trial fibrillation (AF) is one of the most common rhythm disorders encountered in clinical practice. AF occurs in various diseases, including hypertension, myocardial infarction, valvular heart disease, chronic obstructive pulmonary disease (COPD), diabetes mellitus, hyperthyroidism, and others. AF can be a cause of thromboembolic events and heart failure, both of which reduce physical activity. Therefore, it is important to pay attention to predictor(s) associated with the occurrence of AF.

**Background:** P wave ≥0.25 mV in inferior leads (P pulmonale) occurs in chronic lung diseases that underlie atrial fibrillation (AF). The purpose of this study was to elucidate the prognostic value of P pulmonale for development of AF.

**Methods and Results:** Digital analysis of 12-lead electrocardiogram (ECG) was conducted to enroll patients with P pulmonale from among a database containing 308,391 ECGs. In a total of 591 patients (382 men; 56.4±14.8 years) with P pulmonale (follow-up, 46.7±65.6 months), AF occurred in 61 patients (AF group), but did not occur in 530 patients (non-AF group). Male gender was significantly more prevalent in the AF group than in the non-AF group (80.3% vs. 62.8%, P=0.0047). P-wave duration and PQ interval were significantly longer in the AF group than in the non-AF group (115.4±17.2 ms vs. 107.0±17.2 ms, P=0.0003 and 166.3±23.9 ms vs. 153.2±25.4 ms, P=0.0001, respectively). In the total patient group, multivariate Cox proportional-hazards analysis confirmed that male gender (hazard ratio [HR], 2.24; 95% confidence interval [CI]: 1.02–5.49; P=0.045), PQ interval >150 ms (HR, 6.89; 95% CI: 2.39–29.15; P<0.0001), and P-wave axis <74° (HR, 2.55; 95% CI: 1.20–5.41; P=0.016) were associated with AF development. In medication-free patients (n=400), only PQ interval >150 ms (HR, 9.26; 95% CI: 1.75–170.65; P=0.0055) was independently and significantly associated with AF development.

**Conclusions:** PQ interval is the strongest stratifier for AF development in P pulmonale. (Circ J 2014; 78: 329–337)

**Key Words:** Atrium; Electrocardiography; Fibrillation; Prognosis; Pulmonary disease

**COPD is known as a disease underlying the occurrence of AF.**

**P Pulmonale and the Development of Atrial Fibrillation**

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**Atrial fibrillation (AF) is one of the most common rhythm disorders encountered in clinical practice.** AF occurs in various diseases, including hypertension, myocardial infarction, valvular heart disease, chronic obstructive pulmonary disease (COPD), diabetes mellitus, hyperthyroidism, and others. AF can be a cause of thromboembolic events and heart failure, both of which reduce physical activity. Therefore, it is important to pay attention to predictor(s) associated with the occurrence of AF.
nale may not be a specific ECG marker of RAO.

Despite a number of clinical studies regarding P pulmonale, the prognostic value of P pulmonale for the development of AF remains unclear. At Shiga University of Medical Science, >300,000 ECGs obtained from >100,000 patients have been digitally stored for >20 years and are available for assessing long-term outcome. The purpose of this study was to determine the clinical and ECG characteristics of P pulmonale in association with the development of AF. This study benefited from the reproducibility of ECG measures based on computer-processed analysis and the availability of multiple decades of follow-up data.

**Methods**

**Subjects**

We constructed a database for analyzing resting 12-lead ECG recorded at Shiga University of Medical Science. A total of 102,065 patients (49,286 female; 52,779 male) who had ECGs between January 1983 and October 2008 were collected in the database and a total of 308,391 ECGs were done during this period. The 12-lead ECG was recorded for 10s at a sweep speed of 25 mm/s, calibrated to 1 mV/cm in the standard leads. Twelve leads were simultaneously acquired. The ECG signals were recorded with an interval of 2 ms (ie, 500 Hz). Digital data were stored in a server computer with 12-bit resolution. From the database, patients who fulfilled ECG criteria of RAO were chosen using MUSE7.1 (GE Marquette Medical Systems, Milwaukee, WI, USA). Computer-processed ECG defined RAO criteria as P-wave amplitude ≥0.25 mV in lead II, III, or aVF (Figure S1A). Patients with Wolff-Parkinson-White syndrome, ventricular pacing, junctional or idioventricular rhythm and ventricular tachyarrhythmias were excluded. Patients who were <15 years old were also excluded from the analysis. Clinical diagnosis was determined from International Classification of Diseases codes. The research protocol was approved by the Ethics Committee of Shiga University of Medical Science.

