Diurnal variations of the dominant cycle length of chronic atrial fibrillation

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1Department of Cardiology, Lund University Hospital, Lund, Sweden; 2Department of Cardiological Sciences, St. George’s Hospital Medical School, London, United Kingdom; and 3Department of Medicine, Kuopio University Hospital, Kuopio, Finland

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Meurling, Carl J., Johan E. P. Waktare, Fredrik Holmqvist, Antti Hedman, A. John Camm, S. Bertil Olsson, and Marek Malik. Diurnal variations of the dominant cycle length of chronic atrial fibrillation. Am J Physiol Heart Circ Physiol 280: H401–H406, 2001.—High-resolution digital Holter recording was carried out in 21 patients (15 men, 64 ± 12 yr) with chronic atrial fibrillation. Dominating atrial cycle length (DACL) was derived by frequency domain analysis of QRST-reduced electrocardiograms. Daytime mean DACL was 150 ± 17 ms, and nighttime mean was 157 ± 22 ms (P = 0.0002). Diurnal fluctuation in DACL differed among patients: it tended to be virtually absent in those with a short mean DACL, but in those with longer DACL the night-day difference was as much as 23 ms (R = 0.72, P < 0.001, correlation of mean DACL to night-day difference). Mean DACL also correlated with ventricular cycle length (R = 0.40, P < 0.001), particularly at night (r = 0.49). The shorter cycle lengths found in this study during the day are consistent with sympathetic and/or other physiological modulation, but since increased vagal tone shortens atrial refractoriness in most models, parasympathetic influences are not likely to play a major role. Alternatively, atrial effective refractory period may not be the sole determinant of atrial cycle length during atrial fibrillation.

autonomic nervous system; circadian rhythms

VARIABILITY OF HEART RATE in humans ranges from short-term modulations at frequencies corresponding to respiration to significant low-frequency diurnal fluctuations (1, 10, 28). Fluctuations in autonomic nervous system tone acting on the sinus node are an important underlying mechanism (1), but humoral effenter systems are also active (31, 34). However, the whole organism acts as a complex biological system, with diurnal fluctuations in many other parameters such as temperature, blood pressure, metabolism, and activity levels. These may also directly or indirectly alter heart rate.

Diurnal fluctuations in atrial refractoriness have been little studied, but it is well recognized that autonomic tone has a profound effect on refractoriness in normal sinus rhythm (6, 13). In atrial fibrillation (AF), atrial refractoriness is shortened compared with sinus rhythm, but whether it exhibits diurnal variability is unknown. Heart rate during AF is determined by the atrioventricular (AV) nodal conduction (4), but a modulating effect of atrial inputs has been suggested (22, 26).

The aim of this study was to noninvasively detect the presence and to characterize the nature of diurnal variations in atrial electrophysiology during chronic AF. We sought to determine the relationship between fluctuations in AF cycle length and heart rate. The study utilized a noninvasive method, frequency analysis of fibrillatory electrocardiogram (FAF-ECG), which has been validated as a technology for the measurement of atrial cycle length during AF (11).

METHODS

Study population and data acquisition. Recruited patients had chronic (persistent or permanent) AF of >1 mo duration. Exclusion criteria were pharmacological treatment with β-blockers, antiarrhythmic drugs (Ia, Ib, Ic, III), or sympathomimetic agents, diabetes mellitus, overt heart failure, previous cerebrovascular events, or conditions that would possibly cause interference with the autonomic nervous system, such as current alcohol abuse. The study was approved by the local Ethics Committee, and all patients gave written informed consent.

The study investigated 21 outpatients (15 men, mean age 64 ± 12 yr, range 34–78 yr). The median duration of AF was 12 mo (range 1–120 mo), and subjects had undergone a mean of one previous unsuccessful cardioversion (none in 6 patients, 1 in 11 patients, 2 in 2 patients, and 3 in 2 patients). Drug therapy included digoxin in 14 patients, an angiotensin-converting enzyme inhibitor in 8, diltiazem in 3, and verapamil in 1. At echocardiography, left ventricular function was normal in 19 patients and slightly impaired in 2. The mean left atrial diameter was 47 ± 7 mm (range 36–66 mm).

Long-term ECG was recorded in each patient using a digital three-channel Holter recorder (6632 Altair-DISC recorder, SpaceLabs Burdick, East Syracuse, NY) with a

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sampling rate of 1 kHz and an amplitude resolution of 0.16 μV over a ±5-mV range for 17 h. Leads were positioned using a novel quasi-orthogonal three-lead configuration (35), which optimizes acquisition of atrial signal in bipolar recordings.

For analyses of day-night differences, night was defined as 2330–0630 and day as 0730–2130.

