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Prediction of Paroxysmal Atrial Fibrillation in Patients With Congestive Heart Failure: A Prospective Study

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OBJECTIVES We sought to prospectively determine whether patients with congestive heart failure (CHF) at risk for paroxysmal atrial fibrillation (PAF) could be identified by clinical and study variables including the P-wave signal-averaged electrocardiogram (P-SAECG).

BACKGROUND Although it is important to assess the risk of developing PAF in patients with CHF, it still remains difficult to predict the PAF appearance in patients with CHF clinically.

METHODS The study group consisted of 75 patients in sinus rhythm without a history of PAF, whose left ventricular ejection fraction, as measured by radionuclide angiography, was <40%. These patients underwent P-SAECG, echocardiography and 24-h Holter monitoring; in addition, the plasma concentration of atrial natriuretic peptide (ANP) was measured at study entry.

RESULTS An abnormal P-SAECG was found at study entry in 29 of 75 patients. In the follow-up period of 21 ± 9 months, the PAF attacks documented on the ECG significantly more frequently occurred in patients with (32%) rather than without an abnormal P-SAECG (2%) ($p = 0.0002$). The plasma ANP level was significantly higher in patients with rather than without PAF attacks (75 ± 41 vs. 54 ± 60 pg/ml, $p = 0.01$), although there were no significant differences in age, left atrial dimension or high grade atrial premature beats between the groups. The multivariate Cox analysis identified that the variables significantly associated with PAF development were an abnormal P-SAECG (hazard ratio 19.1, $p = 0.0069$) and elevated ANP level ≥60 pg/ml (hazard ratio 8.6, $p = 0.018$).

CONCLUSIONS An abnormal P-SAECG and elevated ANP level could be predictors of PAF development in patients with CHF. (J Am Coll Cardiol 2000;35:405–13) © 2000 by the American College of Cardiology

Atrial fibrillation (AF) occurs in a variety of clinical settings, and congestive heart failure (CHF) is one of the established predisposing conditions for the development of AF (1–3). Some studies have shown that the onset of AF was associated with clinical and hemodynamic deterioration and might predispose to systemic thromboembolism and poorer prognosis (4,5). The ability to define the risk factors for AF in patients with CHF would have important clinical relevance. However, it remains unclear which type of patients with CHF would develop AF.

Recently, other investigators (6–8) and we (9–12) have used the P-wave signal-averaged electrocardiogram (P-SAECG) to assess the risk of paroxysmal atrial fibrillation (PAF) attacks. However, these studies included fewer patients with impaired cardiac function. In patients with CHF, the atrial electrophysiologic property might be modified by hemodynamic overloading (13–15) and neurohumoral activation (16,17), which are frequently observed in CHF. It remains to be clarified whether the appearance of PAF attacks in patients with CHF would also be predicted by the P-SAECG. The aim of this study was to determine prospectively whether patients with CHF at risk for PAF would be identified by clinical and study variables including the P-SAECG.

METHODS

Study patients. This study included 104 consecutive outpatients with stable CHF whose left ventricular ejection fraction (LVEF), as measured by radionuclide angiography, was <40%, and these patients were screened in our heart

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Abbreviations and Acronyms

Ad	= duration of signal-averaged P wave
AF	= atrial fibrillation
ANP	= atrial natriuretic peptide
APB	= atrial premature beat
CHF	= congestive heart failure
LAD	= left atrial dimension
LP_{20}	= root-mean-square voltage for the last 20 ms of signal-averaged P wave
LVEF	= left ventricular ejection fraction
NYHA	= New York Heart Association
PAF	= paroxysmal atrial fibrillation
P-SAECG	= signal-averaged electrocardiogram

failure unit between September 1995 and November 1997. Twenty-nine of 104 patients were excluded because 1) the underlying rhythm was not sinus (chronic AF in 22 patients); 2) there was a history of PAF documented on the ECG (three patients were taking a class Ia or Ic antiarrhythmic drug); 3) three patients were taking amiodarone, which could affect the results of the P-SAECG, because of sustained ventricular arrhythmia; and 4) one patient did not give consent to the follow-up period. A total of 75 patients were enrolled in this study. Each patient gave written, informed consent to participate in this study, which was approved by the Review Committee of the Osaka Prefectural General Hospital.

The mean age of the patients was 65 ± 11 years (range 34 to 85) at study entry. There were 61 men and 14 women. Fifty of them (67%) had ischemic heart disease, and the remaining 25 patients (33%) had nonischemic etiologies. The average New York Heart Association (NYHA) functional classification was 2.1 ± 0.6, with 18% of patients in class I, 57% in class II and 24% in class III congestive heart failure. The LVEF was 30 ± 6% (range 14% to 39%). The interval from the onset of CHF symptom, such as exertional dyspnea, to study entry was 32 ± 27 months (range 3 to 108).

