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ORIGINAL ARTICLE

Elevated 1-h post-load plasma glucose is associated with right ventricular morphofunctional parameters in hypertensive patients

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Abstract

Purpose Emerging data demonstrate that type 2 diabetes mellitus (T2DM) is associated with right ventricular (RV) dysfunction. A cutoff point of 155 mg/dL for the 1-hour (h) post-load plasma glucose, during oral glucose tolerance test (OGTT), identifies patients with normal glucose tolerance (NGT) at high risk to develop T2DM and cardiovascular (CV) disease. We investigated if 1-h post-load glucose may affect RV geometry and function in a group of never-treated hypertensive individuals.

Methods We enrolled 446 Caucasian newly diagnosed hypertensive outpatients. All patients underwent an OGTT and a standard echocardiography. The tricuspid annular plane systolic excursion (TAPSE) and the RV fractional area change (RVFAC) were measured together with systolic pulmonary arterial pressure (s-PAP) and pulmonary vascular resistances (PVR). Insulin sensitivity was evaluated using the Matsuda index.

Results Among all partecipants, 296 had NGT, 100 impaired glucose tolerance (IGT), and 50 T2DM. Considering the cutoff point of 155 mg/dl for 1-h glucose, NGT subjects were stratified into two groups: NGT < 155 ($n = 207$), NGT ≥ 155 ($n = 89$). Subjects NGT ≥ 155 presented a worse metabolic and inflammatory profile than NGT < 155. RV functional parameters (TAPSE, RVFAC, TAPSE/s-PAP, and TAPSE/PVR) were significantly reduced in NGT ≥ 155 subjects compared with NGT < 155 patients. On the contrary, s-PAP and PVR were significantly higher. At multiple regression analysis, 1-h glucose was the strongest predictor of TAPSE in NGT ≥ 155, IGT, and T2DM.

Conclusions The presence of RV impairment in hypertensive NGT ≥ 155 subjects further complicates their CV burden and it may, at least in part, justify the worse clinical outcome in this setting of patients.

Keywords Arterial hypertension Insulin resistance · Post-load glucose · Right ventricle

Introduction

Type 2 diabetes mellitus (T2DM) is characterized by an increased risk for cardiovascular (CV) morbidity and mortality [1]. In particular, even in the absence of other clinical conditions, such as arterial hypertension and coronary artery disease, T2DM is associated with asymptomatic left ventricular dysfunction [2] and, consequently, with heart failure [3, 4]. Among the potential mechanisms responsible for the morphofunctional changes characterizing diabetic cardiomyopathy [5], insulin resistance (IR) could have a pivotal role. In fact, when IR is established, insulin may promote cardiac hypertrophy and fibrosis negatively affecting myocardial function and structure, both directly and indirectly by activating several neurohormonal systems, including the sympathetic nervous (SNS) and the renin–angiotensin–aldosterone (RAAS) ones [6, 7].

Interestingly, emerging data demonstrate that, as previously established for the left ventricle (LV), right ventricle (RV) dimension and function are also impaired in T2DM [8–12], suggesting that both ventricles are influenced by the metabolic abnormalities associated with diabetes. Even if the morphological changes of left chambers may affect RV structure and function, as demonstrated in hypertensive individuals [13], the mechanisms underlying RV involvement in T2DM are not completely elucidated. Keeping in mind the

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established impact of RV on clinical prognosis [14, 15], understanding the pathophysiological mechanisms occurring in individuals with T2DM and dysglycemia conditions is crucial. In this regard, experimental in vitro and in vivo models have suggested that IR may have an important role in promoting pulmonary vascular disease and pulmonary arterial hypertension (PAH), thus affecting RV [16, 17]. Moreover, patients with PAH and T2DM exhibit a worse prognosis compared with individuals without metabolic disorders, probably due to impaired RV compensation [18].

Several studies have shown that IR and glucose intolerance may negatively affect myocardial function, even before the occurrence of overt T2DM [19–21]. In the last decade, it has been demonstrated that a cutoff point of 155 mg/dL for the 1-h post-load plasma glucose, during an oral glucose tolerance test (OGTT), is able to identify subjects with normal glucose tolerance (NGT) at high risk for T2DM [22, 23]. Moreover, NGT patients with 1-h post-load glucose ≥155 mg/dl show an unfavorable metabolic and inflammatory profile, including a higher degree of IR and subclinical CV organ damage [24–27], in particular LV hypertrophy and diastolic dysfunction [28, 29].

To our knowledge, there are no data regarding the association between post-load glucose and RV morphofunctional pattern. Thus, we addressed the question of whether glucose tolerance status, and in particular 1-h post-load plasma glucose levels, may affect RV geometry and function in a group of never-treated hypertensive individuals.

Materials and methods

Study population

We enrolled 446 Caucasian newly diagnosed hypertensive outpatients (250 men and 196 women, aged 40–70 years [mean ± SD: 48.9 ± 7.7]) participating in the Catanzaro Metabolic Risk Factors Study (CATAMERIS). Diagnosis of arterial hypertension was performed according to current guidelines [30]. Causes of secondary hypertension were excluded by appropriate clinical and biochemical tests. Other exclusion criteria were history or clinical evidence of CV complications, chronic gastrointestinal disease associated with malabsorption, history of any malignant or chronic respiratory disease, alcohol or drug abuse, and liver or kidney failure. No patient had ever been treated with antihypertensive drugs. All subjects underwent anthropometrical evaluation and 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 using the American Diabetes Association criteria [31]. 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] [32]. The local ethic 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.

