% of the control atria (p < 0.01). Curves describing the relationship between the corrected sinus node recovery time and the cycle length of overdrive pacing were smooth and predictable in 72% of the donor atria, but in only 17% of the recipient (p < 0.01) and 20% of the control atria (p < 0.01). In transplant patients pacing was performed for both 60- and 15-second overdrive periods; recovery phenomena were qualitatively and quantitatively the same for the two durations of pacing. We conclude that the cardiac autonomic nervous system has considerable influence on the postspacing recovery phenomenon of the normal human sinus node. This may account, in part, for the insensitivity of the sinus node recovery time in detecting sinus node dysfunction.

SINUS NODE STIMULATION, achieved by atrial pacing at rates exceeding the spontaneous sinus rate, produces a period of depression of automaticity after the cessation of pacing.1 The extent of this overdrive suppression has been used clinically to assess the integrity of sinus node function in animals and man.2,8 However, prolongation of the sinus node recovery time (SNRT) and the occurrence of secondary pauses have been insensitive markers of deranged sinus node function.6,8 This insensitivity is probably explained by the inability of investigators to control the multiple factors that may modulate the extent of postspacing suppression, including intrinsic sinus node automaticity, conduction disease within the perinodal and atrial tissue, variability of blood demand and supply, ionic milieu, and autonomic nervous system activity. The purpose of this study was to measure the impact of the cardiac autonomic nervous system on the recovery of the normal sinus node in man. Patients without evidence of sinus node dysfunction and human cardiac transplant recipients were studied. The latter group was selected because of the coexistence in each patient of both the denervated sinus node of the donor heart and the innervated sinus node of the recipient's remnant atrium.

Materials and Methods

Eighteen cardiac recipients, 1–8 years after transplantation, gave consent for this atrial pacing study at the time of their annual invasive cardiovascular evaluation. Only transplant subjects who had a normal cardiovascular status were studied. This normal status included absence of rejection documented by endomyocardial biopsy, absence of significant coronary artery stenosis as assessed by coronary angiography, normal supine arterial pressure, no complicating illness, and apparently normal function of the donor sinus node. The latter was determined by the presence of a mean resting heart rate of 85 beats/min or greater, which is characteristic of the denervated state10–14 without relative bradycardia (rates below 80 beats/min), sinus pauses, or sinus arrhythmia on a minimum of 20 ECGs recorded during the preceding year. In addition, treadmill exercise testing was performed in each transplant patient to document the presence of the normal exercise response for the denervated state.15 None of these patients showed evidence of cardiac reinnervation. Previous studies in our cardiac recipients failed to document reinnervation,15,16 and no evidence has been acquired in subjects surviving beyond 11 years after transplantation to suggest that autonomic reinnervation of the human cardiac allograft occurs.

Records from 20 control patients were reviewed and analyzed retrospectively (table 1). Ten of the control patients had coronary artery disease and had undergone electrophysiologic study, including the determination of SNRT at least four pacing cycle lengths, as part of a research investigation appended to diagnostic catheterization or as a separate diagnostic study. Ten other patients had undergone electrophysiologic study for diagnosis and therapy of recurrent supraventricular tachycardia or syncope. None of these control subjects had taken medications, except for diazepam, for 48 hours before study. None of them had cardiomegaly, congestive heart failure or

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### Table 1. Clinical Characteristics of the Control Subjects

