Circadian Modulation of Atrial Cycle Length in Human Chronic Permanent Atrial Fibrillation: A *Non-Invasive Assessment Using Long-Term Surface ECG*

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Objectives: Short-term autonomic influences on the electrophysiological properties (EP) of the atrial myocardium are well known, but the role of long-term sympathovagal influences on EP is less clear. This study aimed at finding if a circadian pattern could be identified in atrial EP, using the fibrillatory wave (F wave) of surface ECG recordings as a surrogate of atrial refractoriness in patients with chronic permanent atrial fibrillation (AFib).

Methods: 24-hour two-channel Holter ECG were obtained in 20 consecutive patients (mean age 70 ± 8 years) with nonvalvular, chronic and permanent AFib, free of antiarrhythmic agents except digoxin. Digitized ECG were analyzed by a custom software. After QRST substraction of detected complexes, the residual F waves (5-min duration) were computed by a Fourier algorithm. The dominant frequency peak of the power spectrum obtained has been shown to correspond to the dominant atrial cycle length (DACL). 24-hour recordings were analyzed separately during the day (8 active and awake consecutive hours) and at night (4 resting and asleep consecutive hours), and DACL was calculated hourly for each diurnal and nocturnal periods.

Results: Spectra could be reliably studied in 17 patients (85%). The DACL showed a significant circadian pattern with a mean 3.3% increase, from 151 ms in the diurnal period to 156 ms at night ($P < 0.001$). A significant positive relation was found between circadian day-night changes of DACL and the baseline DACL value ($P < 0.05$). Mean ventricular heart rate decreased from 87 beats/min during the diurnal period to 71 beats/min at night ($P < 0.001$).

Conclusion: Spectral analysis of the F wave can be successfully achieved from long-term Holter recordings. In chronic permanent AFib, the DACL still shows a circadian rhythmicity with an increase from day to night. In addition to atrial refractoriness, the amplitude of DACL circadian modulation could represent a new index of atrial electrical remodeling. A.N.E. 2000;5(3):000–000

atrial fibrillation; electrocardiology, Holter ECG; autonomic nervous system; circadian rhythm

Atrial electrical activity including sinus, ectopic, and fibrillatory waves can be assessed from the surface ECG by applying QRS waveform cancellation.[1–3] The early clinical applications of this method were automatic detection of atrial fibrillation (Afib) or of second-degree AV block episodes, recognition of atrioventricular dissociation, mainly from short-term 12-lead resting ECG. More recently, that technique of ventricular activity cancellation was applied to noninvasive analysis of the electrophysiological (EP) properties of the atria, which was available only through invasive ECG recordings. Previous reports have shown that the frequency content of the residual fibrillatory waveform accurately reflects the mean intracardiac atrial cycle length.[4–8]

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The modulation of the EP properties of the atrial myocardium by the autonomic nervous system has been extensively studied.[9-11] In particular, it is well known that both vagal stimulation and acetylcholine application result in sustained Afib by shortening the atrial refractory period. Using surface ECG recordings and QRS substraction, Ingemansson and co-authors found that the frequency spectrum of the fibrillatory wave is influenced by the short-term autonomic variations of a tilt test, with a decrease in the atrial cycle length.[12]

In a 24-hour time frame, many biological phenomena show long-term fluctuations with peaks and troughs of several variables. Such long-term patterns have been reported for Afib onsets and duration.[13,14] Regarding the raw EP properties of the human heart, the existence of circadian variations have been rarely explored, with the exception of heart rate and heart rate variability.[15,16] Using repeated hourly programmed electrical stimulation in patients with implanted pacemakers, Kong et al. found a significant daily rhythmic variation of ventricular refractoriness.[17] By sequential bedside EP testing, Cinca et al. showed that conventional EP parameters, in particular atrial refractory period (RP), have long-term modulation.[18]

This study aimed at finding whether a circadian pattern could be noninvasively identified for atrial EP properties from spectral analysis of the fibrillatory wave calculated on 24-hour surface ECG recordings in a selected group of patients with chronic permanent atrial fibrillation.

