P-Wave Morphologic Characteristics Predict Cardiovascular Events in a Community-Dwelling Population

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Background: There have been few reports on the relationship between P-wave characteristics and long-term cardiovascular events.

Methods: A nested case-control study was conducted as part of the Jichi Medical School cohort study, which enrolled 12,490 subjects in a community-dwelling population. The mean follow-up period was 10.7 years. The P-wave characteristics of 526 patients who suffered cardiovascular events (fatal/nonfatal stroke, fatal/nonfatal myocardial infarction, and sudden death) within the follow-up period (case group) were compared with those of 1578 matched controls (control group). The P-wave morphology was classified as normal, deflected, and notched type in precordial leads. A broad P wave was defined as a maximum P-wave duration of more than 120 ms in any of the 12 leads.

Results: The mean age was 64 ± 8 years and the percentage of males was 54% in both groups. A notched P wave at baseline was observed in 10.1% of the case group and 6.0% of the control group ($P = 0.001$). A notched P wave was a significant predictor of cardiovascular events after adjustment for covariates (odds ratio = 1.59; 95% confidence interval = 1.08–2.33). Among the patients with left ventricular hypertrophy as evaluated by the Sokolow–Lyon criteria or Cornell product criteria, there was no significant difference in cardiovascular events between those with and those without a notched P wave, but in the absence of left ventricular hypertrophy, patients with a notched P wave suffered more cardiovascular events than those without a notched P wave by each criteria.

Conclusion: P-wave morphologic characteristics were effective for predicting cardiovascular events.

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electrocardiography; P wave; cardiovascular event

The P wave on electrocardiography (ECG) reflects atrial electrical propagation. P-wave duration is an indicator of intraatrial conduction time, and there have been reports that the high signal-averaged P-wave duration^{1,2} and high P-wave duration from the 12-lead surface ECG³ are markers of risk for atrial fibrillation. However, the relationship

between P-wave duration and cardiovascular disease remains unclear.

On the other hand, P-wave morphology reflects interatrial conduction.^{3,4} Several studies have reported that the P-wave morphology from signal-averaged ECG and 12-lead surface ECG^{3,5–7} were also markers of risk for atrial fibrillation as

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with the P-wave duration, however, the relationship between P-wave morphology and cardiovascular disease remains uncertain.

Therefore, the aim of this study was to evaluate the relationship among P-wave duration, P-wave morphology, and cardiovascular events.

METHODS

Study Population

This study was conducted as a part of the Jichi Medical School (JMS) Cohort study, which was designed to clarify the risk factors of cardiovascular and cerebrovascular diseases in the Japanese general population. The details of the protocol of the JMS Cohort Study have been reported elsewhere.⁸ Baseline data were collected between April 1992 and July 1995. The mean duration of follow-up was 10.7 years.

Follow-Up System

Repeat examinations were used to follow most subjects every year. Those examined were asked whether they had any history of stroke or myocardial infarction (MI). Subjects with such a history were asked for the time of these incidents and the names of the hospitals where they were treated. Subjects who did not come to the screening examination were contacted by mail or phone. Medical records at hospitals in the area were also checked to determine if these subjects had been hospitalized. Hospitals were responsible for reporting cases of sudden death. Public health nurses also visited the subjects to obtain additional information. If an incident case was suspected, forms for stroke incidence were filled out and duplicate computer tomography films or magnetic resonance imaging films for strokes were obtained.⁹

Diagnostic Criteria

The diagnostic criterion for stroke was sudden onset of a focal and nonconvulsive neurological deficit that lasted for more than 24 hours.¹⁰ Stroke events included ischemic stroke (cerebral infarction and cerebral embolism), hemorrhagic stroke (cerebral hemorrhage and subarachnoid hemorrhage), and undefined type of stroke. We excluded transient ischemic attacks in which the neurological deficit cleared completely within 24 hours from the onset of symptoms.

In subjects who were suspected of having had myocardial events, information about the symptoms, ECG, cardiac enzymes, and necropsy findings (if available) were collected. MI was considered to be present in cases with (1) definite ECG findings (ST segment elevation on ECG), (2) cases with typical or atypical or inadequately described symptoms, together with probable ECG and abnormal enzymes, (3) cases with typical symptoms and abnormal enzymes with ischemic or noncodable or unavailable ECG, or (4) fatal cases, whether sudden or not, with gross appearance of fresh MI and/or recent coronary occlusion found at necropsy.¹¹

Sudden death was defined as death attributable to cardiac causes, heralded by abrupt loss of consciousness, or within 1 hour after the onset of acute symptoms, or an unwitnessed, unexpected death of someone seen in a stable medical condition within 24 hours previously with no evidence of a noncardiac cause. If death was witnessed and occurred within 1 hour after the start of symptoms, we assumed it to be a sudden death, without additional review of medical records.¹² In the case of an unwitnessed death, we sought evidence of cardiac and stroke causes by searching all available information.

