Dynamic Behavior and Autonomic Regulation of Ectopic Atrial Pacemakers

Heikki V. Huikuri, MD; Aino-Maija Poutiainen, MD; Timo H. Mäkikallio, MD; M. Juhani Koistinen, MD; K.E. Juhani Airaksinen, MD; Raul D. Mitrani, MD; Robert J. Myerburg, MD; Agustin Castellanos, MD

Background—Heart rate (HR) variability reflects the neural regulation of normal pacemaker tissue, but the autonomic nervous regulation of abnormal atrial foci originating outside the sinus node has not been well characterized. We compared the HR variability of tachycardias originating from the ectopic foci and the sinus node.

Methods and Results—R-R–interval variability was analyzed from 24-hour Holter recordings in 12 patients with incessant ectopic atrial tachycardia (average HR 107±14 bpm), 12 subjects with sinus tachycardia (average HR 106±9 bpm), and 24 age- and sex-matched subjects with normal sinus rhythm (average HR 72±8 bpm). Time- and frequency-domain HR variability measures, along with approximate entropy, short- and long-term correlation properties of R-R intervals (exponents $\alpha_1$ and $\alpha_2$), and power-law scaling (exponent $\beta$), were analyzed. Time- and frequency-domain measures of HR variability did not differ between subjects with ectopic and sinus tachycardia. Fractal scaling exponents and approximate entropy were similar in sinus tachycardia and normal sinus rhythm, but the short-term scaling exponent $\alpha_1$ was significantly lower in ectopic atrial tachycardia (0.71±0.16) than in sinus tachycardia (1.16±0.13; P<0.001) or normal sinus rhythm (1.19±0.11; P<0.001). Abrupt prolongations in R-R intervals due to exit blocks from the ectopic foci or instability in beat-to-beat R-R dynamics were the major reasons for altered short-term HR behavior during ectopic tachycardias.

Conclusions—HR variability obtained by time- and frequency-domain methods does not differ between ectopic and sinus tachycardias, which suggests that abnormal atrial foci are under similar long-term autonomic regulation as normal pacemaker tissue. Short-term R-R–interval dynamics are altered toward more random behavior in ectopic tachycardia, which may result from a specific autonomic disturbance or an intrinsic abnormality of ectopic atrial pacemakers. (Circulation. 1999;100:1416-1422.)

Key Words: tachycardia ■ arrhythmia ■ heart rate ■ intervals

Heart rate (HR) is normally determined by the rate of depolarization of the dominant cardiac pacemaker. Because temporal changes in cardiac interbeat intervals are mediated by phasic vagal and sympathetic outflow, measurement of HR variability from long-term ECG recordings has considerable potential to assess the role of the autonomic nervous system in the regulation of pacemaker tissue.1–6 Beginning with the original observations of Akselrod et al1 on the typical spectral patterns of HR variability during normal sinus rhythm, a large amount of data has been published on the characteristics of HR variability in healthy subjects and patients with various cardiac diseases.2–6 Recently, analysis methods based on nonlinear dynamics have been developed to describe the complex behavior of cardiac interbeat intervals.7–11 The studies using these new methods have shown typical self-similar or fractal-like features in the R-R–interval dynamics of normal sinus rhythm9–13 and have also implicated abnormal HR behavior of patients with structural heart disease.10–13

The neural regulation and dynamics of the richly innervated sinus node are well characterized,1–6,9–13 but there is little information on the dynamic behavior of pacemakers originating outside the sinus node. Therefore, we studied the characteristics of HR variability of incessant ectopic atrial tachycardias. We also sought to determine whether there are differences in HR behavior between normal sinus rhythm, sinus tachycardia, and ectopic atrial tachycardia by analyzing the fractal correlation properties and complexity of R-R–interval variability.