Measurements. Before entering this study, patients underwent radionuclide angiography. At entry, all patients underwent P-SAECG, standard 12-lead ECG, 24-h Holter monitoring and echocardiography; 6-min walk distance was also measured. Furthermore, venous blood was sampled for assay of plasma neurohormones.

RADIONUCLIDE ANGIOGRAPHY. All patients underwent ECG-gated blood pool scintigraphy at rest in the supine position using a conventional rotating gamma camera (Prism 2000, Picker, Bedford, Ohio) equipped with a low energy, high resolution, parallel-hole collimator. Patients were given 740 MBq of technetium-99m–labeled human serum albumin (Nihon Medi-Physics, Nishinomiya, Japan). The camera was positioned in the modified left anterior oblique projection to isolate the left ventricle from other cardiac structures, and data acquisition was then performed. Then, LVEF was calculated using the standard program (18).

P-WAVE SIGNAL-AVERAGED ELECTROCARDIOGRAPHY. The methodology of P-SAECG recording and analysis has been described previously (9–11). The P-SAECG was recorded from a modified X, Y and Z lead system using the VCM-3000 (Fukuda Denshi, Ltd., Tokyo, Japan). All of the digital data were stored on a floppy disk. The standard lead I was used as the X lead. Lead aVF was used as the Y lead. Similarly, the precordial lead V_1 was used as the Z lead. The signal from each lead was amplified up to 5 μV/cm and passed through a low bandpass filter of 300 Hz (the slope; 12 dB/octave) and a high bandpass filter of 40 Hz (the slope; 18 dB/octave), and then converted from analog-to-digital data to a 12-bit accuracy at the sampling rate of 1 kHz. A specially filtered P wave derived from the selected dominant sinus P wave of lead II or V_1 served as a reference signal for all processing. After passing through a P-wave recognition program to eliminate ectopic atrial beats, signals >200 beats were averaged on a trigger point within the specially filtered P wave. If the noise level remained >1 μV, even after 200 beats averaging, the averaging was continued until the peak noise level was reduced to <1 μV. The filtered signals for the X, Y and Z leads were combined into a spatial magnitude: $(X^2 + Y^2 + Z^2)^{1/2}$. The onset and offset of the filtered P wave were defined as signals during the interval when signals showed a persistent level of 1 μV. The duration (Ad) and the root-mean-square voltage for the last 20 ms (LP_{20}) of the signal-averaged P wave were measured in the vector magnitude. Percent variation (day to day) of Ad and LP_{20} in patients with CHF were 1.3 ± 0.4% and 8.8 ± 4.3% (n = 32), respectively.

An abnormal P-SAECG was defined as Ad >132 ms and LP_{20} <2.3 μV, each of which was the 90th percentile value obtained from 132 normal control subjects (66 men and 66 women, average age 38 ± 17 years [range 14 to 80]) who had neither clinical symptoms nor signs suggestive of organic heart disease on chest radiography or standard ECG. The Ad and LP_{20} were 118 ± 10 ms and 3.2 ± 0.9 μV, respectively. An abnormal P-SAECG was observed in only 3 (2.3%) of the 132 normal control subjects.

STANDARD ELECTROCARDIOGRAPHY. The P-wave duration and the PR interval were measured in lead II of the scalar ECG recorded at a chart speed of 200 mm/s, and the presence of P mitrale (left atrial enlargement) was also examined in lead V_1 (a negative P wave of 0.04 s in duration and 0.1 mV in depth).

HOLTER MONITORING. Twenty-four-hour dual-channel Holter ECG recordings were obtained with a Marquette Electronics (Milwaukee, Wisconsin) 8000 Holter monitoring system. Holter data were evaluated by the number and characteristics of atrial premature beats (APBs), graded into the following five categories: no APBs; <10 APBs/h; 10 to

100 APBs/h; >100 APBs/h; and couplets or more of APBs. The presence of the last two categories of APB was considered as high grade atrial ectopic activity.

