Optimal analysis of the signal averaged P wave in patients with paroxysmal atrial fibrillation

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Abstract

Objective—To define the ability of analysis of the signal averaged P wave to identify patients with paroxysmal atrial fibrillation (AF) and establish whether differences in quantitative variables between patients and controls are due to concurrent cardiopulmonary disease, greater atrial dimension, or to unrelated changes in atrial electrophysiology.

Design—An observational parallel group study.

Setting—Cardiac department of a busy district general hospital.

Patients—58 participants without cardiopulmonary disease (24 with paroxysmal AF and 34 controls, group A) and 57 with cardiac or respiratory conditions (31 with paroxysmal AF and 26 controls, group B). Mean (range) age of patients was 54 (25–71) and controls 53 (34–78) for group A and 65 (45–81) and 62 (36–78) respectively for group B. Left atrial size was similar in patients and controls in each group (mean (SEM)) group A: 2.39 (0.1) v 2.19 (0.07) cm; group B: 2.51 (0.10) v 2.71 (0.12) cm).

Main outcome measures—Analysis of the P wave after P-wave-specific signal averaging. Filtered P wave duration and spatial velocity were calculated. Energies contained in frequency bands from 20, 30, 40, 60, and 80 to 150 Hz after spectral analysis were expressed as absolute values (P20, P30 etc) and ratios of high to low frequency energy (PR20, PR30, etc).

Results—Duration and peak spatial velocity were increased in patients with paroxysmal AF (median (interquartile range) duration group A: 144 (137–155) v 136 (129–143) ms, $P = 0.007$; group B: 155 (144–159) v 142 (136–151) ms, $P = 0.002$; peak spatial velocity group A: 16.5 (14.1–21.2) v 14.5 (11.7–18.1) mV/s, $P = 0.02$; group B: 18.9 (14.8–21.8) v 14.3 (12.6–17.6) mV/s, $P = 0.01$). Energy contained in frequency bands from 20, 30, 40, 60 and 80 to 150 Hz was expressed as absolute values (P20, P30, P40, P60, and P80) and percentage energy ratios. P30, P60, and P80 were significantly greater in patients with AF in group A (for example P60: 3.9 (3.0–5.3) v 3.1 (2.0–4.3) $\mu V^2.s$, $P = 0.02$) and P20, P30, and P40 were increased in those with AF in group B (for example P40: 16.7

(9.9–20.8) v 10.8 (8.1–14.8) $\mu V^2.s$, $P = 0.02$). A score developed from logistic regression analysis of duration and P60 identified patients with paroxysmal AF with a sensitivity of 81% and specificity of 73%.

Conclusions—Increased P wave duration and magnitude are associated with paroxysmal AF with and without additional cardiopulmonary disease. The discriminant ability of the signal averaged P wave is improved by analysis of duration and a magnitude variable. These results invite prospective assessment of the ability of the signal averaged P wave to predict paroxysmal AF in unselected patients.

(Br Heart J 1995;74:413–418)

Keywords: paroxysmal atrial fibrillation; signal averaged P wave

Investigations of the P wave of the 12 lead electrocardiogram have shown repeatedly that cardiac disease, leading to atrial hypertrophy or dilatation, may affect its duration and amplitude.^{1–5} More recently changes in low noise highly amplified P waves have been explored during sinus rhythm in patients with paroxysmal atrial fibrillation (AF).^{6–10} Most studies, however, have not addressed the potential influence of concurrent cardiac disease that may affect atrial activation on P wave morphology. As paroxysmal AF is often associated with cardiac disease that leads to atrial volume or pressure overload the abnormal findings reported may simply be related to a different prevalence of cardiac disease between patients and controls.

The role of the high resolution P wave as a predictor of individual risk of paroxysmal AF has yet to be defined. Significant differences in group mean values may not translate into effective discriminant indices of abnormality when single variables are analysed. We have therefore undertaken a multivariate analysis of multiple time and frequency domain variables from high resolution P waves obtained using signal averaging in patients with paroxysmal AF and controls to identify potentially discriminant groups of P wave variables. We have also ensured that patients and controls were matched for the presence or absence of concurrent cardiac or pulmonary disease.

