Automatic P Wave Analysis Over 24 Hours in Patients with Paroxysmal or Persistent Atrial Fibrillation

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Background: Patients with atrial fibrillation (AF) often exhibit abnormalities of P wave morphology during sinus rhythm. We examined a novel method for automatic P wave analysis in the 24-hour-Holter-ECG of 60 patients with paroxysmal or persistent AF and 12 healthy subjects.

Methods: Recorded ECG signals were transferred to the analysis program where 5–10 P and R waves were manually marked. A wavelet transform performed a time-frequency decomposition to train neural networks. Afterwards, the detected P waves were described using a Gauss function optimized to fit the individual morphology and providing amplitude and duration at half P wave height.

Results: >96% of P waves were detected, $47.4 \pm 20.7\%$ successfully analyzed afterwards. In the patient population, the mean amplitude was 0.073 ± 0.028 mV (mean variance 0.020 ± 0.008 mV²), the mean duration at half height 23.5 ± 2.7 ms (mean variance 4.2 ± 1.6 ms²). In the control group, the mean amplitude (0.105 ± 0.020 ms) was significantly higher ($P < 0.0005$), the mean variance of duration at half height (2.9 ± 0.6 ms²) significantly lower ($P < 0.0085$).

Conclusions: This method shows promise for identification of triggering factors of AF.
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arrhythmia; atrial fibrillation; electrocardiography; P-wave amplitude; P-wave duration; Holter

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia¹ with great clinical and socioeconomic impact.^{2–6} Many efforts have been made so far to detect possible trigger factors or warning signs from the 12-lead-surface-electrocardiogram (ECG) which could predict occurrence or recurrence of AF episodes.^{7–9} Patients suffering from AF often exhibit abnormalities of their P-wave morphology corresponding to an intra-atrial conduction delay.¹⁰ Various studies using manual measurement of P waves¹¹ or signal-averaged ECG (SAECG)^{12,13} analysis have shown that P-wave parameters might be valuable mark-

ers for risk stratification of AF. Especially P-wave duration and its variance, maximum P-wave duration ("P maximum") and P-wave dispersion (i. e., difference between the maximum and minimum duration in the standard ECG-leads) have been examined in recent studies.^{7–9,14–17} However, only short ECG sections of several minutes could be analyzed because of time- and staff-consuming measurement methods so far. Dynamic, circadian behavior of P waves has therefore not been studied yet, but could reveal important information about pathomechanism and trigger factors of AF. The aim of the present study was to test the applicability of

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a new method for automatic detection and analysis of P waves in the 24-hour-Holter-ECGs¹⁸ of a mixed population of patients with paroxysmal as well as persistent AF after successful electrical cardioversion.

METHODS

Study Population

The patient population consisted of 60 patients with AF (36 male, 24 female, mean age 60.0 ± 12.2 years); 43 patients had paroxysmal AF, 17 patients had been cardioverted electrically because of persistent AF and were included the day after cardioversion.

Twenty-three patients were suffering from lone AF, 19 had coronary heart disease, 10 systemic hypertension, three dilated cardiomyopathy, and five valvular heart disease. Each patient underwent physical examination, standard 12-lead surface ECG, two-dimensional echocardiography, and also coronary angiography if clinically indicated.

The mean left ventricular ejection fraction (LVEF) in the patient population was $60.7 \pm 13.3\%$. The lowest LVEF values were found in the three patients with dilated cardiomyopathy (30%, 30%, and 50%), the highest mean LVEF in the subgroup with systemic hypertension ($70.5 \pm 7.6\%$). In the two biggest subgroups, patients with coronary heart disease had a mean LVEF of $52.1 \pm 13.8\%$, patients with lone AF a mean LVEF of $65.9 \pm 7.2\%$ (Table 1).

The control group consisted of 12 healthy subjects (nine male, three female, mean age 51.3 ± 12.0 years) with no evidence of cardiovascular diseases. Subjects were included after systemic arterial hypertension was ruled out and their standard 12-lead surface ECG showed no significant abnormalities.

Baseline ECG data of both study groups derived from their 12-lead ECGs are shown in Table 2. There were significant differences concerning mean P-wave amplitude, PR interval, QRS time and QTc time (corrected QT time). In contrast, data comparison of the control group and the subgroup suffering from lone AF revealed no significant differences at all (Table 3).