Laboratory determinations

Plasma glucose was measured by the glucose oxidation method (Beckman Glucose Analyzer II; Beckman Instruments, Milan, Italy), and plasma insulin concentration was determined by a chemiluminescence-based assay (Roche Diagnostics).

Creatinine was measured by using Jaffe methodology. Values of estimated glomerular filtration rate (e-GFR) were calculated by using the equation proposed by investigators in the chronic kidney disease epidemiology (CKD-EPI) collaboration [33].

Echocardiographic measurements

Tracings were taken using a VIVID-7 Pro ultrasound machine (GE Technologies, Milwaukee, WI) with patients in a partial left decubitus position, an annular phased array 2.5-MHz transducer was used. Echocardiographic readings were made in random order by the investigator, who had no knowledge of patients' BP and other clinical data. The mean values from at least five measurements of each parameter for each patient were computed.

Morphofunctional parameters of left chambers

Measurements of interventricular septal and posterior wall thickness and LV internal diameter were made at end-diastole and end-systole. LVM was calculated using the Devereux equation and normalized by body surface area (LVMI) [34]. LV diastolic function was evaluated according to the American Society of Echocardiography (ASE) [35]. The following parameters were evaluated: peak transvalvular flow velocity in early diastole (E wave), peak transvalvular flow velocity in late diastole (A wave), and E-to-A ratio. 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.

Morphofunctional parameters of right chambers

Proximal RV outflow tract (RVOT) diameter and right atrium (RA) area were obtained according to ASE recommendations [34, 36]. The tricuspid annular motion was

recorded at the RV-free wall for tricuspid annular plane systolic excursion (TAPSE) that explains longitudinal right function. RV fractional area change (RVFAC), a reliable measure of the global RV contractility was measured from the apical four-chamber view as (end-diastolic area)–(end-systolic area)/end-diastolic area × 100 [36]. From the subcostal view, the measurement of inferior vena cava diameter at end-expiration and during an inspiratory manoeuvre has allowed an estimate of RA pressure. Tricuspid regurgitant velocity was derived from the application of continuous wave Doppler along the tricuspid regurgitant jet, from apical four-chamber projections or from the parasternal RV inflow view, if the regurgitant jet was eccentric. Systolic pulmonary arterial pressure (s-PAP) was calculated through the Bernoulli equation, and pulmonary vascular resistances (PVR) were estimated using the following formula: TRV peak/RVOT time velocity integral (TVI) × 10 + 0.16 [36, 37]. Moreover, for a more complete RV function evaluation, also the TAPSE/s-PAP ratio, an index of RV length/force relationship, and RV ejection efficiency (RVEe) as TAPSE/PVR ratio were calculated because these are not affected by the quality of LV dysfunction [38, 39].

Statistical methods

To test the differences among groups, analysis of variance (ANOVA) for clinical and biological data was performed, followed by the Bonferroni post hoc test for multiple comparisons. Chi-squared test was considered for categorical variables. Linear regression analysis was performed to relate TAPSE, s-PAP, and PVR with different covariates [age, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), e-GFR, high sensitivity C-reactive protein (hs-CRP), fasting, 1-h and 2-h post-load plasma glucose and insulin levels, Matsuda index and LVMI]. Afterward, variables achieving statistical significance, smoking and gender, as dicotomic values, were inserted in a stepwise multivariate linear regression model to determine the independent predictors of TAPSE, s-PAP, and PVR. Correlational analysis was carried out for the whole study population and according to different glucose tolerance groups. Data are reported as mean ± SD and differences were considered significant at $P < 0.05$. All comparisons were performed using the statistical package SPSS 20.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

Study population

Among 446 patients evaluated by OGTT, 296 showed NGT, 100 impaired glucose tolerance (IGT), and 50 presented T2DM. Considering the cutoff point of 155 mg/dl for 1-h post-load plasma glucose, NGT subjects were stratified into two groups: 207 patients with 1-h post-load plasma glucose < 155 mg/dl (NGT<155), and 89 subjects with 1-h post-load plasma glucose ≥ 155 mg/dl (NGT ≥ 155).

In Table 1, the demographic, clinical, and biochemical characteristics of the study population are reported according to different metabolic states. There were no significant differences among groups regarding gender distribution, age, and smoking. Anthropometric parameters, PAD, total and HDL cholesterol were also not significantly different. A significant increase of fasting, 1-h and 2-h post-load glucose and insulin was observed according to the worsening of glucose tolerance, accounting for the reduction of MATSUDA/ISI. In addition, from the first to the fourth group there was a significant increase of SBP, triglyceride, and hs-CRP values as well as a reduction in e-GFR. Of interest, NGT ≥ 155 presented a lower insulin sensitivity ($P < 0.0001$) and higher triglyceride ($P = 0.044$) and hs-CRP values ($P = 0.001$) when compared with NGT < 155, showing a metabolic and inflammatory profile similar to IGT individuals.