Methods

Patient Population

Inpatients and outpatients of the Oulu University Hospital (n=19) and the University of Miami School of Medicine (n=5) with fast HR
in standard 12-lead ECG and in 24-hour ambulatory ECG recordings
were included in the study. All patients had elevated HRs observed
incidentally (n = 3) on a routine examination or brought to attention
because of symptoms (n = 21) causing referral to a hospital. Twelve
patients had ectopic atrial tachycardia (6 women and 6 men, mean
age 30 ± 12 years), and 12 had inappropriate sinus tachycardia (9
women and 3 men, mean age 32 ± 8 years). The characteristics of
the patients are shown in Tables 1 and 2.

The control group with normal sinus rhythm consisted of healthy
subjects without clinical or echocardiographic evidence of structural
heart disease (12 women and 12 men, mean age 34 ± 12 years). These
subjects were enrolled from populations described in detail previ-
ously14–16 and were matched with respect to age and sex to the
patients with ectopic atrial tachycardia. All patients and control
subjects gave informed consent for 24-hour ECG recordings.

Definitions of Tachycardias
Incessant ectopic atrial tachycardia was defined according to the
following criteria: (1) a resting daytime HR > 100 bpm, (2) an
average HR of > 90 bpm on 24-hour ECG recordings, and (3) an
abnormal p-wave axis and/or abnormal p-wave morphology in ≥2
precordial leads and in 1 bipolar limb lead on a 12-lead ECG. Inappropriate sinus tachycardia was defined as a resting daytime HR
> 100 bpm with a normal p-wave morphology and axis obtained
from standard 12-lead ECGs recorded on ≥2 separate days and an
average HR of > 90 bpm on 24-hour ECG recording. None of the
patients had a secondary cause for sinus tachycardia or ectopic atrial
tachycardia. The symptoms and duration of arrhythmias are shown in
Tables 1 and 2.

Electrophysiological Studies
Seven patients with a 12-lead ECG suggesting ectopic atrial
tachycardia and 4 with inappropriate sinus tachycardia underwent a
clinically indicated electrophysiological study. Quadripolar catheters
(7F) were positioned in the lateral portion of the high right atrium
and the low septal right atrium to record a His bundle electrogram,
the coronary sinus, and the right ventricular apex. In 4 cases with
inappropriate sinus tachycardia, a “halo” catheter consisting of 10
bipolar pairs was positioned along the crista terminalis in the right
atrium with the tip of the catheter at the coronary sinus ostium.
Surface leads I, II, and V1 and intracardiac electrograms, filtered
from 30 to 250 Hz, were recorded on an electrostatic paper at a paper
speed of 100 mm/s or in a computer-based digitized amplifier/rec-
order system with optical disk storage (ART Inc).

Detailed mapping and ablation of the ectopic atrial tachycardias
were performed with a 7F ablation catheter with a deflectable tip and

---

**TABLE 1. Characteristics of Patients With Ectopic Atrial Tachycardia**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, y</th>
<th>Duration of Symptoms, mo</th>
<th>Location of Ectopic Focus</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>38</td>
<td>48</td>
<td>*Right atrial auricle</td>
<td>Palpitation</td>
</tr>
<tr>
<td>2</td>
<td>9</td>
<td>42</td>
<td>Left atrium</td>
<td>Tiredness, vomiting</td>
</tr>
<tr>
<td>3</td>
<td>20</td>
<td>48</td>
<td>*Right atrium, interatrial septum</td>
<td>Palpitation</td>
</tr>
<tr>
<td>4</td>
<td>26</td>
<td>10</td>
<td>*Lateral right atrium, crista terminalis region</td>
<td>Palpitation</td>
</tr>
<tr>
<td>5</td>
<td>43</td>
<td>30</td>
<td>Right atrium</td>
<td>Palpitation</td>
</tr>
<tr>
<td>6</td>
<td>42</td>
<td>360</td>
<td>*Right atrium, posterior from AV node</td>
<td>Palpitation</td>
</tr>
<tr>
<td>7</td>
<td>44</td>
<td>108</td>
<td>*Inferolateral right atrium, crista terminalis region</td>
<td>Tachycardia, tinnitus</td>
</tr>
<tr>
<td>8</td>
<td>19</td>
<td>10</td>
<td>*Right atrium, interatrial septum</td>
<td>Palpitation</td>
</tr>
<tr>
<td>9</td>
<td>30</td>
<td>12</td>
<td>Left atrium</td>
<td>Palpitation</td>
</tr>
<tr>
<td>10</td>
<td>21</td>
<td>3</td>
<td>*Right atrial auricle</td>
<td>Palpitation</td>
</tr>
<tr>
<td>11</td>
<td>41</td>
<td>12</td>
<td>Left atrium</td>
<td>Palpitation</td>
</tr>
<tr>
<td>12</td>
<td>23</td>
<td>6</td>
<td>Right atrium</td>
<td>Palpitation</td>
</tr>
</tbody>
</table>

