

# Microalbuminuria as a marker of cardiac damage in essential hypertension

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**Abstract.** – A subclinical elevation in urinary albumin excretion (UAE) microalbuminuria is frequently seen in essential hypertension.

The level of blood pressure appears to be an important factor in the development of microalbuminuria. Moreover there is some evidence to indicate that microalbuminuria may be an early marker of increased cardiovascular risk.

Aim of this study was to evaluate the prevalence of UAE in hypertensives with normal left ventricular mass and to study any association with blood pressure level and with possible modification in left ventricular function.

A group of 112 subjects diagnosed as having stage 1-2 essential hypertension were included in the study. Patients underwent urinary collection to evaluate UAE and to 24/hours arterial blood pressure monitoring. Moreover a complete echocardiography was performed. According with UAE levels patients were divided into three groups: A: UAE 0-15 mg/24 h, B: UAE 16-29 mg/24 h, C: UAE 30-300 mg/24 h.

We found a significant correlation between 24/h SBP, 24/h DBP and UAE. We observed a significant correlation between impaired diastolic function and UAE.

UAE is influenced by BP levels with better correlation with 24/h systolic values. UAE is associated with subclinical decrease of left ventricular function and may be an early marker of cardiac involvement.

*Key Words:*

Microalbuminuria, Blood pressure, Essential hypertension, Cardiac damage.

## Introduction

Microalbuminuria is considered an important predictor of overt renal disease and cardiovascular events in diabetic patients<sup>1</sup>. During the last decade there has been a

growing interest in the study of microalbuminuria in essential hypertension<sup>2-3</sup>. In primary hypertension microalbuminuria is significantly associated with raising blood pressure values and with signs of organ damage<sup>4</sup>. Several studies showed a correlation between microalbuminuria and left ventricular mass in hypertension<sup>5-6</sup>. Increased urinary albumin excretion is often detected in hypertensive patients with fundoscopic changes. While a weak correlation between blood pressure casual measurements and microalbuminuria was found, a stronger association is evident between increased urinary albumin excretion (UAE) and ambulatory blood pressure values<sup>7</sup>. There are no observations demonstrating that impaired diastolic function, an early marker of hypertensive cardiac damage, is related to subclinical albuminuria. Aim of this study was to evaluate the prevalence of microalbuminuria in stage 1-2 hypertensives with normal ventricular mass, and to seek a possible association with changes in left ventricular function.

## Methods

### *Subjects*

This study was performed in 1997-2000 as a part of a screening of a patients afferent to our hypertension center in Catholic University in Rome. 112 individuals Caucasian males diagnosed as having stage 1-2 essential hypertension, according to Joint National Committee, JNC 1997<sup>8</sup>, with normal echo left ventricular mass according with Devereux<sup>9</sup>, were selected from a population of 1800 patients. The mean age was  $44 \pm 12$  yrs. All of the patients no received antihyper-

tensive treatment or medication known to affect blood pressure. Those who had previously received treatment (n = 34) had their antihypertensive medication withdrawn for at least 1 month before the study.

We excluded patients with secondary hypertension, diabetes, impaired glucose tolerance, cardiac disease, renal disease and particularly all had normal renal function with normal creatinine clearance and without macroproteinuria or abnormalities in the urine.

Blood sample was collected from which we have evaluated plasma renin activity by radioimmunoassay (Techno Genetics RIA Kit; sensitivity 0.012 ng/ml, variability coefficient < 4%).

In order to evaluate the presence of microalbuminuria, each subject underwent two separate 24-hour urinary collections and 24-hour blood pressure monitoring, after a week of pharmacological wash-out, and of eating a standard diet with controlled sodium, potassium and protein intake (145-155 mmol/day and 40-55 mmol/day and 70 g/day respectively). Moreover all the patients underwent a complete echocardiographic study.

#### **Urinary albumin excretion**

Urinary albumin excretion for two separate 24-h urine collections was measured using an immunonephelometric assay (Behring Institute Mannheim, Germany). For each patient, the UAE was considered as the mean of value obtained in the two separate 24h urine collections. According to UAE levels patients were divided into three different groups and considered as normoalbuminuric, Group A: UAE 0-15 mg/24h, borderline microalbuminuric, Group B: UAE 16-29 mg/24h, and microalbuminuric, Group C: UAE 30-300 mg/24 h.

#### **Ambulatory blood pressure recording**

The 24-hour ambulatory monitoring (ABPM) was performed using an oscillometric-based device (model 090207; SpaceLabs Medical Inc.) and the Ambulatory Blood Pressure Report Management System delivered by SpaceLabs Medical Inc. Redmond WA. Blood pressure readings were taken every 15 minutes during the daytime and the nighttime period.