MATERIAL AND METHODS

Study Population

Patients with chronic atrial fibrillation were enrolled in the study if they met the following criteria: (1) documented chronic Afib for > 1 month, without occasional pattern of atrial flutter or atrial tachycardia on surface ECG (2) age between 18 and 80 years, and (3) absence of any drug with known EP or autonomic influences, in particular betablockers, but digoxin administration was allowed to lower the mean heart rate. All patients who had these three criteria were consecutively and prospectively enrolled, and no other clinical criteria were used to exclude patients.

During the period between January and May 1999, 20 patients meeting the inclusion criteria were diagnosed in our institution. There were 4 females and 16 males. The mean age was 70 ± 8 years (range: 52–79 years). In this population, chronic permanent Afib lasted for more than 5 months as a minimum.

Lone atrial fibrillation was present in 13 patients. In the 7 other patients, underlying pathologic findings were: hypertension (n = 5), stable coronary artery disease (n = 2), and mild mitral regurgitation (n = 1). Only one male patient had a left ventricular dysfunction (ejection fraction < 35%). Eleven of 20 patients were under digoxin at the time of Holter recording.

24-hour ECG Monitoring

ECG was continuously monitored for 24 hours using two-channel Holter recorders. Patients were advised to keep their normal sleep-wake schedule.

Holter ECG was always performed with the routine bipolar lead configuration used in the laboratory. Lead 1 was recorded between manubrium (−) and the fifth rib (+) on the left anterior axillary line (CM5) and lead 2 was recorded between the right (−) and the left (+) fifth ribs (CC5).

The ECG data were digitized at 200 samples per second and QRS labeling and editing were performed on a standard ELATEC system (ELA Medical, Le Plessis Robinson, France). Beat detection and morphological classification were carefully reviewed for all patients. In this study, we used the hourly ventricular heart rates (R-R series) provided by the ELATEC system.

Recordings with at least > 18 hours of good quality data and with atrial fibrillation as the basic rhythm were considered.

Analysis of Atrial Activity

The Holter analysis protocol is outlined in Figures 1 and 2. The digital ECG data were transferred from the ELATEC system to a personal computer for Afib analysis, using the FAF-ECG software (Frequency analysis of Fibrillatory ECG) developped at the Lund University Hospital (Lund, Sweden) and previously described in detail.[5] F1-F2

ECG segments manually selected for analysis were resampled at 1,000 Hz with a resolution of 12 bits. The QRST complexes were substracted from the original signal and the resulting baseline fibrillatory signal was used for frequency analysis (Fourier transformation). The frequency spectrum was displayed in the 3- to 12-Hz range (corresponding to the human atrial cycle length).

