Cardiovascular Topics

Effect of insulin resistance on left ventricular remodelling in essential hypertensives: a cross-sectional study

Bernard Kianu Phanzu, Aliocha Nkodila Natuhoyila, Eleuthère Kintoki Vita, Benjamin Longo-Mbenza, Jean-René M'Buyamba Kabangu

Abstract

Background: In clinical practice, left ventricular hypertrophy (LVH) is defined by physical findings and electrocardiographic criteria, which are useful but imperfect tools, echocardiographic criteria and cardiac magnetic resonance imaging. In echocardiography, LVH is defined not by left ventricular wall thicknesses but by left ventricular mass. The latter is calculated according to Devereux's formula, and is increased by insulin resistance/hyperinsulinaemia. It is however unclear whether insulin resistance, hyperinsulinaemia, or both, is actually causative and what their collective or individual influence is on the components of Devereux's formula and parameters of left ventricular diastolic function. This study evaluated the associations of the homeostatic model assessment for insulin resistance (HOMAIR) and fasting plasma insulin levels with components of Devereux's formula and parameters of left ventricular diastolic function.

Methods: Relevant clinical data were collected from 220 hypertensive patients recruited between January and December 2019. The associations of components of Devereux's formula and parameters of diastolic function with insulin resistance were tested using binary ordinal, conditional and classical logistic regression models.

Results: Thirty-two (14.5%) patients (43.9 ± 9.1 years), 99 (45%) patients (52.4 ± 8.7 years) and 89 (40.5%) patients (53.1 ± 9.8 years) had normal left ventricular geometry, concentric left ventricular remodelling and concentric left ventricular hypertrophy, respectively. In multivariable adjusted analysis, 46.8% of variation in interventricular septum diameter (R^2 = 0.468; overall p = 0.001) and 30.9% of E-wave deceleration time (R^2 = 0.309; overall p = 0.003) were explained by insulin level and HOMAIR, 30.1% of variation in left ventricular end-diastolic diameter (R^2 = 0.301; p = 0.013) by HOMAIR alone, and 46.3% of posterior wall thickness (R^2 = 0.463; p = 0.002) and 29.4% of relative wall thickness (R^2 = 0.294; p = 0.007) by insulin level alone.

Conclusions: Insulin resistance and hyperinsulinaemia did not have the same influence on the components of Devereux's formula. Insulin resistance appeared to act on left ventricular end-diastolic diameter, while hyperinsulinaemia affected the posterior wall thickness. Both abnormalities acted on the interventricular septum and contributed to diastolic dysfunction via the E-wave deceleration time.

Keywords: hyperinsulinaemia, insulin resistance, left ventricular remodelling, diastolic dysfunction, hypertension

Submitted 27/6/20; accepted 24/4/23

Cardiovasc J Afr 2023; **34**: 00–00 www.cvja.co.za

DOI: 10.5830/CVJA-2023-024

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Hypertensive patients with insulin resistance (IR) are at increased cardiovascular risk compared to hypertensive patients without IR.[1] Likewise, the presence of target-organ damage, including left ventricular hypertrophy (LVH), is associated with a poor prognosis in hypertensive patients.[2] International guidelines therefore recommend considering hypertensive patients with target-organ damage, including LVH, as being at high cardiovascular risk.[3-5]

Hypertension-induced LVH is a known corollary not only of barometric overload secondary to high blood pressure, but also of various metabolic abnormalities induced by IR[6,7] and hyperinsulinaemia.[8,9] LVH represents a phenotype of the formidable capacity of the heart to adapt to various constraints in order to maintain a cardiac output sufficient to meet the metabolic needs of the whole organism. This left ventricular (LV) remodelling is defined as the set of changes in the size, shape and function of the left ventricle.[10]

LVH has a poor prognosis.[2,10-12] It is defined not by the ventricular wall thickness, but by the left ventricular mass (LVM), calculated according to the formula of Devereux, also known as Penn's formula,[13] as:

$$\text{LVM (g)} = 0.8 \times 1.04\,[(\text{LVED} + \text{IVS} + \text{PWT})^3 - \text{LVED}^3] + 0.6\text{ g},$$

where LVED indicates left ventricular end-diastolic diameter, IVS indicates interventricular septal thickness and PWT indicates posterior wall thickness. Therefore, any factor that increases LVM might affect at least one of the following components: LVED and/or IVS and/or PWT.

Because IR and hyperinsulinaemia increase LVM, the purpose of this study was to assess the collective and isolated influence of IR/hyperinsulinaemia on each component of the Devereux formula and on diastolic functional parameters.

