Influence of microalbuminuria on left ventricular geometry and function in hypertensive patients with type 2 diabetes mellitus

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Key words:
Diabetes mellitus; Echocardiography; Hypertension; Left ventricular hypertrophy.

Background. **An increased urinary albumin excretion (UAE) is associated with an augmented risk of cardiovascular disease in diabetic patients and in non-diabetic subjects. Left ventricular hypertrophy has been demonstrated to be a powerful predictor of cardiovascular morbidity and mortality in arterial hypertension and when the ventricular geometry is concentric the relation is even stronger. This echocardiographic and Doppler study was designed to evaluate the influence of microalbuminuria on the left ventricular geometry and function in hypertensive patients with type 2 diabetes mellitus.**

Methods. **Forty-two patients (16 males, 26 females, mean age 59.6 ± 6.7 years) with mild-to-moderate essential hypertension and type 2 diabetes mellitus were enrolled in the study. Twenty-one patients had an elevated UAE (group 1) and 21 a normal UAE (group 2). M-mode (under two-dimensional control) and Doppler echocardiography were performed after a 4-week washout period off antihypertensive therapy.**

Results. **The left ventricular mass index was found to be greater than the partition value of 51 g/m$^{2.7}$ in both groups but was significantly higher ($p < 0.001$) in group 1. The midwall fractional shortening was significantly lower ($p < 0.001$) in group 1 in comparison with group 2. The E/A ratio was impaired in both groups but was more significantly reduced ($p < 0.02$) in group 1. There was a significantly higher prevalence of a left ventricular concentric hypertrophy pattern (19/21 patients, $p < 0.001$) in group 1.**

Conclusions. **In hypertensive patients with type 2 diabetes mellitus, an elevated UAE is associated with an increased left ventricular mass index, a higher prevalence of a concentric left ventricular hypertrophy pattern, a depressed midwall systolic performance and a markedly impaired diastolic function..**

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Introduction

An elevated urinary albumin excretion (UAE) in the absence of clinical albuminuria (microalbuminuria) is associated with an increased risk of cardiovascular disease both in type 1 and type 2 diabetic patients[1-4] as well as in non-diabetic subjects[5]. Conversely, left ventricular hypertrophy (LVH) has been demonstrated to be a powerful predictor of cardiovascular morbidity and mortality in arterial hypertension[6], and when the left ventricular geometry is concentric the relation is even stronger[7]. Few data concerning the relationship between microalbuminuria and LVH in patients with essential hypertension and diabetes mellitus are available[8-12].

Thus, using Doppler echocardiography, we assessed the left ventricular geometry and function in hypertensive, type 2 diabetic patients with and without microalbuminuria.

Methods

Patient population. Forty-eight consecutive patients (20 males, 28 females, mean age 59.6 ± 6.7 years) with mild-to-moderate essential hypertension[13] and type 2 diabetes mellitus diagnosed on the basis of the National Diabetes Data Group criteria[14] were recruited. Twenty-three patients (mean blood pressure 146/92 ± 7/4 mmHg) had a UAE (by radioimmunoassay) ranging between 30 and 300 mg/24 hours in two distinct 24-hour urine samples collected during a 7-day period before enrollment, while 25 patients (mean blood pressure 148/90 ± 7/5 mmHg) had a UAE < 30 mg/24 hours. The inclusion criteria were

as follows: 1) type 2 diabetes mellitus well controlled by oral antidiabetic drugs; 2) sitting and standing diastolic blood pressures of 90 to 109 mmHg; 3) sitting and standing systolic blood pressures of 140 to 179 mmHg; 4) the absence of chronic renal failure (plasma creatinine ≤ 1.3 mg/dl); 5) the absence of cerebrovascular disease, autonomic neuropathy, congestive heart failure, cardiomyopathy, cardiac arrhythmias, angina pectoris or previous myocardial infarction.

Any causes of secondary hypertension were excluded by routine investigation. All subjects gave their informed consent to be enrolled in the study which was approved by the local medical ethics committee. All patients underwent a 4-week washout period during which antihypertensive (but not antidiabetic) drugs were discontinued. Clinical examination, ECG and laboratory investigations (including the standard determination of plasma creatinine levels, plasma levels of glucose, and glycosylated hemoglobin) were obtained weekly during the washout period. The blood pressure was measured by the same observer using a mercury sphygmomanometer. The systolic and diastolic pressures were defined by Korotkoff phase 1 and 2 respectively. M-mode (under two-dimensional control) and pulsed Doppler echocardiography were performed at the end of the washout period.

