Circadian Behavior of P-Wave Duration, P-Wave Area, and PR Interval in Healthy Subjects

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Background: The prolongation of P-wave duration has long been shown to indicate the presence of high risk for atrial fibrillation. The circadian variation of P-wave characteristics and their dynamic adaptation to heart rate changes was not tested before.

Methods: To evaluate the diurnal pattern of P-wave duration, P area, and PR interval and of their linearly fitted relation with RR interval, 50 healthy volunteers (25 men, mean age 34 ± 10 years) underwent 24-hour ambulatory electrocardiographic (ECG) recording with digital 12-lead Holter recorders. The median P-wave duration, P area, and PR interval were calculated from the average 12-lead ECG constructed from each 10-second ECG recording. Single harmonic regression analysis was performed to reveal the presence of circadian variation in the aforementioned ECG parameters.

Results: The P area ($P < 0.0001$, $R^2 = 0.78$), the PR interval ($P < 0.0001$, $R^2 = 0.92$), the P area / RR slope ($P < 0.0001$, $R^2 = 0.55$), and the PR/RR slope ($P < 0.0001$, $R^2 = 0.42$) showed a highly significant circadian variation while the periodic nature of P-wave duration ($P = 0.016$, $R^2 = 0.32$) and of the P duration / RR slope ($P = 0.011$, $R^2 = 0.18$) was only indicated by harmonic regression analysis.

Conclusions: P-wave duration, P area, and PR interval show a significant circadian variation in healthy subjects. The relations between P area/RR,PR/ RR, and P duration/RR also demonstrate a significant diurnal pattern. **A.N.E. 2001;6(2):92–97**

P-wave duration; P area; PR; circadian variation

Abnormalities in atrial conduction and refractoriness are associated with the occurrence of atrial fibrillation (AF).[1] The prolongation of the P-wave duration is an established indicator of an interatrial conduction disturbance,[2] and prolonged P-wave duration is commonly used to predict paroxysmal AF.[3-7] Multiple physiological factors may influence P-wave duration and morphology, e.g., the changes in left atrial volume,[8,9] left atrial pressure,[10] autonomic tone,[11] or atrial conduction characteristics.[2] Many of these factors, and particularly autonomic tone, display significant variability over 24 hours, resulting in a significant diurnal variation of P-wave characteristics.[12] The relation of P-wave duration and RR interval may reflect the adaptation of atrial conduction to the changes in cycle length and be of prognostic importance in patients with atrial arrhythmias. Previous data on the diurnal variation of P-wave characteristics are of limited nature,[12] due to the lack of the appropriate recording technology. Recent progress in Holter technology allows comprehensive analysis of P-wave dynamics based on densely sampled 12-lead ECG recordings.

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Using advanced Holter technology, this study investigated the diurnal patterns of P-wave duration, P area, and PR interval and of their relation with the underlying RR interval in a population of healthy volunteers.

METHODS

The study population consisted of 50 healthy volunteers (25 men, mean age 34 ± 10, range 19–59 years) without a history of cardiovascular disease. All participants had normal physical examination and a normal 12-lead resting electrocardiogram (ECG). None of them received any cardiotropic drugs. The study was approved by the local Ethics Committee and all participants gave an informed consent.

Ambulatory ECG Recording

Each study participant underwent ambulatory 24-hour ECG recording using digital 12-lead ECG Holter recorders SEER MC (Marquette Medical Systems, Milwaukee, WI), with the modified 12-lead and 10-electrode Mason-Likar system.[13] The recorders were programmed to obtain a 10-second 12-lead ECG every 2 minutes. The sampling rate of the recordings was 250 Hz with 12-bit A/D conversion.

Data Analysis

From each 10-second ECG sample, a representative "median beat" was constructed for each of the 12 standard ECG leads using a commercial interpretive algorithm (12SL, Marquette Medical Systems, Milwaukee, WI).[14] Data analysis of the ECG patterns was based on these median P-QRS-T complexes. From each median complex, the P-wave duration, the P-wave area, and the PR interval were calculated in each of the 12 leads using the ECG Research Workstation Software Package Version 1.0 (Marquette Medical Systems, Milwaukee, WI). The onset and offset points of the component waves—P and QRS—were delineated using previously described recognition algorithms.[15,16] The median values of P-wave duration (P duration), P-wave area (P area), and PR interval were calculated from the results obtained in the individual leads.

