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Increased plasma levels of N-terminal brain natriuretic peptide (NT-proBNP) in type 2 diabetic patients with vascular complications

THESE

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Résumé

Les concentrations plasmatiques du peptide natriurétique de type B sont augmentées chez les diabétiques de type 2 atteints de complications vasculaires

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Les concentrations plasmatiques du peptide natriurétique de type B (BNP), ou de sa pro-hormone (NT-proBNP), sont reconnues depuis peu comme marqueur de choix de la dysfonction cardiaque. Les diabétiques de type 2 sont à haut risque de développer des complications cardiovasculaires. L'objectif de cette étude a été de déterminer si les concentrations plasmatiques de NT-proBNP étaient comparables chez des diabétiques de type 2 avec ou sans complications vasculaires .

Méthodes

Nous avons mesuré le NT-proBNP plasmatique chez 54 diabétiques de type 2, 27 sans complications micro- ou macrovasculaires et 27 présentant des complications soit micro- soit macrovasculaires, soit les deux. Le même dosage a été effectué chez 38 témoins sains, appariés pour l'âge et le sexe avec les diabétiques.

Résultat

Le NT-proBNP plasmatique était plus élevé chez les diabétiques avec complications (médiane 121 pg/ml, intervalle interquartile 50-240 pg/ml) que chez ceux sans complications (37 pg/ml, 21-54 pg/ml, P < 0,01). Comparés au groupe témoin (55 pg/ml, 40-79 pg/ml), seuls les diabétiques avec complications vasculaires avaient un NT-proBNP plasmatique significativement augmenté (P < 0,001). Chez les diabétiques la maladie coronarienne et la néphropathie (définie selon l'excrétion urinaire d'albumine) étaient chacune associée de façon indépendante avec une augmentation des concentrations plasmatiques de NT-proBNP.

Conclusion

Chez les diabétiques de type 2 souffrant de complications micro- ou macrovasculaires, les concentrations plasmatiques de NT-proBNP sont augmentées par rapport à celles des malades indemnes de complications vasculaires. L'augmentation de sécrétion de ce peptide est associée de façon indépendante avec la maladie coronarienne et la néphropathie. La mesure du NT-proBNP plasmatique pourrait donc être utile pour dépister la présence de complications micro- ou macrovasculaires.

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Increased plasma levels of N-terminal brain natriuretic peptide (NT-proBNP) in type 2 diabetic patients with vascular complications

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SUMMARY

Aims: The plasma levels of either brain natriuretic peptide (BNP) or the N-terminal fragment of the prohormone (NT-proBNP) have recently gained extreme importance as markers of myocardial dysfunction. Patients with type 2 diabetes are at high risk of developing cardiovascular complications. This study was aimed to assess whether plasma NT-proBNP levels are at similar levels in type 2 diabetics with or without overt cardiovascular diseases.
Methods: We assayed plasma NT-proBNP in 54 type 2 diabetics, 27 of whom had no overt macro- and/or microvascular complications, while the remaining ones had either or both. The same assay was carried out in 38 healthy control subjects age and sex matched as a group with the diabetics.
Results: Plasma NT-proBNP was higher in diabetics (median 121 pg/ml, interquartile range 50-240 pg/ml,) than in those without complications (37 pg/ml, 21-54 pg/ml, P < 0.01). Compared with the controls (55 pg/ml, 40-79 pg/ml), only diabetics with vascular complications had significantly increased plasma NT-proBNP levels (P < 0.001). In the diabetics, coronary heart disease and nephropathy (defined according to urinary excretion of albumin) were each independently associated with elevated values of plasma NT-proBNP.
Conclusions: In type 2 diabetes mellitus, patients with macro- and/or micro-vascular complications exhibit an elevation of plasma NT-proBNP levels compared to corresponding patients with no evidence of vascular disease. The excessive secretion of this peptide is independently associated with coronary artery disease and overt nephropathy. The measurement of circulating NT-proBNP concentration may therefore be useful to screen for the presence of macro- and/or microvascular disease.

