Original Paper

Urinary Protein Excretion Is Associated with Left Ventricular Hypertrophy in Treatment-Naïve Hypertensive Patients in an African Hospital Setting

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Yaoundé, Cameroon**Key Words**

Proteinuria · Left ventricular hypertrophy · Hypertension

Abstract

Background: Left ventricular hypertrophy (LVH) is an independent predictor of fatal and non-fatal cardiovascular events in hypertensive patients. Current guidelines for the management of hypertension are based on cardiovascular risk stratification. This study evaluated the possibility that an inexpensive, simple random, single-void urinary protein-to-creatinine ratio (UPCR) would be associated to left ventricular (LV) mass in a black African setting, and therefore direct appropriate management of these patients. **Methods:** We measured echocardiographic LV mass and a random spot UPCR in 34 untreated newly diagnosed hypertensive patients attending the cardiology consultation unit at the Yaoundé General Hospital. LV mass was indexed to height (in $m^{2.7}$) to obtain the LV mass index (LVMI). A regression model was used to verify the independent association between UPCR and LVMI. **Results:** The mean age of our patients was 52.65 years, and the mean systolic and diastolic blood pressures were 152.44 and 92.84 mm Hg, respectively. The prevalence of LVH was 41.2%. UPCR was higher in patients with LVH compared to those without ($p = 0.043$). There was a significant correlation between UPCR and LVMI ($r = 0.581$, $p < 0.001$). In the multiple linear regression model, UPCR was associated with LVMI independent of systolic blood pressure ($p < 0.001$). **Conclusion:** Random spot UPCR is associated with an increased LV mass and may be very useful in screening and guiding appropriate management of high-risk untreated hypertensive patients.

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The findings of this study have not been published elsewhere.

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Introduction

Left ventricular hypertrophy (LVH), which is the primary cardiac manifestation of hypertension, is a potent predictor of fatal and non-fatal cardiovascular (CV) events [1]. Proteinuria has recently been identified as a CV risk marker in hypertensive patients [2]. Whether LVH is the link between proteinuria and CV events is still a matter of debate [3, 4]. However, the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC) VII advocates more aggressive treatment of hypertension in patients with proteinuria and LVH [5]. The association between proteinuria and left ventricular (LV) mass has been inconsistent [6–11]. Moreover, studies carried out in Africa have used the semi-quantitative dipstick to measure proteinuria and electrocardiography (ECG) to assess the LV mass [12, 13].

Current guidelines for the management of hypertension are based on CV risk stratification [14], thus making the screening for target organ lesions such as LVH very important. In Cameroon, like in most sub-Saharan African countries, ECG and echocardiography machines are only available in urban areas. It is therefore necessary to validate simple tools which can predict or detect target organ damage such as LVH in hypertensive patients and thus direct appropriate treatment. Therefore, we sought to determine the relationship between urinary protein excretion (UPE) and LV mass in untreated hypertensive Cameroonians with normal renal function.

Methods

Study Design, Setting and Participants

In this cross-sectional analytic study, we consecutively recruited 42 untreated, newly diagnosed (<3 months) stage 1 and 2 hypertensive patients attending the cardiology consultation unit at the Yaoundé General Hospital from August 2011 to February 2012. The subjects were aged between 35 and 74 years. Hypertension was defined as a systolic blood pressure (SBP) ≥ 140 mm Hg or a diastolic blood pressure (DBP) ≥ 90 mm Hg on two separate visits [5].

Eight participants with the following conditions after blood and urine testing were excluded: fasting glycemia >1.26 g/l ($n = 1$), serum creatinine >1.6 mg/dl ($n = 1$), proteinuria $>1+$ ($n = 5$) and lost to follow-up ($n = 1$). Other exclusion criteria were anemia (hemoglobin <11 g/dl for females and <12 g/dl for males), underlying renal and liver disease, secondary forms of hypertension, active infection, pregnancy, congestive heart failure, myocardial infarction, hypertrophic cardiomyopathy and aortic valvular diseases. In the remaining 34 subjects, blood pressure was measured thrice in the sitting position after a 5-min rest with a 3-min interval between readings, using an electronic sphygmomanometer (OMRON® 705IT) of standard cuff size (23×12 cm). The means of the last two readings were used for SBP and DBP [5].

