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Original Article

Insulin resistance-related differences in the relationship between left ventricular hypertrophy and cardiorespiratory fitness in hypertensive Black sub-Saharan Africans

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Abstract: Background: Left ventricular hypertrophy (LVH) is associated with impaired cardiorespiratory fitness (CRF), a surrogate marker of poor outcome. Insulin resistance (IR) plays a central role in all stages of cardiovascular disease continuum. This study evaluates IR-related differences in the relationship between left ventricular mass (LVM) and CRF in asymptomatic newly diagnosed hypertensive Black sub-Saharan Africans. Methods: In this cross-sectional observational study, 126 asymptomatic newly diagnosed hypertensive participants (50.5 ± 9.5 years) underwent comprehensive resting transthoracic echocardiographic examination and maximal incremental cardiopulmonary exercise test (CPET). CRF was estimated in maximal oxygen uptake (VO2max). CPET results were compared between participants with and without LVH. Multivariate analysis examined the influence of IR on the observed differences. Results: Those with LVH had lower VO2max (15.7 ± 5.5 mL min^{-1} kg^{-1} vs. 18.4 ± 3.7 mL min^{-1} kg^{-1}; $P = 0.001$) than those without LVH. In patients with IR, LVM ($r = -0.261$, $P = 0.012$), LVM indexed to body surface area (LVMIbsa; $r = -0.229$, $P = 0.027$), and LVM indexed to height to an allometric power of 2.7 ($LVMIh^{2.7}$; $r = -0.351$, $P = 0.001$), and VO2max were negatively correlated. In hypertensive patients without IR, these same parameters and VO2max have no significant correlation. Body mass index (BMI), LVM, and LVMIbsa emerged as independent determinants of VO2max, explaining 46.9% of its variability (overall $P = 0.001$) in IR participants, a relationship not found in participants without IR. Conclusions: IR may participate in the deterioration of CRF associated with LVH. Measures to improve insulin sensitivity should be considered for improving CRF and therefore the prognosis of insulin-resistant hypertensive patients. Targeting IR in hypertensive patients with LVH could improve prognosis.

Keywords: Cardiorespiratory fitness, cardiopulmonary exercise test, insulin resistance, left ventricular hypertrophy, Sub-Saharan Africans

Introduction

Insulin resistance (IR) and left ventricular hypertrophy (LVH) are associated with hypertension [1, 2]. Insulin resistance plays a major role in the genesis of arterial hypertension, left ventricular hypertrophy, and cardiovascular disease in general.

The link between IR and hypertension was initially highlighted by Welborn et al. [3] then later confirmed by the European Group for the IR Study [4]. IR and compensatory hyperinsulinemia are thought to play a major role in the genesis of hypertension by multiple and complex mechanisms, in particular by an increased reabsorption of sodium in the renal tubules, a sympathetic hyperstimulation and a decrease in vascular compliance via an increased calcium concentration in vascular smooth muscle cells [1].

During hypertension, the heart undergoes left ventricular remodeling which consists of a

series of changes in its size, shape and function [5]. LVH, one of the phenotypes of this remodeling, has poor prognostic value [6-8]. Its genesis would be multifactorial because it is due, not only to the barometric overload linked to arterial hypertension, but also to metabolic factors including IR. Indeed, IR and compensatory hyperinsulinemia, independently of their effect on systemic blood pressure, have been shown to promote cardiomyocyte hypertrophy and matrix deposition, either directly or through stimulation of the Renin Angiotensin System and the Sympathetic Nervous System [9, 10]. Studies have shown that IR contributes to the development of LVH and left ventricular dysfunction. However, the role of IR in the pathophysiology of LVH is controversial. Some studies have shown that IR is independently associated with LVH [11, 12]. Others, however, have not found such an association [13, 14]. In a case-control study, we recently found that IR increased the risk of LVH eight-fold in asymptomatic Black sub-Saharan African hypertensive patients [15].

IR plays a central role in all stages of cardiovascular disease continuum, from the development of risk factors to the onset of cardiovascular events and death. It is indeed involved in the genesis of dyslipidemia [16, 17], essential hypertension [18], diabetes mellitus [19], hyperuricemia [20], and endothelial dysfunction [21, 22]. In hypertensive patients, IR is associated with the development of hypertension-mediated organ damage, including LVH [12], microalbuminuria [23], benign nephroangiosclerosis [24], intima-media thickness [25], carotid plaque [26], arterial stiffness [27], and peripheral arterial disease [28]. In addition, although IR is associated with traditional risk factors, it may independently influence the occurrence of cardiovascular events, including stroke [29], acute coronary syndrome [30], heart failure [31], and sudden cardiac death [32]. Moreover, IR is associated with cardiovascular and all-cause mortality [33]. It appears, therefore, that IR is either the main culprit or an accomplice at every step of cardiovascular disease continuum in general and hypertensive heart disease in particular. Echocardiographic LVH is known to be a powerful, independent risk factor of cardiovascular morbidity and mortality in essential hypertension, even after adjusting for age, smoking, obesity, blood pressure (BP), pulse pressure, treatment and level of hypertension control, diabetes mellitus, lipid abnormalities, and so forth [34]. However, whether this association is independent of IR remains unclear.