The cardiovascular events were defined as fatal/nonfatal stroke, fatal/nonfatal MI, and sudden death. Diagnosis of the cardiovascular events was determined under the consensus of all the members of the diagnostic committee.

Subjects

At baseline, there were a total of 12,490 participants in the JMS Cohort Study at baseline. After excluding 1610 subjects with inadequate follow-up, including subjects with no ECG recording ($n = 1285$), immeasurable ECG findings ($n = 28$), atrial fibrillation ($n = 53$), or no blood pressure data ($n = 160$), and subjects who declined follow-up ($n = 84$), 10,880 subjects remained and were entered into the analysis.

There were 526 cardiovascular events during the follow-up period (case group). These patients were matched for age (to within 2 years) and gender on a 3-to-1 basis to 1578 control subjects (control group), and we analyzed the P-wave duration and morphologic characteristics in both groups, but not in the whole population.

Information about medical history and lifestyle was obtained with a questionnaire at baseline.

Smoking status was judged as smoking, ex-smoking, or never smoking. Alcohol drinkers were defined as subjects who drank at least 20 g/day. Body mass index was calculated as weight (kg)/height (m)². The systolic blood pressure and diastolic blood pressure at baseline were measured with a fully automated sphygmomanometer, BP203RV-II (Nippon Colin, Komaki, Japan).¹³ Blood pressure was measured once after resting for at least 5 minutes in a sitting position. Hypertension was defined as systolic blood pressure ≥ 140 mmHg and/or ≥ 90 mmHg, or medicated hypertension. Diabetes mellitus was defined by a fasting glucose level >7.0 mmol/L (126 mg/dL), a random nonfasting glucose level >11.1 mmol/L (200 mg/dL), or the use of an oral hypoglycemic agent or insulin. Hyperlipidemia was defined by a total cholesterol level >5.7 mmol/L (220 mg/dL), a triglyceride level >1.7 mmol/L (150 mg/dL), or the use of an oral lipid-lowering agent according to the Japan Atherosclerosis Society Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases.¹⁴

ECG Analysis

ECG was measured at a paper speed of 25 mm/s and gain of 10 mm/mV (or 5 mm/mV) using ECG devices available at the participating institutes (FCP130-A9, FCP145-M4, and FCP270-M5; Fukuda Denshi, Japan, among other suppliers.). Both SL voltage (SV1+RV5) and Cornell voltage (RaVL+SV3, with 6 mm added for women) were measured.^{15,16} QRS duration was taken from the beginning of the first detected Q wave to the end of the last S wave. QT interval was measured from the beginning of the QRS complex to the end of the T wave. QRS duration was measured manually from lead II (or lead I or III if the measurement of QRS duration was difficult from lead II) on a single heartbeat. Cornell product (CP) was calculated as the product of Cornell voltage times QRS duration afterward. Sokolow-Lyon-left ventricular hypertrophy (SL-LVH) was defined as >38 mm (3.8 mV), and CP-LVH was defined as 2440 mm $\times$ ms according to a previous report of the Losartan Intervention for Endpoint Reduction in Hypertension Study.¹⁷ The heart rate adjusted QT interval (QTc) was calculated using the Bazett [QTc = QT/(RR^{1/2})] formula.¹⁸ Major ST change was defined according to a past report.¹⁹

Figure 1. P-wave morphology pattern. (A) Normal type, (B) deflected type, (C) notched type. Black arrow: deflected P wave. White arrow: notched P wave.

