Association between insulin resistance and left ventricular hypertrophy in asymptomatic Black sub-Saharan African hypertensive patients: A case-control study

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Abstract

Background: Conflating information exists regarding the association between insulin resistance (IR) and left ventricular hypertrophy (LVH). Here, we described the associations between parameters of obesity, fasting insulinaemia, homeostasis model assessment of insulin resistance (HOMA-IR) and LVH in Black patients with essential hypertension. 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 relationships 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 analyses, 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 conditional logistic regression in multivariate analysis. The coefficients of determination (R^2), the adjusted ORs and their 95% CIs were calculated to determine the association between LVH and the independent variables.

Results: Eighty-eight cases (52 men) were compared to 132 controls (81 men). Nineteen percent (19%) of left ventricular mass (LVM) variation was predicted by age; 31.3%, by the duration of hypertension; 44.4%, by body mass index (BMI); 42.5%, by waist circumference (WC); 20%, by glycaemia; 44.8%, by insulinaemia; and 43.7%, by HOMA-IR. In multiple linear regression analysis, duration of hypertension, BMI, insulinaemia and HOMA-IR 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) and IR by 8 (aOR: 8.4, 95% CI (3.7-15.7), p <0.001). Conclusions: Obesity and IR appear to be the main predictors of LVH in Black sub-Saharan African hypertensive patients. The comprehensive management of cardiovascular risk factors should be emphasized with particular attention to obesity and IR. A prospective Black sub-Saharan population-based study with serial imaging remains essential to better understand subclinical LV deterioration over time and to confirm the role of IR in Black sub-Saharan individuals with hypertension.

Background

Hypertensive patients with insulin resistance (IR) are at increased risk of cardiovascular events compared to hypertensive patients without IR [1]. Similarly, the presence of hypertension-mediated organ damage (HMOD), including left ventricular hypertrophy (LVH), has well-established adverse prognostic significance [2].

IR is classically defined as an impaired biological response to insulin stimulation of target tissues [3]. Gerald M. Reaven’s pioneering works suggest that there is a pathophysiological link between IR and almost all cardiovascular risk factors. Indeed, 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 for assessing insulin-mediated glucose uptake in humans [4]. Using this test, he established the importance of IR in human disease, especially in type 2 diabetes [5, 6]. In a non-diabetic patient population, he illustrated the role of IR in the development of essential
hypertension [7], the osmotic balance [8], stimulation of the sympathetic nervous system [9], hypercoagulability [10], decreased clearance of urinary uric acid with resultant hyperuricaemia [11], increased postprandial lipaemia and accumulation of residual lipoproteins [12], the occurrence of lipid abnormalities such as hypertriglyceridaemia [13], low HDL-c [14], and a decrease in the diameter of LDL-c particles [15].

LVH is a HMOD and full-fledged cardiovascular risk factor, and it is associated with poor prognostic value [16-19]. Despite extensive studies, the pathophysiology of cardiac hypertrophy remains incompletely understood [20]. Both genetic [21, 22] and environmental factors [23, 24] are involved in this pathophysiology. IR is one of the environmental factors that are cited as being involved in the occurrence of LVH [24-26].

However, conflicting information exists regarding the association between IR and LVH in hypertensive patients. We sought to assess this relationship among a hypertensive sub-Saharan Black population.

**Methods**

**Study design and setting**

This was 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 » (« cardiology centre ») with highly qualified and regularly retrained personnel, that provides cardiovascular explorations such as Doppler echocardiography, a coronary scanner and cardiopulmonary exercise testing. A cardiovascular rehabilitation unit, the only one in central Africa, is also operational there.

**Patient selection**

Consecutive asymptomatic hypertensive patients aged 20 years or older attending the outpatient clinic of the CMK Pôle de cardiologie between January and December 2019 were screened for clinical or laboratory evidence of secondary hypertension and renal or hepatic disease. Patients in whom a cause of secondary hypertension was found, as well as patients in whom renal or hepatic disease was diagnosed, were not included in this study. All other patients were invited by written informed consent forms to participate in this study and underwent cardiac Doppler ultrasound.

