Comparison of Positive Cases for B-type Natriuretic Peptide and ECG Testing for Identification of Precursor Forms of Heart Failure in an Elderly Population

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SUMMARY

Plasma B-type natriuretic peptide (BNP) levels have been reported to be elevated in various types of cardiac disorders and in precursors of CHF. To elucidate the potential ability of BNP testing to identify individuals with structural cardiac disease (ie, hypertensive heart disease, coronary heart disease, valvular heart disease) among community-dwelling elderly persons, cases which were positive on BNP testing were compared to those positive on ECG testing.

In the initial phase, we performed plasma BNP measurements and ECG in 856 participants (age ≥ 65 years) selected from a general population. From within this group, subjects with an abnormal ECG (n = 125) were selected according to the Minnesota code. Subjects with elevated BNP were selected independently on the basis of plasma levels (n = 112). In the next phase, subjects in both groups were invited to complete Rose’s angina questionnaire and to undergo physical examination and transthoracic echocardiography. In this subject group (positive in ECG testing and/or BNP testing), the two tests had comparable sensitivity (65% versus 59%; NS) and specificity (40% versus 41%; NS) for identifying hypertensive heart disease (n = 17). For coronary heart disease (n = 12), the two tests had also comparable sensitivity (58% versus 42%; NS) and specificity (39% versus 41%; NS). However, for selection of valvular heart disease (n = 7), BNP testing had higher sensitivity than ECG testing (100% versus 14%; P < 0.01) with comparable specificity (43% versus 40%; NS).

Several types of structural heart disease, in particular valvular heart disease, could be identified exclusively by BNP testing, suggesting that BNP measurement can make a significant contribution to screening for CHF precursors when used in combination with ECG in elderly populations. (Int Heart J 2005; 46: 477-487)

Key words: B-type natriuretic peptide, Screening, Coronary artery disease, Hypertensive heart disease, Valvular heart disease, General population, Elderly

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ALTHOUGH the mortality rate for CHF has improved slightly over the last decade, once CHF has developed, the prognosis is still unacceptably poor. To improve outcomes such as survival and readmission rates, the importance of primary and secondary prevention of CHF has been emphasized. It would therefore be important to establish screening techniques to identify individuals at high risk of CHF due to asymptomatic structural heart disease as designated by class Stage B in the ACC/AHA guideline. Several multicenter randomized trials have demonstrated that when asymptomatic individuals with this type of cardiac disorder can be identified, angiotensin converting enzyme inhibitors effectively reduce the risk of progression to cardiovascular events, including new onset of CHF, in subjects at high risk with or without left ventricular systolic dysfunction.

Although resting ECG recording is widely used for identifying various kinds of heart disease in a screening setting, the prevalence of abnormal ECG findings rises exponentially with age. In fact, ECG abnormalities have been reported to be present in approximately 30% of elderly individuals in the general population. This suggests that an abnormal resting ECG frequently appears in the absence of significant structural heart disease in aged subjects.

The heart has been recognized as an endocrine organ that releases A-type natriuretic peptide and B-type natriuretic peptide (BNP). Cardiac production of BNP and circulating levels of this peptide have been reported to be increased in patients with several kinds of structural heart disease including hypertensive heart disease, left ventricular systolic dysfunction, coronary heart disease, and valvular heart disease. It is therefore possible that measurement of plasma BNP levels could play a role in the identification of individuals at high risk of CHF due to various forms of structural heart disease. However, the utility of plasma BNP testing when compared to ECG testing for screening for these types of cardiac disease remains unknown, especially in the elderly general population. Therefore, the aim of the present study was to examine the potential ability of BNP testing to identify individuals with structural cardiac disease (ie, hypertensive heart disease, coronary heart disease, or valvular heart disease) among community-dwelling elderly persons by comparing cases that were positive on BNP testing with those that were positive on ECG testing.

