

Association between insulin resistance and left ventricular hypertrophy in sub-saharan hypertensive black patients with preserved ejection fraction: A case control study

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Abstract

Background:

Conflicting information exists regarding the association between insulin resistance (IR) and left ventricular hypertrophy (LVH).

We described the associations between parameters of obesity, fasting insulinemia, HOMAIR with LVH in black patients with essential hypertension.

Materials and Methods:

A case-control study was conducted at the Centre Médical de Kinshasa (CMK), the Democratic Republic of the Congo, between January and December 2019. Cases and controls were hypertensive patients with and without LVH, respectively. The relationship between obesity indices, physical inactivity, parameters of glucose metabolism and lipid disorders and LVH were assessed using linear and logistic regression analyses in simple and univariate exploratory analysis, respectively. When differences were observed between LVH and the independent variables, the effect of potential confounders was studied by adjustment in multiple linear regression and in conditional logistic regression in multivariate analysis. The coefficients of determinations (R^2), the adjusted ORs and their 95% CI were calculated to determine the association between the LVH and the independent variables

Results:

Eighty-eight cases (52 men) were compared to 132 controls (81 men). Nineteen percent of left ventricular mass (LVM) variation (19%) was predicted by age, 31.3% by the duration of hypertension, 44.4% by BMI, 42.5% by WC, 20% by glycemia, 44.8% by insulinemia and 43.7% by HOMAIR. In multiple linear regression analysis, duration of hypertension, Body Mass Index (BMI), insulinemia and HOMAIR explained 68.3% of the variability in the increase in LVM. In the logistic model obesity multiplied the risk of LVH by 3 (aOR: 2.8, 95% CI (1.06-7.4), $p = 0.038$), IR by 8 (aOR: 8.4, 95% CI (3.7-15.7), $p < 0.001$).

Conclusion:

Obesity and IR appear to be the main predictors of LVH. The comprehensive management of cardiovascular risk factors should be emphasized with particular attention to obesity and insulin resistance. A prospective black sub-saharan population based study with serial imaging remain essential to better understand subclinical LV deterioration over time and to confirm the role of insulin resistance in black sub-saharan hypertensives.

Background

Hypertension is a major contributor to global mortality and incapacity [1]. In 2018, the World Health Organization (WHO) listed hypertension as one of the two main global risk factors of death and disability

for all ages, alongside smoking [2]. The number of people with systolic blood pressure (SBP) of 140 mm Hg or higher was estimated to have increased from 442 million in 1990 to 874 million in 2015, when this SBP level was responsible for 14% of total deaths and 143 million disability-associated life-years [3]

Hypertension is a major challenge, especially for sub-Saharan African countries where its prevalence, which was 30.0% according to a pooled data from 33 surveys published between 2000 and 2013[4], is experiencing dramatic growth. Hypertension in sub-Saharan Africa affects younger people, is poorly controlled and often leads to target organ damage at an earlier age and with more severe cardiovascular complications [2, 5].

Hypertensive patients with insulin resistance (IR) are at increased risk of cardiovascular events compared to hypertensive patients without IR [6]. Similarly, the presence of target organ damage (TOD), including LVH has a negative prognostic value in hypertensive patients [7, 8]. The European Guidelines on the management of hypertension recommend that hypertensive patients with a target organ, including LVH, be considered at a higher risk of cardiovascular events [9].

The high prevalence of IR in the hypertensive population was first highlighted in 1966 by Welborn et al. from a sample of 19 non-diabetic hypertensives [10]. Two decades later, this finding was confirmed from the results of other research studies with more participants. Ferrannini in 1987 was the first researcher to state hypertension was a state of insulin resistance [11].

In 1997, the existence of a link between IR and hypertension was definitively confirmed by the European Group for the Study of Insulin Resistance (EGIR) which demonstrated that regardless of age, gender or body mass index, the level of blood pressure is positively correlated with insulin resistance and insulinemia [12].

Gerald M. Reaven, fondly remembered as the father of IR because of his contribution to understanding the central role of IR in cardiovascular disease, developed the insulin suppression test; the first quantitative method to assess insulin-mediated glucose uptake in humans [13]. Using this test, he established the importance of IR in human disease, and especially in type 2 diabetes [14, 15]. In a non-diabetic patient population, he illustrated the role of insulin resistance in the development of, essential hypertension [16], the osmotic balance [17], stimulation of the sympathetic nervous system [18], hypercoagulability [19], decreased clearance of urinary uric acid with resultant hyperuricemia [20], increased postprandial lipemia and accumulation of residual lipoproteins [19] and occurrence of lipid abnormalities such as hypertriglyceridemia [21], low HDL-c [22], and a decrease in the diameter of LDL-c particles [23].

IR also plays a key role in the development of left ventricular remodeling (LVR) [24, 25]. LVH, one of the phenotypes of LVR linked to hypertension, has a poor prognostic value [7, 26, 27]. Both mechanical and hemodynamic factors as well as the trophic role of insulin in hypertension favor the occurrence of LVH [28]. Genetic factors as well as environmental factors also play their role [29–31] in the development of

LVH and its resultant consequences. The link between echographic LVH and cardiovascular risk has been largely documented in the literature [26, 32–37].

There exists, however, conflicting information regarding the association between insulin resistance and left ventricular hypertrophy in hypertensive patients. We sought to assess such relationship among a hypertensive sub-saharan black population

Material And Methods

Study design and setting

This is a case-control study conducted at the Centre Médical de Kinshasa (CMK) between January and December 2019. The CMK is a reference clinic, working on international standards and norms, with a cardiology unit named « pôle de cardiologie » with highly qualified and regularly retrained personnel, that provides cardiovascular explorations such as doppler echocardiography, coronary scanner and cardiopulmonary exercise testing. A cardiovascular rehabilitation unit, the only one in central Africa, is also operational there.

