One-Hour Postload Plasma Glucose Levels and Diastolic Function in Hypertensive Patients

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OBJECTIVE—To address whether glucose tolerance status, and in particular 1-h postload plasma glucose levels, may affect diastolic function in 161 never-treated hypertensive white subjects. Impaired left ventricular relaxation, an early sign of diastolic dysfunction, represents the first manifestation of myocardial involvement in diabetic cardiomyopathy. A plasma glucose value ≥155 mg/dL for the 1-h postload plasma glucose during an oral glucose tolerance test (OGTT) is able to identify subjects with normal glucose tolerance (NGT) at high risk for type 2 diabetes and with subclinical organ damage.

RESEARCH DESIGN AND METHODS—Subjects underwent OGTT and standard echocardiography. Diastolic function was assessed by pulsed Doppler transmitral flow velocity and tissue Doppler imaging. Insulin sensitivity was assessed by Matsuda index.

RESULTS—Among the participants, 120 had NGT, 26 had impaired glucose tolerance (IGT), and 15 had type 2 diabetes. According to the 1-h postload plasma glucose cutoff point of 155 mg/dL, we divided NGT subjects as follows: NGT <155 mg/dL (n = 90) and NGT ≥155 mg/dL (n = 30). Those with NGT ≥155 mg/dL had higher left atrium dimensions ($P < 0.0001$) and isovolumetric relaxation time (IVRT) ($P = 0.037$) than those with NGT <155 mg/dL. By contrast, early/late transmitral flow velocity and all tissue Doppler parameters were significantly lower in those with NGT ≥155 mg/dL than in those with NGT<155 mg/dL. At multiple regression analysis, 1-h glucose was the major determinant of left atrium area, IVRT, septal e′, septal e′-to-a′ ratio, lateral e′, and lateral e′-to-a′ ratio.

CONCLUSIONS—The main finding of this study is that 1-h postload plasma glucose is associated with left ventricular diastolic dysfunction. Subjects with NGT ≥155 mg/dL had significantly worse diastolic function than those with NGT<155 mg/dL.

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Impaired left ventricular relaxation, characterized by reduced early and increased late diastolic flow, is an early sign of diastolic dysfunction. It provides independent prognostic information in the general population, free of clinical signs of heart failure (1), as well as in different clinical settings, including essential hypertension (2), congestive heart failure (3), myocardial infarction (4), and left ventricular hypertrophy (LVH), and in the elderly (5). It represents the first manifestation of myocardial involvement in diabetes (6) and may precede the clinical appearance of diabetes itself (7), suggesting that diastolic dysfunction is not exclusively a complication of diabetes but rather a coexisting condition.

On the other hand, type 2 diabetes (T2D) is recognized, independently of coronary artery disease or hypertension, as an independent risk factor for heart failure that is one of the major causes of cardiovascular morbidity and mortality (8). A possible explanation is that the metabolic abnormalities characterizing T2D may affect the cardiac structure, promoting the LVH and diastolic dysfunction appearance (6). In addition, subjects with impaired glucose tolerance (IGT) or impaired fasting glucose (IFG) are characterized by an unfavorable cardiovascular risk profile (9).

Recently, a cutoff of 155 mg/dL for 1-h postload plasma glucose during the oral glucose tolerance test (OGTT) has been shown to be able to identify subjects who are at high risk for T2D (10). Moreover, 1-h postload plasma glucose value is strongly associated with carotid intima-media thickness (IMT) (11) and reduced estimated glomerular filtration rate (eGFR) (12), which are well-established subclinical organ damage and independent predictors for cardiovascular events.

Even if there are several findings demonstrating a strong association between T2D or IGT and diastolic dysfunction, at this moment there are no data supporting the association between postload glucose and diastolic dysfunction. We designed this study to address whether glucose tolerance status, and in particular 1-h postload plasma glucose levels, may affect diastolic function in a group of never-treated hypertensive white subjects.

