Relation of Left Ventricular Function, Mass, and Volume to NT-proBNP in Type 1 Diabetic Patients

Anne Sofie Astrup, md[1]
Won Yong Kim, md[2,3]
Lise Tarnow, md[1]
René M. Botnar, phd[4]
Cheryl Simonsen, rt[3]
Lau Brix, msc[3]
Lotte Pietraszek[1]
Peter Riis Hansen, md[5]
Warren J. Manning, md[6]
Hans-Henrik Parving, md[7]

OBJECTIVES — To measure left ventricular mass (LVM), left ventricular volumes, and left ventricular function (LVF) in a cohort of type 1 diabetic patients and to correlate measures of imaging to NH_2-terminal pro-brain natriuretic peptide (NT-proBNP).

RESEARCH DESIGN AND METHODS — In a cross-sectional study, all patients with type 1 diabetes underwent cardiovascular magnetic resonance imaging. We included 63 patients with diabetic nephropathy and 73 patients with normoalbuminuria.

RESULTS — All patients had normal global LVF. LVM was increased in patients with diabetic nephropathy compared with patients with persistent normoalbuminuria. Patients with nephropathy had smaller left ventricular volumes and increased levels of NT-proBNP. Linear regression analysis in patients with diabetic nephropathy showed that NT-proBNP and creatinine were associated with LVM.

CONCLUSIONS — Increased LVM is identified in asymptomatic type 1 diabetic patients with nephropathy compared with normoalbuminuric patients. Elevated levels of NT-proBNP were associated with increased LVM, which are both markers of increased cardiovascular risk.

Diabetes Care **31**:968–970, 2008

Cardiovascular disease remains the leading cause of mortality and morbidity in diabetic patients. The increased mortality in type 1 diabetic patients is primarily due to a poor prognosis in patients with diabetic nephropathy. Since ~40% of type 1 diabetic patients with diabetic nephropathy develop cardiovascular disease (1), it may be beneficial to diagnose cardiac disease early in this population. We have already shown a higher coronary plaque burden in asymptomatic individuals with type 1 diabetes and diabetic nephropathy than in patients with persistent normoalbuminuria (2).

RESEARCH DESIGN AND METHODS

— We randomly included 136 patients with type 1 diabetes: 63 with diabetic nephropathy and 73 with persistent normoalbuminuria. All patients were without symptoms or clinical history of cardiovascular disease. The selection of patients and clinical measurements have previously been described (2).

NH_2-terminal pro-brain natriuretic peptide (NT-proBNP) was analyzed by Roche Diagnostics with an immunoassay (3). All 136 patients underwent cardiovascular magnetic resonance imaging (CMR) (Intera 1.5 T MR; Philips, Best, Netherlands). Left ventricular volumes and left ventricular mass (LVM) were measured using a steady-state free procession breath-hold cine sequence. Left ventricular wall stress at end-systole was calculated (4).

To estimate left ventricular filling pressures by CMR, transmitral flow and myocardial tissue velocities were measured (5). To evaluate coronary and aortic plaque burden, subjects underwent black-blood vessel wall imaging according to previously validated protocols (2,6,7).

In analysis of correlations with LVM, variables used in all linear regression analyses were those that were significantly associated with LVM in a univariate analysis: sex, age, creatinine, smoking, systolic blood pressure, diastolic blood pressure, total cholesterol, BMI, hemoglobin, A1C, and NT-proBNP. Univariate correlations of clinical and CMR variables to NT-proBNP were described with *r* values.

RESULTS

Clinical data, NT-proBNP, and CMR parameters are shown in Table 1. NT-proBNP was significantly increased in patients with nephropathy than in normoalbuminuric patients.

All patients had normal global left ventricular function (LVF). LVM, LVM index, and heart rate were higher in patients with nephropathy. Left ventricular end-diastolic and end-systolic volumes tended to be smaller in those with diabetic nephropathy. Consequently, left ventricular end-systolic wall stress was smaller in patients with nephropathy than in patients with normoalbuminuria. The noninvasively estimated filling pressures (peak flow velocity/peak velocity muscle) were similar in both groups.

