Detection of Patients with Hypertrophic Cardiomyopathy at Risk for Paroxysmal Atrial Fibrillation during Sinus Rhythm by P-Wave Dispersion

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Summary

Background: Paroxysmal atrial fibrillation (PAF) in hypertrophic cardiomyopathy (HCM) is associated with poor prognosis. Previous studies have shown good correlation between P-wave dispersion (Pd) and occurrence of PAF. However, Pd in patients with HCM for predicting PAF has not been studied.

Hypothesis: The aim of the study was to determine whether Pd could identify patients with HCM who are likely to suffer from PAF.

Methods: Twenty-two patients with HCM with a history of PAF (Group 1) and 26 patients with HCM without a history of PAF (Group 2) were studied. Maximum (Pmax) and minimum (Pmin) P-wave durations, as well as P-wave dispersion (Pd = Pmax – Pmin) were calculated from 12-lead surface electrocardiograms (ECG).

Results: P-wave dispersion was significantly different between the groups (Group 1: 55 ± 6 ms vs. Group 2: 37 ± 8 ms; $p < 0.001$), while Pmax (Group 1: 134 ± 11 ms vs. Group 2: 128 ± 13 ms; $p = 0.06$) and Pmin (Group 1: 78 ± 9 ms vs. Group 2: 81 ± 7 ms; $p = 0.07$) was not significantly different. Patients with a history of PAF had higher left atrial diameter than the patients without PAF (Group 1: 52 ± 8 mm vs. Group 2: 48 ± 10 mm; $p = 0.02$). A cut-off value of 46 ms for Pd had a sensitivity of 76% and a specificity of 82% in discriminating between patients with and without PAF.

Conclusion: This study suggests that P-wave dispersion could identify patients with HCM who are likely to develop PAF.

Key words: hypertrophic cardiomyopathy, atrial fibrillation, P-wave dispersion

Introduction

Hypertrophic cardiomyopathy (HCM) is one of the recognized predisposing conditions for the development of paroxysmal atrial fibrillation (PAF).^{1, 2} Atrial fibrillation (AF) episodes are associated with systemic thromboembolism and poor prognosis in patients with HCM.³

A prolonged intra- and interatrial electrical conduction time, an increased fragmentation of the intra-atrial electrocardiogram (ECG), and an increased dispersion of atrial refractoriness are well-known electrophysiologic characteristics predisposing to AF^{4–6} and are reflected in P-wave morphology and duration on the 12-lead ECG.⁷ Heterogeneity of structural properties of the atrial myocardium in HCM predisposes to generation of unidirectional block of premature impulses, thus causing atrial reentry.⁸ Fananapazir *et al.*,⁹ in a study of 155 patients with HCM who had undergone electrophysiologic study, reported that 66% had prolonged sinoatrial conduction time. The presence of prolonged and fractionated atrial electrograms was also shown to be associated with the induction of PAF.¹⁰

Alterations of P-wave duration have been studied in several clinical settings, such as idiopathic PAF, ischemic heart diseases, after coronary artery bypass surgery, hypertension, and congestive heart failure.^{11–16} Recently, P-wave dispersion (Pd) has been proposed to be a useful index for identifying the risk for AF in several clinical conditions.^{11, 15} Thus, in the present study, we investigated whether Pd could be used to discriminate between patients with HCM with and without a history of PAF.

Methods

Patient Selection

Forty-eight patients (30 men and 18 women; mean age 43 ± 11) with HCM were retrospectively selected for this study.

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Patients were categorized into two groups. Group 1 consisted of 22 patients with a history of PAF and Group 2 of 26 patients without a history of PAF. Hypertrophic cardiomyopathy was defined as the presence of a hypertrophied, nondilated left ventricle demonstrated by M-mode, two-dimensional, and Doppler echocardiography in the absence of other cardiac or systemic disease that might produce left ventricular (LV) hypertrophy.¹⁷ The AF episode was designated as paroxysmal if the episode was terminated spontaneously. Patients were excluded if they met the following conditions: (1) treatment with antiarrhythmic drugs other than beta blocker or verapamil, (2) persistent or permanent AF, (3) other cardiovascular or systemic disease or permanent pacemaker, and (4) moderate or severe mitral regurgitation.

Patient Characteristics

All patients in Group 1 ($n = 22$; mean age 44 ± 12) and in Group 2 ($n = 26$; mean age 42 ± 13) were in sinus rhythm and none were taking type I or type III antiarrhythmic agents. Patients were in New York Heart Association (NYHA) class I or II.

