One-Hour Postload Plasma Glucose Levels and Left Ventricular Mass in Hypertensive Patients

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OBJECTIVE—Left ventricular hypertrophy (LVH), an independent risk factor for cardiovascular (CV) morbidity and mortality, recognizes a multifactorial pathogenesis. A plasma glucose value ≥155 mg/dL for the 1-h postload plasma glucose during an oral glucose tolerance test (OGTT) identifies subjects with normal glucose tolerance (NGT) at high risk for type 2 diabetes. We addressed the question if glucose tolerance status, particularly 1-h postload plasma glucose levels, affects left ventricular mass (LVM) and cardiac geometry in essential hypertension.

RESEARCH DESIGN AND METHODS—We enrolled 767 never-treated hypertensive subjects, 393 women and 374 men (mean age 49.6 ± 8.5 years). All patients underwent an OGTT for the evaluation of glucose tolerance and standard echocardiography. LVM was calculated using the Devereux formula and normalized by body surface area (LVM index [LVMI]). Insulin sensitivity was assessed by the Matsuda index. Among all participants, 514 had NGT, 168 had impaired glucose tolerance (IGT), and 85 had type 2 diabetes. According to the 1-h postload plasma glucose cutoff point of 155 mg/dL, we divided normotolerant subjects into two groups: NGT <155 mg/dL (n = 356) and NGT ≥155 mg/dL (n = 158).

RESULTS—Subjects in the NGT ≥155 mg/dL group had worse insulin sensitivity than subjects in the NGT <155 mg/dL group (Matsuda index 63.9 vs. 88.8; $P < 0.0001$). Men with NGT ≥155 mg/dL had a higher LVMI than men with NGT <155 mg/dL (126.6 vs. 114.3 g/m^2; P = 0.002) and a different LVH prevalence (41.1 vs. 25.8%; $P < 0.0001$). At multiple regression analysis, 1-h glucose resulted in the major determinant of LVMI in normotolerant, IGT, and diabetic groups.

CONCLUSIONS—These data show that NGT ≥155 mg/dL subjects, compared with NGT <155 mg/dL subjects, have a higher LVMI and a greater prevalence of LVH similar to that of IGT and diabetic patients.

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Left ventricular hypertrophy (LVH) represents an independent risk factor for cardiovascular (CV) morbidity and mortality in essential hypertension (1) and in the general population (2). Left ventricular mass (LVM) increase is not only the consequence of adaptative cardiac remodeling to pressure overload, but it recognizes a complex and multifactorial pathogenesis. In fact, several studies have demonstrated that hypertension explains only a 10–25% variation of LVM, confirming the hypothesis that other nonhemodynamic factors such as salt retention (3) and genetic (4), hormonal, and metabolic factors (5) are involved in the LVM increase.

It is known that type 2 diabetes is an independent risk factor for heart failure independently of coronary artery disease or hypertension (6). A possible explanation is that the metabolic abnormalities characterizing type 2 diabetes may affect the cardiac structure, promoting the LVH appearance (7,8). In addition, subjects with impaired glucose tolerance (IGT) and/or impaired fasting glucose (IFG) are characterized by an unfavorable CV risk profile (9). Rutter et al. (7) demonstrated that glucose metabolism worsening, tested by an oral glucose tolerance test (OGTT), is more strongly associated with LVH in women than in men. Similarly, women in the Hoorn study showed eccentric or concentric LVH according to IGT (8).

Recently, a cutoff point of 155 mg/dL for the 1-h postload plasma glucose during an OGTT identifies subjects with normal glucose tolerance (NGT) at high risk for type 2 diabetes (10). Moreover, a 1-h postload plasma glucose value is strongly associated with carotid intima-media thickness (IMT) (11), a subclinical organ damage and an independent predictor for CV events (12).

Taken together, we designed this study to address the question if glucose tolerance status, and in particular 1-h postload plasma glucose levels, may affect LVM and geometry in a group of never-treated hypertensive Caucasian subjects.