A cardiopulmonary exercise test (CPET) provides several parameters with proven prognostic value. Among these parameters, cardiorespiratory fitness (CRF) has a predictive value of all-cause mortality in both normal subjects and subjects with cardiovascular disease [35] and in all age categories [36] and genders [37], as well as in virtually all patient populations, independent of other traditional risk factors [38]. It can then be used to estimate the risk of morbidity and mortality.

The present study aims to evaluate IR-related differences in the relationship between left ventricular mass (LVM) and CRF in asymptomatic newly diagnosed hypertensive Black sub-Saharan Africans.

Materials and methods

We performed a cross-sectional multicentric analysis of data from 126 nondiabetic participants with newly diagnosed essential hypertension. Participants were consecutively selected during outpatient consultations at five hospitals with individualized cardiology units (University Hospital of Kinshasa, the General Provincial Reference Hospital of Kinshasa, the Centre Médical de Kinshasa (CMK), the Lomo-Médical Clinic, and the Ngaliema Clinic) in Kinshasa, the capital of the Democratic Republic of the Congo, from October 1 to December 27, 2019.

Anamnestic data were collected in each of the five aforementioned recruitment hospitals by trained interviewers. Whereas anthropometric, echocardiographic, carbohydrate homeostasis, and CPET parameters were obtained at CMK, the only cardiology center in central Africa where CPET is performed.

Patient selection

The study entry criterion was an age of 20 years and older, newly diagnosed hypertension and the absence of clinical, imaging, and biology evidence of secondary hypertension and renal or hepatic disease. The selected patients were

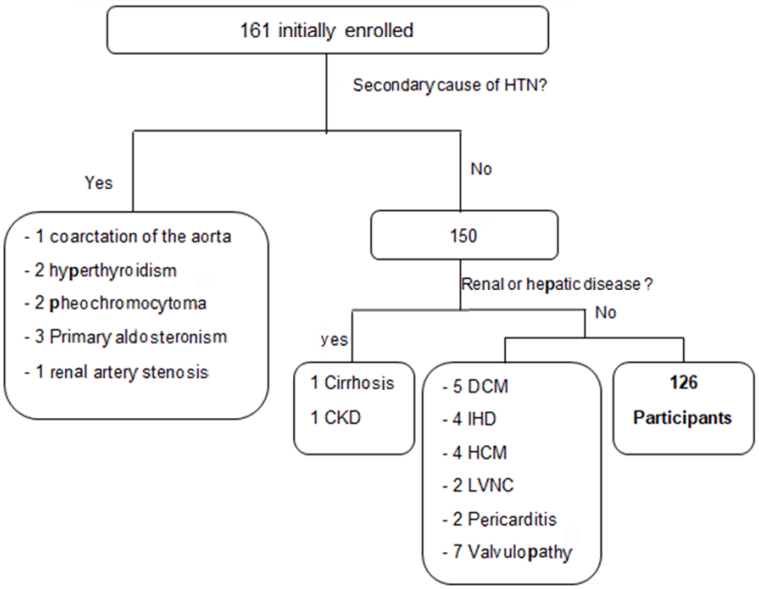

Figure 1. Flow chart summarizing the participant's inclusion. HTN = hypertension, CKD = chronic kidney disease, IHD = ischemic heart disease, HCM = hypertrophic cardiomyopathy, LVNC = left ventricular non compaction.

invited to sign written informed consent forms to participate in this study and underwent comprehensive carbohydrate homeostasis test, echocardiography and CPET. Patients diagnosed with heart disease unrelated to hypertension were excluded from the study.

Overall, 161 consecutive asymptomatic newly diagnosed hypertensive patients were initially enrolled. 11 of them were ineligible because of secondary causes of high BP (9 patients), chronic kidney disease (1 patient), and liver cirrhosis (1 patient). Of the remaining 150 patients, 24 were excluded due to diagnoses of heart disease unrelated to high BP. **Figure 1** presents the recruitment flowchart.

Study procedures

Anamnestic data: Anamnestic data was collected using a standard questionnaire. This included questions about demographic data (age, sex), lifestyle habits (heavy alcohol consumption, current smoking, sedentary behavior), medical history including cardiovascular risk factors (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 (antidiabetic treatment and other treatments including statins, antiplatelet agents, hypouricemics, oral contraception, hormone replacement therapy).

Physical examination: 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) and a derived variable (body mass index [BMI]). The WC was measured to the nearest 0.1 cm using a measuring tape directly applied to the skin along a horizontal line passing through the umbilicus. BMI was obtained by dividing the weight (kg) by the square of height (m^2).

BP: BP was noninvasively measured by 24-hour ambulatory BP monitoring using a TONOPORT V (GE Healthcare, Freiburg, Germany) recorder. Participants were asked to maintain his/her usual way of life during the recording.

