

# Plasma Brain Natriuretic Peptide Concentration: Impact of Age and Gender

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<b>OBJECTIVES</b>	We wished to examine the effects of age and gender on plasma brain natriuretic peptide (BNP) concentration in a population-based study.
<b>BACKGROUND</b>	Measurement of BNP concentration is approved for use in the diagnosis of heart failure and may aid in the detection of left ventricular dysfunction. Although BNP is approved for clinical use, there are few data regarding the range of BNP observed in persons without cardiovascular disease or cardiac dysfunction. These data are essential for the interpretation of BNP.
<b>METHODS</b>	In 2,042 randomly selected residents of Olmsted County, Minnesota, >44 years old, BNP (Shionogi and Biosite assays), Doppler echocardiography, and medical record review were performed. A normal subset of subjects (n = 767) in sinus rhythm without cardiovascular, renal, or pulmonary disease or diabetes; on no cardiovascular medications; and with normal systolic, diastolic, and valvular function was identified.
<b>RESULTS</b>	Within the normal subset, the distribution of BNP differed by age, gender, and assay system. With both assays, BNP increased significantly with age and was significantly higher in women than men, leading to age-, gender-, and assay-specific reference ranges. Receiver operating characteristic analysis for the ability of BNP to detect an ejection fraction $\leq 40\%$ was performed in each age/gender stratum in the entire cohort (n = 2,042) and confirmed that discriminatory values for BNP for detection of reduced ejection fraction were higher in women and older persons and were different between the two assays.
<b>CONCLUSIONS</b>	Interpretation of BNP should include consideration of age-, gender-, and assay-specific partition values. (J Am Coll Cardiol 2002;40:976-82) © 2002 by the American College of Cardiology Foundation

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Brain natriuretic peptide (BNP) is a member of the family of genetically distinct natriuretic peptides synthesized and released by cardiomyocytes in response to increased transmural wall stress (1). Although this response is critical for cardiorenal regulation, the increase in plasma BNP concentration has diagnostic implications as well. Indeed, BNP may be useful for the detection of asymptomatic left ventricular (LV) dysfunction (2,3) and the diagnosis (4,5) and management (6) of congestive heart failure (CHF). Whereas most previous studies have utilized an immunoradiometric assay (Shionogi), recent Food and Drug Administration approval of a point-of-care assay (Biosite Triage) for use in the diagnosis of CHF has made the possibility of using BNP in clinical practice a reality.

The range of BNP observed in subjects without cardiovascular disease or cardiac dysfunction has not been well established. Although a few studies suggest that age and gender may influence circulating natriuretic peptide levels (7-9), the magnitude of these effects and their potential

importance in the interpretation of BNP remains unclear. Therefore, we measured BNP with two commercially available assays in a population-based cohort. In subjects without cardiovascular disease or cardiac dysfunction (n = 767), we assessed the influence of the assay used, age, and gender on BNP. We evaluated the influence of clinical factors, renal function, and cardiac structural parameters on BNP, as age/gender-related changes in these factors could mediate associations between BNP and age/gender. In the entire cohort (n = 2,042), we determined whether the BNP that identified subjects having systolic dysfunction (ejection fraction [EF]  $\leq 40\%$ ) with optimal sensitivity and specificity varied with age, gender, and assay.

## METHODS

This study was approved by the Mayo Institutional Review Board.

**Study setting.** The characteristics of the Olmsted County, Minnesota, population and the unique resources for population-based epidemiologic research in Olmsted County have been previously described (10,11).

**Population sampling, subject recruitment, and enrollment.** A random sample of the population >44 years was invited to participate. A sampling fraction of 7% was applied within each of the gender and age (five-year) specific strata.

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Manuscript received March 4, 2002; accepted May 31, 2002.

**Abbreviations and Acronyms**

- BNP = brain natriuretic peptide
- CHF = congestive heart failure
- CI = confidence interval
- E/A = early-to-late filling velocities
- EF = ejection fraction
- HRT = hormone replacement therapy
- LV = left ventricular
- ROC = receiver operating characteristic
- 2-D = two-dimensional

Of the 4,203 subjects invited, 2,042 (47%) participated. Analysis of the medical records of 500 nonparticipants revealed no clinically significant differences between participants and nonparticipants. Subjects gave written consent and underwent echocardiography and phlebotomy.