Participants with heart disease unrelated to high blood pressure were excluded. Each participant who met echocardiographic diagnostic criteria for LVH was matched for sex and age with two hypertensive patients without LVH.

A total of 267 participants were initially selected to participate in the study, 106 with LVH and 161 without LVH. Of these, 47 were excluded due to dilated cardiomyopathy in 20 participants (8 with LVH and 12 without LVH), ischaemic 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 LVH. The flow chart in Figure 1 summarizes the selection of cases and controls.

**Study procedures**

**Anamnestic data**

Demographic data (age and sex), lifestyle habits (heavy alcohol consumption, current smoking, and sedentary behavior), medical history including cardiovascular risk factors (age at diagnosis of high blood pressure, history of diabetes mellitus, dyslipidaemia, hyperuricaemia, and menopause) and previous cardiovascular events (stroke, ischaemic heart disease, heart failure, chronic kidney disease, and cardiovascular surgery), and current medication use for chronic disease (antihypertensive treatment, antidiabetic treatment and other treatments including statins, antiplatelet agents, hypouricaemics, oral contraception, and hormone replacement therapy) were collected during an in-person directed interview using an 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, and hip measurement) according to WHO recommendations and a derived variable (body mass index (BMI)) as follows:

- Body weight was measured to the nearest 100 g using a validated electronic balance with the participants upright in light clothing without shoes;
- Height was obtained to the nearest centimeter using a measuring rod, with the participant standing, barefoot and bareheaded;
- Waist circumference was measured to the nearest 0.1 cm 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 [27] as follows: \( \text{BSA (m}^2) = \frac{\text{height (cm)}}{725} \times \text{weight (kg)}^{0.425} \times 0.00718413 \); and
- BMI was obtained by dividing the weight (kg) by the square of height (m²)

**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 participants were asked to maintain their 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 [28] using a Vivid T8 (GE Health care, Freiburg, GERMANY) 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 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 performed 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: \(\frac{2 \times \text{LVPWd}}{\text{LVEDd}}\). In accordance with international recommendations [29], the parameters of LV diastolic function were measured by recording transmitial flow velocity using conventional Doppler echocardiography. With pulsed wave Doppler (PW), transmitial 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 view with color flow imaging for optimal alignment of PW Doppler with blood flow. The 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. Moreover, E, A and DT were measured as the averages of five consecutive cardiac cycles, and 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 carried out 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 (\(e',\text{ cm/s}\)) was measured over five cardiac cycles, and the mean was calculated. The calculated \(E/e'\) ratio was used as a parameter of left ventricular filling pressure (LVFP).

**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 « BIOLABO » test (France).

The insulin concentration was assessed with EDTA plasma by ELISA. The optical density reading was performed on a string read from the firm HUMAREADER HUMAN (Germany).
Assessments of glycated haemoglobin were performed with plasma treated with EDTA by the electrophoretic method using HYRYS HYDRASIS from the firm SEBIA (France).

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

**Operational Definitions**

**Lifestyle data**

Sedentary was defined as sitting for more than 7 hours a day [30]. Cigarette smoking was defined as regular smoking for at least 30 days preceding the interview date regardless of the number of cigarettes smoked [31].

Excessive alcohol consumption was defined as drinking more than 2 glasses of beer or its equivalent every day for at least a year [32].

**Anthropometric parameters**

Overweight was defined as a BMI between 25 and 29.9 kg/m\(^2\) of BSA [33].

Obesity was defined as a BMI equal to or greater than 30 kg/m\(^2\) of BSA [33]. Abdominal obesity was defined as a waist circumference of more than 102 cm and > 88 cm for men and women, respectively [33].

**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 ABPM [34].

**Paraclinical data**

Diabetes mellitus was defined as a fasting blood glucose ≥ 10 mmol/l with a glycated haemoglobin level greater than 7% [35].

Hyperinsulinaemia was been defined as fasting insulin > 90 mmol/L.

IR was defined as a HOMA-IR of ≥ 2.5 [36].

Dyslipidaemia was defined as an HDL-cholesterol level of <1.03 mmol/L for males or <1.04 mmol/L for females, an LDL-cholesterol level ≥ 3.38 mmol/L, a total cholesterol level ≥ 5.17 mmol/L, and/or a triglyceride level ≥ 1.69 mmol/L [37].

