JACC: CARDIOVASCULAR IMAGING
VOL. 2, NO. 2, 2009

ISSN 1936-878X/09/$36.00
PUBLISHED BY ELSEVIER INC.
DOI:10.1016/j.jcmg.2008.12.006

iREVIEWS

STATE-OF-THE-ART-PAPER

B-Type Natriuretic Peptides and Echocardiographic Measures of Cardiac Structure and Function

Richard W. Troughton, MB, ChB, PhD, FRACP,
A. Mark Richards, MD, PhD, DSc, FRACP
Christchurch, New Zealand

Echocardiography and the B-type natriuretic peptides (BNPs) provide powerful incremental assessment of cardiac function, clinical status, and outcome across the spectrum of cardiac disease. There is strong evidence to support their integrated use in the diagnosis and management of cardiovascular disease. Amino-terminal pro-B-type natriuretic peptide (NT-proBNP) or BNP may guide more effective use of echocardiography in screening for asymptomatic left ventricular dysfunction; Doppler echocardiography improves the accuracy of heart failure diagnosis in the setting of intermediate BNP or NT-proBNP levels. Combined assessment of peptides and echocardiography provides more powerful stratification of risk across all stages of heart failure, and integrated use of both tests may identify subjects with valvular disease at greatest risk for progression and guide decision-making for timely intervention. (J Am Coll Cardiol Img 2009;2:216–25) © 2009 by the American College of Cardiology Foundation

Since their discovery and characterization, B-type natriuretic peptides have become firmly established as biomarkers for heart failure diagnosis and for prognosis across the spectrum of cardiovascular disease (1–3). The relationship between the B-type peptides and echocardiographic measures of cardiac structure and function has been widely explored. Peptide measurements provide information complementary or incremental to echocardiography for assessment of cardiac function, clinical status, and outcome. We review these data and consider the potential clinical applications of echocardiography integrated with B-type natriuretic peptide testing.

B-type Natriuretic Peptides

The natriuretic peptide family includes atrial, B-type (BNP), C-type natriuretic peptide, and urodilatin. BNP is secreted primarily by atrial and ventricular cardiomyocytes and—like atrial natriuretic peptide—has vasodilator, lusitropic, and natriuretic actions; it also inhibits cardiac sympathetic traffic, renin-angiotensin-aldosterone activity, and cardiac fibrosis (3).

The BNP gene encodes pre-pro-BNP, a 134-amino acid (aa) molecule from which BNP signal peptide is cleaved to produce

From the University Department of Medicine, University of Otago, Christchurch, Christchurch, New Zealand. Dr. Troughton has received honoraria from Roche Diagnostics as part of their Speaker's Bureau (<$10K). Dr. Richards has received honoraria and research grants from Roche Diagnostics and Advisory Committee fees and grant support from Inverness/Biosite.

Manuscript received December 4, 2008, accepted December 9, 2008.

proBNP (amino acids 1 to 108) (4). ProBNP and its two cleavage products, the inactive amino-terminal pro-B-type natriuretic peptide (NT-proBNP) (aa 1 to 76) and the bioactive molecule BNP (aa 77 to 108) (Fig. 1) are all present in the circulation. Although secretion of BNP and NT-proBNP is equimolar, BNP is actively cleared through natriuretic peptide C-receptors and by neutral endopeptidase, resulting in significantly lower plasma levels and a shorter half-life (21 min) than NT-proBNP (70 min), for which clearance mechanisms beyond renal filtering are less certain. Further processing of proBNP, NT-proBNP, and BNP within the circulation produces truncated forms presumably variably recognized by immunoassays and possessing variable bioactivity (5). This appears to have little impact on clinical application of current well-validated immunoassays for BNP and NT-proBNP (5).

BNP is not stored but is synthesized and secreted constitutively in response to cardiomyocyte stretch (4). Increased ventricular or atrial wall stress, reflecting volume or pressure overload, is the primary driver of myocyte stretch-mediated secretion, but ischemia, neurohormones, and cytokines also stimulate or modify BNP gene expression (4).

Plasma levels of B-type natriuretic peptides. Validated commercial assays are available for BNP and NT-proBNP (6). Each assay has different performance characteristics and recognizes different epitopes on the BNP or NT-proBNP molecule. Although there is generally strong correlation between assays, absolute peptide values may vary considerably, so clinicians should know the reference range and performance characteristics of their local assay (6,7).

Plasma levels of BNP and NT-proBNP increase with age and are lower in men than in women (8). Levels are inversely related to body mass index and lean mass (9) and increase with worsening glomerular filtration rate (10). Even in stable subjects, peptide levels vary with repeat testing as a consequence of assay characteristics and biological variation (11). Relative variation is greater in normal subjects, in whom absolute levels are low. In disease states, absolute levels are higher and relative variation is lower. In stable heart failure subjects, changes of more than 23% for NT-proBNP or 43% for BNP are likely to indicate a change beyond that due to background biological variation (11).

BNP and Echocardiographic Indexes of Cardiac Function

Given synthesis primarily by cardiomyocytes, it is not surprising that the greatest secretion of B-type peptides is from the left ventricle (LV). BNP and NT-proBNP levels correlate positively with LV dimensions, volumes, and mass in a variety of settings and populations and are inversely related to LV ejection fraction (LVEF) (3,12–15). Peptide levels are higher with left ventricular hypertrophy (LVH) (14) and are higher still in subjects with LVH and clinical heart failure.(16)

Diastolic function. The strongest correlations have been reported for BNP with LV diastolic wall stress consistent with stretch-mediated BNP secretion (Fig. 2) (15). BNP levels increase with greater severity of overall diastolic dysfunction, independent of LVEF, age, sex, body mass index, and renal function, and the highest levels are seen in subjects with restrictive filling patterns (Fig. 3) (17–19). Peptide levels correlate with indexes of filling pressure—including transmitral early filling velocity (E) and its ratio to early diastolic annular velocity (E/Ea)—as well as with indexes of compliance and myocardial relaxation (18,19). In subjects with normal LVEF, elevated NT-proBNP (>600 pg/ml) or BNP (>100 pg/ml) are the strongest independent predictors of severe diastolic dysfunction; low peptide levels (<140 pg/ml) exhibit very high negative predictive value (>90%) for diastolic dysfunction (19).