Of the 2,042 participants, 1,020 had no history of cardiovascular, renal, or pulmonary disease and were on no cardiovascular medications. Of these, 75 were excluded because of an abnormal two-dimensional (2-D) echocardiogram, 64 were excluded by an inability to characterize diastolic function, and 114 had abnormal diastolic function. Thus, 767 subjects had normal EF (>50%), no wall motion abnormalities, normal diastolic function, no valve disease, and normal sinus rhythm; these make up the normal subgroup. The criteria used to establish the normal subgroup resulted in small numbers in the oldest (age 75 to 83) normal subgroup, where there were 18 women and two men. In this age group, the majority of excluded subjects were excluded because of the presence of known cardiovascular disease (72% of women excluded, 84% of men excluded) and a minority were excluded purely on the basis of diastolic dysfunction (10% of women excluded, 7% of men excluded).

**Medical record review.** All Olmsted County care providers have maintained a unified medical record, which is indexed by the Rochester Epidemiology Project. Each subject's medical record was reviewed by trained nurse chart abstractors using established criteria for hypertension (12), myocardial infarction (13), and congestive heart failure (10). Clinical diagnoses of coronary artery disease, obstructive lung disease, renal failure, and dia-

betes were recorded. Medication questionnaires were completed by each subject.

**Doppler echocardiography.** All echocardiograms were performed by one of three registered diagnostic cardiac sonographers with the same echocardiographic instrument (HP-2500) according to protocol and interpreted by a single echocardiologist (M. M. R.). Two-dimensional and color Doppler imaging were performed to screen for valvular stenosis or regurgitation.

In each subject, measurement of EF by M-mode (modified Quinones formula), quantitative 2-D (BiPlane Simpsons) and semiquantitative 2-D (visual estimate) methods was attempted as previously described (14-17). For analysis in the normal subgroup, subjects had normal EF (>40%) by all three methods. For analysis in the entire population, the visual estimation of EF was used.

Pulsed-wave Doppler examination of mitral (before and with Valsalva maneuver) and pulmonary venous inflow as well as Doppler tissue imaging of the mitral annulus was performed in each subject. Diastolic function was categorized as normal, impaired relaxation without evidence of increased filling pressures ("impaired relaxation"), impaired relaxation associated with moderate elevation of filling pressures ("pseudonormal filling"), and advanced reduction in compliance ("restrictive filling"), as previously described (18-21). Decreases in the ratio of the mitral early to late filling velocities (E/A ratio) indicate a reduction in early diastolic filling related to impairment of LV relaxation. We defined impaired relaxation as an E/A ratio  $\leq 0.75$ , reflecting the average lower confidence interval for the E/A ratio in subjects aged >45 years in a previous normal cohort (22). Doppler indices used to discriminate pseudonormal or restrictive from normal are independent of age.

Left ventricular dimension and mass (M-mode) and left atrial volume (2-D) were indexed to body surface area.