The study was designed according to the Declaration of Helsinki; written informed consent was obtained from all study subjects.

Holter ECG Recording

The ECG signals of each subject were recorded digitally on a "flash card" over a 24-hour-period using a commercial Holter system (Elatec "Synesis," 2 ECG channels with 200 Hz sampling rate; Ela, Le Plessis Robinson Cedex, France). The two electrodes (Medicotest "Blue Sensor" Q-00-A; Medicotest, Andernach, Germany) which were used to analyze the selected ECG lead were placed on the upper *manubrium sterni* and over the left ventricular apex.

The recorded data were transferred to a personal computer, decompressed and converted into a format compatible to the analysis program.

P-Wave Detection

After the data were read by the analysis program, 10–15 P waves were manually marked over a defined ECG period of 5 minutes. The exact number of P waves necessary to be marked as templates differed individually and depended on the variability of the P-wave morphology in each data recording. Afterwards, a discrete wavelet transform performed an adaptive time-frequency decomposition of the presented pattern. By the multiresolution representation it was possible to describe the signal

Table 1. Baseline Clinical Characteristics of the Study Patients with Atrial Fibrillation

Cardiac Disease	Number of Pat.	Gender [m/f]	Mean Age [years]	Mean LVEF [%]
None (=lone atrial fibrillation)	23	12/11	53.3 ± 13.6	65.9 ± 7.2
Coronary heart disease	19	15/4	68.3 ± 6.2	52.1 ± 13.8
Systemic hypertension	10	5/5	62.0 ± 8.7	70.5 ± 7.6
Dilated cardiomyopathy	3	3/0	56.0 ± 6.2	36.7 ± 11.5
Valvular heart disease	5	1/4	58.2 ± 14.3	64.0 ± 8.9
All patients	60	36/24	60.0 ± 12.2	60.7 ± 13.3

Number or mean value with standard deviation; pat. = patients; m = male; f = female; LVEF = left ventricular ejection fraction.

Table 2. Baseline ECG Data of the Two Study Groups Derived from Standard 12-Lead Electrocardiograms

Baseline ECG Data	Controls	Patients	P
Number of subjects	12	60	–
Mean P-wave duration [ms]	97.3 ± 6.5	98.7 ± 20.4	0.7367 (n. s.)
Mean P-wave amplitude [mV]	0.173 ± 0.034	0.144 ± 0.049	0.0316
Mean PR interval [ms]	185.5 ± 16.3	215.0 ± 41.2	0.0318
Mean QRS time [ms]	77.3 ± 4.7	90.5 ± 18.4	0.0151
Mean QT interval [ms]	366.4 ± 21.6	382.0 ± 40.9	0.2089 (n. s.)
Mean QTc interval [ms]	388.6 ± 14.0	411.8 ± 51.6	0.0071

Mean value with standard deviation; n. s. = not significant.

structure by only a few coefficients in the wavelet domain (Fig. 1).

Next, the actual classification was done using three-layer feed forward neuronal networks, which were trained by the chosen set of coefficients, each of those representing a neuron in the input layer. The hidden layer was chosen to be large enough to solve the learning problem and small enough to prevent over-adaption. The output layer had only one neuron in order to decide between an event and no event (Fig. 2). After successful detection, the defined ECG segment was plotted on screen with the marked P waves. Each marker was shown with its individual probability of actually representing a real P wave. The sensitivity could be influenced by manually changing the "threshold" value (Fig. 3).¹⁹

In case of a sufficient P-wave detection over the period of 5 minutes, the R waves were marked in analogy. Five marked R waves in the defined segment were usually enough to get a certain separation, which was then continued throughout the whole data set. By gathering this information, a better separation of P waves could be achieved in noisy recordings with the necessity of high sensitivity values on costs of an acceptable P-wave specificity. Due to the fact that P waves usually appear within

a certain time range before an R wave, an additional selective criterion was available. Thus, a faster P-wave detection mode was finally performed within the whole 24-hour-recording.

P-Wave Measurement

In a second step, the detected P waves were measured automatically by the analysis program. Our novel method founded on the assumption that most of all non-pathologic P waves have a morphology very similar to a Gauss function. Hence, a modified Gauss function with parameters optimized to fit the individual P wave as exactly as possible ("Gauss fit") seemed to be a sufficient description (Fig. 4).

