Selective Vagal Denervation of the Atria Eliminates Heart Rate Variability and Baroreflex Sensitivity While Preserving Ventricular Innervation

Chuen-Wang Chiou, MD; Douglas P. Zipes, MD

**Background**—The purpose of this study was to test whether radiofrequency catheter ablation (RFCA) of 3 epicardial fat pads that resulted in efferent vagal denervation of the atria and sinus and atrioventricular nodes also denervated the ventricles.

**Methods and Results**—Vagal innervation of the ventricles was determined by measuring prolongation of ventricular effective refractory period induced by bilateral vagal stimulation (20 Hz, 10 V, 4 ms). Changes in heart rate variability (HRV) and baroreflex sensitivity (BRS) were also examined. We found that RFCA of the 3 epicardial fat pads vagally denervated the sinus and AV nodes and atria without affecting vagal innervation of the ventricles, indicating that efferent vagal fibers to the ventricles do not travel through the 3 epicardial fat pads. Parameters of time-domain variables decreased significantly; the total-power, high-frequency, and low-frequency components of frequency-domain variables decreased significantly; and the ratio of the low- and high-frequency components increased significantly after chronic vagal denervation. Vagally modulated sinus arrhythmia and BRS were also eliminated after chronic vagal denervation. These data also indicate that HRV and BRS represent vagal activity at the level of the sinus node and may not accurately reflect efferent vagal activity at the ventricular level.

**Conclusions**—Selective vagal denervation of the sinus and AV nodes and atria decreased HRV and eliminated BRS while preserving ventricular innervation. (Circulation. 1998;98:360-368.)

**Key Words:** vagus nerve • heart rate • reflex

Previous studies have demonstrated that increased sympathetic activity predisposes the heart to ventricular fibrillation, whereas augmented vagal tone exerts a protective and antifibrillatory effect. Both experimental and clinical studies also indicate a strong correlation between indexes of either impaired vagal reflexes or reduced vagal tone and a greater incidence of sudden cardiac death after myocardial infarction. At the atrial level, in contrast, heightened vagal tone promotes the genesis of atrial fibrillation. We have shown previously that long-term vagal denervation of the atria can be produced by RFCA of 3 epicardial fat pads located (1) between the superior vena cava and aortic root, superior to the right pulmonary artery (SVC-Ao fat pad), (2) at the junction of the inferior vena cava and left atrium (IVC-LA fat pad), and (3) over the right pulmonary veins (RPV fat pad). Vagal denervation supersensitivity results, but induction of atrial fibrillation is made more difficult, presumably because of increased electrophysiological homogeneity. However, if this manipulation, antiarrhythmic for the atria, caused efferent vagal denervation to the ventricles, it might be more arrhythmogenic for the ventricles. Accordingly, one purpose of the present study was to determine the effects of RFCA of the SVC-Ao, IVA-LA, and RPV fat pads on the efferent vagal innervation to the ventricles.

Heart rate variability and baroreflex sensitivity have been widely used to reflect the autonomic activity in the heart. Numerous studies have also demonstrated that analysis of baroreflex sensitivity or heart rate variability can identify subgroups at both lower and higher risk for sudden death. However, we have shown previously that sinus node function may not always represent an “autonomic barometer” of autonomic activity in the ventricle. Therefore, the second purpose of the study was to determine whether we could eliminate or reduce the response of heart rate variability and baroreflex sensitivity without affecting efferent vagal innervation of the ventricles.

**Methods**

**Overview**

Dogs underwent a right lateral thoracotomy; 5 received RFCA of the 3 fat pads, and 5 had a sham procedure. After full recovery, heart rate variability and baroreflex sensitivity were measured with the dogs in a conscious state. Finally, they underwent an open-chest electrophysiological study to determine ERP response to vagal stimulation and were then euthanized.