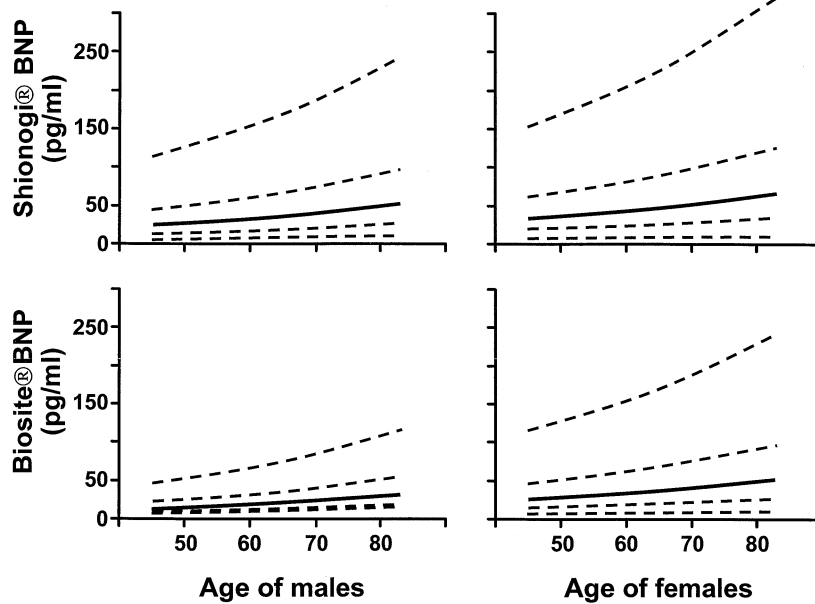
**BNP analysis.** Blood for BNP was collected in the fasting state in ethylenediaminetetraacetic acid-treated tubes and placed on ice. After centrifugation at 2,500 rpm and 3°C, the plasma was stored at -80°C.

Plasma BNP was determined by immunoradiometric assay (nonextracted) using antibody to human BNP (Shionogi Co. Ltd., Tokyo, Japan), as previously described (23). The intra-assay (within-day) and interassay (total)

**Table 1.** Plasma BNP (Biosite [BNP-B] and Shionogi [BNP-S] Assays) by Age and Gender in Normal Subjects

Gender BNP	Age 45-54		Age 55-64		Age 65-74		Age 75-83	
	n	Median (25th, 75th)	n	Median (25th, 75th)	n	Median (25th, 75th)	n	Median (25th, 75th)
Women								
Biosite	180	18 (10, 32)	135	27 (15, 43)	56	29 (19, 52)	17	67 (28, 89)
Shionogi	194	28 (13, 55)	141	32 (18, 68)	59	45 (20, 111)	18	58 (26, 172)
Men								
Biosite	181	7 (3, 13)	111	11 (5, 20)	40	18 (7, 37)	2	21 (17, 24)
Shionogi	193	17 (9, 34)	118	31 (14, 49)	42	28 (10, 58)	2	38 (31, 44)

The median 25th and 75th percentiles are shown.  
BNP = brain natriuretic peptide.



**Figure 1.** Plasma brain natriuretic peptide (BNP) concentration as a function of age for each gender and assay system. The nomogram demonstrates the 5th, 25th, 50th, 75th, and 95th percentiles for BNP according to age.

coefficients of variation were both 8% and were consistent across concentrations of BNP.

One-milliliter aliquots of frozen plasma were shipped to Biosite Diagnostics (San Diego, California), and the non-extracted samples were batch-analyzed by a fluorescence immunoassay (5,24). The within-day coefficient of variation (9.4% to 15.2%) and total coefficient of variation (10.1% to 16.2%) increased from low to high BNP.

**Statistical methods.** Because the variability of BNP increased with its mean level, the natural log transformation was used in the regression analyses to satisfy modeling assumptions. Nomograms based on age and gender were established using the least-squares regression fit of log-transformed BNP with age and gender as predictor variables. From the fitted model, the 5th, 25th, 50th, 75th, and 95th percentiles were estimated and back-transformed to the natural scale. An interaction term with age and gender was also evaluated to determine if the association of age with BNP differed between the genders.

Unadjusted and adjusted associations of BNP were evaluated using Spearman's correlation coefficient and linear least-squares regression, respectively. For adjusted associations, a model with age and gender was fit and, in turn, variables were added to see if there was significant residual association that could be explained by these characteristics.

The ability of BNP to detect an EF  $\leq$ 40% was evaluated using receiver operating characteristic (ROC) curves within age/gender-specific strata. The optimal discriminatory value was identified as the BNP value that had a combined sensitivity/specificity at the smallest distance to 100%/100%, respectively (23).