Methods

This was a cross-sectional study conducted in the Centre Médical de Kinshasa (CMK) between January and December 2019. The CMK is a reference clinic with a cardiology centre named Pôle de Cardiologie, where cardiovascular explorations such as Doppler echocardiography, coronary scanning and cardiopulmonary exercise testing are performed. It operates with highly qualified, regularly retrained personnel.

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 Public Health School prior to its commencement. Each participant provided written, informed consent to participate in the study. All respondents were debriefed on the results of the study.

Two hundred and twenty asymptomatic hypertensive patients (133 men, 60.4%), aged 51.5 ± 9.7 years, were consecutively enrolled during out-patient consultations at the Pôle de Cardiologie of the CMK between January and December 2019. The inclusion criteria were age of 20 years and above and absence of clinical or laboratory evidence of secondary hypertension, renal or hepatic disease. Patients with heart disease unrelated to high blood pressure were excluded from participation.

Demographic data (age, gender), lifestyle habits (heavy alcohol consumption, current smoking, sedentary behaviour), medical history including cardiovascular risk factors (age at diagnosis of high blood pressure, history of diabetes mellitus, dyslipidaemia, hyperuricaemia, menopause), previous cardiovascular events (stroke, ischaemic heart disease, heart failure, chronic kidney disease, cardiovascular surgery), and current medication use for chronic disease (antihypertensive treatment, antidiabetic treatment and other treatments including statins, antiplatelet agents, hypo-uricaemics, oral contraception and hormone replacement therapy) were collected during an in-person directed interview using an *ad hoc* questionnaire.

Anthropometric parameters measured by a trained observer consisted of measurements of body weight, height, and waist and hip circumference according to WHO recommendations. Body weight was measured in kilograms using a validated electronic balance on a stable and flat surface, with participants in light clothing and shoes. The reading was taken to the nearest 100 g. Height was measured with a measuring rod, to the nearest centimetre, with participants standing barefoot and bareheaded. Body mass index (BMI) was obtained by dividing the weight (kg) by the height (m) squared.

Waist circumference was measured to the nearest 0.1 cm, using a measuring tape applied directly to the skin along the horizontal line passing through the umbilicus. Body surface area (BSA) was calculated using the DuBois formula,[14] as follows:

BSA = height 0.725 × weight 0.425 × 0.007184.

Blood pressure was measured non-invasively by 24-hour ambulatory blood pressure monitoring using a Tonoport V (GE Healthcare, Freiburg, Germany) type recorder. During this recording, the participant was asked to maintain his usual way of life.

LV measurements were obtained according to the updated 2015 American Society of Echocardiography and European Association of Cardiovascular Imaging guidelines for cardiac chamber quantification,[15] using a Vivid T8 (GE) type ultrasound system equipped with 3.5-MHz transducers. Two-dimensionally guided M-mode echocardiography was performed in the parasternal long-axis view. IVS, LVED and PWT were measured at end-diastole at a level just below the mitral valve leaflets. Simultaneous ECG was used to correlate measurements with the cardiac cycle. Diastolic wall thickness was measured at the onset of the QRS wave. LVM was calculated according to the American Society of Echocardiography simplified cubed equation linear method using the equation of Devereux (see above).[13]

LVM was indexed by BSA and by height$^{2.7}$. The relative wall thickness (RWT) of the left ventricle was calculated as (2 × PWT)/LVED.

In accordance with international recommendations,[16] the parameters of LV diastolic function were measured by recording transmitral flow velocity using conventional Doppler echocardiography. With pulsed-wave (PW) Doppler, 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), A (peak A-wave velocity) and deceleration time of early filling (DT) were recorded in the apical four-chamber view with colour-flow imaging for optimal alignment of PW Doppler with blood flow. PW Doppler sample volume (1–3 mm axial size) was placed between the mitral leaflet tips using low wall filter setting (100–200 MHz) and low signal gain, so that the optimal spectral waveforms would not display spikes. 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 was 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.

For all analyses, a blood sample was taken between 7:00 and 9:00 from the cubital vein of the patient who had been fasting since 22:00 the previous day. All analyses were carried out at the CMK laboratory. For the determination of serum uric acid, total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglycerides, blood was collected in a dry tube and the assay was performed by colorimetric spectrophotometer (Helios Epsilon, Milwaukee, USA).

The blood glucose test was performed on plasma oxalate by colorimetric method using standard reagents (Biolabs) and was

measured by the Helios Epsilon spectrophotometer. The dosage of insulin was performed on EDTA plasma by ELISA. Reading the optical density was done on a string read from the firm Humareader Human (Germany).