Patient selection

Consecutive asymptomatic patients with probably essential hypertension aged 20 years or more attending the outpatient clinic at the CMK Pôle de cardiologie between January and December 2019 were screened for clinical or laboratory evidence of secondary hypertension, renal or hepatic disease. They were invited by written informed consent to participate in the present study. Those with high blood pressure unrelated heart disease were not enrolled. Each participant who met the criteria for echocardiographic diagnosis of LVH was matched for gender and age with two hypertensive patients without left ventricular hypertrophy.

A total of 267 participants were screened, 106 with left ventricular hypertrophy and 161 without left ventricular hypertrophy. Of these, 47 were excluded due to dilated cardiomyopathy in 20 participants (8 with LVH and 12 without LVH), ischemic cardiopathy in 14 participants (5 with LVH and 9 without LVH), significant valvulopathy in 5 participants (2 with LVH and 3 without LVH), pericarditis in 5 participants without LVH, and hypertrophic cardiomyopathy in 3 participants with LVH. The final analysis therefore included 220 participants 88 (40%) with and 132 (60%) without left ventricular hypertrophy.

Study procedures

Anamnestic data

Demographic data (age, sex), lifestyle habits (heavy alcohol consumption, current smoking, sedentary behavior), medical history including cardiovascular risk factors (age at diagnosis of high blood pressure, history of diabetes mellitus, dyslipidemia, hyperuricemia, menopause) and previous cardiovascular events (stroke, ischemic heart disease, heart failure, Chronic Kidney Disease, cardiovascular surgery), and

current medication use for chronic disease (antihypertensive treatment, anti-diabetic treatment and other treatments including statins, antiplatelet agents, hypouricemics, oral contraception, hormone replacement therapy) were collected during an in-person directed interview using ad hoc questionnaire.

Anthropometric data

Anthropometric parameters were measured by a final year medical student who had also undergone a study-training session held by the authors. The student measured both primary variables (weight, height, waist size, hip measurement) according to WHO recommendations and a derived variable (body mass index (BMI) as :

- Body weight was measured to the nearest 100 g using a validated electronic balance the participants upright in light clothing without shoes ;
- The height was obtained to the nearest centimeter using a measuring rod, , with the participant standing, barefoot and bareheaded;
- The waist circumference to the nearest 0.1 cm, was measured using a measuring tape applied directly to the skin along a horizontal line passing through the umbilicus.
- The body surface area (BSA) was calculated using the DuBois formula [38] as follows: $BSA = \text{Height}^{0.725} \times \text{Weight}^{0.425} \times 0.007184$.
- BMI was obtained by dividing the weight (Kg) by the square of height (m^2)

Blood pressure

BP was measured non-invasively by 24 hour-ambulatory blood pressure monitoring (ABPM) using a TONOPORT V (GE Health care, Freiburg, GERMANY) type recorder. During this recording, the participant was asked to maintain his usual way of life.

Echocardiographic data

Left ventricular measurements were taken according to the 2015 American Society of Echocardiography and the European Association of Cardiovascular Imaging updated guidelines for cardiac chamber quantification [39] using a Vivid T8 (GE) type ultrasound system equipped with 3.5 MHz transducers. Two-dimensional guided M-mode echocardiography was performed on a parasternal long-axis view. Interventricular septum (IVS) thickness in diastole (IVSd), left ventricular posterior wall (PW) thickness in diastole (LVPWd), and left ventricular end-diastolic diameter (LVEDd), all measured in mm were assessed at a level just below the mitral valve leaflets at end-diastole. Simultaneous ECG was done to correlate left ventricular measurements with the cardiac cycle. Diastolic wall thickness was measured at the onset of the QRS wave. LVM was calculated based on the American Society of Echocardiography simplified cubed equation linear method using the following equation : $LVM \text{ (grams)} = 0.8 \times 1.04 \times [(LVEDd + IVSd + LVPWd)^3 - (LVEDd)^3] + 0.6 \text{ g}$. LVM was indexed to BSA and to height as mass/BSA and mass/height^{2.7}. The relative wall thickness (RWT) of the left ventricle (LV) was calculated as follows: $(2 \times LVPWd) /$

LVEDd. In accordance with international recommendations [40], the parameters of LV diastolic function were measured by recording transmitral flow velocity using conventional doppler echocardiography. With pulsed wave Doppler (PW), transmitral flow velocity was recorded from the apical transducer position with the sample volume situated between the mitral leaflet tips. E (Peak E-wave velocity) and A (Peak A-wave velocity) and Deceleration time of early filling (DT), were recorded in apical four-chamber with color flow imaging for optimal alignment of PW Doppler with blood flow. PW Doppler sample volume (1–3 mm axial size) was placed between mitral leaflet tips, using low wall filter setting (100–200 MHz) and low signal gain, so that the optimal spectral waveforms should not display spikes and. Both E, A and DT were measured as the averages of five consecutive cardiac cycles. The E/A ratio was calculated. Tissue Doppler echocardiography, which measures the velocity of the regional cardiac wall, was performed by activating the tissue doppler echocardiographic function, as for two dimensional and M-mode echocardiography. Mitral annular velocities were recorded from the apical window. Sample volumes were located at the lateral site of the mitral annulus. Peak early diastolic mitral annular velocity (E', cm/s) was measured over five cardiac cycles and the mean calculated. The ratio E/e' was used as a parameter of left atrial pressure, which is elevated with progression of LV diastolic dysfunction. These parameters, obtained by tissue doppler echocardiography, were also used as parameters of LV diastolic function.