**Surgical Preparation**

Ten conditioned mongrel dogs of either sex weighing 20 to 30 kg were used in the study. The dogs were premedicated with antibiotics...
(cefazoline 500 mg IM) and a muscle relaxant (pancuronium bromide 2 mg IV) and anesthetized initially with sodium thiopental 20 mg/kg. Anesthesia was maintained by ventilation with 1% to 3% isoflurane gas mixed with oxygen at a rate of 1.0 to 2.0 L/min. Under sterile surgical conditions, a right lateral intercostal thoracotomy was performed, the ribs and lungs were retracted, and the pericardium was incised. A right pericardial window was created to expose the right atrium.

**Vagal Denervation Procedure**

The RF energy was delivered to the SVC-Ao, IVC-LA, and RPV fat pads through a 7F deflectable quadripolar catheter with a 4-mm tip electrode (EP Technology or Mansfield) in 5 of the 10 dogs (denervated group) as we described previously. The catheter tips were positioned manually on the epicardial surface of the heart under direct visualization to ensure optimal tissue contact and energy delivery. Continuous unmodulated RF current of 300 to 750 kHz with a power output setting of 30 to 35 W was delivered from a RF generator (EP Technologies) for a duration of 60 seconds. The catheter tip was flushed with small amounts of saline during epicardial RF energy delivery to prevent excessive heat formation. Serum electrolytes, pH, base excess, and blood gases were monitored during surgical procedures and were obtained daily for 3 days after surgery. After RFCA of 3 epicardial fat pads, the chest was closed in layers, negative pressure was reestablished in the pleural cavity, and the animal was allowed to recover. Antibiotics were administered for 5 days after surgery, and analgesics were given as needed.

The other 5 dogs underwent a similar operation but without a denervation procedure (sham-operated group).

**24-Hour Holter ECG and Heart Rate Variability**

All 24-hour Holter ECG recordings were performed by means of 3-channel bipolar Rosin Holter recorders. The tapes were subsequently analyzed by the PREDICTOR HRVECG arrhythmia analysis program allowing detection of normal sinus beats and supraventricular and ventricular extrasystoles. After automatic analysis of the tape, the data file was visually reviewed and edited by the investigators. Heart rate variability was performed with the PREDICTOR HRVECG heart rate variability analysis program. Aberrant ECG complexes, such as premature ventricular beats, electrical noise, or other aberrant ECG signals, and their adjacent RR intervals were rejected from the RR interval generation process and heart rate variability analysis.

**Time-Domain Measures**

Time-domain measures were the SD of all normal RR intervals in the entire 24-hour ECG recording (SDNN), the SD of the average normal RR intervals for all 5-minute segments (SDANN), the mean squared successive difference interval (the square root of the mean of the squared differences between adjacent normal RR intervals over the entire 24-hour recording, MSSD), and the percentage of sinus cycles differing from the preceding cycle by >50 ms over the entire 24-hour recording (PNN50).

**Frequency-Domain Measures**

The power spectral analysis of normal to normal intervals was computed by fast Fourier transformation on 5-minute segments over the 24-hour period. The PREDICTOR HRVECG system provides 4
TABLE 1. Changes in Holter Variables After Chronic Vagal Denervation of the Atria and Sinus and AV Nodes or After Sham Operation

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>After</th>
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<tbody>
<tr>
<td>A. Denervated dogs (N=5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Min HR, bpm</td>
<td>44±9</td>
<td>107±13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean HR, bpm</td>
<td>85±14</td>
<td>140±22</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Max HR, bpm</td>
<td>226±20</td>
<td>196±34</td>
<td>NS</td>
</tr>
<tr>
<td>VPC, n/N</td>
<td>0/5</td>
<td>0/5</td>
<td></td>
</tr>
<tr>
<td>Sinus arrhythmia, α/N</td>
<td>5/5</td>
<td>0/5</td>
<td></td>
</tr>
<tr>
<td>B. Sham-operated dogs (N=5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Min HR, bpm</td>
<td>43±9</td>
<td>41±9</td>
<td>NS</td>
</tr>
<tr>
<td>Mean HR, bpm</td>
<td>85±15</td>
<td>87±15</td>
<td>NS</td>
</tr>
<tr>
<td>Max HR, bpm</td>
<td>225±20</td>
<td>226±19</td>
<td>NS</td>
</tr>
<tr>
<td>VPC, n/N</td>
<td>0/5</td>
<td>0/5</td>
<td></td>
</tr>
<tr>
<td>Sinus arrhythmia, α/N</td>
<td>5/5</td>
<td>0/5</td>
<td></td>
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N indicates numbers of dogs; Min, minimal; HR, heart rate; Max, maximal; n, number of dogs with ventricular premature complex (VPC); and α, number of dogs with sinus arrhythmia. Values are mean±SD. A, Min and mean HR significantly increased, max HR was not significantly changed, the occurrence of VPCs was not increased, and the sinus arrhythmia was abolished after chronic vagal denervation. B, Min, mean, and max HR and the occurrence of VPCs and sinus arrhythmias were not significantly changed after sham operation.