Hyperinsulinaemia was defined as a fasting insulin level > 90 mmol/l and IR was defined by a HOMAIR ≥ 2.5.[17] Normal LVM was defined as ≤ 115 g/m^2 or ≤ 48 g/m$^{2.7}$ in males and ≤ 95 g/m^2 or ≤ 44 g/m$^{2.7}$ in females, with LVH defined as LVM exceeding those values.[18]

Four LV geometric patterns were defined as follows:[18,19] normal geometry (normal LVM and RWT ≤ 0.42); concentric remodelling (normal LVM and RWT > 0.42); concentric hypertrophy (LVH and RWT > 0.42); and eccentric hypertrophy (LVH and RWT ≤ 0.42).

Three patterns of diastolic dysfunction were defined as follows:[20,21] abnormal relaxation (grade I: E/A ratio < 1 and prolonged deceleration time); pseudo-normal 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 by left atrial area > 20 cm^2 of body surface area.[15]

Statistical analysis

Data are presented as number (*n*) and relative frequencies (%) for categorical variables and average (± standard deviation) for quantitative variables. Paired comparisons were carried out by Pearson's chi-squared or Fischer's exact test, as appropriate, for categorical variables, and multiple comparison of continuous variables (means and medians) by ANOVA and the *H*-test of Kruskal–Wallis. ANOVA tests, which were found to be significant at the threshold of $p < 0.05$, were supplemented by the Scheffé *post hoc* test, comparing the different groups two to two.

The influence of HOMAIR and insulinaemia on the LV and diastolic parameters was investigated by linear regression in simple exploratory analysis, respectively. Correlation coefficients (*r*) were calculated to determine the degree of association between LV and diastolic parameters, and HOMAIR on one hand and insulinaemia on the other. When differences were observed between the ultrasound parameters and HOMAIR or insulin level, the effect of potential confounders was studied by adjustment in multiple linear regression.

Finally, the determination coefficients (R^2), were calculated to determine the degree of association between the ultrasound parameters of the left ventricle and HOMAIR or insulin level. The significance threshold was $p < 0.05$. Statistical analyses were performed using XLStat 2020 (Oxford, UK) and SPSS (Statistic Package for Social Sciences) 20 for Windows version 24 software (Chicago, USA).

Results

Socio-demographic and clinical characteristics of the patients according to LV geometry are shown in Table 1. Thirty-two (14.5%) patients (43.9 ± 9.1 years), 99 (45%) patients (52.4 ± 8.7 years) and 89 (40.5%) patients (53.1 ± 9.8 years) had normal LV geometry, concentric LV remodelling and concentric LVH, respectively. No cases of eccentric LV hypertrophy were found. Compared to participants with normal LV geometry, those with LVH were significantly older, obese, sedentary, insulin-resistant and had more often a history of hypertension, dyslipidaemia,

Table 1. Sociodemographic and clinical characteristics of patients according to LV geometry

Variables	*All* (n = *220*)	*Normal LVG* (n = *32*)	*CR* (n = *99*)	*Concentric LVH* (n = *89*)	p-*value normal LVG vs CR*	p-*value normal LVG vs concentric LVH*	p-*value concentric LVH vs CR*
Age (years)	51.5 ± 9.7	43.9 ± 9.1	52.4 ± 8.7	53.1 ± 9.8	< 0.001	< 0.001	0.605
Gender					0.527	0.746	0.674
Male	133 (60.5)	18 (56.3)	62 (62.6)	53 (59.6)			
Female	87 (39.5)	14 (43.8)	37 (37.4)	36 (40.4)			
T2DM	26 (11.8)	4 (12.5)	13 (13.1)	9 (10.1)	0.930	0.708	0.674
Known HTN	136 (61.8)	12 (37.5)	63 (63.6)	61 (68.5)	0.009	0.002	0.523
ND HTN	84 (38.2)	20 (62.5)	36 (36.4)	28 (31.5)	0.010	0.002	0.480
Overweight	86 (39.1)	15 (46.9)	49 (49.5)	22 (24.7)	0.799	0.020	0.258
Obesity	112 (50.9)	10 (31.3)	36 (36.4)	66 (74.2)	0.601	< 0.001	0.005
Abdominal obesity	97 (44.1)	5 (15.6)	37 (37.4)	55 (61.8)	0.022	< 0.001	< 0.001
Sedentary	123 (55.9)	6 (18.8)	45 (45.5)	72 (80.9)	0.007	< 0.001	< 0.001
Dyslipidaemia	173 (78.6)	18 (56.3)	79 (79.8)	76 (85.4)	0.009	0.007	0.315
High AI	93 (42.3)	8 (25.0)	39 (39.4)	46 (51.7)	0.141	0.010	0.092
Hyperuricaemia	51 (23.2)	3 (9.4)	19 (19.2)	29 (32.6)	0.199	0.011	0.036
Uncontrolled HTN	182 (82.7)	28 (87.5)	85 (85.9)	69 (77.5)	0.820	0.226	0.136
BMI (kg/cm^2)	30.2 ± 5.0	28.2 ± 4.8	28.7 ± 4.0	32.6 ± 5.1	0.560	< 0.001	< 0.001
SBP (mmHg)	135.9 ± 7.9	132.2 ± 7.9	133.8 ± 6.9	138.9 ± 7.8	0.273	< 0.001	0.926
DBP (mmHg)	81.0 ± 9.0	79.8 ± 7.5	79.9 ± 9.7	82.5 ± 8.6	0.957	0.118	0.054
WC (cm)	103.3 ± 12.4	95.4 ± 9.8	100.4 ± 9.8	109.4 ± 13.1	0.013	< 0.001	< 0.001
HR (bpm)	67.9 ± 13.7	69.1 ± 17.2	70.5 ± 11.5	62.1 ± 13.5	0.600	0.021	< 0.001
Hyperinsulinaemia	19 (8.6)	2 (6.3)	8 (8.1)	9 (10.1)	0.740	0.523	0.634
Insulin resistance	44 (20.0)	1 (3.1)	0 (0.0)	43 (48.3)	0.097	< 0.001	< 0.001