Biochemical measurements: For all analyses, we obtained a blood sample between 7 a.m. and 9 a.m. from the cubital vein of the patient, after an overnight fast. The blood glucose test was performed on plasma oxalate by the colorimetric method using Biolabo standard reagents (Biolabo S.A.S., Les Hautes Rives, Maizy, France) and measured by the HELIOS Epsilon spectrophotometer. The dosage of insulin was performed on EDTA plasma by enzyme-linked immunosorbent assay. Optical density readings were performed on a string read from the firm HUMAREADER HUMAN (Germany). The Homeostatic Model Assessment for Insulin Resistance (HOMAIR) was calculated as HOMAIR = fasting insulin (μU/mL) × fasting glucose (mmol/L)/22.5 [32]. HbA1c was measured using the immunoturbidimetric technique with the biochemistry analyzer COBAS C111.

Echocardiographic measurements: Two-dimensionally guided M-mode echocardiography

was performed using standard methods 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 Healthcare) ultrasound system equipped with 3.5-MHz transducers. Echocardiographic examinations were performed and interpreted by the same cardiologist who was unaware of the patient data. Interventricular septum thickness in diastole (IVSd), left ventricular posterior wall thickness (PWT) in diastole (LVPWd), and left ventricular end-diastolic diameter (LVEDd), all measured in millimeters, were assessed at a level just below the mitral valve leaflets at end diastole, on the leading edge to the leading edge. LVM was calculated based on the American Society of Echocardiography simplified cubed equation linear method: LVM (g) = 0.8 × 1.04 × [(LVEDd + IVSd + LVPWd)^3 - (LVEDd)^3] + 0.6 g. LVM was indexed to body surface area (BSA) and to height$^{2.7}$ as LVM/BSA and LVM/height$^{2.7}$. The relative wall thickness (RWT) of the left ventricle (LV) was calculated as follows: (2 × LVPWd)/LVEDd. Parameters of LV diastolic function were measured in accordance with international recommendations [40], using both pulsed wave Doppler and pulsed tissue Doppler. Peak E-wave velocity (E; Cm/s), peak A-wave velocity (A; Cm/s), deceleration time (DT) of early filling (ms), and peak early diastolic mitral annular velocity (e', cm/s) were measured over five cardiac cycles, and the mean was calculated.

CPET: All participants performed maximal CPET using a cycle ergometer (eBike, GE Medical Systems, GmbH, Freiburg, Germany). Participants were asked to refrain from eating for at least 2 hours before the test, strenuous exercise for at least 24 hours before the CPET, caffeine on the day of the test, and smoking at least 8 hours before the test. They were further advised to wear comfortable clothing and exercise-appropriate footwear. Immediately before exercise testing, participants were encouraged to make maximal effort. The system was calibrated before each test based on the manufacturer's instructions. We used an incremental exercise protocol tailored to each patient's characteristics (age, gender, maximal predicted capacity, corrected by the level of estimated physical activity) [41]. Gas exchange and ventilatory variables were analyzed using Medisoft cardiorespiratory instrumentation (Medisoft Ergocard CPX, 5503 Sorinnes, Belgium). Standard 12-lead electrocardiograms were obtained at rest and during the exercise and recovery phases with CardioSoft V6.73 (GE Medical Systems). Continuous BP measurement and heart rate recordings were performed every minute, and the Borg scale was used to rate the perceived exertion at each stage. Pulse oximetry was also measured throughout the CPET. Exercise was discontinued in the event of any of the following: severe angina, decrease or insufficient increase in BP despite workload increase, ST-segment elevation (not corresponding to a myocardial infarct territory), severe or poorly tolerated arrhythmias, signs of low cardiac output, neurological signs such as ataxia (confusion, vertigo, etc.), technical problems preventing proper monitoring (electrocardiogram recording and/or BP measuring), and patient request [42]. CPET was considered maximal when respiratory exchange ratio (RER) was ≥1.1 [43]. CRF was expressed as the maximal oxygen uptake (VO2max). The VO2max was defined as the highest value reached at the end of the maximal CPET. Participants were categorized into three groups according to percentiles of CRF level: low (<25th), intermediate (25th-75th), and high (>75th).