RESEARCH DESIGN AND METHODS

Study population

We enrolled 767 Caucasian hypertensive outpatients who were free of complications (393 men and 374 women aged 40–70 years [mean ± SD 49.6 ± 8.5]) and participating in the Catanzaro Metabolic Risk Factors Study (CATAMERIS). Causes of secondary hypertension were excluded by appropriate clinical and biochemical tests. Other exclusion criteria were history or clinical evidence of coronary and valvular heart disease, congestive heart failure, hyperlipidemia, peripheral vascular disease, chronic gastrointestinal disease associated with malabsorption, chronic pancreatitis, history of any malignant disease, history of alcohol or drug abuse, liver or kidney failure, and treatment to modify glucose metabolism. No patient had ever been treated with antihypertensive drugs. All subjects underwent anthropometrical

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evaluation: weight, height, BMI, and waist circumference (WC).

After a 12-h fast, a 75-g OGTT was performed with 0, 30, 60, 90, and 120 min sampling for plasma glucose and insulin. Glucose tolerance status was defined on the basis of OGTT using the World Health Organization criteria. Insulin sensitivity was evaluated using the Matsuda index (insulin sensitivity index [ISI]) calculated as follows: 10,000/square root of [fasting glucose (millimoles per liter) × fasting insulin (milliunits per liter)] × [mean glucose × mean insulin during OGTT]. The Matsuda index is strongly related to the euglycemic-hyperinsulinemic clamp, which represents the gold standard test for measuring insulin sensitivity (13). An ethics committee approved the protocol, and informed written consent was obtained from all participants. All investigations were performed in accordance with the principles of the Declaration of Helsinki.

Blood pressure measurements

Clinic blood pressure readings were obtained from the left arm of supine patients, after 5 min of quiet rest, with a mercury sphygmomanometer. A minimum of three blood pressure readings were taken on three separate occasions at least 2 weeks apart. Baseline blood pressure values were the average of the last two of three consecutive measurements obtained at intervals of 3 min. Patients with a clinic systolic blood pressure (SBP) >140 mmHg and/or diastolic blood pressure (DBP) >90 mmHg were defined as hypertensive.

Laboratory determinations

Plasma glucose was measured by the glucose oxidation method (Beckman Glucose Analyzer II; Beckman Instruments, Milan, Italy). Triglyceride and total and HDL cholesterol concentrations were measured by enzymatic methods (Roche Diagnostics, Mannheim, Germany). Plasma insulin concentration was determined by a chemiluminescence-based assay (Roche Diagnostics).

Echocardiograms

Tracings were taken with patients in a partial left decubitus position using a VIVID-7 Pro ultrasound machine (GE Technologies, Milwaukee, WI) with an annular phased array 2.5-MHz transducer. Echocardiographic readings were made in random order by the investigator, who had no knowledge of patients' blood pressure and other clinical data. Only frames with optimal visualization of cardiac structures were considered for reading. The mean values from at least five measurements of each parameter for each patient were computed. Having the same experienced sonographer perform all studies in a dimly lit and quiet room optimized the reproducibility of measurements. In our laboratory, the intraobserver coefficients of variation (CVs) were 3.85% for posterior wall (PW) thickness, 3.70% for interventricular septal (IVS) thickness, 1.50% for left ventricular internal diameter (LVID), and 5.10% for LVM.

M-mode measurements

Tracings were recorded under two-dimensional guidance, and M-mode measurements were taken at the tip of the mitral valve or just below. Measurements of IVS thickness, PW thickness, and LVID were made at end-diastole and end-systole. LVM was calculated using the Devereux equation (14) and normalized by body surface area (LVM index [LVMI]). Partition values for LVH were taken with the cutoff value of 125 g/m^2 for both women and men, as suggested by Casale et al. (15).

Patterns of left ventricular geometry

Relative wall thickness (RWT) was measured at end-diastole as the ratio of the (IVS + PW)/LVID. A value of 0.45 was considered to be the cutoff for normal.

Concentric remodeling or concentric LVH was defined by an RWT >0.45.

Statistical analysis

ANOVA for clinical and biological data was performed to test the differences among groups, and the Bonferroni post hoc test for multiple comparisons was further performed. The χ^2 test was used for categorical variables. Correlation coefficients were calculated according to Pearson's method. Linear regression analysis was performed to relate LVMI to the following covariates: age, BMI, WC, SBP, DBP, fasting, 1-h and 2-h postload plasma glucose levels, fasting insulin, Matsuda index, and high-sensitivity C-reactive protein (hs-CRP). Subsequently, variables reaching statistical significance and sex, as a dicotomic value, were inserted in a stepwise multivariate linear regression model to determine the independent predictors of LVMI. Correlation analysis was performed for the whole study population and according to different groups of glucose tolerance. Data are reported as means ± SD. Differences were assumed to be significant at $P < 0.05$. All comparisons were performed using the statistical package SPSS 16.0 for Windows (SPSS, Chicago, IL).