Based on the Levenberg-Marquardt method,²⁰ several reference values were needed to perform the automatic Gauss fit: the amplitude, the mean value, and the full-width at half maximum (FWHM). The maximum inside the data window was chosen as reference amplitude, its position as mean value, and an empiric value valid for all data sets as FWHM.

Besides, the number of data points had to be known to define the beginning and the end of the wave. Due to a high physiological variability of

Table 3. Baseline ECG Data of the Control Group and the Patient Group with Lone Atrial Fibrillation

Baseline ECG Data	Controls	Lone AF	P
Number of subjects	12	23	–
Mean P-wave duration [ms]	97.3 ± 6.5	95.0 ± 20.4	0.6641 (n. s.)
Mean P-wave amplitude [mV]	0.173 ± 0.034	0.147 ± 0.056	0.0986 (n. s.)
Mean PR interval [ms]	185.5 ± 16.3	196.7 ± 36.6	0.8035 (n. s.)
Mean QRS time [ms]	77.3 ± 4.7	85.7 ± 14.0	0.0812 (n. s.)
Mean QT interval [ms]	366.4 ± 21.6	375.2 ± 50.2	0.6335 (n. s.)
Mean QTc interval [ms]	388.6 ± 14.0	395.2 ± 67.8	0.0844 (n. s.)

Mean value with standard deviation; n. s. = not significant).

Figure 1. Multi-resolution representation of an ECG by wavelet coefficients. The values of the coefficients are translated into a three-dimensional plot using a linear frequency scale.

these limits, different data windows with an increasing width were placed around the marked P wave, and a separate Gauss fit was calculated for each window width. The fit with the lowest chi-square value achieved the best adaptability. Finally, this chi-square had to be tested for statistical significance using a standard probability function $Q(\chi^2|\nu)$.

In case the P-wave marker—representing the center of gravity in the time series—was not equivalent with the P-wave maximum, an asymmetric curve could have been selected inside the data window. Thus, the data window was shifted horizontally over the time series until the first and the last data point inside the window were of the same height. Additionally, typical side effects caused by drifts and offsets were prevented automatically by setting the lowest value of the window to "0" and shifting all other values vertically corresponding to their difference.

Optimized by these techniques,¹⁸ a Gauss fit was performed for all detected P waves in the entire data set in order to achieve automatic measurement. Since a mathematical Gauss function has in fact no beginning or ending, the normal P-wave du-

ration had to be replaced by the "duration at half height," that is the full width of the function at its half maximum (corresponding to FWHM; Fig. 5).

Finally, the Gauss fit was able to deliver the mean P-wave amplitude and the mean P-wave duration at half height with their standard deviations and the mean variances of both parameters. The variances were chosen as valuable markers for the extent of variability possibly related to dynamics of atrial substrate.

Statistical Analysis

Statistical analysis of all measured P-wave parameters was performed using Mann-Whitney Test for unpaired values (non-parametric test). $P < 0.05$ was considered statistically significant. All data are presented as mean value with standard deviation.

RESULTS

Detection Rate

The mean detection rate of P waves throughout a 24-hour-recording was 96.2% (with a range from

Figure 2. Structure of a feed forward multilayer neural network using a frequency dependent connection. The neurons of the input layer are assigned to one single neuron in the hidden layer according to the frequency bands of the associated wavelet coefficients. The figure depicts seven input neurons out of three frequency bands (f1–f3) connected to one of the three hidden neurons which are all linked to the one output neuron.

92.6% to 99.9%) in relation to all detected R waves after supraventricular premature beats were sorted out by the detection algorithm based on prematurity.

Analysis Rate

Automatic P-wave analysis was obtained in $47.4 \pm 20.7\%$ of detected P waves. This corresponds to $35,599 \pm 16,683$ P waves automatically detected and analyzed. The high standard deviation is caused by the variation in signal quality and noise levels of the recorded ECG data.

P-Wave Measurement

In the patient population, the mean P-wave amplitude was 0.073 ± 0.028 mV, its mean variance 0.020 ± 0.008 mV². The mean P-wave duration at half height was 23.5 ± 2.7 ms, its mean variance 4.2 ± 1.6 ms².