Operational definitions: Hypertension was defined as an average systolic BP >130 mmHg and/or average diastolic BP >80 mmHg on 24-hour ambulatory blood pressure monitoring (ABPM) [44]. Newly diagnosed hypertension was defined as arterial hypertension for which a confirmatory diagnosis has just been obtained within 48 hours by ABPM and for which antihypertensive therapy has not yet been initiated. Sedentary was defined as sitting for more than 7 hours per day [45]. Hyperinsulinemia was defined as fasting insulin glucose level >90 mmol/L. IR was defined as a HOMAIR of ≥2.5 in accordance with the accepted criteria [46]. LVH was defined as LVM of >115 g/m^2 or >48 g/m$^{2.7}$ for men when indexed to BSA or height, respectively, and >95 g/m^2 or >44 g/m$^{2.7}$ for women when indexed to BSA or height, respectively. Three patterns of diastolic dysfunction were defined as follows [47, 48]: abnormal relaxation (grade I of diastolic dysfunction: E/A ratio of <1 and prolonged DT), pseudonormal relaxation (grade II: E/A ratio of

Table 1. Participant characteristics according to the presence of LVH

Variable	Overall n = 126	With LVH n = 51	Without LVH n = 75	*p* value
Age (years)	50.5 ± 9.5	50.2 ± 10.0	50.7 ± 9.3	0.784
Gender				0.259
Male	82 (65.1)	31 (60.8)	51 (68.0)	
Female	44 (34.9)	20 (39.2)	24 (32.0)	
Sedentary time (hours)	9.9 ± 2.2	11.4 ± 1.9	8.8 ± 1.7	0.000
BMI (kg m^{-2})	30.0 ± 4.6	32.0 ± 4.8	28.7 ± 4.1	0.000
WC (cm)	102.7 ± 11.0	105.8 ± 11.4	100.5 ± 10.3	0.023
FPG (mmol L^{-1})	5.5 ± 6	6.4 ± 1	6.2 ± 1.1	0.070
FI (pmol L^{-1})	93.1 ± 38.3	119.5 ± 39.9	75.1 ± 24.3	0.000
HOMAIR	1.9 ± 0.8	2.3 ± 0.8	1.42 ± 0.47	0.000
E/A	1.24 ± 0.44	1.15 ± 0.45	1.33 ± 0.43	<0.001
DT (Cm/s)	208 ± 43	204 ± 45	209 ± 47	0.498
E/e'	5.9 ± 1.7	6.6 ± 2.8	5.3 ± 1.5	<0.001
VO2max/kg (ml min^{-1} kg^{-1})	17.3 ± 4.7	15.7 ± 5.5	18.4 ± 3.7	0.001

BMI = body mass index; WC = waist circumference; FPG = fasting plasma glucose; FI = fasting insulin; HOMAIR = Homeostatic Model Assessment for Insulin Resistance; E/A = transmitral ratio between early and late ventricular filling velocity; DT = deceleration time; E/e' = transmitral early diastolic velocity to pulsed tissue Doppler-derived annular early diastolic velocity ratio; VO2max/kg = peak exercise oxygen consumption per body weight.

>1 and intermediate values of DT), and restrictive patterns (reversible and irreversible, grades III-IV, respectively; E/A ratio of >2 and shortened DT). Normal left ventricular filling pressure was defined by an E/é ratio of <8 [49]. Elevated left ventricular filling pressure was defined by a E/e' lateral of >12 [49]. Dilation of the left atrium was defined as an area of the OG of >20 cm^2 of body surface [39].

Statistical analysis

Statistical analysis of the data was performed using SPSS for Windows version 24. Descriptive analyses included the mean and standard deviation for quantitative data with Gaussian distribution, median and interquartile space for non-normally distributed data, and the relative (%) and absolute (n) proportions for categorical data. Student *t*-test was performed to compare two means. Analysis of variance (ANOVA) was used for multiple comparisons. ANOVA tests significant at the $P<0.05$ level were supplemented by a post hoc Cheffée test. To compare the medians of two groups, we used Mann-Whitney *U* test, and for more than two medians, we used the Kruskal-Wallis H test. Linear regression testing was applied to verify Pearson simple correlation between clinical, laboratory, and ultrasound parameters with extreme percentiles of VO2max. Pearson coefficients (*r*) were calculated to assess this association. When differences were observed between clinical, laboratory, and ultrasound findings and VO2max categories, the effect of potential confounders was investigated by conditional linear regression fitting in multivariate analysis. Finally, coefficients of determination (R^2) were calculated to determine the degree of variability between clinical, biological, and ultrasound findings and VO2max. The significance level was retained as $P<0.05$.

Ethical considerations

This research was conducted in strict compliance with the recommendations of the Helsinki Declaration III. Study approval was obtained from the National Health Ethics Committee (No. 219/CNES/BN/PMMF/220).

Results

Participants general characteristics

Overall, 126 hypertensive participants were included in the final analysis. **Table 1** summarizes the general characteristics of the study population. The mean age of patients was 50.5 ± 9.5 years, with a predominance of men (sex ratio (M/F), 1:9). Comparison between patients