Echocardiographic parameters according to glucose tolerance

Table 2 shows the main echocardiographic parameters of left and right chambers according to glucose tolerance status. From the first to the fourth group, there was a significant increase of LVMI and a reduction of e'/a' showing a worsening of diastolic function. Notably, NGT ≥ 155 subjects showed a LVMI value significantly higher and a worse diastolic function in comparison with NGT < 155 subjects, but were not significantly different from IGT ($P = 0.999$) and T2DM patients ($P = 0.999$). Regarding the right chamber, both RA area and RVOT values significantly increased from the first to the fourth group and the value of s-PAP and PVR were significantly higher. In addition, a significant reduction of RV function parameters was observed as demonstrated by lower values of TAPSE, RVFAC, TAPSE/s-PAP, and RVEe. Of interest, NGT ≥ 155 subjects showed significantly higher values of s-PAS ($P = 0.011$), PVR (0.020), RA area ($P = 0.010$), and RVOT ($P = 0.022$) in comparison with NGT < 155 but similar to IGT. Similarly, RV functional parameters were significantly reduced in NGT ≥ 155 subjects compared with NGT < 155 patients. In particular, the first group compared with the latter presented significantly lower values of TAPSE ($P = 0.005$), TAPSE/s-PAP ($P < 0.0001$), RVEe ($P = 0.006$); however, there were no significant differences between NGT ≥ 155 and IGT for all the above-mentioned RV functional parameters.

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

Variables	All ($n = 446$)	NGT < 155 ($n = 207$)	NGT ≥ 155 ($n = 89$)	P^a	IGT ($n = 100$)	Newly diagnosed T2DM ($n = 50$)	P^b
Gender, m/f	250/196	106/101	52/37	0.253	58/42	34/16	0.155[c]
Age, years	48.9 ± 7.7	48.5 ± 9.2	49.4 ± 6.3	0.974	49.2 ± 6.1	49.4 ± 5.8	0.718
Current smokers, *n* (%)	79 (18)	42 (20)	18 (20)	0.989	10 (10)	9 (18)	0.143[c]
Waist, cm	102.6 ± 12.2	101.1 ± 12.5	103.2 ± 11.9	0.883	103.8 ± 11.2	105.1 ± 12.9	0.107
BMI, Kg/m^2	30.5 ± 5.1	29.9 ± 5.2	31.2 ± 5.6	0.252	30.9 ± 4.2	31.0 ± 5.4	0.127
Systolic BP, mmHg	139.2 ± 16.1	136.9 ± 15.2	139.1 ± 15.1	0.999	143.3 ± 17.8	140.0 ± 16.4	0.013
Diastolic BP, mmHg	85.5 ± 10.4	85.7 ± 10.6	84.6 ± 9.9	0.999	86.1 ± 10.0	85.0 ± 11.3	0.752
Fasting glucose, mg/dl	97.5 ± 19.5	91.3 ± 10.1	95.1 ± 12.0	0.468	99.8 ± 13.0	122.5 ± 40.2	<0.0001
1-h glucose, mg/dl	162.7 ± 49.7	123.1 ± 20.2	182.5 ± 27.8	<0.0001	184.3 ± 27.2	248.1 ± 46.0	<0.0001
2-h glucose, mg/dl	132.4 ± 48.5	100.6 ± 19.3	114.0 ± 17.0	<0.0001	161.8 ± 16.6	237.9 ± 26.9	<0.0001
Fasting insulin, μU/ml	13.7 ± 8.5	11.6 ± 6.4	12.3 ± 6.3	0.999	17.3 ± 10.8	16.9 ± 10.5	<0.0001
1-h insulin, μU/ml	106.2 ± 66.2	101.0 ± 64.8	125.7 ± 72.8	0.040	108.6 ± 62.8	86.1 ± 57.1	0.011
2-h insulin, μU/ml	89.4 ± 66.9	67.3 ± 50.2	80.4 ± 52.9	0.032	135.0 ± 85.4	107.7 ± 62.9	<0.0001
Matsuda/ISI	61.4 ± 46.1	76.1 ± 50.9	55.9 ± 44.2	<0.0001	43.5 ± 26.8	39.4 ± 32.6	<0.0001
Total cholesterol, mg/dl	205.5 ± 40.5	204.9 ± 41.5	201.1 ± 31.1	0.999	210.0 ± 43.7	205.0 ± 44.5	0.405
HDL cholesterol, mg/dl	50.5 ± 13.8	51.4 ± 13.3	50.8 ± 13.6	0.090	49.1 ± 13.7	49.3 ± 16.1	0.518
Triglyceride, mg/dl	137.9 ± 72.1	132.8 ± 74.9	150.1 ± 71.7	0.044	154.4 ± 72.6	151.2 ± 63.5	0.047
hs-CRP, mg/l	2.5 ± 1.5	2.1 ± 1.1	2.8 ± 1.4	0.001	2.9 ± 1.7	3.1 ± 1.2	<0.0001
e-GFR, ml/min/1.73 m^2	100.2 ± 26.2	104.3 ± 23.6	98.3 ± 22.9	0.621	97.1 ± 31.9	93.1 ± 27.5	0.014

NGT normal glucose tolerance, *IGT* impaired glucose tolerance, *T2DM* type 2 diabetes mellitus, *BMI* body mass index, *BP* blood pressure, *ISI* insulin sensitivity index, *hs-CRP* high-sensitivity C-reactive protein, *e-GFR* estimated glomerular filtration rate