Laboratory measurements

For all analyses, a blood sample was taken from the cubital vein between 7 a.m. and 9 a.m. following an overnight fast that started at 10pm the previous day. All analyses were carried out at the CMK laboratory. Blood was collected in a dry tube for the assessment of serum uric acid level, total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides,. Serum was used for the analysis. The assay was performed by the standard colorimetric method. Readings were measured using the colorimetric spectrophotometer brand HELIOS Epsilon (Milwaukee, USA). The blood glucose test was performed on plasma oxalate by colorimetric method using standard reagents Biolabo.

The insulin dose was assessed on EDTA plasma by ELISA. Optical density reading was done on a string read from the firm HUMAREADER HUMAN (Germany).

Assessments of glycated hemoglobin were performed on plasma treated with EDTA by the electrophoretic method using HYRYS HYDRASIS from the firm SEBIA (France).

Serum creatinine was measured by the method of simple colorimetric Jaffe. Readings were assessed by colorimetric spectrophotometer (Spectrum 2100 brand, South Africa).

Operational Definitions

Lifestyle data

Sedentary was defined as sitting for more than 7 hours a day [41].

Cigarette smoking was defined as regular smoking for at least 30 days preceding the interview date regardless of the number of cigarettes smoked [42].

Excessive alcohol consumption was defined as drinking more than 2 glasses of beer or its equivalent every day for at least a year [43].

Anthropometric parameters

Overweight was defined as a BMI between 25 and 29.9 Kg/m² of body surface area [44].

Obesity was defined as a BMI equal to or greater than 30 Kg/m² of body surface area [44]. Abdominal obesity was defined as a waist circumference of more than > 102 cm and > 88 cm for men and women respectively [44].

Bioclinical data

Poor control of arterial hypertension was defined as an average systolic blood pressure greater than 130 mmHg and/or average diastolic BP greater than 80 mmHg on 24-hour ambulatory blood pressure monitoring [45].

Paraclinical data

Diabetes mellitus was defined as a fasting blood glucose ≥ 10 mmol/l with a glycosylated hemoglobin level greater than 7% [46].

Hyperinsulinemia was defined as fasting insulin > 90 pmol/L.

Insulin resistance was defined as a HOMA-IR of ≥ 2.5 [47].

Dyslipidemia was defined as a HDL-cholesterol level of <1.03 mmol/L for males or <1.04 mmol/L for females, and/or an LDL-cholesterol level ≥ 3.38 mmol/L, and/or a total cholesterol level ≥ 5.17 mmol/L, and/or a triglyceride level ≥ 1.69 mmol/L [48].

The atherogenicity index (AI) was calculated by the total cholesterol to HDL-C ratio. The atherogenicity index was considered high when this ratio was greater than 5 [49].

Hyperuricemia was defined as a uric acid of > 420 mmol/L [50].

Echographic data

Normal LVM was defined as ≤ 115 g/m² or ≤ 48 g/m^{2.7} for males and ≤ 95 g/m² or ≤ 44 g/m^{2.7} for females ; LVH was defined as LVM exceeding these values in males and female patients respectively. Four LV geometric patterns were defined as follows [51, 52] : normal geometry (normal LVM and RWT ≤ 0.42), concentric remodeling (normal LVM and RWT > 0.42), eccentric hypertrophy (LVH and RWT ≤ 0.42) and concentric hypertrophy (LVH and RWT > 0.42).

Three patterns of diastolic dysfunction (DD) were defined as follows [53, 54]: abnormal relaxation (grade I of DD: E/A ratio <1 and prolonged deceleration time), pseudonormal relaxation (grade II: E/A ratio >1 and intermediate values of deceleration time), and restrictive patterns (reversible and irreversible, grade III–IV respectively; E/A ratio > 2 and shortened deceleration time).

The dilation of the left atrium was defined as an area of the OG of > 20 cm² of body surface [39].

Statistical Analyses

Data were presented in the form of absolute (n) and relative (%) frequencies for categorical variables and as averages (\pm standard deviation) for quantitative variables. Paired comparisons between the cases and controls were made using Pearson square Chi-square test or the Fisher Exact test as appropriate for categorical variables and using Student's t-test for continuous variables.

Linear regression was used to determine factors predictive of LVM variations. The following variables were entered in the univariate analysis : parameters of obesity (WC, HC, BMI), parameters of glucose metabolism (Fasting glucose, HBA1c, fasting insulinemia, and HOMAIR), parameters of lipid metabolism (TC, HDL-c, LDL-c, Triglycerides), parameters of renal function (creatinine and uricemia), parameters of phosphocalcic metabolism (calcium, ionized calcium, phosphore). When significant associations were observed between LVM and the independent variables, the effect of potential confounders was studied by adjustment in multiple linear regression.

Simple logistic regression was used to determine factors predictive of LVH. The following variables were entered in the univariate analysis : Medical & social history (Known HTN, ND HTN, Cigaret smoking, excessive alcohol consumption, Menopausal), sedentary, uncontrolled HTN, dislipidemia, High AI, diabetes mellitus, hyperinsulinemia, hyperuricemia and insulin resistance. When associations were observed between LVH and the independent variables, the effect of potential confounders was studied by adjustment in conditional logistic regression (multivariate analysis).

The significance threshold retained was then $p < 0.05$. Statistical analyzes were performed using XLStat 2020 and SPSS (Statistic Package for Social Sciences) for Windows version 24 software

Ethical considerations

This research was conducted in strict compliance with the recommendations of the Helsinki Declaration III. Approval to conduct the study was obtained from the ethics committee of the University of Kinshasa School of Public health. Each participant provided written informed consent for to participate in the study. All respondents were debriefed on the results of the study.