RESEARCH DESIGN AND METHODS

The study group consisted of 161 outpatients with uncomplicated hypertension, 101 men and 60 women aged 38–65 years (mean ± SD 43.7 ± 11.7 years), participating in the CAtanzaro MEtabolic RIsk factors Study (CATAMERIS). All patients were Caucasian and underwent physical examination and review of their medical history. Causes of secondary hypertension were excluded by appropriate clinical and biochemical tests. Other exclusion criteria were history or clinical evidence of coronary or valvular heart disease, congestive heart failure, hyperlipidemia, peripheral vascular disease, chronic

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gastrointestinal diseases associated with malabsorption, chronic pancreatitis, history of any malignant disease, history of alcohol or drug abuse, liver or kidney failure, and treatments able to modify glucose metabolism. No patient had ever been treated with antihypertensive drugs. All subjects underwent anthropometrical evaluation: weight, height, and BMI.

After 12-h fasting, 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 (WHO) 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 euglycemic-hyperinsulinemic clamp, which represents the gold standard test for measuring insulin sensitivity (13). The ethics committee approved the protocol, and informed written consent was obtained from all participants. All of the investigations were performed in accordance with the principles of the Declaration of Helsinki.

Blood pressure measurements

Readings of clinic blood pressure were obtained in the left arm of the 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. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were recorded at the first appearance (phase I) and the disappearance (phase V) of Korotkoff sounds. Baseline blood pressure values were the average of the last two of the three consecutive measurements obtained at intervals of 3 min. Patients with a clinic SBP >140 mmHg and/or 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, LDL, 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 the patient 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 or 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. Subjects with a left ventricular ejection fraction <50% were excluded from this study. In our laboratory, the intraobserver coefficients of variation were 3.85% for posterior wall thickness, 3.7% for interventricular septal thickness, 1.5% for left ventricular internal diameter, and 5.1% for left ventricular mass (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 interventricular septal thickness, posterior wall thickness, and left ventricular internal diameter were made at end diastole and end systole, as recommended by the American Society of Echocardiography (14). LVM was calculated using the Devereux formula and normalized by body surface area (LVMI).

Diastolic function. Left ventricular diastolic function was evaluated according to diagnostic criteria proposed by the American Society of Echocardiography (15). Evaluation of left atrium volume was obtained using the apical four-chamber and two-chamber views. Pulsed Doppler transmitral flow velocity profile was obtained from the apical four-chamber view, and the sample volume was positioned at the tip of the mitral valve leaflets. The following parameters were evaluated for diastolic function: peak transvalvular flow velocity in early diastole (E wave), peak transvalvular flow velocity in late diastole (A wave), E-to-A ratio, deceleration time (DT) (time measured between peak E velocity and the point where the deceleration slope of the E velocity crosses the zero baseline), and isovolumic relaxation time (IVRT) (time elapsed between aortic valve closure and mitral valve opening). E-to-A ratio between 1 and 2 was defined as normal.

Pulsed wave tissue Doppler imaging (TDI) was performed at the junction of the septal and lateral mitral annulus. Early diastolic (septal e′ and lateral e′) and late diastolic (septal a′ and lateral a′) velocities were recorded; ratio of E-to-e′ (average) was also calculated. The intraobserver coefficients of variation for measurement of diastolic parameters ranged from 1.8 to 4.1%.

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. Correlational coefficients were calculated according to Pearson's method. Linear regression analysis was performed to relate parameters of diastolic function with the following covariates: age, BMI, SBP, DBP, fasting and 1- and 2-h postload plasma glucose levels, fasting and 1- and 2-h postload insulin, Matsuda index, and LVMI. Subsequently, variables reaching statistical significance and sex, as dichotomic value, were inserted in a stepwise multivariate linear regression model to determine the independent predictors of diastolic dysfunction. Correlational 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—Of 161 patients examined by OGTT, 120 had normal glucose tolerance (NGT), 26 had IGT, and 15 had newly diagnosed T2D. A 1-h postload plasma glucose cutoff point of 155 mg/dL during OGTT was used to stratify NGT subjects into two groups: 90 patients with 1-h postload plasma glucose <155 mg/dL (NGT <155) and 30 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 were no significant differences among groups for sex, age, BMI, SBP, DBP, and total cholesterol. From the first to the fourth group, there was a significant increase of triglyceride ($P = 0.002$) and a significant reduction of HDL cholesterol ($P = 0.034$). Obviously, a progressive increase of fasting and 1-h and 2-h postload glucose parallels the worsening