Table 2. Participant characteristics according to IR

Variable	With IR n = 33	Without IR n = 93	*p*
Age (years)	50.6 ± 9.8	50.5 ± 9.5	0.958
Gender			0.014
Male	27 (81.8)	55 (59.1)	
Female	6 (18.2)	38 (40.9)	
Sedentary time (hours)	11.4 ± 2.1	9.3 ± 1.9	0.000
BMI (kg m^{-2})	33.3 ± 4.7	29.9 ± 4.7	0.001
WC (cm)	108.3 ± 12.9	100.9 ± 9.8	0.006
FPG (mmol l^{-1})	6.6 ± 0.1	6.4 ± 2.0	0.065
FI (pmol L^{-1})	192.3 ± 68.1	86.9 ± 41.1	0.000
HOMAIR	3.9 ± 1.4	1.6 ± 0.5	0.000
LVED (mm)	59.8 ± 19.9	44.4 ± 6.4	0.000
IVS (mm)	12.3 ± 1.6	11.3 ± 1.6	0.004
PWT (mm)	12.1 ± 1.4	11.3 ± 1.5	0.003
LVM (g)	270.4 ± 97.3	182.3 ± 58.3	0.000
LVMIbsa (g m^{-2})	127.7 ± 29.9	88.5 ± 21.7	0.000
$LVMIh^{-2.7}$ (g $m^{-2.7}$)	95.9 ± 59.8	47.3 ± 25.9	0.000
LAA (cm^{-2})	16.4 ± 2.7	15.9 ± 4.6	0.573
E/A ratio	1.1 ± 0.09	2.1 ± 2.3	0.002
DT (ms)	215.7 ± 44.8	204.3 ± 43.5	0. 001
E/e'	7.5 ± 0.3	5.1 ± 1.4	0.001
VO2max (ml min^{-1} kg^{-1})	13.7 ± 6.2	18.6 ± 3.3	0.000

BMI = body mass index; WC = waist circumference; FPG = fasting plasma glucose; FI = fasting insulin; HOMAIR = Homeostatic Model Assessment for Insulin Resistance; LVED = left ventricular end-diastolic diameter; IVS = interventricular septum; PWT = posterior wall thickness; LVM = left ventricular mass; LVMIbsa = left ventricular mass indexed to body surface area; $LVMIh^{-2.7}$ = left ventricular mass indexed to height to allometric power of 2.7; DT = deceleration time; LAA = left atrial area; E/A = transmitral ratio between early and late ventricular filling velocity; E/e' = transmitral early diastolic velocity to pulsed tissue Doppler-derived annular early diastolic velocity ratio; DT = deceleration time; VO2max (ml min^{-1} kg^{-1}) = peak exercise oxygen consumption in milliliter per minute per kg of body weight.

with LVH and those without LVH indicated that the two subgroups were similar in age and sex ratio. However, the mean BMI, WC, fasting insulin, HOMAIR, and sedentary time were significantly higher in patients with LVH ($P<0.05$). Contrarily, hypertensive patients with LVH had lower VO2max than those without LVH. Regarding diastolic function parameters, patients with LVH had significantly lower E/A ratios, with a longer DT and a higher E/e' ratio, although it was normal. **Table 2** shows the comparison between insulin-resistant and non-insulin-resistant participants. The two subgroups had a similar mean age, with a significantly higher proportion of men in the IR subgroup. IR participants had significantly greater BMI, WC, LVED, IVS, PWT, LVM, LVMIbsa, LVMIh and sedentary time than those without IR. A comparison of the diastolic function parameters showed that participants with IR had a significantly lower E/A ratio and greater E/e' with significantly longer DT. Participants with IR had an overall lower VO2max than those without IR. **Table 3** shows a Gaussian distribution of VO2max over the entire study population.

Correlates of CRF

Table 4 shows that the mean values of BMI, FI, HOMAIR, LVED, LVM, LVMIbsa, LVMIh, and E/e' significantly decreased with increasing percentile of VO2max. On the other hand, the E/A ratio increased with the increase in the percentile of VO2max. In contrast, participants with different percentiles of CRF had similar age, WC, FPG, ST, IVS, PWT, RWT, DT, and LAA. **Table 5** shows that VO2max was negatively related to BMI, FI, HOMAIR, LVM, LVMIbsa, and LVMIh. In contrast, LVED and E/A were positively related to VO2max. **Table 6** presents the results of the multiple linear regression analysis. This table shows that insulin, HOMAIR, LVMIh, and E/A ratio emerged as independent determinants of VO2max, explaining 53.1% of its variability. **Table 7** shows that LVM and LVMIh significantly decreased as the percentiles of VO2max increased in both IR and non-IR participants, whereas E/A ratio significantly increased with increases in the percentiles of VO2max in participants both with and without IR.

Correlates of CRF according to IR status

Table 8 indicates that BMI, LVED, LVM, LVMIbsa, LVMIh, and DT were negatively correlated with VO2max in patients with IR. On the other hand, the E/A ratio positively correlated with VO2max in patients with IR, but this correlation was not significant in hypertensive patients without IR. **Table 9** illustrates the results of multiple regression analysis. BMI, LVM, and LVMIbsa emerged as independent determinants of VO2max, explaining 46.9% of its variability in insulin-resistant participants, although

Table 3. Fitness level categories

Variable	N	Low fitness <25th P n (%)	Intermediate fitness [25th-75th P] n (%)	High fitness >75th P n (%)
VO2max (ml min^{-1} kg^{-1})	120	12 (9.5)	95 (75.4)	19 (15.1)
Me (extreme)		12.5 (10.0-14.0)	18.0 (15.0-21.0)	24.0 (22.0-26.0)

VO2max = peak VO2; P = percentile value.