**Digital Analysis of ECG**

MUSE7.1 identified identical P wave using the template matching technique. A point that had an area ≥160 μV/ms from baseline was considered to be P-wave onset, and a point that had an area ≤160 μV/ms toward baseline was considered to be P-wave offset. The duration, amplitude, and area of total P wave in leads II, III, aVF and V1 were measured using matrix parameters available in MUSE7.1. P-wave area was constructed by integrating the duration and amplitude. The duration, amplitude, and area of the initial and terminal portions of P wave in lead V1 were also measured. We also calculated duration×amplitude of P-wave initial and terminal portions in lead V1 as a force value. For the ECG measurement, a median complex was computed as follows: (1) all P waves of the same morphology were aligned in time; and (2) the algorithm generated a representative P wave from the median voltages that were found at each successive sample time. P-wave duration was measured from the earliest onset in any lead to the latest offset in any lead. PR interval, QRS duration, and QT interval were measured in a similar manner, and the average of the 10-s recording time was used. Standardized, computerized ECG criteria according to a 12-lead ECG analysis program were used to diagnose abnormal intraventricular morphologies. Given that all measurements of 12-lead ECG were digitally performed using MUSE7.1, neither intra-observer nor inter-observer vari-
ability occurred in this study.

**Follow-up**

The occurrence of AF was set as the primary outcome. We compared the patients who had AF during the follow-up period (the AF group) and those who did not (the non-AF group). In patients who developed AF during follow-up, we compared clinical characteristics and ECG variables between the AF group and the non-AF group. The follow-up period was defined as the interval between the first day and the last day when ECG was done.

**Statistical Analysis**

Continuous variables are presented as mean±SD and categorical variables, as observed number of patients (percentage). To compare patient characteristics and ECG characteristics between groups, t-test was used for continuous variables and $\chi^2$ test for categorical variables. Receiver operating characteristic curve was used to determine a cut-off point for prognostic factors optimizing the sensitivity and specificity of ECG variables for the development of AF. The Kaplan-Meier curve was used to describe the difference between 2 groups and log-rank test was used for examining the difference. Cox proportional hazard analysis was used to estimate multivariate adjusted hazard ratios (HRs) accounting for confounders (age, gender, presence of various diseases, and ECG variables). Variables were included in the Cox model if they were significant at $P<0.1$. Because chronotropic drugs (ie, $\beta$-blockers, calcium channel

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**Table 2. Baseline ECG Characteristics**

