Aims: P-wave terminal force in lead V1 (PTFV1) is an electrocardiogram marker of increased left atrial pressure and may be a noninvasive and early detectable marker for future cardiovascular events in the general population compared to serum B-type natriuretic peptide (BNP) concentration. The clinical significance of PTFV1 in the contemporary general population is an area of unmet need. We aimed to demonstrate the correlation between PTFV1 and BNP concentrations in a contemporary representative Japanese population.

Methods: Among 2,898 adult men and women from 300 randomly selected districts throughout Japan (NIPPON DATA2010), we analyzed 2,556 participants without cardiovascular disease (stroke, myocardial infarction, and atrial fibrillation). Elevated BNP was defined as a value of ≥ 20 pg/mL based on the definition from the Japanese Circulation Society guidelines.

Results: In total, 125 (4.9%) participants had PTFV1. Participants with PTFV1 were older with a higher prevalence of hypertension, major electrocardiographic findings, and elevated BNP concentrations (13.5 [6.9, 22.8] versus 7.8 [4.4, 14.5] pg/mL; P<0.001). After adjustment for confounders, PTFV1 was correlated with elevated BNP (odds ratio, 1.66; 95% confidence interval, 1.05–2.62; P=0.030). This correlation was consistent among various subgroups and was particularly evident in those aged <65 years or those without a history of hypertension.

Conclusions: In the contemporary general population cohort, PTFV1 was independently related to high BNP concentration. PTFV1 may be an alternative marker to BNP in identifying individuals at a higher risk of future cardiovascular events in the East Asian population.

Key words: B-type natriuretic peptide, Electrocardiogram, P-wave terminal force in lead V1, East Asian, NIPPON DATA2010

Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide in both men and women1). There is considerable evidence that the onset of CVD may be delayed or prevented through interventions
aimed at modifying risk factors for CVD. Many studies provide an evidence-based approach for risk assessment to lower the high burden of these risk factors and CVD in the general population.

P-wave terminal force in lead V1 (PTFV1) is a 12-lead electrocardiogram (ECG) marker of increased left atrial pressure, and it is a common finding in apparently healthy middle-aged subjects; it is associated with increased risk of atrial fibrillation (AF), stroke, and death in populations with high cardiovascular risk. Eranti et al. reported that PTFV1 was associated with increased risk of AF and death in the general population; however, their subjects were enrolled between 1966 and 1972, did not reflect the contemporary living environment, and had insufficient baseline information to adjust for potential confounders. Thus, the clinical significance of PTFV1 in the contemporary general population is an area of unmet need.

**Aim**

Since the National Integrated Project for Prospective Observation of non-communicable Disease and its Trends in the Aged 2010 (NIPPON DATA2010) cohort is currently in the process of investigating participant prognosis, we aimed to demonstrate the correlation between PTFV1 and B-type natriuretic peptide (BNP) concentration in a contemporary representative Japanese population; the latter is a known biomarker of left ventricular dysfunction and has also been reported to be associated with incident AF, stroke, and other major CVDs in both Western and Asian populations. This is the first study to investigate the correlation between these two biological markers. Moreover, PTFV1 may have the potential to be a noninvasive and earlier detectable marker for future cardiovascular events in the general population compared to serum BNP concentration. This study will provide additional value in terms of evidence for appropriate screening to identify those at high risk of developing future cardiovascular events among healthy individuals.

**Methods**

**Study Population**

NIPPON DATA2010 is a prospective cohort study on CVDs established in 2010. The study was performed in participants of the National Health and Nutrition Survey of Japan in November 2010 (NHNS2010) and Comprehensive Survey of Living Conditions in June 2010 (CSC2010); these studies were conducted by the Ministry of Health, Labor, and Welfare of Japan. The details regarding NHNS2010 and CLSC 2010 have been reported previously.

In NHNS2010, 300 unit blocks throughout Japan were randomly selected. Trained staff members explained the aim and methods of NIPPON DATA2010 to the 3,873 participants aged 20 years or older who underwent blood examinations for NHNS2010. A total of 2,898 participants (1,239 men and 1,659 women; participation rate, 74.8%) subsequently responded to the survey for NIPPON DATA2010, which included electrocardiographic analysis, urinalysis, additional blood tests, and a questionnaire related to CVD. Staff obtained written informed consent from all participants before enrollment, and the Institutional Review Board of Shiga University of Medical Science (No. 22-29, 2010) and Keio University School of Medicine (20180108) approved this study. All procedures performed in this study were in accordance with the principles of the declaration of Helsinki.