Mean systolic 24 hours blood pressure (SBP/24 h) and mean diastolic 24-hours blood pressure (DBP/24 h) were calculated.

#### **Echocardiographic and doppler studies**

A M-mode /2D/Doppler echocardiography was performed in all the patients using a commercially available phased array echocardiography - doppler system (Hewlett Packard model 77020 Sonos 1000) that had 2.5 or 3.5 transducers for M - mode and two-dimensional echocardiography, and 2.0 or 2.5 transducers for Doppler echocardiography.

Two dimensional targeted M-mode echocardiography was performed with the patients in the partial left lateral decubitus position. The M-mode cursor was directed through the center of two dimensional parasternal short-axis image at or just distal to the tips of mitral valve leaflets. Particular care was taken to achieve image planes orthogonal to the left ventricular anatomic long axis and to optimize definition of endocardial and epicardial interfaces. Mitral inflow was sampled by placing the doppler-wave sample volume at the level of the mitral annulus with optimal adjustment of gain and filtration to achieve the acoustically purest frequency and narrowest spectral envelope obtainable.

Left ventricular end-diastolic (EDV) and end-systolic (ESV) volumes were calculated as the cube function of the corresponding cavity dimensions<sup>10</sup>. Ejection fraction was calculated as:  $(EDV-ESV) / EDV \times 100$ .

The peak velocity (E) of early diastolic filling was taken at the maximal excursion of leading edge of the mitral time velocity integral, and the late diastolic filling rate (A) was determined from the maximal excursion of the time velocity integral with atrial contraction. We calculated E/A ratio as measure of the balance between early and late diastolic filling<sup>11</sup>.

As previously described decrease in this ratio have been shown to reflect increasing impairment in left ventricular diastolic function.

#### **Statistical analysis**

Multiple regression analysis was performed between UAE values, clinic and 24-hour blood pressure and indices of diastolic function.

Statistical analysis was performed using SigmaStat software.

P < 0.05 was considered significant.

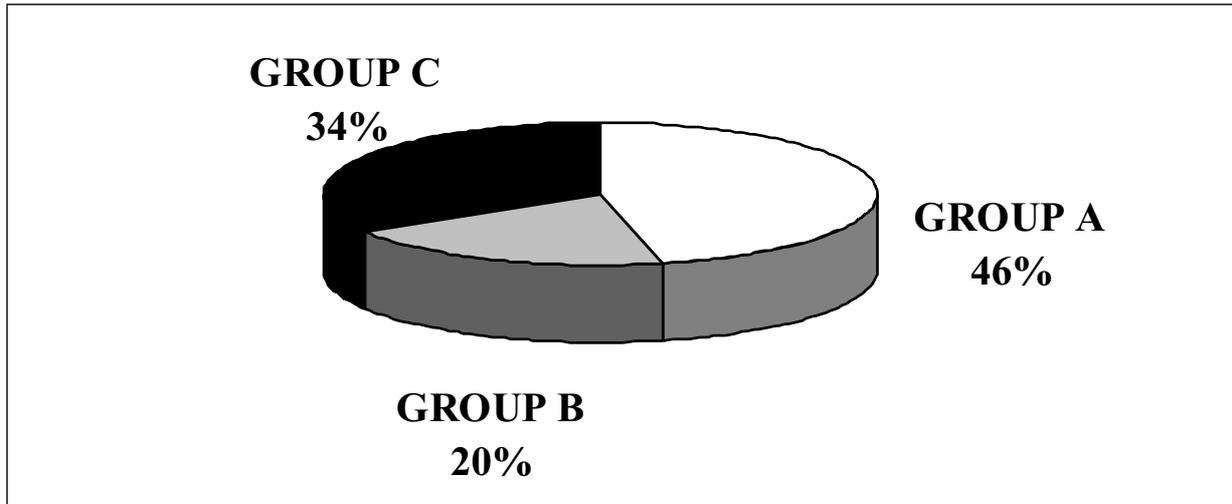


Figure 1. UAE distribution in 112 hypertensive patients.

### Results

According to our results 52 pts (46%) were normoalbuminuric (Group A), 22 pts (20%) borderline (Group B), and 38 (34%) microalbuminuric (Group C) (Figure 1).

The analysis of the three subsets revealed no significant differences in age, body mass index, serum creatinine level and plasma renin activity.