BNP and NT-proBNP levels also reflect left atrial size, correlating positively with left atrial volume, particularly in the general population and in patients with heart failure with preserved systolic function (13,20,21). In acutely decompensated heart failure or in subjects with advanced systolic heart failure, the relationship between left atrial volume and BNP appears diminished, possibly reflecting proportionately greater peptide secretion from the left and right ventricles in this context.

Right ventricle. The right ventricle (RV) contributes to plasma levels of BNP or NT-proBNP, with either normal or impaired LVEF. Levels of both peptides correlate with measures of RV size and function, increasing with greater dilatation and systolic dysfunction, and with increasing RV pressure estimates (18,22).

ABBREVIATIONS AND ACRONYMS

aa = amino acid
ADHF = acute decompensated heart failure
BNP = B-type natriuretic peptide
E/Ea = transmitral early filling velocity/early diastolic annular velocity
LVEDP = left ventricular end diastolic pressure
LVEF = left ventricular ejection fraction
LVH = left ventricular hypertrophy
NT-proBNP = amino-terminal pro-B-type natriuretic peptide
PCWP = pulmonary capillary wedge pressure
RV = right ventricle

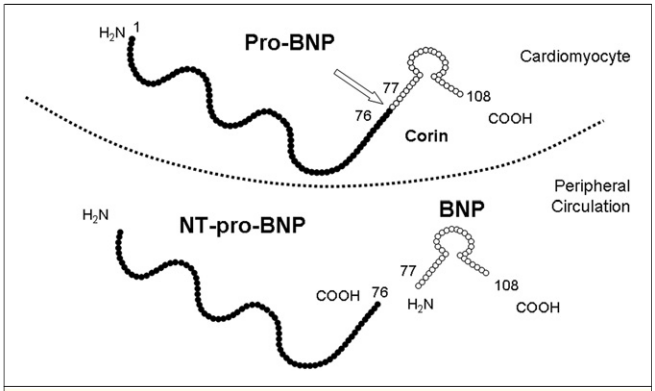

Figure 1. B-Type Natriuretic Peptide Molecular Forms and Processing

Pro-B-type natriuretic peptide (proBNP) is synthesized primarily within cardiomyocytes and is largely cleaved to form bioactive BNP and the inert marker molecule amino-terminal proBNP (NT-proBNP), the major circulating forms. Further processing within the circulation produces truncated forms of all 3 peptides that can be identified in plasma. Modified with permission from Lam et al (5).

Detection of Elevated Left Ventricular Filling Pressures

Plasma levels of the B-type peptides reflect measurements of LV filling pressure, but the relationship is often modest and dependent on clinical context (23). In patients undergoing routine coronary angiography (24), BNP and/or NT-proBNP correlate strongly with LV end diastolic pressure (LVEDP) and exhibit modest accuracy for detection of raised LVEDP (23,24). Smaller studies in subjects with stable systolic dysfunction demonstrate similar strong correlations between BNP or NT-proBNP and either LVEDP or pulmonary capillary wedge pressure (PCWP) (25,26). In this context, peptide levels are elevated and exhibit good specificity but reduced sensitivity and overall accuracy for detection of elevated filling pressures (25). When LV ejection fraction is preserved but diastolic function is impaired, the correlation between BNP or NT-proBNP and invasively measured filling pressures is weaker (r = ~0.45), but negative predictive values (~90%) for elevated LVEDP remain high (19). In acute decompensated heart failure (ADHF), where background BNP or NT-proBNP levels are significantly elevated, the correlation between peptide levels and filling pressure is weaker, especially in advanced heart failure or unselected intensive care patients (23,27). Changes in peptide levels during therapy for ADHF reflect clinical and hemodynamic changes, but peak peptide changes lag behind the latter (27,28).

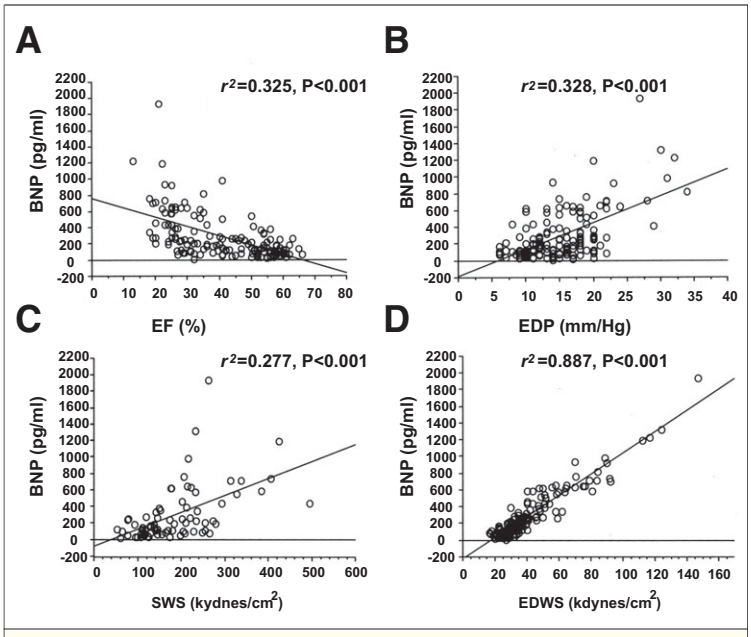

Figure 2. Relationship of B-Type Natriuretic Peptide to Indexes of Left Ventricular Function

Hemodynamic, imaging and B-type natriuretic peptide (BNP) data from 160 subjects with systolic or diastolic heart failure demonstrating that BNP levels correlate with indexes of left ventricular function including: **(A)** ejection fraction (EF), **(B)** end diastolic pressure (EDP), **(C)** systolic wall stress (SWS), and **(D)** end diastolic wall stress (EDWS). Adapted with permission from Iwanaga et al. (15).