Variables are presented as mean ± SD or *n* (%).
LVG: left ventricular geometry; CR: concentric remodelling; LVH: left ventricular hypertrophy; T2D: type 2 diabetes mellitus; HTN: hypertension; ND HTN: newly diagnosed hypertension; AI: atherogenic index; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; WC: waist circumference; HR: heart rate.

Table 2. Biological and ultrasound characteristics of patients according to LV geometry

Variables	*Total* (n = *220*)	*Normal* (n = *32*)	*CR* (n = *99*)	*Concentric LVH* (n = *89*)	p-*value normal LVG vs CR*	p-*value normal LVG vs concentric LVH*	p-*value concentric LVH vs CR*
Glycaemia (mmol/l)	5.8 ± 1.9	5.2 ± 1.2	5.4 ± 1.6	6.4 ± 2.2	0.517	0.004	0.004
TC (mmol/l)	5.5 ± 1.0	5.0 ± 1.0	5.5 ± 1.0	5.5 ± 1.0	0.015	0.017	0.999
LDL-C (mmol/l)	3.7 ± 1.1	3.3 ± 1.1	3.7 ± 1.1	3.9 ± 1.1	0.076	0.009	0.215
Triglycerides (mmol/l)	1.14 ± 0.6	0.91 ± 0.4	1.11 ± 0.6	1.25 ± 0.6	0.081	0.003	0.112
HDL-C (mmol/l)	1.21 ± 0.3	1.27 ± 0.3	1.28 ± 0.4	1.13 ± 0.3	0.897	0.025	0.004
AI	4.8 ± 1.6	4.1 ± 0.9	4.7 ± 1.9	5.2 ± 1.6	0.088	0.004	0.054
HbA_{1c} (%)	6.1 ± 1.3	5.7 ± 1.0	5.9 ± 1.0	6.4 ± 1.6	0.327	0.022	0.010
Creatinine (mmol/l)	84.5 ± 19.0	84.5 ± 18.1	84.3 ± 15.8	84.6 ± 22.5	0.952	0.982	0.915
Uric acid (mmol/l)	367.1 ± 94.6	317.1 ± 78.6	363.6 ± 90.7	388.2 ± 97.9	0.010	0.003	0.075
Insulin (mmol/l)	92.9 ± 41.8	68.2 ± 21.4	73.3 ± 25.8	123.2 ± 43.0	0.314	< 0.001	< 0.001
Calcium (mmol/l)	2.33 ± 0.2	2.32 ± 0.3	2.34 ± 0.2	2.30 ± 0.2	0. 667	0.674	0.173
Ionised calcium (mmol/l)	1.21 ± 0.2	1.24 ± 0.2	1.21 ± 0.1	1.20 ± 0.1	0.462	0.277	0.496
Phosphorus (mmol/l)	1.08 ± 0.2	1.14 ± 0.5	1.08 ± 0.2	1.06 ± 0.2	0.328	0.210	0.495
Hb (mg/dl)	13.4 ± 1.4	13.6 ± 1.6	13.4 ± 1.4	13.3 ± 1.3	0.499	0.295	0.614
HOMAIR	1.79 ± 0.8	1.42 ± 0.8	1.39 ± 0.5	2.37 ± 0.8	0.802	< 0.001	< 0.001
LVED (mm)	44.3 ± 4.6	45.7 ± 2.6	41.9 ± 4.0	46.5 ± 4.4	< 0.001	0.335	< 0.001
IVS (mm)	11.5 ± 1.7	9.0 ± 1.2	11.2 ± 1.3	12.7 ± 1.1	< 0.001	< 0.001	< 0.001
PWT (mm)	11.4 ± 1.6	9.0 ± 0.8	11.2 ± 1.3	12.5 ± 0.9	< 0.001	< 0.001	< 0.001
SWT	22.9 ± 3.1	18.1 ± 1.9	22.3 ± 2.4	25.2 ± 1.6	< 0.001	< 0.001	< 0.001
LVEF	64.6 ± 5.1	63.8 ± 4.4	65.5 ± 4.9	63.7 ± 5.4	0.083	0.925	0.018
LVM (g)	183.0 ± 48.4	139.5 ± 24.6	160.9 ± 34.3	222.8 ± 38.5	0.001	< 0.001	< 0.001
LVMIh ($g/m^{2.7}$)	44.4 ± 11.1	34.4 ± 5.2	38.4 ± 6.4	54.7 ± 8.4	0.002	< 0.001	< 0.001
LVMIbsa (g/m^2)	91.2 ± 20.8	71.9 ± 10.5	81.8 ± 15.1	108.6 ± 15.6	0.008	< 0.001	< 0.001
RWT	0.52 ± 0.1	0.40 ± 0.1	0.54 ± 0.1	0.55 ± 0.07	< 0.001	< 0.001	0.433
E (cm/s)	0.99 ± 0.7	1.31 ± 0.9	1.00 ± 0.5	0.86 ± 0.9	0.015	< 0.001	0.183
E/A ratio	0.99 ± 0.2	1.15 ± 0.1	0.75 ± 0.2	0.71 ± 0.2	< 0.001	< 0.001	0.173
DT (ms)	201.9 ± 40.0	178.1 ± 29.4	197.8 ± 39.2	215.3 ± 39.6	0.011	< 0.001	0.003
Sa (cm/s)	12.4 ± 1.4	12.9 ± 1.2	12.3 ± 1.2	12.4 ± 1.6	0.015	0.109	0.626
LAA (cm^2)	15.7 ± 3.3	13.8 ± 1.9	14.9 ± 2.8	17.3 ± 3.5	0.040	< 0.001	< 0.001
sPAP (mmHg)	26.4 ± 2.9	24.5 ± 1.9	26.5 ± 2.7	27.0 ± 3.1	0.002	< 0.001	0.239