ECHOCARDIOGRAPHY. Two-dimensional echocardiography was performed with a Toshiba SSH-160A recorder equipped with 2.5- or 3.75-MHz transducers. The standard technique was employed for sizing the left ventricle and atrium (19). Left ventricular dimension was measured at end-diastole on the R wave of the ECG-derived QRS complex just below the level of the mitral leaflets through the standard left parasternal window. Left atrial dimension (LAD) was measured as the distance from the leading edge of the posterior aortic wall to the leading edge of the posterior left atrial wall at end-systole. Mitral and tricuspid valve regurgitations were diagnosed by color Doppler echocardiography and quantified using a 4+ grading system. Mitral diastolic flow velocity was assessed by pulsed Doppler echocardiography from the apical four-chamber view by positioning the sample volume between the leaflets at the level of their tips in diastole. The ratio of maximal late to early diastolic velocities was also measured and averaged from five consecutive cycles.

HORMONE ANALYSIS. Blood sampling for plasma neurohormone determination was done from an intravenous cannula after the patient had rested for at least 30 min in the supine position. The plasma concentration of atrial natriuretic peptide (ANP) (20) and aldosterone, as well as plasma renin activity, was measured in EDTA-plasma by a radioimmunoassay technique, and the plasma norepinephrine concentration was also determined in EDTA-plasma by high performance liquid chromatography (21) at Shionogi Biomedical Laboratories (Osaka, Japan). Intraassay and interassay coefficients of variation of ANP were 4.7% and 5.8%, respectively.

Follow-up. All patients were followed up every two weeks for the initial eight weeks and every four weeks thereafter, and examined by standard ECG or portable ECG monitoring to observe the cardiac rhythm. Furthermore, 24-h Holter monitoring and echocardiography were repeated two and six months after study entry and every six months thereafter. The primary physicians taking care of the patients had no knowledge of the results of P-SAECG or other measurements.

The development of PAF was the primary end point in the present study. Paroxysmal atrial fibrillation was defined as an arrhythmia of supraventricular origin associated with a grossly irregular ventricular rhythm and no visible P or flutter waves that lasted for >1 min and did not persist for 6 months. Chronic AF was defined as AF sustained for >6 months. The development of PAF was considered secondary in the present study if LAD at study entry was >44 mm (mean ± 2 SD of normal control subjects) or there was a gradual increase in LAD without improvement in cardiac function during the follow-up period.

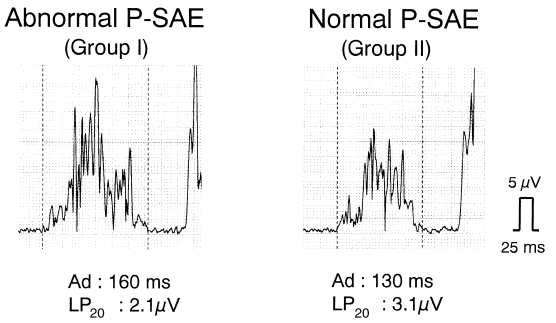

Figure 1. Representative tracings of P-SAE (P-SAECG) in a patient who developed PAF (**left,** group I) and a patient who did not develop PAF (**right,** group II) during the follow-up period. Note that the signal-averaged P-wave duration is longer and the terminal portion of the signal-averaged P wave is lower in the group I patients than in the group II patients. The abnormality of the P-SAECG was Ad >132 ms and LP_{20} <2.3 μV (positive in group I; negative in group II).

Statistical analysis. Data are presented as the mean value ± SD. The Mann-Whitney *U* test and the Fisher exact test were used to compare differences of continuous and discrete variables, respectively, in patients with and without an abnormal P-SAECG. The event (PAF)-free rates in patients with and without an abnormal P-SAECG were calculated using the Kaplan-Meier method, and the difference between them was detected using the log-rank test.

The Mann-Whitney *U* test and the Fisher exact test were also used to compare differences in patients with and without PAF development. Variables for which a difference ($p < 0.1$) was observed between the two groups were analyzed in the univariate Cox proportional hazard model, and variables such as age, LAD and ANF were dichotomized to make the hazard ratio maximal. The determination of prognostic significance of an abnormal P-SAECG, Holter reading, echocardiogram and plasma neurohormone level was explored by the multivariate Cox proportional hazards regression model analysis. McNemar's test was used to compare sensitivity, specificity and predictive accuracy among the different criteria for prediction of PAF development, and the Fisher exact test was used for comparing positive and negative predictive values among them.

All statistical analyses except for McNemar's test were carried out using the Stat-View statistical package, version 4.5. A p value <0.05 was considered statistically significant.