The atherogenicity index (AI) was calculated by the total cholesterol-to-HDL-c ratio. The AI was considered high when this ratio was greater than 5 [38].
Hyperuricaemia was defined as a uric acid level > 420 mmol/L [39].

**Echographic data**

LVH was defined as LVM > 115 g/m$^2$ or > 48 g/m$^{2.7}$ for males when indexed to BSA or to height, respectively, and > 95 g/m$^2$ or > 44 g/m$^{2.7}$ for females when indexed to BSA or to height, respectively.

Four LV geometric patterns were defined as follows [40]: normal geometry (normal LVM and RWT $\leq$ 0.42), concentric remodelling (normal LVM and RWT > 0.42), eccentric hypertrophy (LVH and RWT $\leq$ 0.42) and concentric hypertrophy (LVH and RWT > 0.42).

Three patterns of diastolic dysfunction (DD) were defined as follows [41, 42]: 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).

Normal LVFP was defined by an E/e’ ratio <8 [43]. Elevated LVFP was defined by an E/e’ lateral > 12 [43]

The dilation of the left atrium (LA) was defined as an area of the LA of > 20 cm$^2$ of body surface [44].

**Statistical Analyses**

Data were presented in the form of absolute (n) and relative (%) frequencies for categorical variables and as averages (± standard deviation) for quantitative variables. Paired comparisons between the cases and controls were made using Pearson square Chi-square test or the Fisher’s 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 insulinaemia, and HOMA-IR), parameters of lipid metabolism (TC, HDL-c, LDL-c, and triglycerides), parameters of renal function (creatinine and uricaemia), parameters of phosphocalcic metabolism (calcium, ionized calcium, and phosphorus). 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 and social history (duration of HTN, cigarette smoking, excessive alcohol consumption, and menopause), sedentary lifestyle, uncontrolled HTN, dyslipidaemia, High AI, diabetes mellitus, hyperinsulinaemia, hyperuricaemia and IR. 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 analyses 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

As illustrated in Table 1, cases and controls did not differ significantly with respect to the matching variables. The proportion of newly diagnosed hypertensive patients was similar between cases and controls. The mean duration of hypertension in known hypertensive participants was significantly longer in participants with LVH than in those without LVH. Compared to patients without LVH, patients with LVH had significantly higher (p ≤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) with significantly higher RWT, E-wave deceleration time, E/e' ratio (although within normal limits), triglyceridaemia, AI, glycaemia, HbA1c,insulinaemia, HOMA-IR, IR and hyperuricaemia (Table 2). Conversely, the HDL-c level and E/A ratio were significantly lower in patients with LVH.

Table 1 General characteristics of Black hypertensive patients stratified by the presence or absence of LVH
| Characteristics                           | LVH+ n=88 | LVH- n=132 | p value |
|------------------------------------------|-----------|-----------|---------|
| **Demographic characteristics**          |           |           |         |
| Age (years)                              | 52.6±10.6 | 50.3±9.5  | 0.096   |
| Sex                                      | 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   |
| Duration of HTN                          | 5.0 (1.0-8.0) | 4.0 (2.0-6.0) | 0.014 |
| ND HTN                                   | 28(31.8)  | 56(42.4)  | 0.149   |
| Cigarette smoking                        | 87(98.9)  | 132(100.0) | 0.400  |
| Alcohol intake                           | 85(96.6)  | 128(97.0) | 0.582   |
| Menopause                                | 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   |
| 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 biological characteristics of Black hypertensives stratified by the presence or absence of LVH
| Variables                | LVH+       | LVH-       | P     |
|--------------------------|------------|------------|-------|
|                           | n=88       | n=132      |       |
| **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|
| LVMth (g/m<sup>2.7</sup>)| 54.7±8.4   | 37.6±6.6   | <0.001|
| LVMlbsa (g/m<sup>2</sup>)| 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|
| E/e’ ratio               | 7.4 (4.9 – 7.5) | 5.5 (4.5-7.0) | <0.001|
| LAA (cm<sup>2</sup>)     | 17.3±3.5   | 14.7±2.7   | 0.001 |
| SPAP (mmHg)              | 26.9±3.1   | 26.0±2.7   | 0.019 |
| **Biological parameters**|            |            |       |
| TC (mmol/L)              | 5.5±1.0    | 5.4±1.0    | 0.305 |
| LDL-c (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 |
| HDL-c (mmol/L)           | 1.1±0.3    | 1.3±0.4    | 0.003 |
| Glycaemia (mmol/L)       | 6.3±2.1    | 5.4±1.6    | <0.001|
| HbA1C (%)                | 6.3±1.6    | 5.9±1.1    | 0.016 |
| Insulinaemia (mmol/L)    | 122.8±43.1 | 72.7±25.8  | <0.001|
| AI                       | 5.2±1.6    | 4.6±1.8    | 0.008 |
| HOMA-IR                  | 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 (mmol/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
Phosphorus (mmol/L) | 1.06±0.2 | 1.09±0.3 | 0.333
Dyslipidaemia | 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
Hyperinsulinaemia | 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