Key-words: Diabetes mellitus, type 2 · Natriuretic peptide, brain · Myocardial diseases · Coronary disease · Diabetic nephropathy.

RÉSUMÉ

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Résultat : Le NT-proBNP plasmatique était plus élevé chez les diabétiques avec complications (médiane 121 pg/ml, intervalle interquartile 50-240 pg/ml) que chez ceux sans complications (37 pg/ml, 21-54 pg/ml, P < 0,01). Comparés au groupe témoin (55 pg/ml, 40-79 pg/ml), seuls les diabétiques avec complications vasculaires avaient un NT-proBNP plasmatique significativement augmenté (P < 0,001). Chez les diabétiques la maladie coronarienne et la néphropathie (définie selon l'excrétion urinaire d'albumine) étaient chacune associée de façon indépendante avec une augmentation des concentrations plasmatiques de NT-proBNP.
Conclusion : Chez les diabétiques de type 2 souffrant de complications micro- ou macrovasculaires, les concentrations plasmatiques de NT-proBNP sont augmentées par rapport à celles des malades indemnes de complications vasculaires. L'augmentation de sécrétion de ce peptide est associée de façon indépendante avec la maladie coronarienne et la néphropathie. La mesure du NT-proBNP plasmatique pourrait donc être utile pour dépister la présence de complications micro- ou macrovasculaires.

Mots-clés : Diabète de type 2 · Peptide natriurétique · Maladie coronarienne · Maladies cardiaques · Néphropathie diabétique · Complications vasculaires.

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Introduction

Brain natriuretic peptide (BNP) is a 32-amino-acid peptide first described in porcine brain [1], and later found to be synthetized also by cardiac myocytes [2]. In humans the left ventricle subjected to an increased wall tension is the main source of BNP. In the circulation, the peptide is present not only as BNP, but also as an inactive N-terminal pro-BNP (NT-proBNP) resulting from the cleavage of the precursor form of BNP (proBNP). The actions of BNP are similar to those of the atrial natriuretic peptide (ANP), which is produced primarily by atrial tissue, and include enhanced renal sodium and water excretion, vasorelaxation, and suppression of the activity of the renin-angiotensin-aldosterone system. Abnormally high plasma levels of BNP and/or NT-proBNP have been found in a number of pathological states, in particular in patients with cardiac failure or hypertrophy [2-5]. This led to consider the measurement of these peptides as a useful tool for the early detection of left-ventricular abnormalities.

Patients with type 2 diabetes represent a high risk population in terms of cardiovascular and renal complications [6-8]. Such patients show a disproportionate increase in left-ventricular dysfunction and left-ventricular hypertrophy [9]. Increased plasma BNP levels have been reported in certain patients with type 2 diabetes, in association with coronary heart disease [10], and BNP screening has been proposed for the easy identification of subclinical diabetic cardiomyopathy [9]. Other studies suggest that elevated plasma BNP level could also be a marker of incipient microvascular complications, including diabetic nephropathy [11] and retinopathy [12].

In a recent study, BNP levels were reported to be a reliable predictor of cardiac and all-cause mortality in diabetic patients [13]. Actually, elevated plasma levels of NT-proBNP have been reported in type 2 diabetics without overt cardiovascular disease compared with non-diabetic controls [14], but it is still unclear whether there exists a difference in terms of BNP secretion between type 2 diabetes with or without macro- and/or microvascular disease. The present study was carried-out in a cohort of unselected patients with type 2 diabetes in an attempt to answer this specific question.