**Signal processing.** The Holter recordings were transferred to a personal computer for standard automated analysis, visual inspection, overreading, and manual correction using commercial software (Vision Premier, SpaceLabs Burdick). A 5-min segment was further chosen in each hour of each recording. The search for such a segment and, subsequently, in the analysis of atrial cycle length was driven by the quality of the original. The same procedure was repeated for each hour of each recording. Initially, the segment of the first 5 min of the hour was taken. If there was low signal-to-noise ratio (i.e., noise amplitude similar to fibrillatory wave amplitude), more than 2% high-amplitude noise (noise $R$-wave amplitude), or baseline wander, the segment was rejected. In such a case, the preceding and following 5-min regions were inspected to identify the closest segment of acceptable quality. If none could be found, the hour was rejected.

The selected 5-min segments were analyzed using the FAF-ECG method, which has been described in detail elsewhere (11). Briefly, QRST complexes were subtracted, and frequency domain analysis was performed on the residual ECG signal within the 3- to 12-Hz range using a fast Fourier transform. The peak frequency in the generated spectrum, expressed as a cycle length, constituted the dominant atrial cycle length (DACL). The method is illustrated in Fig. 1. For this analysis the DACL was obtained from a bipolar lead with the positive electrode at a low C1 position (6th intercostal space, right sternal border) and with the indifferent electrode in a left subclavicular position (35). This lead has a superior atrial signal resolution and corresponds approximately to the conventional unipolar V1 lead, in which the DACL has been shown to correlate closely with invasively measured right atrial free wall fibrillatory cycle length (11).

All frequency spectra were visually inspected to confirm sufficient quality allowing an accurate DACL determination. Optimum-quality spectra exhibit a single sharp spectral peak in the expected range for DACL (5–11 Hz) with minimum low-frequency components in the 3- to 5-Hz range (<50% of DACL power). Spectra were of acceptable quality in the presence of a single spectral peak with low-frequency components with power between 50 and 150% of the DACL power. Where two spectral peaks were present within the 3- to 12-Hz band, the component with the highest amplitude was automatically chosen by the FAF-ECG software, but all such cases were manually confirmed.

Heart rate was expressed as mean R-R interval, calculated by the commercial Holter software for each 5-min segment.

**Statistics.** Unless otherwise specified, values are means ± SD. Wilcoxon test was used for comparison between paired samples. Spearman ranked correlation coefficients and the U test were used elsewhere. Since there was significant variation between subjects in mean DACL, the hourly DACL values were normalized for selected analyses. This was performed by dividing the individual DACL values by the mean of all valid DACL values for the given subject. $P < 0.05$ was considered statistically significant. All statistical analyses were performed using STATISTICA for Windows (version 5.1, StatSoft, Tulsa, OK).

**RESULTS**

**Data availability.** One patient was excluded because the recording contained only 2 h that could be analyzed. The calculations were made on the basis of the remaining 20 patients.

The mean duration of analyzable recording was 15.5 h (range 12–16 h). The median starting hour was 1500 (range 0700–1700), and the finishing hour was 0600 (range 0100–2100). Of the potential 310 sequences of 5 min each, a segment suitable for analysis was found in 305 (98%) cases. The median offset from the hour to the beginning of the segments was 5 min (range 0–30 min), with the daytime median offset (7 min) being larger than the nighttime offset (2 min).
Manual correction of the DACL was needed on one analyzed segment (the automated analysis identified an outlier peak of a bimodal distribution, while the other peak corresponded to adjacent hours).

Diurnal fluctuations in AF cycle length. Mean DACL was 154 ± 20 ms but varied significantly between patients, ranging from 125 to 186 ms, and through the day (Fig. 2). The DACL exhibited significant diurnal fluctuations, with a shorter mean DACL during the day (mean 150 ± 17, range 124–179) than at night (mean 157 ± 22, range 125–195, P = 0.0002). There was significant interpatient variation in the mean DACL for the recording. The normalized DACL values are presented in Fig. 3.

There was a significant correlation between mean DACL and the standard deviation of DACL values for patients (r = 0.78, P = 0.00004), with longer DACL being associated with a greater standard deviation (i.e., the DACL variability increased with increasing DACL values). Likewise, the magnitude of the difference between daytime and nighttime mean DACL was strongly related to the mean DACL (Fig. 4). Those patients with short DACL exhibited little diurnal variation, while those with longer mean DACL exhibited night-day differences of up to 23 ms (P = 0.0004; Fig. 4).

Of the patient characteristics studied, none showed a significant relationship with the mean DACL or with the magnitude of the night-day difference (Table 1).