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

	NGT <155	NGT ≥155	IGT	T2D	*P*
n	90	30	26	15	
Male/female	54/36	22/8	18/8	7/8	0.373*
Age (years)	41.9 ± 12.5	44.7 ± 11.6	47.1 ± 11.3	48.1 ± 6.7	0.090
BMI (kg/m^2)	28.5 ± 4.1	28.1 ± 4.7	29.1 ± 5.1	29.8 ± 5.6	0.624
SBP (mmHg)	129.9 ± 13.4	131.3 ± 9.7	131.6 ± 9.2	134.0 ± 4.3	0.602
DBP (mmHg)	81.3 ± 10.7	80.1 ± 8.4	83.7 ± 10.3	86.1 ± 6.2	0.186
Fasting glucose (mg/dL)	87.5 ± 7.9	91.2 ± 9.2	94.4 ± 10.6	108.2 ± 10.2	<0.0001
1-h glucose (mg/dL)	119.6 ± 23.7	176.2 ± 21.2	179.5 ± 33.2	239.3 ± 18.9	<0.0001
2-h glucose (mg/dL)	100.8 ± 17.9	113.5 ± 14.3	156.8 ± 13.7	248.2 ± 18.1	<0.0001
Fasting insulin (μU/mL)	11.1 ± 6.2	15.5 ± 9.1	13.7 ± 7.3	23.9 ± 8.1	<0.0001
1-h insulin (μU/mL)	77.9 ± 37.2	139.8 ± 70.1	129.1 ± 115.3	101.3 ± 24.0	<0.0001
2-h insulin (μU/mL)	57.6 ± 34.1	103.6 ± 55.1	153.1 ± 105.9	149.6 ± 30.5	<0.0001
MATSUDA index/ISI	89.2 ± 38.2	49.1 ± 20.7	54.8 ± 45.5	28.2 ± 11.9	<0.0001
Total cholesterol (mg/dL)	197.5 ± 38.4	195.7 ± 31.5	211.1 ± 24.6	201.1 ± 37.1	0.325
HDL cholesterol (mg/dL)	50.5 ± 12.5	45.1 ± 12.7	45.7 ± 14.8	41.9 ± 13.6	0.034
Triglycerides (mg/dL)	113.2 ± 61.4	139.2 ± 87.8	134.5 ± 65.3	187.2 ± 100.3	0.002

Data are means ± SD unless otherwise indicated. *χ^2 test.

of glucose tolerance ($P < 0.0001$). Fasting and postload insulin values were higher in the NGT ≥155 group and IGT subjects in comparison with those in the NGT<155 group and diabetic patients, respectively. All of these parameters account for the reduction of MATSUDA index/ISI.

Echocardiographic parameters and glucose tolerance

Echocardiographic parameters for the study population, according to glucose tolerance groups, are reported in Table 2. T2D patients had the highest LVMI value ($P = 0.020$), and clinically relevant, NGT ≥155 subjects showed an LVMI value not significantly different from IGT patients ($P = 0.691$) but significantly higher than NGT <155 subjects ($P = 0.042$).

It is interesting to note that the left atrium volume and IVRT values significantly increased from the first to the fourth group ($P < 0.0001$) and that NGT ≥155 subjects showed both parameters significantly higher than NGT <155 subjects ($P < 0.0001$ for left atrium and $P = 0.037$ for IVRT). Moreover, left atrium dimensions in NGT ≥155 subjects were similar to those of the IGT group and T2D patients; NGT ≥155 subjects showed an IVRT value similar to that of IGT subjects ($P = 0.614$) and T2D patients ($P = 0.120$). By contrast, E-to-A ratio significantly decreased from the first to the fourth group ($P < 0.0001$), and it was significantly lower in NGT ≥155 than in NGT<155 subjects. No significant differences among groups were observed for the DT duration ($P = 0.391$).

E-to-e′ ratio significantly increased from the first to the fourth group ($P < 0.044$) and in NGT ≥155 subjects was significantly higher than in NGT <155 subjects ($P < 0.036$) and similar to that of diabetic patients. All remaining tissue Doppler parameters were significantly decreased from the first to the fourth group, confirming the progressive impairment of left ventricular diastolic dysfunction from the first to the fourth group of glucose tolerance. It is important to remark that NGT ≥155 subjects had the same characteristics observed in IGT and T2D patients.

