Postoperative Sinus Node Dysfunction in the Transplanted Heart*

Impaired Automaticity but Normal Refractoriness

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We describe the use of the extrastimulus technique to define the range of sinus node (SN) effective refractoriness (SNERP) in the denervated transplanted human heart. SNERP could be successfully determined in 18 of 28 patients corresponding to 25 of 43 SN studies and ranged from 210 to 360 ms at a basic pacing cycle length of 500 ms (95% confidence limits: 252.5 to 396.2 ms), which is shorter than reported in the innervated native heart. Sixteen data sets in 12 patients showed normal SN function and nine sets of measurements in seven patients showed abnormal SN function (corrected SN recovery time >590 ms). While recovery time was profoundly abnormal (279.7 ± 94 vs 7,854.8 ± 10,454, p < 0.001), the SNERP did not differ significantly between the groups (274.3 ± 40 vs 286 ± 42 ms at 500 ms, p = 0.5) and was normal at a range of 220 to 340 ms even in those patients with grossly impaired SN recovery (SNERP in patients with normal SN function: 210 to 360 ms at 500 ms). This study demonstrates that SN refractoriness in the transplanted human heart is shorter than previously reported in innervated controls and suggests that posttransplantation SN dysfunction is characterized by impaired automaticity rather than impaired refractoriness. (Chest 1992; 101:603-06)

Formal testing of sinus node (SN) function currently includes measurement of SN recovery time (SNRT) and sinoatrial conduction time (SACT). Another feature of the SN tissue, refractoriness, is not routinely evaluated.

Recently, logistics of premature stimulation have been applied to measure SN refractoriness.1 Subsequently, this technique has been used to define the SN effective refractory period (SNERP) in the native human heart.2,3 Some investigators have reported that SNERP might enable better delineation of normal and impaired SN function,2,3 while others were unable to reproduce these results.4

In contrast, no data are as yet available on the SNERP in the transplanted human heart despite a high incidence of SN dysfunction in this patient population.5-9 The purpose of the present study was to define the range of the SNERP in the indefinitely denervated,10 transplanted human heart in the setting of normal and impaired postoperative SN function.

METHODS

Study Population

Measurement of SNERP was attempted in 28 cardiac transplant recipients. These 28 patients represent all consecutive patients in sinus rhythm who had undergone transplants between May 1990 and February 1991. Recipient age was 45 ± 13 years; donor age was 31 ± 8 years.

SN Studies

Including successful determination of SNERP, a total of 25 SN function studies were performed in 18 patients (one to four SN studies per patient, mean 1.4 ± 0.8) a mean of 13 ± 5 days after transplantation. None of the patients was receiving drugs influencing impulse formation or conduction during the study. Maximum SNRT was determined by bipolar atrial pacing at ten cycle lengths between 600 and 300 ms. Pacing was performed for 1 min at twice diastolic threshold using a Medtronic 5325 device and temporary atrial pacing wires inserted at the end of the operation. All measurements were made from the pacing artifact to the beginning of the ensuing donor p wave in the lead best delineating its onset. Donor and recipient sinus activity could be clearly delineated in all patients by the temporal relationship and the vector of the p wave (leads 1, 2, 3). Corrected SN recovery time (CSNRT) was calculated by subtracting spontaneous sinus cycle length. A value of 520 ms was accepted as the upper limit of normal for the CSNRT in the denervated transplanted heart.5,7 Sinoatrial conduction was evaluated by the method of Narula et al.11

Determination of SN Refractoriness

The SNERP was determined by programmed atrial stimulation at basic cycle lengths (S1-S1) of 500 or 600 ms, as appropriate. Premature atrial stimuli (S2) were introduced after each eighth beat at progressively premature intervals (S1-S2) in steps of 10 to 20 ms. According to Kerr et al.,1 the SNERP was defined as the longest premature interval that resulted in incomplete interpolation of S2. Incomplete interpolation was identified by abrupt shortening of the S2-A3 recovery interval of at least 50 ms over a decremental step in coupling interval of only 10 to 20 ms. Echo beats were distinguished in terms of the time interval between the last preectopic

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stimulus (S1) and the postectopic beat (A3) and defined as a subsequent A3 appearing earlier than it would have in the absence of A2.