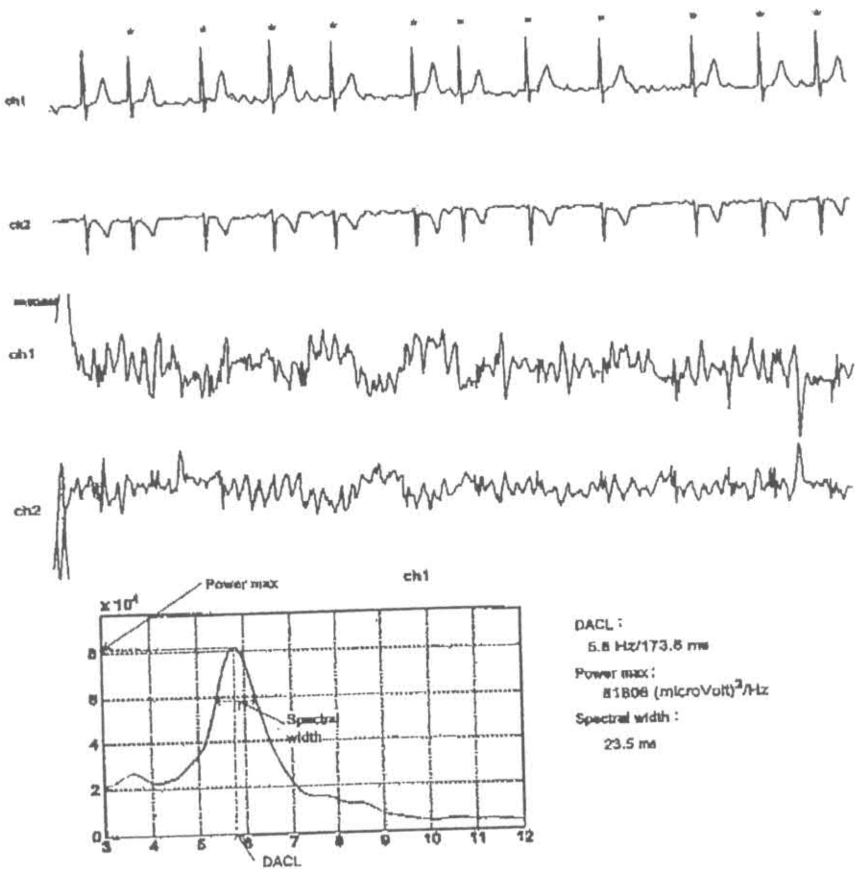

Figure 1. ECG processing. **Upper panel:** ECG tracings from two-channel Holter ECG recordings. Asterisks indicate QRS complex detection. **Mid-panel:** residual atrial electrical signal after QRST cancellation (same segment as in upper panel). **Lower panel:** frequency spectrum of the fibrillatory wave in channel 1 (range: 3–12 Hertz). Three parameters are extracted from the spectrum: the frequency of the dominant peak (DACL), the spectral amplitude of the dominant peak (Power max), and the spectral width defined as the difference in cycle lengths at the 75% level of amplitude interceptions. ch1 = channel one; ch2 = channel two; DACL = dominant atrial cycle length.

The frequency parameters obtained from the frequency spectrum are shown in Figure 1: the dominant frequency component converted in milliseconds (1/Hz) and named dominant atrial cycle length (DACL), and the width of the spectral component defined as the difference in cycle lengths at the 75% level of amplitude interceptions.

The protocol for selection of ECG segments is outlined in Figure 2. The first 5-minute ECG segment of each hour was analyzed with the FAF software and the distribution of the resulting spectrum was examined. If the distribution was monomodal (a single frequency component present in the 3- to 12-Hz interval) the corresponding ECG segment was retained and the next hour was processed. In case of multimodal distribution (> 2 components) the ECG segment was rejected and the neighboring 5-minute ECG periods (forward and backward, without time overlap) were analyzed. In addition, the FAF method was applied on both ECG Holter leads, and the lead with the largest amplitude of the fibrillatory activity was selected, provided the same lead was always used for the 24-hour processing.

Circadian Variation of Atrial Electrical Activity

The mean ventricular heart rate decreased from 87 beats/min during the diurnal period to 71 beats/min at night ($P < 0.001$).

In 15 (88%) of the 17 patients, the FAF method applied to Holter lead 1 (CM5) provided the most reliable (monomodal) spectra. In the other two patients bipolar lead 2 (CC5) was selected because repeated multimodal spectra were obtained in lead 1.

The DACL median values were 151 and 156 ms during the day and at night, respectively. It showed a significant circadian pattern with a mean 3.3% increase, (from 151 ms to 156 ms, $P < 0.001$). F3 Figure 3 shows a representative example of the frequency spectrum variation between day and T1 night. Table 1 outlines that this circadian variation was consistently found in each patient (with only 1 exception for patient 16). The range of circadian modulation in our population was 0–21 ms. Exclusion of patient 15 with the largest day-night variation did not affect our results. F4 Figure 4 is a graphical display of the hourly DACL variations in a representative patient (patient 7).

Within each circadian period, the hourly DACL variability was larger during the day than at night (12.5 ms vs 7.5 ms, respectively, $P < 0.001$).

There was no correlation between day-night changes in ventricular heart rates and day-night changes in median DACL.