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Accepted for publication
16 May 1995

Patients and methods

PATIENT GROUPS

Participants were recruited from cardiac and gastroenterology outpatient clinics at the Royal Sussex County Hospital, Brighton. Additional controls were recruited from an endoscopy list and normal volunteers. Participants were investigated by clinical history and examination, routine biochemistry and haematology, thyroid function tests (in patients with paroxysmal AF), chest radiograph, 12 lead electrocardiogram, echocardiogram (including Doppler and color flow examination), and treadmill exercise test. This was not performed in patients with known ischaemic heart disease or in normal controls.

Participants were divided into two groups: group A comprised 58 patients without detectable cardiac or respiratory disease, of whom 24 had documented attacks of paroxysmal AF and 34 were controls, while group B comprised 57 patients in whom cardiopulmonary disease was diagnosed including, 31 with paroxysmal AF and 26 controls. Ambulatory monitoring was not performed in group A as the risk of asymptomatic arrhythmia in such a normal group was felt to be low. In group B controls who could have had asymptomatic arrhythmia, however, at least 24 h of normal ambulatory electrocardiographic monitoring was required before inclusion into the study. During the recruitment of participants we selected controls so that each control group comprised individuals with a similar age and sex distribution to its respective patient group. Additionally, group B controls were also selected to present a similar range of cardiopulmonary conditions to those of group B patients.

SIGNAL AVERAGED P WAVE RECORDINGS

Our methodology for selective P wave averaging has been described previously.¹¹ Importantly, this technique ensures that only P waves with the same shape as the participant's most frequently occurring P wave are averaged.

A vector magnitude plot of the P wave was generated after averaging and the P wave limits defined automatically by the computer as we have reported,¹¹ except that the frequency cut off of the filter we used for the current analysis was 40 Hz and the P wave end was defined as the point where the vector magnitude exceeded the minimum PR segment voltage by three standard deviations of the mean baseline value. P wave duration and root mean square (RMS) voltage were calculated between these limits. Because of interest in the possible existence of low amplitude terminal P wave signals ("atrial late potentials") in patients with paroxysmal AF,¹² we also determined the RMS voltage of the terminal 10, 20, and 30 ms of the P wave (RMS10, RMS20, RMS30).

Spatial velocity is the rate of change of voltage within the P wave signal in each orthogonal lead. It is a measure of the higher frequency magnitude of the P wave and the rapidity of directional change of the P wave vector during atrial activation. Spatial velocity was calcu-

lated by digitally differentiating the signal from each lead and then combining the three leads to produce a vector magnitude plot. The mean, peak, and ratio of peak to mean spatial velocity were calculated.

Spectral analysis was performed on the entire P wave as we have previously described.¹¹ For the analysis presented in this paper we filtered signals with a high pass of 15 Hz before Fourier transformation to attenuate large low frequency components. P wave energy was estimated by summing the energies contained in frequency bands extending from 20, 30, 40, 60, and 80 to 150 Hz. We expressed these as absolute values (P20, P30, P40, P60, and P80) and percentage energy ratios (PR20, PR30, PR40, PR60, and PR80). For example, if P30 was the summation of the energies contained in frequency bands between 30 and 150 Hz, PR30 was the ratio of P30 to the summation of energies contained in frequency bands between 10 and 30 Hz multiplied by 100.

STATISTICAL METHODS

As the data were not all normally distributed results are expressed as median (interquartile range) except left atrial size (mean (SEM)). Comparisons between patients and controls within groups A and B were performed using the Mann-Whitney U test for independent samples. Comparisons across all four groups were made with the Kruskal-Wallis test.¹³ For both tests $P < 0.05$ (two tailed) was considered significant. Where significant differences were found between groups the 95% confidence intervals for these differences are given. Correlation coefficients between left atrial diameter and various P wave variables were sought by Spearman rank test.

A multivariate analysis of the factors associated with the occurrence of paroxysmal AF was conducted using logistic regression.¹⁴ The computer package BMDP¹⁵ was used to find estimates and their standard errors. The logistic regression equation was used to develop a score to help identify patients who were likely to have paroxysmal AF. The discriminant ability of this score and univariate parameters derived from the P wave were explored using receiver operator curves in which the sensitivity (percentage of patients with paroxysmal AF correctly classified) was plotted against the specificity (percentage of controls correctly identified) for a range of cut off values.