Results

Characteristics of cases and controls

Compared to patients without LVH, patients with LVH had significantly higher ($p \leq 0.05$) BMI, WC, HC and average 24-hour systolic blood pressure. There was a significantly higher proportion of sedentary persons among patients with LVH (Table 1, at the end of the document text file) with significantly higher relative wall thickness, E-wave deceleration time, triglyceridemia, AI, glycemia, HbA1c, insulinemia, HOMAIR, IR and hyperuricemia (Table 2, at the end of the document text file). Conversely, HDL-c level and E/A ratio were significantly lower in patients with LVH. Cases and controls did not differ significantly with respect to the matching variables (Tables 1 and 2)

Table 1

General characteristics of black hypertensive patients at CMK hospital stratified by the presence or absence of left ventricular hypertrophy, January to December 2019

Characteristics	LVH+ n = 88	LVH- n = 132	p value
Demographic characteristics			
Age (years)	52.6 ± 10.6	50.3 ± 9.5	0.096
Gender			0.421
Male	52(59.1)	81(61.4)	
Female	36(40.9)	51(38.6)	
Medical & social history			
Known HTN	60(68.2)	76(57.6)	0.074
ND HTN	28(31.8)	56(42.4)	0.149
Cigaret smoking	87(98.9)	132(100.0)	0.400
Alcohol intake	85(96.6)	128(97.0)	0.582
Menopausal	14(38.9)	27(52.9)	0.141
Anthropomorphic measurements			
BMI (Kg/m ²)	32.6 ± 5.1	28.7 ± 4.3	< 0.001
WC (Cm)	109.3 ± 13.2	99.3 ± 10.0	< 0.001
HC (Cm)	112.7 ± 9.9	103.8 ± 9.2	< 0.001
Overweight	22(25.0)	64(48.5)	< 0.001
Total obesity	65(73.9)	47(35.6)	< 0.001
abdominal Obesity	34(61.4)	43(32.6)	< 0.001
Lifestyle history			
Sedentarity	71(80.7)	52(39.4)	< 0.001
Treatment history & examination findings			
Uncontrolled HTN	20(22,7)	18(13,6)	0,060
SBP (mmHg)	138,8 ± 7,8	133,4 ± 7,2	0,048

HTN = hypertension ; ND HTN = newly-diagnosed hypertension ; WC = Waist circumference ; BMI = Body mass index ; HC = hip circumference ; HR = Heart rate ; SBP = Systolic Blood Pressure ; DBP = Diastolic Blood Pressure.

Characteristics	LVH+ n = 88	LVH- n = 132	p value
DBP (mmHg)	82,5 ± 8,7	79,9 ± 9,1	0,087
HR (bpm)	62.1 ± 13.5	70.0 ± 13.4	0.199
HTN = hypertension ; ND HTN = newly-diagnosed hypertension ; WC = Waist circumference ; BMI = Body mass index ; HC = hip circumference ; HR = Heart rate ; SBP = Systolic Blood Pressure ; DBP = Diastolic Blood Pressure.			

Table 2

Echographic and biologic characteristics of black hypertensive patients at CMK hospital stratified by the presence or absence of left ventricular hypertrophy, January to December 2019

Variables	LVH+ n = 88	LVH- n = 132	P
Echocardiographic measurements			
LVED (mm)	46.5 ± 4.4	42.9 ± 4,1	< 0.001
IVS (mm)	12.7 ± 1.1	10.7 ± 1.5	< 0.001
PWT (mm)	12.5 ± 0.8	10.7 ± 1.5	< 0.001
SWT (mm)	25.2 ± 1.6	21.3 ± 2.9	< 0.001
LVEF (%)	63.8 ± 5.4	65.1 ± 4.9	0.062
LVM (g)	222.2 ± 38.4	156.8 ± 34.8	< 0.001
LVMlh (g/m ^{2,7})	54.7 ± 8.4	37.6 ± 6.6	< 0.001
LVMlbs (g/m ²)	108.5 ± 15.7	79.7 ± 15.0	< 0.001
RWT	0.55 ± 0.1	0.50 ± 0.1	0.001
E (Cm/s)	0.85 ± 0.6	1.08 ± 0.6	0.029
E/A ratio	0.71 ± 0.2	0.99 ± 0.2	0.034
DT (ms)	215.8 ± 39.4	172.8 ± 37.7	< 0.001
LAA (Cm ²)	17.3 ± 3.5	14.7 ± 2.7	0.001
SPAP (mmHg)	26.9 ± 3.1	26.0 ± 2.7	0.019
Biologic parameters			
TC (mmol/L)	5.5 ± 1.0	5.4 ± 1.0	0.305
LDLc (mmol/L)	3.8 ± 1.1	3.6 ± 1.1	0.126
Triglycerides (mmol/L)	1.25 ± 0.6	1.05 ± 0.6	0.027
HDLc (mmol/L)	1.1 ± 0.3	1.3 ± 0.4	0.003

LVED = Left ventricular end-diastolic diameter ;IVS = interventricular septal thickness; PWT = Posterior wall thickness; SWT = Sum of wall thickness; LVEF = Left ventricular ejection fraction; LVM = left ventricular mass; LVMlh = left ventricular mass indexed to height^{2,7}; LVMbs = left ventricula mass indexed to body surface area ; RWT = relative wall thickness; E = mitral E wave; E/A = ratio of peak early and late diastolic flow velocities ; DT = deceleration time; LAA = left atrium area; SPAP = systolic pulmonary arterial pressure; TC = total cholesterol; LDLc = low density lipoprotein; LDL-c = low density lipoprotein ; HDLc = high density lopoprotein; AI = atherogenicity index ; HbA1C = glycated haemoglobin; T2DM = vtype 2 diabetes melitus; HOMAIR = Homeostatic Model Assessment for Insulin Resistance; IR = insulin resistance.