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; LVM\textsubscript{h}= left ventricular mass indexed to height\textsuperscript{2.7}; LVM\textsubscript{bsa}= left ventricular 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; LDL\textsubscript{c}=low density lipoprotein; LDL-c= low density lipoprotein ; HDL\textsubscript{c}= high density lopoprotein; AI= atherogenicity index ; HbA1C= glycated haemoglobin; T2DM=type 2 diabetes melitus; HOMAIR= Homeostatic Model Assessment for Insulin Resistance; IR= insulin resistance.

**Determinants of Left Ventricular mass**

In the simple linear regression, as illustrated in Table 3, there was a significant and positive relationship between LVM and age, duration of hypertension, BMI, WC, Glycaemia, insulinaemia, and HOMA-IR.

**Table 3** Simple linear regression showing determinants of left ventricular mass in Black patients with essential hypertension
| 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|
| Glycaemia (mmol/L)         | 0.201 | 1.19 | 0.003 |
| Insuline (mmol/L)          | 0.448 | 0.12 | <0.001|
| HOMA-IR                    | 0.437 | 5.80 | <0.001|

HTN=hypertension ; BMI=body mass index ; WC= waist circumference ; HOMA-IR= homeostatic model assessment for insulin resistance.

Nineteen percent (19%) of LVM variation was predicted by age ; 31.3%, by the duration of hypertension ; 44.4%, by BMI ; 42.5%, by WC ; 20%, by glycaemia ; 44.8%, by insulinaemia ; and 43.7%, by HOMA-IR (Figure 2 and b).

In multiple linear regression, patient’s predicted LVM was equal to 0.56 (hypertension duration) + 0.67 (BMI) + 0.08 (Insulin levels) +0.27 (HOMAIR).

The duration of hypertension, BMI, insulin and HOMA-IR predicted 68.3% of the patient’s LVM (Table 4).

**Table 4.** Multiple linear regression showing determinants of left ventricular mass in Black patients with essential hypertension
| Variables                  | LVM Ih |     |     |
|---------------------------|--------|-----|-----|
|                           | $\beta$ | 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|
| Glycaemia (mmol/L)        | 0.06   | 0.46| 0.903|
| Insuline (mmol/L)         | 0.08   | 0.04| 0.034|
| HOMA-IR                   | 0.27   | 1.81| 0.021|

$R^2 = 0.683$, overall p $\leq 0.001$

HTN=hypertension ; BMI= body mass index ; WC= waist circumference ; HOMA-IR= homeostatic model assessment for insulin resistance

\[ Y = 0.56 X_1 + 0.67 X_2 + 0.08 X_3 + 0.27 X_4 + 6.84 \]

With $Y = \text{LVM Ih}; X_1 = \text{HTN duration}; X_2 = \text{BMI}; X_3 = \text{Insuline}; X_4 = \text{HOMA-IR}$

**Determinants of LVH**

In univariate analysis, global obesity, abdominal obesity, sedentary status, AI, hyperuricaemia, and 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).