As testing a scoring system on the data from which it was derived can lead to an over optimistic assessment of its diagnostic ability cross validation was used to obtain a more reliable estimate. In this approach each participant in turn is excluded during the fitting process and his or her paroxysmal AF status predicted. Prediction error rates can be then calculated.

Results

PATIENT GROUPS

Table 1 gives details of each group. Table 2 summarises the cardiopulmonary conditions

Table 1 Characteristics of the patient groups studied

	Group A		Group B	
	PAF	Controls	PAF	Controls
No	24	34	31	26
Mean (range) age (years)	54 (25–71)	53 (34–78)	65 (45–81)	62 (36–78)
Sex (M : F)	12 : 12	18 : 16	22 : 9	18 : 8
Mean (SEM) left atrial diameter (cm)*	2.4 (0.1)	2.2 (0.1)	2.5 (0.1)	2.7 (0.1)

*Technically suitable measurements of left atrial diameters were available in 40 controls and 50 patients with paroxysmal atrial fibrillation (PAF).

Table 2 Cardiopulmonary disease in group B*

Definition	Patients	Controls
Chronic stable hypertension: all receiving drug treatment, none taking β blockers or verapamil at time of recording	6	5
Ischaemic heart disease: positive exercise test; documented myocardial infarction or > 50% stenosis in at least one coronary artery on coronary angiogram; none taking β blockers at time of recording	11	13
Mitral regurgitation: at least grade I mitral regurgitation on Doppler echocardiogram	5	3
Aortic Stenosis: > 70 mm Hg AV gradient on Doppler echocardiogram	2	0
Aortic valve replacement	1	3
Sino-atrial disease: sustained bradycardia < 40 beats/min and or pauses of > 2.5 s (3 s at night) on ambulatory monitoring	4	1
Left ventricular EF < 40%: assessed by MUGA or echocardiogram	3	3
Previous myocarditis: clinical diagnosis by flu-like illness, left ventricular impairment plus or minus enzyme increase, or both, arrhythmia, and chest pain	1	1
Asymmetric septal hypertrophy: no outflow tract gradient on Doppler echocardiogram	2	1
Chronic obstructive airways disease: Obstructive pattern of airflow limitation on pulmonary function tests with limitation of patient by dyspnoea	3	1
AV nodal re-entry tachycardia: diagnosed at electrophysiological study	0	1

*Some patients had more than one diagnosis. AV, atrioventricular; MUGA, multiple gated acquisition scan.

present in group B, together with our criteria for categorising patients into diagnostic groups. Patients in group B were slightly older than those in group A (63 (36–81) v 53 (25–78) years) and had slightly greater left atrial diameters (2.6 (0.1) v 2.3 (0.1) cm, $P = 0.004$). However, patients and controls had similar characteristics within each group.

Table 3 Time domain analysis

Variable	Group A				Group B				
	PAF	Controls	<i>p</i> value	95% confidence interval difference	PAF	Controls	<i>p</i> value	95% confidence interval difference	Overall <i>p</i> value*
Noise (μ V)	0.11 (0.09–0.17)	0.13 (0.10–0.21)	NS	—	0.15 (0.10–0.21)	0.19 (0.11–0.21)	NS	—	NS
Duration (ms)	144 (137–155)	136 (129–143)	0.007	2–14	155 (144–159)	142 (136–151)	0.002	4–17	<0.01
RMS (μ V)	9.2 (7.7–10.4)	8.2 (6.8–9.6)	NS	—	9.5 (8.2–10.5)	8.1 (7.5–9.3)	0.05	0–2.0	NS
RMS10 (μ V)	1.3 (0.7–2.8)	2.2 (1.2–3.6)	0.04	0.04–1.4	1.5 (1.0–3.0)	1.6 (1.0–3.1)	NS	—	NS
RMS20 (μ V)	2.8 (1.5–4.1)	3.4 (2.4–4.1)	NS	—	3.0 (1.8–4.4)	3.4 (1.7–4.9)	NS	—	NS
RMS30 (μ V)	4.7 (3.0–5.9)	4.0 (3.1–6.1)	NS	—	4.3 (2.8–6.2)	4.6 (3.3–6.0)	NS	—	NS
Mean SV (mV/s)	5.1 (4.4–5.7)	4.5 (4.1–5.0)	0.06	–0.01–0.9	5.3 (4.2–5.8)	4.7 (4.2–5.8)	NS	—	NS
Peak SV (mV/s)	16.5 (14.1–21.2)	14.5 (11.7–18.1)	0.02	0.6–5.4	18.9 (14.8–21.8)	14.3 (12.6–17.6)	0.01	0.8–6.3	<0.01
Peak/Mean SV	3.3 (2.8–4.0)	3.1 (2.7–3.5)	NS	—	3.6 (3.0–4.1)	3.0 (2.7–3.5)	0.01	0.1–0.9	0.02