Correlational analysis

A linear regression analysis was performed to test the correlation between echocardiographic parameters and different covariates (Table 3). One-hour postload glucose was linearly correlated with IVRT ($r = 0.426$; $P < 0.0001$) and left atrium volume ($r = 0.366$; $P = 0.0001$)

Table 2—*LVMI and echocardiographic parameters of left ventricular diastolic function according to glucose tolerance*

	NGT <155	NGT ≥155	IGT	T2D	*P*
n	90	30	26	15	
LVMI (g/m^2)	90.5 ± 21.1	99.5 ± 19.9	97.2 ± 23.2	108.4 ± 16.7	0.020
Left atrium volume/BSA (mL/m^2)	15.8 ± 4.2	18.7 ± 4.6	19.4 ± 3.7	20.5 ± 3.6	<0.0001
E-to-A ratio	1.3 ± 0.4	1.0 ± 0.3	0.9 ± 0.2	0.9 ± 0.7	<0.0001
DT (ms)	185.6 ± 48.8	201.6 ± 64.3	194.2 ± 44.5	201.9 ± 49.6	0.391
IVRT (ms)	107.5 ± 24.6	120.5 ± 40.1	116.1 ± 20.1	152.3 ± 38.1	<0.0001
Tissue Doppler parameters					
Septal e′ (cm/s)	12.2 ± 3.1	9.6 ± 3.3	8.9 ± 3.6	7.9 ± 1.5	<0.0001
Septal e′-to-a′	1.4 ± 0.5	0.9 ± 0.5	0.7 ± 0.4	0.7 ± 0.2	<0.0001
Lateral e′ (cm/s	13.1 ± 3.9	10.7 ± 3.5	8.4 ± 3.3	9.2 ± 2.6	<0.0001
Lateral e′-to-a′ ratio	1.7 ± 1.3	1.0 ± 0.6	0.9 ± 0.5	0.8 ± 0.4	<0.0001
E-to-e′ ratio	10.8 ± 3.6	12.4 ± 3.5	13.8 ± 6.3	12.3 ± 3.2	0.044

Data are means ± SD unless otherwise indicated. BSA, body surface area.

Table 3—*Linear regression analysis (R/P) between diastolic function parameters and different covariates*

	Left atrium volume/BSA	E-to-A ratio	DT	IVRT	Septal e′	Septal e′-to-a′ ratio	Lateral e′	Lateral e′-to-a′ ratio	E-to-e′ ratio
Age (years)	0.275/<0.0001	−0.332/<0.0001	0.063/0.215	0.215/0.003	−0.278/<0.0001	−0.231/0.002	−0.122/0.062	−0.105/0.092	0.141/0.037
SBP (mmHg)	0.073/0.179	−0.022/0.389	−0.064/0.209	0.196/0.006	−0.146/0.032	−0.129/0.052	0.113/0.077	0.051/0.261	0.173/0.014
DBP (mmHg)	−0.068/0.194	−0.016/0.421	−0.148/0.031	0.077/0.167	−0.042/0.300	−0.059/0.229	−0.048/0.274	0.011/0.445	−0.023/0.386
BMI (kg/m^2)	−0.021/0.397	0.069/0.194	−0.014/0.431	−0.060/0.226	−0.054/0.247	−0.101/0.101	−0.117/0.069	0.001/0.493	0.075/0.172
Fasting glucose (mg/dL)	0.031/0.350	−0.153/0.026	0.092/0.122	0.253/0.001	−0.296/<0.0001	−0.271/<0.0001	−0.208/0.004	−0.110/0.082	0.030/0.352
1-h glucose (mg/dL)	0.366/0.001	−0.238/0.001	0.092/0.122	0.426/<0.0001	−0.389/<0.0001	−0.502/<0.0001	−0.427/<0.0001	−0.384/<0.0001	0.161/0.020
2-h glucose (mg/dL)	0.111/0.080	−0.218/0.003	0.108/0.087	0.322/<0.0001	−0.341/<0.0001	−0.441/<0.0001	−0.412/<0.0001	−0.322/<0.0001	0.092/0.123
Fasting insulin (μU/mL)	−0.044/0.291	0.035/0.331	0.170/0.016	0.249/0.001	−0.196/0.006	−0.284/<0.0001	−0.219/0.003	−0.169/0.016	0.019/0.407
1-h insulin (μU/mL)	0.021/0.397	−0.040/0.306	0.122/0.062	0.134/0.045	−0.080/0.157	−0.218/0.003	−0.241/0.001	−0.151/0.028	0.072/0.181
2-h insulin (μU/mL)	0.063/0.213	−0.078/0.162	0.105/0.092	0.137/0.041	−0.180/0.011	−0.252/0.001	−0.303/<0.0001	−0.160/0.022	0.130/0.050
Matsuda/ISI	−0.070/0.188	0.088/0.134	−0.136/0.043	−0.104/0.094	0.177/0.012	0.290/<0.0001	0.300/<0.0001	0.187/0.009	−0.045/0.284
LVMI (g/m^2)	0.181/0.011	−0.139/0.039	0.046/0.280	0.202/0.005	−0.289/<0.0001	−0.362/<0.0001	−0.159/0.022	−0.079/0.159	0.143/0.035