The mean 24-hour, nighttime (00.00 to 06.00 h), and daytime (10.00 to 16.00 h) values of P duration, P area, and PR interval were calculated for each subject. Nighttime and daytime periods were chosen according to previously published papers on the circadian variation of ECG intervals.[17]

The relations of P duration, P area, and PR interval with the underlying RR interval were determined by linear regressions. These were calculated for the entire 24-hour recording period, for the nighttime (00.00 to 06.00 h), and the daytime (10.00 to 16.00 h).

To investigate circadian patterns, the mean hourly values of P duration, P area, and PR interval were considered. Furthermore, linear regressions between P duration, P area, and PR interval with the underlying RR interval were calculated for every sequential 30-minute period of the day. The circadian pattern of the slopes of P duration/RR, P area/RR, and PR/RR regression equations for every half-hour of the day was also investigated.

Statistical Analysis

Continuous variables are expressed as mean ± standard error of the mean (SEM). The inter-individual differences between daytime and nighttime values were examined using paired Student's *t*-test. The periodic nature of each parameter considered was examined using a single harmonic regression model.[18] The following harmonic regression equation was used:

$$Y = b_0 + b_1 \text{ sine } (2\pi t/24) + b_2 \text{ cosine } (2\pi t/24)$$

where t is the time of the day in hours. A P value < 0.05 was considered statistically significant.

RESULTS

The mean 24-hour, nighttime (00.00 to 06.00 h), and daytime (10.00 to 16.00 h) values of all the parameters analyzed in this study are presented in Table 1. Significant differences between the nighttime and the daytime values of heart rate, P area, PR interval, P area/RR slope, and PR/RR slope, were demonstrated. The P area showed lower values during the nighttime compared to the daytime, whereas the PR interval showed higher values during the nighttime than during the daytime. The PR interval showed a positive relation to the RR interval, while P area and P duration showed a negative relation to the RR interval (Fig. 1). The P area/RR slope showed a highly significant difference between the daytime and the nighttime values, whereas the PR/RR slope showed a rather weak,

Table 1. Twenty-four Hour, Nighttime (00.00 to 06.00 h) and Daytime (10.00 to 16.00 h) Values of Heart Rate (HR), P Wave Duration (P Duration), P Wave Area (P Area), PR Interval (PR), P Duration/RR Slope, P Area/RR Slope, and PR/RR Slope

Parameters	24-hour	Nighttime	Daytime	P Value
HR (bpm)	75.9 ± 0.9	64.4 ± 1	83.3 ± 1.1	< 0.001
P duration (ms)	93.5 ± 1.4	93.9 ± 1.6	92.7 ± 1.4	0.126
P area (mV · ms)	1.858 ± 0.097	1.669 ± 0.096	2.018 ± 0.107	< 0.001
PR (ms)	149.4 ± 2.6	157.6 ± 3.1	142.6 ± 2.3	< 0.001
P duration/RR slope	−0.004 ± 0.002	−0.006 ± 0.002	−0.012 ± 0.004	0.128
P area/RR slope	−0.0018 ± 0.0001	−0.0009 ± 0.0001	−0.0025 ± 0.0002	< 0.001
PR/RR slope	0.044 ± 0.004	0.013 ± 0.005	0.025 ± 0.004	0.014

Probability values are for comparisons between nighttime and daytime values.

although significant, difference between the daytime and the nighttime values. The P duration/RR slope did not differ between the daytime and the nighttime.

To test the significance of the linear relation of P duration, P area, and PR interval with the underlying RR interval, the null hypothesis that the slope of the respective linear regression equations for the 24-hour recording period is equal to 0, was examined.[19] The regression coefficient of the P area/RR regression equation was highly significant ($P < 0.0001$) in 47 patients, significant at the level of $P = 0.0003$ in one patient, and was not significant in two. The regression coefficient of the PR/RR regression equation was highly significant ($P < 0.0001$) in 44 patients, significant at the level of $P < 0.05$ in four patients, and was not significant in two. Finally, the regression coefficient of the P duration/RR regression equation was highly significant ($P < 0.0001$) in 28 patients, significant at the level of $P < 0.01$ in 9 patients, significant at the level of $P < 0.05$ in 2 patients, and was not significant in 11.