**RESULTS**

**The association of BNP with age and gender in the normal subgroup (n = 767).** The distribution of the normal subgroup by age/gender and corresponding BNP is shown in Table 1. Adjusting for age, BNP was higher in women than men and increased with age within each gender. Plasma BNP was 32% higher in women than men (confidence interval [CI] = 15% to 51%,  $p < 0.001$ ) by Shionogi assay and 80% higher by Biosite assay (CI = 50% to 116%,  $p < 0.001$ ). Nomograms for BNP as a function of age, gender, and assay are reported (Fig. 1). The age/gender-specific reference ranges (5th and 95th percentile) for each assay as derived from the regression fit are provided in Table 2. The association between gender and BNP remained similar across all age ranges for both assays ( $p > 0.90$ ).

We sought to determine if age/gender-related changes in BNP were due to age- or gender-related changes in clinical

**Table 2.** Age and Gender-Specific Ranges (5th-95th Percentiles) for Plasma BNP (pg/ml) (Biosite and Shionogi Assays) Derived From the Regression Analysis in Normal Subjects

Gender BNP	Age 45-54	Age 55-64	Age 65-74	Age 75-83
Women				
Biosite	8-73	10-93	13-120	16-155
Shionogi	7-157	9-192	11-233	13-284
Men				
Biosite	4-40	5-52	7-67	9-86
Shionogi	6-120	7-146	8-177	10-216

BNP = brain natriuretic peptide.

**Table 3.** Variables Examined for Association With Age, Gender, and Plasma BNP Concentration in Normal Subjects

	Age		Gender		Log of Shionogi BNP		Log of Biosite BNP	
	Spearman CC	p Value	Spearman CC	p Value	Spearman CC	p Value	Spearman CC	p Value
Age	NA	NA	0.134	0.0002	0.173	< 0.0001	0.283	< 0.0001
Gender	0.134	0.0002	NA	NA	0.183	< 0.0001	0.421	< 0.0001
Body surface area	-0.198	< 0.0001	-0.705	< 0.0001	-0.147	< 0.0001	-0.345	< 0.0001
Systolic blood pressure	0.255	< 0.0001	-0.080	0.0274	0.021	0.5531	-0.006	0.8773
Diastolic blood pressure	-0.023	0.5198	-0.339	< 0.0001	-0.088	0.0152	-0.186	< 0.0001
Creatinine	-0.000	0.9894	-0.682	< 0.0001	-0.111	0.0026	-0.232	< 0.0001
Creatinine clearance	-0.510	< 0.0001	-0.454	< 0.0001	-0.193	< 0.0001	-0.369	< 0.0001
LV dimension index	0.079	0.0426	0.449	< 0.0001	0.134	0.0006	0.263	< 0.0001
LV mass index	0.047	0.2265	-0.325	< 0.0001	-0.003	0.9371	-0.150	0.0002
LA volume index	0.006	0.8790	-0.131	0.004	0.139	0.0002	0.096	0.0118

BNP = brain natriuretic peptide; CC = correlation coefficient; LA = left atrial; LV = left ventricle; NA = not appropriate.

factors, renal function, or cardiac structural parameters. Table 3 displays the variables considered as potentially associated with BNP. Several of these parameters were associated with BNP but were also associated with age and/or gender, as indicated in Table 3. Only age, gender, and left atrial volume index were independently associated with BNP (Table 4). Within each gender and assay group, BNP increased according to left atrial volume index.

To further evaluate the association between gender and BNP, we determined whether BNP was different in the presence or absence of hormone replacement therapy (HRT). As measured by the Biosite assay, there was a relationship between HRT and BNP among women. Of the 388 women in the normal subgroup, 186 (48%) were taking HRT. Controlling for age, BNP was 21% higher in women on HRT than in women not on HRT (CI 6% to 40%,  $p < 0.005$ ) (Fig. 2). Plasma BNP was 99% higher in women on HRT than in men (CI 75% to 125%,  $p < 0.005$ ) and was 64% higher in women not on HRT than in men (CI 44% to 85%,  $p < 0.005$ ). Similar trends were observed with the Shionogi assay, but the difference in BNP between women with or without HRT was not significant (data not shown).