Urinary protein-to-creatinine ratio (UPCR) was measured on a random spot, single-void urine specimen. Laboratory measurement of both variables was carried out using the Ortho-clinical vitros® 250 system analyzer: creatinuria was assessed quantitatively by an enzymatic colorimetric two-point rate method and proteinuria was measured using a colorimetric method.

Echocardiographic Measurements

Two-dimensional guided M-mode echocardiograms were obtained by the same cardiologist using an HITACHI Hi-vision echograph. M-mode tracings were recorded on strip-chart papers at 50 mm/s. To reduce bias, the cardiologist was blinded to the results of urinalysis.

The LV internal diameter in diastole (LVIDD), interventricular septum thickness (IVSTD) and posterior wall thickness in diastole (PWTD) were measured according to the American Society of Echocardiography (ASE) convention. LV mass was calculated using the formula

$$\text{LV mass (g)} = 0.8 (1.04 ([\text{LVIDD} + \text{PWTD} + \text{IVSTD}]^3 - [\text{LVIDD}]^3) + 0.6 \text{ g}$$

as adjusted by Devereux et al. [15]. Indexation was done through division by height (in $\text{m}^{2.7}$) [15, 16] to obtain the LV mass index (LVMI).

Table 1. Characteristics of the study population (n = 34)

Characteristics	Mean ± SD
Age, years	52.65 ± 3.42
SBP, mm Hg	152.44 ± 3.80
DBP, mm Hg	92.84 ± 2.73
UPCR, mg/g	66.44 ± 12.72
LVMI	44.47 ± 3.98
Body mass index	29.90 ± 1.97
LVH, %	41.2
Left atrial dimension, mm	36.27 ± 1.22
SUA, mg/dl	5.95 ± 0.72

Table 2. Factors associated with LVH (mean ± SD)

Characteristics	No LVH (n = 20)	LVH (n = 14)
Age, years	51.55 ± 4.58	54.21 ± 5.19
Sex (M/F)	8/12	8/6
UPCR, mg/g	53.11 ± 9.43	85.50 ± 25.16*
Body mass index	30.04 ± 2.42	29.70 ± 3.42
SBP, mm Hg	147.95 ± 4.59	158.86 ± 5.46**
DBP, mm Hg	91.38 ± 3.68	94.93 ± 3.92
SUA, mg/dl	5.76 ± 0.92	6.37 ± 1.10
Left atrial dimension, mm	35.46 ± 1.67	37.44 ± 1.63
* p < 0.05; ** p < 0.01.		

LVH was defined as an LVMI >47 g/m^{2.7} in women and an LVMI >50 g/m^{2.7} in men [16]. All echocardiographic variables were measured thrice and the mean value was calculated.

Ethical approval for the study was obtained from the national ethics committee, and all subjects gave their written informed consent.

Statistical Analysis

Data were recorded and analyzed using the SPSS 20.0 Inc. 2011 Chicago USA software, and were reported as mean ± standard deviation (SD) for continuous variables and as percentages for categorical variables. Comparisons among groups were done using the Mann-Whitney U test. The correlation between UPCR and LVMI was verified by Pearson's correlation coefficient. Multiple linear regression analysis was performed for continuous variables, with LVMI as the dependent variable. UPCR, serum uric acid (SUA) and SBP were taken as covariates. A value of p < 0.05 was considered statistically significant.

Results

Patient Characteristics

Sixteen males and 18 females were studied, with a sex (M/F) ratio of 0.9. The mean UPCR was 66.44 mg/g, and the prevalence of LVH was 41.2% (table 1).

Factors Associated with LVH

UPCR, SBP and SUA were higher in patients with LVH compared to those without (p = 0.043, p = 0.01 and p = 0.138, respectively; table 2).

Table 3. Multiple linear regression

Variable	Beta ± SD	Standardized beta
Constant	−40.83 ± 7.00	
UPCR (mg/g)	0.18 ± 0.14	0.583 [†]
SUA (mg/dl)	0.54 ± 0.25	0.098
SBP (mm Hg)	0.46 ± 0.04	0.438**

** p < 0.01; [†] p < 0.001.
Dependent variable: LVMI; R² = 0.534, n = 34.

Correlation between UPCR and LVMI

There was a significant correlation between UPCR and LVMI ($r = 0.581$, $p < 0.001$). This correlation remained significant even after controlling for age, BMI, SBP, DBP and SUA (partial $r = 0.620$, $p < 0.001$). When considering only the male patients, the correlation between UPCR and LVMI was stronger ($r = 0.629$, $p = 0.009$) than when only the female patients were considered ($r = 0.554$, $p = 0.017$).