ECGs were manually analyzed by the use of a magnifying glass by one blinded cardiologist having no information about the patients. The maximum P-wave duration was defined as the longest interval between the earliest onset of the wave (positive deflection crossing the isoelectric line) and the latest offset in any of the 12 leads. A broad P wave was defined as a maximum P-wave duration of more than 120 ms.^{1,20}

P-wave morphology was divided into three subgroups (normal, deflected, and notched) in standard limb leads (I, II, and III) and augmented unipolar limb leads on the left arm, right arm, and left foot (aVL, aVR, and aVF) according to a previous report.³ P waves were defined as "deflected" if the electrocardiogram presented a deviation from a smooth fluent wave without showing a clear bifid pattern (Fig. 1, Panel B). P waves were found to be "notched" if the peak-to-peak distance in the M-shape was more than 1 mm (0.04 second; Fig. 1, Panel C). The levels of intra- and interobserver agreements were found to be acceptable in the determination of notched P waves (intraobserver agreement: κ statistic = 0.53; interobserver agreement: κ statistic = 0.46).

Ethical Issues

The internal review board of the Jichi Medical University School of Medicine approved this study. Written informed consent for the study was obtained individually from all of the subjects during the mass screening examination health checkup.

Statistical Analysis

Data are shown as the mean $\pm$ SD or as a percentage. Student's *t*-test was used to analyze the continuous data of the two study groups. Comparisons of parameters among the groups were made using the chi-square test. The stepwise testing method of multivariate logistic regression analysis was performed to assess the odds ratio and 95% confidence interval of a notched P wave and a broad P wave for cardiovascular events after adjusting for smoking status, history of stroke, and/or MI, systolic blood pressure, triglyceride, glucose, SL-LVH, CP-LVH, major ST change, and QTc duration. SPSS version 15.0 software (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis. A probability value <0.05 was considered statistically significant.

RESULTS

Patients Characteristics

The clinical characteristics of the patients are shown in Table 1. The percentages of current smokers, current drinkers, patients with hypertension and diabetes mellitus, and history of stroke and/or MI were significantly higher in the case group than the control group, and the levels of systolic/diastolic blood pressure, triglyceride, and glucose were significantly higher in the case group than the control group (Table 1).

P-Wave Characteristics in Case Group and Control Group

P-wave characteristics and LVH in the case group and control group at baseline are shown in Table 2. The P-wave duration was similar in both groups, but the percentage of patients with a broad P wave was higher in the case group (Table 2). The percentages of patients with a notched P wave, SL-LVH, and CP-LVH were higher in the case group than the control group (Table 2). The percentages of pa-

Table 1. Baseline Characteristics

Variable	Cases (n = 526)	Controls (n = 1578)	P- Value
Age (yrs)	64.4 $\pm$ 8.3	64.3 $\pm$ 8.1	0.86
Male gender (%)	54.0	54.0	1.00
Body mass index (kg/m ²)	23.0 $\pm$ 3.2	23.1 $\pm$ 3.2	0.86
Smoking status			
Current smoker (%)	31.6	25.2	0.02
Ex-smoker (%)	18.4	20.2	0.02
Nonsmoker (%)	50.0	54.6	0.02
Drinking status			
Current drinker (%)	48.6	47.0	0.54
Ex-drinker (%)	2.5	3.0	0.54
Nondrinker (%)	49.0	50.0	0.68
Hypertension (%)	37.7	20.8	<0.001
Diabetes mellitus (%)	8.7	5.5	0.009
History of stroke (%)	5.5	1.6	<0.001
History of angina pectoris (%)	4.0	2.9	0.24
History of myocardial infarction (%)	2.3	0.7	0.002
Systolic blood pressure (mmHg)	144 $\pm$ 23	134 $\pm$ 21	<0.001
Diastolic blood pressure (mmHg)	84 $\pm$ 13	79 $\pm$ 12	<0.001
Total cholesterol (mg/dL)	192 $\pm$ 35	192 $\pm$ 34	0.90
HDL-cholesterol (mg/dL)	49 $\pm$ 14	50 $\pm$ 13	0.22
Triglyceride (mg/dL)	124 $\pm$ 77	117 $\pm$ 68	0.033
Glucose (mg/dL)	111 $\pm$ 40	104 $\pm$ 25	<0.001

Data are shown as the mean $\pm$ SD or as a percentage.

tients with major ST change were also higher (3.0% vs 0.9%) and the QTc duration was longer (396 $\pm$ 30 vs 389 $\pm$ 28 ms, $P < 0.001$) in the case group than the control group. QRS duration was similar in both groups (88 $\pm$ 17 vs 87 $\pm$ 15 ms, $p = 0.075$). Patients with a notched P wave had a wider P-wave duration than patients without a notched P wave (116 $\pm$ 10 vs 108 $\pm$ 11 ms, $P < 0.001$).