**Discriminatory values of BNP for the detection of systolic dysfunction in the entire cohort (n = 2,042).** Figure 3 displays the ROC curves for the detection of an EF  $\leq 40\%$  within each age stratum by gender and assay. Forty subjects (eight women) had an EF  $< 40\%$ . On each curve, both the BNP representing the upper (95th percentile) reference limit, as derived from the regression fit, and the BNP representing the optimal point on the ROC curve are indicated. The values for the BNP at the upper reference limit and at the optimal point on the ROC curve, and the

corresponding sensitivity and specificity for the detection of an EF  $\leq 40\%$ , are shown in Table 5. The areas under the ROC curves were similar within each age/gender stratum for each assay. However, in general the optimal discriminatory value for BNP increases with age and is higher in women. Only eight female subjects had an EF  $\leq 40\%$  and this significantly limited the power to demonstrate age/gender differences in the optimal discriminatory value for BNP. The available data in women are included to demonstrate the effect on specificity of age/gender-specific partition values derived from the reference population.

## DISCUSSION

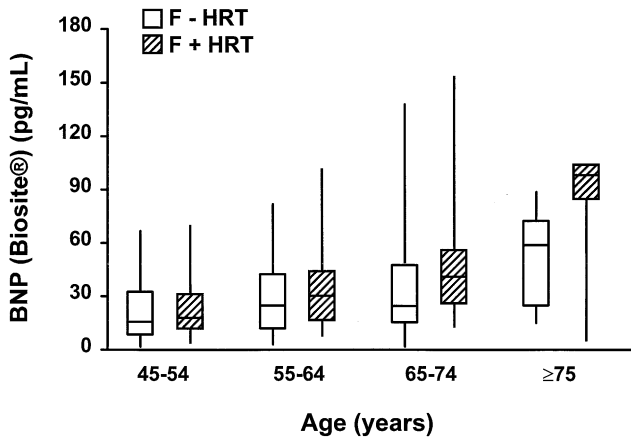
In this population-based study, BNP increased with age and was higher in women than men in a subgroup of subjects without known cardiovascular disease or detectable structural heart disease. These associations were not explained by age- or gender-related changes in blood pressure, renal function, or cardiac structure. The association of female gender and BNP appears to be in part related to estrogen status, as BNP levels were higher in women using HRT. Although the absolute value of BNP varied between the two assays, the associations with age and gender were consistent between assays. In addition, the BNP with optimal sensitivity and specificity for the detection of systolic dysfunction in the entire population increased with age and was higher in women, underscoring the clinical relevance of the relationship among age, gender, and BNP.

**Plasma BNP in the normal subgroup.** The mechanisms whereby age influences BNP are unclear. Previous studies have reported that levels of natriuretic peptides are higher in

**Table 4.** Parameters Independently Associated With BNP

	Log Shionogi BNP			Log Biosite BNP		
	Regression Coefficient	Standard Error	p Value	Regression Coefficient	Standard Error	p Value
Age	0.020	0.004	< 0.0001	0.024	0.003	< 0.0001
Female gender	0.294	0.069	< 0.0001	0.632	0.053	< 0.0001
LA volume index	0.029	0.006	< 0.0001	0.024	0.005	< 0.0001

Regression coefficients indicate effect per year of age or per ml/m<sup>2</sup> for LA volume index. BNP = brain natriuretic peptide; LA = left atrial.