[a]Difference between NGT< 155 and NGT ≥ 155 subjects (Bonferroni post hoc test)

[b]Overall difference among groups (ANOVA)

[c]χ^2 test

Table 2 Morphofunctional echocardiographic parameters of the study population

Variables	All ($n = 446$)	NGT < 155 ($n = 207$)	NGT ≥ 155 ($n = 89$)	P^a	IGT ($n = 100$)	Newly diagnosed T2DM ($n = 50$)	P^b
LVMI, g/ m^2	119.6 ± 23.8	115.2 ± 22.3	122.1 ± 30.4	0.001	122.5 ± 17.2	127.7 ± 25.0	0.002
e'/a'	1.0 ± 0.8	1.2 ± 1.1	0.9 ± 0.4	0.004	0.9 ± 0.4	0.9 ± 0.5	0.004
E/e'	9.4 ± 2.5	9.3 ± 2.3	9.5 ± 2.7	0.900	9.6 ± 2.6	9.6 ± 2.9	0.663
s-PAP, mmHg	31.1 ± 9.4	28.6 ± 9.2	32.2 ± 8.6	0.011	32.4 ± 8.4	36.7 ± 9.8	<0.0001
TAPSE, mm	20.5 ± 4.0	21.6 ± 4.2	20.0 ± 3.7	0.005	19.9 ± 3.6	18.2 ± 3.0	<0.0001
TAPSE/s-PAP	0.7 ± 0.3	0.9 ± 0.4	0.7 ± 0.2	<0.0001	0.7 ± 0.2	0.5 ± 0.2	<0.0001
RA area, cm^2	18.1 ± 5.1	16.7 ± 4.7	18.6 ± 4.9	0.010	18.7 ± 4.8	21.4 ± 4.9	<0.0001
RVOT, cm	2.3 ± 0.4	2.2 ± 0.3	2.3 ± 0.4	0.022	2.3 ± 0.4	2.6 ± 0.4	<0.0001
RVFAC, %	40.3 ± 9.7	42.1 ± 10.3	39.5 ± 9.4	0.176	39.7 ± 9.5	35.4 ± 6.1	<0.0001
PVR, Woods	2.0 ± 0.5	1.9 ± 0.5	2.1 ± 0.5	0.020	2.1 ± 0.5	2.4 ± 0.3	<0.0001
RVEe	11.1 ± 4.5	12.5 ± 4.8	10.7 ± 3.4	0.006	10.3 ± 3.6	7.3 ± 3.1	<0.0001

NGT normal glucose tolerance, *IGT* impaired glucose tolerance, *T2DM* type 2 diabetes mellitus, *LVMI* left ventricular mass index, *RVOT* right ventricular outflow tract, *RVFAC* right ventricular fractional area change, *RA* right atrium, *PVR* pulmonary vascular resistances, *s-PAP* systolic pulmonary arterial pressure, *TAPSE* tricuspid annular plane systolic excursion, *RVEe* right ventricular ejection efficiency

[a]Difference between NGT < 155 and NGT ≥ 155 subjects (Bonferroni post hoc test)

[b]Overall difference among groups (ANOVA)

Table 3 Univariate linear regression analysis between TAPSE and different covariates, in whole study population and in groups with different glucose tolerance

	All		NGT < 155		NGT ≥ 155		IGT		T2DM	
	R	*p*	*r*	*p*	*r*	*P*	*r*	*P*	*r*	*p*
1-h glucose, mg/dl	−0.444	<0.0001	−0.288	<0.0001	−0.513	<0.0001	−0.502	<0.0001	−0.524	<0.0001
LVMI, g/m^2	−0.297	<0.0001	−0.301	<0.0001	−0.237	0.013	−0.265	0.004	−0.159	0.135
2-h glucose, mg/dl	−0.277	<0.0001	−0.074	0.145	−0.116	0.139	−0.065	0.261	−0.320	0.012
Matsuda/ISI	0.204	<0.0001	0.144	0.019	0.076	0.238	0.087	0.193	0.389	0.003
e-GFR, ml/min/m^2	0.194	<0.0001	0.087	0.105	0.087	0.210	0.432	<0.0001	0.211	0.070
Fasting glucose, mg/dl	−0.160	<0.0001	−0.142	0.020	−0.212	0.023	−0.012	0.452	−0.148	0.153
hs-CRP, mg/l	−0.137	0.002	−0.042	0.273	−0.010	0.464	−0.031	0.381	−0.342	0.008
Fasting insulin, μU/ml	−0.088	0.032	0.001	0.495	−0.007	0.473	0.012	0.451	−0.238	0.048
DBP, mmHg	0.072	0.063	0.011	0.438	−0.143	0.091	−0.105	0.152	−0.142	0.162
2-h insulin, μU/ml	−0.063	0.094	−0.011	0.435	−0.174	0.051	−0.091	0.183	−0.138	0.170
Age, yrs	−0.058	0.112	−0.105	0.066	−0.122	0.127	−0.032	0.378	−0.071	0.312
1-h insulin, μU/ml	−0.044	0.179	−0.035	0.308	−0.050	0.320	−0.207	0.020	−0.093	0.261
SBP, mmHg	0.030	0.262	0.005	0.470	−0.234	0.013	−0.102	0.156	−0.038	0.396
BMI, kg/m^2	0.020	0.340	0.109	0.058	0.109	0.154	−0.135	0.090	−0.080	0.290