RESULTS

Clinical and study characteristics of patients with and without an abnormal P-SAECG. Seventy-five patients were dichotomized at study entry on the basis of abnormal P-SAECG criteria. Twenty-nine patients (group I) had an abnormal P-SAECG, whereas the other 46 patients did not (group II). Figure 1 shows the representative tracings of the P-SAECG in groups I and II. The Ad and LP_{20} were

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Table 1. Clinical and Study Characteristics in Patients With and Without an Abnormality of P-SAECG

	With Abnormality (n = 29)	Without Abnormality (n = 46)	p Value
Clinical characteristics			
Age (yrs)	66 ± 13	65 ± 10	NS
Gender (male)	26 (90%)	35 (75%)	NS
Ischemic heart disease	20 (69%)	30 (65%)	NS
Diabetes mellius	6 (21%)	8 (18%)	NS
Hypertension	1 (3%)	7 (14%)	NS
Class Ib antiarrhythmic drugs	10 (34%)	9 (20%)	NS
NYHA functional class	2.1 ± 0.7	2.0 ± 0.6	NS
6-Min walk distance (m)	358 ± 69	383 ± 70	NS
Heart rate (beats/min)	76 ± 12	74 ± 14	NS
Systolic pressure (mm Hg)	124 ± 13	133 ± 20	NS
Diastolic pressure (mm Hg)	73 ± 10	76 ± 11	NS
Radionuclide angiography			
LVEF (%)	30 ± 8	30 ± 7	NS
Holter monitoring			
High grade APB (%)	9 (31%)	14 (30%)	NS
Echocardiography			NS
LVDd (mm)	60 ± 6	61 ± 7	NS
LAD (mm)	39 ± 8	40 ± 6	NS
Neurohumoral pattern			
Atrial natriuretic peptide (pg/ml)	53 ± 46	59 ± 66	NS
Norepinephrine (pg/ml)	406 ± 228	392 ± 207	NS
Aldosterone (pg/ml)	71 ± 57	87 ± 101	NS
Renin (ng/ml per h)	6.6 ± 6.9	5.8 ± 6.5	NS

Data are presented as the number (%) of patients or mean value ± SD.

APB = atrial premature beats; LAD = left atrial dimension; LVDd = left ventricular end-diastolic dimension; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association. P-SAECG = P wave signal-averaged ECG.

143.7 ± 8.1 ms and 1.82 ± 0.3 μV in group I and 135 ± 12 ms and 3.28 ± 1.32 μV in group II, respectively. There were no significant differences in age, gender, use of the class Ib antiarrhythmic agent mexiletine, LVEF, the presence of high grade APB, LAD and plasma concentration of neurohormonal factors between groups I and II (Table 1).

Prediction of PAF attacks by the P-SAECG. In the follow-up period of 21 ± 9 months, 10 of the 75 study patients developed PAF, which was documented by 24-h Holter monitoring in the outpatient clinical setting (n = 8) and at hospital admission for CHF deterioration (n = 2). The development of PAF was considered secondary in 5 of the 10 patients. Five patients experienced palpitation, 2 dyspnea, 1 chest pain and 1 light-headedness associated with PAF attacks, and 1 patient was asymptomatic. In the 2 patients who were hospitalized for CHF deterioration at the first development of PAF, sinus rhythm was restored by electrical cardioversion, whereas the rhythm was spontaneously restored to sinus rhythm in the remaining 8 patients.

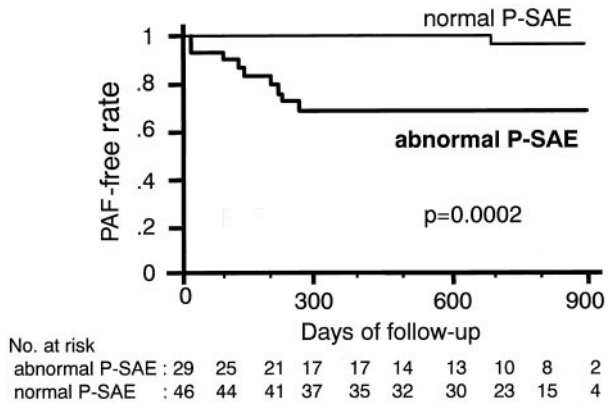

Figure 2. PAF-free rate curves according to Kaplan-Meier analysis in patients with and without an abnormal P-SAE (P-SAECG) (Ad >132 ms and LP_{20} <2.3 μV). The **bold line** (29 patients with the abnormality) and the **narrow line** (46 patients without the abnormality) show the PAF-free rates. The numbers at the bottom are the number of patients in each group at risk for the event (PAF attack) at study entry and after each 100-day period. The PAF-free rate was significantly lower in patients with rather than without an abnormal P-SAECG.

The transition to chronic AF was subsequently observed in one of the 2 patients hospitalized for CHF deterioration.