METHODS

Study population: The subjects recruited for this study were participants in the Iwate-Kenpoku Cohort (I-KENCO) study. The details of the Iwate-KENCO study have been described elsewhere. In brief, the present study was designed to prospectively investigate the risks of acute myocardial infarction, chronic CHF, and stroke in a general adult population in northern Japan. A baseline sur-
vey, which included a self-administered questionnaire on lifestyle, a food-frequency questionnaire, blood pressure measurement, ECG, anthropometrical measurement, and collection of blood and urine samples, was conducted from 2002 to 2004. A follow-up survey has been planned which will assess mortality, migration, and the incidence of cardiovascular disease.

The study subjects were drawn from the community-dwelling adult population of Yamada, a town in the coastal area of Iwate prefecture, Japan. This region has a resident population of 20,815, including 12,703 adults over the age of 40 years (5,752 men and 6,951 women). The study commenced with two screening phases, the first being carried out in June 2003. An invitation to participate in the I-KENCO study was issued to individuals attending a government regulated multiphasic community health screening programme. A total of 1,968 subjects (678 men, 1,290 women) aged 40 years and over agreed to undergo resting ECG recordings and provide blood samples for determination of plasma BNP levels. From within this group, 856 subjects (371 men, 485 women) over the age of 65 years consented to take part in the present study (Figure 1).

**Measurements:** Using a 3-channel device, a 12-lead ECG lasting 16 seconds on average was conducted in the supine position. The ECG tracings were subsequently coded according to the Minnesota code. According to the Pooling

![Figure 1. Summary of the study.](image-url)
major ECG abnormalities consist of ST segment depression (Minnesota code IV.1-2), T-wave inversion (V.1-2), complete or second degree AV block (VI.1-2), complete left or right bundle branch block (VII.1-2), frequent premature beats (VIII.1), and atrial fibrillation or flutter (VIII.3). Subjects showing these types of ECG abnormality were designated as the “abnormal ECG group” (Figure 1).

As the counterpart of the abnormal ECG group, the “elevated BNP group” was independently selected on the basis of a plasma level over 50 pg/mL. Plasma BNP levels were measured by direct radioimmunoassay using monoclonal antibodies specific for human BNP (Shiono RIA BNP kit, Shionogi & Co., Ltd., Japan). While the blood samples for routine testing were being taken, an additional 2 mL sample of venous blood was collected into a test tube containing EDTA-2Na for plasma BNP measurement. Tubes were stored immediately after sampling in an icebox and were transported to the central laboratory within 8 hours of collection. They were then centrifuged at 1,500g for 10 minutes. After separation, samples were stored frozen at -20°C until the time of assay. Cross-reactivity of the antibody was 100% for human BNP and 0.001% for human atrial natriuretic peptide (ANP). The intraassay and interassay coefficients of variation were 5% and 6%, respectively.

Subjects attending the second screening phase underwent a physical examination by a cardiologist blinded to the plasma BNP levels and ECG findings. Cardiac auscultation was performed in all subjects during inspiration and expiration. Subjects were examined in a quiet room, and the results were recorded on a standardized form. Cardiac murmurs were graded on a scale of one to six. To identify subjects with effort angina, the Rose angina questionnaire was completed with the assistance of trained staff prior to physical examination. On the basis of the results of the questionnaire, a cardiologist confirmed the cardiac symptoms and coded the results at the time of the physical examination.

Two-dimensional echocardiography (Cypress, Acuson, Mountain View, CA) was performed in a standard fashion in parasternal long and short axis views and apical two- and four-chamber views with the same protocol. Left ventricular septal and posterior wall thickness, and left ventricular chamber dimensions were measured according to guidelines of the American Society of Echocardiography. Left ventricular ejection fraction was measured by a quantitative 2-D method (biplane Simpson). Color-Doppler imaging was performed to screen for valvular stenosis and regurgitation. The echocardiographic report was compiled immediately after the test by cardiologists or echo-technicians, with the digitally recorded figures being checked after this by an experienced cardiologist (T.S.). These procedures were performed with no knowledge of the plasma BNP levels or ECG findings.
Diagnosis: A diagnosis was made by two cardiologists on the basis of each subject’s medical questionnaire, physical examination including cardiac murmur, and echocardiographic report. Again, this was done with no knowledge of plasma BNP levels. A diagnosis of hypertensive heart disease was made if subjects had echocardiographically-documented left ventricular hypertrophy (13 mm) with elevated blood pressure (systolic blood pressure $\geq 140$ mmHg or diastolic blood pressure $\geq 90$ mmHg) or use of antihypertensive drugs. A diagnosis of coronary heart disease was made if one or more of the following criteria were observed: 1) ongoing medication for angina and/or myocardial infarction; 2) a positive angina questionnaire with subsequent confirmation by a cardiologist; or 3) an abnormal Q wave on ECG tracing with echocardiographic left ventricular wall motion abnormalities. A diagnosis of valvular heart disease was made if a cardiac murmur over 3/6 degree was audible with a color Doppler regurgitation grade of more than 3° and/or a significant valve pressure gradient with reduced valve area. Left ventricular systolic dysfunction was defined as left ventricular systolic dysfunction of less than 40% without coronary artery disease or valvular heart disease.