TAPSE tricuspid annular plane systolic excursion, *NGT* normal glucose tolerance, *IGT* impaired glucose tolerance, *T2DM* type 2 diabetes mellitus, *hs-CRP* high-sensitivity C-reactive protein, *BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *e-GFR* estimated glomerular filtration rate, *ISI* insulin sensitivity index

Correlational analysis

The linear regression analysis between TAPSE and different covariates is reported in Table 3. In the whole study population, TAPSE was significantly correlated with 1-h post-load glucose ($r = -0.444$, $P < 0.0001$), LVMI ($r = -0.297$, $P < 0.0001$), 2-h post-load glucose ($r = -0.277$, $P < 0.0001$), Matsuda/ISI ($r = 0.204$, $P < 0.0001$), e-GFR ($r = 0.194$, $P < 0.0001$), fasting glucose ($r = -0.160$, $P < 0.0001$), hs-CRP ($r = -0.137$, $P = 0.002$), and fasting insulin ($r = -0.088$, $P = 0.032$). In addition, in all subgroups, TAPSE was correlated with 1-h post-load glucose, in particular in NGT ≥ 155 subjects ($r = -0.513$, $P < 0.0001$) and T2DM patients ($r = -0.524$, $P < 0.0001$).

When s-PAP was considered as a dependent variable, in the whole study population it was significantly correlated with 1-h post-load glucose ($r = 0.356$, $P < 0.0001$), LVMI ($r = 0.271$, $P < 0.0001$), hs-CRP ($r = 0.262$, $P < 0.0001$), Matsuda index ($r = -0.242$, $P < 0.0001$), 2 h glucose ($r = 0.240$, $P < 0.0001$), 2-h insulin ($r = 0.176$, $P < 0.0001$), e-GFR ($r = -0.169$, $P < 0.0001$), 1-h insulin ($r = 0.130$, $P = 0.003$), fasting glucose ($r = 0.116$, $P = 0.007$), and fasting insulin ($r = 0.088$, $P = 0.031$). Moreover, the correlation between s-PAP and 1-h post-load glucose remained significant in the different subgroups, particularly in NGT ≥ 155 subjects (Table 4).

Subsequently, as reported in Table 5, PVR were considered as the dependent variable and the analysis showed that in the whole population, PVR were significantly correlated with 1-h post-load glucose ($r = 0.384$, $P < 0.0001$), LVMI ($r = 0.383$, $P < 0.0001$), 2-h post-load glucose ($r = 0.282$, $P < 0.0001$), fasting glucose ($r = 0.188$, $P < 0.0001$), Matsuda ($r = -0.160$, $P < 0.0001$), DBP ($r = 0.104$, $P = 0.014$), e-GFR ($r = -0.101$, $P = 0.016$), hs-CRP ($r = 0.093$, $P = 0.025$), and fasting insulin ($r = 0.087$, $P = 0.034$). The strongest correlation between PVR and 1-h glucose was present in NGT ≥ 155 patients ($r = 0.464$, $P < 0.0001$).

Finally, variables achieving statistical significance, gender, and smoking, as dichotomic values, were inserted in a stepwise multivariate linear regression model to determine the independent predictors of TAPSE, s-PAP, and PVR, respectively (Table 6). In the whole study population, 1-h post-load glucose was the major predictor of TAPSE explaining a 19.7% of its variation ($P < 0.0001$). Also LVMI entered in the model accounting for another 2.8% of TAPSE variation. In NGT < 155 subjects, LVMI and 1-h post-load glucose were the leading predictors of TAPSE, explaining 9.1% and 7.1% of its variation, respectively. Both in NGT ≥ 155, IGT and diabetic subjects, 1-h post-load glucose was the main independent predictor of TAPSE, accounting for 26.3% ($P < 0.0001$), 25.2% ($P < 0.0001$), and 27.4% ($P < 0.0001$) of its variation, respectively. Moreover, in NGT ≥ 155 patients, SBP added another 4.3% ($P = 0.023$). Moreover, 1-h post-load glucose represented the main independent predictor of s-PAP in the whole population and in the different subgroups, accounting for 12.7% ($P < 0.0001$), 3.5% ($P = 0.007$), 19.9 ($P < 0.0001$), 17.6% ($P < 0.0001$), and 16.7% ($P = 0.003$),

Table 4 Univariate linear regression analysis between s-PAP and different covariates, in whole study population and in groups with different glucose tolerance