Doppler echocardiography. All recordings were obtained using an Aloka SSD-870 phased array sector scanner. All echocardiographic and Doppler measurements were made by the same observer on 3 to 5 high quality cycles and averaged for subsequent analysis. The interventricular septum, the left ventricular internal dimensions and the wall thickness as well as the two-dimensional determination of the extent and distribution of hypertrophy were performed in the parasternal short-axis view and using the criteria of the American Society of Echocardiography[15]. The fractional shortening was calculated as LVIDd - LVIDs/LVIDd × 100 where LVIDd = left ventricular internal end-diastolic diameter and LVIDs = left ventricular internal end-systolic diameter. The left ventricular volumes at end-systole and end-diastole were calculated using the method described by Teichholz et al.[16]. The ejection fraction (EF) was calculated on the basis of the values so obtained as follows: EF = LVEDV - LVESV/LVEDV × 100 where LVEDV = left ventricular end-diastolic volume and LVESV = left ventricular end-systolic volume. The stroke volume, calculated as LVEDV - LVESV, was divided by the body surface area to obtain the stroke volume index (SVi). The total peripheral resistance was calculated by standard methods. The ratio of the SVi to the pulse pressure (PP), an estimate of the total arterial compliance, was calculated as SVi/(systolic - diastolic blood pressure) [ml/m^2/mmHg][17].

The left ventricular mass (LVM) was calculated according to the Penn convention[18]. The LVM index was calculated for each patient by dividing the LVM by the height to the power of 2.7 (Cornell adjustment)[19]. The partition value (51 g/m$^{2.7}$) was used to define LVH[17]. The relative wall thickness at end-diastole (RWTd) was calculated as follows[20]: RWTd = 2 PWTd/LVIDd where PWTd = posterior wall thickness at end-diastole.

Four patterns of left ventricular geometry were identified[21]: normal geometry (LVM index < 51 g/m$^{2.7}$, RWT < 0.44), concentric remodeling (LVM index < 51 g/m$^{2.7}$, RWT ≥ 0.44), eccentric hypertrophy (LVM index < 51 g/m$^{2.7}$, RWT < 0.44) and concentric hypertrophy (LVM index > 51 g/m$^{2.7}$, RWT > 0.44). The circumferential end-systolic stress was calculated using the method described by Gaasch et al.[22] as the primary measure of myocardial afterload. The midwall fractional shortening was calculated on the basis of de Simone's criteria[23]. An equation relating the midwall fractional shortening to the circumferential end-systolic stress was used to predict the expected midwall fractional shortening for the observed circumferential end-systolic stress[23]. The ratio between the observed value of the midwall fractional shortening and that predicted on the basis of the circumferential end-systolic stress on the regression equation was used as an index of the left ventricular performance independent of the afterload conditions[7]. Values < 0.78 were considered as indicative of a depressed left ventricular performance[7]. Pulsed Doppler echocardiography was performed using an apical 4-chamber view with the sample volume at the end of the mitral annulus, a site where the change in the diastolic cross-sectional area is minimal[24]. Doppler measurements included the early (E) peak and peak atrial (A) filling velocities and their ratio (E/A). Tracings were recorded at a paper speed of 100 mm/s.

Statistical analysis. Statistical analysis was performed using the Student's paired t-test; p values < 0.05 were considered statistically significant. The results are expressed as means ± SD. The distribution of the geometric patterns of LVH among the two groups of patients was analyzed using the χ^2 test.

Results

Of the 48 patients who met the study inclusion criteria, 6 (2 with an elevated UAE and 4 with a normal UAE) developed severe hypertension (a systolic blood pressure ≥ 180 mmHg or a diastolic blood pressure ≥ 110 mmHg) during the 4-week washout period off antihypertensive therapy and were excluded from the study. Overall, 42 patients were admitted to the study. Of these, 21 patients had an elevated UAE (group 1) while 21 patients had a normal UAE (group 2). The clinical characteristics of the two groups are shown in table I. At the end of the washout period, the

Table I. Characteristics of the study population.

	Group 1 (n=21)	Group 2 (n=21)
Age (years)	58.2 ± 6.5*	60.8 ± 6.8
Sex (M/F)	10/11*	6/15
Duration of diabetes (years)	7.9 ± 5 2*	8.1 ± 5.8
Duration of hypertension (years)	6.9 ± 4.8*	6.7 ± 4.1
Body mass index (kg/m^2)	27.8 ± 5.4*	27.6 ± 5.8
UAE (mg/24 hours)	58.2 ± 34.4*	7.7 ± 3.9
Plasma creatinine (mg/dl)	1.09 ± 0.09*	1.01 ± 0.04
Plasma glucose (mg/dl)	124 ± 16*	118 ± 14
Glycosylated hemoglobin (%)	7.2 ± 1.2*	7.1 ± 1.2

Values are expressed as means ± SD. UAE = urinary albumin excretion. * p = NS compared with group 2.