Variables	LVH+ n = 88	LVH- n = 132	P
Glycemia (mmol/L)	6.3 ± 2.1	5.4 ± 1.6	< 0.001
HbA1C (%)	6.3 ± 1.6	5.9 ± 1.1	0.016
Insulinemia (mmol/L)	122.8 ± 43.1	72.7 ± 25.8	< 0.001
AI	5.2 ± 1.6	4.6 ± 1.8	0.008
HOMAIR	2.36 ± 0.8	1.41 ± 0.6	0.014
Uric acid (mmol/L)	388.3 ± 98.4	352.9 ± 89.5	0.007
Creatinine (mol/L)	84.7 ± 22.6	84.3 ± 16.2	0.854
Calcium (mmol/L)	2.30 ± 0.2	2.3 ± 0.2	0.105
Ionized calcium (mmol/L)	1.20 ± 0.11	1.22 ± 0.2	0.331
Phosphore (mmol/L)	1.06 ± 0.2	1.09 ± 0.3	0.333
Dyslipidemia	75(85.2)	98(74.2)	0.036
High AI	45(51.1)	48(36.4)	0.021
T2DM	20(22.7)	23(17.4)	0.212
Hyperinsulinisme	8(9.1)	11(8.3)	0.514
IR	42(47.7)	2(1.5)	< 0.001
Hyperuricemia	29(33.0)	22(16.7)	0.004
<p>LVED = Left ventricular end-diastolic diameter ;IVS = interventricular septal thickness; PWT = Posterior wall thickness; SWT = Sum of wall thickness; LVEF = Left ventricular ejection fraction; LVM = left ventricular mass; LVMIh = left ventricular mass indexed to height^{2,7}; LVMbs = left ventricula mass indexed to body surface area ; RWT = relative wall thickness; E = mitral E wave; E/A = ratio of peak early and late diastolic flow velocities ; DT = deceleration time; LAA = left atrium area; SPAP = systolic pulmonary arterial pressure; TC = total cholesterol; LDLc = low density lipoprotein; LDL-c = low density lipoprotein ; HDLc = high density lopoprotein; AI = atherogenicity index ; HbA1C = glycated haemoglobin; T2DM = vtype 2 diabetes melitus; HOMAIR = Homeostatic Model Assessment for Insulin Resistance; IR = insulin resistance.</p>			

Determinants Of Left Ventricular Mass

In Simple linear regression, as illustrated in Table 3 (at the end of the document text file), there was a significant and positive relationship between LVM and age, duration of hypertension, BMI, WC, Glycemia, insulinemia and HOMAIR.

Table 3

Simple linear regression showing determinants of left ventricular mass (LVM) in 220 black patients with hypertension at CMK hospital, January to December 2019

Variables	r	β	p
Age in years	0.190	0.22	0.005
HTN duration in years	0.313	0.57	< 0.001
BMI (kg/m ²)	0.444	0.99	< 0.001
WC in cm	0.425	0.39	< 0.001
Glycemia (mmol/L)	0.201	1.19	0.003
Insuline (mmol/L)	0.448	0.12	< 0.001
HOMAIR	0.437	5.80	< 0.001
HTN = hypertension ; BMI = body mass index ; WC = waist circumference ; HOMAIR = Homeostatic Model Assessment for Insulin Resistance.			

Nineteen of LVM (19%) was predicted by age, 31.3% by the duration of hypertension, 44.4% by BMI, 42.5% by WC, 20% by glycemia, 44.8% by insulinemia and 43.7% by HOMAIR (Fig. 1A and Fig. 1B, at the end of the document text file).

In multiple linear regression, patients predicted LVM is equal to 0.56 (hypertention duration) + 0.67 (BMI) + 0.08 (Insulin levels) + 0.27 (HOMAIR).

The duration of hypertension, BMI, insulin and HOMAIR predicted 68.3% of the patients LVM (Table 4, at the end of the document text file).

Table 4

Multiple linear regression showing determinants of left ventricular mass (LVM) in 220 black patients with hypertension at CMK hospital, January to December 2019

Variables	LVM lh		
	β	SE	p
(Constant)	6.84	8.72	0.435
Age (years)	0.14	0.104	0.183
HTN duration	0.56	0.14	< 0.001
BMI (Kg/m ²)	0.67	0.23	0.004
WC (cm)	0.001	0.09	0.994
Glycemia (mmol/L)	0.06	0.46	0.903
Insuline (mmolL)	0.08	0.04	0.034
HOMAIR	0.27	1.81	0.021
R² = 0.683, overall p = 0.001			
HTN = hypertension ; BMI = body mass index ; WC = waist circumference ; HOMAIR = Homeostatic Model Assessment for Insulin Resistance			
Y = 0.56 X₁ + 0.67 X₂ + 0.08 X₃ + 0.27 X₄ + 6.84			
With Y = LVMIh ; X ₁ = HTN duration ; X ₂ = BMI ; X ₃ = Insuline and X ₄ = HOMAIR			

Determinants Of LVH

In univariate analysis, global obesity, abdominal obesity, sedentary, atherogenicity index, hyperuricemia, IR were significant predictors of LVH.

After multivariate adjustment, only total obesity and IR persisted as independent determinants of LVH. Obesity increased the risk of LVH three-fold (OR 2.8, 95% CI 1.06–7.40, p = 0.038) and IR increased it eight-fold (OR 8.4, 95% CI 3.7-15.7, p < 0.001) (Table 5, at the end of the document text file).