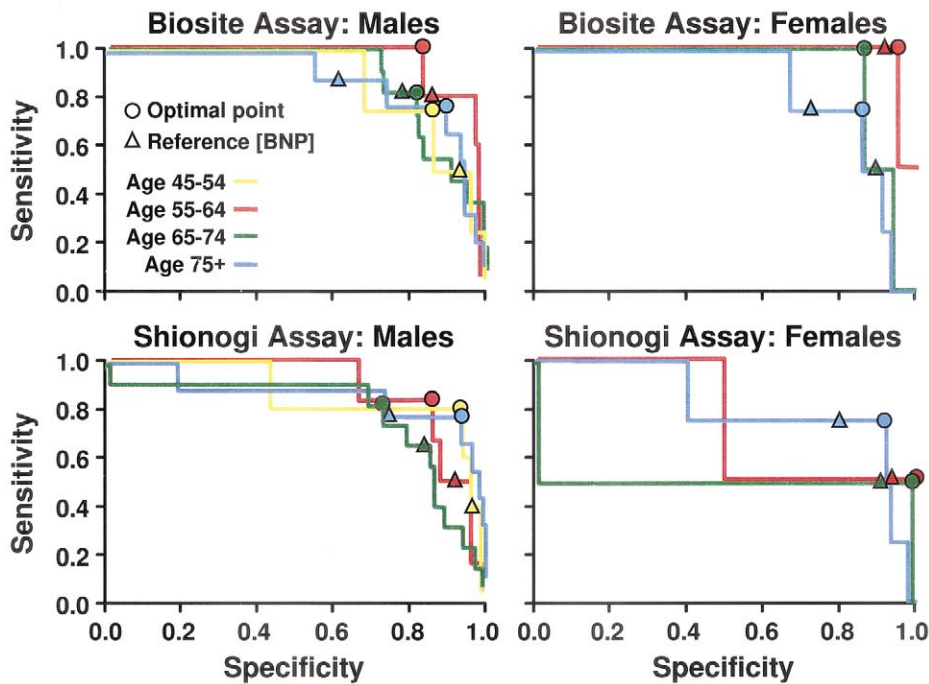
**Figure 2.** Box plot of plasma brain natriuretic peptide (BNP) concentrations (Biosite assay) according to hormone replacement therapy (HRT) status as a function of age in female (F) subjects. The box plots indicate the 5th, 25th, 50th, 75th, and 95th percentiles.

the elderly, but did not exclude those with altered cardiac structure or function (7,9). These investigators suggested that age-related changes in diastolic dysfunction influence BNP. However, in the current study subjects with diastolic dysfunction and the diseases that cause it were excluded. Although age-related alterations in renal function could alter BNP, the effect of age was independent of renal function. The atria and ventricles are sites of BNP production, and age-related changes in cardiac size could influence BNP. However, the effect of age and gender on BNP was independent of atrial volume, LV dimension, and LV mass.

These data would suggest that as yet undefined alterations in BNP production, secretion, or degradation occur with age, and further studies are needed to elucidate the mechanism(s) responsible for this effect. An alternative explanation is that BNP increases in response to age-related alterations in cardiac structure or function that are not detectable by current techniques. Such a mechanism remains speculative and not pertinent to current diagnostic use of BNP, as the prognostic implications of BNP in the absence of detectable structural heart disease have not been defined.

The effect of gender on BNP was also remarkable. This effect was independent of other factors, observed with both assay systems, and substantial. As gender-related differences in endothelin and angiotensin-converting enzyme activity have been reported to be associated with hormonal status (25,26), we investigated the effect of HRT status on BNP and found evidence of a relationship between HRT and BNP. Although preliminary, these data suggest that BNP production may be sensitive to estrogen regulation and represent an area for further study.

After adjusting for age and gender, we found a modest but significant relationship between BNP and left atrial volume index in the normal subgroup. Thus, in the normal state, plasma BNP may be related to the size of the gland that produces it. Although the relationship between BNP and LV mass was not significant after adjustment for age and gender, production of BNP by ventricular myocytes is clearly increased in the presence of hypertrophy. Thus, a



**Figure 3.** Receiver operating curves defining the sensitivity and specificity of brain natriuretic peptide (BNP) (by Shionogi and Biosite assays) for the detection of systolic dysfunction (ejection fraction  $\leq 40\%$ ) in each age strata of men and women. The **open circle** indicates the BNP value at the upper reference limit as derived from the regression fit in each age/gender/assay stratum. The **open triangle** indicates the BNP value with optimal sensitivity and specificity (the "optimal point") on the receiver operating characteristic (ROC) curve.