<table>
<thead>
<tr>
<th>Pt</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Reason for study</th>
<th>Angiographic diagnosis</th>
<th>SNA involved*</th>
<th>ECG abnormality</th>
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<tr>
<td>1</td>
<td>62</td>
<td>M</td>
<td>Protocol</td>
<td>3-vessel CAD, nl, LV</td>
<td>Yes</td>
<td>NI</td>
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<tr>
<td>2</td>
<td>45</td>
<td>M</td>
<td>Protocol</td>
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<td>No</td>
<td>Prev MI</td>
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<tr>
<td>3</td>
<td>56</td>
<td>M</td>
<td>Protocol</td>
<td>1-vessel CAD, seg LV abn</td>
<td>No</td>
<td>NI</td>
</tr>
<tr>
<td>4</td>
<td>45</td>
<td>M</td>
<td>Protocol</td>
<td>2-vessel CAD, nl LV</td>
<td>No</td>
<td>Prev MI</td>
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<tr>
<td>5</td>
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<td>M</td>
<td>Protocol</td>
<td>3-vessel CAD, seg LV abn</td>
<td>?</td>
<td>Prev MI</td>
</tr>
<tr>
<td>6</td>
<td>55</td>
<td>M</td>
<td>Protocol</td>
<td>2-vessel CAD, seg LV abn</td>
<td>No</td>
<td>Prev MI</td>
</tr>
<tr>
<td>7</td>
<td>48</td>
<td>M</td>
<td>Protocol</td>
<td>3-vessel CAD, seg LV abn</td>
<td>Yes</td>
<td>Prev MI</td>
</tr>
<tr>
<td>8</td>
<td>62</td>
<td>F</td>
<td>Protocol</td>
<td>1-vessel CAD, nl LV</td>
<td>No</td>
<td>NI</td>
</tr>
<tr>
<td>9</td>
<td>57</td>
<td>M</td>
<td>Protocol</td>
<td>2-vessel CAD, nl LV</td>
<td>No</td>
<td>NI</td>
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<td>10</td>
<td>64</td>
<td>M</td>
<td>Syncope</td>
<td>Not done</td>
<td>?</td>
<td>Prev MI</td>
</tr>
</tbody>
</table>

*Coronary stenosis proximal to or involving the sinus nodal artery.

Abbreviations: CAD = coronary artery disease; abn = abnormality; LV = left ventricle (on angiogram); nl = normal; prev MI = previous myocardial infarction by ECG; seg = segmented; WPW = Wolf-Parkinson-White; SVT = supraventricular tachycardia; S/P = status post.

hypertension. None had evidence of sinus node dysfunction, as determined by multiple ECGs or by in-hospital and ambulatory monitoring studies or by both. The control patients were 21-67 years old. Fifteen were men and five were women. Among the nine patients with coronary artery disease who had undergone angiographic studies, four had normal left ventriculograms and the other five had segmental left ventricular wall motion abnormalities. Two patients had one-vessel coronary disease, four had two-vessel disease and three had three-vessel disease. Coronary stenosis occurred proximal to the sinus node artery or actually involved the sinus node artery in two of these subjects. In one patient we could not make this determination. There were no differences in sinus node recovery responses between patients with and without coronary artery disease and between the two patients with stenosis before or involving the sinus node artery and those without it. Pharmacologic autonomic blockade was not attempted in the control subjects.

In the 18 transplant patients, bipolar atrial pacing was performed using a square-wave impulse 2 msec long and constant current at twice the atrial capture threshold. Atrial pacing and recording were achieved through a quadrupolar electrode catheter inserted percutaneously through the right internal jugular vein after endomyocardial biopsy. One or more of surface electrocardiographic leads I, aVF, and V1 were recorded simultaneously with an atrial electrogram obtained from the recording pair of electrodes of the quadrapolar catheter (1 cm interpolar distance). Data were recorded directly on photographic paper at speeds of 50-100 mm/sec and were also stored on analog magnetic tape. Pacing at four to seven cycle lengths, usually five or six, between 700 and 300 msec was performed. In each transplant patient, a set of pacing cycle lengths was applied for 60 seconds; the same set was repeated using a pacing duration of 15 seconds. A 30-second intermission was inserted between each pacing intervention.