	All		NGT < 155		NGT ≥ 155		IGT		T2DM	
	R	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
1-h glucose, mg/dl	0.356	<0.0001	0.186	0.004	0.446	<0.0001	0.419	<0.0001	0.409	0.002
LVMI, g/m^2	0.271	<0.0001	0.149	0.016	0.344	<0.0001	0.255	0.005	0.296	0.018
hs-CRP, mg/l	0.262	<0.0001	0.128	0.033	0.246	0.010	0.314	0.001	0.372	0.004
Matsuda/ISI	−0.242	<0.0001	−0.175	0.006	−0.182	0.044	−0.186	0.032	−0.226	0.057
2-h glucose, mg/dl	0.240	<0.0001	0.126	0.035	0.004	0.486	0.012	0.453	0.292	0.020
2-h insulin, μU/ml	0.176	<0.0001	0.026	0.354	0.200	0.030	0.262	0.004	0.277	0.026
e-GFR, ml/min/m^2	−0.169	<0.0001	−0.060	0.195	−0.188	0.039	−0.342	<0.0001	−0.032	0.412
1-h insulin, μU/ml	0.130	0.003	0.002	0.488	0.243	0.011	0.390	<0.0001	0.293	0.020
Fasting glucose, mg/dl	0.116	0.007	0.028	0.346	0.171	0.055	0.061	0.273	0.039	0.394
Fasting insulin, μU/ml	0.088	0.031	0.004	0.476	0.054	0.306	0.007	0.472	0.226	0.057
Age, yrs	0.048	0.156	0.027	0.347	0.084	0.218	0.113	0.131	0.092	0.262
DBP, mmHg	0.035	0.233	0.043	0.269	0.070	0.256	0.027	0.394	0.204	0.078
BMI, kg/m^2	0.023	0.314	0.002	0.488	0.025	0.409	0.190	0.029	0.245	0.043
SBP, mmHg	0.023	0.317	0.053	0.223	0.096	0.186	0.130	0.098	0.152	0.146

s-PAP systolic pulmonary arterial pressure, *NGT* normal glucose tolerance, *IGT* impaired glucose tolerance, *T2DM* type 2 diabetes mellitus, *hs-CRP* high-sensitivity C-reactive protein, *BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *e-GFR* estimated glomerular filtration rate, *ISI* insulin sensitivity index

Table 5 Univariate linear regression analysis between PVR and different covariates, in whole study population and in groups with different glucose tolerance

	All		NGT < 155		NGT ≥ 155		IGT		T2DM	
	R	*p*	*r*	*p*	*r*	*P*	*r*	*p*	*r*	*P*
1-h glucose, mg/dl	0.384	<0.0001	0.320	<0.0001	0.464	<0.0001	0.340	<0.0001	0.350	0.006
LVMI, g/m^2	0.383	<0.0001	0.425	<0.0001	0.292	0.003	0.279	0.003	0.287	0.030
2-h glucose, mg/dl	0.282	<0.0001	0.098	0.080	0.125	0.121	0.013	0.449	0.162	0.131
Fasting glucose, mg/dl	0.188	<0.0001	0.022	0.374	0.241	0.011	0.114	0.129	0.024	0.433
Matsuda index/ISI	−0.160	<0.0001	−0.039	0.288	−0.411	<0.0001	−0.006	0.477	−0.156	0.140
DBP, mmHg	0.104	0.014	0.131	0.030	0.053	0.309	0.093	0.180	0.090	0.268
e-GFR, ml/min/m^2	−0.101	0.016	−0.036	0.305	−0.022	0.420	−0.160	0.056	−0.128	0.188
hs-CRP, mg/l	0.093	0.025	0.003	0.485	0.019	0.431	0.008	0.470	0.284	0.023
Fasting insulin, μU/ml	0.087	0.034	0.111	0.055	0.351	<0.0001	0.011	0.458	0.182	0.103
Age, yrs	0.057	0.116	0.023	0.371	0.026	0.404	0.194	0.026	0.073	0.308
SBP, mmHg	0.052	0.137	0.090	0.099	0.018	0.434	0.058	0.282	0.046	0.374
2-h insulin, μU/ml	0.052	0.138	0.025	0.359	0.022	0.417	0.016	0.439	0.277	0.026
BMI, kg/m^2	0.018	0.353	0.005	0.472	0.037	0.365	0.009	0.465	0.090	0.268
1-h insulin, μU/ml	0.005	0.455	0.007	0.460	0.107	0.160	0.020	0.420	0.125	0.194

PVR pulmonary vascular resistances, *NGT* normal glucose tolerance, *IGT* impaired glucose tolerance, *T2DM* type 2 diabetes mellitus, *hs-CRP* high-sensitivity C-reactive protein, *BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *e-GFR* estimated glomerular filtration rate, *ISI* insulin sensitivity index

Table 6 Stepwise multiple regression analysis on TAPSE, s-PAP, and PVR as dependent variables in whole study population and in groups with different glucose tolerance