Cardiovascular Risk of a Notched P Wave

The stepwise testing method of multivariate logistic regression analysis was performed to assess the odds ratio and 95% confidence interval of a notched P wave and a broad P wave for

Table 2. P-Wave Characteristics and Left Ventricular Hypertrophy in Cases and Controls at Baseline

Variable	Cases (n = 526)	Controls (n = 1578)	Significance (P-Value)
Maximum P-wave duration (ms)			
Mean $\pm$ SD	109.3 $\pm$ 11.9	108.6 $\pm$ 11.2	0.23
Median (25th–75th percentile)	110 (100–120)	110 (100–120)	
Broad P wave (≥ 120 ms (%))	35.9	31.2	0.047
P-wave morphologic characteristics			
Deflected (%)	33.7	31.2	0.29
Notched (%)	10.1	6.0	0.001
ECG -LVH (Sokolow Lyon) (%)	17.7	12.6	0.003
ECG -LVH (Cornell product) (%)	13.1	7.8	<0.001

ECG = electrocardiography; LVH = left ventricular hypertrophy.

Table 3. Adjusted Odds Ratios for Cardiovascular Disease

	Odds ratio (95% CI)	Significance (P-Value)
Current smoking	1.39 (1.10–1.75)	0.006
History of stroke	3.73 (2.02–6.19)	<0.001
History of myocardial infarction	2.45 (0.97–6.19)	0.058
Systolic blood pressure (10 mmHg)	1.18 (1.13–1.24)	<0.001
Glucose (10 mg/dL)	1.05 (1.02–1.09)	0.004
Major ST change	2.00 (0.89–4.46)	0.092
QTc duration (10 ms)	1.06 (1.02–1.10)	0.001
Notched P wave	1.59 (1.08–2.33)	0.018

The stepwise testing method of multivariate logistic regression analysis was performed to assess the odds ratio and 95% confidence interval for cardiovascular events after adjusting for smoking status, history of stroke and/or myocardial infarction, systolic blood pressure, triglyceride, glucose, left ventricular hypertrophy as evaluated by the Sokolow–Lyon criteria, left ventricular hypertrophy as evaluated by the Cornell product criteria, major ST change, QTc duration, a notched P wave, and a broad P wave. CI = confidence interval.

cardiovascular events after adjusting for smoking status, history of stroke and/or MI, systolic blood pressure, triglyceride, glucose, SL-LVH, CP-LVH, major ST change, and QTc duration. After adjustment of these covariates, a broad P wave was not independently associated with cardiovascular events, but a notched P wave was independently associated with cardiovascular events (odds ratio = 1.59; 95% confidence interval = 1.08–2.33; Table 3)

Cardiovascular Risk of a Notched P Wave in Patients with or without LVH

We analyzed the cardiovascular risk of a notched P wave in patients with or without SL-LVH or CP-LVH. Among patients with SL-LVH (N = 291), there was no significant difference in cardiovascular risk between those who had a notched P wave and those who did not (32% vs 32%, P = 1.00), although in the absence of SL-LVH (N = 1813) those who had a notched P wave suffered more cardiovascular events than those who did not (37% vs 23%, P < 0.001; Fig. 2, Panel A). Among patients with CP-LVH (N = 192), there was no significant difference in cardiovascular risk between those who had a notched P wave and those who did not (50% vs 34%, P = 0.17), although in the absence of CP-LVH (N = 1912) those who had a notched P wave suffered more cardiovascular events than those who did not (34% vs 23%, P = 0.006; Fig. 2, Panel B).

We separately analyzed the association between stroke, MI, and a notched P wave. The percentage of patients with a notched P wave was significantly higher in the case group than the control group when the case group was confined to patients with stroke (8.7% vs 5.4%, P = 0.017), marginally higher when it consisted of patients with MI (14.3% vs 7.4%, P = 0.067), and not significantly different when it consisted of cases of sudden death (15.2% vs 8.7%, P = 0.21).

DISCUSSION

Main Findings

The major finding of this study was that a notched P wave was an independent predictor

Figure 2. Cardiovascular events in patients with or without a notched P wave divided by SL-LVH or CP-LVH. CP-LVH = left ventricular hypertrophy as evaluated by the Cornell product criteria; SL-LVH = left ventricular hypertrophy as evaluated by the Sokolow-Lyon criteria.

of cardiovascular events in a community-dwelling population. Among subjects without SL-LVH or CP-LVH, those who had a notched P wave suffered more cardiovascular events than those who did not, and thus notched P waves might play a role in cardiovascular disease before the development of LVH.