*The location of ectopic focus was determined by mapping during the electrophysiological study; in other cases, the focus was determined from a 12-lead ECG.

**TABLE 2. Characteristics of Patients With Sinus Tachycardia**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, y</th>
<th>Duration of Symptoms, mo</th>
<th>EP Testing</th>
<th>Type of Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>39</td>
<td>120</td>
<td>No</td>
<td>Palpitation</td>
</tr>
<tr>
<td>2</td>
<td>47</td>
<td>10</td>
<td>No</td>
<td>Palpitation, sweating</td>
</tr>
<tr>
<td>3</td>
<td>34</td>
<td>1</td>
<td>Yes</td>
<td>Palpitation, left hand paresthesia in exercise</td>
</tr>
<tr>
<td>4</td>
<td>37</td>
<td>7</td>
<td>No</td>
<td>Palpitation</td>
</tr>
<tr>
<td>5</td>
<td>23</td>
<td>6</td>
<td>No</td>
<td>Palpitation</td>
</tr>
<tr>
<td>6</td>
<td>41</td>
<td>8</td>
<td>No</td>
<td>Palpitation</td>
</tr>
<tr>
<td>7</td>
<td>51</td>
<td>360</td>
<td>Yes</td>
<td>Palpitation</td>
</tr>
<tr>
<td>8</td>
<td>56</td>
<td>4</td>
<td>No</td>
<td>Palpitation</td>
</tr>
<tr>
<td>9</td>
<td>52</td>
<td>11</td>
<td>Yes</td>
<td>Palpitation</td>
</tr>
<tr>
<td>10</td>
<td>37</td>
<td>...</td>
<td>No</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>11</td>
<td>50</td>
<td>...</td>
<td>No</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>12</td>
<td>32</td>
<td>...</td>
<td>Yes</td>
<td>Asymptomatic</td>
</tr>
</tbody>
</table>

EP indicates electrophysiological.
a 4-mm distal-tip electrode (Mansfield/Webster). The earliest local intracardiac activation in relation to the p-wave on the surface ECG was used to select the target site for ablation. Radiofrequency energy was applied at the appropriate target sites in a range of 20 to 40 W power for 40 to 60 seconds until termination of ectopic atrial tachycardia.

Criteria of incessant ectopic atrial tachycardia during the electrophysiological study were as follows: (1) an endocardial activation sequence inconsistent with a sinus origin; (2) inability to terminate or reset the tachycardia with appropriately timed premature atrial extrastimuli or rapid atrial pacing; (3) exclusion of intra-atrial, AV, and AV nodal reentry; and (4) sudden restoration of sinus rhythm after radiofrequency ablation of the tachycardia. Inappropriate sinus tachycardia was defined by (1) an activation sequence consistent with a sinus origin (ie, earliest endocardial activation in the lateral high right atrium obtained with the halo catheter) and (2) exclusion of reentry by inability to terminate or reset the tachycardia by atrial extrastimuli or rapid atrial pacing.