The modest relationship between NT-proBNP or BNP and LV filling pressures is consistent with the complexity of factors influencing secretion and clearance. In addition to the effects of age, sex, renal function, and neurohormonal/cytokine status, secretion from the RV and the left atrium contribute to absolute peptide levels. Left ventricular geometry is also important, with dilated ventricles secreting more peptide for a given filling pressure due to greater wall stress and chamber mass (15,18).

A single value for BNP or NT-proBNP is therefore unlikely to provide reliable estimation of filling pressures across individuals, although very low levels retain strong negative predictive values for an elevated filling pressure in most settings (23). Within individuals, however, changes in BNP may reflect changes in filling pressure, as has been demonstrated in subjects with implantable monitoring devices, where serial BNP measurements correlate significantly with ambulatory device-based estimates of filling pressure (29).

In contrast, accurate estimation of LV filling pressures by Doppler echocardiography has been widely validated. Transmitral and pulmonary venous filling indexes and more particularly, the E/Ea ratio, are now established as markers of filling pressure that have been widely adopted across a

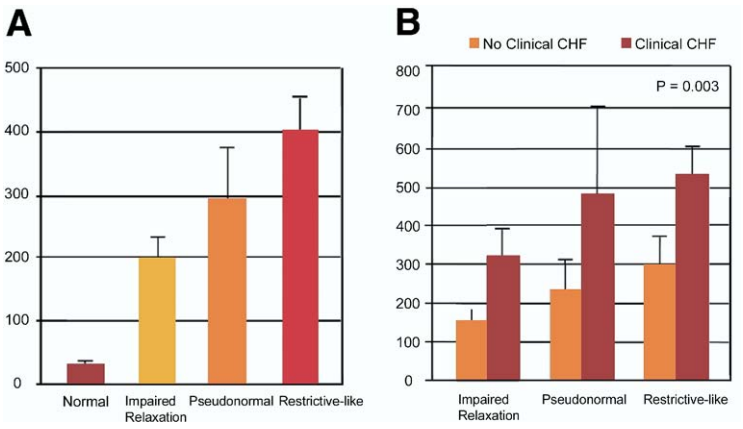

Figure 3. B-Type Natriuretic Peptide and Left Ventricular Diastolic Function

(A) Plasma B-type natriuretic peptide (BNP) levels (pg/ml) are strongly related to overall left ventricular diastolic function assessed by Doppler echocardiography. **(B)** Gradation of BNP levels according to diastolic stage is seen regardless of clinical status, but levels are higher in clinically decompensated heart failure. Adapted with permission from Lubien et al. (17). CHF = congestive heart failure.

broad range of clinical settings (30–32). There have been few comparative studies of echocardiography with BNP, however Dokainish et al. (27) compared validated Doppler echocardiographic indexes with BNP for detection of PCWP >15mm Hg in patients admitted to the intensive care unit. In subjects with established cardiac disease, a BNP level >400 pg/ml demonstrated similar sensitivity (91%) but poorer specificity (51% vs. 91%) and overall accuracy than Doppler indexes such as E/Ea for detection of a PCWP >15 mm Hg. However, in subjects without cardiac disease, BNP proved more sensitive (81% vs. 74%) and specific (83% vs. 72%) than Doppler indexes (27). These findings indicate that in subjects with known cardiac disease, Doppler echocardiography provides superior estimation of elevated filling pressures. Where there is no history of cardiac disease, peptide measurement may be a preferred initial strategy for detecting elevated filling pressure.

Detection of Left Ventricular Systolic and Diastolic Dysfunction

The accuracy of BNP or NT-proBNP in screening for LV structural and functional abnormalities has been tested in community, hospital, and high-risk populations and appears to depend on the abnormality in question and its prevalence within that population (3,13,20,33–35).

In selected subjects referred for echocardiography, BNP has good sensitivity and specificity for detecting systolic (LVEF <40% to 50%) or diastolic dysfunction. Low peptide levels have high negative predictive value; specificity and positive predictive values increase when the prevalence of LV dysfunction is higher (17,36). Maisel et al. (36) demonstrated that a BNP level of ≥75 pg/ml had an overall accuracy of 90% for detecting either systolic (LVEF <50%) or diastolic dysfunction (impaired relaxation pattern or worse on transmitral filling). BNP levels did not differentiate systolic from primary diastolic dysfunction with preserved LVEF. Lubien et al. (17) assessed 294 patients with normal systolic function (LVEF >50%) referred for echocardiography. BNP levels rose with increasing diastolic dysfunction and were higher still if clinical heart failure was present (Fig. 3). A BNP level of 65 pg/ml detected any diastolic dysfunction in this context with a sensitivity of 85%, specificity of 83%, and overall accuracy of 84%. Accuracy was greater when only restrictive filling was considered (17).

Community screening. In community settings, up to one-half of all patients with LV dysfunction may be clinically undetected (37). Several studies have assessed screening of the general population with BNP or NT-proBNP to detect systolic dysfunction (LVEF <50%), increased LV mass, or diastolic dysfunction graded on the basis of transmitral filling as moderate (pseudonormal) or severe (restrictive) (33–35,38,39). The prevalence of LV dysfunction in each study was low (≤6%), but these studies consistently demonstrate a high negative predictive value (93% to 99%) when BNP or NT-proBNP levels are low; values for specificity and overall accuracy are lower (33,35). The lesser accuracy of detection of asymptomatic LV dysfunction by NT-proBNP and BNP in the community setting

may reflect confounding from noncardiac influences, including age, sex, and renal function, in the setting of generally low peptide levels and a low prevalence of LV dysfunction. The effect of body mass on peptide levels may add to background noise that reduces the utility of peptide screening, unlike in heart failure diagnosis, in which the accuracy of threshold peptide cut-points appears less affected by body mass (3,9). The Framingham study group found that use of a single sex-adjusted BNP level did not significantly improve detection of LV systolic dysfunction (diastolic function was not considered) or LVH over standard clinical and electrocardiographic parameters (35). In subjects from Olmsted County, although very low levels of BNP excluded significant LV dysfunction, unadjusted levels appeared suboptimal for routine screening of the general population, with confirmatory echocardiography necessary in up to 40% of the study population and up to 60% of cases missed when a single unadjusted BNP cut-point value was applied (33). The same group compared NT-proBNP to BNP in 1,869 community subjects and found that use of age- and sex-adjusted cut-point factors improved accuracy, with sensitivity and specificity between 90% and 100% for NT-proBNP in detecting LVEF <40% (13). Both NT-proBNP and BNP were less robust when screening for diastolic dysfunction, alone or in combination with systolic dysfunction.