The curves of circadian variation are shown in Figures 2 and 3. The P area (F test $P < 0.0001$; $R^2 = 0.78$), the PR interval (F test $P < 0.0001$; $R^2 = 0.92$), the P area/RR slopes (F test $P < 0.0001$; $R^2 = 0.55$) and the PR/RR slopes (F test $P < 0.0001$; $R^2 = 0.42$) showed a highly significant circadian variation. The circadian variation of P duration and of P duration/RR slopes was also found by harmonic regression analysis (F test $P = 0.016$; $R^2 = 0.32$, and F test $P = 0.011$; $R^2 = 0.18$, respectively).

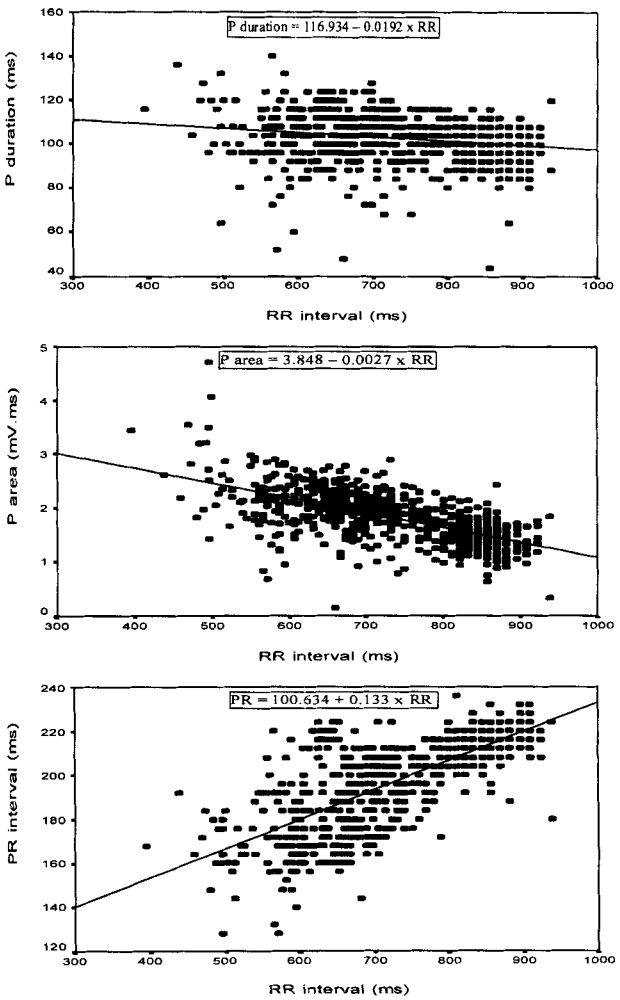

Figure 1. Plots of P duration, P area, and PR interval with the underlying RR interval from the 24-hour recording of a 36-year-old man. Linear regression equations and fitted regression lines are presented. The slopes of the P duration/RR, P area/RR, and PR/RR regression equations were − 0.0192 (95% CI, −0.026 to −0.012), −0.0027 (95% CI, −0.002 to −0.003), and 0.133 (95% CI, 0.123 to 0.142), respectively.