Table 4. Clinical, biological, and echocardiographic characteristics of participants according to VO2max percentiles

Variable	n	VO2max (ml/min/kg)			
		<25th P	25th-75th P	>75th P	*p*
Age (years)	126	50.0 ± 11.5	50.4 ± 9.2	51.1 ± 10.3	0.946
BMI	126	32.2 ± 3.2	30.9 ± 5.1	29.1 ± 4.9	0.200
WC (Cm)	126	101.5 ± 11.9	102.3 ± 10.6	104.9 ± 12.7	0.661
FPG	126	6.6 ± 1.2	6.0 ± 1.5	5.5 ± 1.2	0.061
FI (mmol/L)	126	220.8 ± 85.1	104.2 ± 56.4	98.8 ± 49.7	<0.001
HOMAIR	126	4.1 ± 1.8	2.0 ± 1.2	1.9 ± 0.9	<0.001
ST (hours)	126	10.2 ± 2.5	9.8 ± 2.1	10.3 ± 2.3	0.610
LVED (mm)	126	63.4 ± 22.5	47.2 ± 11.8	44.9 ± 5.7	0.001
IVS (mm)	126	11.2 ± 1.7	11.6 ± 1.6	11.5 ± 1.5	0.674
PWT (mm)	126	11.3 ± 1.6	11.6 ± 1.5	10.8 ± 1.4	0.076
LVM (g)	126	306.7 ± 130.3	198.5 ± 67.9	175.7 ± 47.2	<0.001
LVMIbsa (g m^2)	126	134.1 ± 40.1	96.7 ± 27.0	86.5 ± 16.6	<0.001
LVMIh (g $m^{2.7}$)	126	68.7 ± 15.1	55.3 ± 15.9	40.3 ± 8.7	<0.001
RWT	126	0.56 ± 0.12	0.57 ± 0.38	0.51 ± 0.09	0.746
E/A ratio	126	0.9 ± 0.4	1.2 ± 0.3	1.36 ± 0.50	<0.001
DT (ms)	126	208.3 ± 38.4	207.3 ± 44.3	206.2 ± 47.6	0.990
E/e' ratio	126	7.1 ± 2.5	6.6 ± 2.3	6.0 ± 1.7	<0.001
LAA (cm^2)	126	15.45 ± 2.5	16.3 ± 4.6	15.6 ± 2.8	0.671

BMI = body mass index; WC = waist circumference; FPG = fasting plasma glucose; FI = fasting insulin; HOMAIR = Homeostatic Model Assessment for Insulin Resistance; ST = sedentary time; LVED = left ventricular end diastole; IVS = interventricular septum; PWT = posterior wall thickness; LVM = left ventricular mass; LVMIbsa = left ventricular mass indexed to body surface area; LVMIh = left ventricular mass indexed to $height^{2.7}$; RWT = relative wall thickness; E/A = transmitral ratio between early and late ventricular filling velocity; DT = deceleration time; E/e' = transmitral early diastolic velocity to pulsed tissue Doppler-derived annular early diastolic velocity ratio; LAA = left atrial area.

this relationship was not detected in patients without IR.

Discussion

Ours is the first study to evaluate differences related to IR in the relationship between LVM and CRF in asymptomatic newly diagnosed hypertensive Black sub-Saharan Africans.

Our main findings indicated that LVM is an independent determinant of CRF in IR hypertensive participants, but not in non-IR hypertensive patients. This suggests a detrimental influence of IR on the prognosis for LVH, as independent of other traditional risk factors [38]. CRF is a well-established independent predictor of mortality in almost all patient populations.

Previous studies have demonstrated a significant correlation between CRF and LVM in humans [50], as well as animals [51]. Because hypertension is an IR state [4, 52] and IR is associated with both LVH [11, 12, 53] and impaired CRF [54, 55], the possibility of the interference of IR on the association between

Table 5. Simple linear correlation between clinical, laboratory, and echocardiographic characteristics and CRF parameters VO2max (ml min^{-1} kg^{-1})

Variable	VO2max (ml min^{-1} kg^{-1}) r (p)
BMI	-0.226 (0.011)
FI (mmol/L)	-0.419 (<0.001)
HOMAIR	-0.392 (<0.001)
LVED (mm)	-0.367 (<0.001)
LVM (g)	-0.418 (<0.001)
LVMIbsa	-0.399 (<0.001)
LVMIh	-0.512 (<0.001)
E/A ratio	0.419 (<0.001)

BMI = body mass index; FI = fasting insulin; HOMAIR = Homeostatic Model Assessment for Insulin Resistance; LVED = left ventricular end diastole; LVM = left ventricular mass; LVMIbsa = left ventricular mass indexed to body surface area; LVMIh = left ventricular mass indexed to $height^{2.7}$; E/A = transmitral ratio between early and late ventricular filling velocity.