Table 5
 Logistic regression analysis showing determinants of LVH among 220 black hypertensives from CMK hospital, January to December 2019

Variables	Univariate analysis		Multivariate analysis	
	p	OR (95% CI)	p	aOR (95% CI)
Total Obesity				
No		1		1
Yes	0.000	5.1 (2.8–9.3)	0.038	2.8 (1.06–7.4)
Abdominal Obesity				
No		1		1
Yes	0.000	3.3 (1.9–5.8)	0.275	1.9 (0.6–6.3)
Sedentary				
No		1		1
Yes	0.000	6.4 (3.4–12.1)	0.123	1.9 (0.8–4.5)
High AI				
No		1		1
Yes	0.031	1.8 (1.06–3.2)	0.579	1.3 (0.6–2.9)
Hyperuricemia				
No		1		1
Yes	0.006	2.5 (1.3–4.7)	0.145	2.1 (0.8–5.4)
IR				
No		1		1
Yes	0.000	9.3 (3.8–25.5)	0.000	8.4 (3.7–15.7)
AI = atherogenic index ; IR = insulin resistance				

Discussion

In this study, four factors which explained the bulk of the increase in LVM, (68% of it), were established. These were the duration of hypertension, BMI, insulinemia and HOMAIR. However, only insulin resistance and total obesity emerged as the independent determinants of LVH. We also observed that patients with LVH were more often sedentary, had higher obesity parameters, and more abnormalities in carbohydrate and lipid metabolism compared to patients without LVH. In addition, they also had significantly higher uric acid levels and atherogenicity index, as well as a lower E/A ratio and a longer mitral E wave deceleration time.

Conflicting information exists regarding the involvement of insulin resistance in the development of LVH. Costa et al (1995) did not find any relationship between IR (with insulin measured during glucose tolerance test) and LVM in a small sample of 35 non-obese hypertensive Brazilians [55]. Galvan et al (2000), after adjusting for blood pressure and body mass index (BMI), also found that IR (With insulin sensitivity measured by the insulin clamp technique) was not an independent determinant of LVH in a small sample of 50 Italian nondiabetic subjects[56]. These results are opposite to those found in the present study. The difference in profile of the study population, the sample size and the methods used to diagnose insulin resistance could explain this difference. In our study, HOMAIR was used to diagnose IR. This method has the advantage of a simpler implementation than the hyperinsulinemic euglycemic glucose clamp which is the gold standard method for the determination of insulin sensitivity[57]. HOMAIR has been the subject of numerous validations which have shown a satisfactory correlation with the gold standard method ($r = 0.72$ to 0.82 depending on the studies) with no notable difference according to sex, age, weight, diabetic or hypertensive status [58]. Our results concur however, with data obtained in populations other than black sub-Saharan africans. Sasson et al. (1993) demonstrated a significant association between IR and LVH which was independent of blood pressure level and BMI [59]. Lind et al (1995) also found such an association and demonstrated that hyperinsulinemia was responsible for 43% variation in the left ventricular mass [60]. In a recent prospective population study, Cauwenberghs et al (2018) found that basal insulin resistance / hyperinsulinemia and its worsening during follow-up predicted left ventricular remodelling [61].

The pathophysiological arguments that can support this association are as follows: It is now recognized that LVH is mediated not only by mechanical stress from pressure overload, but also by various neurohormonal substances and metabolic abnormalities that independently exert trophic effects on cardiomyocytes and the extracellular matrix [28, 62]. This is substantiated by the high prevalence of LVH in normotensive type 2 diabetics [63, 64]. Insulin resistance, by multiple and complex mechanisms, has been shown to promote hypertrophy of cardiomyocytes and matrix deposition, regardless of its effect on systemic blood pressure [65].

The transmembrane transport and mitochondrial oxidation of glucose are reduced due to a down regulation of the expression of glucose transporter-4 in response to insulin resistance [66]. Therefore energy metabolism then depends on the oxidation of fatty acids for more than 90% of its needs leading to an increase in plasma levels of fatty acids. The predominant oxidation of fatty acids and reduction in the energy supply from glucose and pyruvates, lead to the formation of end products of non-enzymatic glycation (AGE Advanced Glycation End products), an excess of glycolytic compounds and increased synthesis of ceramide, all of which promote apoptosis. AGE bind to specific receptors, activate a Protein Kinase C whose overexpression stimulates the growth factor of median connective tissue, synthesis of collagen and interstitial fibrosis. Additionally, insulin resistance and an increase in the mitochondrial influx of fatty acids predispose to an overproduction of superoxide ions involved in the genesis of hypertrophy, fibrosis, and left ventricular dysfunction. Furthermore, IR generates reactive oxygen species which are involved in the genesis of LVH and fibrosis [67].

The association between the duration of hypertension and LVH has been highlighted in several previous studies. In the Democratic Republic of Congo, Lepira et al have shown that the duration of hypertension predicted the occurrence of electrical LVH [68]. This association accounts for the influence of the duration of myocardial exposure to chronic barometric overload represented by hypertension.

In the present study we found that hypertensive subjects with LVH had a lower E/A ratio and a longer deceleration time that indicate abnormality in relaxation [52, 54]. The diastolic dysfunction is a consequence of both IR [69, 70] and left ventricular hypertrophy, and underlying myocardial fibrosis [54, 71–74]. In addition, a mitochondrial dysfunction which accompanies insulin resistance state is thought to play a role in both left ventricular hypertrophy and diastolic dysfunction [75]. However, this is still a subject of debate. On the one hand, a certain degree of diastolic dysfunction exists in hypertensive patients long before they develop LVH [76], on the other hand, regression of LVH after antihypertensive treatment does not necessarily lead to the normalization of diastolic function [77]. Nevertheless, some studies found that normalization of the left ventricular mass leads to normalization of diastolic function [78].

Our hypertensive patients with LVH were often sedentary, with higher obesity parameters and more abnormalities in carbohydrate and lipid metabolism. Controversies exist regarding the relationship between sedentary lifestyle and left ventricular mass. Gibbs et al. (2014) observed relationships between sedentary lifestyle and obesity, and higher LVM in Caucasian adults, but not in black populations [79]. In a previous analysis we assessed this association in a population of sub-Saharan blacks and Maghrebis of white skin population, and found that sedentary lifestyle was associated with a lower left ventricular mass among white Maghrebian population but not in sub-Saharan blacks [80]. Likewise, in the present study of sub-Saharan blacks, although a larger proportion of patients with LVH were sedentary, no significant association was found between sedentary lifestyle and left ventricular mass. It is possible that a potential qualitative difference exists in the cardiovascular consequences of sedentary.

