Population-based detection of systolic and diastolic dysfunction with amino-terminal pro-B-type natriuretic peptide

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Background There is limited information regarding the clinical utility of amino-terminal pro-B-type natriuretic peptide (NT-proBNP) for the detection of left ventricular (LV) dysfunction in the community. We evaluated predictors of circulating NT-proBNP levels and determined the utility of NT-proBNP to detect systolic and diastolic LV dysfunction in older adults.

Methods A population-based sample of 1229 older adults (mean age 69.4 years, 50.1% women) underwent echocardiographic assessment of cardiac structure and function and measurement of circulating NT-proBNP levels.

Results Predictors of NT-proBNP included age, female sex, body mass index, and cardiorenal parameters (diastolic dysfunction [DD] severity; LV mass and left atrial volume; right ventricular overload; decreasing ejection fraction [EF] and creatinine clearance). The performance of NT-proBNP to detect any degree of LV dysfunction, including mild DD, was poor (area under the curve 0.56-0.66). In contrast, the performance of NT-proBNP for the detection of EF $\leq$ 40% and moderate-severe DD was strong with area under the curve of >0.90 regardless of age and sex; history of hypertension, diabetes, coronary artery disease; or body mass category. The ability of NT-proBNP to detect EF $\leq$ 40% and/or moderate-severe DD was optimized by using age/sex-specific limits. Of "false-positive" tests, 88% (124/141) were explained after considering cardiorenal determinants of NT-proBNP levels.

Conclusions Amino-terminal pro–B-type natriuretic peptide is a suboptimal marker of mild LV dysfunction, but performs strongly as a marker of EF $\leq$ 40% and/or moderate-severe DD in the community. Most subjects with a positive NT-proBNP test, using age/sex-specific cutoffs, had prognostically significant abnormalities of cardiac structure or function. (Am Heart J 2006;152:941-8.)

The natriuretic peptides are a structurally and functionally distinct group of peptides that play an important role in the regulation of cardiovascular and renal homeostasis. Recent studies have assessed the utility of natriuretic peptides in distinguishing between cardiac and noncardiac dyspnea in the emergency department,[1,2] as a prognostic tool in patients with heart failure[3,4] and acute coronary syndromes,[5,6] and as a guide to medical therapy in patients with chronic heart failure.[7,8] However, in a recent review of the diagnostic utility of natriuretic peptides for the detection of left ventricular (LV) dysfunction and heart failure, it was concluded that the body of evidence is "still a work in progress."[9] In particular, there are several limitations with studies that have sought to establish the clinical utility of natriuretic peptides for the diagnosis of LV dysfunction. Often, such studies are done using convenience samples in which cardiac structure and function are poorly characterized. Furthermore, most studies have focused on the utility of natriuretic peptides for the detection of systolic ventricular dysfunction, ignoring prognostically significant diastolic dysfunction (DD).[10] Another important limitation of previous studies is their failure to evaluate the influence of the multiple determinants of circulating natriuretic peptides on the performance of the tests. Such information on the clinical validation of natriuretic peptide assays is a prerequisite for their optimal use as diagnostic tools in the community.[11]

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The objectives of this study were to determine the clinical and echocardiographic determinants of circulating amino-terminal pro–B-type natriuretic peptide (NT-proBNP) levels in a population-based sample of older adults, establish reference ranges in subjects that have been rigorously assessed to be free of cardiovascular disease, and to evaluate the ability of NT-proBNP to detect subjects with LV systolic dysfunction and DD in the community. We hypothesized that a large proportion of apparent "false positives" could be explained after considering determinants of NT-proBNP levels.

Methods

The Australian Capital Territory Health and Community Care and Australian National University human research ethics committees approved this study in January 2002.

Subjects

A population-based sample of 1388 adults aged 60 to 86 years underwent examination between February 2002 and June 2003 as part of the Canberra Heart Study.[12] All participants provided written and informed consent.

Clinical assessment

Risk factors for heart failure were assessed using a self-administered questionnaire. Body mass index was calculated as the weight in kilograms divided by the square of height in meters. Volume status was assessed clinically according to the jugular venous pressure, the presence of peripheral edema, and cardiorespiratory auscultation. Functional status was assessed using the New York Heart Association classification.[13] Creatinine clearance (CrCl) was calculated by applying relevant data to the Cockcroft-Gault[14] formula.