Methods

We recruited 54 consecutive patients with type 2 diabetes referred to our outpatient clinic. The diagnosis of type 2 diabetes was based on the 1998 WHO criteria [15]. Thirty-eight healthy subjects matched for gender and age served as controls. The latter had all a fasting glycaemia < 6.1 mmol/l, a body mass index (BMI) < 30 kg/m² and a blood pressure (BP) < 140/90 mmHg. They had no past history of heart, lung, kidney, endocrine or liver disease and were not taking any medication. The protocol was approved by the Ethics Committee at our institution, and carried out in accordance with the principles of the Declaration of Helsinki as revised in 2000. Informed consent was obtained in writing from all subjects.

Our diabetic patients were routinely screened for macro- and microangiopathy (history of claudication or stroke, examination of carotid and peripheral arteries, eye fundoscopy by an ophthalmologist). In presence of two or more risk factors on top of diabetes a myocardial radionuclide scintigraphy or a stress echocardiography was performed [16]. This was followed by a coronarography if required. Coronary heart disease was considered present if anyone of the following criteria was met: history of transmural myocardial infarction, history of coronary angioplasty, history of coronary bypass surgery, positive evidence for coronary artery disease on either an exercise tolerance test, a stress echocardiogram, a myocardial scintigraphy, or a coronary angiogram. Ultrasonographic examinations of carotid and peripheral arteries were obtained where appropriate. Diabetic nephropathy was defined as an albumin creatinine/ratio > 2 mg/mmol in a morning urine spot [17,18].

Assay of plasma NT-proBNP

The blood sample used to measure plasma NT-proBNP was collected in a 2.7 ml EDTA-coated tube. After centrifugation, the plasma was stored at -20 °C. NT-ProBNP was determined using an Elecsys proBNP sandwich immunoassay on an Elecsys 2010 analyzer (Roche, Rotkreuz, Switzerland). The interseries coefficient of variation was 3.6% (n = 16) at a level of 263 ng/l and 3.1% (n = 15) at a level of 5812 ng/l. The analytical range extends from 5 to 35000 ng/l. The intra-assay coefficient of variation was 2.9%.

Statistical analysis

Results are presented as means ± SD. Plasma levels of NT-proBNP, due to their skewed distribution, are also summarized as the median and interquartile range. Three groups of subjects (controls, diabetics without any vascular complication, and diabetics with either microvascular or macrovascular complications) were compared with simple parametric analysis of variance (carried out on log-transformed data in the case of plasma NT-proBNP). Where justified by very asymetric distribution not amenable to logarithmic transform, a Kruskall-Wallis test was used instead. When the F (or chi-square) value was significant, pairwise comparisons were carried out with Dunn's test (or its

Abbreviations:

ANP:	atrial natriuretic peptide
BNP:	brain natriuretic peptide.
NT-PROBNP:	N-terminal fragment of pro-BNP
HDL:	high density lipoproteins
LDL:	low density lipoproteins

nonparametric adaptation as described [19]). In diabetic patients, association of plasma NT-proBNP with putative predictors was examined with multiple regression. In this analysis, the values for NT-proBNP were log transformed, categorical independent variables were coded as dummies, and a backward elimination algorithm was used (F to enter 0.25, F to remove 0.10). The alpha level of all tests was set at 0.05. All computations were performed with the JMP software, version 3.2.2 (SAS Institute, Cary, NC).

Results

Characteristics of the study population

The baseline characteristics of the study subjects are summarized in Table I. Diabetic patients were divided into 2 subgroups according to the presence (n = 27) or the absence (n = 27) of micro- and/or macrovascular complications. Among the former patients, 9 exhibited microvascular complications and 5 macrovascular complications only, whereas 13 patients had both types of complications. The body mass index (BMI) as well as systolic and diastolic blood pressures were significantly higher in the

2 groups of diabetics than in controls. Mean plasma HDL-cholesterol levels were significantly lower and plasma triglyceride levels significantly higher in diabetics compared with controls. Significant differences in mean levels of HbA_{1c}, fasting and postprandial plasma glucose, fasting plasma insulin, plasma creatinine, and urinary albumin/creatinine ratio were observed between the 2 groups of diabetics. An exercise tolerance test, a coronary angiogram, a stress echocardiogram and a myocardial radionuclide scintigraphy was performed in 6, 5, 24 and 11 patients, respectively. All patients who underwent the echocardiographical examination showed an ejection fraction above 50%.