The association between obesity and left ventricular hypertrophy appears to be a common finding. However, there exists a divergence as regards the concentric or eccentric geometry pattern of this hypertrophy in obese hypertensive patients. Some authors have found a predominance of eccentric geometry [81] whereas others, including ourselves, have found a predominance of concentric geometry [82, 83]. Concentric geometry is more often attributed to pressure overload whereas eccentric geometry is attributed to volume overload [84]. When hypertension, a condition of pressure overload and obesity, which is a condition of volume overload, coexist, the resulting hypertrophic phenotype would be determined by the predominance of one over the other. This may explain the diverging results in the literature based on the study population. Furthermore, an initially concentric geometry can evolve over time towards an eccentric geometry.

The sedentary-obesity couple is essentially characterized by a chronic caloric excess. Experimental research has shown that prolonged and uninterrupted sitting sessions lead to an increase in blood levels of insulin and glucose. Obesity is linked to insulin resistance via complex mechanisms e.g., inflammation

due to the accumulation of lipids, the inhibitory effect of fatty acid oxidation on glucose oxidation, and the secretion of adipocytokines which have all been associated with the development of local and systemic insulin resistance [85]. Therefore, insulin resistance would bridge the gap between between sedentary lifestyle / obesity and left ventricular hypertrophy.

Significantly higher uric acid levels were found in hypertensives with LVH when compared to hypertensives without LVH. This is in agreement with previous studies which have shown that hypertensives with LVH have higher uric acid levels [86–90]. A large prospective population-based study in Italy found that hyperuricemia is a predictor of LVH [91]. A causal link was suggested since normalization of uric acid levels using hypouricemic treatment led to a reduction in the left ventricular mass [92, 93]. Several mechanisms could be used to explain the increase in LV mass due to hyperuricemia, these include the systemic inflammatory response, oxidative stress [94, 95], activity of the renin system angiotensin aldosterone [96], endothelial dysfunction [97] and the expression of endothelin-1 in cardiac fibroblasts that promotes interstitial fibrosis in myocardium [98]. Furthermore, some indirect effects of hyperuricemia, such as increased BP, parallel decrease in glomerular filtration rate (GFR), deterioration in adhesion and platelet aggregation, and increased aortic stiffness, could further contribute to the development of LVH [99].

Finally, this study found a higher atherogenicity index in hypertensives with left ventricular hypertrophy compared to hypertensives without left ventricular hypertrophy, which suggests an increase risk of coronary events. This aligns to previous study which established that LVH is a risk factor for coronary heart disease mortality [100].

Study Limitations

Our study has to be interpreted within the context of its potential limitations and strengths. First, echocardiographic measurements are prone to measurement errors as a result of signal noise, acoustic artefacts, and angle dependency. We however had an experienced cardiologist with post-graduated training in cardiac imaging perform all echocardiograms. Secondly, the case-control design we used meant we could not really assess cause-effect relationships. Third, the in-hospital and monocentric design makes it risky to extrapolate the results to all sub-Saharan black hypertensives. our study covers a gap, to the extent that, to the best of our knowledge. This is, to the best of our knowledge, the first description of the association between IR and LVH in sub-saharan hypertensive black patients.

Conclusions

Our results showed direct and significant associations between the duration of hypertension, the body mass index, insulinemia and HOMAIR and left ventricular mass. Insulin resistance and obesity emerged as independent determinants of left ventricular hypertrophy in hypertension. We recommend concomitant management of associated cardiovascular risk factors when managing patients with hypertension with particular attention paid to insulin resistance and obesity. A prospective black sub-saharan population

based study with serial imaging remain essential to better understand subclinical LV deterioration over time and to confirm the role of insulin resistance in black sub-saharan hypertensives.

Abbreviations

ABPM

ambulatory blood pressure monitoring

AI

atherogenicity index

BMI

Body mass index

BSA

Body Surface Area

DBP

Diastolic Blood Pressure.

DT

deceleration time

E/A

ratio of peak early and late diastolic flow velocities

E

mitral E wave

HbA1C

glycated haemoglobin

HC

hip circumference

HDLc

high density lipoprotein

HOMAIR

Homeostatic Model Assessment for Insulin Resistance

HR

Heart rate

HTN

hypertension

IR

insulin resistance.

IVS

interventricular septal thickness

LAA

left atrium area

LDLc

low density lipoprotein
LDL-c
low density lipoprotein
LVED
Left ventricular end-diastolic diameter
LVEF
Left ventricular ejection fraction
LVM
left ventricular mass
LVMbs
left ventricula mass indexed to body surface area
LVMlh
left ventricular mass indexed to hight ^{2,7}
ND HTN
newly-diagnosed hypertension
PWT
Posterior wall thickness
RWT
relative wall thickness
SBP
Systolic Blood Pressure
SPAP
systolic pulmonary arterial pressure
SWT
Sum of wall thickness
T2DM
type 2 diabetes melitus
TC
total cholesterol
WC
Waist circumference

Declarations

Ethics approval and consent to participate: Ethics approval and consent to participate the study was approved by the research ethics committee at Public health school of Kinshasa. All participants provided informed consent.

Consent for publication: Not applicable.

Availability of data and materials: Because consent given by study participants did not include data sharing with third parties, anonymized data can be made available to investigators for analysis on reasonable request to the corresponding author.

Competing interests

The authors had no conflicts of interest to declare in relation to this article.