PAF, paroxysmal atrial fibrillation; NS, not significant; RMS, root mean square voltage of the P wave after high pass filtering at 40 Hz; RMS10, RMS 20, RMS 30, RMS value for the terminal 10, 20, and 30 ms of the P wave after high pass filtering at 40 Hz, SV, spatial velocity.

*Comparison across four groups (Kruskal-Wallis test).

TIME DOMAIN ANALYSIS

In normal (A) and diseased (B) groups patients with paroxysmal AF had a longer P wave duration and greater peak spatial velocity than controls (table 3). P wave duration was noticeably increased by the presence of cardiopulmonary disease but changes in RMS voltage and peak spatial velocity were less pronounced (fig 1).

FREQUENCY DOMAIN ANALYSIS

A similar pattern to that seen in the time domain was apparent. Patients with paroxysmal AF and cardiopulmonary disease had the highest P wave energies. Patients with idiopathic paroxysmal AF had significantly greater P wave energy than normal controls (table 4). In contrast to P wave duration, however, very little difference was seen between controls with cardiopulmonary disease and those with normal cardiovascular and respiratory systems (fig 2).

CORRELATION WITH LEFT ATRIAL DIAMETER

Technically suitable measurements of left atrial diameter were available in 50 patients and 40 controls. Correlations were sought between left atrial diameter and each P wave variable for all participants, and separately for participants with paroxysmal AF and controls. Correlation between left atrial size and P wave variables was poor when all participants or only those with paroxysmal AF were examined. Moderate correlations were found between left atrial size and P wave duration ($r = 0.4$, $P < 0.05$), mean spatial velocity ($r = 0.3$, $P < 0.05$), and lower frequency energy (P20, P30, and P40: all $r = 0.3$, $P < 0.05$) in controls.

UNIVARIATE DISCRIMINATION

Receiver operator curves were constructed for P wave duration, peak spatial velocity, ratio of peak to mean spatial velocity, P30, and P60 in all patients, group A, and group B. The cut off value selected for each variable was that which produced approximately equal values for specificity and sensitivity (table 5).

In all participants each of the variables assessed discriminated between patients and controls with sensitivities of 64–71% and

Figure 1 (A) P wave duration and (B) peak spatial velocity in patients and controls. Solid bars represent the interquartile ranges for each patient group. Squares indicate individual patient results. PAF, patients within each group with paroxysmal atrial fibrillation.

Figure 2 Absolute energy contained in frequency bands from (A) 30 (P30) and (B) 80 (P80) to 150 Hz for patients and controls. PAF, patients within each group with paroxysmal atrial fibrillation.

specificities of 60–63%. In patients with concurrent cardiac disease discrimination seemed to be slightly better with sensitivity as high as 76% and specificity 52–68%. The best univariate identifier of paroxysmal AF was filtered P wave duration with an overall sensitivity of 71% and specificity of 61% (fig 3).