Baroreflex Sensitivity Test

Before testing, a venous catheter was placed percutaneously in the cephalic vein to administer medications. The dogs were anesthetized with sodium thiopental 20 mg/kg. A fluid-filled cannula was immediately placed into the right femoral artery and connected to a transducer (Statham p-23 Db, Gould) to monitor arterial pressure.

Two bipolar surface ECG leads were used for continuous ECG monitoring. After catheterization, the dogs were allowed to recover. Ten to 12 hours later, when blood pressure and heart rate values were stable, baroreflex sensitivity was performed according to the method of Smyth et al. The dogs were given injections of phenylephrine HCl, 10 μg/kg (Neo-Synephrine, Winthrop Laboratories) to raise systolic arterial pressure 30 to 50 mm Hg. Each RR interval was plotted as a function of the preceding systolic pressure. A linear regression analysis of these points was performed for the first sustained rise in blood pressure, and baroreflex sensitivity was then estimated as the value of the slope from the regression analysis. The slope was accepted for further analysis only if the correlation coefficient was ≥0.8.

At least 3 such slopes were calculated for each dog, and the mean of these was taken as the baroreflex sensitivity and expressed in ms/mm Hg.

Surgical Preparation for Electrophysiological Study

The surgical preparation for electrophysiological study has been described previously. Briefly, the dogs were anesthetized with pentobarbital (30 mg/kg IV). Additional amounts were given as necessary to maintain anesthesia during the electrophysiological study. Dogs were ventilated with room air by use of a cuffed endotracheal tube and a constant volume cycled respirator (model 607, Harvard Apparatus). Blood pressure and ECG were monitored throughout the study. A His-bundle electrogram was recorded in all dogs with a 7F bipolar electrode catheter (USCI) introduced through the left carotid artery and advanced in a retrograde manner into the noncoronary cusp of the aortic valve. The chest was opened, and a pericardial cradle was created. The heart was autonomically decentralized by isolating, doubly ligating, and transecting both cervical vagi in the neck and subclavian ansae as they exited from the stellate ganglia. Both cervical vagi were stimulated with rectangular pulses of 4-ms duration at a frequency of 20 Hz and at 10 V through 2 Teflon-coated wire electrodes embedded in the distal cut end of each vagal nerve. Six plunge electrodes made of Teflon-coated wire, insulated except for their tips, were inserted 3 to 4 mm beneath the epicardium in the right and left atrial free walls and appendages as cathodes to determine atrial ERP. Three electrodes were placed in the anterior left ventricular subepicardium at distances of ~1 and 3 cm from the AV groove and in the anterior apical region to measure left ventricular ERPs. Another 3 electrodes were placed in the right ventricular outflow tract and basal and apical areas to measure right ventricular ERPs. An anodal electrode was placed in the abdominal wall. ERP responses to vagal nerve stimulation were determined.

Experimental Protocols

Effects of Long-term Vagal Denervation of Sinus and AV Nodes and Atria on Heart Rate Variability and Baroreflex Sensitivity

To test the effects of vagal denervation of the sinus and AV nodes and atria on the heart rate variability and baroreflex sensitivity and to determine whether this denervation procedure was arrhythmogenic, 24-hour Holter recordings were obtained 1 day before and 7 to 10 days after vagal denervation or sham operation. Each dog underwent a baroreflex sensitivity test 7 to 10 days after vagal denervation or sham operation.

