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Cross-Sectional Study

Effect of Insulin Resistance on Left Ventricular Remodeling in Essential Hypertensives: A Cross Sectional Study

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Abstract

Background: In clinical practice, left ventricular hypertrophy is defined not by the left ventricular walls thickness, but by the left ventricular mass. The later is calculated according to the Devereux's formula, and is increased by insulin resistance/hyperinsulinemia. It is however unclear which of insulin resistance, hyperinsulinemia, or both is actually causative and what is their collective or individual influence on the components of Devereux's formula and parameters of left ventricular diastolic function. The present study evaluated the associations of the Homeostatic Model Assessment for Insulin Resistance (HOMAIR) and fasting plasma insulin 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 remodeling 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% in E-wave deceleration time (R^2 =0.309; overall p = 0.003) were explained by insulin 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% ofrelative wall thickness (R^2 = 0.294 ; p= 0.007) by insulin alone.

Conclusion: Insulin resistance and hyperinsulinemia do not have the same influence on the components of Devereux's formula. Insulin resistance appears to act on the left ventricular end diastole diameter, while hyperinsulinemia affects the posterior wall thickness. Both abnormalities act on the interventricular septum and contribute to diastolic dysfunction via the E wave deceleration time.

Keywords: Diastolic dysfunction; Hyperinsulinemia; Hypertension; Insulin resistance; Left ventricular remodeling

Background

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 (TOD) Including Left Ventricular Hypertrophy (LVH), is associated with 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 hyperinsulinemia [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 remodeling is defined as the set of changes in the size, shape and function of the left ventricle [10].

Left ventricular hypertrophy has a poor prognosis [2,10-12]. It is defined not by the ventricular walls thickness, but by the Left Ventricular Mass (LVM) calculated according to the formula of Devereux as LVM (g) = 0.8 (1.04 [(LVED+IVS+PWT)^3 - LVED^3]) + 0.6 g [13], where LVED indicates left ventricular end-diastolic diameter, IVS indicates interventricular septal thickness, and PWT indicates posterior wall thickness. Thus any factor that increases LVM, might affect at least one among the following components: left ventricular end-diastolic diameter and/or the thickness of the left interventricular septum, and / or the thickness of the posterior wall (LVED, and/or IVS, and / or PWT). Because IR and hyperinsulinemia do increase LVM, the purpose of this study was to assess the collective and isolated influence of IR/hyperinsulinemia on each component of the Devereux formula and on diastolic function parameters.

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Methods

Study design and setting

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

Participants selection

Two hundred and twenty hypertensive asymptomatic patients (133 men,60,4%) aged 51.5 ± 9.7 years, were consecutively enrolled during outpatient consultations at the Pôle de Cardiologie of the Center Médical de Kinshasa (CMK), between January and December 2019. The inclusion criteria were age of 20 years and aboveand 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.

Study procedures

Anamnestic data: Demographic data (age, sex),lifestyle habits (heavy alcohol consumption, current smoking, sedentary behavior),medical history including cardiovascular risk factors (age at diagnosis of high blood pressure, history of diabetes mellitus, dyslipidemia, hyperuricemia, menopause) and previous cardiovascular events (stroke, ischemic heart disease, heart failure, Chronic Kidney Disease, cardiovascular surgery), and current medication use for chronic disease (antihypertensive treatment, anti-diabetic treatment and other treatments including statins, antiplatelet agents, hypouricemics, oral contraception, hormone replacement therapy) were collected during an in-person directed interview using ad hoc questionnaire.

Anthropometric data: Anthropometric parameters measured by a trained observer consisted in measurements of body weight, height, 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 participant in light clothing and shoes. The reading was made to the nearest 100 g. Height was measured with a measuring rod, to the nearest centimeter, with 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 the horizontal line passing through the umbilicus. The Body Surface Area (BSA) was calculated using the Dubois formula as follows: BSA = Height 0.725 × Weight 0.425 × 0.007184 [14]. BMI was obtained by dividing the weight (Kg) by the height (m) squared.

Blood pressure

BP was measured non-invasively by 24 Hour-Ambulatory Blood Pressure Monitoring (ABPM) using a TONOPORT V (GE Health care, Freiburg, GERMANY) type recorder. During this recording, the participant was asked to maintain his usual way of life.