| Measurements                  | AF group (n=61) | Non-AF group (n=530) | P-value |
|-------------------------------|----------------|---------------------|---------|
| Heart rate (beats/min)        | 87.3±22.0      | 92.5±18.3           | 0.037   |
| P-wave duration (ms)          | 115.4±17.2     | 107.0±17.2          | 0.0003  |
| P-wave axis (°)               | 73.2±8.0       | 75.7±8.4            | 0.030   |
| PR interval (ms)              | 166.3±23.9     | 153.2±25.4          | 0.0001  |
| P-wave duration (ms) Lead II  | 115.4±17.2     | 106.9±17.3          | 0.0003  |
| P-wave duration (ms) Lead III | 115.0±17.5     | 106.5±17.0          | 0.0002  |
| P-wave duration (ms) Lead aVF | 115.4±17.2     | 106.9±17.2          | 0.0003  |
| P-wave amplitude (μV)         |                |                     |         |
| Lead II                       | 277.2±25.7     | 279.1±34.3          | 0.68    |
| Lead III                      | 212.6±41.8     | 217.9±43.6          | 0.37    |
| Lead aVF                      | 243.7±31.2     | 247.6±36.2          | 0.42    |
| P-wave area (μVxms)           |                |                     |         |
| Lead II                       | 818.7±164.8    | 730.0±130.7         | <0.0001 |
| Lead III                      | 577.7±163.8    | 548.4±134.3         | 0.12    |
| Lead aVF                      | 699.5±156.5    | 637.2±123.3         | 0.0003  |
| P wave in lead V1             |                |                     |         |
| Initial portion               |                |                     |         |
| Duration (ms)                 | 47.7±16.8      | 51.8±27.2           | 0.25    |
| Amplitude (μV)                | 75.8±51.6      | 73.8±57.7           | 0.80    |
| Area (μVxms)                  | 103.0±78.1     | 111.9±106.3         | 0.53    |
| Initial force (s×mm)          | 0.039±0.029    | 0.046±0.052         | 0.30    |
| Terminal portion              |                |                     |         |
| Duration (ms)                 | 64.0±22.5      | 51.7±28.6           | 0.0012  |
| Amplitude (μV)                | –90.2±57.7     | –69.6±55.5          | 0.0064  |
| Area (μVxms)                  | –164.4±120.6   | –110.0±109.7        | 0.0003  |
| Terminal force (s×mm)         | 0.066±0.048    | 0.047±0.046         | 0.0031  |
| QRS-complex duration (ms)     | 93.0±10.4      | 92.1±15.9           | 0.68    |
| QRS-complex axis (°)          | 58.0±32.6      | 56.8±47.9           | 0.86    |
| Complete right BBB            | 0 (0)          | 22 (4.2)            | 0.027   |
| Incomplete right BBB          | 1 (1.6)        | 11 (2.1)            | 0.81    |
| Left BBB                      | 0 (0)          | 3 (0.6)             | 0.42    |
| LVH with strain               | 5 (8.2)        | 31 (5.9)            | 0.49    |
| LVH without strain            | 21 (34.4)      | 176 (33.3)          | 0.86    |
| RVH                           | 1 (1.6)        | 23 (4.4)            | 0.26    |
| S1S2S3 pattern                | 3 (4.9)        | 53 (10.0)           | 0.16    |
| QTc interval (ms)             | 428.4±29.9     | 431.9±28.3          | 0.37    |
| T-wave axis (°)               | 56.0±44.6      | 63.1±41.6           | 0.21    |

Data given as mean±SD or n (%). S1S2S3 pattern reflects an anomalous wavefront that is rightward and superiority oriented, opposed to the electrical forces of the ventricular free wall. BBB, bundle branch block; ECG, electrocardiogram; LVH, left ventricular hypertrophy; RVH, right ventricular hypertrophy. Other abbreviation as in Table 1.
Figure 1. Kaplan-Meier estimates of atrial fibrillation (AF)-free rate in the total group.

Table 3. Independent Predictors of AF in the Total Group

|                  | Univariate | Multivariate |                  |                  |
|------------------|------------|--------------|------------------|------------------|
|                  | HR         | 95% CI       | P-value          | HR               | 95% CI       | P-value |
| Gender (male=1)  | 2.02       | 0.95–4.80    | 0.068            | 2.24             | 1.02–5.49    | 0.045   |
| Age ≥60 years    | 1.38       | 0.68–2.76    | 0.37             | 1.27             | 0.60–2.67    | 0.52    |
| Area of P-wave terminal portion in lead V1 >–115 μV×ms | 2.68 | 1.33–5.75 | 0.0056 | 1.80 | 0.85–4.03 | 0.12 |
| PQ interval >150 ms | 9.28 | 3.31–38.73 | <0.0001 | 6.89 | 2.39–29.15 | <0.0001 |
| QT interval >353 ms | 2.18 | 1.08–4.67 | 0.03 | 0.89 | 0.34–2.31 | 0.76 |
| P-wave axis <74° | 2.74       | 1.38–5.47    | 0.0044           | 2.55             | 1.20–5.41    | 0.016   |
| Heart rate <89 beats/min | 2.37 | 1.16–5.21 | 0.018 | 1.92 | 0.74–5.15 | 0.18 |
| Hypertension     | 1.26       | 0.58–2.56    | 0.54             |                  |              |        |
| Heart failure    | 1.99       | 0.79–4.38    | 0.13             |                  |              |        |
| Valvular disease | 4.42       | 1.64–10.08   | 0.0053           | 2.16             | 0.77–5.20    | 0.13    |

CI, confidence interval; HR, hazard ratio. Other abbreviation as in Table 1.