Nine (31%) of the 29 patients in group I developed PAF, whereas the development of PAF attacks was observed in only 1 (2%) of the 46 patients in group II. Figure 2 shows the event (PAF)-free rate curve according to Kaplan-Meier analysis. Attacks of PAF significantly more frequently occurred in group I than in group II (p = 0.0002). Accordingly, an abnormal P-SAECG gave a sensitivity of 90%, specificity of 69%, positive predictive value of 31% and negative predictive value of 98% for the prediction of the development of PAF in patients with CHF.

Comparison between patients with and those without development of PAF. The clinical and study characteristics of patients with and without PAF development are shown in Table 2. Patients with PAF attacks (PAF group) tended to be older (p = 0.07) than those without PAF attacks (non-PAF group), although there were no significant differences in gender, the presence of ischemic heart disease, diabetes mellitus or hypertension, the use of a class Ib antiarrhythmic agent, beta-blocker or angiotensin-converting enzyme inhibitor, NYHA functional class or LVEF between them. The Ad was significantly longer (p = 0.005) and LP_{20} was lower (p = 0.02) in the PAF group than in the non-PAF group (Fig. 3). So, the incidence of an abnormal P-SAECG was significantly greater (p = 0.001) in the PAF group than in the non-PAF group. By Holter monitoring, high grade APB tended to be observed more frequently in the PAF group than in the non-PAF group (p = 0.07). Echocardiographically, LAD tended to be larger in the PAF group than in the non-PAF group (p = 0.09), although no difference was observed in left ventricular end-diastolic dimension between the two groups.

Table 2. Clinical and Study Characteristics of Patients With and Without the Development of PAF

	PAF (+) (n = 10)	PAF (−) (n = 65)	p Value
Clinical characteristics			
Age (yr)	71 ± 6	64 ± 11	0.07
Gender (male)	8 (80%)	53 (82%)	NS
Ischemic heart disease	9 (90%)	41 (63%)	NS
Diabetes mellius	3 (30%)	12 (18%)	NS
Hypertension	0 (0%)	8 (12%)	NS
Class Ib antiarrhythmic drugs	5 (50%)	14 (22%)	NS
ACE inhibitors	5 (50%)	45 (70%)	NS
Beta-blockers	2 (20%)	16 (32%)	NS
NYHA functional class	2.1 ± 0.9	2 ± 0.6	NS
6-Min walk distance (m)	342 ± 79	379 ± 68	NS
Heart rate (beats/min)	72 ± 12	75 ± 13	NS
Radionuclide angiography			
LVEF (%)	30 ± 8	30 ± 7	NS
P-SAECG			
Abnormality	9 (90%)	20 (31%)	0.001
Ad (ms)	147 ± 8	137 ± 11	0.005
LP_{20} (μV)	1.9 ± 0.2	2.8 ± 1.3	0.02
Standard ECG			
P-wave duration (ms)	119 ± 10	114 ± 11	NS
PR interval (ms)	182 ± 30	171 ± 30	NS
P mitrale	7 (70%)	34 (52%)	NS
Holter monitoring			
High grade APB (%)	6 (60%)	17 (26%)	0.07
Echocardiography			NS
LVDd (mm)	61 ± 5	61 ± 7	NS
LAD (mm)	43 ± 7	39 ± 6	0.09
MR (4-grade score)	1.2 ± 0.7	1.0 ± 0.8	NS
TR (4-grade score)	0.3 ± 0.5	0.4 ± 0.6	NS
A/E ratio	1.31 ± 0.47	1.61 ± 0.56	NS
Neurohumoral pattern			
Atrial natriuretic peptide (pg/ml)	75 ± 41	54 ± 60	0.01
Norepinephrine (pg/ml)	357 ± 157	403 ± 221	NS
Aldosterone (pg/ml)	79 ± 78	81 ± 88	NS
Renin (ng/ml per h)	7.5 ± 8.2	5.9 ± 6.4	NS

Data are presented as the mean value ± SD or number (%) of patients.
A/E = ratio of late to early mitral diastolic velocities; ACE = angiotensin-converting enzyme; PAF = paroxysmal atrial fibrillation; MR = mitral regurgitation; TR = tricuspid regurgitation. Other abbreviations as in Table 1.

In the neurohumoral pattern (Fig. 4), ANP concentration was significantly higher (p = 0.01) in the PAF group than in the non-PAF group, although there were no significant differences in plasma level of norepinephrine, renin or aldosterone. Figure 5 shows the event (PAF)-free rate curve according to Kaplan-Meier analysis. The development of PAF was significantly more frequently observed in patients with than without an elevated ANP level (≥60 pg/ml) (32% [8/25] vs. 4% [2/50], p = 0.001).