No correlations between microalbuminuria and clinic systolic and diastolic blood pressure were observed (Table I). Significant cor-

relation was found between 24-hour systolic blood pressure and UAE (Group B  $p < 0.01$ , Group C  $p < 0.01$ ) (Figure 2). and between 24-hour diastolic blood pressure and UAE (Group C  $p < 0.01$ ) (Table I).

There were no significant changes in left ventricular systolic function of observed patients, whereas we notice a weak significant correlation between abnormal pattern of left ventricular filling rate, as index of left ventricular diastolic function, and the presence of microproteinuria (Group C  $p < 0.05$ ) (Figure 3) (Table I).

Table I. Clinical characteristics, blood pressure and echocardiography parameters of three groups of essential hypertensives according to urinary albumin excretion (UAE).

	Group A UAE 0-15 mg/24 h Pts. 52 (46%)	Group B UAE 16-29 mg/24 h Pts. 22 (20%)	Group C UAE 30-300 mg/24 h Pts. 38 (34%)
Age (years)	44 ± 10	45 ± 11	43 ± 9
B.M.I (Kg/m <sup>2</sup> )	24.2 ± 1.9	25.2 ± 1.6	24.9 ± 1.8
Plasma Creatinine mg/dl	0.87 ± 0.12	0.84 ± 0.15	0.89 ± 0.21
Creatinine Clearance ml/min	101 ± 1.12	104 ± 1.35	102 ± 1.03
U.A.E. (mg/24 h)	9.02 ± 2.6	19.3 ± 5.0	86.3 ± 40.3
Clinic SBP mmHg	169 ± 17	168 ± 16	170 ± 13
Clinic DBP mmHg	102 ± 9	101 ± 7	100 ± 6
24/h SBP mmHg	144.3 ± 7.7	146.4 ± 6.5	147 ± 8.5
24/h DBP mmHg	94.9 ± 2.6	95.5 ± 3.2	96.2 ± 4.1
P.R.A. ng/ml	0.70 ± 0.07	0.71 ± 0.04	0.69 ± 0.09
L.V.M. index (g/m <sup>2</sup> )	94 ± 12	95 ± 17	96 ± 20
E.F.%	62.4 ± 6.4	62.9 ± 3.3	63.2 ± 3.7
E/A ratio	1.1 ± 0.4	1.08 ± 0.3	0.9 ± 0.2

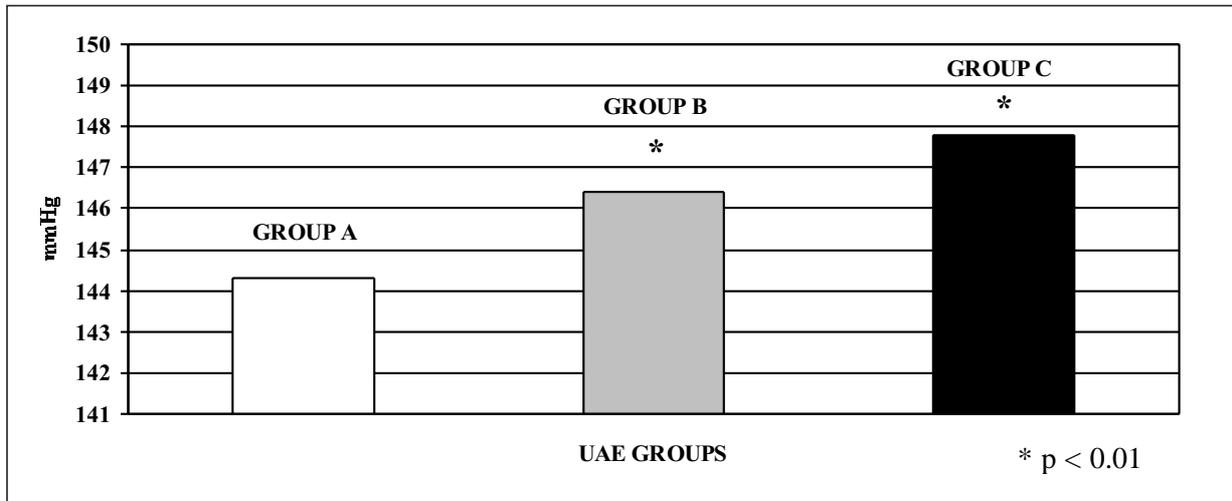


Figure 2. Average 24 hours systolic blood pressure according to UAE groups.

### Discussion

The true prevalence of microalbuminuria in essential hypertension varies in the range 20-40%, according to the selection criteria used<sup>3</sup>.

In our study the high incidence of microalbuminuric patients (34%) is probably due to the greatest number of stage 2 hypertensive patients and to lack of any anti-hypertensive medications.