In the transplant subjects, the same pacing regimen applied to the donor atrium was also applied to the recipient atrium. As a result of the surgical technique used for transplantation, as described by Lower and Shumway,17 posterior portions of the recipient's left and right atria, with sinus node intact, are left in situ for anastomosis of the graft. Thus, each transplant patient has two sinus nodes and sets of atria: the inner-
The recipient determined (fig. graphically14 P donor tures, two sets the tion, separate recipient activated (SNRTmax/SCL). The recipient atrial and donor atrial P waves are visible, and corresponding recipient and donor deflections are shown in the atrial electrogram. (B) Similar recordings from another patient. Recipient atrial activity is not easily distinguished in the surface tracing. The atrial electrogram recording demonstrates independence of the donor and recipient atria, which are dissociated. the donor rate being 103 beats/min and the recipient 70 beats/min.

vated recipient sinus node and remnant atrial structures, and the denervated donor sinus node and atria. The recipient sinus node continues to discharge and drive the remnant atrial tissue, so both recipient and donor P waves can be recorded electrocardiographically14 (fig. 1A). Except for the unusual occurrence of donor-recipient atrial accrochage,14 the two sets of atria beat independently (fig. 1B). In addition, separate recipient and donor atrial electrograms may be recorded and the two sets of atria may be paced independently with an electrode catheter (fig. 2).

In the control group only a 60-second pacing duration was used. All of the patients were paced at at least one cycle length of 400 msec or less, and pacing was not complicated by angina or hemodynamic instability.

The spontaneous sinus cycle length (SCL) was determined by calculating the average cycle length of the 20 consecutive cycles preceding the first pacing intervention. The first five spontaneous recovery cycles after each pacing intervention were measured. The maximum sinus node recovery time (SNRTmax) was defined as the longest postpacing cycle in msec recorded during any of the pacing interventions, and this value was normalized for cardiac rate by dividing it by the spontaneous sinus cycle length in msec (SNRTmax/SCL). The cycle length of pacing at which SNRTmax occurred was noted, and the frequency at which SNRTmax occurred after pacing cycle lengths of 400 msec or shorter was determined. The incidence rate of secondary cycles (cycles 2–5) longer than the initial postpacing recovery cycle was also determined. In this study a delayed pause is defined as a secondary cycle longer than the primary recovery cycle, but not necessarily abnormally long. The corrected sinus node recovery time (CSNRT) was determined by subtracting the average spontaneous sinus cycle length from the recovery cycle. For the maximum CSNRT (CSNRTmax), the longest recovery cycle was used.

These expressions of the sinus node recovery phenomenon were compared using unpaired t tests between the donor and recipient atria and between the control patients and either the donor or recipient atrial responses. One-way analysis of variance of SCL, SNRTmax/SCL and CSNRTmax for the three groups (donor, recipient and control) was carried out before t tests were done. Incidence rates were compared by chi-square analysis.

**Results**

A total of 1980 recovery cycles after 396 pacing interventions was analyzed in the 18 transplant recipients, and 465 recovery cycles after 93 pacing episodes were similarly examined in the 20 control
subjects. Because results from the 60-second and 15-second pacing interventions were quantitatively and qualitatively similar, results of only the 60-second interventions in the transplant recipients are reported in table 2. A one-way analysis of variance of the average spontaneous atrial cycle lengths yielded a significant F value suggesting differences between groups. The SCL was significantly shorter in the donor (643 ± 78 msec) than in the recipient and control atria, which were similar (822 ± 171 msec and 840 ± 204 msec). This more rapid donor sinus rate is characteristic of human cardiac denervation. 10-14

An F value for the SNRTmax normalized for spontaneous sinus rate was also significant. The SNRTmax/SCL was significantly longer in the donor compared with the recipient and control atria (table 2). Normalizing for spontaneous rate might have produced an artifactual difference between the donor and the other sinus nodes due to the marked difference in sinus rates, so the CSNRTmax of the three sinus nodes were compared. The mean CSNRTmax of the donor atria was longest, but not statistically significantly different from that of recipient and control.