Among 2,898 adult men and women, 342 were excluded for the following reasons: missing information in the baseline survey (n=4), no data of 12-lead ECG (n=76), a history of known myocardial infarction or stroke (n=116), specific ECG findings including a moderate or severe Q-wave abnormality (Minnesota Code [MC] 1-1, 1-2), complete atrioventricular block (MC 6-1), Wolff–Parkinson–White syndrome (MC 6-4), AF or atrial flutter (MC 8-3-1 or 8-3-2), or artificial pacemaker (MC 6-8) (n=96). The remaining 2,556 participants were included in the present study (Fig. 1).

**ECG Examination**

A standard 12-lead ECG was recorded in the resting supine position. Each ECG record was manually read independently by two trained researchers according to the MC. In cases where the coding results mismatched, the central committee of ECG reading adjudicated the codes. The main ECG findings examined included left axis deviation (LAD; MC 2-1), right axis deviation (MC 2-2), left ventricular hypertrophy (LVH; MC 3-1 to 3-4), repolarization (ST depression) (MC 4-1 to 4-4), T-wave abnormality (MC 5-1 to 5-5), atrial premature complexes (MC 8-1-1 or 8-1-2), and ventricular premature complexes (MC 8-1-1 or 8-1-2)."
Baseline blood pressures were measured twice in the right arm of seated participants by trained public health nurses using a standard mercury sphygmomanometer after 5 minutes of rest. The mean of the two measurements was used in the present study. Hypertension was defined as a systolic blood pressure of ≥ 140 mmHg, a diastolic blood pressure of ≥ 90 mmHg, use of antihypertensive drugs, or any combination of these.\(^15\)

Casual blood samples were obtained for NHNS2010. Serum was separated and centrifuged soon after blood coagulation. Plasma samples were collected into siliconized tubes containing sodium fluoride and shipped to a central laboratory (SRL, Tokyo, Japan) for analysis.\(^15\)

Plasma glucose was measured using the hexokinase UV method, and hemoglobin A1c (HbA1c) was measured using the latex agglutination inhibition assay according to the standardized method of the Japan Diabetes Society (JDS).\(^15\) In the present study, the HbA1c value was converted into the National Glycohemoglobin Standardization Program (NGSP) value using the following formula: 

\[
\text{HbA1c (NGSP)}\% = 1.02 \times \text{HbA1c (JDS)}\% + 0.25.
\]

Diabetes mellitus was defined as a fasting blood glucose of ≥ 126 mg/dL and/or a non-fasting blood glucose of ≥ 200 mg/dL and/or HbA1c of ≥ 6.5% and/or use of medication. If a blood sample was taken after ≥ 8 hours of fasting, it was defined as a fasting blood sample.\(^15\)

Serum triglyceride, total cholesterol, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol (HDL) cholesterol levels were measured using enzymatic methods, which have been standardized by the Center for Disease Control and prevention/United States Collaborating Center for reference Method.

**Baseline Examination**

The baseline surveys were conducted by trained health professionals at public health centers according to a standardized manual. Height and weight were measured in participants without shoes and with light clothing. Body mass index (BMI) was calculated as weight (kg) divided by the height squared (m\(^2\)). A history of stroke and myocardial infarction was based on self-reports.

Baseline blood pressures were measured twice in the right arm of seated participants by trained public health nurses using a standard mercury sphygmomanometer after 5 minutes of rest. The mean of the two measurements was used in the present study. Hypertension was defined as a systolic blood pressure of ≥ 140 mmHg, a diastolic blood pressure of ≥ 90 mmHg, use of antihypertensive drugs, or any combination of these.\(^15\)

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Serum triglyceride, total cholesterol, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol (HDL) cholesterol levels were measured using enzymatic methods, which have been standardized by the Center for Disease Control and prevention/United States Collaborating Center for reference Method.
Laboratory Network\textsuperscript{21}). Hypercholesterolemia was defined as a low-density lipoprotein cholesterol level of ≥ 140 mg/dL and/or use of medication. Hypertriglyceridermia was defined as a triglyceride level of ≥ 150 mg/dL and/or use of medication. Low HDL cholesterolemia was defined as an HDL-cholesterol level of <40 mg/dL. Dyslipidemia was defined as hypercholesterolemia and/or hypertriglyceridermia with or without low HDL-cholesterol.

Serum creatinine was measured enzymatically, and plasma BNP was measured via chemiluminescent enzyme immunoassay using MI02 Shionogi BNP (Shionogi Co. Ltd., Osaka, Japan). Information on blood chemistry data measurements and their performance has been described elsewhere\textsuperscript{21}). Spot urine samples were also collected and shipped to the same laboratory as blood samples. Urine creatinine and sodium and potassium were measured enzymatically and by selective ion electrode methods, respectively. Estimated 24-h urinary sodium and potassium excretion were estimated using validated formulas\textsuperscript{22}). Urine albumin and protein were measured using immune-nephelometry and pyrogallol red methods.