Although portable echocardiography may provide a more cost-effective approach to screening for LV dysfunction (40,41), integrated use of NT-proBNP using age- and sex-adjusted cut-points could provide helpful screening for systolic dysfunction, but not for isolated diastolic dysfunction (20,42). Importantly, BNP and NT-proBNP may function best in combination with other tests. Combining BNP with electrocardiogram or clinical features increases the positive predictive value and overall accuracy for detection of LV dysfunction (43). Several studies indicate that screening with BNP or NT-proBNP in combination with clinical parameters is cost-effective in reducing the number of formal echocardiographic studies needed to identify LV dysfunction (44). BNP and NT-proBNP may function better as a marker of "cardio-renal dysfunction" rather than specifically for LV dysfunction (20). In this context, peptide values below the 97.5th percentile for the normal population, have high negative predictive value, essentially ruling out cardio-renal abnormalities in asymptomatic subjects (45).

Diagnosis of Heart Failure

The prompt and accurate diagnosis of heart failure facilitates decision making and management in primary care and in the emergency room (3,46,47). However, early diagnosis remains a significant challenge in these settings, with initial diagnoses based on clinical assessment often being incorrect (46,47). BNP or NT-proBNP levels are elevated in patients with ADHF, and multiple studies have demonstrated the value of BNP or NT-proBNP for diagnosis of acute heart failure, regardless of LVEF (46,48,49). In an acutely dyspneic patient, low peptide levels (<100 pg/ml for BNP [49], <300 pg/ml for NT-proBNP [48]) rule out ADHF with a negative predictive value of >95%; very high peptide levels can achieve positive predictive values ≥85% for ADHF (48). In many of these studies, echocardiography was included in the gold standard assessment of ADHF diagnosis. Smaller studies comparing echocardiography with peptide methods show that BNP has similar accuracy to any single echocardiographic index (such as E/Ea) for diagnosis of heart failure; comprehensive Doppler echocardiography provides improved specificity (50–52). Comprehensive echocardiography provides a particular advantage when BNP or NT-proBNP levels fall in the intermediate or "grey" zone. For example, a restrictive transmitral Doppler pattern accurately differentiates acute heart failure from noncardiac causes of acute dyspnea when BNP levels fall between ~100 and ~500 pg/ml (Fig. 4) (50,51). Integrated use of peptide measurement followed by targeted Doppler echocardiography could therefore improve the accuracy of early heart failure diagnosis for up to 30% of acutely dyspneic patients who have intermediate peptide levels at presentation (Fig, 5).

BNP or NT-proBNP levels are higher in heart failure with impaired LV systolic function than when LVEF is preserved, consistent with greater wall stress in the former (15,49). However, peptide levels have limited accuracy in differentiating these two entities and cannot replace echocardiography (49).

Monitoring of Heart Failure

Notwithstanding the biological variation seen with repeat peptide measurements, there is growing evidence that serial measurements of BNP or NT-proBNP may be useful for monitoring clinical status and guiding therapy in heart failure (53,54). The greatest benefits are seen in younger patients with systolic heart failure, in whom reductions in

mortality and heart failure events have been demonstrated with peptide-guided therapy (53–55).

In contrast, the role of serial imaging in heart failure remains unclear and is generally not advocated in stable patients (41). Repeat measurement of 2-dimensional and Doppler indexes may be limited by reproducibility and measurement variability (41). To date, the value of repeat echocardiographic imaging has not been tested in a randomized study, and the few studies comparing serial echocardiographic imaging and peptide measurement suggest the latter may provide more clinically useful information (56,57). Further studies are needed in this area, particularly to assess integrated use of imaging and peptide monitoring. The concept that threshold changes in peptides levels could guide more optimal use of serial or repeated echocardiographic during follow-up warrants testing.

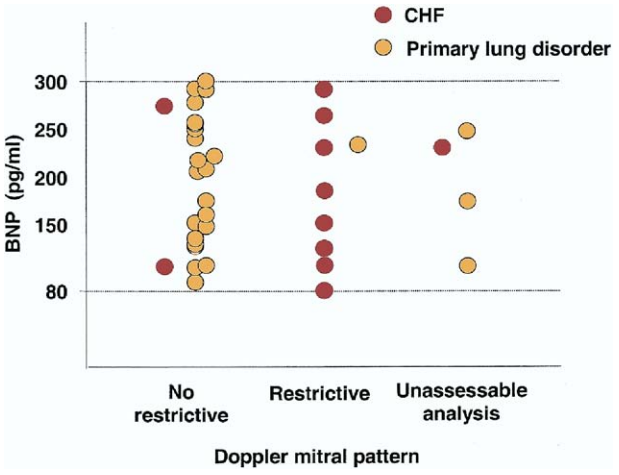

Figure 4. Improved Accuracy of Heart Failure Diagnosis Using BNP and Doppler Echocardiography

Doppler echocardiography facilitates accurate diagnosis of acute decompensated heart failure (ADHF) in subjects with acute dyspnea and intermediate values of B-type natriuretic peptide (BNP). Among 163 patients with acute dyspnea, ADHF was confirmed by a BNP level >300 pg/ml and accurately excluded by a level <80 pg/ml. Doppler echocardiography allowed accurate classification of 33 of 40 subjects with intermediate BNP levels. Adapted with permission from Logeart et al. (52). CHF = congestive heart failure.