Echocardiographic data

Left ventricular measurements were obtained according to the updated 2015 American Society of Echocardiography and European Association of Cardiovascular Imaging guidelines for cardiac chamber quantification using a Vivid T8 (GE) type ultrasound system equipped with 3.5 MHz transducers [15]. Two-dimensionally guided M-mode echocardiography was performed on a parasternal long-axis view. Interventricular Septum Thickness (IVS), Left Ventricular End-Diastolic Diameter (LVED), and Posterior Wall Thickness (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 following equation: LVM (grams) = 0.8 × 1.04 × [(LVED + IVS + PWT)3- (LVED)3] + 0.6 g. LVM was indexed by BSA and by height $^{2.7}$. The Relative Wall Thickness (RWT) of the Left Ventricle (LV) 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 Doppler (PW), transmitral flow velocity was recorded from the apical transducer position with the sample volume situated between the mitral leaflet tips. E (Peak E-wave velocity), A (Peak A-wave velocity) and Deceleration Time of early filling (DT), were recorded in apical four-chamber with color flow imaging for optimal alignment of PW Doppler with blood flow. PW Doppler sample volume (1-3 mm axial size) was placed between mitral leaflet tips using low wall filter setting (100-200 MHz) and low signal gain, so that the optimal spectral waveforms 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 as for two dimensional and M-mode echocardiography. Mitral annular velocities were recorded from the apical window. Sample volumes were located at the lateral site of the mitral annulus. Peak early diastolic mitral annular velocity (E′, cm/s) was measured over five cardiac cycles and the mean calculated. The ratio E/e′ was used as a parameter of left atrial pressure, which is elevated with progression of LV diastolic dysfunction. These parameters, obtained by tissue doppler echocardiography, were also used as parameters of LV diastolic function.

Laboratory Parameters

For all analyzes, a blood sample was taken between 7 a.m. and 9 a.m. from the cubital vein of the patient fasting since 10 p.m. of the previous day. All analyzes were carried out at the CMK laboratory. For the determination of serum uric acid, total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides, blood was collected in a dry tube and the assay performed by colorimetric spectrophotometer (HELIOS Epsilon, Milwaukee, USA). The blood glucose test was performed on plasma oxalate by colorimetric method using standard reagents (Biolabo) and 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).

Operational Definitions

- Hyperinsulinemia was defined as fasting insulin > 90 mmol / L.
- Insulin resistance 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 remodeling (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 (DD) was defined as follow [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 Atrium Area (LAA) >20 cm^2 of body surface [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 Chi-square or Fischer's Exact test as appropriate for categorical variables and multiple comparison of continuous variables (means and medians) by ANOVA and H test of Kruskal Wallis. ANOVA tests found to be significant at the threshold of p<0.05 were supplemented by a post hoc test by Scheffé. The influence of HOMAIR and insulinemia on the left ventricular 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 left ventricular and diastolic parameters, and HOMAIR on the one hand and insulinemia on the other. When differences were observed between the ultrasound parameters and HOMAIR or insulin, the effect of potential confounders was studied by adjustment in multiple linear regression. Finally, the determination coefficients (R2), were calculated to determine the degree of association between the ultrasound parameters of the left ventricle and HOMAIR or insulin. The significance threshold was p <0.05. Statistical analyzes were performed using XLStat 2020 (Oxford, UK) and SPSS (Statistic Package for Social Sciences) 20 for Windows version 24 software (Chicago, USA).

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 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.

Results

Socio-demographic and clinical characteristics of the patients according to left ventricular 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 left ventricular geometry, concentric left ventricular remodeling and concentric left ventricular hypertrophy respectively. No cases of eccentric left ventricular hypertrophy were found. Patients with left ventricular hypertrophy were significantly older than patients with normal left ventricular geometry and more often had a history of hypertension, with higher 24-hour mean systolic blood pressure, while patients with normal ventricular geometry were more often newly diagnosed with hypertension. Patients with LVH were more often sedentary, obese, hyperuricemic, and insulin resistant, and more often with dyslipidemia and high atherogenicity index.

Variables	All n=220	Normal VG n=32	Concentric Remodeling n=99	Concentric LVH n=89	p
Age, Years	51.5±9.7	43.9±9.1	52.4±8.7	53.1±9.8	<0.001
Sex, n (%)					0.802
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)	0.811
Known HTN	136(61.8)	12(37.5)	63(63.6)	61(68.5)	0.007
ND HTN	84(38.2)	20(62.5)	36(36.4)	28(31.5)	0.009
Overweight	86(39.1)	15(46.9)	49(49.5)	22(24.7)	0.001
Obesity	112(50.9)	10(31.3)	36(36.4)	66(74.2)	<0.001
Abdominal Obesity	97(44.1)	5(15.6)	37(37.4)	55(61.8)	<0.001
Sedentary	123(55.9)	6(18.8)	45(45.5)	72(80.9)	<0.001
Dyslipidemia	173(78.6)	18(56.3)	79(79.8)	76(85.4)	<0.005
High AI					
93(42.3)	8(25.0)	39(39.4)	46(51.7)	0.023	
Hyperuricemia	51(23.2)	3(9.4)	19(19.2)	29(32.6)	0.011
Uncontrolled HTN	182(82.7)	28(87.5)	85(85.9)	69(77.5)	0.250
BMI (Kg/cm2)	30.2±5.0	28.2±4.8	28.7±4.0	32.6±5.1	0.000
SBP (mmHg)	135.9±7.9	132.2±7.9	133.8±6.9	138.9±7.8	0.000
DBP (mmHg)	81.0±9.0	79.8±7.5	79.9±9.7	82.5±8.6	0.143
WC (cm)	103.3±12.4	95.4±9.8	100.4±9.8	109.4±13.1	0.000
HR (bpm)	67.9±13.7	69.1±17.2	70.5±11.5	62.1±13.5	0.437
Hyperinsulinemia	19(8.6)	2(6.3)	8(8.1)	9(10.1)	0.848
Insulin resistance	44(20.0)	1(3.1)	0(0.0)	43(48.3)	<0.001