The SNRTmax resulted from shorter overdrive pacing cycle lengths in the donor atria than in recipient or control (fig. 3). SNRTmax occurred at cycle lengths ≤400 msec in 94% of the donor hearts, but in only 28% of the recipient and 10% of control atria. The mean cycle length producing the longest SNRT was 359 ± 46 msec in the donor atria and 491 ± 111 msec in the recipient atria (p < 0.005) (table 2). This value was 499 ± 82 msec for the control group, which was significantly different from that of the donor atria (p < 0.005), but not the recipient atria.

The initial postpacing cycle was usually the longest in all three groups, but occasionally a longer secondary cycle was seen after at least one of the several pacing interventions. This phenomenon occurred in

**Table 2. Measures of Sinus Node Recovery in Donor, Recipient and Control Atria**

<table>
<thead>
<tr>
<th></th>
<th>Donor</th>
<th>Recipient</th>
<th>Control</th>
<th>D vs R</th>
<th>D vs C</th>
<th>R vs C</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average SCL (msec)*</td>
<td>643 ± 78</td>
<td>822 ± 171</td>
<td>840 ± 204</td>
<td>&lt; 0.005</td>
<td>&lt; 0.005</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>SNRTmax†/SCL</td>
<td>1.46 ± 0.16</td>
<td>1.35 ± 0.17</td>
<td>1.34 ± 0.15</td>
<td>0.051</td>
<td>&lt; 0.05</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>CSNRTmax (msec)</td>
<td>300 ± 117</td>
<td>291 ± 171</td>
<td>273 ± 123</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Pacing CL producing longest RT (msec)</td>
<td>359 ± 45</td>
<td>491 ± 111</td>
<td>499 ± 82</td>
<td>&lt; 0.005</td>
<td>&lt; 0.005</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>SNRTmax after pacing CL ≤ 400 msec</td>
<td>17/18 (94%)</td>
<td>5/18 (28%)</td>
<td>2/20 (10%)</td>
<td>&lt; 0.01†</td>
<td>&lt; 0.00001‡</td>
<td>NS‡</td>
<td></td>
</tr>
<tr>
<td>Secondary longer than primary postpacing pause</td>
<td>1/18 (6%)</td>
<td>14/18 (78%)</td>
<td>9/20 (45%)</td>
<td>&lt; 0.001†</td>
<td>&lt; 0.01‡</td>
<td>NS‡</td>
<td></td>
</tr>
<tr>
<td>Organized relationship of RT to pacing CL</td>
<td>13/18 (72%)</td>
<td>3/18 (17%)</td>
<td>4/20 (20%)</td>
<td>&lt; 0.01†</td>
<td>&lt; 0.01‡</td>
<td>NS‡</td>
<td></td>
</tr>
</tbody>
</table>

*F = 8.28, df = 2/54, p < 0.005 (one-way analysis of variance).
†F = 3.51, df = 2/53, p < 0.05 (one-way analysis of variance).
‡Chi-square analysis.
Abbreviations: SCL = sinus cycle length; SNRTmax = maximum sinus node recovery time; CSNRT = corrected maximum sinus node recovery time; CL = cycle length; RT = recovery time; NS = not significant; D = donor; R = recipient; C = control.
only one of the donor atria (6%), but was significantly more frequent in the recipient and control atria (78% and 45%, respectively) (table 2).

The pattern of response to progressively more rapid pacing cycle lengths was examined in the three groups (fig. 4). The relationship was considered organized if the CSNRT rose asymptotically with faster pacing rates or if it rose smoothly to a maximum before decreasing or if the response was flat. The pattern was termed “chaotic” if SNRT varied erratically and independently from the pacing cycle length. An organized pattern was seen in 72% of the donor atrial responses but significantly less frequently in the recipient and control (table 2, figs. 4 and 5).