In the control group, the mean P-wave amplitude (0.105 ± 0.020 ms) was significantly higher ($P < 0.0005$), the mean variance of P-wave duration at half height (2.9 ± 0.6 ms²) significantly lower ($P < 0.0085$) compared to the patient population. The other values showed no statistically significant difference (Table 4).

In addition, we compared the subgroup of patients with lone AF with the healthy control group in order to examine if the differences in P-wave parameters were really due to the associated AF and not mainly caused by the underlying cardiac disease. But also in the lone AF group without any

Figure 3. P-wave detection within an ECG segment. In this case, the R waves have already been detected before. P waves are only marked if the probability P is higher than the entered detection threshold.

Figure 4. a/b Two examples of detected P-waves (original waves: cruxes) and their corresponding optimized Gauss functions (solid lines) calculated by the analysis program.

cardiac disease or other co-morbidities, the mean P-wave amplitude was significantly lower (0.079 ± 0.032 , $P < 0.0075$) compared to the healthy subjects (Table 5).

DISCUSSION

Main Findings

There are several important findings of this study:

First, this is the first study utilizing automatic detection and analysis algorithms for evaluation of the P-wave over a 24-hour-period.

Second, by means of this technique important differences in P-wave dynamics can be found between patients with AF and healthy control subjects. Patients exhibit significantly lower mean P-

wave amplitudes and higher mean variances of P-wave duration at half height. These differences can be explained by inhomogenous conduction through diseased atrial tissue in patients with AF. In the subgroup of patients with lone AF, the mean P-wave amplitude was also significantly lower compared to the healthy control subjects although no cardiac disease or other comorbidities were present in both groups. This suggests that the differences in P-wave parameters between the AF patients as a whole and the control group are—at least predominantly—a result of the associated arrhythmia in the study group and not just an effect of the underlying cardiac disease.

Third, distinct changes of P-wave parameters in the course of the day can be tracked using this automatic 24-hour Holter analysis (Fig. 6A and B). Although we have not been able to identify a specific daily pattern distinguishing AF patients so far, the significantly higher mean variance of P-wave duration at half height in the patient population shows promise that the circadian behavior might be of special interest. Nevertheless, new algorithms for further analysis of the dynamic changes have to be established.

Previous Reports on P-Wave Analysis

Manual measurement of P-wave parameters derived from the 12-lead surface ECG and SAEKG are common methods. They are used to evaluate patients at risk of developing AF.^{8,9,13–16,21–22}

Increased P-wave duration, P-wave dispersion and P maximum were shown to be simple electrocardiographic markers for the prediction of recurrent paroxysmal AF. In analogy to our study, patients with idiopathic AF also exhibited a significantly higher variance of P-wave duration.²¹ P-wave analysis was used to predict AF after coronary artery surgery⁴ or AF recurrence after cardioversion.⁹ Transition to chronic AF in patients with paroxysmal arrhythmia was examined as well.¹³

These reports were all based on 12-lead ECG or SAEKG. In case of manual measurement from the 12-lead-ECG, several auxiliary tools were used in some studies such as magnifying lenses, digital measuring slides etc. In case of SAEKG measurement, P waves derived from the three Frank leads were enhanced by time-domain analysis, signal-averaged and filtered by fast Fourier transform.¹²

Both methods have in common the necessity of a relatively large number of study staff and long

Figure 5. Automatic measurement of an optimized Gauss function representing a P wave.

duration of data analysis compared to our method. Apart from that, only short ECG sections of approximately 5–10 minutes can be analyzed instead of 24-hour-recordings.

Because of intra- and interobserver variability in defining start and end point of a P wave and addi-

tional errors in manual measurement, results also often have poor reproducibility.

In contrast to these methods, our analysis program enables an advanced user to analyze one complete Holter data set in approximately 10 minutes (using a 1 GHz processor). The exact time is

Table 4. Results of Automatic P-Wave Measurement in the Two Study Groups

P-Wave Parameters	Controls	Patients	P
Number of subjects	12	60	–
Mean P-wave duration at half height [ms]	23.1 ± 1.6	23.5 ± 2.7	0.4410 (n. s.)
Mean variance of P-wave duration at half height [ms ²]	2.9 ± 0.6	4.2 ± 1.6	0.0082
Mean P-wave amplitude [mV]	0.105 ± 0.020	0.073 ± 0.028	0.0004
Mean variance of P-wave amplitude [mV ²]	0.025 ± 0.006	0.020 ± 0.008	0.0522 (n. s.)