**Ambulatory ECG Recordings**

All subjects were monitored for 24 hours with an ambulatory ECG recorder with modified V1 and V5 lead placement. All patients and control subjects were nonmedicated at the time of the 24-hour ECG recordings and were encouraged to continue with their normal daily activities during the recordings. The data were sampled digitally and transmitted to a microcomputer for analysis of HR variability. Before the R–R–interval tachograms were analyzed, the recordings were edited to eliminate premature ectopic beats in the sinus tachycardia patients, sinus cycles in the patients with ectopic atrial tachycardia, and segments with intermittent AV block. The editing process was performed by printing full disclosure of the 24-hour ECG recordings at a paper speed of 8 mm/s. All questionable segments with a change in p-wave morphology or R–R intervals on full disclosure were then printed at a paper speed of 25 mm/s to confirm the sinus or ectopic origin of the beats, respectively. Changes in p-wave morphology or AV block were noted and marked, and the corresponding R–R intervals were manually edited from the R–R–interval tachograms before analysis of HR variability. After the ECG data had been transferred to the microcomputer, the R–R–interval series were also edited both manually and automatically from the R–R–interval tachograms. Each R–R–interval time series was passed through a filter to eliminate premature beats and artifacts and to replace the filling gaps. Only recordings with qualified beats for at least a 16-hour period and with >80% of qualified ectopic or sinus beats, respectively, were included in the analyses of HR variability. HR variability, by both traditional and new measures, was analyzed by custom-made analysis programs described in detail previously.

**Time- and Frequency-Domain Analysis of HR Variability**

The time- and frequency-domain measures of HR variability were analyzed by the methods recommended by the Task Force of the European Society of Cardiology. The SD of all normal-to-normal R–R intervals (SDNN) and the difference between the maximum and minimum hourly HR (circadian rhythm) were computed as standard time-domain measures of HR variability. Spectral power was quantified both by fast Fourier transform analysis and by autoregressive analysis in 4 frequency bands. The point power spectrum was logarithmically smoothed in the frequency domain and the power integrated into bins spaced 0.0167 log (Hz) apart. A robust line-fitting algorithm of log (power) on log (frequency) was then applied to the power spectrum between $10^{-2}$ and $10^{2}$ Hz. The slope of this line was calculated ($b$). This spectral range was chosen on the basis of previous observations regarding the linear relationship between log (power) and log (frequency) in this frequency band in human HR time series data. The details of this method have been described elsewhere.

The detrended fluctuation analysis technique was used to quantify the fractal scaling properties of short- and intermediate-term R–R–interval time series. This method is a modified root-mean-square analysis of random walk that quantifies the presence or absence of fractal correlation properties and has been validated for nonstationary time series. In this method, the root-mean-square fluctuation of integrated and detrended time series is measured at each observation window and plotted against the size of the observation window on a log-log scale. The fractal-like signal ($1/f$ signal spectrum) results in an exponent value of 1 ($\alpha=1.0$). The details of this method have been described elsewhere. In the present study, the HR correlations were defined separately for short-term (<11 beats, $\alpha_1$) and longer-term (>11 beats, $\alpha_2$) R–R–interval data (scaling exponents) on the basis of the previous finding of a crossover point on the log-log plot. Both $\alpha_1$ and $\alpha_2$ were analyzed from segments of 8000 R–R intervals and averaged to obtain mean values for the entire recording period.

**Approximate Entropy**

Approximate entropy is a measure that quantifies the regularity of time series. The details of the method used have been described previously. The parameters $m$ and $r$ of the method must be fixed to calculate approximate entropy, and $m=2$ and $r=20\%$ of the SD of the data sets were chosen on the basis of previous findings of statistical validity. Approximate entropy values were computed from 8000 R–R–interval segments and averaged to obtain a mean value of approximate entropy characterizing the entire recording.

**Intravenous Atropine**

Intravenous atropine was given gradually at a dose of 0.02 mg/kg to 11 patients with ectopic atrial tachycardia and 8 patients with inappropriate sinus tachycardia who gave their informed consent to the atropine test. HR was continuously recorded at a paper speed of 25 mm/s until no increase in the average HR was observed during the 2-minute period. The difference between baseline HR and maximum HR after atropine was calculated and compared with normal reference values obtained in previous studies, ie, increase of 20% to 50% over the control rate.

**Statistical Analysis**

Results are expressed as mean±SD. Statistical analysis was performed with 1-way ANOVA with Bonferroni post hoc tests to compare data between the groups. SPSS for Windows version 7.5 was used in the analyses. A value of $P<0.05$ was considered to indicate statistical significance.