Discussion

The purpose of this investigation was to assess the impact of the cardiac autonomic nervous system upon the sinus node recovery phenomenon in the normal human sinus node. We found that heart transplant recipients' innervated remnant sinus nodes responded similarly to the sinus nodes of control patients with apparently normal cardiac innervation and sinus node function. The denervated donor sinus node differed from these latter two groups in several respects. The spontaneous sinus rate was faster, the SNRT\textsubscript{max} was achieved at more rapid overdrive pacing rates, secondary recovery cycles longer than the primary cycle occurred much less frequently, and a more uniform pattern of response to progressively more rapid overdrive pacing rates was observed. In addition, the donor SNRT\textsubscript{max} normalized for spontaneous rate (SNRT/SCL) was significantly longer. The donor CSNRT\textsubscript{max} was not significantly longer, but considerably more rapid pacing rates were required to achieve it. These differences may be a result of the cardiac autonomic nervous system. In previous studies, cardiac transplant recipients have provided a successful model for the study of various cardiac electrophysiologic functions isolated from autonomic nervous system influences,\textsuperscript{10, 11, 16} of the differentiation between direct and autonomically mediated cardiac electrophysiologic effects of a number of drugs,\textsuperscript{12, 16, 18, 22} and of the hemodynamic effects of agents with autonomic nervous system influences.\textsuperscript{23, 24}

The sinoatrial node and perinodal tissue are richly supplied with sympathetic and parasympathetic nerve endings,\textsuperscript{25, 26} and the ability of the autonomic nervous system to influence sinus node automaticity and conduction is well known. However, few data have been reported about the effects of the interaction between the autonomic nervous system and the sinus node upon postpacing sinus node recovery. Dighton showed that some patients with apparent sinus node dysfunction have abnormal responsiveness to autonomic stimuli and others do not.\textsuperscript{27} The frequent fluctuations in heart rate in sleeping animals\textsuperscript{28} and man have been shown to result from autonomic influences. Levy and Zieske\textsuperscript{29, 30} have delineated the complex, yet predictable, interaction between the parasympathetic and sympathetic activities that affect cardiac rate. In an elegant series of experiments, Jose and Collison advocated the value of examining sinus node automaticity in the absence of cardiac autonomic nervous influences.\textsuperscript{31} However, none of these studies have assessed the degree to which nervous influences might control the sinus node recovery phenomenon. While other studies have evaluated the effect of vagus blockade with atropine,\textsuperscript{32} the author is aware of only one study of sinus node recovery in which cardiac denervation was simulated in man with combined chemical blockade by propranolol and atropine. To examine intrinsic automaticity and postpacing recovery of the sinus node, Jordan and associates\textsuperscript{8} used pharmacologic blockade to eliminate autonomic nervous system influences. They found that chemical denervation increased the CSNRT\textsubscript{max} in most patients with the sick sinus syndrome, especially if they had normal intrinsic heart rates. We could not comprehensively compare results from this study with that of Jordan and associates due to differences in data presentation and analysis. However, the use of pharmacologic blockade for this purpose has many practical and theoretical difficulties. Either agent may produce symptoms and can result in alterations in hemodynamic state. Atropine may block the actions of histamine, 5-hydroxytryptamine, and even norepinephrine.\textsuperscript{33} In the presence of atropine, acetylcholine or vagal stimulation may result in an increase in heart rate.\textsuperscript{34} Also, both atropine and propranolol are competitive blocking agents, so one can never be certain that the administered dose of either is adequate to produce complete autonomic blockade. Finally, propranolol may exert membrane effects that could alter sinus node automaticity.\textsuperscript{35} We chose human cardiac transplant recipients for study of autonomic ner-
Figure 4. (A) All sinus node recovery times from the three groups, recipient atria (left), donor atria (center) and control atria (right). Pacing cycle lengths (CL) were slightly different between the control and transplant patient studies. The striking unpredictability of response of the recipient and control atria are contrasted with the smoother, less chaotic responses of the donor atria. Most curves in the donor group are similar to the three organized patterns discussed in the text, while most of the recipient and control curves resemble the chaotic pattern. (B) Donor and recipient atrial responses illustrate the contrasting patterns of response in a single patient. CSNRT = corrected sinus node recovery time.
Figure 5. Multiple electrocardiographic and atrial electrogram recordings in a single transplant patient. The last two overdrive pacing beats at progressively shorter cycle lengths of pacing are shown in order. For each pacing intervention, surface electrocardiographic lead I is recorded simultaneously with the intraatrial electrogram. A bold vertical line is drawn at the beginning of the last paced atrial electrogram and a second bold line is drawn at the beginning of the first spontaneous atrial electrogram of the atria being paced. The tracings are arranged with the last paced beats in exact vertical alignment so that the length of each postpacing pause can be compared to previous and subsequent pauses. With donor pacing in panel A, there is an orderly progression of lengthening postpacing pauses with shortening of the overdrive cycle length. In panel B, the paced recipient atrium showed an unpredictable interrelationship of postpacing pause lengths.