Variables are presented as mean ± SD or *n* (%).
CR: concentric remodelling; TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; HD-C: high-density lipoprotein cholesterol; AI: atherogenic index; HbA_{1c}: glycated haemoglobin; Hb: haemoglobin; HOMAIR: homeostatic model assessment for insulin resistance; LVED: left ventricular end-diastolic diameter; IVS: interventricular septum diameter; PWT: posterior wall thickness; SWT: sum of wall thickness; LVEF: left ventricular ejection fraction; LVM: left ventricular mass; LVMIh: left ventricular mass indexed to $height^{2.7}$; LVMIbsa: left ventricular mass indexed to body surface area; RWT: relative wall thickness; E: peak E-wave velocity; DT: deceleration time; LAA: left atrial area; sPAP: systolic pulmonary arterial pressure.

hyperuricaemia, higher atherogenicity index and higher systolic blood pressure.

Table 1 also shows that for a statistically similar age, high blood pressure history, lipid and uric acid profile, those with concentric LVH were more often obese, sedentary and insulin-resistant. However, those with concentric remodelling, compared to those with normal LV geometry, were more often older, sedentary, and had more often a history of hypertension and dyslipidaemia.

The biological and echocardiographic characteristics are shown in Table 2. For similar total cholesterol and uric acid levels, participants with LVH had lower HDL-C levels, higher glycated haemoglobin and insulin levels, higher HOMAIR, thicker IVS, wider LVED and a higher LVM, with a lower LV ejection fraction than those with concentric remodelling. The E/A ratio was significantly lower for participants with concentric remodelling compared to those with normal LV geometry, and for those with LVH compared to normal LV geometry.

As illustrated in Table 3, as well as in Figs 1 to 6, the correlation between HOMAIR and LVED, IVS, PWT, sum of wall thickness (SWT), LVM indexed to $height^{2.7}$ (LVMIh), LVM indexed to body surface area (LVMIbsa), RWT and E-wave deceleration was 29.8, 41.6, 42.6, 44.1, 43.7, 44.5, 23.9 and 24.9%, respectively.

Multiple linear regression (Table 4) demonstrated that insulin level and HOMAIR explained 46.8% of the increase in IVS (R^2 = 0.468) and 30.9% of the increase in DT (R^2 = 0.309). HOMAIR alone explained 30.1% of the increase in LVED (R^2 = 0.301). Insulin alone explained 46.3% of the increase in PWT (R^2 = 0.463) and 29.4% for RWT (R^2 = 0.294).