Table 4. Baseline Characteristics in Chronotropic Drug-Free Patients

|                  | AF group (n=25) | Non-AF group (n=375) | P-value |
|------------------|-----------------|----------------------|---------|
| Age (years)      | 56.7±13.6       | 55.1±15.1            | 0.60    |
| Gender (male)    | 21 (84.0)       | 228 (60.8)           | 0.014   |
| Lung disease     | 6 (24.0)        | 78 (20.9)            | 0.71    |
| COPD             | 4 (16.0)        | 41 (11.0)            | 0.46    |
| Pulmonary hypertension | 1 (4.0) | 6 (1.6) | 0.44 |
| Bronchial asthma | 1 (4.0)         | 20 (5.4)             | 0.76    |
| Lung cancer      | 1 (4.0)         | 7 (1.9)              | 0.51    |
| Diabetes mellitus | 4 (16.0)    | 58 (15.6)            | 0.95    |
| Cerebral infarction | 0 (0)        | 15 (4.0)             | 0.16    |
| Arteriosclerosis obliterans | 0 (0) | 9 (2.4) | 0.28 |
| Dyslipidemia     | 2 (8.0)         | 32 (8.6)             | 0.92    |
| Hypothyroidism   | 1 (4.0)         | 13 (3.5)             | 0.90    |

Data given as mean±SD or n (%). Abbreviations as in Table 1.
P Pulmonale and AF

Clinical Characteristics
A total of 591 patients (64.6% men; mean age, 56.4±14.8 years) who had P pulmonale were chosen from the database using the 12SL ECG analysis program (GE Marquette Medical Systems) and were enrolled for ECG analysis. In the total patient group, 130 (22.3%) had lung disease; and 276 patients (47.4%), cardiovascular disease. During follow-up, 61 patients (10.3%) developed AF (AF group), while 530 patients did not present AF on ECGs (non-AF group). The number of ECGs done was higher in the AF group than in the non-AF group (17.7±17.9/patient vs. 9.5±15.2/patient; P<0.01).

Table 5. Baseline ECG Characteristics in Medication-Free† Patients

| Measurements                          | AF group (n=25) | Non-AF group (n=375) | P-value |
|---------------------------------------|----------------|----------------------|---------|
| Heart rate (beats/min)                | 87.5±23.6      | 92.3±18.6            | 0.16    |
| P-wave duration (ms)                  | 112.8±14.9     | 106.4±17.1           | 0.068   |
| P-wave axis (°)                       | 43.4±22.5      | 163.0±25.2           | 0.029   |
| PR interval (ms)                      | 112.8±14.9     | 106.3±17.1           | 0.066   |
| Lead II                               | 270.8±16.8     | 277.7±30.3           | 0.26    |
| Lead III                              | 213.4±30.6     | 218.6±39.9           | 0.52    |
| Lead aVF                              | 241.6±20.0     | 247.0±32.8           | 0.41    |
| Lead II                               | 767.4±103.4    | 722.8±124.5          | 0.081   |
| Lead III                              | 562.2±111.5    | 549.8±129.8          | 0.64    |
| Lead aVF                              | 668.9±101.2    | 633.9±120.3          | 0.16    |

P wave in lead V1

| Initial portion                        | AF group (n=25) | Non-AF group (n=375) | P-value |
|---------------------------------------|----------------|----------------------|---------|
| Duration (ms)                         | 60.0±17.7      | 48.6±29.1            | 0.053   |
| Amplitude (μV)                        | 80.2±46.6      | 61.1±51.8            | 0.074   |
| Area (μV×ms)                          | 137.9±98.4     | 93.3±98.1            | 0.028   |
| Initial force (s×mm)                  | 0.052±0.036    | 0.041±0.042          | 0.18    |