Documentation of Paroxysmal Atrial Fibrillation

Episodes of AF were retrospectively determined by careful examination of the patients' medical records and by reviewing all previous ECGs and Holter recordings. When a patient's ECG documentation had not been obtained, an episode of PAF was decided if the patient's history revealed a symptomatic episode of a rapid, grossly irregular heart beat lasting at least 10 min.¹⁸

Twelve-Lead Surface Electrocardiogram

P-wave duration was calculated in all simultaneously recorded 12 leads of the surface ECG. P-wave duration measurements were obtained manually by two of the investigators blinded to the history of patients by using calipers and a magnifying lens for accurate definition of the ECG deflection as defined in previous studies.^{11, 19} The onset of the P wave for positive waves was defined as the point of the first visible upward departure of the trace from the bottom of the baseline. On the other hand, the onset of the P wave for the negative waves was defined as the point of the first downward departure from the top of the baseline. The return to the baseline of the bottom of the trace in positive waves and the return to baseline of the top of the trace in negative waves was considered to be the end of the P wave. If the baseline noise was $> 10 \mu\text{V}$ and/or the peak of the P-wave amplitude from isoelectric line $< 15 \mu\text{V}$, the lead was excluded from the analysis; if the P wave was measurable in at least nine leads, we kept the patient for further analysis. Pmax in any of the 12-lead surface ECGs was calculated and used as a marker of prolonged atrial conduction time. The difference between Pmax and Pmin duration was defined as P-wave dispersion ($\text{Pd} = \text{P max} - \text{P min}$).¹¹ The average values of P wave, maximum and minimum duration, and Pd

that were obtained from two investigators were used for comparison of patients in Group 1 with those in Group 2. Intra- and interobserver coefficients of variation (standard deviation [SD] of differences between two observations divided by mean value and expressed as percent) were found to be 3.8 and 4.1% for Pmax and 4.28 and 4.72% for Pd, respectively.

Statistical Analysis

Data were presented as mean $\pm$ SD. Statistical analysis was performed using the Student's *t*-test for continuous variables and the chi-square test for categorical variables. Pearson's correlation coefficients were utilized to calculate the correlation between different parametric variables. A stepwise logistic regression analysis was used to determine independent predictors of PAF in patients with HCM. A *p* value < 0.05 was considered statistically significant.

Results

Demographic and echocardiographic variables measured in the groups are presented in Table I. There was no significant difference between the groups in age (Group 1: 44 ± 12 years, Group 2: 42 ± 13 years; $p > 0.05$), gender 36% ($n = 8$) women in Group 1 and 38% ($n = 10$) women in Group 2; $p > 0.05$), NYHA, and in the usage of beta blockers and verapamil ($p > 0.05$). Left ventricular ejection fraction (LVEF), septal thickness, mild mitral regurgitation, and LV outflow gradient under basal conditions ($> 30 \text{ mmHg}$) did not differ significantly between the groups ($p > 0.05$, Table I). P-wave dispersion was not associated with the presence of mild mitral regurgitation, the degree of hypertrophy, LVEF, or NYHA class ($p > 0.05$). There was no significant difference in Pd with respect to obstructive and nonobstructive patients in Group 1 ($p > 0.05$).

TABLE I Demographic and echocardiographic variables measured in the groups

	Group 1 ($n = 22$)	Group 2 ($n = 26$)	p Value
Age (years)	44 ± 12	42 ± 13	NS
Gender (n, male)	14	16	NS
NYHA class	1.5 ± 0.3	1.4 ± 0.4	NS
Left atrial diameter (mm)	52 ± 8	48 ± 10	0.02
Mitral regurgitation (n, mild)	8	9	NS
IVST (mm)	15 ± 6	16 ± 5	NS
LVOT gradient $> 30 \text{ mmHg}$ (n)	10	12	NS
LVEF (%)	63 ± 7	62 ± 9	NS

Abbreviations: IVST = interventricular septal thickness, LVOT = left ventricular outflow gradient, LVEF = left ventricular ejection fraction, NYHA = New York Heart Association, Group 1 = patients with a history of paroxysmal atrial fibrillation, Group 2 = patients without a history of paroxysmal atrial fibrillation.

TABLE II Electrocardiographic variables measured in groups

	Group 1 (n = 22)	Group 2 (n = 26)	p Value
P maximum (ms)	134 ± 11	128 ± 13	0.06
P minimum (ms)	78 ± 9	81 ± 7	0.07
P dispersion (ms)	55 ± 6	37 ± 8	0.001

Group definitions as in Table I.