**Poincaré Plot Analysis**

A Poincaré plot is a diagram in which each R–R interval is plotted as a function of the previous R–R interval. Both visual analysis of the graphic display and quantitative analysis of the plots can be used to describe R–R–interval dynamics. The quantitative 2D analysis of these plots has been described in detail previously. The scattergrams of successive R–R intervals were plotted for the entire 24-hour period, and the SD of instantaneous R–R–interval variability (SD1) and of continuous variability (SD2) were then analyzed. The shape of the plot was also classified as complex, torpedo-shaped, or normal, as described previously.

Fractal Analysis of R–R–Interval Variability

The power-law relationship of R–R–interval variability was calculated from the frequency range $10^{-4}$ to $10^{2}$ Hz. The point power spectrum was logarithmically smoothed in the frequency domain and the power integrated into bins spaced 0.0167 log (Hz) apart. A robust line-fitting algorithm of log (power) on log (frequency) was then applied to the power spectrum between $10^{-4}$ and $10^{2}$ Hz, and the slope of this line was calculated ($b$). This spectral range was chosen on the basis of previous observations regarding the linear relationship between log (power) and log (frequency) in this frequency band in human HR time series data. The details of this method have been described previously.

The detrended fluctuation analysis technique was used to quantify the fractal scaling properties of short- and intermediate-term R–R–interval time series. This method is a modified root-mean-square analysis of random walk that quantifies the presence or absence of fractal correlation properties and has been validated for nonstationary time series. In this method, the root-mean-square fluctuation of integrated and detrended time series is measured at each observation window and plotted against the size of the observation window on a log-log scale. The fractal-like signal ($1/f$ signal spectrum) results in an exponent value of 1 ($\alpha=1.0$). The details of this method have been described elsewhere. In the present study, the HR correlations were defined separately for short-term (<11 beats, $\alpha_1$) and longer-term (>11 beats, $\alpha_2$) R–R–interval data (scaling exponents) on the basis of the previous finding of a crossover point on the log-log plot. Both $\alpha_1$ and $\alpha_2$ were analyzed from segments of 8000 R–R intervals and averaged to obtain a mean value of approximate entropy characterizing the entire recording.

**Statistical Analysis**

Results are expressed as mean±SD. Statistical analysis was performed with 1-way ANOVA with Bonferroni post hoc tests to compare data between the groups. SPSS for Windows version 7.5 was used in the analyses. A value of $P<0.05$ was considered to indicate statistical significance.
Results

Time- and Frequency-Domain Measures of HR Variability

Table 3 shows the time- and frequency-domain measures of HR variability in the 3 study groups. None of these measures differed between patients with ectopic atrial tachycardia or sinus tachycardia. However, all traditional HR variability measures expressed in absolute units, including measures obtained by quantitative analysis of Poincaré plots, were reduced in patients with ectopic and sinus tachycardia compared with subjects with normal sinus rhythm (see examples in Figure 1). Despite the reduced overall HR variability, the Poincaré plots showed normal comet-shaped characteristics in cases with ectopic and inappropriate tachycardia (Figure 2). The LF/HF ratio or the LF and HF components analyzed in normalized units did not differ from normal in either ectopic tachycardia or sinus tachycardia. There was also no difference between maximum and minimum HRs (amplitude of the circadian rhythm) between the study groups (Table 3).

Fractal and Complexity Measures of R-R–Interval Variability

The short- and long-term scaling exponents α₁, α₂, the power-law slope β, and approximate entropy did not differ between subjects with sinus tachycardia and those with normal sinus rhythm (Table 3 and Figure 1). Approximate entropy, the long-term scaling exponent α₂, and the power-law slope in cases with ectopic atrial tachycardia also did not differ from those with sinus rhythm. However, the short-term