QRS-complex duration (ms) 90.1±11.0 91.1±14.8 0.74

Table 5 lists the comparison of clinical and demographic characteristics between the AF group and non-AF group. No significant difference in age was seen between the 2 groups. P pulmonale was more prevalent in men than in women in both the AF group and non-AF group. The male predominance was significantly higher in the AF group than in the non-AF group. No significant difference was seen in the prevalence of lung disease between the 2 groups. In contrast, the morbidity of heart disease was signifi-
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**ECG Characteristics**
The ECG variables are listed in Table 2. In the AF group, heart rate was significantly slower, P-wave duration was significantly longer, P-wave axis was significantly more vertical, and PR interval was significantly longer compared to the non-AF group. QRS duration, QT interval, QTc interval, QRS-complex axis, and T-wave axis were not significantly different between the 2 groups. In leads II, III, and aVF, P-wave duration was significantly longer in the AF group than in the non-AF group; but P-wave amplitude was not significantly different between the 2 groups in inferior leads. P-wave area was significantly larger in the AF group than in the non-AF group in inferior leads except lead III. To determine whether LAO was present, the P wave in lead V1 was evaluated. In the P-wave initial portion in lead V1, there was no significant difference in the duration, amplitude, area, or initial force between the AF group and non-AF group. In contrast, in the P-wave terminal portion in lead V1, the duration, amplitude, area, and terminal portion were significantly greater in the AF group than non-AF group. QRS-complex duration, QRS-complex axis, various QRS morphological characteristics, QTc interval, and T-wave axis were not significantly different between the 2 groups.

**Long-Term Outcome**
The mean follow-up period of the non-AF group was significantly longer than that for the AF group (60.8±71.4 months vs. 45.1±64.8 months, P<0.001). For survival analysis, AF occurrence-free Kaplan-Meier plots were constructed according to independent stratifiers of AF development. Figure 1 shows AF occurrence-free rate in the total group. The AF occurrence-free rate was significantly higher in patients with PR interval ≤150 ms than in those with PR interval >150 ms (HR, 9.28: 95% confidence interval: 3.31–38.73; P<0.0001).

Table 3 shows univariate and multivariate analyses in association with AF development. On univariate analysis, male gender, area of P-wave terminal portion in lead V1, PQ interval, QT interval, P-wave axis, heart rate, and valvular disease were associated with the development of AF. Because there was a strong correlation between P-wave duration and PQ interval, P-wave duration was not included in multivariate analysis. On multivariate Cox proportional hazard analysis, male gender, PR interval >150 ms and P axis <74° were identified as independently and significantly associated with the development of AF.

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Table 6. Independent Predictors of AF in Medication-Free Patients

|                       | Univariate | Multivariate |
|-----------------------|------------|--------------|
|                       | HR 95% CI  | P-value      | HR 95% CI  | P-value |
| Gender (male=1)       | 2.01 0.63–9.48 | 0.24          | 1.97 0.57–9.03 | 0.30  |
| Age ≥60 years         | 1.59 0.46–5.25 | 0.45          | 1.21 0.34–4.06 | 0.76  |
| Area of P-wave terminal portion in lead V1 >–77μV×ms | 2.22 0.70–8.31 | 0.18          |         |       |
| PQ interval >150 ms   | 11.22 2.18–205.10 <0.0016 | 9.26 1.75–170.65 0.0055 |         |       |
| QT interval >353 ms   | 2.28 0.72–8.56 | 0.16          |         |       |
| P-wave axis <74°      | 1.58 0.42–5.02 | 0.47          |         |       |
| Heart rate <89 beats/min | 3.26 0.97–14.73 | 0.056         | 2.14 0.60–9.93 | 0.25  |

1Chronotropic and anti-arrhythmic drug free.

Abbreviations as in Table 1,3.
Analysis of Medication-Free Patients

Because of the plausible effects of pharmacological treatment on the development of AF and PR interval, we repeated the multivariate analysis in patients without medications such as β-blocker, calcium antagonist, digitalis and anti-arrhythmic drugs. In all patients enrolled in this study, 400 patients did not receive those medications. The clinical and demographic characteristics of the drug-free patients are listed in Table 4. The prevalence of male gender was significantly higher in the AF group than in the non-AF group, but the prevalence of various diseases was not significantly different between the 2 groups. The ECG characteristics of medication-free patients are listed in Table 5. PR interval was significantly longer in the AF group than in the non-AF group. Figure 2 shows AF occurrence-free rate in patients without medication (follow-up period: AF group, 46.1±62.8 months vs. non-AF group, 58.8±61.4 months; P<0.001). Table 6 shows univariate and multivariate analyses in association with the development of AF. Although PQ interval and heart rate were associated with the development of AF on univariate analysis, multivariate Cox proportional hazard analysis showed that only PR interval >150 ms was independently and significantly associated with the development of AF in patients without medication.