RESULTS

Study population

Of 767 patients examined by OGTT, 514 had NGT, 168 had IGT, and 85 had newly diagnosed type 2 diabetes. A 1-h postload plasma glucose cutoff point of 155 mg/dL during an OGTT was used to stratify NGT subjects into two groups: 356 patients with 1-h postload plasma glucose <155 mg/dL (NGT <155) and 158 individuals with 1-h postload plasma glucose ≥155 mg/dL (NGT ≥155). Table 1 shows the demographic, clinical, and biochemical characteristics of the four study groups.

There was a significant difference in sex distribution among the groups (P = 0.031); in particular, in type 2 diabetic patients and in NGT ≥155, there was a major prevalence of men (63.5 and 54.4%, respectively). In the IGT group, women were more prevalent than men (55.9 vs. 44.0%). On the contrary, there was no significant difference among groups for BMI, DBP, and total and HDL cholesterol. From the first to the fourth group, there was a significant increase in WC (P = 0.008), SBP ($P < 0.0001$), triglycerides (P = 0.001), and in hs-CRP values ($P < 0.0001$). Obviously, a progressive increase of fasting, 1-h and 2-h postload glucose, as well as fasting and 2-h insulin, parallel the worsening of glucose tolerance ($P < 0.0001$), explaining the reduction of Matsuda index/ISI. Moreover, NGT ≥155 had significantly reduced insulin sensitivity ($P < 0.0001$) and increased hs-CRP values (P = 0.001) when compared with NGT <155 and had metabolic and inflammatory profiles similar to IGT individuals.

Echocardiographic parameters and glucose tolerance

Echocardiographic parameters for the study population and for women and men, according to glucose tolerance groups, are reported in Table 2. Considering the whole study cohort, the type 2 diabetic patients had the highest end-diastolic LVID (EDLVID) (P = 0.018) and diastolic PW (dPW) (P = 0.008) values, but there were no significant differences for IVS among groups. Moreover, LVMI

Table 1—*Anthropometric, hemodynamic, and biochemical characteristics of the study population according to glucose tolerance*

	NGT <155	NGT ≥155	IGT	Type 2 diabetes	*P*
n	356	158	168	85	—
Sex (M/F)	179/177	86/72	74/94	54/31	0.031*
Age (years)	48.6 ± 9.6	50.9 ± 7.9	49.7 ± 6.2	49.7 ± 6.2	0.030
BMI (kg/m^2)	29.9 ± 5.6	31.1 ± 6.1	31.1 ± 5.3	31.1 ± 5.4	0.065
WC (cm)	101.2 ± 13.5	103.5 ± 12.9	104.3 ± 12.8	106.1 ± 12,5	0.008
SBP (mmHg)	137.1 ± 15.8	139.4 ± 16.3	143.6 ± 17.7	143.6 ± 19.5	<0.0001
DBP (mmHg)	84.7 ± 10.8	84.5 ± 10.2	85.7 ± 10.4	86.2 ± 11.5	0.473
Fasting glucose (mg/dL)	91.5 ± 10.3	94.7 ± 11.1	98.1 ± 13.1	120.7 ± 33.8	<0.0001
1-hour glucose (mg/dL)	120.2 ± 22.4	184.4 ± 27.5	188.7 ± 34.3	245.8 ± 45.8	<0.0001
2-hour glucose (mg/dL)	101.2 ± 19.7	114.3 ± 17.5	162.1 ± 16.2	242.1 ± 46.1	<0.0001
Fasting insulin (μU/mL)	11.3 ± 6.2	12.7 ± 6.9	15.5 ± 9.8	15.9 ± 10.1	<0.0001
1-hour insulin (μU/mL)	94.5 ± 63.6	105.2 ± 61.4	100.8 ± 49.8	88.1 ± 56.1	0.103
2-hour insulin (μU/mL)	64.1 ± 49.4	76.2 ± 52.6	128.5 ± 76.9	110.1 ± 65.2	<0.0001
Matsuda index/ISI	88.8 ± 61.9	63.9 ± 50.3	48.8 ± 32.5	41.8 ± 29.2	<0.0001
Total cholesterol (mg/dL)	203.5 ± 40.8	201.1 ± 34.7	206.5 ± 41.1	205.3 ± 46.8	0.641
HDL cholesterol (mg/dL)	51.8 ± 14.5	50.8 ± 13.2	50.2 ± 13.1	49.6 ± 15.1	0.430
Triglycerides (mg/dL)	127.9 ± 70.4	125.6 ± 66.1	147.1 ± 77.1	155.4 ± 84.3	0.001
hs-CRP (mg/L)	2.1 ± 1.2	2.7 ± 1.4	2.9 ± 1.7	3.7 ± 1.9	<0.0001