When the circadian changes in atrial activity were plotted against the diurnal or the nocturnal DACL (Fig. 5), a significant positive relation was found ($r = 0.6$, $P = 0.01$ and $r = 0.6$, $P = 0.02$, versus the diurnal and the nocturnal DACL, respectively) indicating that the DACL day-night changes were limited when the baseline DACL value was small. F5

The mean spectral width was 28 ± 8 ms (range: 16–37 ms) during the day and 29 ± 11 ms (range 17–55 ms) at night. This frequency parameter did not show any variation between the two circadian periods.

No significant correlation was found between

Table 1. Circadian Variation of Atrial Cycle Length

Patient	Day (ms)	Night (ms)	CI (ms)
1	143	145	2
2	164	175	11
3	150	153	2
4	164	167	3
5	143	145	2
6	157	164	6
7	159	163	4
8	143	146	3
9	144	148	4
10	152	156	5
11	152	156	5
12	126	129	3
13	130	133	3
14	165	171	6
15	156	177	21
16	154	154	0
17	171	175	4
Mean	151 ± 12	156 ± 14	5

CI = circadian index.

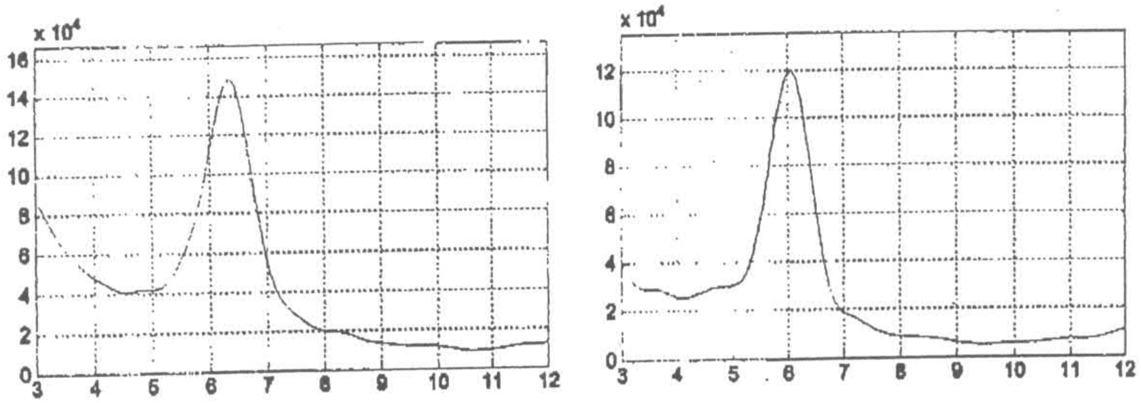

Figure 3. Representative example of DACL circadian changes. **Left:** frequency spectrum of the fibrillatory wave during one hour of the nocturnal period. The DACL is 6 Hz/159 ms. **Right:** the DACL during the day is 6.3 Hz/167 ms.

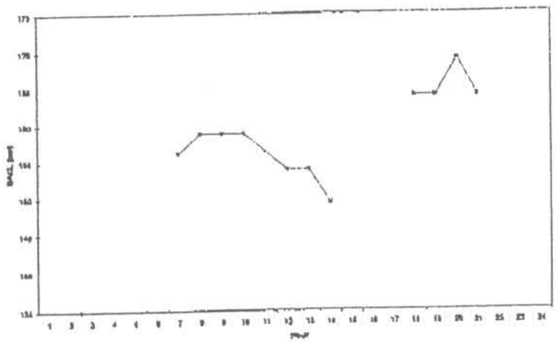

Figure 4. Representative example of DACL circadian rhythmicity. The hourly DACL values are plotted on the vertical axis. This figure shows the DACL increase at night and the larger DACL variability during the diurnal period (patient 7). DACL = dominant atrial cycle length.

atrial activity and patient age. The day-night DACL changes were similar between patients with lone Afib and those with underlying heart disease and between patients with and without digoxin.

DISCUSSION

The present study demonstrates that spectral analysis of the fibrillatory wave can be successfully achieved from 24-hour Holter ECG recordings. This study shows that in a selected group of patients with chronic permanent Afib, and therefore with electrically remodeled atrial cells, the dominant atrial cycle length, although shortened, still follows a moderate but significant circadian rhythmicity, with a 3.3% increase from day to night. This long-term autonomic modulation should be taken into account when assessing fibrillatory activity.