Effects of Long-term RFCA of RPV, IVC-LA, and SVC-Ao Fat Pads on the Vagal Innervation of Sinus and AV Nodes, Atria, and Ventricles

Electrophysiological study was performed immediately after baroreflex sensitivity testing was done. Five consecutive sinus cycle lengths immediately before vagal stimulation were measured and averaged to obtain the spontaneous sinus cycle length. Five consecutive atrio-His intervals were measured during constant right atrial pacing at a cycle length of 400 ms and averaged to obtain AV nodal conduction times. The atrial and ventricular ERPs were determined with unipolar cathodal stimulation at each electrode site by the
extrastimulus technique with a programmable stimulator (Krannert Medical Engineering) and a constant-current isolator as we have described previously.15,27

Sinus cycle length, AV nodal conduction time, atrial ERPs, and ventricular ERPs were determined in the baseline setting and during bilateral vagal stimulation to test the effects of long-term RFCA of the RPV, IVC-LA, and SVC-Ao fat pads on vagal innervation to the sinus and AV nodes, atria, and ventricles.

Data Analysis
Data are presented as mean ± SD. Comparisons within groups were done by paired t test, whereas a group t test was used for comparisons between groups. Differences were considered significant at P < 0.05.

Results
Figure 1 shows the data from electrophysiological studies 7 to 10 days after the chronic vagal denervation procedure (A) or sham operation (B). Figure 1A shows that there was no significant shortening of atrial ERP and no significant prolongation of sinus node cycle length and AV nodal conduction time during bilateral vagal stimulation, indicating that sinus and AV nodes and both atria were completely vagally denervated. Figure 1B shows that there was a marked shortening of atrial ERP and prolongation of sinus node cycle length and AV nodal conduction time during bilateral vagal stimulation, indicating that sham operation did not affect the vagal innervation to the atria and sinus and AV nodes.

Effects of Vagal Denervation of Sinus and AV Nodes and Atria on Holter Variables and Heart Rate Variability
Table 1 shows changes in spontaneous rhythm after chronic vagal denervation of the sinus and AV nodes and atria or after sham operation. Ventricular arrhythmias did not occur before or after vagal denervation or sham operation. Marked sinus arrhythmia was frequently present throughout the Holter study before vagal denervation and disappeared after vagal denervation (Figure 2), indicating that sinus arrhythmia is modulated primarily by vagal tone. The minimal and mean heart rate significantly increased and maximal heart rate was not significantly changed after chronic vagal denervation (Table 1A), indicating that this procedure vagally denervated the sinus node but did not significantly affect sympathetic innervation of the sinus node. Table 1B shows that minimal, mean, and maximal heart rates were not significantly changed after sham operation, indicating that sham operation did not affect the vagal or sympathetic innervation of the sinus node.

Figure 3 illustrates that all the time-domain variables (SDNN, MSSD, PNN50, and SDANN, see above) of the heart rate variability decreased significantly after chronic vagal denervation of the sinus and AV nodes and atria. Figure 4 is an example of the heart period histogram of a dog before and after vagal denervation. Figure 5 shows that there was no significant change in each time-domain variable after sham operation.

Table 2A shows that total power, HF power, LF power, and VLF power of frequency-domain variables significantly decreased and LF/HF ratio significantly increased after chronic vagal denervation of the sinus and AV nodes and atria. These data suggested predominance of sympathetic nervous activity at the sinus node relative to vagal activity after vagal denervation. Table 2B shows that all the frequency-domain variables of the heart rate variability were not significantly changed after sham operation.
Effects of Vagal Denervation of Sinus and AV Nodes and Atria on Baroreflex Sensitivity

Figure 6A shows the regression analysis of baroreflex sensitivity for 1 denervated dog and another sham-operated dog. The baroreflex sensitivity was 12.2 ms/mm Hg for the sham-operated dog and was eliminated for the denervated dog. Figure 6B shows the mean values of baroreflex sensitivity in sham-operated dogs and denervated dogs. The baroreflex sensitivity was completely eliminated in each of the denervated dogs.