Table 6. Multiple correlations

Variable	VO2max (ml min^{-1} kg^{-1})		
	β	ES	*P*
(Constant)	20.312	2.299	0.000
BMI	-0.014	0.065	0.833
FI (mmol/L)	-0.007	0.010	0.004
HOMAIR	-0.337	0.485	0.048
LVED (mm)	-0.052	0.041	0.020
LVM (g)	-0.001	0.006	0.819
LVMIbsa (g m^2)	-0.020	0.015	0.017
LVMIh (g $m^{2.7}$)	-0.033	0.016	0.001
E/A ratio	-0.461	0.316	0.014
	R^2 = 0.531		
Overall *p* value	<0.001		

BMI = body mass index; FI = fasting insulin; HOMAIR = Homeostatic Model Assessment for Insulin Resistance; LVED = left ventricular end diastole; LVM = left ventricular mass; LVMIbsa = left ventricular mass indexed to body surface area; LVMIh = left ventricular mass indexed to $height^{2.7}$; E/A = transmitral ratio between early and late ventricular filling velocity.

LVH and CRF was an eminently plausible hypothesis.

Regensteiner et al. provided a strong argument for a causal link between IR and decreased CRF by demonstrating a significant improvement in CRF after 4 months of treatment with rosiglitazone [56], an insulin sensitizer from the thiazolidinedione group. VO2max, a reflection of CRF, is defined by the interaction between two systems: (1) that of the transport of oxygen from the air to the mitochondria, involving the lungs, heart, blood, and muscles, and (2) that of the mitochondrial metabolic use of the delivered oxygen [57]. All pathophysiological conditions that alter oxygen transport from the air to the mitochondria, as well as its use during exercise, will determine a certain degree of VO2max reduction from the values predicted by age and gender [43]. In fact, studies have shown that IR is associated with impaired lung function [58, 59], reduced capillary alveolar diffusion [60], decreased myocardial perfusion [61], decreased stroke volume, decreased cardiac output [62], endothelial dysfunction [63], increased total peripheral vascular resistance [27], decreased capillary muscle density [64], slowing of the oxygen saturation of tissue hemoglobin [65], and altered mitochondrial function [66].

Interestingly, all of the characteristics that differentiated participants with LVH from those without LVH in the present study have a demonstrated pathophysiological link with IR, whether it is being sedentary [67] and having a higher fasting insulin level [68], a higher BMI [69], larger WC [70], and worse diastolic function parameters [71], expressed by a significantly lower E/A ratio with a longer DT and a higher, although normal, E/e' ratio. Thus, LVH should probably be considered as one of the many risk factors that agglomerate and gravitate around IR to result in the so-called metabolic syndrome. In addition, IR would ultimately be the active ingredient in LVH-related complications and prognosis.

This study also found a negative correlation between BMI and CRF. This correlation was found in all participants; but when dichotomizing the sample according to IR status, this correlation was only found in the subgroup of participants with IR and persisted in multivariate analysis. This assumes that IR would be the link between overall obesity, of which BMI is an index [72], and CRF. Indeed, the BMI is an effective anthropometric indicator to identify IR [73], and IR is related to CRF as demonstrated by Clarke et al. [74]. The fact that this correlation was not found between VO2max and WC, a parameter of abdominal obesity, reopens the debate on the form of obesity (global or abdominal) which is most strongly associated with a poor prognosis. Many authors have found

Table 7. Clinical and echocardiographic characteristics according to CRF levels in participants with and without IR

Variable	VO2max (ml min^{-1} kg^{-1}) in participants with IR				VO2max (ml min^{-1} kg^{-1}) in participants Without IR			
	<25th P	25th-75th P	>75th P	*p*	<25th P	25th-75th P	>75th P	*p*
LVM (g)	314.9 ± 131.8	254.5 ± 82.6	238.6 ± 17.6	0.022	265.4 ± 162.4	185.4 ± 57.1	153.3 ± 30.4	0.019
LVMIh (g m$^{2.7}$)	131.1 ± 59.1	88.5 ± 59.5	52.6 ± 1.9	0.036	117.2 ± 115.6	47.5 ± 22.0	35.9 ± 5.1	0.000
E/A ratio	2.6 ± 1.7	6.7 ± 2.0	6.8 ± 0.16	0.028	0.5 ± 3.3	1.4 ± 1.0	1.7 ± 0.35	0.007

LVM = left ventricular mass; LVMIh = left ventricular mass indexed to height$^{2.7}$; E/A = transmitral ratio between early and late ventricular filling velocity.