Incremental Risk Assessment Using Echocardiography and B-Type Natriuretic Peptides

Echocardiographic indexes of LV systolic and diastolic function are long established prognostic markers in subjects with established cardiovascular disease (58–60). Equally, BNP and NT-proBNP have proven to be among the most powerful independent markers of heart failure events and mortality across the cardiovascular disease spectrum (3).

It is now clear that evaluation of echocardiographic indexes in combination with either BNP or NT-proBNP provides powerful incremental prediction of the risk of new heart failure events or mortality (61–65). This is true for subjects from the general population (61), those with cardiovascular risk factors such as hypertension (65), or after myocardial infarction (64). Integration of BNP levels and Doppler

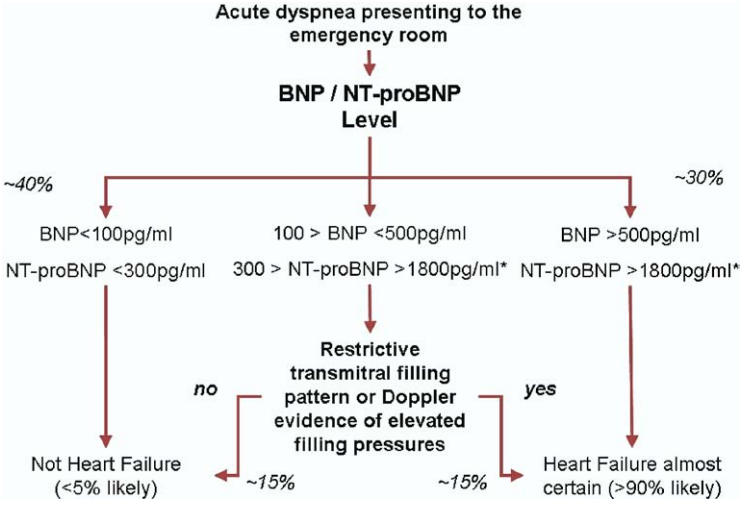

Figure 5. Integrated Use of BNP and Echocardiography for Heart Failure Diagnosis

Algorithm for integrated use of B-type natriuretic peptide (BNP) levels and echocardiography for diagnosis of acute heart failure. *Use of age stratified values for amino-terminal pro-B-type natriuretic peptide (NT-proBNP) provides more accurate test performance: <50 years use NT-proBNP >450 pg/ml; 50 to 75 years use NT-proBNP >900 pg/ml; >75 years use NT-proBNP >1,800 pg/ml (48).

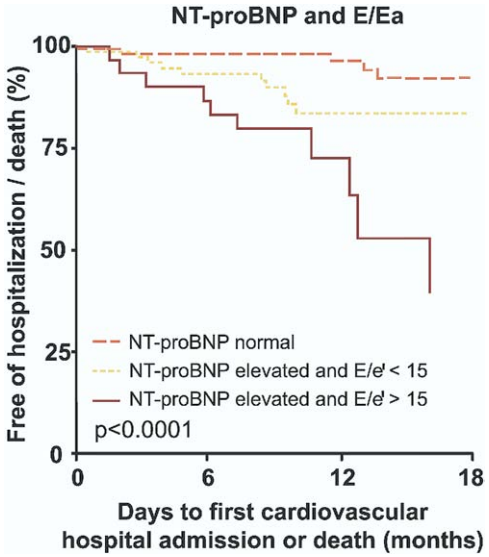

Figure 6. Incremental Risk Stratification Using B-Type Natriuretic Peptide Levels and Doppler Echocardiography

In 268 subjects with dyspnea, the lowest risk for cardiovascular hospitalization or death was seen in subjects with amino-terminal pro-B-type natriuretic peptide (NT-proBNP) <400 pg/ml. In subjects with an elevated NT-proBNP, event rates could be stratified by a ratio of transmitral to mitral annular early diastolic velocity (E/E') above or below 15. Adapted with permission from Whalley et al. (63).

indexes of diastolic function provides powerful incremental prediction in subjects with established heart failure, either at the time of hospitalization (62) or in the community (63). Although abnormalities of either indexes of LV function or of a B-type peptide denote an increased risk of mortality or heart failure, the highest risk is seen in subjects with abnormalities of both LV function and peptide level (Fig. 6) (61–65). Dokainish et al. (62) evaluated 110 subjects hospitalized with heart failure and demonstrated that both BNP levels and E/Ea at discharge were independent predictors of readmission or death. Addition of E/Ea to BNP levels significantly increased the chi-square value of their multivariate model from 17 to 23 and identified nearly all adverse events (47 of 54). These authors suggested that after heart failure hospitalization, an algorithm stratifying patients at discharge by BNP >250 pg/ml and then by E/Ea level >15 could be used to identify most of the subsequent risk of adverse events.

Valvular Heart Disease

Assessment of B-type natriuretic peptide levels in patients with valvular heart disease can provide additional information that may guide decision-making in regard to interventions. Peptide levels rise with increasing severity of aortic stenosis (66,67). Although correlations with transvalvular gradients or indexes of LV function are modest; peptide levels are closely related to symptoms and can assist in their interpretation in this condition. Peptide levels are independent predictors of mortality or heart failure hospitalization in severe aortic stenosis, with BNP levels >100 pg/ml and NT-proBNP levels >600 pg/ml, identifying subjects at higher risk during conservative therapy for moderately severe or severe aortic stenosis (68). Elevated BNP levels also distinguish true from pseudostenosis in low gradient aortic stenosis, with levels >550 pg/ml predicting poor survival after aortic valve replacement in this context (66).

BNP and NT-proBNP levels also increase with greater severity of aortic or mitral regurgitation, reflecting regurgitant volume, LV size and function, and symptomatic status (69,70). Peptide levels identify higher risk for adverse events in subjects with severe aortic regurgitation and preserved LV function (71), suggesting that NT-proBNP in combination with echocardiography could refine prognostic assessment and guide decision-making about timing for intervention.