BSA, body surface area; DT, deceleration time.

and inversely correlated with septal e′-to-a′ ratio ($r = -0.502$; $P < 0.0001$), lateral e′ ($r = -0.427$; $P < 0.0001$), septal e′ ($r = -0.389$; $P < 0.0001$), lateral e′-to-a′ ratio ($r = -0.384$; $P < 0.0001$), E-to-e′ ratio ($r = 0.161$; $P = 0.020$), and E-to-A ratio ($r = -0.238$; $P = 0.001$).

Thus, variables reaching statistical significance and sex, as dichotomic value, were inserted in a stepwise multivariate linear regression model to determine the independent predictors of left ventricular diastolic function parameters (Table 4). In the study population, 1-h postload glucose was the first predictor of left atrium volume, IVRT, and DT, explaining 25.6 ($P < 0.0001$), 18.2 ($P < 0.0001$), and 2.9% ($P = 0.031$) of its variation, respectively. Age, sex, and DBP added another 5.6 ($P = 0.001$), 3.1 ($P = 0.013$), and 2.8% ($P = 0.032$) to explaining left atrium volume, IVRT, and DT, respectively. As for the tissue Doppler parameters, we observed that 1-h postload glucose was retained as the first correlated of septal e′, septal e′-to-a′ratio, lateral e′, and lateral e′-to-a′ ratio, explaining 15.2, 25.2, 18.3, and 14.8% of their variations, respectively. Age and SBP were retained as the independent predictors of E-to-e′ ratio, explaining 8.3% of its variation.

CONCLUSIONS—This study, conducted in a cohort of never-treated and well-characterized hypertensive patients, showed that the worsening of glucose tolerance was associated with an impairment of left ventricular diastolic function. The main finding of this study is that 1-h postload plasma glucose in NGT subjects is associated with left ventricular diastolic dysfunction. This result persists after adjustment for all significant covariates reported in Table 3. Of interest and clinically relevant, NGT ≥155 subjects had significantly worse diastolic function compared with NGT<155 subjects and similar compared with IGT and T2D patients. To our knowledge, this is the first study that demonstrates this association, confirming the usefulness of early diagnosis in the stratification of overall cardiovascular risk; in addition, it highlights the links between early alterations of glucose tolerance and early alterations in cardiac function.