<table>
<thead>
<tr>
<th></th>
<th>Ectopic Atrial Tachycardia (n=12)</th>
<th>Sinus Tachycardia (n=12)</th>
<th>Normal Sinus Rhythm (n=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean 24-h HR, bpm</td>
<td>109±12†</td>
<td>106±9†</td>
<td>72±9</td>
</tr>
<tr>
<td>Minimum HR, bpm</td>
<td>95±15</td>
<td>90±10</td>
<td>56±6</td>
</tr>
<tr>
<td>Maximum HR, bpm</td>
<td>130±13</td>
<td>121±15</td>
<td>95±14</td>
</tr>
<tr>
<td>Difference between maximum and minimum HR, bpm</td>
<td>35±14</td>
<td>31±8</td>
<td>40±14</td>
</tr>
<tr>
<td>SD1, ms</td>
<td>17±12†</td>
<td>15±6†</td>
<td>37±12</td>
</tr>
<tr>
<td>SD2, ms</td>
<td>56±33†</td>
<td>67±14†</td>
<td>145.7±29.3</td>
</tr>
<tr>
<td>SDNN, ms</td>
<td>75±28†</td>
<td>77±16†</td>
<td>176±39</td>
</tr>
<tr>
<td>SDNNi</td>
<td>13±4†</td>
<td>13±3†</td>
<td>21±5</td>
</tr>
<tr>
<td>HF power, ms²</td>
<td>208±256</td>
<td>162±137</td>
<td>1101±750</td>
</tr>
<tr>
<td>Ln, ms²</td>
<td>4.4±1.3†</td>
<td>4.2±0.8†</td>
<td>6.7±0.9</td>
</tr>
<tr>
<td>NU</td>
<td>44.7±7</td>
<td>39±6</td>
<td>38±7</td>
</tr>
<tr>
<td>LF power, ms²</td>
<td>247±286</td>
<td>344±158</td>
<td>1611±960</td>
</tr>
<tr>
<td>Ln, ms²</td>
<td>4.5±1.6†</td>
<td>4.7±1.1†</td>
<td>7.2±0.7</td>
</tr>
<tr>
<td>NU</td>
<td>55±8</td>
<td>60±7</td>
<td>61±6</td>
</tr>
<tr>
<td>LF/HF ratio</td>
<td>1.5±1.2</td>
<td>1.9±1.6</td>
<td>1.9±0.9</td>
</tr>
<tr>
<td>VLF power, ms²</td>
<td>517±472</td>
<td>556±289</td>
<td>2792±1358</td>
</tr>
<tr>
<td>Ln, ms²</td>
<td>5.3±1.3†</td>
<td>5.8±0.8†</td>
<td>7.8±0.6</td>
</tr>
<tr>
<td>ApEn</td>
<td>1.13±0.22</td>
<td>1.05±0.33</td>
<td>1.15±0.16</td>
</tr>
<tr>
<td>α₁</td>
<td>0.71±0.16†</td>
<td>1.16±0.13</td>
<td>1.19±0.11</td>
</tr>
<tr>
<td>α₂</td>
<td>1.06±0.21</td>
<td>1.04±0.19</td>
<td>1.08±0.16</td>
</tr>
<tr>
<td>β</td>
<td>−1.39±0.22</td>
<td>1.39±0.22</td>
<td>−1.26±0.15</td>
</tr>
</tbody>
</table>

SD1, indicates short-term SD analyzed from Poincaré plots; SD2, long-term SD analyzed from Poincaré plots; SDNNi, SDNN normalized with R-R interval length; Ln, natural logarithmic of absolute values; NU, normalized units; and ApEn, approximate entropy.

Values are mean±SD.

†P<0.001 and *P<0.01 compared with normal sinus rhythm with ANOVA and Bonferroni post hoc analysis.

§P<0.001 between ectopic atrial tachycardia and sinus tachycardia.

Fractal and Complexity Measures of R-R–Interval Variability

The short- and long-term scaling exponents α₁, α₂, the power-law slope β, and approximate entropy did not differ between subjects with sinus tachycardia and those with normal sinus rhythm (Table 3 and Figure 1). Approximate entropy, the long-term scaling exponent α₂, and the power-law slope in cases with ectopic atrial tachycardia also did not differ from those with sinus rhythm. However, the short-term
scaling exponent $\alpha_1$ was significantly lower in ectopic atrial tachycardia than in either inappropriate sinus tachycardia or normal sinus rhythm (Table 3; Figures 2 and 3).