Mean value with standard deviation; n. s. = not significant.

Table 5. Results of Automatic P-Wave Measurement in the Control Group and the Patient Group with Lone Atrial Fibrillation

P-Wave Parameters	Controls	Lone AF	P
Number of subjects	12	23	–
Mean P-wave duration at half height [ms]	23.1 ± 1.6	22.8 ± 2.6	0.9723 (n. s.)
Mean variance of P-wave duration at half height [ms ²]	2.9 ± 0.6	3.8 ± 1.2	0.1138 (n. s.)
Mean P-wave amplitude [mV]	0.105 ± 0.020	0.079 ± 0.032	0.0071
Mean variance of P-wave amplitude [mV ²]	0.025 ± 0.006	0.021 ± 0.008	0.1643 (n. s.)

Mean value with standard deviation; AF = atrial fibrillation; n. s. = not significant.

Figure 6. a/b Circadian behavior of P-wave amplitude (A) and P-wave duration at half height (B) (example of a healthy subject).

mainly depending on the available CPU processor and might be reduced even more with advanced hardware.

Automatic measurements provide results independently from any observers and appear therefore highly reproducible.

In our study population, we also compared mean P-wave amplitude and duration, PR interval, QRS time, QT and QTc interval derived from the 12-lead-ECG of AF patients and healthy controls by manual measurement. There were significant differences in mean P-wave amplitude (in analogy to

our findings from the Holter analysis), PR interval, QRS time, and QTc interval. As a result, major differences between the two groups actually could be identified in advance without Holter analysis. But the main aim of our study was to examine the dynamic behavior of P-wave parameters over 24 hours. Whereas, the mean variance of P-wave duration at half height in AF patients was significantly higher compared to the control subjects, there were no significant differences concerning mean P-wave duration derived from the standard surface ECG that only offered a snapshot of a few seconds. In contrast, our method considers an average number of more than 35,500 measured P waves with special regards to the variability of the parameters in the course of the day.

Besides, comparison of the baseline ECG data of our healthy subjects and the subgroup suffering from lone AF showed no statistically significant difference in any of the parameters including P-wave amplitude. This shows that the described method of automatic P-wave analysis is particularly useful in patients with lone AF. In this patient subgroup, significantly lower mean P-wave amplitudes were demonstrated compared to the control group.

Clinical Implications

The ability to document the precise circadian behavior of P-wave parameters for the first time shows promise for identification of predisposing and triggering factors of paroxysmal AF or recurrence after cardioversion in order to guide pharmacological or interventional therapy.

Study Limitations

As shown above, the "Gauss fit" method assumes that P waves have a morphology that is similar to a Gauss function. Holter recordings containing P waves of a very different morphology, for example "P mitrale," might not always be analyzed properly. Therefore, our method was improved to describe obvious pathologic P waves with two peaks as well by performing two separate "Gauss fits," one for each peak. The superposition of these two optimized functions is again very similar to the original P-wave (Fig. 7), but an automatic measurement has not been available yet, since the superposition itself is not a Gauss function any more.

Figure 7. Description of a pathologic P-wave with two peaks ("P mitrale"; original wave: cruxes) using two separate "Gauss fits" (dotted lines). The superposition (solid line) of the two optimized Gauss functions is very similar to the original P-wave.

The measurement of the P-wave duration at half height instead of the normal used full duration is a necessary construction to achieve an automatic analysis independent from an individual definition of start and end point of each P wave. Since Gauss functions themselves have no definite beginning or ending in the mathematical sense, the full width of a function at its half maximum replaces the normal duration value. To what extent this is a reliable analog description still remains open and has to be examined in further studies.

CONCLUSIONS

The results of our study suggest that the new method for automatic detection and analysis of P-waves over a 24-hour period ECG recording successfully measures a high number of P waves in a few minutes, providing the mean P-wave amplitude, the mean duration at half height with the corresponding variances, and the circadian behavior of these parameters with their individual fluctuation during an entire Holter recording. These results show promise for identification of triggering factors and indicators for recurrence of AF. In order to validate the potential of the proposed method for replacing conventional manual P-wave measurement, larger studies have to be performed.

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