In patients with diabetic nephropathy, LVM correlated with NT-proBNP ($r = 0.42$; $P = 0.01$). No other CMR measures or plaque burden measures corre-

From the [1]Steno Diabetes Center, Gentofte, Denmark; the [2]Department of Cardiology, Skejby Hospital, Aarhus University Hospital, Aarhus, Denmark; the [3]MR-Center, Skejby Hospital, Aarhus University Hospital, Aarhus, Denmark; the [4]Department of Nuclear Medicine, Technical University Munich, Munich, Germany; [5]Gentofte Hospital, Gentofte, Denmark; the [6]Department of Medicine, Cardiovascular Division, and the Department of Radiology, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, Massachusetts; and the [7]Department of Medical Endocrinology, Rigshospitalet, Copenhagen, Denmark.

Corresponding author: Anne Sofie Astrup, Steno Diabetes Center, Niels Steensensvej 2, 2820, Denmark. E-mail: ansa@steno.dk.

Received for publication 6 August 2007 and accepted in revised form 23 January 2008.

Published ahead of print at http://care.diabetesjournals.org on 5 February 2008. DOI: 10.2337/dc07-1536.

Abbreviations: CMR, cardiovascular magnetic resonance imaging; LVM, left ventricular mass; LVF, left ventricular function; NT-proBNP, NH_2-terminal pro-brain natriuretic peptide.

Table 1—*Clinical parameters, NT-proBNP, and CMR parameters in 136 type 1 diabetic patients with and without diabetic nephropathy*

	Normoalbuminuria	Diabetic nephropathy	*P*
Sex (male/female)	43/30	36/27	0.837
Age (years)	52 ± 9	48 ± 9	0.011
Duration of diabetes (years)	31 ± 7	34 ± 9	0.017
Duration of nephropathy (years)	0	15 ± 7	—
BMI (kg/m^2)	24.7 ± 2.7	24.4 ± 2.9	0.624
A1C (%)	8.0 ± 0.9	8.8 ± 1.1	<0.0001
Glomerular filtration rate (ml/min per 1.73m^2)	75 ± 12	—	—
Urinary albumin excretion rate (mg/24 h)*	8 (2–29)	209 (3–6,375)	<0.0001
S-creatinine (μmol/l)	89 (61–116)	119 (68–825)	<0.0001
Systolic blood pressure (mmHg)	129 ± 15	135 ± 18	0.065
Diastolic blood pressure (mmHg)	71 ± 6	71 ± 10	0.582
Total cholesterol (mmol/l)	4.8 ± 0.8	4.7 ± 0.8	0.944
HDL cholesterol (mmol/l)	1.9 ± 0.5	1.8 ± 0.5	0.117
LDL cholesterol (mmol/l)	2.5 ± 0.6	2.3 ± 0.8	0.250
Triglycerides (mmol/l)	0.9 ± 0.5	1.2 ± 0.7	0.007
Hemoglobin (mmol/l)	8.5 ± 0.7	7.9 ± 0.8	<0.0001
Smoking (%)	17 (23)	15 (24)	0.943
NT-proBNP (ng/l)	44 (6–621)	77 (5–3,718)	0.016
Statins (%)	20 (27)	36 (57)	<0.0001
Aspirin (%)	19 (26)	45 (71)	<0.0001
RAAS-blockade (%)†	27 (37)	58 (92)	<0.0001
β-Blockers (%)	2 (3)	5 (8)	0.01
Average number of AHT drugs	0.8	2.3	<0.0001
CMR parameters			
LVM unadjusted (g)	90.1 ± 20.8	105.0 ± 29.8	0.001
LVMI adjusted for BSA (g/m^2)	47.4 ± 8.8	56.5 ± 14.3	<0.0001
LVM adjusted for height (g/m$^{2.7}$)	19.9 ± 3.1	23.9 ± 5.6	<0.0001
Ejection fraction (%)	68 ± 8	69 ± 9	0.555
Cardiac output (l/min)	6.3 ± 1.4	6.3 ± 1.4	0.868
Heart rate (beats/min)	75 ± 12	81 ± 11	0.003
E/Ea ratio	7.1 ± 2.7	7.1 ± 3.6	0.931
LVEDV/BSA (ml/m^2)	66.4 ± 13.2	60.8 ± 11.6	0.010
LVESV/BSA (ml/m^2)	21.2 ± 8.4	18.6 ± 7.4	0.054
LVWS (N/m^2)	18.2 ± 0.9	14.4 ± 0.9	0.002
Aortic plaque burden			
n	68	60	
Thoracic plaque frequency	0	2 (3)	0.28
Abdominal plaque frequency	11 (16)	13 (22)	0.7
Coronary plaque burden			
n	33	21	
RCA VW mean thickness (mm)	1.3 ± 0.2	1.7 ± 0.3	<0.001
RCA VW max thickness (mm)	1.6 ± 0.3	2.2 ± 0.5	<0.001
RCA plaque detected	5 (15)	16 (76)	<0.001

