

Left ventricular function, mass, and volumes in type 1 diabetic patients – and relation to NT-proBNP

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ABSTRACT

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

Design and Research Methods: In a cross sectional study, all patients with type 1 diabetes underwent cardiovascular magnetic resonance imaging (CMR). We included 63 patients with diabetic nephropathy and 73 patients with normoalbuminuria.

Results: All patients had normal global LVF. LVM were increased in patients with diabetic nephropathy compared to patients with persistent normoalbuminuria. Patients with nephropathy had smaller left ventricular volumes and levels of NT-proBNP were increased.

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 to normoalbuminuric patients. Elevated levels of NT-proBNP were associated with increased LVM– both markers of increased cardiovascular risk.

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

RESEARCH DESIGN AND METHODS

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

NT-proBNP was analyzed by Roche Diagnostics with an immunoassay (3).

All 136 patients underwent CMR examination (Philips Intera® 1.5 T MR, Best, Netherlands). Left ventricular volumes and mass were measured using a steady state free precession 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 to LVM variables used in all linear regression

analysis were variables that in a univariate analysis were significantly associated with LVM: Gender, age, creatinine, smoking, systolic blood pressure, diastolic blood pressure, total cholesterol, body mass index, hemoglobin, HbA1c, and NT-proBNP. Univariate correlations of clinical and CMR variables to NT-proBNP was described with r values.

RESULTS

Clinical data, NT-proBNP and CMR parameters are shown in the table.

NT-proBNP was significantly increased in patients with nephropathy compared to normoalbuminuric patients.

All patients had normal global LVEF. LVM and LVMI and heart rate were higher in patients with nephropathy. Left ventricular end diastolic volume was smaller, and left ventricular end systolic volume tended to be smaller in patients with diabetic nephropathy. Consequently, left ventricular end-systolic wall stress was smaller in patients with nephropathy compared to patients with normoalbuminuria. The non-invasively estimated filling pressures (E/Ea) were similar in both groups.

In patients with diabetic nephropathy, LVM correlated to NT-proBNP ($r = 0.42$, $p=0.01$). No other CMR measures or plaque burden measures correlated to NT-proBNP. NT-proBNP was positively correlated to systolic blood pressure, urinary albumin excretion, and creatinine, and negatively correlated to GFR, BMI, and hemoglobin, $p<0.01$.

HbA1c was correlated to heart rate variability ($r= -0.28$, $p=0.001$) with higher HbA1c showing a smaller heart rate variation. Furthermore, HbA1c correlated to 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 correlated to LVM in patients

with diabetic nephropathy (estimate 13.5 g increase in LVM per 10 fold increase in NT-proBNP, $p=0.04$). Creatinine was also correlated to LVM (estimate 41.5 g increase in LVM per 10 fold increase in creatinine, $p=0.024$). A negative correlation was found between LVM and 10 year increase in age ($p=0.02$), and gender (male to female, $p<0.0001$); thus the higher age the lower LVM, and females had lower LVM.

In patients with persistent normoalbuminuria, gender (male to female; $p=0.043$) was associated with a smaller LVM, and higher age was related to lower LVM ($p=0.009$).

Analyzing all patients together, increased LVM correlated with increased NT-proBNP, and creatinine, while increased HbA1c, higher age, and gender (male to female) correlated with decreased LVM, $p<0.001$.

CONCLUSIONS

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

No patients had left ventricular hypertrophy according to normal ranges for LVM (8). LVM index in the normoalbuminuric patients were slightly lower (47.4 ± 8.8 ml/m²) than measurements considered to be normal values in non-diabetic subjects (64.7 ± 9.3 ml/m² in males and 52.0 ± 7.4 ml/m² in females) and may reflect differences between the populations (8). In the present study, blood pressure was not correlated to LVM most likely due to intensive antihypertensive treatment. Patients with nephropathy had considerably lower blood pressure compared to earlier studies and would be less likely to have LVH. Our study more accurately reflects cardiovascular function in asymptomatic type 1 diabetics on contemporary renoprotective and cardio protective medication emphasizing the beneficial effect of blood pressure reduction in diabetic patients. We found a negative correlation between HbA1c and LVM showing that patients with high levels of HbA1c had smaller LVM. A possible explanation is that patients with a higher HbA1c 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 higher HbA1c correlated to less heart rate variability. Furthermore, high levels of HbA1c showed an increased heart rate with smaller left ventricular dimensions. Thus, autonomic neuropathy in this normotensive population seems to induce negative left ventricular remodeling.

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TABLE 1. Clinical parameters, NT-proBNP, and CMR parameters in 136 type 1 diabetic patients with and without diabetic nephropathy

	normoalbuminuria	Diabetic nephropathy	p value
Sex (m/f)	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
HbA _{1c} (%)	8.0 ± 0.9	8.8 ± 1.1	<0.001
Glomerular filtration rate (ml/min/1.73m ²)	75 ± 12	-	-
Urinary albumin excretion rate (mg/24h) [‡]	8 (2 – 29)	209 (3 – 6375)	<0.001
S-creatinine (µmol/l)	89 (61 – 116)	119 (68 – 825)	<0.001
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	<0.001
Smoking (%)	17 (23)	15 (24)	0.943
NT-proBNP (ng/l)	44(6-621)	77 (5-3718)	0.016
Statins (%)	20 (27)	36 (57)	<0.001
Aspirin (%)	19 (26)	45 (71)	<0.001
RAAS-blockade (%)*	27 (37)	58 (92)	<0.001
Beta-Blockers (%)	2 (3)	5 (8)	0.01
Average no of AHT drugs	0.8	2.3	<0.001
CMR parameters			

Left ventricular mass 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	<0.001
LVM adjusted for height (g/m ^{2.7})	19.9 ± 3.1	23.9 ± 5.6	<0.001
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			
	Normoalbuminuria (n = 68)	Nephropathy (n = 60)	p value
Thoracic plaque frequency	0 (0)	2 (3)	0.28
Abdominal plaque frequency	11 (16)	13 (22)	0.7
Coronary plaque burden			
	Normoalbuminuria (n = 33)	Nephropathy (n = 21)	p value
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

Table Footer:

Data are n, means ± SD, or medians (range).

‡ Some patients with previously persistent albuminuria receiving antihypertensive medication had a UAE < 300 mg/24 h. Values is the mean of two 24 h urine collections.

Systolic and diastolic blood pressures are means of 24 h measurements.

* Blockade of the renin-angiotensin-aldosteron-system

LVMi = left ventricular mass index

BSA = Body Surface Area ((height in cm x weight in kg)/3600)^{1/2}

LVEDV = Left ventricular end diastolic volume LVESV = left ventricular end systolic volume

E/Ea ratio = peak flow velocity (E) divided by peak velocity muscle (Ea)

LVWS = Left ventricular wall stress (3 x LVESV / (LVM / 1.05) + 1) x Systolic blood pressure

RCA VW = Right Coronary Artery Vessel Wall