Table 3. Correlation between HOMAIR, insulinaemia and LV measurments and diastolic function parameters

	HOMAIR		*Insulin*	
Variables	r	p-*value*	r	p-*value*
LVED (mm)	0.298	< 0.001	0.273	< 0.001
IVS (mm)	0.416	< 0.001	0.468	< 0.001
PWT (mm)	0.426	< 0.001	0.463	< 0.001
SWT	0.441	< 0.001	0.489	< 0.001
LVMIh ($g/m^{2.7}$)	0.437	< 0.001	0.448	< 0.001
LVMIbsa (g/m^2)	0.445	< 0.001	0.472	< 0.001
RWT	0.239	< 0.001	0.288	< 0.001
DT (ms)	0.249	< 0.001	0.304	< 0.001

LVED: left ventricular end-diastolic diameter; IVS: interventricular septum; PWT: posterior wall thickness; SWT: sum of wall thickness; LVMIh: left ventricular mass indexed to $height^{2.7}$; LVMbsa: left ventricular mass indexed to body surface area; RWT: relative wall thickness; DT: deceleration time.

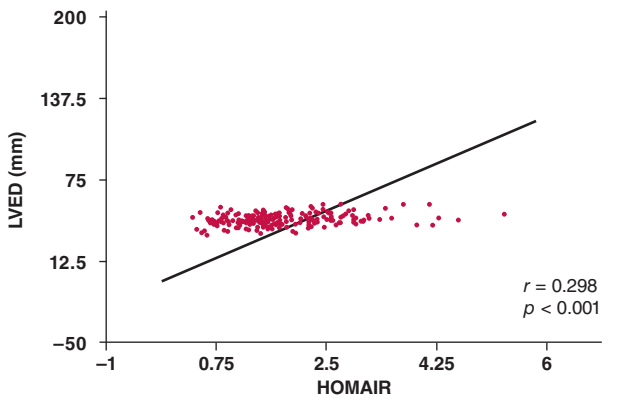

Fig. 1. HOMAIR and left ventricular end-diastole diameter.

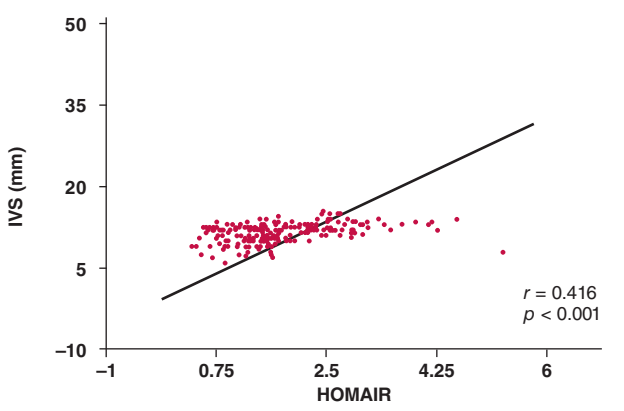

Fig. 2. HOMAIR and interventricular septum.

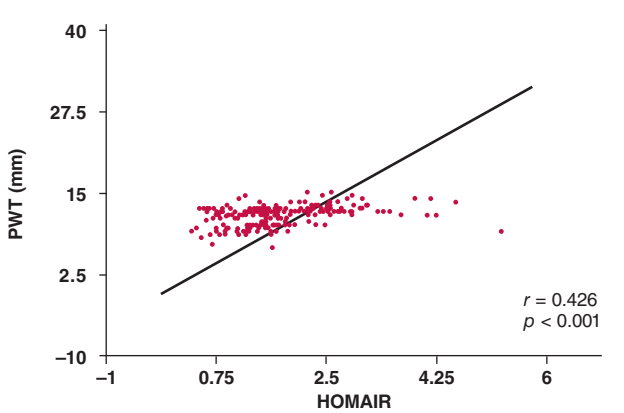

Fig. 3. HOMAIR and posterior wall thickness.

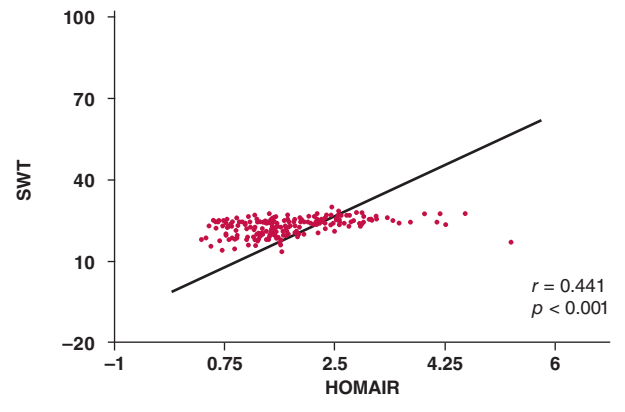

Fig. 4. HOMAIR and sum of wall thickness.