MULTIVARIATE DISCRIMINATION

When stepwise logistic regression was applied to all of the data a model containing P wave duration and RMS voltage was produced. However, as RMS voltage was highly correlated with frequency domain measures of P wave energy, P40, P60, or P80 could be substituted for RMS with a small, but not

Table 4 Frequency domain analysis

Group A					Group B				
Variable	PAF	Controls	p value	95% confidence interval difference	PAF	Controls	p value	95% confidence interval difference	Overall p value*
P20 (μV².s)	47.7 (36.2–63.3)	39.2 (29.5–51.8)	0.08	—	64.3 (45.8–85.7)	42.1 (28.1–56.1)	0.004	7.2–31.3	<0.01
P30 (μV².s)	30.5 (24.6–40.5)	24.4 (16.4–34.3)	0.04	0.2–12.9	34.9 (24.7–50.5)	25.7 (19.2–34.7)	0.02	1.3–18.2	<0.01
P40 (μV².s)	14.6 (9.2–20.5)	11.7 (6.8–17.6)	0.08	—	16.7 (9.9–20.8)	10.8 (8.1–14.8)	0.02	0.6–7.8	0.05
P60 (μV².s)	3.9 (3.0–5.3)	3.1 (2.0–4.3)	0.02	0.2–1.9	4.5 (2.6–5.4)	3.4 (2.9–4.0)	0.06	—	0.02
P80 (μV².s)	1.9 (1.1–2.5)	1.2 (1.0–1.8)	0.01	0.1–0.1	1.5 (1.2–2.7)	1.4 (0.9–1.9)	NS	—	0.03
PR20	261.3 (169.0–323.9)	231.7 (170.3–345.1)	NS	—	246.6 (137.2–408.8)	205.5 (170.4–316.6)	NS	—	NS
PR30	80.0 (63.1–102.7)	77.7 (56.0–102.9)	NS	—	64.6 (41.9–96.5)	70.9 (55.9–88.6)	NS	—	NS
PR40	26.9 (19.0–37.8)	25.9 (17.4–34.7)	NS	—	20.6 (14.3–29.3)	21.1 (15.7–32.1)	NS	—	NS
PR60	6.6 (5.0–8.4)	5.6 (4.0–8.1)	NS	—	4.9 (3.5–6.7)	5.8 (4.1–8.6)	NS	—	NS
PR80	3.0 (1.5–3.5)	2.3 (1.9–3.0)	NS	—	2.0 (1.6–2.6)	2.3 (1.5–3.6)	NS	—	NS

PAF, paroxysmal atrial fibrillation; NS, not significant; P20, p30, p40, p60, p80, energy contained in frequency bands extending from 20, 30, 40, 60, and 80 to 150 Hz; PR20, PR30, PR40, PR60, PR80, energy ratios derived by expressing P20, P30, P40, P60, and P80 as defined above by the energy contained in frequency bands from 10 to 20, 30, 40, 60, and 80 Hz. *Comparisons across four groups (Kruskal-Wallis test).

Table 5 Sensitivities and specificities for different P wave variables treated separately and for duration and P60 combined using logistic regression

Variable	All patients			Group A			Group B		
	Cut off (%)	Sensitivity (%)	Specificity (%)	Cut off (%)	Sensitivity (%)	Specificity (%)	Cut off (%)	Sensitivity (%)	Specificity (%)
Duration (ms)	141	71	61	137	70	56	145	76	64
Peak SV (mV/s)	15.0	66	63	15.0	65	59	14.5	76	52
Mean SV (mV/s)	3.1	67	60	3.1	61	59	3.3	73	64
P30 (μV².s)	28.0	67	61	28.0	61	59	28.0	73	64
P60 (μV².s)	3.6	64	60	3.6	65	63	3.8	66	68
Duration and P60*	45	76	68	36	79	68	50	81	73

Abbreviations defined in tables 3 and 4. *Variables were combined using the multivariate formula described in the text. The output was used as a score for paroxysmal atrial fibrillation (expressed as a percentage between 0 and 100%).

Figure 3 Receiver operator plots for P wave duration alone (-----) and for P wave duration and P60 considered together using logistic regression (—). Increased deviation of the latter curve to the top left of the graph implies increased discriminant ability.

significant, improvement in the fit of the model. Addition of further variables did not improve performance of the formula. As frequency domain estimates of P wave energy gave better univariate discrimination than time domain measurement of RMS voltage duration and P60 were used to predict paroxysmal atrial fibrillation according to the formula:

$$\ln\{p/(1-p)\} = -13.42 (3.18) + 0.082 (0.02) \text{ duration} + 0.37 (0.13) \text{ P60}$$

where duration and P60 are significant at $P < 0.01$ and values in brackets denote the standard error of each coefficient.

