Comparative Impact of Scintigraphic Parameters and B-Type Natriuretic Peptide for the Prediction of Major Cardiac Events in the QGS-Prognostic Value in the Elderly (Q-PROVE) Study

Yuko Igarashi, MD; Taishiro Chikamori, MD; Satoshi Hida, MD; Tadashi Nagao, MD; Hirokazu Tanaka, MD; Yasuhiro Usui, MD; Tsuguhisa Hatano, MD; Takayuki Morishima, MD; Hidefumi Yanagisawa, MD; Akira Yamashina, MD

Background: Although B-type natriuretic peptide (BNP) has emerged as an important predictor for cardiac events, its effect on scintigraphic parameters is unknown.

Methods and Results: The Q-PROVE study is a multicenter study to evaluate the prognostic value of ECG-gated SPECT in 175 Japanese elderly patients. In addition, BNP was assessed in 102 patients. Outcome assessment included cardiac events and noncardiac deaths. Twelve elderly patients (12%) had increased BNP >130 pg/ml. The summed stress score (SSS) was greater in patients with increased BNP than in those with normal BNP. Kaplan-Meier survival estimation indicated event-free survival rates at 3 years of 83%, 78%, 88%, 80%, respectively, in patients with BNP >130 pg/ml, SSS ≥ 7 , summed difference score (SDS) ≥ 2 , and dilated end-diastolic volume (EDV), but 98%, 98%, 100%, 94% in those with BNP ≤ 130 pg/ml, SSS <7, SDS <2 and normal EDV (P=0.006, P=0.005, P=0.0008, P=0.01). Multivariate analysis demonstrated that an SDS was the only independent predictor for subsequent cardiac events (hazard ratio=4.0, P=0.04).

Conclusions: Although BNP may have similar prognostic value to gated SPECT volumetric measurements in elderly patients with known or suspected coronary artery disease, myocardial ischemia as documented by SPECT is still indispensable for detecting high-risk patients compared with BNP alone. (Circ J 2009; 73: 1655–1660)

Key Words: B-type natriuretic peptide; Coronary artery disease; Elderly; Single-photon emission computed tomography

Although B-type natriuretic peptide (BNP) has emerged as an important predictor not only for heart failure but also for myocardial ischemic events,^{1–4} its effect on scintigraphic parameters derived from single-photon emission computed tomography (SPECT) is unknown. We previously reported in the Quantitative gated SPECT Prognostic Value in the Elderly (Q-PROVE) study that stress myocardial SPECT successfully stratified the risk for subsequent cardiac events in 175 elderly patients with a mean age of 79 years.⁵ In addition to the prognostic value of myocardial SPECT, therefore, we performed a post-hoc analysis of the Q-PROVE study to elucidate the prognostic value of BNP in elderly patients with known or suspected coronary artery disease (CAD).

Methods

Subjects

The Q-PROVE study initially enrolled 182 elderly patients aged 75–85 years from 11 institutions.⁵ Consecutive elderly patients who underwent gated SPECT in each institution for the evaluation of known or suspected CAD because of

clinical symptoms, multiple coronary risk factors or abnormal ECG were eligible for enrollment. The following were the exclusion criteria: (1) age <75 years or >85 years, (2) acute heart failure, (3) atrial fibrillation, (4) acute myocardial infarction within 3 months before the SPECT study, (5) coronary revascularization within 3 months after the SPECT study, (6) serious concomitant hepatic or renal disease, (7) malignancy or any other illness with a poor prognosis. Of the 182 patients who participated in this study, 3 patients underwent coronary revascularization within 3 months after the SPECT study, and 4 patients were lost to follow-up. In addition, BNP was not measured within 3 months of the study in 73 patients, which left 102 patients for this post-hoc analysis.

Study Protocol

Applying the inclusion and exclusion criteria for the Q-PROVE study, patients were prospectively evaluated by primary physicians, cardiologists or both who were responsible for the SPECT study, and who assessed the past medical history including classical coronary risk factors. The patients underwent stress/rest myocardial perfusion

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Department of Cardiology, Tokyo Medical University, Tokyo, Japan

Mailing address: Yuko Igarashi, MD, Department of Cardiology, Tokyo Medical University, 6-7-1 Nishi-Shinjuku, Shinjuku-ku, Tokyo 160-0023, Japan. E-mail: yuko50@tokyo-med.ac.jp

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Figure 1. Assignment of myocardial segments for scoring of single-photon emission computed tomography images.