There is a consistent body of evidences demonstrating the association between T2D or insulin resistance and diastolic dysfunction, which is recognized as the first stage of diabetic cardiomyopathy that may lead to chronic heart failure, independent

Table 4—*Stepwise multiple regression analysis on diastolic function parameters as dependent variables in the whole study population*

	Partial R^2	Total R^2	*P*
Left atrium volume/BSA (mL/m^2)			
1-h glucose (mg/dL)	25.6	25.6	<0.0001
Age (years)	5.6	31.2	0.001
E-to-A ratio			
Age (years)	11.0	11.0	<0.0001
1-h glucose (mg/dL)	2.6	13.6	0.031
DT			
Fasting insulin (μU/mL)	2.9	2.9	0.031
DBP (mmHg)	2.8	5.7	0.032
IVRT			
1-h glucose (mg/dL)	18.2	18.2	<0.0001
Sex	3.1	21.3	0.013
Tissue Doppler parameters			
Septal e′			
1-h glucose (mg/dL)	15.2	15.2	<0.0001
Age (years)	3.5	18.7	0.010
Septal e′-to-a′ ratio			
1-h glucose (mg/dL)	25.2	25.2	<0.0001
LVMI (g/m^2)	4.3	29.5	0.002
Lateral e′			
1-h glucose (mg/dL)	18.3	18.3	<0.0001
2-h insulin (μU/mL)	2.0	20.3	0.004
Lateral e′-to-a′ ratio			
1-h glucose (mg/dL)	14.8	14.8	<0.0001
E-to-e′ ratio			
SBP (mmHg)	3.0	3.0	0.029

BSA, body surface area.

of other cardiovascular heart diseases such as hypertension or atherosclerotic ischemic coronary disease (16,17). The development of diabetic cardiomyopathy is likely multifactorial involving several mechanisms including metabolic disturbances, endothelial dysfunction, coronary microvascular impairment, modification in the extracellular matrix, and sympathetic hyperactivity (16,17). All of these factors contribute to the increase of ventricular stiffness, promoting cardiac structure abnormalities such as left ventricular remodeling or hypertrophy. Cardiac fibrosis causes an imbalance between extracellular matrix deposition and degradation within the heart resulting in excessive fibroblast proliferation. In addition, ventricular fibrosis causes progressive stiffening of the ventricular wall resulting in ventricular dysfunction, increase in end diastolic pressure, and atrial dilatation.

Some of these effects could be related to chronic hyperglycemia that induces, in diabetic patients, nonenzymatic glycation of circulating and cellular membrane proteins, leading to the formation of advanced glycation end products (AGEs) and, through protein kinase C activation, to reactive oxygen species production with increased oxidative stress (18). AGEs accumulation, in the myocardium and arterial wall, makes irreversible and stable links with collagen polymers, leading to fibrosis development with reduction of ventricular compliance and increase of LVM, as observed in animal models of IGT (19). Moreover, under chronic hyperglycemia condition, there is an increased turnover of free fatty acids, with a shift of myocardial metabolism toward the oxidation of the latter, with intracellular accumulation of intermediate products that lead, via increased oxidative stress, to deleterious effects (20). In keeping with this, our results, obtained in NGT ≥155 subjects, clearly indicate that these modifications begin early, at a clinically silent phase, and support reconsideration of the notion that NGT subjects are a homogeneous group with a low cardiovascular risk profile.

The activation of both the renin-angiotensin-aldosterone system and sympathetic nervous system is another important mechanism potentially involved in activation of cardiac fibroblasts and collagen production (21), leading to fibrosis and likely subsequent to the development of diastolic dysfunction. Finally, we should not ignore the role of coronary microcirculation abnormalities that may lead to myocardial cell injury and reactive fibrosis/hypertrophy. Of interest, the impairment of coronary microcirculation, occurring without obstructive atherosclerotic lesions on epicardial coronary arteries, induces a reduction of coronary flow reserve, as demonstrated in type 1 diabetic patients (22) and hypertensive subjects (23). The reduction of coronary flow reserve seems to be a direct consequence of elevated glycemia (24). Thus, equally interesting are the results reported by Scognamiglio et al. (25) showing that postprandial hyperglycemia induces myocardial perfusion defects in T2D patients, secondary to deterioration in microvascular function causing a decrease in myocardial blood flow.

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 diastolic dysfunction in NGT hypertensive patients. This has an important clinical implication considering its negative prognostic impact in hypertensive patients. Our data have allowed us to identify a new early predictor of subclinical organ damage and emphasize the importance of performing an OGTT in all subjects affected by essential hypertension, paying attention not only to 2- h but also to 1-h postload plasma glucose values, which are more strongly associated with diastolic dysfunction, in order to better stratify the global cardiovascular risk in hypertensive patients.

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