Statistical analysis: All values are presented as the mean $\pm$ SD. To compare results between the two groups, the unpaired $t$-test or chi-square test was used as appropriate. The sensitivity and specificity between the two tests for each cardiac disorder were determined by calculating the Z value. A $P < 0.05$ was considered statistically significant with a two tailed level.

RESULTS

After the initial screening phase, 88 subjects were assigned to the ECG group and 85 subjects to the BNP group. Twenty-eight of these subjects exhibited both abnormalities (Figure 1), and thus, the total number of subjects in the second screening phase was 145. No significant differences in sex, age, height, weight, cardiovascular disease history, or alcohol and smoking habits were found between the abnormal ECG group and the elevated BNP group (Table). Systemic blood pressure, serum total cholesterol, and serum creatinine levels did not differ significantly between the two groups. After the final screening phase, 45 subjects were identified as having precursor forms of CHF such as hypertensive heart disease ($n = 17$), coronary heart disease ($n = 12$), valvular heart disease ($n = 7$), lone atrial fibrillation ($n = 8$), and left ventricular systolic dysfunction ($n = 1$). Of these 45 subjects, 27 had an ECG abnormality and 30 had elevated BNP. Twelve subjects had positive results in both tests. The sensitivity and specificity for identifying these structural heart diseases from subjects showing abnormal ECG testing and/or elevated BNP levels were comparable (sensitivity, 60% versus 67%; NS: specificity, 42% versus 57%; NS).
In subjects diagnosed as having hypertensive heart disease \((n = 17)\), an ECG abnormality and elevated BNP were observed in 11 and 10 subjects, respectively. Both abnormalities were observed in 4 subjects (Figure 2). In subjects who were positive in ECG testing and/or BNP testing, the two tests had comparable sensitivity (65\% versus 59\%; NS) and specificity (40\% versus 41\%; NS) for identifying hypertensive heart disease.

Twelve subjects as defined by the above definition of coronary artery disease were found in the final screening phase. Three subjects underwent treatment for previous myocardial infarction, six received nitrates from a physician for angina pectoris, and three were identified by the Rose angina questionnaire. The subjects with an abnormal ECG \((n = 7)\) were a completely discrete cohort from those with high BNP \((n = 5)\). No subject had overlapping abnormalities on both tests (Figure 2). The two tests also had comparable sensitivity (58\% versus 42\%; NS) and specificity (39\% versus 41\%; NS) for this type of heart disease.

Seven subjects were diagnosed as having valvular heart disease. None complained of symptoms such as shortness of breath on exercise, whereas all subjects