Outcome Measurement

Till date, no studies have explored the appropriate threshold levels of plasma BNP that indicate an increased risk of the future development of cardiovascular events in the general population. On primary analysis, elevated BNP was defined as a value of ≥ 20 pg/mL, based on the findings of previous publications\textsuperscript{9,14} and the European Society of Cardiology and Japanese guidelines\textsuperscript{2,23}). Sensitivity analyses were performed using different BNP cut-offs (15, 17.5, 20, 30, 40, 50 pg/mL) to confirm the robustness of our result.

Statistical Analysis

First, we compared the baseline characteristics of those with and without PTFV\textsubscript{1}. Normality of continuous variables was tested with the Shapiro–Wilk test and/or Q-Q plot visual assessment, and continuous variables with normal distributions were expressed as mean (standard deviation), and other variables were expressed as median [25\textsuperscript{th} and 75\textsuperscript{th} percentile]. Differences were compared using Student’s t- or Mann–Whitney U tests for continuous variables and the Pearson \( \chi^2 \) or Fisher’s exact tests, as appropriate, for categorical variables.

Second, we performed multivariable logistic regression analysis to determine the correlation between PTFV\textsubscript{1} and elevated BNP. In the logistic regression model, adjustment was made in models 1 and 2. In model 1, we adjusted for age and sex. In model 2, we adjusted for covariates of model 1 along with BMI, hypertension, diabetes mellitus, dyslipidemia, smoking category (never smoker, ex-smoker, and current smoker, with “never smoker” as reference), drinking category (never drinker, ex-drinker, and current drinker, with “never drinker” as reference), serum creatinine, estimated 24-h urinary sodium excretion, and major ECG findings, such as LVH, LAD, and repolarization changes. These variables were determined according to their clinical relevance and statistical significance in correlation with the elevated BNP.

Finally, we performed a subgroup analysis stratified by age (cut-off: 65 years), sex, BMI (cut-off: 22), presence of hypertension, use of antihypertensive drugs, drinking category, and presence of major ECG finding (LVH) to demonstrate the robustness of our finding.

All P-values were two-sided. Results were considered statistically significant at \( P < 0.05 \). All statistical analyses were performed with R 3.4.1 (Foundation for Statistical Computing, Vienna, Austria).

Results

Overall, the mean age of the cohort was 57.8 (15.9) years, and 40.7% were men. Among the 2,556 participants, 125 (4.9%) had PTFV\textsubscript{1}. Table 1 summarizes the baseline characteristics of the study cohort stratified according to the presence of PTFV\textsubscript{1}. Participants with PTFV\textsubscript{1} were older and had a higher proportion of hypertension, major ECG findings (LVH, LAD, and repolarization change), and BNP concentration (13.5 [6.9, 22.8] pg/mL versus 7.8 [4.4, 14.5] pg/mL; \( P < 0.001 \)). Table 2 shows the correlation between PTFV\textsubscript{1} and elevated BNP concentrations using a pre-specified different cut-off. Participants with PTFV\textsubscript{1} had a higher prevalence of elevated BNP than those without PTFV\textsubscript{1}.

Multivariable logistic regression analysis revealed that PTFV\textsubscript{1} was independently correlated with elevated BNP (odds ratio [OR], 1.66; 95% confidence interval [CI], 1.05–2.62; \( P = 0.030 \)) (Table 3). The correlations between PTFV\textsubscript{1} and elevated BNP concentrations were consistent across all subgroups using different BNP cut-offs (Table 4). Fig. 3 shows the results of the subgroup analyses, representing the OR of PTFV\textsubscript{1} for elevated BNP; it demonstrates that PTFV\textsubscript{1} was consistently correlated with elevated BNP concentrations. The impact of PTFV\textsubscript{1} on elevated BNP was more evident in younger participants (age <65 years; OR: 3.74; 95% CI: 1.78–7.86; \( P < 0.001 \)) and in those with no history of hypertension (OR: 2.50; 95% CI: 1.14–5.47; \( P = 0.022 \)). The probability
Discussion