Data are means ± SD, median (range), and *n* (%) unless otherwise indicated. Systolic and diastolic blood pressure values are the mean of 24-h measurements. *Some patients with previously persistent albuminuria receiving antihypertensive medication had a urinary albumin excretion <300 mg/24 h. Values are the mean of two 24-h urine collections. †Blockade of the renin-angiotensin-aldosteron system. AHT, antihypertensive; BSA, body surface area [(height in cm × weight in kg)/3,600]$^{1/2}$; E/Ea ratio, peak flow velocity (E) divided by peak velocity muscle (Ea); LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVMI, LVM index; LVWS, left ventricular wall stress [3 × LVESV/(LVM/1.05) + 1] × systolic blood pressure; RCA VW, right coronary artery vessel wall.

lated to NT-proBNP. NT-proBNP was positively correlated with systolic blood pressure, urinary albumin excretion, and creatinine and negatively correlated to glomerular filtration rate, BMI, and hemoglobin ($P < 0.01$).

A1C was correlated with heart rate variability ($r = -0.28$; $P = 0.001$), with higher A1C showing a smaller heart rate variation. Furthermore, A1C was correlated with heart rate ($r = 0.28$; $P = 0.001$), stroke volume ($r = -0.34$; $P < 0.0001$), left ventricular end-systolic volume ($r = -0.28$; $P = 0.001$), and left ventricular end-diastolic volume ($r = -0.38$; $P < 0.0001$).

In multiple regression analysis, NT-proBNP was correlated with LVM in patients with diabetic nephropathy (with an estimated 13.5-g increase in LVM per 10-fold increase in NT-proBNP; $P = 0.04$). Creatinine was also correlated with LVM (with an estimated 41.5-g increase in LVM per 10-fold increase in creatinine; $P = 0.024$). A negative correlation was found between LVM and a 10-year increase in age ($P = 0.02$) and between LVM and sex ($P < 0.0001$); thus, older-age individuals and women had lower LVM. In patients with persistent normoalbuminuria, sex ($P = 0.043$) was associated with smaller LVM and older age was associated with lower LVM ($P = 0.009$).

In the analysis of all patients together, increased LVM was correlated with increased NT-proBNP and creatinine, whereas increased A1C, older age, and sex were correlated with decreased LVM ($P < 001$).

CONCLUSIONS — The present study showed that asymptomatic type 1 diabetic patients with diabetic nephropathy have larger LVM and higher levels of NT-proBNP than patients with normoalbuminuria. All patients had normal LVF and normal filling pressures in accordance with their clinical status. LVM was correlated with NT-proBNP, creatinine, age, and sex in multiple regression analysis in patients with diabetic nephropathy. NT-proBNP was correlated with well-known cardiovascular risk factors.

