Usefulness of B-type Natriuretic Peptide (BNP) as a screen for left ventricular abnormalities in diabetes mellitus

S Cosson

SUMMARY
Cardiovascular disease is the leading cause of morbidity and mortality in diabetic subjects. Diabetes, independently of the mechanism, is associated with an increased risk of left ventricular hypertrophy, left ventricular dysfunction and coronary artery disease. B-type natriuretic peptide (BNP) is a cardiac neurohormone predominantly released from the cardiac ventricles in response to left ventricular volume expansion and pressure overload. Numerous studies have shown that BNP levels are elevated in asymptomatic or symptomatic left ventricular dysfunction, hypertrophy and coronary artery disease. BNP testing plays an important role in the screening and diagnosis of left ventricular dysfunction by improving the performance of non-specialist physicians in diagnosing heart failure. In clinical practice, BNP testing is best used as a ‘rule out’ test targeted to patients at high risk for left-ventricular dysfunction, such as those with diabetes. Studies are needed to establish if this promising biological tool, in the next future, would assist the management of diabetic patients.

Key-words: Diabetes mellitus · B-type natriuretic peptide · Heart failure · Ventricular function · Diabetic cardiomyopathy.

RÉSUMÉ
Intérêt du dosage de BNP dans le dépistage d’anomalies de la fonction ventriculaire gauche chez le diabétique
Les pathologies cardiovasculaires représentent la première cause de morbidité et de mortalité des patients diabétiques. Le diabète est, indépendamment du mécanisme, associé à une augmentation du risque d’hypertrophie ventriculaire gauche, de dysfonction ventriculaire gauche et de coronaropathie. Le peptide natriurétique de type B (BNP) est une neurohormone cardiaque sécrétée préférentiellement par les ventricules en réponse à une augmentation du volume ou de la pression intraventriculaire. De nombreuses études ont montré que le taux de BNP est augmenté chez les patients avec altération de la fonction ventriculaire gauche (qu’elle soit symptomatique ou non), avec hypertrophie ventriculaire gauche et coronaropathie. Le dosage du BNP est particulièrement utile pour le dépistage et le diagnostic d’une altération de la fonction ventriculaire gauche et permet une amélioration des performances diagnostiques des médecins non spécialistes. En pratique clinique, le dosage du BNP est surtout performant pour sa valeur prédictive négative, pour éliminer une dysfonction ventriculaire gauche chez les patients à haut risque, comme les diabétiques. Des études seront cependant nécessaires pour définir si ce dosage biologique permettra dans le futur une amélioration de la prise en charge des diabétiques.

Mots-clés: Diabète · BNP · Insuffisance cardiaque · Fonction ventriculaire · Cardiomyopathie diabétique.
Cardiovascular disease is the leading cause of morbidity and mortality in diabetic subjects [1]. The most common cardiovascular complications are ischemic cardiomyopathy and left ventricular (LV) dysfunction. Some studies have demonstrated that diabetes is associated with increased LV wall thickness and mass, independently of blood pressure levels and body mass index [2]. Diabetes is also associated with heart failure, mainly through its association with hypertension and coronary artery disease [3]. In addition, the existence of a primary myocardial disease, “diabetic cardiomyopathy”, has been proposed as evidence has accumulated for the presence of myocardial dysfunction in diabetic patients in the absence of ischemic, valvular or hypertensive heart disease [4]. Thus, diabetes, independently of the mechanism, is associated with an increased risk of LV hypertrophy, LV dysfunction and coronary artery disease. Screening for coronary artery disease in diabetes is not easily achieved with non-invasive methods and there is no definitive evidence for a benefit to provide invasive intervention in asymptomatic patients. In contrast, LV abnormalities can be easily detected by non-invasive techniques and there is evidence under treatment of a prognostic benefit, even in asymptomatic patients. Therefore, LV hypertrophy and LV dysfunction are ideal targets for screening and treatment to reduce cardiac deaths in patients with diabetes [5]. Echocardiography is considered the cornerstone of diagnostic evaluation in patients with suspected LV dysfunction but its expense and sometimes limited accessibility has not led to an unselected performance in all patients with diabetes. Brain natriuretic peptide (BNP) is a cardiac neurohormone predominantly released from the cardiac ventricles in response to left ventricular volume expansion and pressure overload. Numerous data reported from studies in patients without diabetes support the idea that the BNP might be used from the diabetologists to select patients for further screening. Indeed, several studies have shown that BNP levels are elevated in asymptomatic or symptomatic LV dysfunction [6], LV hypertrophy [7] and coronary artery disease [8]. The ability to identify patients with left-ventricular dysfunction through the measurement of concentrations of BNP has been studied specifically in patients with diabetes in only one recent study [9]. The purpose of this article is to summarize the physiology, methodology for measurements and clinical applications of BNP testing in order to familiar the diabetologists with a biological test which likely, in the next future, would assist the management of diabetic patients.