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Authors' contributions

Design and concept of study: Kianu Phanzu Bernard

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Figures

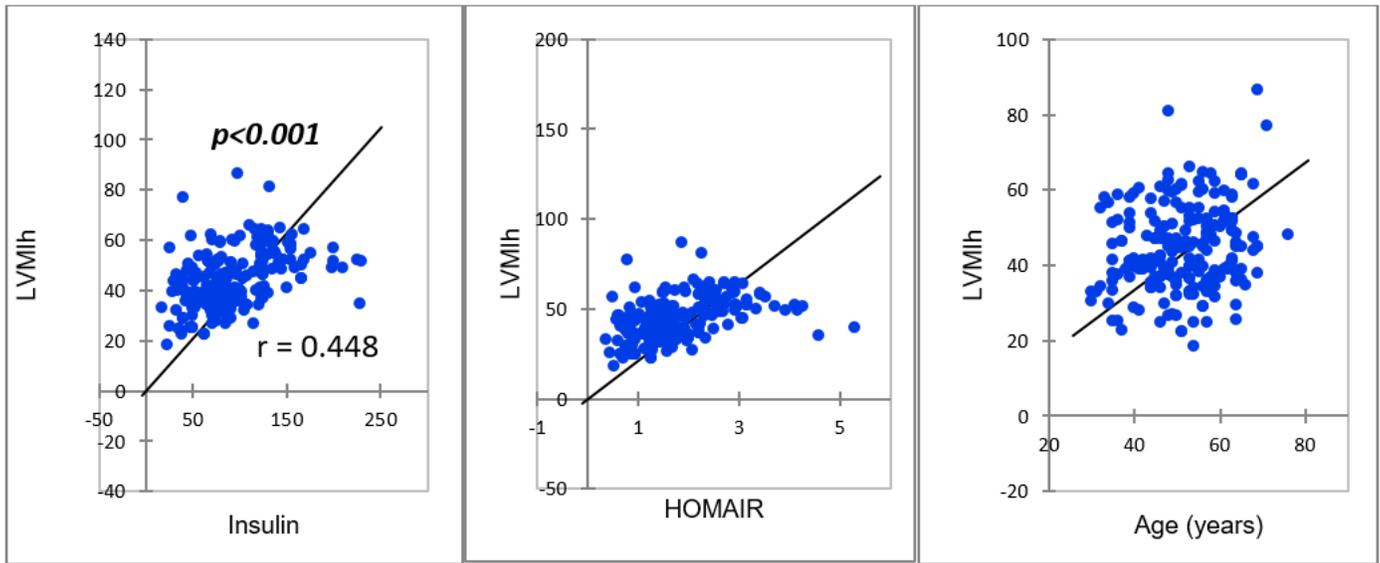


Figure 1A. Explanatory factors for the increase in LVM in simple linear regression.

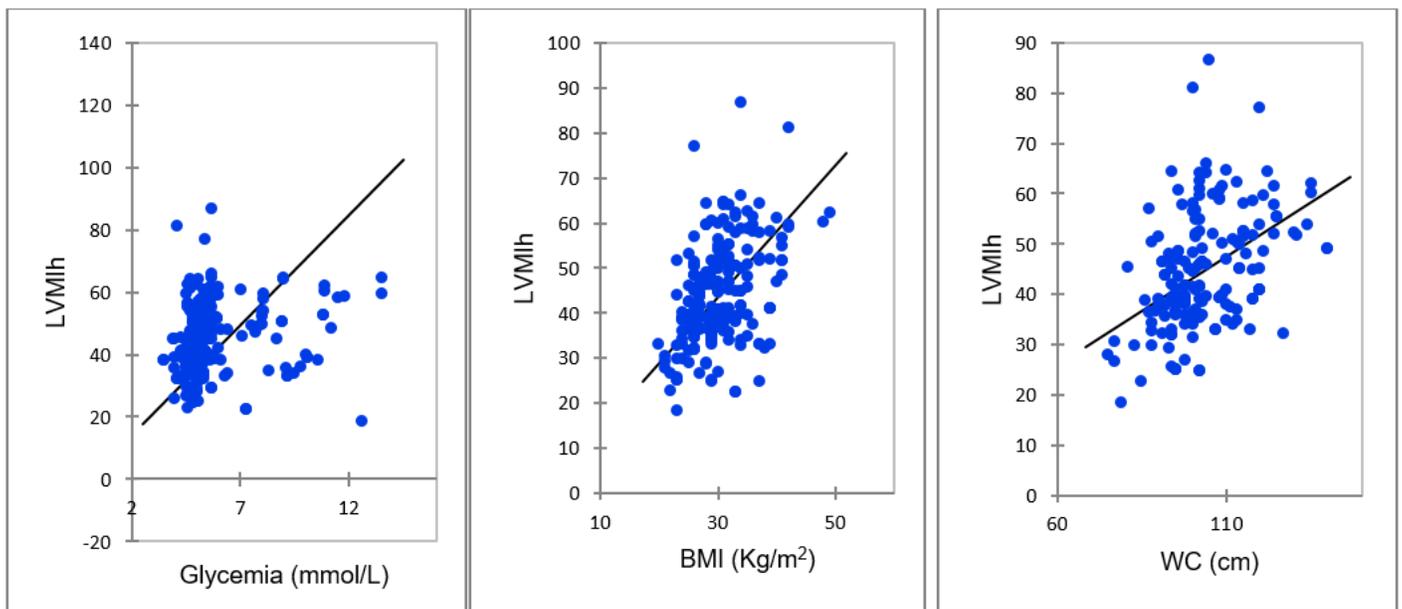


Figure 1B. Explanatory factors for the increase in LVM in simple linear regression

Figure 1

A. Explanatory factors for the increase in LVM in simple linear regression. B. Explanatory factors for the increase in LVM in simple linear regression