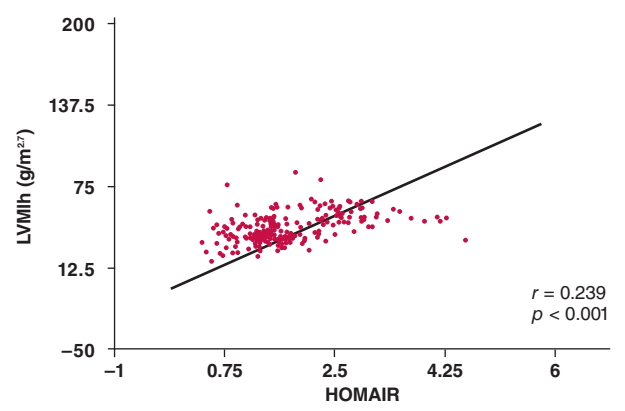

Fig. 5. HOMAIR and left ventricular mass indexed to height$^{2.7}$.

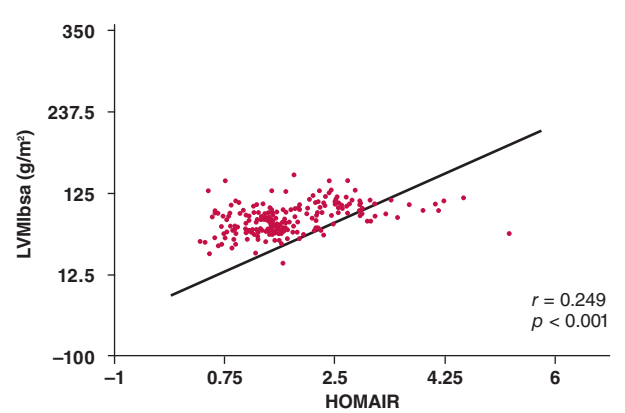

Fig. 6. HOMAIR and left ventricular mass indexed to body surface area.

Discussion

The purpose of this study was to evaluate the association of IR/hyperinsulinaemia with components of Devereux's formula and parameters of LV diastolic function.

The results suggest that IR and hyperinsulinaemia have different effects on components of Devereux's formula, depending on whether they act in synergy or in isolation. IR alone appears to increase LVM only by dilation of LVED, while hyperinsulinaemia alone may increase LVM by a trophic effect on the posterior wall. Only their synergistic action seems to have a trophic effect on the IVS but also a deleterious effect on diastolic function.

These findings make the thorny question of 'the egg and the chicken' between IR and hyperinsulinaemia appear as a watermark. The cause–effect relationship between IR and

Table 4. Multiple linear regression analysis between HOMAIR, insulin and LV echocardiographic parameters

	Equation parameters				
Parameters	β	*SE*	p-*value*	R^2	*Overall* p-*value*
LVED (mm)				0.301	0.001
(constant)	41.375	0.729	0.000		
HOMAIR	1.599	0.823	0.013		
Insulin	0.001	0.017	0.954		
IVS (mm)				0.468	< 0.001
(constant)	9.723	0.254	0.000		
HOMAIR	0.860	0.287	0.016		
Insulin	0.021	0.006	0.000		
PWT (mm)				0.463	< 0.001
(constant)	9.787	0.230	0.000		
HOMAIR	0.063	0.260	0.810		
Insulin	0.016	0.005	0.002		
RWT				0.294	0.011
(constant)	0.467	0.014	0.000		
HOMAIR	0.014	0.016	0.377		
Insulin	0.001	0.000	0.007		
DT ms				0.309	0.003
(constant)	175.610	6.374	0.000		
HOMAIR	6.453	7.203	0.017		
Insulin	0.409	0.145	0.005		

LVED: left ventricular end-diastolic diameter; IVS: interventricular septum; PWT: posterior wall thickness; RWT: relative wall thickness; DT: deceleration time.

hyperinsulinaemia is still debated, since these two conditions are closely associated. It is possible that the two conditions are related by a reciprocal causal relationship, since there are plausible physiopathological explanations justifying the role of the 'chicken or egg' for each of the conditions, respectively.