### BNP

BNP is a member of a family of structurally similar peptide hormones also including atrial natriuretic peptide (ANP), C-natriuretic peptide (CNP) and urodilatin. BNP is produced in the form of a precursor, prepro-BNP, which is cleaved to pro-BNP and released into the blood, where it is finally processed into the 32-amino acid active form and an inactive metabolite, N-terminal pro-BNP (NT-proBNP). Circulating natriuretic peptides are eliminated from the body by two separate mechanisms: enzymatic degradation by neutral endopeptidase and through a clearance receptor. BNP is secreted by atrial and ventricular myocytes, although the major site of production of BNP is the left ventricle. BNP secretion is controlled at the transcriptional level, usually requiring a longer-term stimulus. BNP and particularly its inactive metabolite NT-proBNP are reasonably stable, making them good diagnostic markers. In humans, the half-life of BNP is approximately 20 minutes. However, two studies have shown that BNP levels in whole blood are stable for up to 3 days [10]. Therefore, blood levels of BNP appear to reflect long-term intravascular status rather than short-term fluctuation in blood volume. The most important stimulus for the synthesis of BNP in the heart is an increase in wall stress. Previous studies have found a positive correlation between plasma BNP levels and left ventricular end-diastolic pressure, suggesting that brain natriuretic peptide secretion from the left ventricle may be regulated by end-diastolic wall stretch [11]. Indeed, stretching of the ventricular tissue stimulates brain natriuretic peptide release within 2 minutes [12]. Plasma concentrations in BNP rise in various pathological states, where there is increased cardiac chamber wall stretch, an expanded fluid volume or reduced clearance of peptides (renal failure). BNP causes natriuresis, vasodilatation, inhibition of the sympathoadrenal system, inhibition of the renin-angiotensin system and smooth muscle relaxation.

Measurement of BNP is performed by methods based on immunoassays, mostly radioactive ones. Various research groups developed their own in-house radioimmunoassays, but several immunoassay kits have now become commercially available. At present, there are two natriuretic peptide assays commercially available in both the USA and Europe that can be used in routine clinical and laboratory practice. The first is a rapid fluorescence immunoassay for BNP, which provides results within 15 min on a point-of-care patient testing device (Biosite Diagnostics, San Diego) [13]. This method may be particularly attractive in clinical situations where access to a laboratory is difficult or when a rapid result is required. The second is an electrochemiluminescent assay available for measuring NT-proBNP with a processing time of only 18 min (Roche Diagnostics GmbH, Basel) [14]. A further laboratory-based assay for BNP is available currently in Europe only and is manufactured by Bayer.

### Influence of blood pressure on BNP levels

Several reports have shown that plasma BNP levels are higher in hypertensive patients compared with normoten-
sive hypertensive treatment.

The importance of LV geometry in determining BNP levels has been emphasized in some studies. Indeed, elevated plasma concentrations of BNP appear to be related to the severity of LV hypertrophy rather than blood pressure level. In never-before-treated hypertensive subjects without overt heart failure, BNP concentrations have been shown to be elevated in those subjects with concentric LV hypertrophy, but not in those without LV hypertrophy or in those with remodelling of the left ventricle [7, 16]. In the study of Nishikimi et al. the sensitivity of a BNP value $^2$ 18 pg/ml for predicting LV hypertrophy in hypertensive patients was 60%, with a specificity of 82% [16]. Furthermore, it has been suggested that plasma BNP levels may identify hypertensive patients who are likely to have progressive hypertrophy [17]. One study also demonstrated that long-term ACE therapy can reduce elevated concentrations of BNP and that the reduction is closely related to diminishing LV mass [18]. The mechanisms leading to increased levels of BNP in hypertension could be related to increased LV pressure as well as to local growth factors related to the hypertrophic process or alteration of diastolic function. Thus, BNP levels may be useful for the detection of LV hypertrophy in hypertensive patients and in determining which patients will need intensive hypertensive treatment.