Table 5 and fig 3 show the sensitivities and specificities for this regression formula when applied to all participants, group A, and group B. Important improvements over individual variables are evident with this combination. Overall sensitivity improved to 76% and specificity to 68% using a cut off score of 45%. In group B the sensitivity was 81% with a specificity of 73% using a cut off score of 50%.

Cross validation was performed for all patients and in groups A or B separately for a cut off score of 50%. In all patients a sensitivity of 69% with a specificity of 75% and an overall diagnostic accuracy (percentage of individuals correctly diagnosed) of 72% was achieved. In group B the sensitivity was 65% with a specificity of 85% and a diagnostic accuracy of 74%. The corresponding values were 67%, 74%, and 71% in group A.

Discussion

We found that P waves from patients with paroxysmal AF were longer, had greater spatial velocity, and contained greater energy than those from controls. We observed these differences in patient groups that were selected to control for the confounding influence of concurrent cardiopulmonary disease. Analysis of terminal P wave voltages did not support the existence of "atrial late potentials" that have been reported by others.¹² In part this may be because previous investigators have compared P waves from a heterogeneous group of patients with paroxysmal AF to those from normal controls. Moreover, we have found a low reproducibility for estimates of the terminal P wave voltage when repeated

recordings in the same patients are examined (unpublished observations). A relative increase in high frequency power in the terminal P wave has also been reported in patients with paroxysmal AF¹⁶; but this was not confirmed by our findings, as we did not detect any increase in energy ratios in patients with paroxysmal AF. We have previously shown that spectral analysis of the entire P wave is of greater discriminant value than analysis of only the terminal segment,¹¹ however, and our results are in agreement with others⁶ who have also noted that high and low frequency P wave amplitudes are increased in unchanged proportion in association with paroxysmal AF.

The increased P wave duration and magnitude that we observed in patients with paroxysmal AF cannot be due to coexistent cardiopulmonary disease or greater atrial size, as patients and controls had a similar cardiac or respiratory disease and comparable left atrial diameters. Moreover, we found only moderate correlations between signal averaged P wave variables and left atrial diameter in controls, and none in patients with paroxysmal AF or when all participants were examined. Some effect of atrial pathology was observed on P wave duration (greater in control patients with cardiac or pulmonary disease than in normal controls) that would cause an exaggeration of the difference in P wave duration if we had compared patients with paroxysmal AF and cardiopulmonary disease to normal controls—that is 155 v 136 ms. Thus, when P wave duration is assessed it is important to ensure that patient and control groups are matched for the prevalence of additional cardiac disease. In most of the published studies^{6-9, 12} of the signal averaged P wave in paroxysmal AF differences in P wave duration may have been over estimated by analysis of inadequately matched patient and control groups.

Use of quantitative variables derived from the signal averaged P wave identified patients with paroxysmal AF with reasonable accuracy if duration and a measure of P wave magnitude were used together. The "prospective" diagnostic accuracy is also encouraging at 75% when assessed with cross validation by discriminant analysis. Thus, analysis of the signal averaged P wave using an automatically generated score based on duration and magnitude might be of use for the diagnosis of paroxysmal AF. A more important clinical role may be the use of this technique to predict AF in patients who are already known to be at some risk of arrhythmia and in whom knowledge of those individuals at particularly high risk would be helpful in defining their further management. Patients who could benefit from this approach include those with sinus node disease receiving permanent pacemakers,¹⁷ those after coronary bypass grafting or valvular surgery,^{18, 19} and patients with valvular heart disease or severe left ventricular dysfunction in whom prophylactic anticoagulation might be considered if a high risk of AF was predicted. Further information

concerning the future usefulness of the P wave in arrhythmia diagnosis and prediction must await prospective studies in these patients.

In conclusion, quantitative analysis of the signal averaged P wave in patients with paroxysmal AF showed significant increases in P wave duration and magnitude that were related to the presence or absence of the arrhythmia rather than of concurrent cardiac or respiratory disease. Little relation was found between P wave variables and left atrial diameter. A score derived from these variables using a multivariate approach identified patients with paroxysmal AF with a sensitivity of 76% and specificity of 68% and therefore may be of some use as a diagnostic aid. Further assessment of the clinical utility of the signal averaged P wave for the diagnosis or prediction of paroxysmal AF requires investigation by prospective studies.

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