Table 1: Sociodemographic and clinical characteristics of patients according to left ventricular geometry.

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

The biological and echographic characteristics are shown in table 2. The mean values of glycaemia, total cholesterol, LDL-C, triglyceride, atherogenicity index, HbA1c, uricemia, insulinemia, HOMAIR, mitral E wave deceleration time, left atrium area, and systolic Pulmonary Artery Pressure (sPAP) were significantly higher in patients with LVH compared to those with normal left ventricular geometry, whereas E/A ratio was lower.

As illustrated in table 3, the correlation between HOMAIR and LVED, IVS, PWT, SWT, LVMIh, 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.

Variables	Total N=220	Normal n=32	Concentric Remodeling n=99	Concentric LVH n=89	p
Glycemia (mmol/L)	5.8±1.9	5.2±1.2	5.4±1.6	6.4±2.2	<0.001
TC (mmol/L)	5.5±1.0	5.0±1.0	5.5±1.0	5.5±1.0	0.027
LDL-C (mmol/L)	3.7±1.1	3.3±1.1	3.7±1.1	3.9±1.1	0.047
Triglycerides (mmol/L)	1.14±0.6	0.91±0.4	1.11±0.6	1.25±0.6	0.029
HDL-C. (mmol/L)	1.21±0.3	1.27±0.3	1.28±0.4	1.13±0.3	0.009
AI	4.8±1.6	4.1±0.9	4.7±1.9	5.2±1.6	0.005
HbA1C (%)	6.1±1.3	5.7±1.0	5.9±1.0	6.4±1.6	0.016
Creatinine (mmolL)	84.5±19.0	84.5±18.1	84.3±15.8	84.6±22.5	0.991
Uric Acid (mmolL)	367.1±94.6	317.1±78.6	363.6±90.7	388.2±97.9	0.001
Insulin (mmolL)	92.9±41.8	68.2±21.4	73.3±25.8	123.2±43.0	<0.001
Calcium (mmolL)	2.33±0.2	2.32±0.3	2.34±0.2	2.30±0.2	0.269
Ionized Calcium (mmolL)	1.21±0.2	1.24±0.2	1.21±0.1	1.20±0.1	0.380
Phosphorus (mmolL)	1.08±0.2	1.14±0.5	1.08±0.2	1.06±0.2	0.270
Hb (mg/dl)	13.4±1.4	13.6±1.6	13.4±1.4	13.3±1.3	0.595
HOMAIR	1.79±0.8	1.42±0.8	1.39±0.5	2.37±0.8	<0.001
LVED (mm)	44.3±4.6	45.7±2.6	41.9±4.0	46.5±4.4	<0.001
IVS (mm)	11.5±1.7	9.0±1.2	11.2±1.3	12.7±1.1	<0.001
PWT (mm)	11.4±1.6	9.0±0.8	11.2±1.3	12.5±0.9	<0.001
SWT	22.9±3.1	18.1±1.9	22.3±2.4	25.2±1.6	<0.001
LVEF	64.6±5.1	63.8±4.4	65.5±4.9	63.7±5.4	0.038
LVM (g)	183.0±48.4	139.5±24.6	160.9±34.3	222.8±38.5	<0.001
LVMIh ($g/m^{2.7}$)	44.4±11.1	34.4±5.2	38.4±6.4	54.7±8.4	<0.001
LVMIbsa (g/m^2)	91.2±20.8	71.9±10.5	81.8±15.1	108.6±15.6	<0.001
RWT	0.52±0.1	0.40±0.1	0.54±0.1	0.55±0.07	<0.001
E (Cm/s)	0.99±0.7	1.31±0.9	1.00±0.5	0.86±0.9	0.015
E/A ratio	0.99±0.2	1.15±0.1	0.75±0.2	0.71±0.2	0.010
DT (ms)	201.9±40.0	178.1±29.4	197.8±39.2	215.3±39.6	<0.001
Sa (cms)	12.4±1.4	12.9±1.2	12.3±1.2	12.4±1.6	0.096
LAA (cm^2)	15.7±3.3	13.8±1.9	14.9±2.8	17.3±3.5	<0.001
sPAP (mmHg)	26.4±2.9	24.5±1.9	26.5±2.7	27.0±3.1	<0.001

Table 2: Biological and ultrasound characteristics of patients according to left ventricular geometry.