The pathophysiological mechanisms by which IR promotes LVH and diastolic dysfunction have been the subject of several experimental studies.[22-24] The starting point of a complex metabolic cascade during IR, culminating in structural and functional anomalies of the left ventricle, is the almost exclusive recourse to the metabolism of fatty acids as fuel. Indeed, in a situation of adequate insulin sensitivity, free fatty acids constitute the main fuel for the production of energy[22,25] necessary for uninterrupted and highly endergonic myocardial activity.[22] However, the heart machinery is capable of remarkable metabolic adaptability, allowing it, if necessary, to resort to other sources of energy such as glucose, pyruvate and ketone bodies.[22,26]

On the contrary, in the IR state, this metabolic flexibility is lost.[27] The synthesis of glycogen and the catabolism of proteins in skeletal muscles is impaired, and the activity of lipoprotein lipases in adipocytes is inhibited, resulting in an increased release of free fatty acids and inflammatory cytokines such as interleukin-6, tumour necrosis factor alpha and leptin.[28,29] The heart is therefore integrated in an environment rich in fatty acids and glucose.[30-33] This stimulates the absorption of free fatty acids into the myocardium[33,34] due to upregulation of CD36,[31] which is a powerful transporter of free fatty acids, thus increasing the levels of intracellular fatty acids and the expression of PPAR-α. The excess lipids in the cardiomyocytes are transferred into non-oxidative pathways, leading to the accumulation of toxic lipid species such as ceramides, diacylglycerols, long chain acyl-CoA and acylcarnitines,[35] which contribute to alteration of mitochondrial function, apoptosis and cardiac hypertrophy.[36,37]

Insulin regulates a wide range of functions in the heart, including heart growth.[38] The responsibility for hyperinsulinaemia, which may be a cause or a consequence of IR[39] in the development of LVH,[8,9] and the deterioration of diastolic function[8,40,41] is generally accepted and could be accounted for by the trophic and profibrotic properties of insulin.[8,9,42,43]

The dilator effect of IR on the LVED could be explained by volume overload. The latter is the consequence of insulin-induced sodium retention.[44-47]

Our results indicate that 29.4% of variation in RWT could be explained by insulinaemia, suggesting concentric remodelling. We also found that IR and hyperinsulinaemia increased the DT, which is a parameter of grade I diastolic dysfunction,[19,21] in 31% of patients (R^2 = 0.309). These findings are in accordance with the results of a population-based prospective study by Cauwenberghs *et al.*[48] showing that basal IR and its increase during follow up was positively associated with development of concentric LVH. Similarly, Velagaleti *et al.* assessed the influence of IR on LVM, measured by magnetic resonance imaging, and also concluded that IR caused concentric LVH.[49]

Participants in the study by Cauwenberghs *et al.*, who remained or became IR during follow up, experienced worse changes in E/e′, which is a parameter of diastolic dysfunction.[19,21] Such diastolic dysfunction is probably imputable to IR,[50] with underlying LVH and myocardial fibrosis.[21,51-54] But this is still a subject of debate, as a certain degree of diastolic dysfunction exists in hypertensive patients long before they develop LVH,[55] and regression of LVH after antihypertensive treatment does not necessarily lead to normalisation of diastolic function.[56] Nonetheless, some studies have shown that normalisation of LVM leads to normalisation of diastolic function.[57]

Therefore, IR/hyperinsulinaemia appears to increase cardiovascular risk in patients with hypertension, at least in part, by promoting concentric LVH and diastolic dysfunction. Indeed, concentric LVH is the independent cardiovascular risk factor most strongly associated with a poor prognosis,[12] and diastolic dysfunction is a strong predictor of cardiovascular outcomes in essential hypertension.[58,59]

Strengths and limitations

Our study has to be interpreted within the context of its potential strengths and limitations. To the best of our knowledge, this is the first study to address the question of the collective or individual influence of IR/hyperinsulinaemia on the components of Devereux's formula and on the parameters of diastolic function in Africans.

However echocardiographic measurements are prone to errors as a result of signal noise, acoustic artefacts and angle dependency, although in our study, echocardiography was performed by an experienced cardiologist with post-graduate training in cardiac imaging. Moreover, the cross-sectional design of this study is a limitation, which means that causal relationships cannot be firmly established. Also, measurement of waist circumference at the level of the umbilicus is a possible cause of error as it will vary with the habitus of the individual, obese individuals with protuberant abdominal walls or those with a large umbilical hernia, giving false measurements. Finally, the in-hospital and single-centre design precludes extrapolation of the results to all essential hypertensive patients.

Conclusions

Our study suggests that IR appears to act on LVED, while hyperinsulinaemia affects the PWT. Both conditions act on the IVS and contribute to diastolic dysfunction via E-wave deceleration time. Insulin sensitivity of hypertensive patients should therefore be of concern to the physician managing hypertension, in order to take appropriate measures to improve the prognosis. A prospective, population-based study with serial imaging remains essential to better understand subclinical LV deterioration over time and to confirm the role of IR in essential hypertensives. Even better would be the Mendelian randomisation approach, which would however be costly, time consuming and more difficult to apply.

We gratefully acknowledge Dr Rodolph Amhed, managing director of the Centre Médical de Kinshasa for granting us permission to conduct this study in CMK.

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