SPECT, and were followed up thereafter. The study protocol was approved by the ethical committee in each institution during the enrollment period since July 2001. All participants in this study gave informed consent.

SPECT Imaging

Each institution used ^{99m}Tc -sestamibi, stress/rest myocardial SPECT imaging according to its usual routine, either by exercise stress or by pharmacologic loading, and images were also analyzed in each institution as described previously.^{6,7} The methods were those in routine use at each institution and the method of inducing stress was not particularly regulated. After induction of the stress, a digital gamma camera equipped with a multipurpose or low-energy high-resolution, parallel-hole collimator was rotated over a 180° or 360° arc. The acquisition time was 15–20 min for each patient. SPECT image processing was conducted on a dedicated nuclear medicine computer system using standard filters. Attenuation or scatter correction was not used.

According to the method reported by Berman et al, each SPECT image was divided into 20 segments (**Figure 1**).⁸ The myocardial uptake of ^{99m}Tc -sestamibi was visually evaluated by 2 experienced cardiologists within each institution, blinded to all clinical data, using a 5-grade scale: 0 (normal), 1 (slight reduction of uptake), 2 (moderate reduction of uptake), 3 (severe reduction of uptake) or 4 (absence of radioactive uptake). The score totals for all the segments during exercise and at rest were designated the summed stress scores (SSS) and the summed rest scores (SRS), respectively. The SSS minus SRS was defined as the summed difference score (SDS).⁸ In addition, each reconstructed short-axis ECG-gated SPECT image was processed by the quantitative gated SPECT program (Cedars-Sinai Medical Center, Los Angeles, CA, USA) developed by Germano et al, to automatically calculate the left ventricular end-diastolic volume, left ventricular end-systolic volume and left ventricular ejection fraction.⁹ In the volumetric and functional analyses, the cutoff value for normalcy was set according to gender.¹⁰ The cutoff points for end-diastolic volume, end-systolic volume, and ejection fraction were 88 ml, 33 ml, and 63%, respectively in men, and 59 ml, 17 ml, and 74%, respectively in women.¹⁰ Disagreements in image interpretation, including every score for each SPECT segment, were resolved by consensus.

Follow-up

Patient follow-up was performed by each of the 11 study centers by physician contact or mailing to patients. The follow-up period was defined as the time from the SPECT study until a significant event or the last visit to each institution until the study period endpoint in April 2006.

Significant events were considered to be death, nonfatal myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, malignant arrhythmias, or hospital admission because of heart failure or unstable angina, which were defined as described previously.^{11,12} All patients who were admitted to hospital because of heart failure required roentgenographic evidence of pulmonary congestion. Deaths were classified as either cardiac or noncardiac. Follow-up to event or death was ascertained in 102 of 102 patients by the endpoint of the study period.

Statistical Analysis

Results are expressed as means $\pm$ SD. Student's t-test was used to compare the means of the continuous variables, and categorical variables were analyzed using the chi-square test. To determine a cutoff value of BNP and summed scores for subsequent prognosis, receiver-operating characteristic (ROC) curve analysis was performed. For survival analysis, Kaplan-Meier estimation using a log-rank test was performed. Multivariate analysis of outcome was assessed using the Cox proportional hazard model. A value of $P < 0.05$ was considered as statistically significant. Statistical analyses were performed using the SPSS-PC+ computation program (version 11.0, SPSS Inc, Chicago, IL, USA).

Results

Overall Results

The mean age of the 102 patients who completed follow-up was 79 ± 3 years; there were 59 men and 43 women. For stress SPECT, 35 patients (34%) underwent exercise stress and the remaining 67 (66%) had vasodilator pharmacologic loading. The left ventricular volumetric and functional measurements were successful in 100 patients (98%), but could not be performed in the remaining 2 patients because of frequent extrasystoles.