Detection of left ventricular systolic dysfunction

The diagnostic role of BNP has been studied extensively in patients with heart failure and LV systolic dysfunction. BNP is a useful tool in evaluating possible LV dysfunction and heart failure. Several studies have shown that BNP concentrations increase with increasing severity of New York Heart Association (NYHA) class [19]. Several investigators have shown the usefulness and reliability of BNP-screening tests for rapid heart failure diagnosis. These findings have recently been validated in a multicentre study of 1586 patients presenting to the emergency room with dyspnoea [20]. In this study, concentrations of BNP were highest in patients with decompensated heart failure, intermediate in those with known left-ventricular dysfunction but no acute heart failure exacerbation, and lowest in those without heart failure or left-ventricular dysfunction. Using a threshold of greater than 100 ng/L to diagnose heart failure, BNP did better than other clinical variables [20] and the clinical judgment of the emergency room physician [21]. BNP was especially useful for ruling out heart failure: at a BNP threshold of 50 ng/L, the negative predictive value was 96%.

In a study of 122 consecutive patients with suspected new heart failure referred by general practitioners to a rapid-access heart failure clinic for diagnostic confirmation, a level $^2$ 76 pg/ml had a sensitivity of 97%, a specificity of 84%, a positive predictive value of 70%, and a negative predictive value of 98% for identifying patients with abnormal LV function [22]. As asymptomatic left-ventricular dysfunction is at least as common as symptomatic heart failure, BNP has been used to screen patients in the primary care setting for symptomatic and asymptomatic LV dysfunction. In a community-based study of 1653 subjects who underwent cardiac testing, a BNP level < 18 pg/ml was 97% predictive of normal LV systolic function [23]. Another primary care based study of elderly patients showed that those with echocardiographic left ventricular systolic dysfunction had a higher plasma BNP concentration than those with no evidence of systolic dysfunction (39.3 pmol/l vs 15.8 pmol/l) [24]. A cut-off point of 64 pg/ml gave 92% sensitivity and 65% specificity for the diagnosis of left ventricular systolic dysfunction with a negative predictive value of 99% but with a positive predictive value of only 18%. The authors concluded that a BNP measurement of less than 64 pg/ml would rule out significant left ventricular systolic dysfunction. Epshteyn et al. recently compared BNP levels and echocardiographic findings in patients with diabetes [9]. They divided patients into two groups: patients with clinical indication for echocardiography (n = 172) and those without clinical indication for echocardiography (n = 91). Nearly all patients (mean age 54 ± 1 years) had risk factors for heart disease, including 85% with hypertension and 48% with coronary artery disease. For patients with no symptoms of cardiac heart failure, BNP levels showed a high negative predictive value in ruling out LV dysfunction (91% for BNP values < 39 pg/ml), while in those who had a clinical indication for echocardiography, BNP levels showed a high positive predictive value (96% with BNP levels > 90 pg/ml). Some studies have suggested that BNP testing could be less accurate in detection of asymptomatic LV dysfunction than for clinical diagnosis of heart failure. In part this may be because the degree of elevation of plasma concentration may be much less marked in those who are asymptomatic. In addition, the predictive values of BNP vary with the degree of LV systolic dysfunction. Indeed, BNP concentrations in patients with mild LV systolic dysfunction can overlap with normal concentrations [25, 26]. For example, in the study of Luchner et al., the best predictive values were obtained for the detection of severe LV systolic dysfunction with concomitant hypertrophy and BNP had a sensitivity of 71% and a specificity of 86% to detect this condition [26].