Atrial Electrical Activity in Afib, and the Impact of Remodeling

Our aim was to test the performance of the FAF-ECG method when applied to ambulatory ECG recordings, using a specific model regarding electrophysiological properties of the atrial myocardium. First, in our study population the electrocardiographic presentation was always a complete disorganization of the atrial activity, and the absence of any regular ECG patterns such as atrial flutter or atrial tachycardia was a prerequisite for inclusion. In addition, since Afib lasted for more than 5 months, it is likely that the atrial EP had undergone the remodeling process, according to the concept introduced by Allessie and co-workers from experimental studies in goats.[19] The short DACL values reported here (150 ms) strongly support the existence of an electrical remodeling in our population. Previous invasive studies in humans have also reported a shortening and a loss of the physiologic rate-dependent adaptation of the atrial refractory period facilitating the perpetuation of the arrhythmia in patients with recurrent paroxysmal Afib.[20,21] Therefore, our hypothesis on the existence of a long-term DACL circadian pattern was tested on a specific stable electrical substrate in which, provided that autonomic modulation was still present, it could be less than obvious. As it was found to be present, although moderate but significant, the autonomic modulation validates the sensitivity of this noninvasive approach.

It may be a way to evaluate the stage of remodeling, as well as the DACL. An interesting finding from this study is that the electrophysiological reaction of the atria to autonomic circadian influences is strongly dependent on the baseline atrial cycle length. Figure 5 shows that the patients with the shortest atrial cycle lengths (i.e., 130–140 ms) had a minor long-term circadian modulation (CI: 2–4 ms). Whether the loss of electrical day-night changes is another surrogate of atrial remodeling cannot be ruled out from our data, but undoubtedly requires further investigation, with prospective follow-up of patients referred for persistent atrial fibrillation.

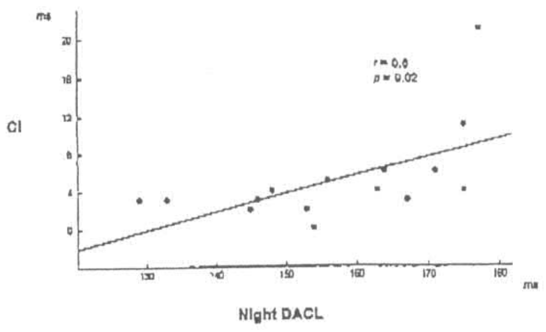

Figure 5. Scatterplot of the relation between DACL day-night changes (CI, vertical axis) and the baseline DACL value at night (horizontal axis). DACL = dominant atrial cycle length; CI = circadian index.

DACL, Local Atrial Fibrillation Interval, and Refractory Period

Previous studies have shown that the dominant atrial cycle length calculated from the body surface ECG is strongly correlated to endocavitary recordings. In particular, there is growing evidence that the DACL is correlated with the median Afib cycle length.[5,7] In vitro experiments in the isolated atrium have shown a correlation between effective refractory periods and atrial fibrillation intervals, the correlation being better with the minimum Afib interval.[22] Kim and co-authors suggested that the measurement of the Afib interval could be used to evaluate the atrial refractory period behavior. Capucci et al. compared the fibrillatory intervals and atrial refractoriness in patients with lone paroxysmal Afib.[23] He confirmed in humans the strict correlation between these two electrophysiological variables. Of note, Bollmann in his study in 10 patients directly measured the atrial refractory periods, and he found a direct correlation with the peak frequency of the surface ECG fibrillatory activity.[7]

Therefore, we can reasonably suggest that the DACL calculated from the surface ECG accurately reflects the atrial fibrillation intervals and is a reliable surrogate of the atrial refractory periods.