	All			NGT < 155			NGT ≥ 155			IGT			T2D		
	Beta	Partial R^2 (%)	*P*	Beta	Partial R^2 (%)	*P*	Beta	Partial R^2 (%)	*P*	Beta	Partial R^2 (%)	*P*	Beta	Partial R^2(%)	*P*
TAPSE															
1-h glucose, mg/dl	−0.401	19.7	<0.0001	−0.267	7.1	<0.0001	−0.502	26.3	<0.0001	−0.546	25.2	<0.0001	−0.598	27.4	<0.0001
LVMI, g/m^2	−0.183	2.8	<0.0001	−0.282	9.1	<0.0001	–	–	–	–	–	–	–	–	–
SBP, mmHg	–	–	–	–	–	–	−0.208	4.3	0.023	–	–	–	–	–	–
Total R^2 (%)		22.5			16.2			30.6			25.2			27.4	
s-PAP															
1-h glucose, mg/dl	0.220	12.7	<0.0001	0.176	3.5	0.007	0.451	19.9	<0.0001	0.327	17.6	<0.0001	0.527	16.7	0.003
hs-CRP, mg/l	0.158	2.6	0.001	–	–	–	0.183	3.3	0.046	0.272	8.9	0.001	–	–	–
LVMI, g/m^2	0.146	2.0	0.001	0.136	1.8	0.048	–	–	–	–	–	–	–	–	–
Matsuda/ISI	−0.100	0.8	0.036	–	–	–	–	–	–	–	–	–	–	–	–
e-GFR, ml/min/m^2	–	–	–	–	–	–	−0.224	4.6	0.021	–	–	–	–	–	–
2-h insulin, µU/ml	–	–	–	–	–	–	0.216	5.4	0.014	–	–	–	0.393	12.7	0.006
1-h insulin, µU/ml	–	–	–	–	–	–	–	–	–	0.254	5.7	0.005	–	–	–
Total R^2 (%)		18.1			5.3			33.2			32.2			29.4	
PVR															
1-h glucose, mg/dl	0.295	14.7	<0.0001	0.290	8.4	<0.0001	0.418	21.5	<0.0001	0.299	11.6	0.001	0.307	12.3	0.013
LVMI, g/m^2	0.287	7.7	<0.0001	0.404	18.1	<0.0001	–	–	–	0.238	7.8	0.005	0.252	8.0	0.023
Matsuda/ISI	–	–	–	–	–	–	−0.357	12.5	<0.0001	–	–	–	-	-	-
Total R^2 (%)		22.4			26.5			34.0			29.4			20.3	

TAPSE tricuspid annular plane systolic excursion, *LVMI* left ventricular mass index, *SBP* systolic blood pressure, *s-PAP* systolic pulmonary arterial pressure, *hs-CRP* high-sensitivity C-reactive protein, *e-GFR* estimated glomerular filtration rate, *ISI* insulin sensitivity index, *PVR* pulmonary vascular resistances, *DBP* diastolic blood pressure

respectively. In the whole population, also hs-CRP, LVMI, and Matsuda entered in the final model that explained 18.1% of s-PAP variation. In NGT < 155 subjects, LVMI added another 1.8% of s-PAP variation, whereas in NGT ≥ 155, 2-h insulin, e-GFR, and hs-CRP entered also in the model accounting for 5.4% ($P = 0.014$), 4.6% ($P = 0.021$), and 3.3% ($P = 0.046$) of the total variance, respectively. In IGT patients, also hs-CRP and 1-h insulin were retained the final model, explaining 8.9% ($P = 0.001$) and 5.7% ($P = 0.005$) of s-PAP variation; finally, of diabetic patients, also 2-h insulin entered in the final model accounting for 12.7% ($P = 0.006$) of its variation. When PVR was considered as the dependent variable, 1-h post-load glucose resulted in the first independent predictor of PVR in the whole study population, explaining 14.7% ($P < 0.0001$) of their variation; also LVMI entered in the model added another 7.7% ($P < 0.0001$). LVMI was the main predictor of PVR in NGT < 155 subjects justifying 18.1% ($P < 0.0001$) of their variation and 1-h glucose added another 8.4% ($P < 0.0001$). In NGT ≥ 155, IGT and diabetic patients 1-h glucose was the major determinant of PVR accounting for 21.5% ($P < 0.0001$), 11.6% ($P = 0.001$), and 12.3% ($P = 0.013$) of PVR variation, respectively. In NGT ≥ 155 subjects, also Matsuda was retained in the model explaining 12.5% ($P < 0.0001$) of its variation. Finally, in IGT and diabetic patients Matsuda accounted for another 7.8% ($P = 0.005$) and 8% ($P = 0.023$) of PVR variation, respectively. No colinearity problem was detected in the multiple regression models.

Discussion

The main finding of the present study is that, in a large cohort of untreated hypertensive patients, there is a progressive worsening of RV morphofunctional parameters according to impairment of glucose tolerance. This is demonstrated by the reduction of RV systolic indices with increase of PVR and s-PAP and the enlargement of right chambers dimensions. The increase in PVR and s-PAP could indicate an increase in RV afterload and, consequently, a major stress for RV wall with the appearance of RV systolic dysfunction. Of interest, NGT ≥ 155 subjects showed RV morphofunctional parameters significantly worse in comparison with NGT < 155 patients, but similar to IGT group. Moreover, after correction for all possible confounding factors, 1-h post-load plasma glucose was the first independent predictor of RV indices in particular in NGT ≥ 155. As already demonstrated by our group [28, 29], LVMI increased and LV diastolic function worsened from the first to the forth group. It is known that the increase in LVM may affect RV structure and function. In particular, high LVM values are associated with a reduced compliance of the LV and an increase in the ventricular filling pressure with possible repercussions on the left atrial pressure and, therefore, on the pulmonary circulation with an increase of the RV afterload. Moreover, we must take into account the ventricular interdependence, justified by the fact that the RV systolic function strongly depends on the contraction of the interventricular septum that is common to the two ventricular chambers. For this reason, all the regression models were adjusted for LVMI. Even if, in the stepwise multiple regression analysis LVMI is one of the major determinants of the RV indexes particularly in NGT < 155 subjects, this association becomes weak with the worsening of glucose tolerance. In fact, in NGT ≥ 155, IGT and T2DM patients 1-h post-load glucose has a predominant effect. Considering the value of the beta coefficient, this effect is particularly evident on the RV systolic function, expressed by TAPSE.