No patients had left ventricular hypertrophy according to normal ranges for LVM (8). LVM indexes in normoalbuminuric patients were slightly lower (47.4 ± 8.8 ml/m^2) than measurements considered normal values in nondiabetic subjects (64.7 ± 9.3 in men and 52.0 ± 7.4 ml/m^2 in women) and may reflect differences between the populations (8). In the present study, blood pressure was not correlated with LVM, most likely due to intensive antihypertensive treatment. Patients with nephropathy had considerably lower blood pressure than patients of earlier studies and would be less likely to have LVH. Our study more accurately re-

flects cardiovascular function in asymptomatic type 1 diabetic patients on contemporary reno- and cardioprotective medication, emphasizing the beneficial effect of blood pressure reduction in diabetic patients. We found a negative correlation between A1C and LVM showing that patients with high levels of A1C had smaller LVM. A possible explanation is that patients with a higher A1C tend to have a higher degree of autonomic neuropathy (9) resulting in a relatively high heart rate with smaller left ventricular dimensions as a consequence to keep the same cardiac output. In accordance, our data showed that higher A1C was correlated with less heart rate variability. Furthermore, high levels of A1C showed an increased heart rate with smaller left ventricular dimensions. Thus, autonomic neuropathy in this normotensive population seems to induce negative left-ventricular remodeling.

References

1. Astrup AS, Tarnow L, Rossing P, Pietraszek L, Hansen PR, Parving HH: Improved prognosis in type 1 diabetic patients with nephropathy: a prospective follow-up study. *Kidney Int* 68:1250–1257, 2005
2. Kim WY, Astrup AS, Stuber M, Tarnow L, Falk E, Botnar RM, Simonsen C, Pietraszek L, Hansen PR, Manning WJ, Andersen NT, Parving HH: Subclinical coronary and aortic atherosclerosis detected by magnetic resonance imaging in type 1 diabetes with and without diabetic nephropathy. *Circulation* 115:228–235, 2007
3. Tarnow L, Hildebrandt P, Hansen BV, Borch-Johnsen K, Parving HH: Plasma N-terminal pro-brain natriuretic peptide as an independent predictor of mortality in diabetic nephropathy. *Diabetologia* 48: 149–155, 2005
4. Arts T, Veenstra PC, Reneman RS: Epicardial deformation and left ventricular wall mechanisms during ejection in the dog. *Am J Physiol* 243:H379–H390, 1982
5. Paelinck BP, De-Roos A, Bax JJ, Bosmans JM, Va-Der G, Dhondt D, Parizel PM, Vrints CJ, Lamb HJ: Feasibility of tissue magnetic resonance imaging: a pilot study in comparison with tissue Doppler imaging and invasive measurement. *J Am Coll Cardiol* 45:1109–1116, 2005
6. Jaffer FA, O'Donnell CJ, Larson MG, Chan SK, Kissinger KV, Kupka MJ, Salton C, Botnar RM, Levy D, Manning WJ: Age and sex distribution of subclinical aortic atherosclerosis: a magnetic resonance imaging examination of the Framingham Heart Study. *Arterioscler Thromb Vasc Biol* 22: 849–854, 2002
7. Kim WY, Stuber M, Bornert P, Kissinger KV, Manning WJ, Botnar RM: Three-dimensional black-blood cardiac magnetic resonance coronary vessel wall imaging detects positive arterial remodeling in patients with nonsignificant coronary artery disease. *Circulation* 106: 296–299, 2002
8. Alfakih K, Plein S, Thiele H, Jones T, Ridgway JP, Sivananthan MU: Normal human left and right ventricular dimensions for MRI as assessed by turbo gradient echo and steady-state free precession imaging sequences. *J Magn Reson Imaging* 17:323–329, 2003
9. Astrup AS, Tarnow L, Rossing P, Hansen BV, Hilsted J, Parving HH: Cardiac autonomic neuropathy predicts cardiovascular morbidity and mortality in type 1 diabetic patients with diabetic nephropathy. *Diabetes Care* 29:334–339, 2006