| Table. Clinical Characteristics of the Two Groups Selected From ECG and BNP Abnormalities |
|--------------------------------------|-----------------|-----------------|-----------------|
| Number                              | 88              | 85              |
| Sex (men/women)                     | 48/40           | 39/46           |
| Age                                 | 70.8 ± 4.6      | 72.2 ± 5.0      |
| Body height (cm)                    | 154.5 ± 9.1     | 152.4 ± 9.4     |
| Body weight (kg)                    | 58.4 ± 9.7      | 57.1 ± 10.5     |
| History \((n)\)                     |                 |                 |
| angina                              | 3               | 3               |
| myocardial infarct                  | 1               | 1               |
| hypertension                        | 36              | 34              |
| diabetes                            | 4               | 5               |
| Alcohol \((n)\)                     |                 |                 |
| no                                  | 51              | 62              |
| yes                                 | 37              | 23              |
| Smoking \((n)\)                     |                 |                 |
| no                                  | 57              | 57              |
| ex/current                          | 31              | 28              |
| Systolic blood pressure (mmHg)      | 133.1 ± 20.7    | 133.2 ± 18.0    |
| Diastolic blood pressure (mmHg)     | 76.2 ± 10.2     | 74.7 ± 9.9      |
| Serum total cholesterol (mg/dL)     | 201.0 ± 37.0    | 195.1 ± 36.2    |
| Serum creatinine (mg/dL)            | 0.76 ± 0.19     | 0.73 ± 0.19     |
| Structural heart disease            |                 |                 |
| Hypertensive heart disease \((n = 17)\) | 11              | 10              |
| Coronary heart disease \((n = 12)\) | 7               | 5               |
| Valvular heart disease \((n = 7)\)  | 1               | 7               | \(P < 0.01\)    |
| Others \((n = 9)\)                  | 8               | 8               | NS              |
exhibited a cardiac murmur (3/6 degree with significant valvular regurgitation or stenosis. Aortic valve abnormalities were found in 4 subjects, and mitral valve abnormalities in 3 subjects. Four subjects showed the dominant lesions of valvular regurgitation, and one subject exhibited aortic valvular stenosis. The remaining two had complex valvular lesions. All seven subjects had elevated BNP, whereas only one subject had an abnormal ECG. BNP testing has higher sensitivity than ECG testing (100% versus 14%; \( P < 0.01 \)) with comparable specificity (43% versus 40%; NS) for identifying valvular heart disease in subjects having an abnormal ECG and/or BNP testing.

Eight subjects exhibited atrial fibrillation without significant valvular lesions or cardiac murmur. All had elevated plasma BNP levels (range 129-156 pg/mL). These 8 subjects were classified as having lone atrial fibrillation. Left ventricular systolic dysfunction was found in only one subject. This individual had an abnormal ECG, but his plasma BNP level was below the cutoff value.

**DISCUSSION**

The present study has compared the ability of ECG and plasma BNP measurement at detecting subclinical forms of structural heart disease in elderly indi-

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**Figure 2.** Cases that had positive ECG and BNP test results for the three major types of structural heart disease.
individuals within a general population. We found that BNP testing appears to be capable of identifying subjects with precursor forms of CHF such as hypertensive heart disease, coronary heart disease, or valvular heart disease who are not detected by ordinary ECG screening testing.

ECG testing has been widely used in screening settings and is the standard diagnostic tool for several types of cardiac disease. However, the sensitivity of ECG for detecting left ventricular hypertrophy that has been proven echocardiographically has been reported to be relatively low. In the present cohort, a major ECG abnormality was found in about 65% of subjects with hypertensive cardiac hypertrophy, while the remaining 35% of subjects with this condition were detected exclusively by BNP testing. These results suggest that either ECG or BNP testing alone may not be an optimal method of screening for left ventricular hypertrophy within an elderly population. This observation is consistent with previously published reports which have demonstrated that either test alone has limited value for identifying subjects with left ventricular hypertrophy within the general population and among a hypertensive population. However, when BNP measurement and ECG are used in combination, screening for hypertensive cardiac hypertrophy may become significantly more accurate.

The most commonly performed screening test for coronary artery disease is most likely the resting ECG. Several studies have demonstrated a significant relationship between ECG abnormalities and risk of death from coronary heart disease. However, some reports have recommended that resting ECG not be used to screen for coronary artery disease in asymptomatic adults with no risk factors. In fact, in clinical practice, patients with angina pectoris do sometimes have a normal ECG tracing. The results of the present study suggest that BNP testing may be able to identify possible coronary artery disease in the absence of significant changes in resting ECG. Patients with unstable angina have been reported to exhibit elevated plasma BNP levels, possibly due to ischemia-induced BNP production from the myocardium. Although no subjects assigned to the coronary artery disease group in the present study showed clinically unstable angina, possible asymptomatic or subclinical myocardial ischemia due to exertion may increase myocardial BNP production and circulating levels. Hence, a number of subjects with coronary artery disease were identified exclusively by BNP testing.