Table II shows the various treatments received at the time of examination. Blockers of the renin-angiotensin system, β-blockers and antiplatelet agents were taken significantly more often in patients with than in those without vascular complications.

Plasma NT-proBNP levels in diabetic patients versus control subjects

Plasma levels of NT-proBNP are depicted in Figure 1. Analysis of variance on the raw data indicated a signifi-

Table I
Characteristics of study participants.

	Controls	Diabetics	
		without vascular complications	with vascular complications
Number of subjects	38	27	27
Duration of diabetes (y.)	-	6.4 ± 6.2	10.8 ± 7.8
Age (y.)	56.0 ± 11.1	54.4 ± 7.7	57.9 ± 7.0
Sex (M/F)	25/13	6/11	22/5
Body mass index (kg/m2)	23.0 ± 2.5	30.4 ± 4.8 [c]	31.4 ± 5.4 [c]
Waist to hip ratio	0.92 ± 0.07	1.01 ± 0.05 [c]	1.04 ± 0.08 [c]
Blood pressure, systolic (mm Hg)	117 ± 10	133 ± 17 [c]	142 ± 16 [c]
Blood pressure, diastolic (mm Hg)	68 ± 8	78 ± 11 [c]	82 ± 9 [c]
Smoking (pack-y.) [a]	1.7 ± 7.2	9.7 ± 23.0 [b]	8.5 ± 13.5 [b]
Plasma glucose, fasting (mM)	4.8 ± 0.5	7.0 ± 1.6 [c]	8.4 ± 2.2 [cd]
Plasma glucose, postprandial (mM)	5.1 ± 0.9	12.4 ± 2.4 [c]	14.2 ± 2.6 [cd]
HbA_{1c} (%)	NA	7.3 ± 1.1	8.2 ± 1.3 [d]
HDL-cholesterol (mM)	1.62 ± 0.34	1.29 ± 0.36 [c]	1.30 ± 0.30 [c]
LDL-cholesterol (mM)	2.96 ± 0.89	2.85 ± 0.71	2.75 ± 0.87
Triglycerides (mM)	0.94 ± 0.47	1.87 ± 0.80 [c]	2.09 ± 1.92 [c]
Plasma creatinine (μM)	89 ± 10	87 ± 15	104 ± 26 [cd]
Urine albumine/creatinine ratio [a]	0.6 ± 0.5	0.8 ± 0.6	32.4 ± 83.9 [cd]

Means ± SD. NA not available.
[a] non parametric statistical analysis (Kruskall-Wallis test).
[b] P < 0.05.
[c] P < 0.01 vs controls.
[d] P < 0.01 diabetics with vs diabetics without vascular complications.

cantly higher dispersion of data in diabetics with vascular complications, in comparison with the other two groups (P < 0.001, Levene's test). Subsequent analyses were carried out on log-transformed data. Plasma pro-BNP was on the average higher in diabetics with (median 121 pg/ml, inter-

Table II
Number of patients (%) on various therapies.

	Diabetics without vascular complications	Diabetics with vascular complications	
Insulin	13 (48%)	19 (70%)	NS
Oral antidiabetics	19 (70%)	15 (56%)	NS
ACE-I or AT1-receptor blocker	14 (52%)	21 (78%)	P < 0.05
β-blocker	0	12 (44%)	< 0.001
Diuretic	8 (30%)	13 (48%)	NS
Calcium antagonist	7 (26%)	9 (33%)	NS
Statin	10 (37%)	16 (59%)	NS
Antiplatelet agents	9 (33%)	24 (89%)	P < 0.001