*χ^2 Test.

values significantly increased from the first to the fourth group (P = 0.002). Notably, NGT ≥155 subjects showed an LVMI value not significantly different from IGT (P = 0.999) and type 2 diabetic patients (P = 0.999) but significantly higher compared with NGT <155 subjects. Also, RWT was significantly different among the study groups (P = 0.013).

The prevalence of LVH significantly increased from the first to the fourth group (P = 0.001) and NGT ≥155 subjects showed an LVH prevalence significantly higher than NGT <155 subjects (P < 0.0001) and similar to that of IGT (P = 0.435) and type 2 diabetic patients (P = 0.896). No significant differences among groups were observed for the LVH pattern (P = 0.999).

In women, EDLVID, diastolic IVS (dIVS), dPW, and LVMI were not significantly different among groups, whereas RWT was significantly higher in IGT and type 2 diabetic patients (P = 0.018). The LVH prevalence was 27.7% in NGT <155 subjects, 36.1% in NGT ≥155 subjects, 34% in IGT, and 41.9% in type 2 diabetic patients; this distribution was not significantly different (P = 0.406).

In men, with worsening glucose tolerance, EDLVID (P = 0.010) and LVMI significantly increased (P = 0.001). There was no significant difference for dIVS and dPW among groups. Notably, NGT ≥155 subjects showed an LVMI value significantly higher than NGT <155 subjects (P = 0.044), but not significantly different from IGT and type 2 diabetic patients. LVH prevalence was 24% in NGT <155 subjects, 45.3% in NGT ≥155 subjects, 39.2% in IGT, and 40.7% in type 2 diabetic patients, with a significantly different distribution among groups (P < 0.0001). NGT ≥155 subjects showed an LVH prevalence similar to IGT (P = 0.532) and type 2 diabetic (P = 0.719) patients but showed a significantly higher prevalence than NGT <155 subjects (P < 0.0001). Finally, no significant differences among groups were observed for the LVH pattern (P = 0.891).

Table 2—*Echocardiographic parameters according to glucose tolerance in the whole study population and according to sex*

	NGT <155	NGT ≥155	IGT	Type 2 diabetes	*P*
n	356	158	168	85	—
EDLVID (cm)	4.89 ± 0.40	4.93 ± 0.39	4.87 ± 0.43	5.03 ± 0.36	0.018
dIVS (cm)	1.07 ± 0.18	1.10 ± 0.18	1.10 ± 0.18	1.11 ± 0.14	0.065
dPW (cm)	0.97 ± 0.18	0.98 ± 0.18	1.02 ± 0.18	1.02 ± 0.14	0.008
LVMI (g/m^2)	114.8 ± 32.6	122.4 ± 39.1	122.8 ± 33.3	127.9 ± 27.9	0.002
RWT	0.42 ± 0.07	0.43 ± 0.07	0.44 ± 0.07	0.42 ± 0.05	0.013
LVH [*n* (%)]	92 (25.8)	65 (41.1)	61 (36.3)	35 (41.1)	0.001
Women					
n	177	72	94	31	—
EDLVID (cm)	4.82 ± 0.39	4.87 ± 0.39	4.76 ± 0.42	4.81 ± 0.44	0.397
dIVS (cm)	1.05 ± 0.18	1.07 ± 0.16	1.09 ± 0.19	1.10 ± 0.15	0.225
dPW (cm)	0.95 ± 0.20	0.93 ± 0.13	0.97 ± 0.15	0.96 ± 0.17	0.059
LVMI (g/m^2)	115.4 ± 33.1	117.4 ± 32.8	120.2 ± 33.5	119.7 ± 25.4	0.673
RWT	0.42 ± 0.08	0.41 ± 0.05	0.44 ± 0.07	0.44 ± 0.07	0.018
LVH [*n* (%)]	49 (27.7)	26 (36.1)	32 (34.0)	13 (41.9)	0.406
Men					
n	179	86	74	54	—
EDLVID (cm)	4.96 ± 0.40	4.97 ± 0.39	5.01 ± 0.39	5.16 ± 0.22	0.010
dIVS (cm)	1.09 ± 0.18	1.13 ± 0.19	1.11 ± 0.17	1.12 ± 0.14	0.326
dPW (cm)	0.99 ± 0.16	1.03 ± 0.21	1.06 ± 0.21	1.04 ± 0.14	0.027
LVMI (g/m^2)	114.3 ± 32.1	126.6 ± 43.5	126.1 ± 32.9	132.6 ± 28.5	0.001
RWT	0.42 ± 0.07	0.44 ± 0.08	0.44 ± 0.06	0.42 ± 0.04	0.071
LVH [*n* (%)]	43 (24.0)	39 (45.3)	29 (39.2)	22 (40.7)	0.002