Effects of Chronic Vagal Denervation of Sinus and AV Nodes and Atria on Vagal Innervation of the Ventricles

Figure 7 shows the values of vagally induced ERP prolongation at left and right ventricular sites in the denervated and sham-operated dogs. There was no significant difference in vagally induced prolongation of ventricular ERP between the denervated and sham-operated dogs, indicating that this denervation procedure did not affect efferent vagal innervation to both ventricles.

Discussion

Major Findings

The major conclusions from this study are that selective vagal denervation of the sinus and AV nodes and atria by use of RFCA of the RPV, IVC-LA, and SVC-Ao fat pads abolished vagally modulated sinus arrhythmia, markedly decreased heart rate variability, and eliminated baroreflex sensitivity without affecting vagal innervation of the ventricles. This denervation procedure did not cause any ventricular arrhythmias.

Effects of Vagal Denervation on Heart Rate Variability and Baroreflex Sensitivity

Clinical10-12 and experimental7-9 data demonstrated that depressed heart rate variability and baroreflex sensitivity are closely associated with increased cardiac mortality after myocardial infarction. The mechanism(s) responsible for depressed vagal activity and/or enhanced sympathetic activity after myocardial infarction is not known and may be multifactorial, including cardiac and peripheral autonomic responses. Furthermore, damage to the sinus node itself may
alter its responses to autonomic stimulation. Alterations in nitric oxide modulation of vagal and sympathetic actions may be important. Nevertheless, these responses are useful in risk-stratifying patients. In the present study, although selective vagal denervation of sinus and AV nodes and atria by use of RFCA of 3 epicardial fat pads eliminated the baroreflex sensitivity and markedly decreased heart rate variability, the vagal effects in the ventricles were preserved. This finding supports the conclusion that this denervation procedure should not affect any potential protective effects of vagal tone on the ventricles. It also supports the conclusion that the degree of vagal effects at the sinus node does not necessarily reflect that of vagal effects at the ventricular level and provides additional support to the concept that reduced heart rate variability and baroreflex sensitivity are only manifestations of changes that can result from a complex interaction between efferent neural sympathetic and vagal activities and sinus node pacemaker function. Conceivably, this finding could explain false-positive or negative results of heart rate variability or baroreflex sensitivity.

### TABLE 2. Changes in Frequency-Domain Variables of Heart Rate Variability After Chronic Vagal Denervation of the Atria and Sinus and AV Nodes or After Sham Operation

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
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<tbody>
<tr>
<td><strong>A. Denervated dogs (N=5)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total power (0.00-1.00 Hz), bpm²/Hz</td>
<td>378 279±71 759</td>
<td>10 247±6299</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HF power (0.15-0.50 Hz), bpm²/Hz</td>
<td>242 865±63 613</td>
<td>765±113</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LF power (0.04-0.15 Hz), bpm²/Hz</td>
<td>98 316±23 524</td>
<td>7106±5021</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>VLF power (0.00-0.04 Hz), bpm²/Hz</td>
<td>34 164±9136</td>
<td>2360±1436</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LF/HF ratio</td>
<td>0.4±0.1</td>
<td>8.8±4.7</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td><strong>B. Sham-operated dogs (N=5)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total power (0.00-1.00 Hz), bpm²/Hz</td>
<td>308 636±117 353</td>
<td>315 566±139 781</td>
<td>NS</td>
</tr>
<tr>
<td>HF power (0.15-0.50 Hz), bpm²/Hz</td>
<td>128 329±42 055</td>
<td>134 383±64 275</td>
<td>NS</td>
</tr>
<tr>
<td>LF power (0.04-0.15 Hz), bpm²/Hz</td>
<td>135 319±75 008</td>
<td>132 439±61 597</td>
<td>NS</td>
</tr>
<tr>
<td>VLF power (0.00-0.04 Hz), bpm²/Hz</td>
<td>44 223±20 809</td>
<td>44 542±20 502</td>
<td>NS</td>
</tr>
<tr>
<td>LF/HF ratio</td>
<td>1.1±0.5</td>
<td>1.0±0.1</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are mean±SD. A, Total, HF, LF, and VLF powers significantly decreased and LF/HF ratio significantly increased after chronic vagal denervation. B, All frequency-domain variables were not significantly changed after sham operation.