A mean level of BNP was 73.5 ± 137.7 pg/ml (3.4–1,310 pg/ml). Weak but significant correlations were observed between BNP and SSS ($r=0.32$; $P=0.001$), SRS ($r=0.25$; $P=0.001$) and SDS ($r=0.22$; $P=0.03$). The ROC curve analysis revealed a BNP level of 130 pg/ml as the cutoff point for the prognosis of elderly patients in this cohort. Accordingly, using 130 pg/ml as the cutoff, the clinical characteristics of patients who had a high BNP level (>130 pg/ml) and those who had a low BNP level (≤ 130 pg/ml) are shown in **Table 1**. Age, gender, and the prevalence of classical coronary risk factors were similar in the 2 groups (**Table 1**). Although 40 patients (39%) had had a previous myocardial infarction, coronary revascularization or both, the frequency of revascularization history was more common in patients with a high BNP level than in

Table 1. Clinical Characteristics of 102 Elderly Patients With Known or Suspected Coronary Artery Disease

	BNP >130 pg/ml (n=12)	BNP ≤130 pg/ml (n=90)	P value
M/F	10/2	49/41	NS
Age (years)	80±2	79±4	NS
Hypertension	1 (8%)	16 (18%)	NS
Hypercholesterolemia	4 (33%)	43 (48%)	NS
Diabetes mellitus	5 (42%)	29 (32%)	NS
Current smoker	0 (0%)	9 (10%)	NS
Remote history of revascularization			
PCI	6 (50%)	15 (17%)	0.02
CABG	0 (0%)	6 (7%)	NS
Remote history of MI	5 (42%)	22 (24%)	NS

BNP, B-type natriuretic peptide; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; MI, myocardial infarction.

Table 2. Scintigraphic Data According to BNP Level

	BNP >130 pg/ml (n=12)	BNP ≤130 pg/ml (n=90)	P value
End-diastolic volume (ml)	120±74	75±31	NS
End-systolic volume (ml)	73±70	34±22	NS
Ejection fraction (%)	47±17	57±13	0.01
Summed stress score	17.7±14.6	8.0±8.3	0.04
Summed rest score	14.9±15.1	7.4±7.8	NS
Summed difference score	2.8±5.1	0.6±3.8	NS

BNP, B-type natriuretic peptide.

Table 3. Comparison of Clinical Characteristics of Patients With and Without Cardiac Events

	Cardiac event (+) (n=14)	Cardiac event (–) (n=88)	P value
M/F	10/4	49/39	NS
Age (years)	80±3	79±4	NS
Hypertension	3 (21%)	14 (16%)	NS
Hypercholesterolemia	5 (36%)	42 (48%)	NS
Diabetes mellitus	5 (36%)	29 (33%)	NS
Smoking	5 (36%)	29 (33%)	NS
BNP >130 pg/ml	6 (43%)	6 (7%)	0.001
Medications			
ACEI/ARB	6 (43%)	39 (43%)	NS
β-blockers	0 (0%)	2 (2%)	NS
CCBs	9 (64%)	56 (64%)	NS
Diuretics	3 (21%)	9 (10%)	NS
Statins	4 (29%)	38 (43%)	NS
Aspirin	9 (64%)	56 (64%)	NS
Warfarin	1 (7%)	7 (8%)	NS

BNP, B-type natriuretic peptide; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; CCBs, calcium-channel blockers.

those with a low level (**Table 1**). ECG-gated SPECT showed that the SSS was greater in patients with a high BNP level than in those with a low BNP level. Although the ejection fraction was lower in patients with a high BNP level than in those with a low BNP level, end-diastolic volume, end-systolic volume, SRS, and SDS were similar in the 2 groups (**Table 2**).

During a mean follow-up of 3.4±0.6 years (median, 3.8 years), 17 patients had significant events, of whom 3 patients died from noncardiac causes, and the remaining 14 patients had cardiac events: cardiac death in 2, heart failure that needed hospital admission in 4, percutaneous coronary intervention in 6, coronary artery bypass grafting in 1, unstable angina in 1. The clinical characteristics of patients who subsequently had cardiac events and those who were free of cardiac events are shown in **Table 3**. Age, gender, the prevalence of classical coronary risk factors and medications were similar in patients with and without cardiac

events, although patients with a high BNP level were more frequently observed among those with cardiac events than among those without (**Table 3**). ECG-gated SPECT showed that end-diastolic volume, SSS and SDS were greater in patients with cardiac events than in those without, whereas end-systolic volume, ejection fraction and SRS were similar in the 2 groups (**Table 4**).

BNP, Gated SPECT and Prognosis

Kaplan-Meier survival estimation was performed based on a BNP with a cutoff of 130 pg/ml. The cardiac event-free survival rate in patients with a low BNP level was 99% at 1 year and 98% at 3 years, which was higher than the 100% at 1 year and 83% at 3 years in patients with a high BNP level ($P=0.006$, log-rank=7.7) (**Figure 2A**).