supine systolic and diastolic blood pressures and heart rate were similar in both groups (Table II). There was no significant difference between the two groups in the left ventricular EF and fractional shortening (Fig. 1). The LVM index was found to be greater than the partition value of 51 g/m$^{2.7}$ in both groups, but was significantly higher ($p < 0.001$) in hypertensive, diabetic, group 1 patients in comparison with hypertensive, diabetic, group 2 patients (Fig. 2). The ratio between the observed value of the midwall fractional shortening and that predicted on the basis of the circumferential end-systolic stress was significantly lower ($p < 0.001$) in group 1 (Fig. 3). The E/A ratio was impaired in both groups, but was more significantly reduced ($p < 0.02$) in group 1 (Fig. 4). There was no significant difference between the two groups in the SVi/PP while a significant increase of the total peripheral resistance ($p < 0.001$) was observed in group 1 (Table III). The distribution of the geometric patterns of the LVH was different between the two groups: a significantly higher prevalence of a concentric hypertrophy pattern ($p < 0.001$) was found in group 1 patients in comparison with group 2 (Table IV). Eccentric hypertrophy was found in 2/21 patients of group 1 (Table IV). In group 2, 5 patients had a normal geometry, 7 had a concentric remodeling and an eccentric hypertrophy pattern was observed in 9 patients (Table IV).

Table II. Systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) in the two study groups at the end of the washout period off antihypertensive therapy.

	Group 1	Group 2
SBP (mmHg)	168 ± 6*	170 ± 8
DBP (mmHg)	98 ± 4*	97 ± 6
HR (b/min)	73 ± 10*	70 ± 9

Values are expressed as means ± SD. * p = NS compared with group 2.

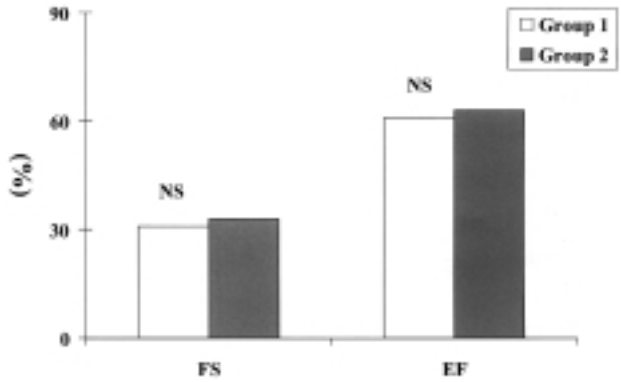

Figure 1. *Ejection fraction (EF) and fractional shortening (FS) in the two study groups. NS = not significant compared with group 2.*

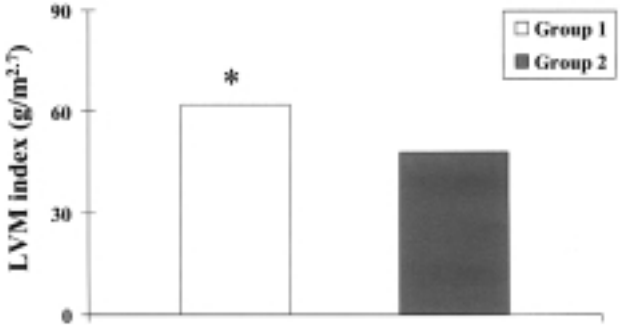

Figure 2. *Left ventricular mass (LVM) index in the two study groups. * p < 0.001 compared with group 2.*

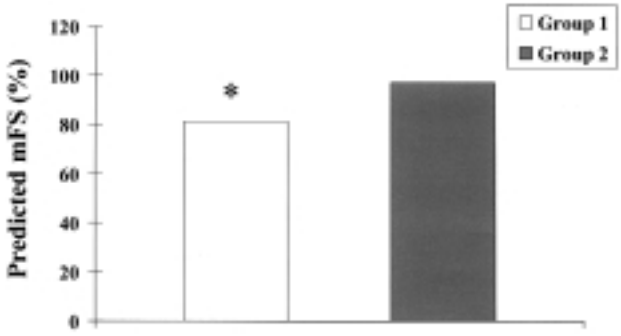

Figure 3. *Predicted midwall fractional shortening (mFS) in the two study groups, as calculated on the basis of the circumferential end-systolic stress. * p < 0.001 compared with group 2.*

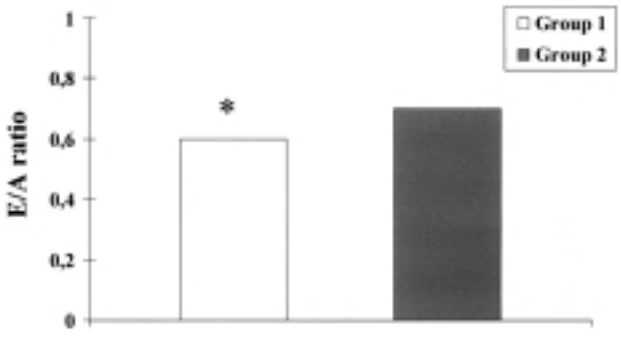

Figure 4. *The ratio between the peak early and atrial filling velocities (E/A ratio) in the two study groups. * p < 0.02 compared with group 2.*

Table III. Total peripheral resistance (TPR) and ratio of stroke volume index to pulse pressure (SVi/PP) in the two study groups.