The premature interval was decreased until encountering atrial effective refractory period. Since endocardial recordings were not performed, we were not able to distinguish between atrial and AV nodal effective refractory period. However, if S2 is not conducted via the AV node during premature atrial stimulation at short coupling intervals, it may be assumed that the atrial effective refractory period is equal or shorter (<5) than that given coupling interval. Thus, even without atrial recordings, premature atrial stimulation may give a gross representation about the magnitude of the atrial effective refractory period in this clinical model, which is important since SNERP can be determined only if it is longer than the atrial effective refractory period.

**Data Analysis**

Data are expressed as means ± standard deviation. Comparisons were made by Student's t test. Nonparametric methods and medians/range were used where normal approximations did not seem to be applicable. A p value <0.05 was considered significant in all analyses.

**Results**

**Identification of the SNERP**

The SNERP could be successfully identified in 18 (64.3 percent) of 28 patients and, in terms of the absolute number of SN studies performed, in 25 (58.13 percent) of 43 SN studies. Figure 1 gives a representative example of the determination of SNERP and Figure 2 gives the corresponding graphic representation. At a basic cycle length (S1-S1) of 500 ms and a coupling interval (S1-S2) of 300 ms, the resulting recovery interval (S2-A3) is 950 ms. With shortening of S1-S2 to 290 ms S2-A3 prolongs to 1,080 ms, presumably due to prolongation of retrograde (atriosinus) conduction. Further decreasing the coupling interval (S1-S2) to 280 ms results in a sudden shortening of S2-A3 to 750 ms and interpolation of S2. Since the encompassing interval S1-A3 is still longer (1,030 ms) than the spontaneous (and hence the reset) return cycle (950 ms), this indicates incomplete interpolation. According to in vitro studies of Kerr et al,1 this represents the SNERP. Following the aforementioned assumptions, the atrial effective refractory period was ≤250 ms in this patient and thus, shorter than the SNERP. The CSNRT indicated SN dysfunction (Table 1: patient 7, fourth measurement).

At times there was a more gradual transition from reset to interpolation as is illustrated in Figure 3. However, in the patient given in Figure 3 (patient 5, Table 1), a break in the S2-A3 response curve ≥50 ms could be identified at a coupling interval of 330 ms

![Figure 1](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21640/)

_Figure 1. Upper panel: Reset response. The S2-A3 return cycle approximately equals the spontaneous recovery cycle without a premature beat. Middle panel: This also represents a reset response. The lengthening of S2-A3 most likely is due to prolongation of atriosinus conduction. This was often seen immediately before transition to incomplete interpolation. Lower panel: A sudden decrease is observed in the S2-A3 interval with shortening of the premature interval from 290 to 280 ms. According to Kerr et al,1 this represents the effective refractory period of the sinus node (SNERP). See text for further details._

![Figure 2](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21640/)

_Figure 2. Graphic representation of the SNERP determination in Figure 1. The recovery interval S2-A3 is plotted as a function of the coupling interval S1-S2. At a premature interval of 280 ms, a sudden break is observed in the S2-A3 response curve. This represents the SNERP. CL = cycle length._

Sinus Node Dysfunction in Transplanted Heart (Heinz et al)
since shorter premature intervals consistently resulted in shorter S2-A3 return cycles.

In ten patients corresponding to 18 sets of measurements, the SNERP could not be measured at any cycle length evaluated. Echo beats made determination of SNERP impossible in three patients (eight data sets). Atrial flutter was inadvertently induced on one occasion in one patient. In another patient, inadvertent induction of atrial fibrillation precluded determination of the SNERP. In the remaining five patients (eight sets of measurements), there was no obvious explanation for the inability to record a transition from reset to incomplete interpolation.

SNERP in Patients with Normal and Impaired Postoperative SN Function

Sixteen SN studies in 12 patients showed normal SN function (group 1) and nine sets of measurements in seven patients showed impaired SN function (group 2) on the basis of CSNRT values (Table 1). There were no significant differences in SNERP between groups 1 and 2 (Table 1). For example, patient 15 showed profound sinus bradycardia and striking SN depression for about 24 s during which junctional rhythm prevailed; SNERP, however, was 260 ms at a pacing cycle length of 600 ms. Confidence limits (±95 percent) ranged from 252.5 to 296.2 ms vs 246.5 to 325.4 ms for group 1 vs group 2, respectively.