It is important to emphasize that, the relationship between 1-h glucose and RV indexes is significantly more robust than that with 2-h glucose, not just in NGT ≥ 155 subjects but even in IGT and T2DM individuals. In previous studies, our group has demonstrated that 1-h post-load glucose ≥ 155 mg/dl is associated with a worse cardiometabolic risk burden in IGT subjects or in pre-diabetic individuals diagnosed by HbA1c. Thus, 1-h post-load glucose values allow to identify subjects at higher risk of T2DM and CVD, more efficaciously than 2-h post-load glucose levels [40, 41].

According with this, the present study confirms that NGT ≥ 155 subjects, compared with NGT < 155 patients, are characterized by a worse metabolic and inflammatory profile; that appears similar to the one observed for the IGT and T2DM groups.

In fact, NGT ≥ 155 subjects showed higher degree of IR as demonstrated by reduced Matsuda index and increased hs-CRP levels. Moreover, they presented a worse CV phenotype as demonstrated by reduced e-GFR and increased LVMI, all independent predictor of adverse clinical outcome in different settings of patients.

The novelty of the study is that not only LV but also RV is affected by early glucose metabolism disorders. This is clinically relevant, because most studies on diabetic cardiomyopathy have mainly considered LV, but RV may have a crucial role too. In particular, previous studies showed an impairment in RV function in diabetic subjects [8–12]. According with this, Widya et al. reported a significant reduction of diastolic and systolic RV indices in uncomplicated T2DM patients, evaluated by magnetic resonance imaging, when compared with healthy subjects [12]. In addition, before the occurrence of overt T2DM, other conditions characterized by an altered glucose metabolism, including the metabolic syndrome, may affect RV structure and function [42, 43]. It is plausible that, conditions as hyperglycemia and IR, may affect both ventricles. In particular, during chronic high glucose levels, myocardial

energy production by glucose is decreased and there is a shift toward the oxidation of free fatty acids (FFA) with depletion of glucose transporters (GLUT)-1 and -4, thus promoting IR. Hyperglycemia and IR also promote a proinflammatory status with increased oxidative stress and mythocondrial dysfunction, whicht associated with increased advanced glycation end products lead to myocardial fibrosis. The reduction of insulin-like growth factor-1 and the activation of RAAS and SNS, all conditions associated with hyperglycemia/IR, are other important mechanisms involved in cardiac damage [44, 45]. Moreover, during chronic hyperglycemia it is important to take into account the microangiopathy of the alveolar capillaries and pulmonary arterioles, that may justify increased RV afterload and, in the long run, RV dysfunction [46]. Obviously, since these mechanisms have not been investigated in the study, they remain at this stage pathophysiological hypotheses.

Thus, the present data indicate that, even before the onset of clinically diagnosed diabetes, glucose metabolism disorders can have a significant impact not only on left cardiac sections, but also on the right heart. The present data are clinically relevant because it has been demonstrated that RV dysfunction may affect the course and the prognosis of different clinical conditions [14, 15, 47].

In particular, several studies have demonstrated that, independently of LV ejection fraction, the RV systolic performance is an independent prognostic factor in patients with chronic and acute heart failure [14, 15]. Moreover, in patients with inferior wall acute myocardial infarction (AMI), the persistent RV dysfunction was associated with a significantly lower 8-year survival rate after hospital discharge, because of a higher incidence of left- and right-sided cardiac failure and recurrent AMI [47].

Several limitations of the study should be considered. First, the evaluation of RV has been performed by echocardiography, which is an operator-dependent method; however, it is inexpensive, easily accessible and widespread in clinical practice. Second, the results were observed in hypertensive patients with high 1-h post-load glucose, and it may not be confirmed in other settings of patients; moreover, we have to consider the lack of clinical follow-up data.

Also the lack of HbA1c values, among parameters included in the analysis, should be considered a limitation of the study. However, the strengths are represented by the evaluation of a large cohort, with complete metabolic assessment, without pharmacological treatment, to exclude possible bias.

In conclusion, the present results confirm the predictive role of 1-h post-load plasma glucose on cardiac damage, not only for left chambers but also for RV, thus highlighting the importance to perform an OGTT in all hypertensive patients taking into account not only 2-h but also 1-h post-load glucose levels to improve the stratification of global CV risk. The demonstration of RV impairment in hypertensive NGT ≥ 155 subjects, further complicates their CV burden and it may, at least in part, justify the increased risk for all-cause mortality in this setting of patients as indicated by recent evidence [41, 48].

According with this, in the 30-year follow-up report of the Israel Study of Glucose Intolerance, Obesity and Hypertension, 1-h glucose value ≥ 155 mg/dl is an important predictor of all-cause mortality (28% increased risk) in NGT subjects, also after adjusting for gender, age, smoking, BMI, and blood pressure [48].

Recently, a petition review further emphasizes the high risk of T2DM and the increased CV burden in subjects with elevated 1-h post-load glucose levels and the document proposes to replace current OGTT criteria for diagnosing prediabetes with the 1-h post-load plasma glucose ≥ 155 mg/dl [49].

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures, that have been performed in humans, were in accordance with the ethical standards of the institutional ethic committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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