Correlational analysis

A linear regression analysis was performed to test the correlation between LVMI and different covariates (Table 3). In the whole study population, LVMI was significantly correlated with age ($P = 0.002$), BMI ($P < 0.0001$), WC ($P < 0.0001$), SBP ($P = 0.014$), 1-h and 2-h postload glucose ($P < 0.0001$), fasting insulin ($P < 0.0001$), Matsuda index/ISI ($P < 0.0001$), and hs-CRP ($P < 0.0001$). In NGT <155 subjects, LVMI was significantly correlated with age ($P = 0.011$), BMI ($P < 0.0001$), WC ($P < 0.0001$), 1-h postload glucose ($P = 0.006$), fasting insulin ($P = 0.028$), Matsuda index/ISI ($P = 0.037$), and hs-CRP ($P = 0.002$). In NGT ≥155 subjects, LVMI correlated with BMI ($P = 0.005$), WC ($P = 0.004$), 1-h postload glucose ($P < 0.0001$), and insulin (fasting, $P = 0.034$; 1-h postload, $P = 0.015$; 2-h postload, $P = 0.004$). In IGT patients, LVMI was correlated with 1-h postload glucose ($P < 0.0001$), fasting insulin ($P = 0.002$), Matsuda index/ISI ($P = 0.007$), and hs-CRP ($P < 0.0001$). Finally, in diabetic patients, LVMI was statistically correlated with BMI ($P < 0.0001$), WC ($P = 0.002$), 1-h ($P < 0.0001$) and 2-h postload glucose ($P < 0.0001$), fasting ($P < 0.0001$) and 1-h postload insulin ($P = 0.012$), and hs-CRP ($P < 0.0001$).

Thus, variables reaching statistical significance and sex, as a dichotomic value, were inserted in a stepwise multivariate linear regression model to determine the independent predictors of LVMI variation (Table 4). In the whole population, 1-h postload glucose was the major predictor of LVMI, explaining 8.9% of its variation ($P < 0.0001$). Other independent predictors were WC, fasting insulin, hs-CRP, 2-h postload glucose, age, and sex, explaining 18.7% of the LVMI variation. In NGT <155 subjects, the main predictor of LVMI was waist, accounting for 4.0% of its variation ($P < 0.0001$); hs-CRP, age, and fasting insulin explained a further 7.0% of its variation. In NGT ≥155 subjects, IGT, and type 2 diabetic patients, 1-h postload glucose was the strongest predictor of LVMI, accounting for 27.9% ($P < 0.0001$), 15% ($P < 0.0001$), and 25.1% ($P < 0.0001$) of its variation in the respective models. In NGT ≥155 subjects, 1-h postload insulin and SBP were retained as independent predictors of LVMI, explaining another 4.5% of its variation. In IGT patients, hs-CRP, sex, and fasting insulin were entered in the analysis, and the final model accounted for 27.5% of LVMI variation. In type 2 diabetic patients, BMI, fasting insulin hs-CRP, and sex were also significantly included in the final model, accounting for a further 19.3% ($P < 0.0001$), 9.3% ($P < 0.0001$), 4.9% ($P = 0.005$), and 2.3% ($P = 0.049$), respectively. The entire model explained 53.9% of LVMI variation.