ACE-I=Angiotensin converting enzyme inhibitor.
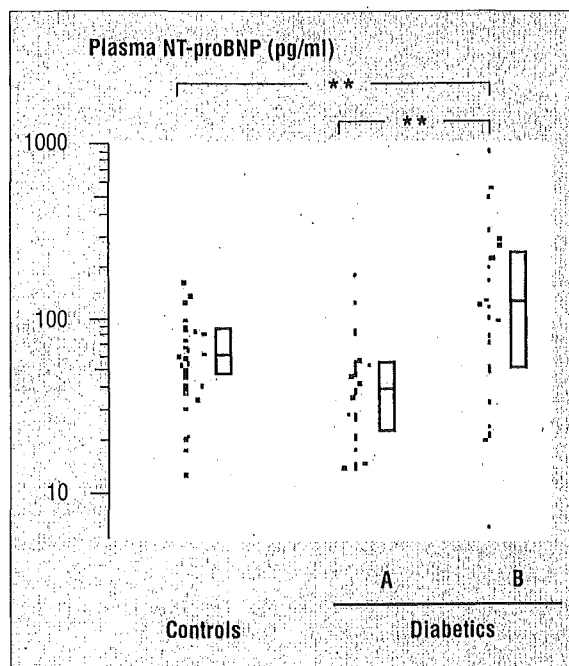NS=not significant.

Figure 1
A) diabetics without vascular complications. B) diabetics with vascular complications. Small dots: individual values. Horizontal bars within rectangles: medians and interquartile range. Statistical analysis: parametric analysis of variance on log-transformed data. ** P < 0.01

quartile range 50-240 pg/ml, P < 0.01) than in those without vascular complications (median 37 pg/ml, interquartile range 21-54 pg/ml). Compared with the controls (median 55 pg/ml, interquartile range 40-79 pg/ml), only diabetics with vascular complications had significantly increased plasma NT-proBNP levels (P < 0.001). Expressed as means ± SD, the plasma NT-proBNP levels averaged 62 ± 34 pg/ml in controls, compared with 194 ± 230 and 46 ± 37 pg/ml in diabetic patients with and without complications, respectively.

Association of plasma NT-proBNP levels with specific vascular complications in diabetic patients

In diabetic patients, the presence of either nephropathy, retinopathy, or coronary artery disease, but not of peripheral arteriopathy or arterial hypertension was associated, on univariate tests, with significantly higher plasma levels of NT-proBNP (Table III). Only 4 patients had cerebrovascular disease, precluding any meaningful comparison concerning this specific complication. Because many patients presented with more than one of the conditions listed in Table III, a multivariable approach was applied next, showing that nephropathy and coronary heart disease were each independently associated with elevated values of plasma NT-proBNP (Table IV). Notably, all but one of the 19 patients with nephropathy were hypertensive, whereas 11 of the 35 diabetics without nephropathy were normotensive (P = 0.03, univariate chisquare test).

Discussion

The plasma levels of brain natriuretic peptides are now widely accepted as markers of myocardial dysfunction. In principle, either the active C-terminal (BNP), or the inactive N terminal moieties (NT-proBNP) of the 108 amino acids prohormone convey similar information regarding abnormalities of cardiac function [20]. When screening for abnormalities of cardiac function, the assay of NT-proBNP rather than BNP may be advantageous because a longer biologic half-life (70 minutes, versus 20 minutes for BNP) [21] makes the circulatory levels of this peptide somewhat less susceptible to short-term fluctuations, resulting in a better intraindividual reproducibility of the assay [22]. For this reason, we chose to assay the N-terminal peptide in the present study. In the control group of healthy subjects, we obtained a mean NT-proBNP level (± SD) of 62 ± 32 pg/ml, in reasonable agreement with the values reported by Hunt and associates in similar conditions (10.8 ± 6.8 pmol/l, equivalent to 92 ± 57 pg/ml) [23].