**Table 5** Logistic regression analysis showing determinants of LVH among Black hypertensive patients
| Variables          | Univariate analysis | Multivariate analysis |
|-------------------|---------------------|-----------------------|
|                   | p   | OR (95% CI)   | p   | aOR (95% CI) |
| **Total Obesity** |      |               |      |              |
| No                | 1   | 1             | 1    | 1            |
| Yes               | 0.000 | 5.1 (2.8-9.3) | **0.038** | 2.8 (1.06-7.4) |
| **Abdominal Obesity** |    |               |      |              |
| No                | 1   | 1             | 1    | 1            |
| Yes               | 0.000 | 3.3 (1.9-5.8) | 0.275 | 1.9 (0.6-6.3) |
| **Sedentary**     |      |               |      |              |
| No                | 1   | 1             | 1    | 1            |
| Yes               | 0.000 | 6.4 (3.4-12.1)| 0.123 | 1.9 (0.8-4.5) |
| **High AI**       |      |               |      |              |
| No                | 1   | 1             | 1    | 1            |
| Yes               | 0.031 | 1.8 (1.06-3.2)| 0.579 | 1.3 (0.6-2.9) |
| **Hyperuricaemia**|     |               |      |              |
| No                | 1   | 1             | 1    | 1            |
| Yes               | 0.006 | 2.5 (1.3-4.7)| 0.145 | 2.1 (0.8-5.4) |
| **IR**            |      |               |      |              |
| No                | 1   | 1             | 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 that explained the bulk of the increase in LVM (68%), were established. These were the duration of hypertension, BMI, insulinaemia and HOMA-IR. However, only IR 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, AI, and E/e’ ratio as well as a lower E/A ratio and e’ 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. [45] 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 Brazilian subjects. Galvan et al. [46], 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 non-diabetic subjects. 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, HOMA-IR 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 [47]. HOMA-IR 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 [48]. There is no agreed HOMA-IR threshold for defining IR in the sub-Saharan Black African population. The cut-off of 2.5 used in the present study has been used in various Black Central African [49], African-American [50], European American [51], Caucasian [36] and Asian [52, 53] studies. Our results concurred, however, with data obtained in populations other than Black sub-Saharan Africans. Sasson et al. [54] demonstrated a significant association between IR and LVH, which was independent of blood pressure level and BMI [59]. Lind et al [55] also found such an association and demonstrated that hyperinsulinaemia was responsible for 43% of the variation in the left ventricular mass. In a recent prospective population study, Cauwenberghs et al [56] found that basal insulin resistance / hyperinsulinaemia and its worsening during follow-up predicted left ventricular remodelling.

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 [22, 57]. This is substantiated by the high prevalence of LVH in normotensive type 2 diabetic individuals [58, 59]. Insulin resistance, by multiple and complex mechanisms, has been shown to promote cardiomyocyte hypertrophy and matrix deposition, regardless of its effect on systemic blood pressure [60].

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 [61]. 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 (AGEs or advanced glycation end products), an excess of glycolytic compounds and increased synthesis of ceramide, all of which promote apoptosis. AGEs bind to specific receptors, activate 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 [62].
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 [63] showed that the duration of hypertension predicted the occurrence of electrical LVH. 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 participants with LVH had a lower E/A ratio and a longer deceleration time that indicated abnormalities in relaxation [41, 42, 64] associated with normal LVFP, as evidenced by a normal E/e’ ratio ([8] [43] with almost normal LAA. The presence of an isolated relaxation abnormality without an impact on filling pressures is believed to be due to the relatively short duration of HTN (5 years and 4 years in participants with LVH and patients without LVH, respectively). Diastolic dysfunction is a consequence of both IR [65, 66] and of LVH and the underlying myocardial fibrosis [42, 67-70]. In addition, the mitochondrial dysfunction that accompanies IR state is thought to play a role in both LVH and diastolic dysfunction [71]. 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 [72]; on the other hand, regression of LVH after antihypertensive treatment does not necessarily lead to the normalization of diastolic function [74].