Predictors of the development of PAF in patients with CHF. The Cox proportional hazard model analysis was used to determine the prognostic power of age, the abnormality of P-SAECG, the presence of high grade APB, LAD and plasma level of ANP. Table 3 shows the results of univariate and multivariate Cox proportional hazard model analyses for the prediction of PAF development. By univariate analysis, an abnormal P-SAECG, an elevated ANP level (≥60 pg/ml) and the presence of high grade APB were significantly related to PAF development. By multivariate analysis, an abnormal P-SAECG and an elevated ANP level

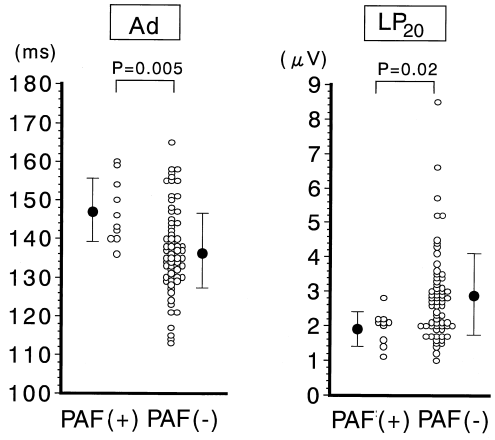

Figure 3. Plots of Ad and LP_{20} in patients with and without the development of PAF. The Ad was significantly longer and the LP_{20} was smaller in patients with rather than without the development of PAF.

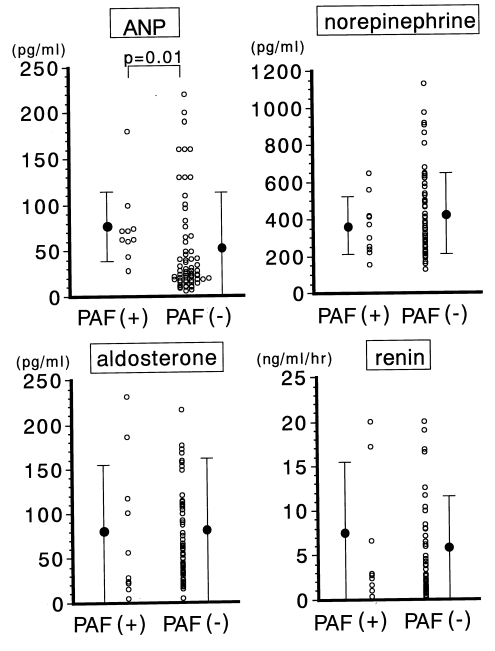

Figure 4. Plots of neurohumoral pattern in patients with and without the development of PAF. The ANP concentration was significantly higher in patients with rather than without the development of PAF, although there were no differences in the plasma level of norepinephrine, aldosterone or renin between the groups.

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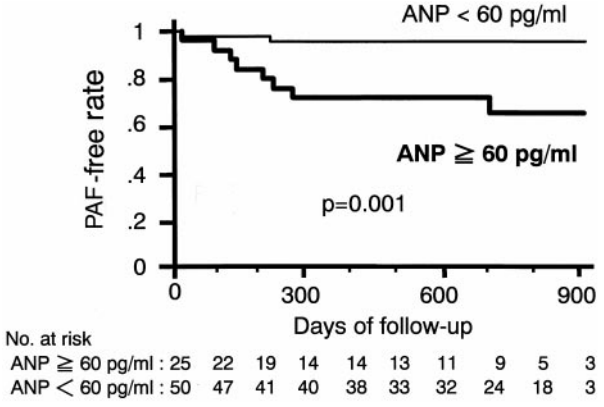

Figure 5. The PAF-free rate curves according to Kaplan-Meier analysis in patients with and without an elevated ANP level. The **bold line** (25 patients with an elevated ANP level ≥60 pg/ml) and the **narrow line** (50 patients without an elevated ANP level) show the PAF-free rate. The numbers at the bottom are the number of patients in each group at risk for the event (PAF attack) at study entry and after each 100-day period. The PAF-free rate was significantly lower in patients with rather than without an elevated ANP level.

were independently related to PAF development. The combination of abnormal P-SAECG and an elevated ANP level gave a sensitivity of 70%, specificity of 94%, positive predictive value of 64% and negative predictive value of 94% for the identification of patients at risk for PAF development (Table 4). Predictive accuracy (91%) for the combination significantly increased ($p < 0.01$), as compared with that for abnormal P-SAECG (72%) or elevated ANP level alone (75%).