DISCUSSION

The study shows that P duration, P area, and PR interval show a significant dynamic behavior in

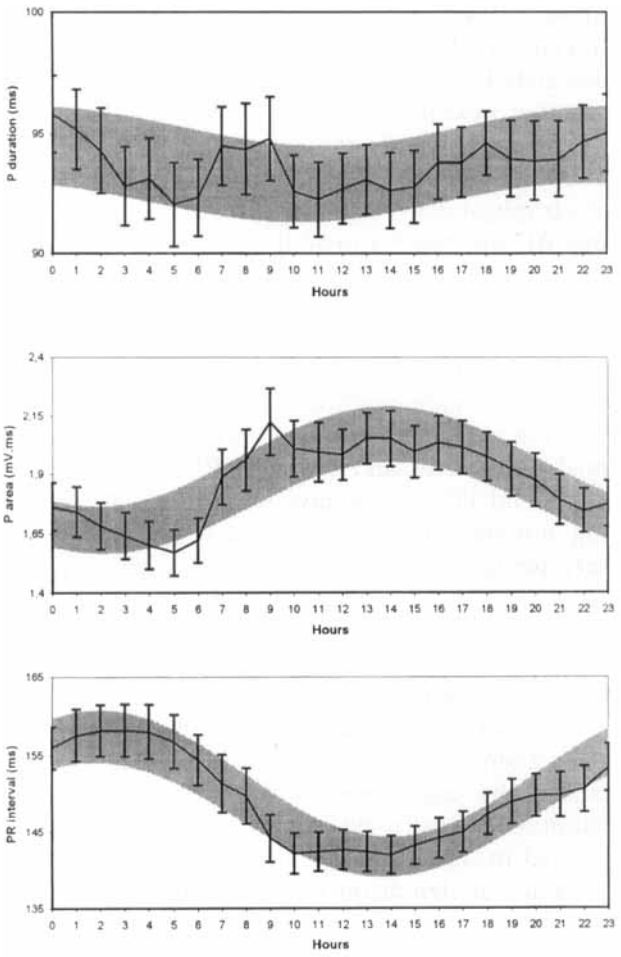

Figure 2. Mean hourly P duration, P area, and PR intervals plotted against the time of the day. Vertical bars represent the standard error of the mean. The shaded areas represent the fitted single harmonic curves ± the standard error of the mean.

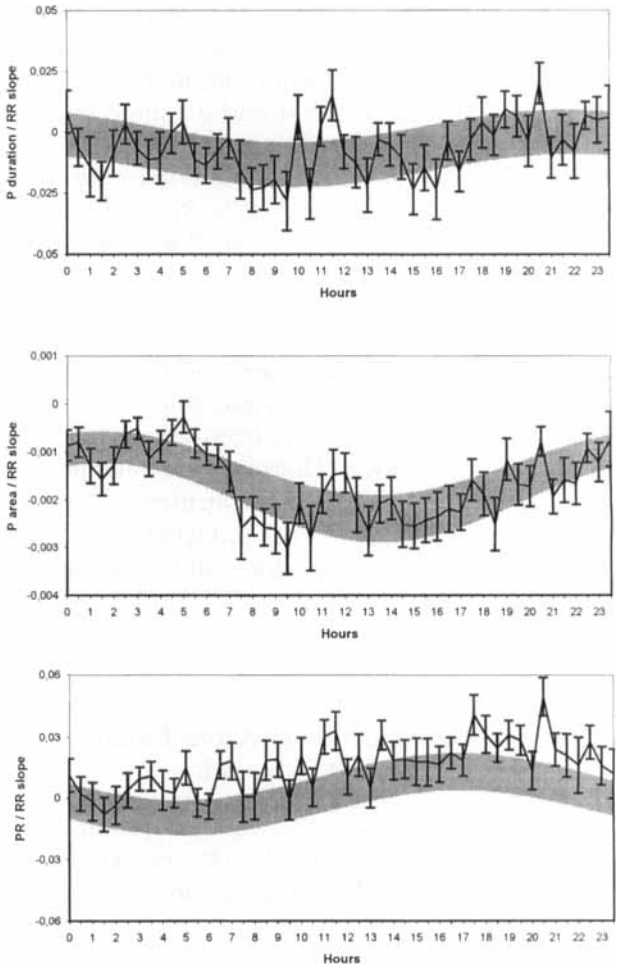

Figure 3. Mean hourly P duration/RR, P area/ RR, and PR/RR slopes plotted against the time of the day. Vertical bars represent the standard error of the mean. The shaded areas represent the fitted single harmonic curves ± the standard error of the mean.

healthy subjects. The relations between P area/RR, PR/RR, and P duration/RR also demonstrate a significant diurnal pattern.