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 a sedentary lifestyle and LVM. Gibbs et al. [75] observed relationships between sedentary lifestyle and obesity and increased LVM in Caucasian adults but not in Black populations. In a previous analysis, we assessed this association in a sub-Saharan Blacks population and White Maghrebi population and found that sedentary lifestyle was associated with a lower LVM in the White Maghrebi population but not in the sub-Saharan Black population [76]. Likewise, in the present study of sub-Saharan Black patients, although a larger proportion of patients with LVH were sedentary, no significant association was found between sedentary lifestyle and LVM. It is possible that a potential qualitative difference exists in the cardiovascular consequences of sedentary behaviours.

The association between obesity and LVH 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 [77], whereas others, including ourselves, have found a predominance of concentric geometry [78, 79]. Concentric geometry is more often attributed to pressure overload, whereas eccentric geometry is attributed to volume overload [80]. When hypertension, a condition of pressure overload and obesity, coexist, the resulting hypertrophic phenotype would be determined by the predominance of one over the other. This may explain the divergent results in the literature based on the study population. Furthermore, an initially concentric geometry can evolve over time towards an eccentric geometry.

The sedentary behaviour-obesity combination 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 IR 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 IR [81]. Therefore, IR would bridge the gap between sedentary lifestyle/obesity and LVH.

Significantly higher uric acid levels were found in hypertensives with LVH than in those without LVH. This is in agreement with previous studies which have shown that hypertensives with LVH have higher uric acid levels [82]. A causal link was suggested since normalization of uric acid levels using hypouricaemic treatment led to a reduction in the LVM[83, 84]. Several mechanisms could be used to explain the increase in LVM due to hyperuricaemia, including the systemic inflammatory response, oxidative stress [85, 86], activity of the renin angiotensin aldosterone system [87], endothelial dysfunction [88] and the expression of endothelin-1 in cardiac fibroblasts that promotes interstitial fibrosis in myocardium [89]. Furthermore, some indirect effects of hyperuricaemia, such as increased BP, a parallel decrease in glomerular filtration rate, deterioration in adhesion and platelet aggregation, and increased aortic stiffness, could further contribute to the development of LVH [90].

Finally, this study found a higher AI in hypertensive participants with LVH than in those without LVH, which suggests an increase risk of coronary events. This aligns with a previous study that established that LVH is a risk factor for coronary heart disease mortality [91].

Study limitations

Our study must 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. In addition, it is important to keep in mind the intraobserver variability of transthoracic 2D echocardiography, which is not as good as the real-time 3D technique [28, 92]; however, in the present study, echocardiography was performed by an experienced cardiologist with post-graduate training in cardiac imaging. Second, the case-control design we used meant we could not truly assess cause-effect relationships. Third, the in-hospital and monocentric desing makes it risky to extrapolate the results to all sub-Saharan Black hypertensive patients. Our study covers a gap, in that, to the best of our knowledge, this is the first description of the association between IR and LVH in Black sub-Saharan African hypertensive patients.

Conclusions

Our results showed direct and significant associations between the duration of hypertension, BMI, insulinaemia and HOMA-IR and LVM. IR and obesity emerged as independent determinants of LVH in hypertension. These results might indicate that in addition to haemodynamic factors related to high blood pressure, changes in LVM in hypertensive patients may be mediated by IR. Early detection and effective management of IR should be considered in all hypertensive patients to prevent or delay the
development of LVH and its consequences. In addition, these results should stimulate further research to assess the efficacy and safety of pharmacological and nonpharmacological insulin sensitization measures on IR in hypertensive patients, even non-diabetic patients.

A prospective Black sub-Saharan population-based study with serial imaging remains essential to better understand subclinical LV deterioration over time and to confirm the role of IR in Black sub-Saharan hypertensive patients.

**List Of 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

HDL-c=high density lipoprotein

HMOD = hypertension-mediated organ damage

HOMAIR=Homeostatic Model Assessment for Insulin Resistance

HR=Heart rate

HTN=hypertension

IR=insulin resistance.

IVS=interventricular septal thickness

LAA=left atrium area

LDL-c=low density lipoprotein
LVED=Left ventricular end-diastolic diameter
LVEF=Left ventricular ejection fraction
LVM=left ventricular mass
LVMlbs=left ventricular mass indexed to body surface area
LVMlh=left ventricular mass indexed to height $^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 declare that they have no competing interests.

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Authors' contributions

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