To analyze the SPECT data, the cutoff values were set according to ROC curve analysis as follows: 7 for the SSS, 3 for the SRS and 2 for the SDS. In addition, gender-spe-

Table 4. Comparison of Scintigraphic Parameters of Patients With and Without Cardiac Events

	Cardiac event (+) (n=14)	Cardiac event (-) (n=88)	P value
End-diastolic volume (ml)	119±70	74±30	0.04
End-systolic volume (ml)	68±63	34±23	NS
Ejection fraction (%)	50±15	57±13	NS
Summed stress score	16.4±12.3	8.0±8.7	0.002
Summed rest score	11.8±11.4	7.7±8.8	NS
Summed difference score	4.6±6.3	0.3±3.1	<0.0001

Figure 2. Kaplan-Meier survival estimates for cardiac events according to B-type natriuretic peptide (BNP). (A) Patients with BNP ≤ 130 pg/ml (n=90; solid line), and patients with BNP > 130 pg/ml (n=12; dashed line). A significant difference was found between these 2 groups (P=0.006 by log-rank test). Kaplan-Meier survival estimates for cardiac events according to the summed stress score (SSS). (B) Patients with SSS < 7 (n=51; solid line), and patients with SSS ≥ 7 (n=51; dashed line). A significant difference was found between these 2 groups (P=0.005 by log-rank test).

Figure 3. Kaplan-Meier survival estimates for cardiac events according to the summed difference score (SDS). (A) Patients with SDS < 2 (n=69; solid line), and patients with SDS ≥ 2 (n=33; dashed line). A significant difference was found between these 2 groups (P=0.0008 by log-rank test). Kaplan-Meier survival estimates for cardiac events according to end-diastolic volume (EDV) as assessed by gated SPECT. (B) Patients with normal EDV (n=53; solid line), and patients with dilated EDV (n=47; dashed line). A significant difference was found between these 2 groups (P=0.01 by log-rank test).

Table 5. Predictors for Cardiac Events by the Cox Proportional Hazard Model

	Univariate analysis		Multivariate analysis	
	Cox HR (95%CI)	P value	Cox HR (95%CI)	P value
Age	1.1 (0.96–1.31)	0.15		
Men	1.6 (0.52–5.32)	0.40		
Hypertension	0.8 (0.21–2.80)	0.69		
Hypercholesterolemia	0.7 (0.23–2.09)	0.52		
Diabetes mellitus	1.5 (0.50–4.60)	0.46		
Smoking	0.04 (0.00–738)	0.53		
SSS ≥ 7	4.8 (1.07–21.7)	0.04	2.1 (0.40–10.6)	0.39
SRS ≥ 3	34.0 (0.21–5,652.2)	0.18		
SDS ≥ 2	6.7 (1.87–24.2)	0.004	4.0 (1.05–15.5)	0.04
Dilated ESV	1.9 (0.52–6.68)	0.34		
Dilated EDV	4.1 (1.13–14.6)	0.03	2.6 (0.69–9.48)	0.28
Reduced EF	0.4 (0.05–2.90)	0.35		
BNP >130 pg/ml	6.7 (1.41–12.5)	0.01	2.1 (0.66–6.72)	0.21

HR, hazard ratio; CI, confidence interval; SSS, summed stress score; SRS, summed rest score; SDS, summed difference score; ESV, end-systolic volume; EDV, end-diastolic volume; EF, ejection fraction; BNP, B-type natriuretic peptide.

cific normalcy for the volumetric analysis derived from the J-ACCESS database was applied.¹⁰ Kaplan-Meier survival curves, which showed statistical significance by the univariate analyses, are shown in **Figures 2 and 3**. The cardiac event-free survival rate in patients with a SSS <7 was 98% at 1 year and 98% at 3 years, which was higher than the 85% at 1 year and 78% at 3 years in those with a SSS ≥ 7 ($P=0.005$, log-rank=8.1) (**Figure 2B**). The cardiac event-free survival rate in patients with a SDS <2 was 100% at 1 year and 100% at 3 years, which was also significantly higher than the 97% at 1 year and 88% at 3 years in those with a SDS ≥ 2 ($P=0.0008$, log-rank=11.3) (**Figure 3A**). Kaplan-Meier survival estimates revealed that the cardiac event-free survival rate in patients with normal end-diastolic volume was 94% at 1 year and 94% at 3 years, which was higher than the 87% at 1 year and 80% at 3 years in those with dilated end-diastolic volume ($P=0.01$, log-rank=6.2) (**Figure 3B**).