P-wave dispersion was highly significant in discriminating between the groups (Table II, Fig. 1). Patients with a history of PAF scored higher Pd values than patients without a history of PAF (55 ± 6 ms vs. 37 ± 8 ms; $p > 0.001$). However, maximum and minimum P-wave durations (P max: 134 ± 11 vs. 128 ± 13 ms; $p = 0.06$, P min: 78 ± 9 vs. 81 ± 7 ms; $p = 0.07$ in Groups 1 and 2, respectively) did not significantly differentiate between the groups. Furthermore, higher left atrial (LA) diameter was associated with the presence of a history of PAF, although its predictive importance was less salient than that of Pd (52 ± 8 vs. 48 ± 10 mm in Groups 1 and 2, respectively; $p = 0.02$). Only the Pd remained as a significant independent predictor of PAF in the multivariate analysis ($p = 0.01$). There was a weak correlation between age and Pd ($r = 0.38$; $p > 0.05$), but there was no correlation between LA diameter and Pd ($p = 0.6$).

A cut-off value of 46 ms for Pd had a sensitivity of 76% and a specificity of 82% in discriminating patients with from those without PAF.

Discussion

The principal finding of this study is that P-wave dispersion could be used to discriminate between patients suffering from HCM with and without a history of PAF.

Patients in Group 1 had significantly increased dispersion of P-wave duration, although maximum and minimum P-wave durations did not differ significantly from those in Group 2. Higher Pd on the surface ECG is thought to reflect the heterogeneity of structural and electrophysiologic properties of

atrial myocardium and inhomogeneous propagation of atrial impulse which predisposes to reentry.²⁰ Dilaveris *et al.*^{11, 12, 15} studied Pd in patients with idiopathic PAF, with coronary artery disease and spontaneous angina, and with hypertension separately. Authors have shown higher dispersion of P wave in patients who developed AF. In addition, signal-averaged P-wave duration measurement emerged to be a reliable index for determining the risk for AF in a variety of clinical conditions.^{21–23} Cecchi *et al.*²⁴ conducted the only study with patients suffering from HCM to assess the relation between P-wave duration and the occurrence of AF by using signal-averaged ECG. Our study, however, is the first one carried out to evaluate Pd in discriminating patients with HCM prone to develop PAF.

Aging has many well-known effects on the electrophysiologic properties and pathologic aspects of the atrial myocardium,²⁵ such as fibrosis causing intra-atrial conduction defects. In many studies, age > 60 years was found to be an independent predictor of the frequency of AF.^{23, 26} Although an association between P-wave duration and age has been shown,²⁷ the relation between age and Pd is not known. We found a weak correlation between age and Pd, and as a consequence, age had a negligible confounding effect on the correlation between Pd and the occurrence of PAF.

The most common cause of increased LA size and AF in patients with HCM is the presence of obstruction concomitant with mitral regurgitation. Furthermore, both systolic and diastolic LV dysfunction may also lead to a significant LA enlargement and arrhythmia.^{28, 29} In our study, LA maximum diameter differed significantly between Group 1 and Group 2 patients. This confirms the findings of other studies.^{23, 26, 30} However, in multivariate analysis the significance was less important than that of Pd. This can be explained by the fact that the highly anisotropic properties of the atrial myocardium due to microarchitectural changes in HCM are more important in the genesis of AF paroxysms than cavity size. Indeed, the ECG pattern of LA enlargement is thought to be an independent indicator of the abnormal interatrial conduction, occurring independent of an increased LA size but related to prolongation of interatrial conduction time due to multiple factors.^{31, 32} In the present study, we also found only Pd as a significant predictor of PAF in multivariate analysis.

Limitations

There are some unavoidable limitations to this study as a result of its retrospective nature. Given the very slow progression of AF generation in patients with HCM, a prospective study would be impractical for any clinical investigation. Left atrial diastolic functions found to be abnormal in all forms of HCM irrespective of LV outflow tract obstruction and distribution of hypertrophy have not been assessed in our study.³³ It is likely that HCM involves the heart as a whole and that increased Pd precedes and represents a pathologic process in the atria that creates an environment for PAF to occur. Further prospective clinical studies are needed to evaluate the role of Pd in predicting PAF in patients with HCM.

FIG. 1 Comparison of P-wave durations and P-wave dispersion between the groups. Group 1: Patients with a history of paroxysmal atrial fibrillation; Group 2: Patients without a history of paroxysmal atrial fibrillation. Pd = P-wave dispersion. □ = Group 1, ■ = Group 2.

It is a recognized fact that low P-wave onset and offset amplitudes constitute the main source of error in manual measurement of P waves. On-screen manual evaluation of P-wave duration is likely to be more precise compared with on-paper evaluation. However, it was shown that consistent clinically relevant results were obtained irrespective of the method used for P-wave measurements.³⁴

Conclusion

This study demonstrated that Pd could identify patients with HCM who are likely to develop PAF, which can lead to rapid deterioration of the clinical status by reducing diastolic filling and cardiac output. Thus, early detection of patients with HCM at risk of developing AF may have important implication in choosing preventive measures and treatment strategies.

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