Conclusions

Integrated use of echocardiography and plasma B-type natriuretic peptide levels provides powerful incremental assessment of cardiac function, clinical status, and outcome across the spectrum of cardiac disease. NT-proBNP or BNP may guide more effective use of echocardiography in screening for asymptomatic LV dysfunction. Doppler echocardiography improves the accuracy of heart failure diagnosis in the setting of intermediate BNP or NT-proBNP levels. Combined assessment of peptides and echocardiography provides more powerful stratification of risk across all stages of heart failure. Integrated use of both tests may identify subjects with valvular disease at greatest risk for progression and facilitate timely intervention.

Reprint requests and correspondence: Dr. Richard W. Troughton, University Department of Medicine, University of Otago, Christchurch, PO Box 4345, Christchurch, New Zealand. *E-mail: richard.troughton@cdhb.govt.nz.*

REFERENCES

1. Mukoyama M, Nakao K, Hosoda K, et al. Brain natriuretic peptide as a novel cardiac hormone in humans. Evidence for an exquisite dual natriuretic peptide system, atrial natriuretic peptide and brain natriuretic peptide. J Clin Invest 1991;87:1402–12.
2. Hunt PJ, Yandle TG, Nicholls MG, Richards AM, Espiner EA. The amino-terminal portion of pro-brain natriuretic peptide (Pro-BNP) circulates in human plasma. Biochem Biophys Res Commun 1995;214: 1175–83.
3. Daniels LB, Maisel AS. Natriuretic peptides. J Am Coll Cardiol 2007;50: 2357–68.
4. Martinez-Rumayor A, Richards AM, Burnett JC, Januzzi JL Jr. Biology of the natriuretic peptides. Am J Cardiol 2008;101:3–8.
5. Lam CS, Burnett JC Jr., Costello-Boerrigter L, Rodeheffer RJ, Redfield MM. Alternate circulating pro-B-type natriuretic peptide and B-type natriuretic peptide forms in the general population. J Am Coll Cardiol 2007;49:1193–202.
6. Tang WH, Francis GS, Morrow DA, et al. National Academy of Clinical Biochemistry Laboratory Medicine practice guidelines: Clinical utilization of cardiac biomarker testing in heart failure. Circulation 2007;116: e99–109.
7. Hammerer-Lercher A, Ludwig W, Falkensammer G, et al. Natriuretic peptides as markers of mild forms of left ventricular dysfunction: effects of assays on diagnostic performance of markers. Clin Chem 2004;50: 1174–83.
8. Redfield MM, Rodeheffer RJ, Jacobsen SJ, Mahoney DW, Bailey KR, Burnett JC Jr. Plasma brain natriuretic peptide concentration: impact of age and gender. J Am Coll Cardiol 2002; 40:976–82.
9. Das SR, Drazner MH, Dries DL, et al. Impact of body mass and body composition on circulating levels of natriuretic peptides: results from the Dallas Heart Study. Circulation 2005; 112:2163–8.
10. Vickery S, Price CP, John RI, et al. B-type natriuretic peptide (BNP) and amino-terminal proBNP in patients with CKD: relationship to renal function and left ventricular hypertrophy. Am J Kidney Dis 2005;46:610–20.
11. Ordonez-Llanos J, Collinson PO, Christenson RH. Amino-terminal pro-B-type natriuretic peptide: analytic considerations. Am J Cardiol 2008;101:9–15.
12. Groenning BA, Raymond I, Hildebrandt PR, Nilsson JC, Baumann M, Pedersen F. Diagnostic and prognostic evaluation of left ventricular systolic heart failure by plasma N-terminal pro-brain natriuretic peptide concentrations in a large sample of the general population. Heart 2004;90: 297–303.
13. Costello-Boerrigter LC, Boerrigter G, Redfield MM, et al. Amino-terminal pro-B-type natriuretic peptide and B-type natriuretic peptide in the general community: determinants and detection of left ventricular dysfunction. J Am Coll Cardiol 2006;47:345–53.
14. Yamamoto K, Burnett JC Jr., Jougasaki M, et al. Superiority of brain natriuretic peptide as a hormonal marker of ventricular systolic and diastolic dysfunction and ventricular hypertrophy. Hypertension 1996;28: 988–94.
15. Iwanaga Y, Nishi I, Furuichi S, et al. B-type natriuretic peptide strongly reflects diastolic wall stress in patients with chronic heart failure: comparison between systolic and diastolic heart failure. J Am Coll Cardiol 2006;47: 742–8.
16. Yamaguchi H, Yoshida J, Yamamoto K, et al. Elevation of plasma brain natriuretic peptide is a hallmark of diastolic heart failure independent of ventricular hypertrophy. J Am Coll Cardiol 2004;43:55–60.
17. Lubien E, DeMaria A, Krishnaswamy P, et al. Utility of B-natriuretic peptide in detecting diastolic dysfunction: comparison with Doppler velocity recordings. Circulation 2002;105: 595–601.
18. Troughton RW, Prior DL, Pereira JJ, et al. Plasma B-type natriuretic peptide levels in systolic heart failure: importance of left ventricular diastolic function and right ventricular systolic function. J Am Coll Cardiol 2004;43: 416–22.
19. Tschope C, Kasner M, Westermann D, Gaub R, Poller WC, Schultheiss HP. The role of NT-proBNP in the diagnostics of isolated diastolic dysfunction: correlation with echocardiographic and invasive measurements. Eur Heart J 2005;26:2277–84.
20. Abhayaratna WP, Marwick TH, Becker NG, Jeffery IM, McGill DA, Smith WT. Population-based detection of systolic and diastolic dysfunction with amino-terminal pro-B-type natriuretic peptide. Am Heart J 2006; 152:941–8.
21. Lim TK, Ashrafian H, Dwivedi G, Collinson PO, Senior R. Increased left atrial volume index is an independent predictor of raised serum natriuretic peptide in patients with suspected heart failure but normal left ventricular ejection fraction: implication for diagnosis of diastolic heart failure. Eur J Heart Fail 2006;8: 38–45.
22. Mariano-Goulart D, Eberle MC, Boudousq V, et al. Major increase in brain natriuretic peptide indicates right ventricular systolic dysfunction in patients with heart failure. Eur J Heart Fail 2003;5:481–8.
23. Bansal M, Marwick TH. Natriuretic peptides and filling pressure at rest and stress. Heart Fail Clin 2008;4: 71–86.
24. Omland T, Aakvaag A, Vik-Mo H. Plasma cardiac natriuretic peptide determination as a screening test for the detection of patients with mild left ventricular impairment. Heart 1996; 76:232–7.
25. Parsonage WA, Galbraith AJ, Koerbin GL, Potter JM. Value of B-type natriuretic peptide for identifying significantly elevated pulmonary artery wedge pressure in patients treated for established chronic heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. Am J Cardiol 2005;95:883–5.
26. Maeda K, Tsutamoto T, Wada A, Hisanaga T, Kinoshita M. Plasma brain natriuretic peptide as a biochemical marker of high left ventricular end-diastolic pressure in patients with symptomatic left ventricular dysfunction. Am Heart J 1998;135:825–32.
27. Dokainish H, Zoghbi WA, Lakkis NM, et al. Optimal noninvasive assessment of left ventricular filling pressures: a comparison of tissue Doppler echocardiography and B-type natriuretic peptide in patients with pulmonary artery catheters. Circulation 2004;109:2432–9.
28. Kazanegra R, Cheng V, Garcia A, et al. A rapid test for B-type natriuretic peptide correlates with falling wedge pressures in patients treated for decompensated heart failure: a pilot study. J Card Fail 2001;7:21–9.
29. Braunschweig F, Fahrleitner-Pammer A, Mangiavacchi M, et al. Correlation between serial measurements of N-terminal pro brain natriuretic peptide and ambulatory cardiac filling pressures in outpatients with chronic heart failure. Eur J Heart Fail 2006;8: 797–803.
30. Nagueh SF, Middleton KJ, Kopelen HA, Zoghbi WA, Quinones MA. Doppler tissue imaging: a noninvasive technique for evaluation of left ventricular relaxation and estimation of filling pressures. J Am Coll Cardiol 1997;30:1527–33.