Lifestyle factors

A validated, interviewer-administered physical activity questionnaire[15] was used to document time spent on physical activity during the preceding week, adjusting for the intensity of the activity. Data were collected on smoking status (nonsmoker or current smoker), alcohol consumption (none, ≤20 g/d, and >20 g/d), and daily consumption of caffeine-containing tea and coffee.

Cardiac structure and function

Transthoracic echocardiography was performed according to a standardized protocol, and studies were evaluated offline by a cardiologist who was blinded to the participant's clinical data. Left ventricular ejection fraction (EF) was quantified by the biplane Simpson method. Abnormal LV systolic function was categorized according to EF and the presence of regional wall motion abnormalities. Left ventricular DD was graded into 3 categories (mild, moderate, and severe) using Doppler evaluation of the mitral and pulmonary venous inflow and tissue Doppler imaging of the lateral mitral annulus motion as previously described.[16,17] In a stratified subsample of 50 participants, interobserver reproducibility for grading of systolic and diastolic function was very good ($\kappa_{systolic}$ = 0.88 and $\kappa_{diastolic}$ = 0.89). Left ventricular mass and maximum left atrial volume were estimated by the area-length method[18] and indexed for height and body surface area, respectively. Aortic and mitral valve function were quantified using Doppler methods. The presence of right ventricular (RV) volume or pressure overload was determined using 2-dimensional images of the right ventricle from the parasternal long and apical 4-chamber views and the RV systolic pressure estimated by Doppler assessment of tricuspid regurgitant jet.

Table I. Characteristics of the study population (N = 1229)

Women	616 (50.1)
Age (y)	69.4 (6.5)
Hypertension	828 (67)
Diabetes	171 (14)
Coronary artery disease	214 (17)
BMI ≥30 kg/m^2	358 (29)
Congestive heart failure	86 (7.0)
Atrial fibrillation*	51 (4.2)
CrCl <60 mL/min	308 (25)
EF ≤40%	27 (2.2)
Moderate-severe DD, any EF	91 (7.4)
Moderate DD-NEF	68 (5.5)
Severe DD-NEF	2 (0.2)

Data are expressed as mean (SD) or n (%). *BMI*, Body mass index; *DD-NEF*, DD, EF >50%, and no regional wall motion abnormalities.
*Diastolic function grade could not be determined in 23 subjects with atrial fibrillation.

Amino-terminal pro–B-type natriuretic peptide levels

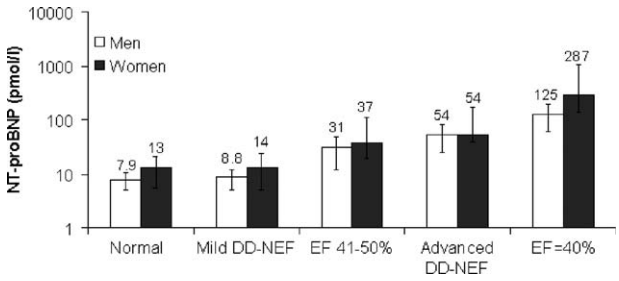
Venous blood was collected in serum tubes, centrifuged, and stored at −70 °C until analysis. Amino-terminal pro–B-type natriuretic peptide levels were measured using a commercially available and fully automated electrochemiluminescence sandwich immunoassay on an Elecsys 1010 (proBNP, Roche Diagnostics, Basel, Switzerland). This immunoassay has a within-run coefficient of variability (CV) of 0.7% to 1.6% and a between-run coefficient of variability of 5.3% to 6.7%.[19]

Statistical analysis

Data are summarized as means ± SD for continuous variables or as frequency percentages for categorical variables. Amino-terminal pro–B-type natriuretic peptide levels were positively skewed and natural log transformation was required to satisfy statistical modeling assumptions for regression analyses. For the entire cohort, echocardiographic and clinical variables were assessed for their univariate association with NT-proBNP using Spearman ρ correlation. Variables with statistically significant associations with log NT-proBNP in the univariate analysis were included in the stepwise multivariable linear least-squares regression analysis, starting with a full model (Stata version 7.0, Stata Corporation, College Station, TX).