Predictors of Cardiac Events

Thirteen variables related to clinical and scintigraphic findings (**Tables 3,4**) were considered potential predictors for the occurrence of subsequent cardiac events during follow-up, and were included in the multivariate analysis using the Cox proportional hazard model. The analysis revealed that only SDS ≥ 2 was an independent predictor of cardiac events (hazard ratio (HR)=4.0, $P=0.04$) (**Table 5**). The analysis was repeated without setting a cutoff point in order to exclude a potential confounding effect in the process of selecting the cutoff points. The BNP and SPECT data were included in the Cox proportional hazard model as numerical variables and the analysis again showed that the SDS was the only independent predictor for subsequent cardiac events (HR=1.1, $P=0.04$).

Discussion

Since the discovery of BNP, the measurements of this left ventricular-derived peptide for the management of patients with heart failure has become routine clinical practice.^{14–18} Furthermore, recent studies showed that the BNP level predicted subsequent prognosis not only in patients with heart failure but also in those with CAD.^{1,3,4} In the present post-hoc analysis of the Q-PROVE study, a high BNP level >130 pg/ml was significantly associated with subsequent

cardiac events in 102 elderly patients with known or suspected CAD. The cardiac event-free survival rate in patients with a high BNP level was 83% at 3 years, which was lower than the 98% at 3 years in patients with a low BNP level (**Figure 2A**). When the patient population of the current study consisting of 102 elderly patients with a mean age of 79 years is taken into consideration, BNP may have a clinical role in risk stratification even in elderly patients aged 75 years or more who are suspected of having CAD.

In the prognostication and risk stratification of patients with known or suspected CAD, nuclear cardiology is providing accumulating evidence applicable to daily practice.^{19–21} In the present study, gated SPECT also showed event-free survival rates at 3 years of 78%, 88%, and 80%, respectively, in patients with a SSS ≥ 7 , SDS ≥ 2 , and dilated end-diastolic volume, but 98%, 100%, and 94%, respectively in those with a SSS <7 , SDS <2 and normal end-diastolic volume (**Tables 3–5**). Thus, elderly patients with normal or mildly abnormal myocardial perfusion and normal left ventricular volume have a good prognosis. These observations are consistent with previous reports.^{22–25} To compare the prognostic impact of BNP with scintigraphic parameters, both BNP and scintigraphic parameters were evaluated by multivariate analysis. The Cox proportional hazard model revealed that the SDS was the only independent predictor of outcomes (**Table 5**). Thus, although BNP may have a similar prognostic value to scintigraphic parameters in elderly patients with known or suspected CAD, myocardial ischemia as documented by SPECT is still indispensable for better detection of high-risk patients.

Normalcy for the BNP level differs according to age, gender and other factors.²⁶ In this study based on elderly patients aged 75 years or more, a cutoff point of 130pg/ml was determined by ROC curve analysis and was higher than the BNP level for heart failure in middle-aged patients.¹⁵ The left ventricular volumetric analysis as assessed by gated SPECT showed larger end-diastolic and end-systolic volumes in patients with a high BNP level than in those with a low BNP level, though this did not reach statistical significance because of the wide variation of these measurements. In contrast, the left ventricular ejection fraction was reduced significantly in patients with a high BNP level. These observations are consistent with previous studies in which the BNP level was increased in elderly subjects and/or those with impaired left ventricular systolic function.^{1,27,28}

In addition, BNP showed weak but significant correlations with scintigraphic summed scores. However, the best correlation was observed between BNP and the SSS, which represents the combination of myocardial scar and stress-induced ischemia. Previous studies reported significant increase in the BNP level after stress myocardial SPECT, particularly in those in whom myocardial ischemia was documented.^{29,30} Therefore, it is reasonable that the 2 markers, which are influenced not only by cardiac function but also by myocardial ischemia, showed a good relationship.

Although our results indicate the superiority in prognostic value of stress myocardial SPECT to BNP in elderly patients with suspected CAD, the current study was a post-hoc analysis of the Q-PROVE study. Thus, these preliminary results need confirmation through a series of large-scale, prospective clinical trials.

Conclusion

Although BNP may have a similar prognostic value to gated SPECT volumetric measurements in elderly patients with known or suspected CAD, myocardial ischemia as documented by SPECT is still indispensable for better detection of high-risk patients compared with BNP alone.

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