The major finding of this study was that 1) almost 5% of participants had PTFV₁ in a contempo-
PTVF1 reflects left atrial abnormalities associated with left atrial pressure, size, atrial conduction pattern, and left ventricular diastolic dysfunction. The prognostic impact of PTFV1 on cardiovascular outcomes has been established among high-risk second prevention populations. Liu et al. also demonstrated that PTFV1 was associated with cardiac death or hospitalization for heart failure in prior myocardial infarc-
tion patients. However, till date, the clinical significance of PTFV in the general population is less well established. Eranti et al. reported that PTFV was associated with increased risk of AF and death in the general population; however, their subjects were enrolled between 1966 and 1972, did not reflect the contemporary living environment, and showed insufficient baseline characteristic information to adjust for potential confounders. Thus, the clinical significance of PTFV in the contemporary general population is an area of unmet need. Our study contributes to a growing body of literature on the clinical significance of PTFV in the contemporary general population.

There are several potential explanations for the correlation between PTFV and elevated BNP. First, PTFV may be an early manifestation of increased intra-atrial pressure and left ventricular diastolic dysfunction. In cases of left atrial remodeling and early diastolic dysfunction, left ventricular filling pressure rises without clinical manifestations; this may lead to elevated BNP. Another potential explanation is that PTFV may reflect a left atrial overload, which may be associated with an increased risk of future incidence of AF. Several studies have reported that AF is associated with elevated BNP in the general population. These findings suggest that PTFV could be a surrogate marker of elevated BNP or indicate a prodromal stage.

The use of screening ECG in healthy individuals is controversial. The United States preventive services Task Force recommends against screening with resting or exercise ECG to prevent cardiovascular events in asymptomatic adults at low risk of cardiovascular events. However, the current evidence to assess the balance of benefits and harms of screening with ECG to prevent cardiovascular events in asymptomatic adults with intermediate or high cardiovascular risk is insufficient. Similarly, the American College of Cardiology/American Heart Association guidelines provide ECG with class IIa recommendations for cardiovascular risk assessment in asymptomatic adults with hypertension or diabetes. In Japan, screening ECGs are recommended as part of the worksite annual health checkup and are mandated for all employees under legal regulations on industrial safety and health. Moreover, mass health screening, including ECGs, is provided to most community dwellers in Japan. The reason for this inconsistency is partly due to a lack of studies assessing the impact of frequently seen but non-specific ECG findings such as PTFV. Major ECG findings including left atrial enlargement, LVH, LAD, and repolarization change, demonstrated statistically significant association with long-term cardiovascular outcomes; however, these are clinically negligible findings due to their scarcity. Our study demonstrated that PTFV, a precursor finding of left atrial enlargement, is frequently observed on ECG, and has an additive and clinically meaningful impact. Moreover, the correlation between PTFV and BNP was consistent even among subjects without a history of hypertension or major EGG findings; this may justify the performance of ECG screening in an apparently healthy population. On a 12-lead ECG, the PTFV may be a useful marker for identifying individuals at a higher risk of future cardiovascular events, particularly in countries where ECGs are commonly performed in the general population.

Several studies have shown a significant association between plasma BNP and N-terminal pro-BNP levels and cardiovascular events in the general population. However, the appropriate threshold levels of plasma BNP that indicate an increased risk of future cardiovascular events in the general population with no cardiovascular history remain controversial. The Framingham study conventionally applied a single cut-off (the 80th percentile) to examine the association between high BNP levels and cardiovascular events. Linssen et al. demonstrated that N-terminal pro-BNP levels of >87.5 pg/mL were associated with all-cause mortality and CV events in the general population; they also observed a gradual increase in the risk of mortality and CV events with increasing levels of NT-proBNP, without a clear cut-off. Nakamura et al. showed that the adjusted HR was significantly increased from the ninth plasma BNP decile in men and the tenth decile in women. For reassurance, we confirmed the robustness of our results using several cut-offs.

The findings of this study should be interpreted in the context of some limitations and considerations. First, due to the nature of an observational study, some unmeasured or unmeasurable variables may have influenced the outcomes; however, the robustness of our results was confirmed through several statistical analyses. Moreover, no studies have identified the appropriate threshold levels of plasma BNP that indicate an increased risk of future development of cardiovascular events in the general population; therefore, further studies must be conducted to evaluate the association between PTFV and the longitudinal outcomes. However, considering the magnitude of the effect of elevated BNP on long-term major adverse cardiovascular and cerebrovascular events, we believe our results contribute to a growing body of literature on the utility of PTFV.

Conclusion

In this contemporary general population cohort,
PTFV1 was found to be independently related to high BNP concentrations. PTFV1 on a 12-lead ECG may be a noninvasive, simple, and useful marker to identify individuals at a higher risk of future cardiovascular events in the modern-day East Asian population.

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Disclosures

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