Amino-terminal pro–B-type natriuretic peptide reference ranges were derived in subjects without atrial fibrillation, myocardial infarction, hypertension, diabetes, past or current clinical heart failure, renal impairment (creatinine ≥150 μmol/L), or echocardiographic evidence of abnormal cardiac structure/function (indexed LA volume [LAVI]

Figure 1



Median (bars) and interquartile range (error bars) for NT-proBNP levels according to sex and LV function. Amino-terminal pro–B-type natriuretic peptide levels are presented in the logarithmic scale. *DD-NEF*, DD, normal LV EF (EF >50%), and no regional wall motion abnormalities; *advanced DD-NEF*, moderate or severe DD-NEF.

>28 mL/m^2, LV hypertrophy, abnormal LV systolic function, any DD, more than mild mitral or aortic valve disease, and elevated RV systolic pressure). Subjects on vasoactive medication were excluded from the reference group. Analytical methods used on the entire cohort were used to determine associations of NT-proBNP in the reference subgroup, and the result of the multivariable regression analysis was used to determine which parameters required partitioning to more accurately reflect NT-proBNP reference levels. From the least-squares regression model for log (NT-proBNP) with age and sex as predictor variables, 5th to 95th percentiles were estimated and back-transformed to the natural scale to derive sex-specific reference NT-proBNP ranges.

The ability of NT-proBNP to detect varying degrees of LV systolic and/or DD in the entire cohort was assessed using receiver operating characteristic (ROC) analysis. The overall performance for the test over its entire range was quantified using the areas under the ROC curve (AUCs) within age- and sex-specific strata and compared using the method of DeLong et al.[20] Clinical and echocardiographic associations with false-positive NT-proBNP tests were determined using logistic regression analysis.

Results

The characteristics of 1229 subjects that completed all investigations relevant to this study are described in Table I. Amino-terminal pro–B-type natriuretic peptide levels are presented in Figure 1, stratified by sex and LV function. There was a large overlap in NT-proBNP levels between groups with normal LV function and mild DD with EF >50% (DD-NEF). However, NT-proBNP levels increased progressively with deteriorating LV function thereafter (all $P < .0001$). Amino-terminal pro–B-type natriuretic peptide levels in subjects with advanced DD-NEF were higher than those with an EF of 41% to 50% ($P = .002$), but lower than subjects with EF ≤40% ($P < .001$).

Table II. Multivariable associations with NT-proBNP levels in the entire cohort

Predictor (increment)	β*	95% CI	P
Age (per 1 y)	1.03	1.02-1.04	<.0001
Women	1.39	1.27-1.51	<.0001
Volume overload	1.16	1.03-1.31	.017
Functional class			
NYHA class II	1.13	1.03-1.23	.007
NYHA class III	1.48	1.18-1.86	.001
NYHA class IV	4.32	1.16-16.1	.03
LV systolic function			
RWMA, EF >50%	1.40	1.15-1.71	.001
EF 41%-50%	1.82	1.48-2.24	<.0001
EF 31%-40%	2.38	1.65-3.42	<.0001
EF ≤ 30%	2.98	1.86-4.76	<.0001
LV diastolic function			
Mild DD	0.94	0.87-1.03	.176
Moderate DD	2.24	1.85-2.70	<.0001
Severe DD	4.87	2.62-9.04	<.0001
LV mass index (per 5 g/m)	1.02	1.01-1.03	<.0001
Left atrial volume index (per mL/m^2)	1.01	1.01-1.02	<.0001
RV volume/pressure overload	1.28	1.00-1.67	.049
CrCl (per mL min^{-1} 1.73 m^2)	0.99	0.99-0.99	<.0001
BMI (per kg/m^2)	0.98	0.97-0.99	.004
Pulse pressure (per 5 mm Hg)	1.03	1.01-1.04	.001
Atrial fibrillation	2.69	2.02-3.59	<.0001

Adjusted R^2 for model = 0.60. *NYHA*, New York Heart Association; *RWMA*, regional wall motion abnormalities.
*The β coefficient is back-transformed to natural scale.