Detection of left ventricular diastolic dysfunction

Several studies have shown that BNP levels may also reflect diastolic dysfunction. Some demonstrated that there is a close relationship between BNP levels and diastolic
Doppler parameters of LV filling in patients with systolic heart failure [27]. Indeed, the patients with the transmitral restrictive pattern, a marker of severe heart failure, have the higher BNP levels. BNP in the setting of normal systolic function also correlates with the presence or absence of diastolic abnormalities on echocardiography. Lang et al. first found that BNP was elevated in patients with isolated diastolic dysfunction, although they did not relate the levels to the pattern of diastolic abnormality [28]. Krishnaswamy et al. demonstrated in patients with symptoms of heart failure and a normal systolic function by echocardiography, that BNP levels > 57 pg/ml had a positive predictive value of 100% for diastolic abnormalities [29]. Lubien et al. [30] studied 294 patients with normal systolic function referred for Doppler echocardiography to evaluate LV diastolic function. Patients with normal LV systolic and diastolic function had significantly lower mean BNP concentrations (33 ± 3 pg/mL) compared to patients with abnormal LV diastolic function (286 ± 31 pg/mL); BNP levels correlated with severity of LV diastolic dysfunction. A BNP value of 62 pg/mL had a sensitivity of 85%, a specificity of 83%, and an accuracy of 84% for detecting diastolic dysfunction. In the study by Maisel et al. [31], when patients with heart failure with preserved systolic function (ejection fraction of greater than 45%) were compared with patients without heart failure, a BNP value of 100 pg/ml had a sensitivity of 86%, a negative predictive value of 96%, and an accuracy of 75% for detecting abnormal diastolic dysfunction. Thus, elevated BNP levels could help reinforce the diagnosis of diastolic dysfunction in patients with normal systolic function. Although measurement of BNP cannot distinguish between systolic and diastolic LV dysfunction, a low BNP in patients with normal systolic function can be used to rule out clinically significant diastolic dysfunction. The accuracy of BNP to detect diastolic dysfunction, an early marker of diabetic cardiomyopathy, needs to determined in the diabetic population. For this purpose we sought to determine whether plasma BNP is a valuable tool to detect subclinical LV diastolic dysfunction in a selected population of 48 normotensive, asymptomatic, type 2 diabetic patients free of coronary artery disease [32]. All patients had a BNP level within the normal range while isolated diastolic dysfunction (normal systolic function) was observed by echocardiography. The conclusion of this preliminary study was that BNP is unable to identify diabetic patients with asymptomatic isolated diastolic dysfunction.

Detection of myocardial ischemia

Several studies have shown that the level of BNP is higher among patients with myocardial ischemia. A correlation between elevated BNP levels and stable angina was found by Marumoto et al. [33] who investigated BNP levels during exercise in 35 patients with stable angina and normal resting LV function. Exercise caused a significantly greater increase in BNP in the patients with angina as compared with controls. The degree of elevation was correlated with the size of the ischemic territory as measured with the use of nuclear single-photon-emission computed tomography imaging. Similar relationships have been seen in patients with unstable angina [34]. In a small study of patients with unstable angina (n = 33), stable angina (n = 20), and control subjects (n = 20), blood samples for BNP were obtained within 24 hours of chest pain. BNP levels were significantly higher in the unstable angina group than both the control and the stable angina groups. Furthermore, plasma levels of BNP decreased significantly after medical treatment to relieve angina. BNP have also been shown to increase transiently after uncomplicated percutaneous transluminal coronary angioplasty (PTCA), even when intracardiac filling pressures remain unchanged [35]. In addition, a pronostic value of BNP in patients with acute coronary syndromes was recently demonstrated. Indeed, the level of B-type natriuretic peptide, measured in the first few days after an acute coronary event, predicts the long-term risk of death and nonfatal cardiac events across the spectrum of acute coronary syndromes [36]. In patients with a myocardial infarction, BNP levels rise rapidly during the first 24 hours and then tend to stabilize [37]. Plasma BNP concentrations rise in proportion to the size of the infarct and are inversely associated with ejection fraction [37]. Measurement of the level of B-type natriuretic peptide between one and four days after a transmural infarction provides prognostic information that is independent of the LV ejection fraction and other important base-line variables [38]. A higher plasma level of B-type natriuretic peptide is associated with an increased likelihood of ventricular remodeling and an increased risk of heart failure and death. The mechanism for the increase in BNP after ischemia has not been fully clarified. In patients with reversible ischemia, a transient increase in LV wall stress may be sufficient to cause an elevation in BNP levels [39]. In patients with MI, although mechanical wall stress is thought to play a significant role, it has been suggested that myocardial necrosis also contributes to the increase in BNP [37]. BNP production has been shown to be significantly greater from infarcted regions than from noninfarcted tissue. Thus, elevated BNP levels may not only indicate LV dysfunction but also be a marker for myocardial ischemia.

Limitations of diagnostic use of BNP

There are several important limitations to note when considering the diagnostic role of BNP.