Table 8. Simple linear correlation between clinical and echocardiographic parameters with VO2max in patients with and without IR

Variable	VO2max (ml min^{-1} kg^{-1})	
	With IR	Without IR
	r (p)	r (p)
BMI	-0.394 (0.003)	0.174 (0.332)
LVED (mm)	-0.225 (0.030)	-0.080 (0.657)
LVM (g)	-0.261 (0.012)	-0.101 (0.574)
LVMIbsa (g m^2)	-0.229 (0.027)	-0.032 (0.861)
LVMIh (g m$^{2.7}$)	-0.351 (0.001)	-0.091 (0.646)
E/A	0.255 (0.014)	0.184 (0.036)
DT (mm)		

BMI = body mass index; LVED = left ventricular end diastole; LVM = left ventricular mass; LVMIbsa = left ventricular mass indexed to body surface area; LVMIh = left ventricular mass indexed to height$^{2.7}$; E/A = transmitral ratio between early and late ventricular filling velocity; DT = deceleration time.

abdominal obesity to be associated with a poorer prognosis [75, 76], but other authors have found no difference [77, 78].

In addition, a positive and independent correlation was found between CRF and LVED. Brinker et al. found the same in a large population of 2925 participants [79]. The explanation for this correlation would come, at least in part, from Franck Starling's law, which states that the force of contraction of the heart muscle during systole is proportional to its stretch at the end of diastole [80]. This force of myocyte contraction is an essential component of cardiac output [81], which is itself an essential component of the CRF [82].

Furthermore, a positive correlation between VO2max and E/A ratio, a parameter of diastolic function, was found. In line with our results, Grewal et al. but also Brinker et al. showed that CRF was strongly and inversely associated with LV diastolic dysfunction [79, 83].

Interestingly, by dichotomizing the sample based on IR status, the correlation between VO2max and LVED, as well as that between VO2max and E/A, was only found in insulin-resistant participants. This result which, to our knowledge, is unprecedented, probably suggests that it is in an IR situation that Franck Starling's law is imposed with rigor, and that good diastolic relaxation proves to be more effective for the maintenance of good CRF.

The present study used HOMAIR as a surrogate for IR. The HOMAIR index has been the subject of numerous validations, which have shown satisfactory correlation with the reference technique, the hyperinsulinemic euglycemic clamp (r = 0.72-0.82, depending on the studies) with no notable difference by sex, age, weight, presence of diabetes mellitus, or presence of high BP [84].

LVM was echographically determined in the present study. Although cardiac magnetic resonance is considered the gold standard for evaluating LVM, echocardiography is a well-validated, harmless, and widely available method with reliable performance for LVM assessment and classification of LVH, with limited influence of image quality [85].

Study limitations

Our study must be interpreted within the context of its potential strengths and limitations. To the best of our knowledge, this study is the first to demonstrate that the effects of LVM on CRF are primarily driven by the degree of IR in asymptomatic newly diagnosed hypertensive Black sub-Saharan Africans. However, the cross-sectional design of this study is one of its limitations, meaning that causal relationships cannot be firmly established. In addition, the inhospital design precludes extrapolation of the results to all Black sub-Saharan Africans

Table 9. Multiple correlations between clinical and echocardiographic parameters and VO2max (ml min^{-1} kg^{-1}) in patients with and without IR

Variable	With IR n = 33			Without IR n = 93		
	B	ES	p	β	ES	p
(Constant)	27.830	3.184	0.000	-7.645	14.559	0.604
BMI	-0.230	0.081	0.006	0.487	0.297	0.113
LVED (mm)	0.010	0.069	0.883	0.035	0.121	0.777
LVM (g)	0.033	0.015	0.027	0.002	0.020	0.915
LVMIbsa (g m^2)	-0.068	0.030	0.026	0.058	0.059	0.333
LVMIh (g $m^{2.7}$)	-0.050	0.032	0.124	-0.025	0.051	0.625
E/A	-0.430	0.501	0.393	-1.172	0.914	0.211
	R^2 = 0.469			R^2 = 0.384		
Overall *p* value	0.001			0.616		

BMI = body mass index; LVED = left ventricular end diastole; LVM = left ventricular mass; LVMIbsa = left ventricular mass indexed to body surface area; LVMIh = left ventricular mass indexed to height$^{2.7}$; E/A = transmitral ratio between early and late ventricular filling velocity.

with essential hypertension. Furthermore, because of signal noise, acoustic artifacts, and angle dependency, echocardiographic measurements are prone to error. In addition, keeping in mind that the intraobserver variability of transthoracic two-dimensional echocardiography is inferior to the real-time three-dimensional technique is important [86, 87]. However, in the present study, echocardiography was performed by an experienced cardiologist with postgraduate training in cardiac imaging.

Conclusions

Our results suggest that the effects of LVM on CRF are primarily driven by the degree of IR. A prospective, population-based study of Black sub-Saharan Africans remains essential to confirm the detrimental influence of IR on LVH-related CRF impairment and therefore on the traditionally poorer prognosis of hypertension in this population. Our results could indicate that early detection and effective management of IR should be considered in all hypertensive patients. Measures targeting IR should help improve the prognosis of hypertensive patients.

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Disclosure of conflict of interest

None.

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