In spite of the high prevalence of myocardial dysfunction in diabetes, there is surprisingly little specific data concerning the plasma levels of brain natriuretic peptides

Table III
Plasma levels of NT-proBNP (pg/ml) in diabetics with and without specific vascular complications.

Vascular Complication	Absent	Present	P
Nephropathy			
number of patients	35	19	
plasma NT-proBNP	38 (21-56)	136 (83-284)	< 0.0001
Retinopathy			
number of patients	41	13	
plasma NT-proBNP	47 (23-82)	126 (77-262)	0.011
Coronary heart disease			
number of patients	42	12	
plasma NT-proBNP	44.5 (22-91)	147.5 (78-296)	0.0008
Peripheral arteriopathy			
number of patients	44	10	
plasma NT-proBNP	47.5 (22-126)	102 (54-217)	
Treated arterial hypertension			
number of patients	42	12	
plasma NT-proBNP	37.5 (23-54)	57 (28-174)	0.13

Table IV
Independent predictors of plasma NT-proBNP levels in diabetic patients. Stepwise multivariable regression of log-transformed plasma levels of NT-proBNP, using backward elimination. Variables initially included in model: age, sex, duration of diabetes, and presence of specific vascular complications (nephropathy, retinopathy, coronary heart disease, peripheral arteriopathy, and treated arterial hypertension, each included as a separate dummy variable). Ranges in parentheses are 95% confidence intervals.

Predictor	Predicted fold increase in plasma NT-proBNP	P value
Nephropathy	1.70 (1.49-1.94)	< 0001
Coronary heart disease	1.54 (1.32-1.78)	0.006

in this pathology. The available studies mostly sought to establish whether the presence of microvascular complications was a determinant of plasma BNP levels, and therefore enrolled patients with or without microalbuminuria or retinopathy, but without overt evidence of heart disease. Results were variable. In 100 subjects with type 2 diabetes who had normal blood pressure and cardiothoracic ratio, no history of coronary heart disease, and no ultrasound evidence of left ventricular hypertrophy, Isotani et al. found mostly normal plasma levels of BNP which did not differ between subjects with and without microangiopathy [24]. Asakawa and associates reported the same findings in

another cohort of 100 type 2 diabetics without evidence of cardiac or macrovascular complications [10]. In contrast, data by Yano et al. collected in 42 type 2 diabetics with characteristics similar to those in the Isotani study indicate higher plasma BNP levels in presence than in absence of microalbuminuria (16.7 ± 2.4 vs 9.6 ± 1.3 pg/ml, mean ± SEM, P < 0.01) [11]. Finally, Siebenhofer et al. examined 71 type 1 diabetic patients who had normal echocardiography, no history of coronary artery disease and no end-stage renal disease. Median levels of plasma NT-proBNP were more than four-fold higher in subjects with micro-(187 pg/ml) or macroalbuminuria (193 pg/ml) than in normoalbuminuric subjects (43 pg/ml, P = 0.016 versus both other groups) [25]. Finally, plasma NT-proBNP were measured in 253 patients with type 2 diabetes without overt cardiovascular disease and compared with those determined in 230 matched controls [14]. The diabetic patients showed significantly higher NT-proBNP values than normal counterparts.

In contrast with these studies, no exclusion criteria were applied in the present work, so that patients with and without overt vascular disease were included. Consequently, the collected data are reasonably representative of what may be expected in daily practice, with the caveat that none of our patients had end-stage renal disease. In patients devoid of overt micro-and macrovascular complications, plasma NT-proBNP was not elevated (46 ± 37 pg/ml, mean ± SD) in comparison with a control group matched for age and sex (62 ± 34 pg/ml). In presence of complications by contrast, both the dispersion and mean value of this marker were abnormally high (194 ± 230 pg/ml). Figure 1 shows the