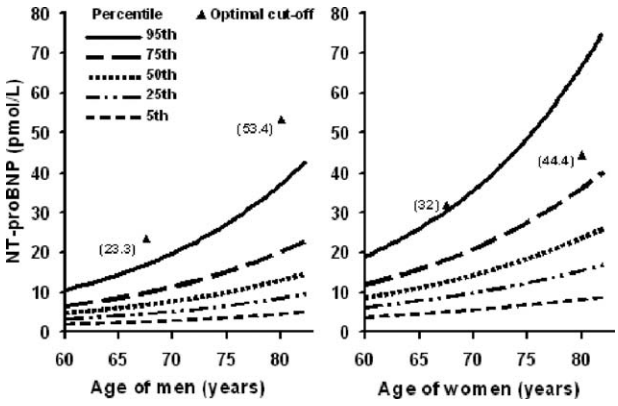
Associations with NT-proBNP in the entire cohort

In univariate analysis, age ($\rho = 0.46$), CrCl ($\rho = -0.41$), and LAVI ($\rho = 0.41$) were most strongly correlated with NT-proBNP levels. Associations between NT-proBNP and clinical and echocardiographic variables in the entire cohort in the multivariable analysis are reported in Table II.

Associations with NT-proBNP in the reference subgroup (n = 201)

In univariate analysis, increasing age ($\rho = 0.34$, $P < .0001$) and LAVI ($\rho = 0.15$, $P < .03$); female sex ($P < .0001$); decreasing CrCl ($\rho = -0.31$ $P < .0001$); and coffee consumption ($P < .038$) were associated with increased NT-proBNP levels. There was no association between NT-proBNP and heart rate ($\rho = -0.07$, $P < .33$), physical activity levels over the preceding week ($\rho = -0.03$, $P < .65$), tobacco smoking ($P < .53$), or tea ($P < .79$) consumption. Amino-terminal pro–B-type natriuretic peptide levels were not higher in healthy women on hormone replacement therapy ($P < .64$), even after adjusting for age ($P < .51$). Age, sex, and LAVI were the only independent predictors of NT-proBNP levels in the reference subgroup. The addition of LAVI marginally improved the multivariable model for the prediction of NT-proBNP levels ($R^2 = 0.24$-0.25) and did not

Figure 2



Amino-terminal pro–B-type natriuretic peptide reference ranges are illustrated as 5th, 25th, 50th, 75th, and 95th percentile levels. Cutoff NT-proBNP levels based on 95th percentiles and age/sex-specific optimal discriminatory points for the detection of EF ≤40% and/or moderate-severe DD are compared.

significantly alter the β coefficients for age and sex. Thus, for simplicity, results of the multivariable analysis with age and sex as the only predictor variables were used to construct nomograms for NT-proBNP reference levels (Figure 2).

Amino-terminal pro–B-type natriuretic peptide utility to detect LV dysfunction in entire cohort

The performance of NT-proBNP to detect any degree of LV dysfunction, including mild DD-NEF, was poor (AUC 0.56-0.66). In contrast, the performance of NT-proBNP for the detection of EF ≤40% or moderate-severe DD-NEF was strong with AUC levels consistently >0.90 (Table III), regardless of age and sex; history of hypertension, diabetes, coronary artery disease; or body mass category (Figure 3). Given the prevalence of disease in the study population and characteristics of the test performance, further analysis of NT-proBNP performance has been limited to the detection of EF ≤40% and/or moderate-severe DD, as it is likely that this approach will represent the optimal use of NT-proBNP for the detection of LV dysfunction in the community.

Age and sex had a greater impact on 95th percentile reference limits than on optimal discriminatory NT-proBNP levels for the detection of EF ≤40% and/or moderate-severe DD (Figure 2). Accordingly, the disparity between optimal discriminatory and reference limits was most evident for women aged ≥75 years.

Using the derived NT-proBNP cutoffs (Table III), 7.4% (2/27) with an EF ≤40% and 26% (18/70) with moderate-severe DD-NEF were missed with NT-proBNP testing. Of the 141 subjects with false-positive tests, only 17 individuals did not have an identifiable cardiorenal cause for an elevated NT-proBNP level. Clinical and echocardiographic predictors of false-positive NT-proBNP tests are described in Table IV.

Discussion

In this large population-based cohort of older adults, some of the complexities of using NT-proBNP as a tool for the detection of LV dysfunction have been identified and explored.

Determinants of NT-proBNP

An understanding of the determinants of NT-proBNP is a prerequisite for its optimal use as a diagnostic tool for LV dysfunction in the community. Our results serve as a guide not only to determine the extent to which each demographic and cardiorenal factor influences circulating NT-proBNP levels, but also to identify the potential sources of false-positive NT-proBNP tests.