31. Ommen SR, Nishimura RA, Appleton CP, et al. Clinical utility of Doppler echocardiography and tissue Doppler imaging in the estimation of left ventricular filling pressures: A comparative simultaneous Doppler-catheterization study. Circulation 2000;102:1788–94.
32. Lester SJ, Tajik AJ, Nishimura RA, Oh JK, Khandheria BK, Seward JB. Unlocking the mysteries of diastolic function: deciphering the Rosetta Stone 10 years later. J Am Coll Cardiol 2008;51:679–89.
33. Redfield MM, Rodeheffer RJ, Jacobsen SJ, Mahoney DW, Bailey KR, Burnett JC Jr. Plasma brain natriuretic peptide to detect preclinical ventricular systolic or diastolic dysfunction: a community-based study. Circulation 2004;109:3176–81.
34. Bibbins-Domingo K, Ansari M, Schiller NB, Massie B, Whooley MA. Is B-type natriuretic peptide a useful screening test for systolic or diastolic dysfunction in patients with coronary disease? Data from the Heart and Soul Study. Am J Med 2004;116:509–16.
35. Vasan RS, Benjamin EJ, Larson MG, et al. Plasma natriuretic peptides for community screening for left ventricular hypertrophy and systolic dysfunction: the Framingham Heart Study. JAMA 2002;288:1252–9.
36. Maisel AS, Koon J, Krishnaswamy P, et al. Utility of B-natriuretic peptide as a rapid, point-of-care test for screening patients undergoing echocardiography to determine left ventricular dysfunction. Am Heart J 2001;141:367–74.
37. McDonagh TA, Morrison CE, Lawrence A, et al. Symptomatic and asymptomatic left-ventricular systolic dysfunction in an urban population. Lancet 1997;350:829–33.
38. Vasan RS, Benjamin EJ, Larson MG, et al. Plasma natriuretic peptides for community screening for left ventricular hypertrophy and systolic dysfunction: The Framingham Heart Study. JAMA 2002;288:1252–9.
39. McDonagh TA, Cunningham AD, Morrison CE, et al. Left ventricular dysfunction, natriuretic peptides, and mortality in an urban population. Heart 2001;86:21–6.
40. Lim TK, Dwivedi G, Hayat S, Collinson PO, Senior R. Cost effectiveness of the B type natriuretic peptide, electrocardiography, and portable echocardiography for the assessment of patients from the community with suspected heart failure. Echocardiography 2007;24:228–36.
41. Marwick TH, Schwaiger M. The future of cardiovascular imaging in the diagnosis and management of heart failure, part 2: clinical applications. Circ Cardiovasc Imaging 2008; 1:162–70.
42. Bibbins-Domingo K, Ansari M, Schiller NB, Massie B, Whooley MA. B-type natriuretic peptide and ischemia in patients with stable coronary disease: data from the Heart and Soul study. Circulation 2003;108:2987–92.
43. Ng LL, Loke I, Davies JE, et al. Identification of previously undiagnosed left ventricular systolic dysfunction: community screening using natriuretic peptides and electrocardiography. Eur J Heart Fail 2003;5:775–82.
44. Heidenreich PA, Gubens MA, Fonarow GC, Konstam MA, Stevenson LW, Shekelle PG. Cost-effectiveness of screening with B-type natriuretic peptide to identify patients with reduced left ventricular ejection fraction. J Am Coll Cardiol 2004;43:1019–26.
45. Corteville DC, Bibbins-Domingo K, Wu AH, Ali S, Schiller NB, Whooley MA. N-terminal pro-B-type natriuretic peptide as a diagnostic test for ventricular dysfunction in patients with coronary disease: data from the Heart and Soul Study. Arch Intern Med 2007;167:483–9.
46. Mueller C, Scholer A, Laule-Kilian K, et al. Use of B-type natriuretic peptide in the evaluation and management of acute dyspnea. N Engl J Med 2004;350:647–54.
47. Wright SP, Doughty RN, Pearl A, et al. Plasma amino-terminal pro-brain natriuretic peptide and accuracy of heart-failure diagnosis in primary care: a randomized, controlled trial. J Am Coll Cardiol 2003;42:1793–800.
48. Januzzi JL, van Kimmenade R, Lainchbury J, et al. NT-proBNP testing for diagnosis and short-term prognosis in acute destabilized heart failure: an international pooled analysis of 1256 patients: the International Collaborative of NT-proBNP Study. Eur Heart J 2006;27:330–7.
49. Maisel AS, McCord J, Nowak RM, et al. Bedside B-type natriuretic peptide in the emergency diagnosis of heart failure with reduced or preserved ejection fraction. Results from the Breathing Not Properly Multinational Study. J Am Coll Cardiol 2003;41:2010–7.
50. Dokainish H, Zoghbi WA, Lakkis NM, Quinones MA, Nagueh SF. Comparative accuracy of B-type natriuretic peptide and tissue Doppler echocardiography in the diagnosis of congestive heart failure. Am J Cardiol 2004;93:1130–5.
51. Huang CH, Tsai MS, Hsieh CC, Wang TD, Chang WT, Chen WJ. Diagnostic accuracy of tissue Doppler echocardiography for patients with acute heart failure. Heart 2006;92: 1790–4.
52. Logeart D, Saudubray C, Beyne P, et al. Comparative value of Doppler echocardiography and B-type natriuretic peptide assay in the etiologic diagnosis of acute dyspnea. J Am Coll Cardiol 2002;40:1794–800.
53. Troughton RW, Frampton CM, Yandle TG, Espiner EA, Nicholls MG, Richards AM. Treatment of heart failure guided by plasma aminoterminal brain natriuretic peptide (N-BNP) concentrations. Lancet 2000;355:1126–30.
54. Jourdain P, Jondeau G, Funck F, et al. Plasma brain natriuretic peptide-guided therapy to improve outcome in heart failure: the STARS-BNP Multicenter Study. J Am Coll Cardiol 2007;49:1733–9.
55. Coletta AP, Cullington D, Clark AL, Cleland JGF. Clinical trials update from European Society of Cardiology meeting 2008: TIME-CHF, BACH, BEAUTIFUL, GISSI-HF, and HOME-HF. Eur J Heart Fail 2008; 10:1264–7.
56. Gackowski A, Isnard R, Golmard JL, et al. Comparison of echocardiography and plasma B-type natriuretic peptide for monitoring the response to treatment in acute heart failure. Eur Heart J 2004;25:1788–96.
57. Wasywich CA, Whalley GA, Walsh HA, Gamble GD, Doughty RN. The relationship between BNP and E/Ea in patients hospitalized with acute heart failure. Int J Cardiol 2008;125: 280–2.
58. Gruppo Italiano per lo Studio della Sopravvivenza Nell'infarto M, Nicolosi GL, Latini R, et al. The prognostic value of predischarge quantitative two-dimensional echocardiographic measurements and the effects of early lisinopril treatment on left ventricular structure and function after acute myocardial infarction in the GISSI-3 Trial. Eur Heart J 1996;17:1646–56.
59. Yu CM, Sanderson JE, Marwick TH, Oh JK. Tissue Doppler imaging a new prognosticator for cardiovascular diseases. J Am Coll Cardiol 2007;49: 1903–14.
60. Moller JE, Whalley GA, Dini FL, et al. Independent prognostic importance of a restrictive left ventricular filling pattern after myocardial infarction: an individual patient meta-analysis: Meta-Analysis Research Group in Echocardiography acute myocardial infarction. Circulation 2008;117:2591–8.
61. Olsen MH, Hansen TW, Christensen MK, et al. N-terminal pro-brain natriuretic peptide, but not high sensitivity C-reactive protein, improves cardiovascular risk prediction in the general population. Eur Heart J 2007; 28:1374–81.