BNP is not a stand-alone diagnostic test and it must be used and interpreted in a wider clinical context. Clinicians must be aware that several clinical circumstances can alter the interpretation of BNP concentrations. Small increases in BNP are not specific for LV dysfunction, because several disorders are also associated with increases in BNP, such as...
right-ventricular dysfunction, renal insufficiency. Indeed, BNP concentrations increase in proportion to the degree of right ventricular dysfunction in several disorders associated with right-ventricular pressure overload or structural abnormalities in the right ventricle. For example, raised BNP concentrations have been described in patients with primary pulmonary hypertension, chronic obstructive pulmonary disease, pulmonary embolism, congenital heart disease, and arrhythmogenic right-ventricular dysplasia [40-43]. However, the amount of BNP elevation seems to be less than that seen with processes leading to dysfunction of the left ventricle. Among patients with acute pulmonary embolism, plasma BNP levels help prognosticate and differentiate between a benign versus a complicated hospital course [44]. In chronic renal failure, natriuretic peptides are often markedly elevated [45]. A decrease in plasma BNP concentrations after hemodialysis has also been described [46]. Extracellular volume expansion, a diminished or abolished renal clearance and concomitant myocardial dysfunction may all contribute to this elevation. Zoccali et al., recently showed that in uremic patients, the plasma BNP concentration is determined mainly by LV mass and ejection fraction [47]. In addition, beta-blockade may have a variable effect on circulating BNP concentrations [48]. A decrease in plasma BNP concentrations after hemodialysis has also been described [46]. Extracellular volume expansion, a diminished or abolished renal clearance and concomitant myocardial dysfunction may all contribute to this elevation.

Zoccali et al., recently showed that in uremic patients, the plasma BNP concentration is determined mainly by LV mass and ejection fraction [47]. In addition, beta-blockade may have a variable effect on circulating BNP concentrations, and ACE inhibitors and diuretics will reduce BNP concentrations [48]. Finally, when considering use of BNP to screen patients who are asymptomatic, one should remember that the normal range of BNP is specific to age, sex, and assay [49, 50].

**Conclusion**

BNP testing plays an important role in the screening and diagnosis of LV dysfunction in non-selected populations. On the basis of current evidence, plasma BNP testing is of most value by improving the performance of non-specialist physicians in diagnosing heart failure. The convincing results of several studies could be extended to the patients with diabetes in whom BNP could be a useful tool in evaluating possible LV dysfunction and heart failure. In clinical practice, BNP testing could be best used as a ‘rule out’ test targeted to patients at high risk for left-ventricular dysfunction, such as those with diabetes. BNP should not replace echocardiography and full cardiological assessment but used for selecting patients for further cardiac evaluation. A low BNP level may preclude the need for echocardiography in some patients, especially those who have no symptoms of heart failure. Elevated BNP levels, on the other hand, may indicate the presence of LV dysfunction whether the patient has symptoms or not, warranting further cardiac workup. Still, further studies are needed to unequivocally state that BNP testing would assist the management of diabetic patients.

**References**

34. Marumoto K, Hamada M, Hiwada K. Increased secretion of atrial
35. Tateishi J, Masutani M, Ohyanagi M, Iwasaki T. Transient increase in
36. De Lemos J, Morrow D, Bentley J, et al. The prognostic value of
37. Morita E, Yasue H, Yoshimura M, et al. Increased plasma levels of
38. Omland T, Aakvaag A, Bonarjee VVS, et al. Plasma brain natriuretic peptide as an indicator of left ventricular systolic dysfunction and
39. de Lemos JA, Morrow DA. Brain natriuretic peptide measurement in
40. Nagaya N, Nishikimi T, Okano Y, et al. Plasma brain natriuretic peptide levels increase in proportion to the extent of right ventricular dys-
41. Bando M, Ishii Y, Sugayama Y, Kitamura S. Elevated plasma brain natriuretic peptide levels in chronic respiratory failure with cor pul-
42. Bolger AP, Sharma R, Li W, et al. Neurohormonal activation and the
44. Kucher N, Printzen G, Goldhaber SZ. Prognostic role of brain natriu-
46. Haug C, Metzle A, Steffgen I, Grunert A. Changes in brain natriu-
retic peptide and atrial natriuretic peptide plasma concentrations during
47. Zoccali C, Mollamaci F, Benedetto FA, et al. Cardiac natriuretic pep-
tides are related to left ventricular mass and function and predict mor-