Our findings provide valuable insight into the relationship between natriuretic peptides and diastolic function, a topic of recent dispute. Lubien et al[21] have observed that BNP levels increased with progressive stages of DD in clinic-based patients with preserved systolic function and reported that the performance of BNP for the detection of mild DD-NEF was good (AUC 0.87). However, since then, several studies with differing study populations have provided conflicting results.[22–24] In this population-based sample, we have shown that NT-proBNP was a poor marker of mild DD-NEF, but levels were increased in subjects with moderate or severe DD-NEF, in whom LV filling pressures were raised. In a proportion of subjects with elevated NT-proBNP levels, we observed that preload-dependent, instantaneous diastolic function grade was only mildly impaired despite structural evidence to suggest long-term exposure to increased LV filling pressures, manifested as left atrial enlargement.[25] The overrepresentation of such cases with "mild" DD grade in populations referred for LV assessment may account for the differences between our findings and those from clinic-based studies.

In this study, we have extended previous efforts [16,24,26,27] to examine the relationship between age, sex, and NT-proBNP levels in subjects free of any identifiable cardiovascular disease. Comprehensive Doppler-echocardiographic methods were used to exclude subjects with DD-NEF from the reference subgroup, and subjects with a dilated left atrium or significant renal dysfunction were excluded for the derivation of reference limits because these conditions have been recognized as subclinical markers of increased cardiovascular risk[10,28] and were associated with increasing levels of NT-proBNP in our cohort. In addition, we

Table III. Amino-terminal pro–B-type natriuretic peptide performance for detection of LV dysfunction

	Prevalence		NT-proBNP cutoff		Sens	Spec			Missed	Negative
	n (%)	AUC	pmol/L	pg/mL	%	%	LR+	LR-	Cases (%)	Echos (%)
Men, 60-86 y (n = 613)*										
Moderate DD	46 (7.5)	0.91	30	254	83	85	5.4	0.21	17	69
EF ≤40%	21 (3.4)	0.92	53	452	86	91	9.2	0.16	14	75
EF ≤50%	55 (9.0)	0.82	24	206	76	81	4	0.29	24	72
Women, 60-86 y (n = 616)*										
Moderate DD	45 (7.3)	0.90	32	270	89	86	6.5	0.13	11	66
EF ≤40%	6 (1.0)	0.99	84	710	100	96.1	25	0	0	78
EF ≤50%	20 (3.3)	0.85	35	296	70	84.2	4.4	0.36	30	87
Men, 60-74 y (n = 458)										
EF ≤40% and advanced DD-NEF	32 (7.0)	0.92	23	197	84	89	7.8	0.18	16	63
EF ≤50% and advanced DD-NEF	54 (12)	0.86	18	151	78	88	6.3	0.25	22	54
Men, 75-86 y (n = 155)										
EF ≤40% and advanced DD-NEF	20 (13)	0.86	53	452	85	79	4.1	0.19	15	62
EF ≤50% and advanced DD-NEF	32 (21)	0.84	50	426	81	80	4.2	0.23	19	48
Women, 60-74 y (n = 470)										
EF ≤40% and advanced DD-NEF	22 (4.7)	0.89	32	270	82	89.7	8	0.2	18	72
EF ≤50% and advanced DD-NEF	31 (6.6)	0.86	32	270	68	90.2	6.9	0.36	32	67
Women, 75-86 y (n = 146)										
EF ≤50% and advanced DD-NEF	28 (19)	0.91	44	375	86	86	6.3	0.17	14	52
EF ≤40% and advanced DD-NEF	23 (16)	0.89	44	375	83	83	4.8	0.21	17	40

LR+, Positive likelihood ratio; *LR−*, negative likelihood ratio; *missed* cases, proportion of subjects with LV dysfunction who would have been missed with NT-proBNP test; *Sens*, sensitivity; *Spec*, specificity.
*Because of the low numbers of subjects with EF ≤40%, age-pooled analyses were performed to compare the test performances for the detection of "predominantly" systolic dysfunction or DD.