Relationship between fluctuations in AF cycle length and heart rate. There was a significant correlation between the mean R-R interval and DACL (r = 0.30, P < 0.000001), with long DACL corresponding to long R-R intervals. The correlation was higher during the night (r = 0.44, P = 0.000001) than during the day (r = 0.27, P = 0.001; Fig. 5).

DISCUSSION

This study has shown that 1) the AF cycle length during chronic AF exhibits diurnal variability, with longer cycle lengths (i.e., slower AF revolution) occurring at night; 2) there is a correlation between the AF cycle length and ventricular cycle length, particularly at night; and 3) there are marked interpatient differences in the diurnal variability of the AF cycle length, with higher variability in patients with a longer mean AF cycle length.

Diurnal rhythms and changes in AF cycle length. The diurnal pattern of variation of atrial cycle length found in this study is in keeping with circadian changes in atrial refractoriness during sinus rhythm (6) and atrial pacing (6, 13). Previous work has shown that atrial cycle length closely correlates with atrial refractory period during AF (15, 17, 36), and the former may therefore be used as an index of the latter. However, this has been tested in laboratory conditions and has not been validated under varying autonomic influences or other diurnal physiological variations.
A circadian rhythm is seen in a range of physiological variables, including arterial (24) and pulmonary (19) blood pressure, body temperature, blood pH, hormone levels (25, 31, 34), and autonomic tone (10, 12). Furthermore, there are diurnal differences in levels of physical exertion, respiratory rate, and body posture. A number of these factors are likely to be interrelated and may contribute to diurnal changes in atrial electrophysiology. However, a physiologically plausible direct effector mechanism exists probably for only four modulators, i.e., autonomic modulations, including those due to postural changes, core body temperature, atrial stretch, and hormonal changes.

Temperature-induced changes in cardiac refractory period are demonstrable (32) but are mainly seen with major body temperature alterations, rather than with small physiological fluctuations. The effect of atrial stretch on atrial effective refractory period has been studied by AV synchronous pacing (3, 16), which has additional hemodynamic effects. Klein et al. (16) found a strong correlation between changes in atrial effective refractory period and both right atrial pressure and left atrial diameter. In contrast, Calkins et al. (3) found no such effect with or without prior autonomic blockade. Data from isolated cell preparations suggest that significant changes in cardiac refractory period occur only at supraphysiological levels of stretch (27). The levels of circulating catecholamines may affect atrial electrophysiology. However, catecholamine levels are intrinsically linked to other parts of the autonomic nervous system, and no data are available on electrophysiological effects of other diurnally varying hormones. Hence, it seems plausible to propose that the observed diurnal changes in atrial cycle length are largely mediated by autonomic tone fluctuations.

Increased sympathetic and vagal tone decreases the atrial refractory period (20, 30, 38), but the effect of electrophysiological properties on fibrillating human atrial tissue is less clear. Some recent data suggest that the chronic fibrillating atrium is more under sympathetic than vagal control (26, 33), but other studies have shown that adrenergic compounds do not affect the chronically fibrillating atrium (32). Unless increased vagal tone has the opposite effect during AF to that observed in normal conditions, the present study supports the hypothesis that either the sympathetic tone is the dominant determinant of changes in atrial cycle length during AF or dominant AF cycle frequency is less closely determined by atrial effective refractory period than is presently presumed. Preserved vagal tone is known to offer an antiarrhythmic defense in the ventricle. Hence, it might exhibit similar effects in the fibrillating atria, e.g., by slowing and/or partially blocking excitation propagation. In such a scenario, an excitable gap of a larger-than-negligible size may exist within fibrillating atrium under dominant vagal influence.

In the present study, the variation in refractoriness appeared to show a single diurnal peak, but more complex patterns of circadian fluctuations in atrial electrophysiology have been suggested to occur. Yamashita et al. (37) found that the probability of paroxysmal AF onset, maintenance, and termination had diurnal distributions that varied from a single peak to

Table 1. Influence of recorded variables on mean DACL and night-day differences in DACL

<table>
<thead>
<tr>
<th>Feature present</th>
<th>Feature absent</th>
<th>DACL, ms</th>
<th>N-D difference</th>
<th>Mean DACL</th>
<th>N-D difference</th>
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<tbody>
<tr>
<td>Digoxin treatment</td>
<td>152</td>
<td>8</td>
<td>156</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>ACE inhibitor treatment</td>
<td>159</td>
<td>8</td>
<td>147</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Normal LV function</td>
<td>181</td>
<td>6</td>
<td>153</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>AF duration &gt; mean</td>
<td>155</td>
<td>7</td>
<td>154</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Age &gt; mean</td>
<td>149</td>
<td>7</td>
<td>170</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>LA diameter &gt; mean</td>
<td>155</td>
<td>6</td>
<td>155</td>
<td>8</td>
<td></td>
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</tbody>
</table>

DACL, dominant atrial cycle length; ACE, angiotensin-converting enzyme; LV, left ventricular; AF, atrial fibrillation; LA, left atrial; N-D, night-day. All differences are nonsignificant (P > 0.05, U test for discrete state variables, Spearman R ranked correlation coefficient for other variables).