Table 1—Sinus Node Effective Refractory Period in Patients with Normal and Impaired Sinus Node Function*

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>SCL, ms</th>
<th>CSNRT, ms</th>
<th>SACT, ms</th>
<th>SNERP 500, ms</th>
<th>A-ERP, 500, ms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 (normal SN function)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>632</td>
<td>268</td>
<td>54</td>
<td>280</td>
<td>≤330</td>
</tr>
<tr>
<td>2</td>
<td>800</td>
<td>340</td>
<td>80</td>
<td>290</td>
<td>≤280</td>
</tr>
<tr>
<td>3</td>
<td>706</td>
<td>134</td>
<td>47</td>
<td>210</td>
<td>≤240</td>
</tr>
<tr>
<td>4</td>
<td>550</td>
<td>130</td>
<td>58</td>
<td>280</td>
<td>≤240</td>
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<tr>
<td>5</td>
<td>625</td>
<td>235</td>
<td>57</td>
<td>300</td>
<td>≤260</td>
</tr>
<tr>
<td>6</td>
<td>632</td>
<td>248</td>
<td>74</td>
<td>210</td>
<td>≤290</td>
</tr>
<tr>
<td>7</td>
<td>625</td>
<td>315</td>
<td>280</td>
<td>≤220</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>612</td>
<td>248</td>
<td>250</td>
<td>≤210</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>632</td>
<td>414</td>
<td>77</td>
<td>300</td>
<td>≤300</td>
</tr>
<tr>
<td>10</td>
<td>612</td>
<td>223</td>
<td>58</td>
<td>220</td>
<td>≤240</td>
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<tr>
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<td>577</td>
<td>294</td>
<td>67</td>
<td>300</td>
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<tr>
<td>11</td>
<td>597</td>
<td>232</td>
<td>56</td>
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<td>≤230</td>
</tr>
<tr>
<td>13</td>
<td>677</td>
<td>313</td>
<td>66</td>
<td>260</td>
<td>≤230</td>
</tr>
<tr>
<td>14</td>
<td>1,000</td>
<td>3,030</td>
<td>170</td>
<td>310</td>
<td>≤350</td>
</tr>
<tr>
<td>15</td>
<td>677</td>
<td>893</td>
<td>96</td>
<td>320</td>
<td>≤210</td>
</tr>
<tr>
<td>16</td>
<td>1,053</td>
<td>24,027</td>
<td>88</td>
<td>†260</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>1,250</td>
<td>3,750</td>
<td>150</td>
<td>†300</td>
<td>≤180</td>
</tr>
<tr>
<td>18</td>
<td>571</td>
<td>27,129</td>
<td>240</td>
<td>≤360</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>545</td>
<td>655</td>
<td>220</td>
<td>≤300</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>647.2</td>
<td>248</td>
<td>64.7</td>
<td>274.4</td>
<td></td>
</tr>
<tr>
<td>± SD</td>
<td>±67</td>
<td>±10</td>
<td>±40</td>
<td>±10</td>
<td></td>
</tr>
</tbody>
</table>

| Group 2 (impaired SN function) | | | | | |
| 7 | 619 | 1,461 | 110 | 290 | ≤260 |
| 8 | 612 | 1,961 | 280 | ≤250 |
| 13 | 923 | 3,657 | 96 | 340 | ≤270 |
| 14 | 1,000 | 2,030 | 170 | 310 | ≤350 |
| 15 | 677 | 893 | 96 | 320 | ≤210 |
| 16 | 1,053 | 24,027 | 88 | †260 |
| 17 | 1,250 | 3,750 | 150 | †300 | ≤180 |
| 18 | 571 | 27,129 | 240 | ≤360 |
| 19 | 545 | 655 | 220 | ≤300 |
| Mean | 905.1 | 2,030 | 94 | 256 |
| ± SD | ±255 | ±56 | ±42 | ±10 |
| p | 0.13 | 0.001 | 0.2 | 0.54 |

*SCL = sinus cycle length; CSNRT = corrected sinus node recovery time; SACT = sinoatrial conduction time (Narula et al. method); SNERP = sinus node effective refractory period at indicated cycle length; A-ERP = estimate of the atrial effective refractory period at cycle length indicated.
†Did not measure due to SN depression at this cycle length.
‡Medians; p by Wilcoxon nonparametric rank-sign test.