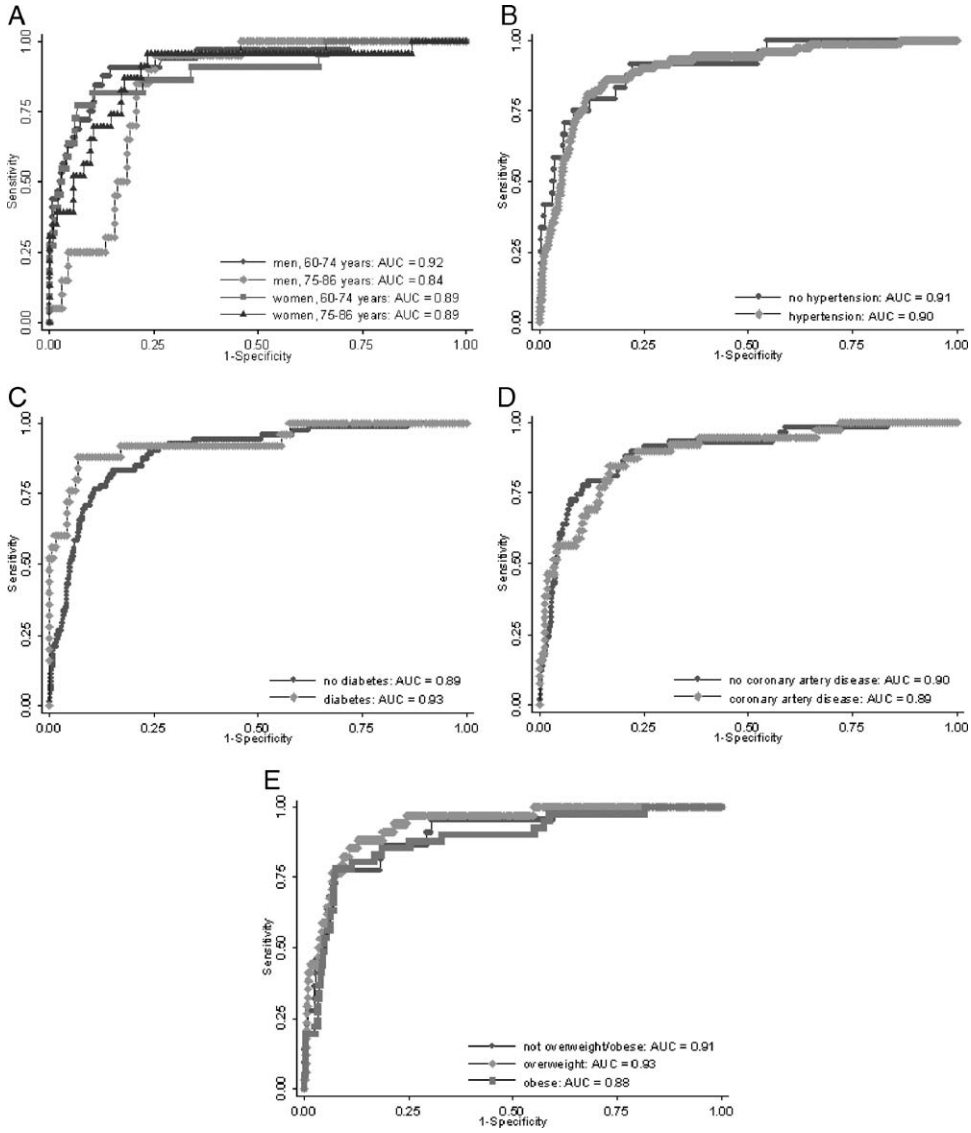
evaluated the potential for lifestyle factors to account for higher NT-proBNP levels in women and with increasing age. Despite our efforts, age and sex were reconfirmed as major determinants of NT-proBNP levels. Accordingly, we have presented reference limits that are stratified according to age and sex. Data from longitudinal studies are required to determine if the increase in NT-proBNP levels with advancing age is related to occult pathophysiologic rather than physiologic influences, in which case age-specific references limits may be unwarranted. As we found that age and sex had a greater impact on 95th percentile reference limits than on optimal discriminatory NT-proBNP levels, we would advise against the use of 95th reference limits as cutoffs for the detection of LV dysfunction as this approach would result in a reduction in test sensitivity and thus an increased proportion of missed cases, particularly for women aged ≥75 years.