Multiple Linear Regression

We entered UPCR, SUA and SBP into a multiple linear regression model to identify factors independently linked to LV mass. UPCR was independently associated to LVMI ($r = 0.583$, $p < 0.001$), as was SBP ($r = 0.438$, $p = 0.001$), with more than 50% of the variation in LVMI being explained by this model (table 3). The equation derived here is:

$$\text{LVMI} = 0.18 \text{ UPCR} + 0.46 \text{ SBP} - 40.83.$$

Discussion

To the best of our knowledge, studies that have demonstrated a relationship between proteinuria and LV mass using spot UPCR and echocardiography in black African hypertensive patients are scarce. We found that UPE, evaluated by a simple, inexpensive, single-void UPCR, is associated with LV mass in treatment-naïve hypertensive patients.

UPCR was higher in our patients with LVH. Our findings are similar to the results of previous studies [3, 10, 11]. For example, in Italy, Dell'omo et al. [3] described microalbuminuria and SBP to be higher in untreated hypertensive men with LVH compared to those without. Saitoh et al. [10] in Japan and Post et al. [11] in the USA reported proteinuria, albumin-creatinine ratio and SBP to be significantly higher in untreated hypertensive patients with LVH. We did not find any effect of age, sex and BMI on LV mass contrary to other studies [3, 10, 17]. Isa et al. [17] found height and BMI but not age and weight to be associated with LVH in newly diagnosed hypertensive Nigerians. Saitoh et al. [10] on their part found age but not sex and BMI to be associated with LVH, and Dell'omo et al. [3] showed age, height and BMI but not weight to be associated with LVH.

This disparity with our results could be explained by the fact that our patients were older and heavier compared to the patients analyzed in the other studies. However, similar to our findings, Post et al. [11] did not find any link between LVH and age and BMI in black American hypertensive men.

Correlation between Proteinuria and LVMI

Proteinuria correlated positively with LV mass even after correcting for the effect of SBP (partial $r = 0.620$, $p < 0.001$). This result is similar to other studies from Europe, Asia, the United States and Africa [3, 4, 10–12]. Our study is, however, at variance with the Italian study by Palatini et al. [6] who found no correlation between urinary albumin excretion and LV mass in stage 1 untreated hypertensive white subjects. The lack of association in their study could be explained by several factors: their study included only patients with grade 1 hypertension. Moreover, their patients were much younger and had much lower mean blood pressure readings. They used 24-hour UPE, which is unreliable if not validated by measuring 24-hour urinary creatinine concomitantly.

In our study, the correlation between UPCR and LVMI was stronger in men than in women. This is in agreement with previous studies [9, 18] that reported LVH to be more frequently observed in males. Our findings of a correlation in women differs from those of Redon et al. [7] who found a correlation between microalbuminuria and LVH in men, but not in women, with mild hypertension in Spain. However, our female patients were older and thus at a greater cardiovascular risk compared to theirs.

In this study, UPCR and SBP were the only factors independently associated with LVMI. Although the identified predictors of LVMI account for more than 50% of the variation in LVMI, it remains unexplained why UPE should predict LVMI. Whether the two parameters are a consequence of the same pathophysiological mechanism or one leads to the other is not yet clearly elucidated. However, the pressure-independent association between both variables as found in this study suggests there might be some factors other than blood pressure that drives proteinuria and elevates LV mass, perhaps via transforming growth factor-beta 1 (TGF- β 1) [19]. Upregulation of TGF- β 1 has been shown to be linked with CV and renal alterations in hypertensive patients [19]. Alternatively, increased LV mass might mediate UPE, maybe via natriuretic peptides [20]. Overall, these factors should certainly act concomitantly, with no single factor being the sole cause. The above hypothesis is speculative as a cross-sectional analysis cannot assume causality.

In conclusion, despite the small number of patients in this study, random spot UPCR was associated with increased LV mass in our setting and may be very useful as a routine screening tool and therefore guide appropriate management of high-risk untreated hypertensive patients.

Study Limitations

The fact that only one urine sample was used to quantify UPE is a limitation of our study. Using the average UPCR from three urine samples would have been more reproducible. Moreover, we did not perform ambulatory blood pressure measurement in this study; hence, the possibility of certain patients having white-coat hypertension could not be completely excluded.

Disclosure Statement

The authors have no conflict of interest to declare.

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