individual values of plasma NT-proBNP in the control subjects and the 2 groups of diabetics. Further analyses showed that presence of coronary artery disease and nephropathy were two independent predictors of plasma NT-proBNP in the diabetic subjects (Table III). The first association is of course highly expected, as coronary heart disease is a major cause of myocardial dysfunction. The association of plasma NT-proBNP with nephropathy, defined according to urinary excretion of albumin, is consistent with the Isotani as well as the Siebenenhofer studies mentioned above [24, 25] and could be due to a number of factors. It could reflect an altered clearance of the peptide by the diseased kidney. Although this possibility cannot be discounted on the basis of our data, it seems unlikely when considering studies in patients with terminal renal failure, in whom the plasma levels of BNP were essentially normal in absence of ultrasonographically detectable myocardial dysfunction [26]. A more plausible link between nephropathy and elevated NT-proBNP implies endothelial dysfunction, which is known to play a pivotal role in the pathogenesis of vascular disease in diabetics [27]. Microalbuminuria not only predicts the future progression of renal disease in patients with type 2 diabetes, but also represents a strong predictor of cardiovascular complications [28]. Notably, microalbuminuria is regarded nowadays as an indicator of endothelial dysfunction [29]. Finally, short term infusions of BNP have caused microalbuminuria in previously normoalbuminuric type 1 diabetics [30], raising the possibility that abnormally high plasma levels of BNP-secondary to cardiac dysfunction -could elicit or amplify a cardinal diagnostic feature of diabetic nephropathy.

Not surprisingly, the treatment was heavier in patients with than in those without vascular complications (Table II). Significant differences were observed with regard to the use of blockers of the renin-angiotensin system, β-blockers and antiplatelet agents. Whether such differences in drug regimen might influence BNP secretion has to be considered, but no clear answer can be given based on data presented herein.

The aim of the present study was not to investigate the relationship between plasma BNP levels and left ventricular mass or function. This explains why only a fraction of our patients underwent an echocardiogram or a myocardial scintigraphy. The primary aim was to assess whether the measurement of BNP might serve as an indicator of macro-and/or microvascular disease in patients with type 2 diabetes. Our findings show that this is indeed the case as increased NT-proBNP levels were independently associated with both overt coronary artery disease and diabetic nephropathy.

References

1. Sudoh T, Kangawa K, Minamino N, Matsuo H. A new natriuretic peptide in porcine brain. Nature 1988;332:78-81
2. Levin ER, Gardner DG, Samson WK. Natriuretic peptides. N Engl J Med 1998;339:321-8
3. Cowie MR, Mendez GF. BNP and congestive heart failure. Progress Cardiovasc Dis 2002;44:293-321
4. Maisel AS, Krishnaswamy P, Nowak RM, et al. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. N Engl J Med 2002;347:161-7
5. 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
6. Murray CJ, Lopez AD. Evidence-based health policy--lessons from the Global Burden of Disease Study. Science 1996;274:740-3
7. Butler R, MacDonald TM, Struthers AD, Morris AD. The clinical implications of diabetic heart disease. Eur Heart J 1998;19:1617-27
8. Waeber B, Feihl F, Ruilope L. Diabetes and hypertension. Blood Pressure 2001;10:311-21
9. Struthers AD, Morris AD. Screening for and treating left-ventricular abnormalities in diabetes mellitus: a new way of reducing cardiac deaths. Lancet 2002;359:1430-2
10. Asakawa H, Fukui T, Tokunaga K, Kawakami F. Plasma brain natriuretic peptide levels in normotensive Type 2 diabetic patients without cardiac disease and macroalbuminuria. J Diab Complic 2002;16:209-13
11. Yano Y, Katsuki A, Gabazza EC, et al. Plasma brain natriuretic peptide levels in normotensive noninsulin-dependent diabetic patients with microalbuminuria. J Clin Endocrinol Metab 1999;84:2353-6
12. Nagai T, Imamura M, Inukai T, Mori M. Brain natriuretic polypeptide in type 2 NIDDM patients with albuminuria. J Med 2001; 32:169-80
13. Bhalla MA, Chiang A, Epshteyn VA, et al. Prognostic role of B-type natriuretic peptide levels in patients with type 2 diabetes mellitus. J Am Coll Cardiol 2004;44:1047-52
14. Magnusson M, Melander O, Israelsson B, Grubb A, Groop L, Jovinge S. Elevated plasma levels of Nt-proBNP in patients with type 2 diabetes without overt cardiovascular disease. Diabetes Care 2004; 27:1929-35
15. Alberti KG, Zimmet PZWdc. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med 1998;15:539-53
16. Consensus Development Conference on Insulin Resistance. American Diabetes Association. Diabetes Care 1998;21:310-4
17. Jermendy G, Farkas K, Nadas J, Daroczy A, Peterfai E. Practical aspects of measuring microalbuminuria in diabetic patients. Diab Nutr Metab 2001;14:195-200
18. Gerstein HC, Mann JF, Yi Q, et al. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. JAMA 2001;286:421-6
19. Glantz SA. Primer of Biostatistics. New York. McGraw-Hill. 3rd edition. 1992;350-2
20. Hammerer-Lercher A, Neubauer E, Muller S, Pachinger O, Puschendorf B, Mair J. Head-to-head comparison of N-terminal pro-brain natriuretic peptide, brain natriuretic peptide and N-terminal pro-