Full disclosures of Holter recordings and ECG printouts of patients with ectopic atrial tachycardia showed sudden, abrupt prolongations in R-R intervals (exit blocks from ectopic foci) without evidence of a change in p-wave morphology or AV block in 6 patients throughout the 24-hour recordings (Figure 4). In 5 cases with a low $\alpha_1$ value, no abrupt changes in R-R intervals were observed, but the ectopic foci showed continuous instability in beat-to-beat behavior during the entire recording period. Unstable beat-to-beat R-R-interval behavior and exit blocks were more commonly observed during sleep than in the daytime.

**HR Responses to Intravenous Atropine**

HR increased from $104\pm16$ bpm to $134\pm11$ bpm ($P<0.001$) after intravenous atropine administration in patients with ectopic tachycardia. The mean increase of HR was 30±14 beats (range 11 to 65 bpm). In 2 patients, the increase in HR was smaller than the reference values reported for healthy subjects with normal sinus rhythm (<20% increase from baseline). In subjects with inappropriate sinus tachycardia, HR increased from $108\pm15$ to $137\pm18$ bpm. The mean increase of HR was $29\pm13$ bpm (range 15 to 49 bpm). Two subjects with sinus tachycardia had a smaller increase in HR than the normal reference range.

**Discussion**

HR variability values obtained by time- and frequency-domain analysis methods over a 24-hour period did not differ between ectopic atrial tachycardia and sinus tachycardia, which suggests that atrial arrhythmic foci are under similar long-term phasic regulation as the sinus node. It appears that autonomic regulation of cardiac rhythm is not limited to effects on those specialized pacemaker tissues richly innervated by vagal and sympathetic fibers but may also influence the abnormal atrial pacemaker tissue. In contrast, short-term correlation properties of R-R-interval behavior were not similar during sinus and ectopic tachycardia. These differences in short-term HR behavior may result from a specific autonomic disturbance that controls the discharge of the ectopic foci or from an intrinsic electrophysiological abnormality of these foci.

**Abnormalities in Time- and Frequency-Domain HR Variability**

Autonomic regulation of sinus tachycardia and ectopic tachycardia can be compared by use of traditional analysis methods because of the similar average HR between the 2 rhythms. The results suggest that vagal outflow both to ectopic foci and to sinoatrial cells and their responsiveness to vagal input are similar, because phasic vagal tone is the major factor in the genesis of HR variability. The concept is also supported by the observation that atropine resulted in a similar increase in average HR during ectopic and sinus tachycardia.

HR variability analyzed in absolute units was reduced in both types of tachycardia compared with normal sinus rhythm. Reduced overall HR variability in inappropriate sinus tachycardia has also been reported previously. The mechanism for differences in overall HR variability is difficult to interpret, however, because traditional HR variability analysis methods may fail to reveal specific autonomic abnormalities in cases with markedly elevated HR. Several factors that increase HR itself, regardless of the cause of increase, reduce the overall HR variability. Therefore, the pattern
of reduced overall R-R–interval variability in patients with inappropriate sinus tachycardia or ectopic tachycardia may result not only from a reduced vagal input but also from enhanced intrinsic automaticity of pacemaker cells or an elevated sympathetic input. The traditional methods of analyzing HR variability in absolute units may not be able to document the specific autonomic disturbance as a mechanism of arrhythmias in these cases. Notably, the LF/HF ratio and the LF and HF components analyzed in normalized units did not differ from normal either in ectopic or sinus tachycardia, which suggests that there are no marked abnormalities in the phasic influences of the autonomic nervous system on either ectopic foci or sinoatrial cells causing inappropriate sinus tachycardia. Recent studies in which direct muscle sympathetic nerve activity has been used as a reference index have suggested that the LF and HF spectral components analyzed in normalized units may provide information on sympathetic and vagal outflow, respectively, in subjects without structural heart disease.23 The increase in HR was within the normal limits after atropine in the majority of patients with sinus and ectopic tachycardias, which also suggests that abnormal vagal function may not be the predominant autonomic disturbance of these tachycardias.24