Circadian Variation of P-Wave Characteristics

Analysis of standard 12-lead or signal-averaged ECG in patients with paroxysmal AF has repeatedly shown a longer P-wave duration in patients with the arrhythmia compared with that in controls.[3-7] Although the effects of autonomic tone on the P-wave duration have already been demonstrated,[11] data on the diurnal variation of P-wave characteristics were rather sparse in the past.[12]

In this study, a significant circadian variation was immediately apparent for P area and PR interval, while the periodic nature of P duration was only indicated by a detailed single harmonic regression analysis. Furthermore, no significant differences were noticed between daytime and nighttime values of P duration, whereas longer PR intervals and lower P areas (i.e., flatter P waves) were demonstrated during the night compared to the daytime. These findings may indicate an autonomic influence on the investigated ECG parameters, although the contribution of other factors like atrial volume changes cannot be ruled out.[20,21]

The lability of P-wave abnormalities in normal subjects has already been reported by Forfang and Erikseen.[22] The changes in P-wave amplitude during physical daily activities such as body positional

changes, respiration, or exercise have been demonstrated previously.[23,24] In a previous study, Myrtek et al.[12] showed a significant variation in P-wave amplitude and PR interval and a rather stable P duration over 23 hours. This is in accord with our results. The stability of P duration measurements over sequential recordings has been demonstrated previously.[25] Unlike P duration, P area showed a highly significant circadian variation and lower values were noticed throughout the nighttime. This finding may be due to diurnal changes in the autonomic control, the atrial volume, or just in changes in the body position. In previous studies, high frequency P-wave energy has been associated with atrial refractoriness.[7] Therefore, a relation between P area and atrial refractoriness cannot be ruled out. Further, similarly conducted studies performed during autonomic provocative testing, like positional changes or during the administration of autonomically active agents are needed to draw definite conclusions.

Dynamic Relation of P-Wave Parameters to RR Interval

The dynamic P-wave/RR interval relation has not been previously reported. In the present study, P area/RR and PR/RR regression slopes showed a very apparent circadian pattern, whereas the circadian variation of the P duration/RR slope was only established by the single harmonic regression analysis. Furthermore, the P area/RR and the PR/RR regression slopes were significantly steeper during the daytime than during the nighttime, while no significant differences were noticed between the daytime and the nighttime values of the P duration/RR slope. The highly significant difference observed between the daytime and the nighttime P area/RR slopes may imply that the changes in the P area from the daytime to the nighttime are due to other factors than just simple adaptation to changes in heart rate, such as positional or atrial volume changes.

This is the first approach to evaluate the dynamic relation between P wave and RR interval in a healthy population. The patterns of the relationship depend on the physiological basis and the techniques of data processing. To simplify the technique, we used simple linear regression in the present study. However, we do not know whether the relation between the P wave and the RR interval is linear under dynamic conditions. Furthermore, we do not know whether this dynamic behavior of the P wave/RR relation is actually associated with atrial electrophysiology and whether possible alterations of these diurnal patterns may have any clinical significance. Similarly conducted studies in patients with abnormal atrial electrophysiology, e.g., in patients with paroxysmal AF, are needed to address this question.

Study Limitations

The circadian variation of P-wave characteristics and the dynamic relation between P-wave and RR was not evaluated on a beat-to-beat basis. Rather, median P-waves and averaged RR intervals from 10-second ECG recordings were used. By averaging, a higher signal-to-noise ratio, which is necessary for an accurate quantitative analysis, can be obtained,[15] while the beat-to-beat changes of P-wave characteristics and their relation with RR variability are lost. Furthermore, the calculation of the median value from the 12 ECG leads for all the P-wave parameters used in this study, has possibly strengthened the accuracy of our results, but precluded the assessment of any possible interlead variations. Finally, no echocardiography was performed in our healthy volunteers to rule out the presence of significant but not clinically apparent heart disease.

CONCLUSIONS

P duration, P area, and PR interval show a significant circadian variation in healthy subjects. The relations between P area/RR, PR/RR, and P duration/RR also demonstrate a significant diurnal pattern.

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