atrial natriuretic peptide in diagnosing left ventricular dysfunction. Clinica Chimica Acta 2001;310:193-7

21. Pemberton CJ, Johnson ML, Yandle TG, Espiner EA. Deconvolution analysis of cardiac natriuretic peptides during acute volume overload. Hypertension 2000;36:355-9

22. Wu AH, Smith A, Wieczorek S, et al. Biological variation for N-terminal pro- and B-type natriuretic peptides and implications for therapeutic monitoring of patients with congestive heart failure. Am J Cardiol 2003;92:628-31

23. Hunt PJ, Richards AM, Nicholls MG, Yandle TG, Doughty RN, Espiner EA. Immunoreactive amino-terminal pro-brain natriuretic peptide (NT-PROBNP): a new marker of cardiac impairment. Clinical Endocrinology 1997;47:287-96

24. Isotani H, Kameoka K, Sasaki I, Hida H, Kakutani S, Tasaki T. Plasma brain natriuretic peptide levels in normotensive type 2 diabetic patients without cardiac disease. Diabetes Care 2000;23:859-60

25. Siebenhofer A, Ng LL, Plank J, Berghold A, Hodl R, Pieber TR. Plasma N-terminal pro-brain natriuretic peptide in Type 1 diabetic

patients with and without diabetic nephropathy. Diabet Med 2003; 20:535-9

26. Cataliotti A, Malatino LS, Jougasaki M, et al. Circulating natriuretic peptide concentrations in patients with end-stage renal disease: role of brain natriuretic peptide as a biomarker for ventricular remodeling. Mayo Clin Proc 2001;76:1111-9

27. El-Atat F, McFarlane SI, Sowers JR. Diabetes, hypertension, and cardiovascular derangements: pathophysiology and management. Current Hypertens Rep 2004;6:215-23

28. Mattock MB, Morrish NJ, Viberti G, Keen H, Fitzgerald AP, Jackson G. Prospective study of microalbuminuria as predictor of mortality in NIDDM. Diabetes 1992;41:736-41

29. Feldt-Rasmussen B. Microalbuminuria, endothelial dysfunction and cardiovascular risk. Diabetes Metab 2000;26 (suppl 4):64-66

30. McKenna K, Smith D, Moore K, Glen A, Tormey W, Thompson CJ. Brain natriuretic peptide increases urinary albumin and alpha-1 microglobulin excretion in Type 1 diabetes mellitus. Diabet Med 2001; 18:973-8