Prognostic significance of the development of PAF. In the present study, 6 of 10 patients who developed PAF subsequently experienced major events (four hospital admissions for CHF deterioration, one sudden death and one brain embolism), whereas major events were observed in 9 of 65 patients without PAF development (four hospital admissions for CHF deterioration and five sudden deaths). Although there was no significant difference in mortality between patients with and those without PAF development, major events were significantly more frequently observed in patients with rather than without the development of PAF (60% vs. 14%, $p < 0.01$).

DISCUSSION

A number of electrophysiologic factors play a role in the development of AF (22). Atrial fibrillation is generally believed to result from multiple microreentry (23). Like all other reentrant arrhythmias, one of these factors in AF is a depressed atrial conduction. It was reported that the electrophysiologic abnormality of the atrial muscle in patients with PAF could be detected by P-SAECG (6,7,9,10,12), and prospective studies showed that P-SAECG would be useful for the prediction of PAF occurrence after cardiac surgery (8) and the transition to chronic AF in patients with PAF (11). However, in previous studies, the study groups mainly consisted of patients with relatively preserved cardiac function. In patients with CHF, which is one of the most frequent precursors of AF, the atrial electrophysiologic property might be modified by hemodynamic overloading (13–15) and neurohumoral activation (16,17), which are frequently observed in CHF. There have been no investigations to determine whether P-SAECG could be used to assess the risk of PAF in patients with CHF. This prospective study demonstrated that an abnormal P-SAECG could define a high risk group of patients with CHF who may develop PAF, and that the combination of an abnormal P-SAECG and an elevated ANP level would identify the higher risk subset for the development of PAF in patients with CHF.

P-SAECG in patients with CHF. In the present study, patients with CHF who developed PAF had a significantly longer Ad than those without PAF. Furthermore, Ad in patients with CHF who did not develop PAF was also longer, as compared with that in control subjects. A recent study showed that Ad in patients with CHF would depend more on the level of left atrial pressure rather than on LAD (15). In the present study, Ad significantly correlated with left ventricular end-diastolic pressure ($r = 0.32$, $p < 0.05$ [$n = 40$]) but not with LAD. We think that Ad in patients with CHF may be determined by hemodynamic overload, in addition to the electrophysiologic substrate characterized

Table 3. Univariate and Multivariate Cox Proportional Hazard Analysis for the Identification of Patients at Risk for PAF

	Univariate Analysis		Multivariate Analysis	
	p Value	Hazard Ratio (95% CI)	p Value	Hazard Ratio (95% CI)
Abnormal P-SAECG	0.0071	17.6 (2.2–135.8)	0.0069	19.1 (2.3–162.3)
ANP ≥60 pg/ml	0.064	8.6 (1.8–40.7)	0.018	8.6 (1.8–50.9)
High grade APB	0.04	3.7 (1.0–13.2)	0.89	1.1 (0.2–6.3)
Age >66 years	0.05	4.7 (0.99–22.0)	0.48	2.0 (0.3–13.2)
LAD >41 mm	0.06	3.6 (0.94–14.1)	0.11	3.3 (0.8–14.7)

ANP = atrial natriuretic peptide; high grade APB = >100 APBs/h or couplets or more of atrial premature beats (APBs); CI = confidence interval. Other abbreviations as in Table 1.

Table 4. Prediction of the Development of Paroxysmal Atrial Fibrillation by an Abnormal P-SAECG Elevated ANP Level and a Combination of the Two

	Abnormal P-SAECG	Elevated ANP	Abnormal P-SAECG and Elevated ANP
Sensitivity	90% (9/10)	80% (8/10)	70% (7/10)
Specificity	69% (45/65)	74% (48/65)	94%* (61/65)
Positive predictive value	31% (9/29)	32% (8/25)	64% (7/11)
Negative predictive value	98% (45/46)	96% (48/50)	94% (61/64)
Predictive accuracy	72% (54/75)	75% (56/75)	91%† (68/75)

*$p < 0.001$. †$p < 0.01$ vs. abnormal P-SAECG or elevated ANP. The numbers in parentheses are the number of patients. Abbreviations as in Table 3.

by slow inhomogeneous conduction of atrial impulse (24–26). This consideration is also supported by the experimental findings that the atrial stretch induced by increased cardiac loading due to heart failure produced profibrillatory changes in atrial conduction (13).