Amino-terminal pro–B-type natriuretic peptide detection of LV dysfunction in the community

Given the prevalence of various degrees of systolic dysfunction and DD in the study population, the characteristics of the test performance, and the emerging evidence that DD is prognostically significant regardless of whether it is associated with reduced EF, [10,29] we suggest that the diagnostic utility of NT-proBNP would be optimized in the community by using cutoffs for the detection of EF ≤40% and/or advanced DD. We agree with a recent report that overall performance of the test as assessed by ROC analysis was best for the strategy to detect EF ≤40%[27] as the NT-proBNP levels were highest for these subjects. However, as previously documented, the prevalence of EF ≤40% is low in the community and most subjects are in the clinical stage of disease.[10,12] In contrast, advanced DD-NEF is more common in the community, and often unaccompanied by symptoms of congestive heart failure.[10,17] Using thresholds for the detection of EF ≤40%, which are similar to cutoffs reported recently in another population-based study,[27] many cases with prognostically significant DD-NEF and milder degrees of systolic dysfunction will be missed without an accompanying gain in the positive predictive value of the test.

We have confirmed recent observations that, owing to the relatively low prevalence of advanced LV dysfunction in the community, the diagnostic performance of natriuretic peptides in the general population is adversely affected by a high false-positive rate, resulting in a large proportion of subjects with a positive NT-proBNP test who will subsequently undergo an echocardiogram without confirmation of an EF <40% and/or advanced DD.[27] However, on closer inspection, we have shown that most subjects with false-positive tests had prognostically significant cardiorenal disease. This finding has several important clinical implications. First, before ordering a NT-proBNP

Figure 3



Overall performance of NT-proBNP for the detection of EF ≤40% and/or moderate-severe DD, according to (**A**) age and sex (*P* = .26); history of (**B**) hypertension (*P* = .83); (**C**) diabetes (*P* = .31); (**D**) coronary artery disease (*P* = .90); or (**E**) body mass category (*P* = .35).

test in patients with atrial fibrillation or renal impairment, clinicians should be aware that NT-proBNP levels are more likely to be raised without accompanying echocardiographic evidence of abnormal cardiac structure or function. Second, most subjects with a positive NT-proBNP test are likely to have cardiac disease for which secondary preventive measures are indicated. Additional studies are required to determine whether screening for stage B heart failure[30] with natriuretic peptides can be used as a cost-effective strategy to reduce the growing burden of congestive heart failure in our aging community.

Our results should not be extrapolated to patients presenting with acute dyspnea for investigation. Because natriuretic peptide levels are also raised by noncardiac causes of acute dyspnea, NT-proBNP cutoff levels have been set higher to optimize the diagnosis of acute heart failure in the emergency department.[2] Moreover, the overall performance of the test is also likely to vary depending on the setting in which it is used, although a recent study has shown that even in the emergency department, the performance of NT-proBNP for the diagnosis of acute heart failure was very good (AUC 0.94).[2]

Table IV. Cardiorenal predictors of false-positive NT-proBNP tests

	Entire cohort (N = 1229)	False positive (n = 141)	Adjusted OR
Atrial fibrillation	51 (4.2)	21 (15)	3.8*
CrCl <60 mL/min	308 (25)	70 (50)	2.6*
Increased LV mass	140 (11)	25 (17)	NS
LAVI ≥28 mL/m^2	317 (26)	69 (49)	2.2*
RWMA, EF >50%	49 (4.0)	17 (12)	5.4*
EF 41%-50%	75 (6.1)	26 (18)	3.3*
Mild DD-NEF	291 (24)	31 (22)	NS
RV overload†	26 (2.1)	8 (5.7)	3.9*

NS, Not statistically significant; *LAVI*, indexed LA volume.
*$P < .005$.
†Ejection fraction >50%, no LV RWMA.

Limitations

Echocardiographic methods are imperfect "gold" standards for the classification of systolic and diastolic function. However, these methods are currently accepted as the reference standard for the assessment of LV function in clinical practice, and we could not justify the evaluation of diastolic function in survey participants with invasive tests. Although our sample of older adults represents a suitable population for which natriuretic peptides would have potential use in the diagnosis or screening of heart failure, study findings may not be valid in younger subjects. As most of the sample was white, our results may not be applicable to nonwhite populations.

Conclusions

Amino-terminal pro–B-type natriuretic peptide is a suboptimal marker of mild LV dysfunction, but performs strongly as a marker of EF ≤40% and/or moderate-severe DD in the community. Most subjects with a positive NT-proBNP test, using age/sex-specific cutoffs, had prognostically significant abnormalities of cardiac structure or function.

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