Atrial Activation Pattern and Atrial Fibrillation

It has been reported that P-wave morphology in surface 12-lead ECG was associated with the onset of atrial fibrillation.⁵ P-wave morphology is regulated by the activation pattern of the right and left atriums. It has been shown that the latter half of the P wave represents left atrial activation, and a notched P wave indicates a delay of left atrial activation.^{3,21} Cosio et al. showed that the property of interatrial conduction showed individual differences, and Bachmann's bundle was important for interatrial conduction.²² A conduction delay in the Bachmann's bundle causes interatrial block, and it has been reported that a partial interatrial block

was associated with a notched P wave on inferior leads.²³ Interatrial delay plays an important role in atrial fibrillation,²⁴ and Platonov et al. showed that a notched P wave on unfiltered signal-averaged ECG was associated with paroxysmal atrial fibrillation.²⁵ Recently, it has been reported that abnormal unfiltered and band-pass filtered signal-averaged P-wave morphology is associated with nonsudden cardiac death as well as atrial fibrillation.²⁶ The relationship between a notched P wave and stroke events might be explained through the onset of atrial fibrillation.

P Wave and Hemodynamic Status

The association between the P wave and hemodynamic status remains unclear. A broad P wave on signal-averaged electrocardiogram has been associated with higher pulmonary capillary wedge pressure in patients with chronic heart failure.²⁷ It has also been shown that left ventricular filling pressure was related with left atrial size,²⁸ and thus left atrial load due to diastolic failure might affect the P wave. Kizer et al. showed that left atrial diameter independently predicted incident cardiovascular events after adjustment for established clinical, echocardiographic, and inflammatory risk factors in a population-based cohort.²⁹ Left atrial diameter has been reported to be a marker of clinical/subclinical diastolic failure, and an abnormality of P-wave morphology might cause cardiovascular disease through diastolic failure. Atrial structural remodeling plays an important role in atrial fibrillation with congestive heart failure.³⁰ Gerdtts et al. showed that baseline left atrial diameter/height predicted the incidence of cardiovascular events, and greater left atrial diameter reduction during follow-up was associated with greater reduction in LVH, absence of new-onset atrial fibrillation, or mitral regurgitation.³¹ In a recent paper in which abnormal P-wave morphology was shown to be a predictor of atrial fibrillation and cardiac death, the authors suggested that there may be an association between abnormal P-wave morphology and left atrial enlargement.²⁶ These results suggest that left atrial remodeling might be effective as a marker of hypertensive organ damage in addition to left ventricular remodeling.

In this study, a broad P wave was not an independent risk for cardiovascular events. In previous studies, an increase of P-wave duration was associated with an increase of left atrial volume,³² and

diastolic dysfunction and elevated filling pressures were shown to lead to elevated filling pressures and atrial remodeling, predisposing to atrial fibrillation.³³ These hemodynamic changes might play a role in the increase of cardiovascular events. It has been shown that the P-wave duration increases with age.³⁴ In the present study, however, the control group was matched for age, and thus further studies will be needed to evaluate the mechanism of P-wave duration, because the significance of the cardiovascular risk of high P-wave duration disappeared after adjustment for covariates. The median and percentiles were actually identical, and the mean was very close in this study. The difference between the average, median, and the percentage of patients with prolonged P wave might have been attributable to the distribution of P waves in the cases being wider than that in the controls.

The methods of single tracing ECG have been broadly used in the clinical setting. Further studies will be needed to examine the relation among P-wave morphology determined by a single tracing ECG, atrial fibrillation, and cardiovascular disease.

Study Limitations

This study had several limitations that bear mentioning. First, the number of patients with CP-LVH was relatively small, and thus the lack of significance in cardiovascular risk between those who had a notched P wave and those who did not among patients with CP-LVH might have been due to a lack of statistical power. Second, we did not assess left ventricular function by ultrasound cardiography. Thus, the P-wave morphologic characteristics and cardiovascular events might have been affected by left ventricular function. And finally, we could not obtain ECG data during the follow-up period, and therefore we could not know the onset of atrial fibrillation or how atrial fibrillation affected the occurrence of stroke events.

CONCLUSION

P-wave morphologic characteristics were effective for predicting cardiovascular events.

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