The presence of valvular heart disease in the present elderly cohort was approximately 1%. This rate is lower than those reported previously among other ethnic groups. This may be due to differences in diagnostic criteria for valvular heart disease between the previous studies and the present one. A cardiac murmur over 3/6 degree was required to fulfill our criteria, whereas previous reports used Doppler assessment only and did not take into account the results of cardiac aus-
Several reports have suggested that the number of patients with degenerative cardiac valve disorder is increasing with the rising age of the population.\textsuperscript{25)} This type of heart disease eventually leads to CHF, stroke, endocarditis, and sometimes sudden death. It is therefore important that this disorder be recognised early so that medical therapy can be initiated and potential cardiovascular events can be averted. This would also facilitate appropriate timing of referral for surgery with consequent minimization of morbidity and mortality. Although the diagnostic ability of clinical evaluation including ECG testing for symptomatic and asymptomatic valvular heart disease has been reported to be unsatisfactory,\textsuperscript{26)} plasma BNP levels have been shown to be elevated even in patients with asymptomatic aortic and mitral valve disease.\textsuperscript{9,10)}

Only one subject in the present elderly population had left ventricular systolic dysfunction with an ejection fraction $< 40\%$. This prevalence is clearly lower than those found in the United States and Europe. However, this value is comparable to that in our previous report conducted in a Japanese population participating in a multiphasic health examination programme.\textsuperscript{13)} As the predominant etiology in this instance was coronary heart disease, the low prevalence of left ventricular systolic dysfunction in this population may have been due to the low prevalence of coronary heart disease.

**Clinical Implications:** The most prevalent precursors of CHF in the general population are hypertensive cardiac hypertrophy, coronary heart disease, and a combination of the two. In addition, valvular heart disease due to degenerative etiology may also be an important cause underlying cardiovascular events in the elderly.\textsuperscript{25)} Moser and Hebert have reported that a blood pressure reduction strategy for 3 to 5 years in an apparently healthy population is effective in reducing the onset of heart failure by half.\textsuperscript{27)} The HOPE trial has also demonstrated that one type of angiotensin converting enzyme inhibitor reduced the rate of new CHF onset by approximately 20\% in patients with atherosclerotic disease and cardiovascular risks irrespective of their baseline left ventricular ejection fraction.\textsuperscript{4)} The calcium channel blocker nifedipine has been reported to reduce the need for valve replacement surgery by approximately 20\% in asymptomatic patients with aortic regurgitation.\textsuperscript{28)}

**Limitations:** We did not carry out detailed examinations (ie, echocardiography, physical examination, and angina questionnaire) in cases who had negative results for BNP and/or ECG testing so true negative and false negative cases could not be identified. However, our aim was to compare the potential ability of the two forms of testing to identify subjects with various kinds of heart failure precursors in an elderly population, because it remains unknown whether BNP measurement could provide unique diagnostic information independent of standard ECG testing. Several reports have demonstrated that the cutoff level for
“abnormal” plasma BNP depends on sex and age in the general population.\textsuperscript{29,30) On this basis, we should have used a sex-age dependent cutoff value for plasma BNP levels when selecting the BNP group. However, the levels reported in these studies vary.\textsuperscript{29,30) The present study therefore set 50 pg/mL as the cutoff level in both genders. This was done because a previous study of ours using identical assay methodology showed that this was the most useful cutoff point for the detection of several types of structural cardiac disorder.\textsuperscript{13}) Another limitation of the present study was the possibility of bias in the selection of the subject population. However, the trends in the prevalence of hypertension, history of stroke, serum total cholesterol levels, and body mass index in the present cohort were similar to those reported in a randomly selected Japanese adult population.\textsuperscript{31)}

In conclusion, several types of structural heart disease, especially valvular heart disease, could be identified exclusively by BNP testing. This suggests that BNP measurement may make a significant contribution to screening for CHF precursors when used in combination with ECG in elderly populations.

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