Vagal system influences upon the sinus node recovery phenomenon because, due to anatomic cardiac denervation, pharmacologic blockade would be unnecessary.

Some of the differences between the denervated and the innervated atria might be explained as follows: Withdrawal of vagal nervous input to the sinus node and surrounding myocardium may improve transmission of closely coupled impulses across the perinodal tissue into the sinus node. The effective frequency of driven sinus nodal depolarization at more rapid pacing rates might thereby be increased, resulting in greater overdrive suppression, accounting for the appearance of $SNRT_{max}$ at shorter pacing cycle lengths (fig. 3) and the absence of a shortening of $SNRT$ at those cycle lengths (figs. 4 and 5A) in the denervated donor.
heart. Shortening of SNRT at faster drive rates in normally innervated hearts possibly results from reflex vagal withdrawal and sympathetic stimulation induced by rate-related mild hypotension. This reflex would be absent in the denervated donor heart. The variability of the postpacing pause (as manifested by an unpredictable relationship between its length and the rate of overdrive pacing and by the appearance of delayed postpacing pauses) in normally innervated hearts may be a result of fluctuating autonomic tone resulting from the hemodynamic or direct mechanical effects of rapid pacing. Such fluctuation would not be unexpected in a feedback system in which the effector (the cardiac autonomic nervous system) responds, but not immediately, to possibly multiple and suddenly changing stimuli.

There are potential criticisms of this study. The remnant recipient sinus node may well not behave normally for two reasons. First, the normal blood supply to the recipient atrium and sinus node is interrupted by the surgical procedure. We assume that the remnant tissue subsists on a blood supply derived from bronchial, intercostal and mediastinal collateral vessels, as well as on nutrition supplied by intracavitary blood. Second, these remnant sinus nodes and atria had resided in patients with end-stage heart disease before transplantation. Thus, it is possible that some or all of the remnant sinus nodes are diseased. However, these 18 transplant recipients did not have preexisting diagnoses of sinus node disease. In addition, and most important, the recipient sinus nodes responded in a fashion similar to the control group, suggesting that recipient sinus node recovery function was normal under the test circumstances. In previous studies,11, 12, 14, 15, 19, 20 the recipient atria have responded normally to the chronotropic effects of physiologic and pharmacologic interventions, which further defines the intactness of recipient sinus node function.

Another potential criticism concerns the integrity of the donor sinus nodes. One could suggest that these nodes were injured by the transplant procedure and that the overriding factor leading to the differences in this study was an undefined effect of surgery rather than a result of autonomic denervation. While this seems unlikely, it cannot be conclusively eliminated. The fact that electrocardiographic monitoring showed no abnormalities of atrial rate, that other aspects of cardiac function were entirely normal, and that rejection and coronary artery disease were absent, suggests that sinus node function was normal and that any differences between the donor sinus nodal responses and those of the recipients' and controls' sinus nodes were due to cardiac autonomic nervous system influences.

It is interesting that different durations of atrial pacing (60 seconds vs 15 seconds) produced the same patterns and degrees of postspacing suppression in the transplant atria. This result suggests that metabolic products elaborated during pacing may not influence the recovery phenomenon, at least on a quantitative basis. Further, it appears that production or modula-

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