Autonomic Modulation of DACL

Our study shows that there is a mean 5 ms prolongation of the DACL at night (i.e., a 5 ms prolongation of the atrial refractoriness). The magnitude of this prolongation may seem relatively small, although comparable with the only published data (to the best of our knowledge) on the long-term circadian variations of cardiac electrophysiological parameters. Cinca and co-authors assessed the atrial refractoriness by repeated bedside EP testing during a 24-hour period, and they found a significant prolongation of the refractory period between 2:00 AM and 9:00 AM. In this study, the atrial refractoriness was normal at baseline (233 ms in a population without documented atrial arrhythmias) and the long-term variations reached a percentage of only 5.5%.[18] Our findings obtained from shorter DACL (150 ms) are concordant with the report from Cinca, but a noninvasive approach is obviously preferable to determine 24-hour variations in electrical properties, being suitable in larger populations.

The day-night DACL changes observed in our population have to be considered with respect to electrical and structural atrial changes associated with chronic Afib. Structural changes were identified long before EP abnormalities were discovered, and it is known that Afib is also associated with atrial dilatation, fibrosis, and loss of normal atrial architecture.[24-26] In fact, these structural changes may be the origin of the heterogeneous EP properties. The combination of EP and structural abnormalities may lead to an impaired response of the atria to autonomic stimulation.

More recently, Bollmann also using Holter ECG, calculated the frequency content of the fibrillatory baseline, in a group of six subjects with persistent Afib. The temporal variations of the peak frequency were only determined every 4 hours, using 1-minute ECG segments.[8] In this study, the long-term variations did not reach statistical significance, and Bollmann concluded that the peak frequency was constant over 24 hours. However, our methodology using 5-minute ECG segments extracted on an hourly basis might be better adapted to demonstrate circadian variations in the DACL. In addition, we evaluated 17 patients with chronic Afib lasting at least for 1 month, whereas Bollmann recruited patients with persistent Afib, defined as Afib throughout the entire recording.

Autonomic nervous control of the cardiovascular system shows a circadian rhythm,[27] and there is general agreement that at night parasympathetic activity predominates over a reduced sympathetic activity. Autonomic modulation of the cardiac EP properties has been extensively studied: vagal stimulation alone shortens the atrial refractory periods, and adrenergic stimulation alone decreases this parameter or has little effect on it.[9,11,28,29] Our findings that the atrial refractoriness increases at night is at first glance discordant with the direct effects of an isolated vagal stimulation. However, Ingemansson reported that the sympathetic stimulation induced by upright tilting globally shortens the DACL, despite a concomittant parasympathetic withdrawal with potential opposite EP effects.[12] The study of Ingemansson indicates that the effects of an autonomic limb variation can be dominant over the variation of the other limb. Using the same logic, one can therefore hypothetize that the sympathetic withdrawal at night could be dominant over the parasympathetic increase. Finally, it is well known that multiple interactions exist between the two limbs of the autonomic nervous system. In particular, the importance of the temporal factor of activation has been repeatedly demonstrated, and this phenomenon could modulate direct autonomic effects.[30]

Study Limitations

Our results were obtained in a group of patients with a mean age of 70 ± 8 years, ranging from 52 to 79 years. The progressive attenuation of neural autonomic influences on the cardiovascular system with aging is well known, and the relatively small amplitude of the circadian atrial variations might be related to this characteristic of our population. However, we did not find a relation between the CI and patient age.

In the majority of our patients, the atrial fibrillation was lone. Our findings cannot be extrapolated to other types of chronic Afib, in particular to patients with underlying valvular heart disease and impaired left ventricular function.

In this study, we used a routine hook-up electrode configuration from two-channel Holter recordings (CM5 and CC5). We cannot exclude that ECG presentation would have been different on other ECG leads (i.e., possible local organization of the atrial arrhythmia), and we cannot conclude whether one of the two atria is mostly responsible for our results.

CONCLUSION

Our study conducted in a selected population shows that a noninvasive approach to atrial electrophysiology is feasible. The existence of a long-term modulation of atrial refractoriness in chronic permanent Afib should be taken into account when studying drug regimen or Afib onset-offset during night and day. In addition to atrial refractoriness itself, the amplitude of DACL circadian modulation could represent a new index of atrial electrical remodeling.

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