62. Dokainish H, Zoghbi WA, Lakkis NM, et al. Incremental predictive power of B-type natriuretic peptide and tissue Doppler echocardiography in the prognosis of patients with congestive heart failure. J Am Coll Cardiol 2005;45:1223–6.
63. Whalley GA, Wright SP, Pearl A, et al. Prognostic role of echocardiography and brain natriuretic peptide in symptomatic breathless patients in the community. Eur Heart J 2008;29:509–16.
64. Richards AM, Nicholls MG, Espiner EA, et al. B-type natriuretic peptides and ejection fraction for prognosis after myocardial infarction. Circulation 2003;107:2786–92.
65. Olsen MH, Wachtell K, Tuxen C, et al. N-terminal pro-brain natriuretic peptide predicts cardiovascular events in patients with hypertension and left ventricular hypertrophy: a LIFE study. J Hypertens 2004;22:1597–604.
66. Bergler-Klein J, Mundigler G, Pibarot P, et al. B-type natriuretic peptide in low-flow, low-gradient aortic stenosis: relationship to hemodynamics and clinical outcome: results from the Multicenter Truly or Pseudo-Severe Aortic Stenosis (TOPAS) study. Circulation 2007;115:2848–55.
67. Gerber IL, Stewart RA, Legget ME, et al. Increased plasma natriuretic peptide levels reflect symptom onset in aortic stenosis. Circulation 2003;107:1884–90.
68. Weber M, Hausen M, Arnold R, et al. Prognostic value of N-terminal pro-B-type natriuretic peptide for conservatively and surgically treated patients with aortic valve stenosis. Heart 2006;92:1639–44.
69. Gerber IL, Stewart RA, French JK, et al. Associations between plasma natriuretic peptide levels, symptoms, and left ventricular function in patients with chronic aortic regurgitation. Am J Cardiol 2003;92:755–8.
70. Sutton TM, Stewart RA, Gerber IL, et al. Plasma natriuretic peptide levels increase with symptoms and severity of mitral regurgitation. J Am Coll Cardiol 2003;41:2280–7.
71. Weber M, Hausen M, Arnold R, et al. Diagnostic and prognostic value of N-terminal pro B-type natriuretic peptide (NT-proBNP) in patients with chronic aortic regurgitation. Int J Cardiol 2008;127:321–7.

Key Words: natriuretic peptides ■ echocardiography ■ left ventricular function ■ Doppler echocardiography.