	Group 1	Group 2
TPR (dynes/s/cm^5)	2067 ± 485*	1755 ± 439
SVi/PP (ml/m^2/mmHg)	0.59 ± 0.08**	0.63 ± 0.13

Values are expressed as means ± SD. * $p < 0.001$ compared with group 2; ** p = NS compared with group 2.

Table IV. Left ventricular geometric patterns in the two study groups.

	Group 1	Group 2
Normal geometry	0	5
Concentric remodeling	0	7
Eccentric hypertrophy	2	9
Concentric hypertrophy	19*	0

* $p < 0.001$ compared with group 2.

Discussion

Diabetes mellitus is associated with accelerated atherosclerosis and an increased prevalence of cardiovascular disease[25]. Although the link between diabetes and cardiovascular disease is not fully understood, loss of the modulatory role of the endothelium could be implicated in the pathogenesis of diabetic vascular complications[25]. In hypertensive subjects, type 2 diabetes mellitus was associated with a higher LVM, more concentric left ventricular geometry and a lower myocardial function independent of age, sex, body size and arterial blood pressure[26]. These cardiovascular abnormalities are known to predict higher rates of cardiovascular events in both asymptomatic and symptomatic subjects[27] and may contribute in part to the high rates of coronary heart disease and heart failure observed among diabetic patients.

Microalbuminuria is defined as abnormally elevated UAE below the level of clinical albuminuria. This represents a UAE rate of 20-200 μg/min, equal to 30-300 mg/24 hours. The prevalence of microalbuminuria in essential hypertension and diabetes is about the same: 25% (range 14-31%) and 20% (range 9-27%) respectively[28]. In both conditions microalbuminuria is associated with an increased risk of fatal and non-fatal cardiovascular disease and all-cause mortality[1-5]. Dysfunction of the vascular endothelium has been suggested as constituting a link between microalbuminuria and atherosclerotic cardiovascular disease in essential hypertension[29,30] and type 2 diabetes mellitus[31].

Concentric LVH, an increased LVM and low myocardial contractility have been considered prognostically significant cardiovascular abnormalities[6,7]. Few data are available concerning the relationship between microalbuminuria and echocardiographic abnormalities of the left ventricular geometry and function in hypertensive, diabetic subjects[8-12]. In patients with stage II-III hypertension and electrocardiographic LVH, an abnormal left ventricular geometry and a high LVM were associated with a high urine albumin/creatinine ratio independent of age, systolic blood pressure, diabetes and race suggesting parallel cardiac and microvascular damage[10]. In a group of 249 untreated hypertensive subjects, the prevalence of normal geometry was found to be significantly higher in normoalbuminuric compared with microalbuminuric subjects[12].

This study was designed to evaluate the relationship between microalbuminuria and the left ventricular geometric shape (normal, concentric remodeling, eccentric hypertrophy and concentric hypertrophy) and left ventricular systolic and diastolic function in patients with mild-to-moderate essential hypertension and type 2 diabetes mellitus. There was no significant difference between group 1 and group 2, for age, sex, body mass index and biochemical control of diabetes mellitus. The blood pressure was also similar in both groups. The results of the present study show that microalbuminuria is associated with an increased LVM index, a higher prevalence of the geometric pattern of concentric LVH, a decreased midwall ventricular performance and a markedly impaired diastolic function. Thus, in hypertensive patients with type 2 diabetes mellitus, microalbuminuria identifies a subset of patients with left ventricular abnormalities associated with the highest cardiovascular risk. This finding may partially account for the worse cardiovascular outcomes associated with the presence of an increased UAE both in hypertensive and diabetic subjects. In patients with arterial hypertension, a reduced SVi/PP, an indirect measure of arterial compliance, has been reported to be associated with a concentric left ventricular geometry (both remodeling and hypertrophy)[17]. A decreased arterial compliance has also been shown to be a predictor of cardiovascular morbid events independent of age and LVM[17]. In our patients, the SVi/PP was not significantly reduced in group 1, the group with the higher prevalence of concentric LVH. This finding could be related to real biological differences between diabetic and non-diabetic hypertensive patients or else merely reflect the small number of subjects enrolled in the present study. However, it must be stressed that in group 2, the geometric pattern of concentric left ventricular remodeling was present in 7/21 patients. Larger trials are needed to evaluate the relationship between a concentric left ventricular geometry and the SVi/PP even in diabetic hypertensive patients and to determine the effective role of microalbuminuria.

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