Discussion

This study defines the range of the SN refractoriness in the denervated, transplanted human heart. The cardiac transplant remains denervated indefinitely. As expected, the SNERP in our transplant cohort was shorter than previously reported in innervated controls. This observation is in line with previous reports on a shortening of SNERP with parasympathetic blockade. Likewise, β-sympathetic blockade and parasympathetic stimulation prolonged refractoriness. Sympathetic stimulation is expected to shorten SNERP and circulating catecholamines may have additionally contributed to the shorter SNERP values in our postoperative patients since both preceding heart failure and the perioperative state lead to sympathetic activation. Therefore, it should be acknowledged that the range of SNERP obtained in this study must not necessarily be applicable to the chronic postoperative state.

When previously proposed normal values for the SNERP of <440 ms at a pacing cycle length of 500 ms are applied to our study population, the SNERP would have been classified as normal in all our patients. However, because of the chronically denervated state of the transplanted heart, these normal limits cannot be directly applied to our study population. Beyond the absence of parasympathetic influences, however, the relatively short SNERP suggests that it was actually normal in all our patients since deprivation of autonomic influences, on average, may account for a

**Figure 3.** Example of a more gradual transition from reset to interpolation. After all, a jump ≥50 ms could be identified at a coupling interval of 330 ms. At coupling intervals <330 ms, the resulting S2-A3 intervals are consistently shorter than at longer premature intervals. Basic pacing cycle length is 500 ms.
shortening of 11.2 percent only.3
The SNERP did not differ significantly in our
patients with normal and impaired postoperative SN
function. This is inconsistent with observations of Kerr
et al2,3 while other investigators have also found a lack
of significant differences between patients with normal
and impaired SN function.4
Several explanations exist for this discrepancy. First,
in most of our patients, SNERP could be compared at
the same pacing cycle length, while different pacing
cycle lengths were compared in a previous series.3
With the SNERP prolonging at shorter pacing cycle
lengths, this may account for some of the differences
between patients with normal and impaired SN func-
tion.
Second, differences in stratification may account for
the aforementioned incongruities. In a previous study,
SN dysfunction was delineated on clinical grounds
while CSNRT was prolonged only in 3 of 12 patients
with SN dysfunction.2 In contrast, our study popula-
tion was stratified on the basis of CSNRT values and
prolonged CSNRT is an accepted indicator of SN
dysfunction in the transplanted, denervated state.5-8
In the pharmacologically or surgically denervated
heart, the CSNRT is a more reliable indicator of SN
dysfunction and produces more organized results.12,13
Accordingly, prolonged CSNRT has been interpreted
in terms of a postoperative sick sinus syndrome14 that
may persist up to 28 months following cardiac trans-
plantation.9 It may be argued that prolonged CSNRT
might be a laboratory artifact. This view, however, is
not supported by the association with—in view of the
denervated state—often profound sinus bradycardia
in patients with pathologic CSNRT. A heart rate of 50
beats/min or lower has been considered abnormal in
the denervated, transplanted human heart.12
Third, SN disease in the innervated heart may fall
into one of two categories, that is, it may represent an
“intrinsic” or “extrinsic” sick sinus syndrome. In the
extrinsic sick sinus syndrome, there is an exaggerated
response to autonomic, respectively, parasympathetic
influences. Supersensitivity to parasympathetic stimu-
li in extrinsic SN dysfunction may explain the perni-
tent prolongation in SNERP, since SN refractoriness
is prolonged with parasympathetic stimulation.3
The fourth explanation and the most interesting
aspect of our study is that SN dysfunction after
transplantation may behave somewhat differently than
the sick sinus syndrome in the native heart. In the
native heart, SN dysfunction might be characterized
by prolonged refractoriness of the sinoatrial region
with or without prolongation of CSNRT while post-
transplantation SN dysfunction might merely repre-
sent disturbance of automaticity. As has been outlined
above, the SNERP values in our transplant cohort
may be regarded as normal including those measure-
ments with otherwise pathologic SN function. Thus,
we interpret our findings in terms of a different entity
of the posttransplantation sick sinus syndrome, char-
acterized by abnormal automaticity but normal refrac-
toriness. Further work on this issue will have to show
whether this point of view is correct.

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