**Abnormalities in Short-Term Correlation Properties of R-R–Interval Dynamics**

A potential advantage of the new methods of analyzing R-R–interval variability based on complexity and fractal analysis is that they can provide information on the autonomic regulation of pacemaker tissue independent of the rate of pacemaker firing.8–13 The fractal and complexity measures are not related to moment statistics (means and variance), and they are able to reveal subtle abnormalities in dynamic behavior that are undetectable by traditional analysis techniques.8–13 Fractal-like correlation properties in R-R–interval dynamics, ie, values of $\sim 1.0$ of all scaling exponents, were observed in the present study during both normal sinus rhythm and sinus tachycardia. Similar fractal-like behavior in R-R–interval dynamics over different time scales has also been described in previous studies of subjects with normal sinus rhythm.7,10–12

An increase in the randomness of short-term HR behavior, expressed as a reduction in the short-term scaling exponent, was a typical feature of the ectopic tachycardias and resulted either from abrupt prolongations in the R-R intervals or from continuous instability in the beat-to-beat behavior of R-R intervals. An ECG analysis of Holter recordings revealed that the prolongations in R-R intervals resulted from abrupt exit blocks from the ectopic foci. Anecdotal cases of exit blocks from ectopic atrial foci have also been reported previously in short-term ECG recordings.25

Two potential mechanisms may explain the unstable or random R-R–interval behavior of ectopic tachycardias. First, it is possible that the exit blocks from the ectopic foci result from a specific electrophysiological abnormality similar to that observed in the diseased sinus node. Second, there may be a specific autonomic mechanism behind this abnormality. Accentuated sympathovagal interaction caused by high sympathetic outflow together with a concomitant increase in phasic vagal outflow may result in uncorrelated short-term HR behavior. Experiments in healthy volunteers have shown that incremental doses of norepinephrine infusion with baroreflex-mediated vagal activation result in similar abrupt prolongations of sinus intervals as observed in the present

![Figure 4](https://example.com/figure4.png)

Figure 4. ECG printouts of Holter recordings of 2 patients with ectopic atrial tachycardia (EAT). In upper recording (#1), unstable R-R–interval dynamics were observed during tachycardia without change in p-wave morphology or PQ duration. In lower recording (#2), Mobitz type II exit blocks from ectopic foci were observed during tachycardia. Unstable R-R–interval dynamics and exit blocks occurred more frequently during sleep than in daytime in both of these patients.
study in patients with ectopic tachycardia. A reduced short-term scaling exponent and random beat-to-beat HR dynamics have also been observed in patients with heart failure with high levels of norepinephrine. A complex interaction between norepinephrine and acetylcholine at the presynaptic and postsynaptic levels of the target tissue has been described, which may facilitate the random firing of both normal and abnormal pacemakers. Unstable R–R–interval dynamics were most commonly observed in the present study during the sleeping hours, when vagal activity is high, which also supports the view that altered beat-to-beat dynamics in ectopic tachycardias result from increased phasic vagal outflow together with enhanced responsiveness to sympathetic influences of the ectopic foci.

Implications
Analysis of the fractal characteristics of cardiac interbeat dynamics revealed abnormal dynamic behavior that was not uncovered by the traditional analysis methods of HR variability, which confirms that the new analysis methods based on fractals and nonlinear dynamics add significantly to the ability, which confirms that the new analysis methods based on fractals and nonlinear dynamics add significantly to the diagnostic performance of the conventional methods used to assess abnormal HR behavior. Long-term ECG recordings may also help to differentiate between inappropriate sinus tachycardia and ectopic atrial tachycardia in cases in which the 12-lead ECG does not yield a definitive diagnosis.

Acknowledgments
This research was supported by grants from the Academy of Science, Finland; the Finnish Foundation for Cardiovascular Research; and a contract with the Finnish Life and Pension Insurance Companies, Helsinki, Finland.

References