Discussion

The present study has elucidated the detailed clinical and ECG characteristics in patients with P pulmonale and the prognostic implication of P pulmonale for developing AF. In the present cohort, the major findings are: (1) approximately 10% of patients with P pulmonale developed AF during the follow-up; (2) no disease was significantly associated with the development of AF; and (3) PQ interval >150 ms was an independent risk stratifier of the development of AF.

P Pulmonale

Several studies reported that P pulmonale was observed in COPD.11-18 Because atrial depolarization spreads from the right atrium to the left atrium, the first portion of the P wave is attributed to the excitation of the right atrium. When an amount of right atrial musculature increases parallel to the frontal plane, P pulmonale results. Abildskov et al reported a close association of an increased amount of atrial musculature in the enlarged right atrium of human specimens with the tall P wave.19 Furthermore, hemodynamic correlation with the amplitude of P wave in inferior leads was not observed.20 Zuckerman et al postulated that a vertically straight position was attributed to P pulmonale in COPD.21 In addition, Chou and Helm reported that P pulmonale was present in patients with left ventricular dysfunction.13 Taken together, several mechanisms contribute to the formation of P pulmonale. In this study, P pulmonale was present not only in COPD but also in heart disease. Of note, P pulmonale was more frequently observed in patients with heart disease than in patients with COPD in this study, suggesting that overload occurred in both atria, rather than RAO alone, in the present subjects. Left-sided heart failure can cause pulmonary hypertension, subsequently leading to right-sided heart failure. This suggests that right-sided heart failure might have been involved in the present study. Therefore, heart disease has the potential to increase the amplitude of the initial portion of the P wave in inferior leads. Although we do not know how many patients had right-sided heart disease, it is possible that right- and left-sided heart failure might coexist in some patients, because intracardiac pressure of the right-sided chambers is passively increased in left-sided heart failure.

P Pulmonale and AF

Although COPD is one of the diseases underlying AF, the prognostic value of P pulmonale for the development of AF has not been fully investigated. This study showed that AF developed in 10.3% of the total patient group and in 6.3% of the medication-free patients. In the present database, AF was present in 4.1% of the male patients and in 1.9% of the female patients. In a general Japanese population aged ≥40 years, the prevalence of AF was reported to be 1.6%.22 Another report showed that the prevalence was 4.4% in men and 2.2% in women even aged ≥80 years in Japan.23 Annual AF incidence was reported to be 9.3/1,000 patient-years in Japanese subjects aged ≥40 years.24 In the present study, the overall incidence of AF development was 115/1,000 patient-years. Therefore, patients with P pulmonale were at high risk for the development of AF, which is suggestive of a propensity toward occurrence of AF in the atrium representing P pulmonale on ECG. Regarding the relationship between P pulmonale and AF development, the prevalence of heart disease was higher in the AF group than the non-AF group; but the prevalence of COPD was identical between the 2 groups. The present results are different to previously reported risk stratifications. de Vos et al reported that COPD was an independent factor of progression from paroxysmal to sustained AF in addition to age and underlying heart disease.26 After adjustment, the HATCH score (hypertension, age >75 years, prior transient ischemic attack or stroke, COPD, and heart failure) was validated as an independent predictor for the progression of AF in cardiology practice patients. The discrepancy between the present results and those of previous studies might be due to the presence of COPD patients in the present cohort, the pulmonary function of whom was not so severe.

We reported that the magnitude of both the initial and terminal portions of biphasic P wave in lead V1 was associated with the development of AF, suggesting that RAO and LAO may share similar fundamental mechanisms.27 Organic heart disease might cause chronic stretch and atrial dilation, which seems to be important stimuli for chronic atrial structural remodeling (cellular hypertrophy, fibroblast proliferation, and tissue fibrosis), thus enabling maintenance of AF.28,29 Consistent with these fundamental mechanisms, RAO represented by P wave was found to be a novel risk stratifier for the development of AF.