![Fig. 5. Relationship between ventricular rate (x-axis) and DACL (y-axis) at night (A) and during the day (B). Relationship is stronger at night, with a steeper slope of the regression line.](image-url)
trimodal patterns. Their study included many more subjects than the present one (212 vs. 21 patients), and the more complex diurnal patterns were demonstrable only in the younger subset of their patients.

**Interpatient differences in variability of AF cycle length.** The variability of AF cycle length was less expressed in subjects with shorter mean DACL, suggesting that patients with short atrial refractoriness are less receptive to presumed autonomic modulation. High-frequency atrial depolarization leads to a progressive shortening of the refractory period, a phenomenon named electrical remodeling (9, 36). There was no trend for arrhythmia duration to be longer in those with a short AF cycle length in the present study, possibly because maximum remodeling occurs within 1 or 2 mo (8, 36). There was a trend for older subjects to have longer AF cycle length. This is consistent with previous studies showing that atrial refractory period increases with age in sinus rhythm (23).

None of the examined clinical parameters predicted mean DACL or night-day differences. However, the present study was not of sufficient size to fully explore the influence of multiple cofactors influencing AF electrophysiology. There was a relationship between mean DACL and night-day difference (Fig. 4) and a possible clustering of the subjects’ results with respect to these parameters. In Fig. 2, there might be a suggestion of subpopulations, rather than a smooth random distribution of mean DACL and night-day difference in DACL. Presently and without further confirmation, it is difficult to speculate whether this reflects distinct electrophysiological mechanisms for the maintenance of AF in different patient groups, e.g., focally mediated AF (14), AF related to delayed interatrial conduction (7), and inherited AF (2). Although “focal AF” is mainly described in paroxysmal AF (14), there are data suggesting that it also mediates persistent AF in some patients (18). Alternatively, some patients may have a genetically determined ability to develop a higher and more severe degree of electrical remodeling.

**Relationship of AF and ventricular cycle length.** This study found a strong correlation between fluctuations in AF cycle length and ventricular rate. This may reflect a similar response of both fibrillating atria and the AV node to diurnal fluctuations of autonomic nervous system tone and other physiological variables or a direct effect of changes in atrial cycle length on ventricular rate. Other observations suggest an inverse relationship between atrial and ventricular cycle lengths during AF (5, 22), and thus it is the net effect of diurnal variations in physiological parameters that results in a direct, rather than an inverse, relationship.

Under normal conditions (39) and during AF (21, 26, 29), sympathetic discharge reduces AV nodal refractory period while increased vagal tone increases it. The role of atrial inputs in the ventricular rhythm during AF are complex and incompletely understood. Since depolarizations of the atrial input to the AV node occur at intervals of ≈200 ms, yet there is marked beat-to-beat variation in the ventricular cycle length during AF, factors other than AV nodal effective refractory period are involved. It is believed that concealed conduction of the AF impulses into the AV node and electrotonic modulation of AV nodal propagation participate in the determination of ventricular rate (22). The present study found that the net result is a direct relationship between atrial and ventricular cycle length in physiological conditions.

**Limitations of the study.** The study used 17-h, rather than 24-h, Holter recordings, a limitation imposed by the technology available. Although no statistical differences between different daytime and different nighttime hours could be found (data not shown), we cannot exclude an effect of the underrepresentation of certain daytime segments. Because of the variable quality of ambulatory recordings, we were unable to select segments precisely on the hour in a large proportion of segments. Segments during any activity beyond mild exertion are likely to have been unsuitable for analysis, leading to an underestimation of true diurnal changes. The study also required some operator selection, and despite the subjective criteria applied, this may have introduced bias.

The FAF-ECG method was validated in controlled laboratory settings on supine subjects, and thus a confounding effect of posture, activity, or other variables is possible. However, the quality of spectra (amount of low-frequency signal, sharpness of peaks) in this study was comparable to that in previous studies. Moreover, there are no signal modulations likely to be encountered during ambulatory recordings that fall within the examined frequency range. It is therefore unlikely that the findings were due to confounding factors, rather than to alterations in AF cycle length.

The precise intracardiac site corresponding to the DACL from the lead used in this study has not been tested but is likely to be the right atrial free wall. Assessment of other parts of the atria was therefore not performed. Finally, the DACL can only be used as an assessment of atrial refractoriness as long as there are no significant changes in atrial conduction velocity.

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