Prediction of the development of AF in patients with CHF. It was reported that the onset of AF in patients with CHF was associated with clinical and hemodynamic deterioration and might predispose to systemic thromboembolism and poorer prognosis (5). Furthermore, Middlekauf et al. (4) showed that AF in patients with CHF, whether paroxysmal or chronic, would be a marker for increased risk of death. In the present study, patients with PAF development experienced major events (hospital admission for CHF deterioration, sudden death and brain embolism) more frequently than those without PAF development, although there was no significant difference in mortality between them. Therefore, patients with CHF at risk for PAF should be monitored more frequently and should possibly have a more aggressive approach to the treatment of heart failure and thromboembolism.

The Framingham study reported that CHF was the most powerful independent precursor of AF, with a relative risk of approximately sixfold (1,3). It has also been shown that CHF increased the likelihood of recurrence of AF after electrocardioversion to sinus rhythm (27). Thus, the association between CHF and AF is well documented. However, the factors that predispose to PAF development have not been elucidated in patients with CHF. In this study, we demonstrated that an abnormal P-SAECG and an elevated ANP level at study entry would be useful predictors of the development of PAF in patients with CHF. Pozzoli et al. (5) reported that the occurrence of AF in patients with CHF could not be predicted by any baseline variable. In their study, the duration of the P wave was measured from the standard 12-lead ECG, but ANP was not measured. The difference between these two studies would be due to methodologic problems. In contrast, in the present study, there were no significant differences in age, LAD or the presence of diabetes mellitus or hypertension between patients with and those without the development of PAF. The result suggests that such risk factors of AF in the general population reported in the Framingham study (3) might not be predictive of the development of AF in patients with CHF.

ANP and the development of AF in patients with CHF. An increased level of ANP has been associated with a poor prognosis in patients with CHF (28,29). In some studies (30,31), the influence of chronic AF on the ANP level has been investigated in patients with CHF, and it was reported that ANP was further elevated in patients with CHF and chronic AF, as compared with those in sinus rhythm. The ANP itself might modulate the atrial electrophysiologic properties, because it was reported that ANP infusion shortened the atrial effective refractory period (32). However, no information has been available on the relation between ANP and the development of AF in patients with CHF. In the present study, plasma ANP level was significantly higher in patients with CHF with rather than without PAF development, and elevated ANP level was a risk factor for PAF development independently of an abnormal P-SAECG. The results suggest that ANP might provide prognostic information on the development of PAF in patients with CHF.

High levels of ANP have been reported in patients with increased atrial pressure associated with CHF (33). The main stimulus of release of ANP prohormone from the atrium is atrial wall stress. We speculate that the relation between high ANP level and AF development in patients with CHF might be indirectly brought about by left atrial wall stress and that the development of AF might not be a direct result of a high ANP level. Increased atrial pressure in patients with CHF induces higher wall stress, which not only stimulates the secretion of ANP from atrial myocytes but may also produce profibrillatory changes in atrial electrophysiologic properties by stretching the atrial wall. This speculation is supported by the following data in the present study. In patients with an elevated ANP level or an abnormal P-SAECG, improvement in cardiac function with an increase in LVEF measured by radionuclide angiography >5% one year after study entry was observed in 19 patients (ejection fraction 30 ± 6% to 44 ± 10%). In these patients, left ventricular end-diastolic dimension (61 ± 7 to 57 ± 6 mm, $p = 0.02$) and LAD (42 ± 5 to

39 ± 5 mm, p = 0.01) significantly decreased one year after study entry, which might result in the decrease in wall stress. The decreases in ANP level (52 ± 50 to 26 ± 20 pg/ml, p = 0.02) and signal-averaged P-wave duration (143 ± 7 to 140 ± 7 ms, p = 0.03) were also observed one year after study entry in these patients. These data suggest that in patients with CHF who were then effectively treated, an elevated ANP level or an abnormal P-SAECG might be related to wall stress, taking a corresponding improvement in ANP level and P-SAECG with a decrease in wall stress into consideration.

Study limitations. First, although patients were carefully followed up, it could not be ruled out that some patients with PAF might remain undocumented if their attack was brief or not so severe. Second, in this study, we studied only consecutive stable outpatients who had mild to moderate CHF. The results of our study should not be generalized to inpatients with severe CHF. Further study is needed to address this issue. Third, the positive predictive value of an abnormal P-SAECG was still low (32%), although the positive predictive value was increased (63%) by combination of an abnormal P-SAECG and elevated ANP level. Further prospective study is needed to verify the prognostic value of ANP as a predictor of AF development in patients with CHF, as ANP critical level was determined retrospectively in this study.

Conclusions. We concluded that an abnormal P-SAECG could be a predictor of PAF development in patients with CHF and that the combination of an abnormal P-SAECG and an elevated ANP level might identify the higher risk subset for PAF development in patients with CHF.

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