**Table 5.** Sensitivity and Specificity of BNP for Detection of Systolic Dysfunction at the Discriminatory Value for BNP as Determined by the ROC Analysis and at the 95th Percentile Reference Limit by Age, Gender, and Assay System

	Men Biosite BNP			Women Biosite BNP			Men Shionogi BNP			Women Shionogi BNP		
	BNP	SENS	SPEC	BNP	SENS	SPEC	BNP	SENS	SPEC	BNP	SENS	SPEC
Discriminatory (BNP)												
Age 45-54	24	75%	86%	ND	ND	ND	91	80%	93%	ND	ND	ND
Age 55-64	43	100%	82%	109	100%	95%	89	83%	85%	777	50%	100%
Age 65-74	75	82%	81%	98	100%	86%	107	83%	74%	743	50%	99%
Age ≥75	356	78%	90%	219	75%	86%	672	78%	93%	528	75%	92%
95th percentile reference (BNP)												
Age 45-54	40	40%	95%	73	ND	96%	120	40%	95%	157	ND	94%
Age 55-64	52	80%	86%	93	100%	92%	146	50%	92%	192	50%	94%
Age 65-74	67	82%	79%	120	50%	90%	177	67%	84%	233	50%	91%
Age ≥75	86	89%	62%	155	75%	73%	216	78%	74%	284	75%	80%

BNP is in pg/ml.

BNP = brain natriuretic peptide; ND = no systolic dysfunction detected among females age 45-54; SENS = sensitivity; SPEC = specificity.

stronger relationship between plasma BNP and LV mass or left atrial volume may be apparent if subjects with cardiovascular disease are included.

**Implications for use of BNP as a diagnostic test.** Previous studies have reported the sensitivity and specificity of BNP for the detection of CHF or LV dysfunction (2-5). These studies derived a single abnormal (partition) value for BNP by ROC analysis and have not examined the use of age- or gender-specific partition values. For the Biosite assay, values of 75 to 80 pg/ml have been reported as partition values for detection of ventricular dysfunction (with and without symptoms) or diagnosis of CHF (5,24). For the Shionogi assay, values of 17.9 to 79 pg/ml have been reported for detection of ventricular dysfunction or CHF in highly variable populations (2,8,23,27,28). Although we found that the area under the ROC curves was similar among the age/gender strata, the optimal partition value for the detection of systolic dysfunction differed by assay, age, and gender.

These data suggest that age-, gender-, and assay-specific partition values should be used to interpret BNP. The ultimate partition values used may also depend on the abnormality being screened for (CHF vs. asymptomatic LV dysfunction), its severity, the implications of false positives or negatives and, importantly, on the population being studied. The operating characteristics of diagnostic tests may vary according to the population to which they are applied (11). Even though patients with severe CHF have very high BNP, age/gender effects still need to be considered when choosing a partition value. A previous study that utilized the Biosite assay to measure BNP reported that a BNP of 80 pg/ml is diagnostic of CHF in symptomatic patients presenting for urgent care (5). Although the average BNP value in patients with CHF was very high, and the performance of the test was outstanding, the study population was young (mean age 63 years) and predominately men (94%). In the current study, a value of 80 pg/ml would be abnormal in most male age groups (Table 2, Fig. 1) but would be well within the 95th percentile for women. A higher partition value may be needed in women or older

patients where use of age- and gender-specific partition values may enhance the predictive characteristics of the test, particularly avoiding specificity problems in the elderly.

**Limitations.** The population of Olmsted County, Minnesota, is primarily white, and thus we are unable to investigate potential influence of ethnicity on BNP. Our study was confined to subjects >44 years of age.

**Conclusions.** In this population-based cohort, we found that BNP increases with age and is higher in women among subjects without cardiovascular disease or cardiac dysfunction. The magnitude of the effects of age and gender on BNP in the normal subgroup suggested that both parameters need to be considered when interpreting BNP, and indeed, the optimal discriminatory value of BNP for the detection of systolic dysfunction in the population was higher in women and older persons. Although the ultimate partition value for BNP used in clinical practice will be influenced by a number of variables, these data suggest that age-, gender-, and assay-specific values will be needed.

#### Acknowledgments

The authors are indebted to the study sonographers, Trudy Wellik, Mary Wenzel, and Joan Lusk; and the data analysts, Lynn Urban and Matthew Johnson for their technical expertise.

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