CONCLUSIONS—This study, conducted in a large cohort of untreated hypertensive subjects, showed that worsening glucose tolerance was associated with an LVM increase in the whole study population and men, but not in women. Clinically relevant, NGT ≥155 subjects had LVMI values significantly higher than NGT <155 subjects and similar to IGT and type 2 diabetic patients. This condition was particularly evident in men. Obviously, as expected, LVMI was significantly greater in men than in women.

Similarly, the prevalence of LVH, which is an important predictor of CV events, increased consistently from NGT <155 subjects to type 2 diabetic patients. It is important to remark that NGT ≥155 subjects have, in the whole population, the same LVH prevalence of type 2 diabetic patients; whereas in men, it is even greater (45.3 vs. 40.7%). In addition, stepwise multiple regression analysis retained 1-h postload plasma glucose as the first independent predictor of LVM in all groups (Table 4). In particular, it explains the 27.9% of LVM variation in NGT ≥155 subjects, 25.1% in type 2 diabetic patients, 15% in the IGT group, and 8.9% in the whole study population.

Our results are in agreement with other previously published data, although these studies have not investigated the association between postload plasma glucose and cardiac mass. In particular, women enrolled in both the Framingham (7) and Hoorn (8) studies showed, with worsening of glucose tolerance, a progressive increase of LVM values. In addition, Verdecchia et al. (16) reported, in first-diagnosis hypertensive NGT patients, the 2-h postload insulin, but not plasma glucose, as the main determinant of LVM. This discordance is due, at least in part, to the different categorization of NGT subjects, divided by us into two groups on the basis of 1-h

Table 3—*Univariate linear regression analysis between LVMI and different covariates, in the whole study population and in groups with different glucose tolerance*

	All		NGT <155		NGT ≥155		IGT		Type 2 diabetes	
	R	*P*	*R*	*P*	*R*	*P*	*R*	*P*	*R*	*P*
One-hour glucose (mg/dL)	0.299	<0.0001	0.134	0.006	0.528	<0.0001	0.387	<0.0001	0.501	<0.0001
hs-CRP (mg/L)	0.214	<0.0001	0.152	0.002	−0.041	0.302	0.329	<0.0001	0.368	<0.0001
Fasting insulin (μU/mL)	0.199	<0.0001	0.101	0.028	0.145	0.034	0.222	0.002	0.408	<0.0001
BMI (kg/m^2)	0.177	<0.0001	0.182	<0.0001	0.204	0.005	0.083	0.144	0.460	<0.0001
WC (cm)	0.169	<0.0001	0.201	<0.0001	0.210	0.004	0.089	0.125	0.317	0.002
Two-hour glucose (mg/dL)	0.147	<0.0001	−0.033	0.267	0.131	0.051	0.006	0.471	0.452	<0.0001
Age (years)	0.105	0.002	0.122	0.011	0.038	0.318	0.109	0.079	0.081	0.231
SBP (mmHg)	0.079	0.014	0.076	0.077	0.117	0.072	−0.029	0.352	0.068	0.267
Fasting glucose (mg/dL)	0.046	0.103	−0.011	0.417	0.074	0.178	−0.038	0.311	−0.066	0.274
DBP (mmHg)	−0.030	0.204	−0.057	0.140	−0.010	0.449	−0.017	0.411	−0.044	0.346
Matsuda index/ISI	−0.143	<0.0001	−0.095	0.037	−0.103	0.099	−0.187	0.007	−0.193	0.039
One-hour insulin (μU/mL)	0.058	0.054	0.011	0.415	0.173	0.015	0.011	0.445	0.245	0.012
Two-hour insulin (μU/mL)	0.034	0.171	0.016	0.380	0.213	0.004	0.054	0.242	0.175	0.055

Table 4—*Stepwise multiple regression analysis with LVMI as the dependent variable in the whole study population and in groups with different glucose tolerance*