**Figure 5.** Changes in SDNN, MSSD, PNN50, and SDANN before and 7 to 10 days after sham operation (all P >0.05). See text for details. Abbreviations as in Figure 3.
Changes in Frequency-Domain Variables After Vagal Denervation of the Sinus and AV Nodes and Atria

For the frequency-domain measures, standard frequency bands presented in the literature contain HF power (0.15 to 0.40 Hz), LF power (0.04 to 0.15 Hz), VLF power (0.003 to 0.04 Hz), and ULF power (≤0.003 Hz). HF and LF components account for 5% of total power, and the ULF and VLF components account for the remaining 95% of total power. According to the suggestion of the recent Task Force of the ESC and NASPE,³¹ vagal activity is the major contributor to the HF component. Disagreement exists with respect to the LF component. Some studies³²–³⁵ suggest that LF is a quantitative marker of sympathetic modulation; other studies³⁶,³⁷ view LF as reflecting both sympathetic activity and vagal activity. The LF/HF ratio is considered by some investigators to mirror sympathovagal balance or to reflect sympathetic modulation. Although spectral analysis of heart rate variability in survivors of myocardial infarction³⁸,³⁹ suggested that the ULF and VLF components carry the highest predictive value, the physiological correlate of these components is unknown. In the present study, vagal denervation of the sinus and AV nodes and atrial muscle resulted in a large loss of power in all bands, including the LF and VLF, and an increase of LF/HF ratio. These data suggest that vagal activity may be contributing to all components of frequency-domain variables and that LF/HF ratio can be used as an indicator of sympathovagal balance.

Selective Vagal Innervation of the Sinus and AV Nodes, Atria, and Ventricles

Previous studies⁴⁰–⁴³ have demonstrated that different groups of vagal ganglia innervate the sinus and AV nodal regions, selectively regulating heart rate and AV nodal conduction. Ganglia associated with the vagal pathway to the sinus node are located in the RPV fat pad, whereas the ganglia associated with the vagal pathway to the AV node are located in the IVC-LA fat pad. Our previous study¹⁵ demonstrated that these 2 fat pads also contain some vagal fibers to both atria. In addition, we also reported that another fat pad, the SVC-Ao fat pad, receives most of the efferent vagal fibers to both atria. In the present study, vagal innervation of the sinus and AV nodes and atria were completely eliminated by RFCA of these 3 fat pads, whereas the vagal innervation of the ventricles were still preserved, indicating that efferent vagal fibers to the ventricles do not travel through these 3 fat pads.
Methodological Considerations and Study Limitations

Because a previous study\textsuperscript{44} showed that even small amounts of pentobarbital markedly inhibit spontaneous baroreceptor discharge, all dogs in this study underwent baroreflex sensitivity testing in the conscious state. For the frequency-domain measures, the heart rate variability analysis program used in this study provided only 3 measurement frequency bands, so we set the HF power at 0.15 to 0.40 Hz, LF at 0.04 to 0.15 Hz, and VLF at 0.00 to 0.04 Hz. Because we did not assess sympathetic innervation to the sinus and AV nodes and atria in the present study, we cannot state whether the sympathetic supply was still preserved after complete efferent vagal denervation. Nevertheless, the minimal and mean heart rates increased and the maximal heart rate did not change after vagal denervation, which suggests that sympathetic inputs to the sinus node were preserved. In addition, because the LF/HF ratio is a useful index of sympathetic-parasympathetic balance, significant increases in LF/HF ratio after vagal denervation might also indirectly support the notion that most of the sympathetic inputs to the sinus node were still preserved.

Acknowledgments

This study was supported in part by the Herman C. Krannert Fund and by grant HL-52323 from the National Heart, Lung, and Blood Institute of the National Institutes of Health. The authors thank Ed Berbari, PhD, for assistance in heart rate variability analysis and Claude J. Arnott for technical assistance.

References


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