In the total patient group, the duration, amplitude, and area of the P-wave terminal portion in lead V1 were significantly greater in the AF group than in non-AF group. Similarly, the area of the P-wave terminal portion in lead V1 was significantly greater in the AF group than in the non-AF group in the medication-free patients. These findings indicate that the left atrium was more overloaded in the AF group than in the non-AF group. Therefore, it is possible that AF might originate from the pulmonary vein.

It is noteworthy to mention the relationship between the development of AF and underlying disease in P pulmonale. Although patients with chronic lung disease and heart disease are generally at high risk for the development of AF, no disorders were associated with the development of AF in the present study. To clarify what kind of disease is associated with the development of AF in the presence of P pulmonale, more
studies are necessary.

**PQ Interval and AF**

To our knowledge, the present study is the first investigation based on P pulmonale patients, showing that PQ interval was independently associated with the development of AF after adjustment of confounding factors. The number of patients who took medication was relatively low. In addition, the results did not change after exclusion of individuals with medication, including drugs affecting the cardiac conduction system.

Prior studies have raised the possibility that slowed intra- or inter-atrial conduction may directly increase the risk of AF, and increased atrial conduction time or intra-atrial block may manifest as prolongation of PR interval. Therefore, we used PR interval results in delayed and ineffective mitral valve closure and diastolic mitral regurgitation, thus leading to heart failure.

There are several potential explanations for the observed association of prolonged PR interval with the development of AF. Anatomical abnormalities such as fibrosis and calcification near the atrioventricular node have been reported to be associated with prolongation of PQ interval. Autonomic as well as structural cardiac abnormalities may cause prolongation of PQ interval. Because the present patients were aged 56.4±14.8 years, it is unlikely that prolonged PR interval was caused by enhanced vagal tone. Therefore, age-related blunting of the catecholaminergic effect on the atrioventricular node could also result in the same ECG manifestation.

**Study Limitations**

There are several limitations worth noting. First, the reasons for undergoing ECG have not been thoroughly documented; namely, the tests were ordered according to physician discretion. Therefore, it is possible that the more frequent the ECGs, the higher the likelihood of detecting AF. Second, the intermittent or asymptomatic nature of AF may lead to underestimation of AF development. Third, clinical information on the patient cohort, such as echocardiographic markers, was not included in the analysis. Fourth, we did not classify clinical types of AF, which in turn means the severity of AF was not considered in this study. Fifth, because ECGs were done according to physician decision, the time interval between ECGs was not constant. Therefore, this method might affect the significant difference of the number of ECGs done between the AF group and non-AF group, and some episodes of AF incidence might have been missed. Sixth, the correlation between PR interval and P-wave duration needs to be mentioned. P-wave duration represents the time during which the RA and LA depolarize; while PR interval represents the depolarization of the atria and the atrioventricular node. Because there was a strong correlation between P-wave duration and PQ interval, P-wave duration was not included in multivariate analysis. We thought that PR interval might reflect the right-sided atrial abnormality more precisely than P-wave duration. Therefore, we used PR interval as a covariate. Last, we did not analyze the prognostic value of P pulmonale depending on type of AF: paroxysmal, persistent, or permanent. A larger patient group is needed to determine differential characteristics according to AF type.

**Study Implications**

This study provides information for decision-making in cardiac practice: usefulness for early detection of patients in an effort to prevent the development of AF. Patients who have P pulmonale and prolonged PR interval would be recommended to have frequent ECGs to prevent complications relating to AF, irrespective of presence of heart disease or chronic lung disease. In addition, we recommend opportunistic screening for AF by pulse palpation. Therefore, the ECG characteristics identified in the present study potentially enable stratification of patients at risk for cardiovascular morbidity. To determine whether prophylactic anticoagulation therapy is necessary in patients with P pulmonale, more studies are needed, especially involving the general population.

**Disclosures**

Conflict of interest: None.

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Supplementary Files

Supplementary File 1

Figure S1. (A) Initial 12-lead electrocardiogram (ECG) showing typical P pulmonale (tall P wave in inferior leads) in a 55-year-old man.

Please find supplementary file(s):
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