	All		NGT <155		NGT ≥155		IGT		Type 2 diabetes	
	Partial R^2 (%)	*P*	Partial R^2 (%)	*P*	Partial R^2 (%)	*P*	Partial R^2 (%)	*P*	Partial R^2 (%)	*P*
One-hour glucose (mg/dL)	8.9	<0.0001	—	—	27.9	<0.0001	15.0	<0.0001	25.1	<0.0001
WC (cm)	3.5	<0.0001	4.0	<0.0001	—	—	—	—	—	—
Fasting insulin (μU/mL)	2.3	<0.0001	1.4	0.018	—	—	2.3	0.023	9.3	<0.0001
hs-CRP (mg/L)	1.6	<0.0001	2.8	0.001	—	—	6.5	<0.0001	4.9	0.005
Two-hour glucose (mg/dL)	1.2	0.001	—	—	—	—	—	—	—	—
Age (years)	0.8	0.008	2.8	0.001	—	—	—	—	—	—
Sex (M/F)	0.4	0.041	—	—	—	—	3.7	0.005	2.3	0.049
BMI (kg/m^2)	—	—	—	—	—	—	—	—	12.3	<0.0001
One-hour insulin (μU/mL)					2.8	0.013				
SBP (mmHg)					1.7	0.048				
Total R^2 (%)	18.7	—	11.0	—	32.4	—	27.5	—	53.9	—

postload glucose. In agreement with Verdecchia et al. (16), in the NGT ≥155 group, postload insulin was retained in the multivariable analysis as an independent predictor of LVMI; notably, the impact of postload insulin in our population was less than for postload glucose. These findings emphasize the role of 1-h metabolic modifications in early identification of subjects at high risk.

Another important finding is that NGT ≥155 subjects have both hs-CRP and insulin resistance (IR) levels similar to IGT that are considered at high risk for both type 2 diabetes and CV disease (17). The coexistence of an increased LVM contributes to further amplify their CV risk profile. In addition, our data consent to reconsider the concept that NGT subjects are a homogeneous group with a low CV risk. Nevertheless, the evidence that NGT ≥155 subjects have cardiac modifications similar to IGT subjects confirms that the major pathogenetic mechanism promoting organ damage is IR. Finally, the present results are in agreement with previously published data demonstrating that subclinical inflammation participates in IR development and its progression to type 2 diabetes.

The direct effect of plasma glucose and its associated abnormalities, as the proinflammatory state and IR/hyperinsulinemia, may explain the increase of LVM (5). It is well known that chronic hyperglycemia promotes the formation of advanced glycation end products (AGEs) and, through protein kinase C activation, to reactive oxygen species production (18). AGEs make irreversible and stable links with collagen polymers, leading to fibrosis development, as observed in animal models (19). Moreover, under chronic hyperglycemia, there is an increased turnover of free fatty acids, with a shift of myocardial metabolism toward the oxidation of the latter (20). Our results clearly indicate that these modifications begin early, at a clinically silent phase.

In addition, IR/hyperinsulinemia increases LVM by the insulin binding to its receptors and to IGF-I receptors, expressed in the myocardium (21). IGF-I stimulates hypertrophy and differentiation of cardiomyocytes, as demonstrated in in vivo and in vitro studies (21,22). Moreover, hyperinsulinemia may cause renal sodium retention, affecting cardiac preload, which is another factor involved in LVM increase (23). The activation of both the renin-angiotensin-aldosterone system and sympathetic nervous system are other important mechanisms potentially involved in cardiac mass increase promoting oxidative stress, stimulating cardiac fibroblast, and increasing heart rate and cardiac overload (24).

In conclusion, the most clinically relevant information from this study is that there is a statistically significant and direct correlation between 1-h postload plasma glucose and LVM in hypertensive patients. Particularly, in men but not in women, NGT ≥155 subjects showed an LVH prevalence significantly higher than NGT <155 subjects and similar to IGT and type 2 diabetic patients. Our data have allowed us to identify a new early predictor of organ damage and emphasize the importance to perform an OGTT in all hypertensive subjects, paying attention not only to 2-h but also to 1-h postload plasma glucose values, which are more strongly associated with LVM, to better stratify the global CV risk in hypertensive patients.

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A.S. researched the data and wrote the manuscript. S.M. researched the data and contributed to the discussion. G.C. researched the data. L.G. researched the data. E.S. and F.A. reviewed and edited the manuscript. G.S. designed the study, analyzed the data, and reviewed and edited the manuscript. F.P. designed the study, analyzed the data, wrote the manuscript, and reviewed and edited the manuscript.

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