Variables are presented as mean ± SD or n (%).

TC = Total Cholesterol; LDLc = Low-Density Lipoprotein; HDLc = High-Density Lipoprotein; AI = Atherogenic Index; HbA1C = Glycated Haemoglobin; Hb = Haemoglobin; HOMAIR = Homeostatic Model Assessment for Insulin Resistance; LVED = Left Ventricular End-Diastolic; 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.

Multiple linear regression (Table 4) demonstrated that insulin 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 ($R^2 = 0.294$).

Variables	HOMAIR		Insulin	
	r	p	R	p
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

Table 3: Correlation between HOMAIR, insulinemia and left ventricular mensurations and diastolic function parameters.

LVED = Left Ventricular End-Diastole 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.

Parameters	Equation parameters				
	β	SE	P	R2	Overall p
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**		

Table 4: Multiple linear regression analysis between HOMAIR, Insulin and LV echographic parameters.

LVED = Left Ventricular End-Diastole Diameter; IVS = Interventricular Septum; PWT = Posterior Wall Thickness; RWT = Relative Wall Thickness; DT = Deceleration Time

Discussion

The purpose of the present study was to evaluate the associations of insulin resistance/hyperinsulinemia with components of Devereux's formula and parameters of left ventricular diastolic function.

The results suggest that insulin resistance and hyperinsulinemia have different effects on components of Devereux's formula depending on whether they act in synergy or in isolation. Insulin

resistance alone appears to increase LVM only by dilation of LVED while hyperinsulinemia 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.

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 necessary for uninterrupted and highly endergonic myocardial activity [22,25]. 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 inhibited, resulting in an increased release of free fatty acids and inflammatory cytokines such as IL-6, TNFα 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 hyperinsulinemia, which may be a cause or a consequence of insulin resistance in the development of left ventricular hypertrophy and the deterioration of diastolic function [8,9,39-41], is generally accepted and could be explained accounted for by trophic and profibrotic properties of insulin [8,9,42,43].

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

Our results indicate that 29.4% of variation in RWT could be explained by insulinemia suggesting a concentric remodeling. We also found that IR and hyperinsulinemia do increase the DT which is a parameter of a grade I diastolic dysfunction in 31% (R2 = 0.309) [19,21]. These findings are in accordance with the results of a population-based prospective study by Cauwenberghs, et al. [48], showing that basal insulin resistance and its increase during follow-up, waspositively associated with development of concentric LVH. Similarly, Velagaleti et al. assessed the influence of IR on LVM measured by MRI, and also concluded that IR caused concentric LVH [49]. Participants in Cauwenberghs et al. study, who remained or became insulin resistant during follow-up experienced worse changes in E/e', which is a parameter of DD [19,21]. Such a diastolic dysfunction is probably imputable to IR with underlying left ventricular hypertrophy and myocardial fibrosis [21,50-54]. But this is, however, still a subject of debate as a certain degree of diastolic dysfunction exists in hypertensive patients long before they develop LVH [55], and as LVH regression of after antihypertensive treatment does not necessarily lead to normalization of diastolic function [56]. Nonetheless, some studies have shown that normalization of the left ventricular mass leads to normalization of diastolic function [57].

Therefore, IR/hyperinsulinemia 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 and diastolic dysfunction is a strong predictor of cardiovascular outcomes in essential hypertension [12,58,59].

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 insulin resistance / hyperinsulinemia on the components of Devereux's formula and on the parameters of diastolic function in the Africans. However echocardiographic measurements are prone to errors as a result of signal noise, acoustic artefacts, and angle dependency although in the present 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. Finally, the in-hospital and single-center design precludes extrapolation of the results to all essential hypertensive patients.

Conclusion

Our study suggests that insulin resistance appears to act on left ventricular end diastole diameter, while hyperinsulinemia affects the posterior wall thickness. Both conditions do act on the interventricular septum and contribute to diastolic dysfunction via the 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 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 insulin resistance in essential hypertensives.

Authors Contribution

Design and concept of study: KPB.

Acquisition of data: KPB.

Manuscript draft: KPB.

Supervision: KVE, LMB, MJR.

Statistical analysis: NNA.

All authors read and approved the final manuscript.

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