Actually, pathogenic mechanisms of microproteinuria in essential hypertension are not clearly known and it is likely that more than one factor is operative<sup>12</sup>.

Atrial natriuretic factor may play a role as a mediator of hyperfiltration<sup>13</sup>, and probably there is also a genetic tendency to develop microalbuminuria in association with essential hypertension<sup>14</sup>.

Haemodynamical changes like as the increased intraglomerular pressure could be responsible for hyperfiltration and consequent worsening of proteinuria<sup>15</sup>.

On the other hand is well known that high blood pressure lead to anatomical changes, like as nephroangiosclerosis with altered glomerular selectivity and further increased protein flux<sup>16</sup>.

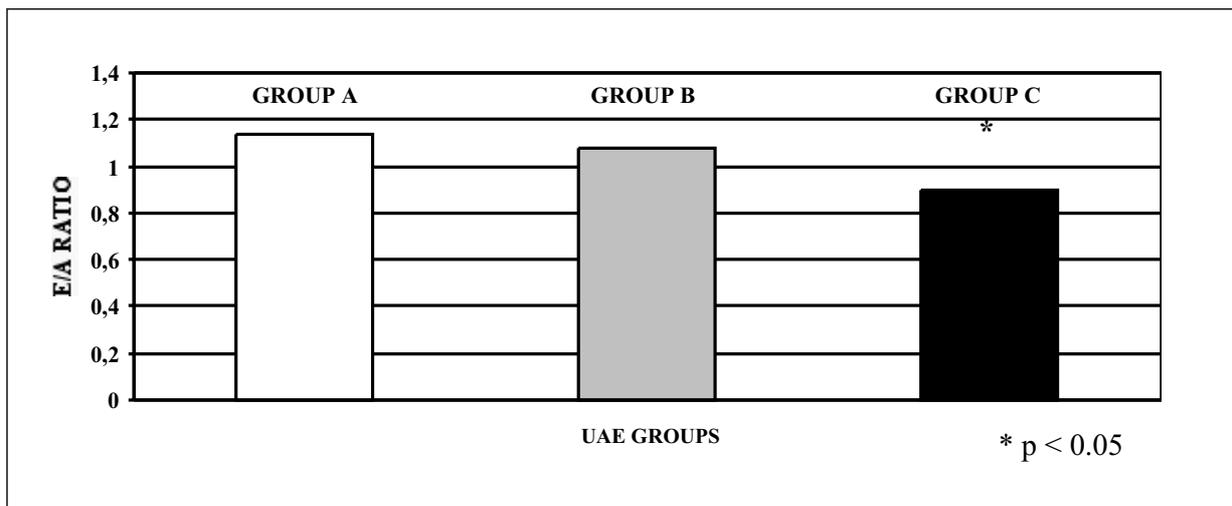


Figure 3. Diastolic function variations according to UAE groups.

We didn't find a significant correlation between UAE and casual blood pressure values, while we noted a strong relation between UAE and 24 hour blood pressure suggesting a pathophysiological link between transcapillary protein leak and arterial blood pressure<sup>17-18</sup>.

This stronger correlation could be explained by the multiplicity and better quality of ambulatory blood pressure measurement.

Recently several studies have reported an increased prevalence of cardiovascular end points in hypertensive patients with dipstick-positive proteinuria, compared with those with normal protein excretion<sup>19-20</sup>.

Yudkin et al<sup>4</sup>, in patients aged more than 40 years, observed that cardiovascular complication such as coronary artery disease or peripheral arterial disease were more frequent in patients with microalbuminuria. Moreover, within a mean follow up period of 3,6 years, death was more frequent in those with microalbuminuria. In patients with treated essential hypertension, Samuelsson et al<sup>21</sup> reported that proteinuria at entry was higher in those patients who developed cardiovascular complication than in those who had no cardiovascular events within a 10-year follow up period.

Our preliminary results in this area suggest that the finding of left ventricular diastolic dysfunction in hypertensives patients without left ventricular hypertrophy and without overt proteinuria may be linked to early glomerular changes.

In conclusion, in middle age essential hypertensives microalbuminuria is a marker for a presence of higher values of blood pressure throughout a 24 hours period; furthermore our results suggest that microalbuminuria is associated with the presence of subclinical decrease of left ventricular diastolic function, and emphasize the role of microalbuminuria as a marker of early cardiac damage in essential hypertension<sup>22</sup>.

Further studies need to be performed in order to explore the pharmacological possibility of prevention and normalization of diastolic dysfunction and microproteinuria in this risk-laden group patients.

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