Impaired Glucose Tolerance, but Not Impaired Fasting Glucose, Underlies Left Ventricular Diastolic Dysfunction

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OBJECTIVE—Glucose intolerance is recognized as a predictor of congestive heart failure (CHF). However, the association of postprandial hyperglycemia or fasting hyperglycemia with CHF has not been clarified. We determined the impact of the total spectrum of glucose abnormalities on left ventricular (LV) geometry and diastolic function.

RESEARCH DESIGN AND METHODS—Two hundred and eighty-seven Japanese subjects who visited the university hospital to be checked for glucose intolerance or known type 2 diabetes were consecutively recruited. Participants underwent an oral glucose tolerance test if they had no history of diabetes, and LV geometry and LV systolic and diastolic function were analyzed by Doppler echocardiography.

RESULTS—The frequency of LV diastolic dysfunction in subjects with normal glucose tolerance, impaired fasting glucose (IFG), impaired glucose tolerance (IGT), newly detected diabetes, and known diabetes were 13, 22, 50, 51, and 61%, respectively ($\chi^2 = 54.2$, $P < 0.0001$). IGT was a predictor for LV diastolic dysfunction after adjusting for age, sex, systolic blood pressure, and heart rate (odds ratio 3.43 [95% CI 1.09–11.2]), but IFG was not (0.49 [0.06–3.08]). IGT was a predictor after adjusting for established CHF risk factors but was no longer significant after adjusting for BMI and homeostasis model assessment of insulin resistance.

CONCLUSIONS—In this hospital-based registry of subjects without CHF, the prevalence of LV diastolic dysfunction was higher in subjects with IGT but not in those with IFG. Results suggest that IGT, as well as newly detected and known diabetes, could be linked to an increased risk of cardiovascular events, partly through LV diastolic dysfunction.

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Major cardiovascular events or mortality are related to prevailing hyperglycemia, particularly postprandial, but not fasting hyperglycemia (1,2). Abnormalities of the postprandial state are especially hazardous to endothelial function and are important contributing factors to the development of atherosclerosis (3,4). Hyperglycemia also is recognized as a predictor of congestive heart failure (CHF) (5–7), the major cause of cardiovascular morbidity and mortality. However, the association of postprandial hyperglycemia or fasting hyperglycemia with CHF has not been clarified.

In patients hospitalized for CHF, 30–40% present only with left ventricular (LV) diastolic dysfunction but not with LV systolic dysfunction (8,9). Patients with LV diastolic dysfunction manifest more subtle symptoms and signs than those with LV systolic dysfunction, and the identification often could be delayed or missed. In a large-scale community study, the prevalence of LV diastolic dysfunction was shown to be strongly associated with diabetes (odds ratio 2.3), as was hypertension (2.8), LV hypertrophy (LVH) (7.6), and having a previous myocardial infarction (4.3) (10). But the association of the total spectrum of glucose abnormalities and LV diastolic function remains unclear.

We therefore evaluated the impact of the spectrum of glucose abnormalities, namely, impaired fasting glucose (IFG), impaired glucose tolerance (IGT), newly detected diabetes, and known diabetes, on LV geometry and LV diastolic function in a hospital-based registry.

RESEARCH DESIGN AND METHODS

A total of 287 Japanese participants who visited the university hospital by self-referral or by recommendation for further check-up of glucose intolerance or known type 2 diabetes were consecutively recruited. Participants were excluded if they had a history of coronary heart disease, cerebrovascular disease, peripheral vascular disease, symptomatic arrhythmia, or congestive heart failure (CHF). After an overnight fast, subjects underwent a 75-g oral glucose tolerance test if they did not have known diabetes. They were divided into groups of those who had normal glucose tolerance (NGT) ($n = 104$), IFG ($n = 18$), IGT and/or IFG ($n = 52$), or newly detected diabetes ($n = 72$), according to World Health Organization criteria (11). A group of subjects with known diabetes ($n = 41$), who had been treated with diet and/or oral hypoglycemic agents and insulin, also were recruited. The study protocol complied with the ethical principles for medical research involving human subjects of the World Medical Association Declaration of Helsinki and ethical guidelines for clinical studies issued by the Ministry of Health, Labor, and Welfare of Japan. All subjects gave informed consent.

Echocardiographic measurements

Echocardiography was performed on a ProSound SSD-5500 (Aloka) with a 2.5-MHz transducer by observers (N.H., Y.O., and T.A.) blinded to the clinical data obtained. Subjects were examined in the

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left lateral decubitus position using standard parasternal, short-axis, and apical views.

LV diastolic dysfunction was evaluated using standardized diagnostic criteria proposed by the Canadian consensus on diastolic dysfunction by echocardiography and were classified as normal, impaired relaxation, pseudonormal, and restrictive patterns (12) with modifications (13). The transmitral peak E velocity, peak A velocity, acceleration and deceleration time (time elapsed between peak E velocity and the point where the extrapolation of the acceleration and deceleration slope of the E velocity crosses the zero baseline), and isovolumic relaxation time (aortic valve closure spike to the beginning of mitral flow) were measured at end expiration. On the color M-mode echocardiography in the apical four-chamber view, flow propagation velocity (FPV) was measured as the slope of the first color aliasing velocity from the mitral annulus in early diastole to 4 cm distally into the LV capacity (13). LV diastolic function was defined as having a normal (FPV ≥45 cm/s and isovolumetric relaxation time [IRT] <100 ms), mildly impaired relaxation (FPV <45 and IRT ≥100), pseudonormal (FPV <45 and 60≤ IRT <100), and severely restrictive (FPV <45 and IRT <60) patterns. No subject had echocardiographically detectable regional-wall motion abnormalities, and subjects who had ejection fractions <50% were excluded. All cardiac valves were examined to rule out significant valvular disease. LV mass was calculated using the following equation (14): LV mass (g) = 0.8×1.04 [$(\text{LVEDD} + \text{IVST} + \text{PWT})^3 - (\text{LVEDD})^3$] + 0.6, where LVEDD is LV end-diastolic internal diameter, IVST is interventricular septal thickness, and PWT is posterior-wall thickness.

Biochemical measurements

Venous blood samples were obtained in tubes containing EDTA sodium and in polystyrene tubes without an anticoagulant, separated by centrifugation, and stored at –80°C until assayed. Plasma glucose concentration was measured by a glucose oxidase method, insulin by an enzyme-linked immunosorbent assay, and HbA_{1c} by an affinity-binding assay. Serum concentrations of total cholesterol, HDL cholesterol, and triglycerides were measured by routine enzymatic methods, and the concentration of LDL cholesterol was calculated using the Friedewald method (15).

Statistical analysis

Values were expressed as means ± SD, unless otherwise indicated. Multigroup comparisons of variables were done by one-way or two-way ANOVA followed by the Tukey-Kramer honestly significant difference test or by the Fisher exact-probability test. Multiple logistic regression analysis was done to adjust confounding factors. Variables were treated as continuous, except for the categorical class of LV diastolic function (normal vs. abnormal [mild, pseudonormal, or severely restricted]), the class of glucose intolerance (NGT, IFG, IGT, and/or IFG; newly detected diabetes; and known diabetes), and sex, which were treated as nominal. We investigated the independent variables in five sets of models in a hierarchical fashion: unadjusted; adjusted for age and sex; adjusted for age, sex, and other established risk factors for CHF (systolic blood pressure, smoking, total cholesterol, and LV mass index); adjusted for age, sex, BMI, and homeostasis model assessment (HOMA) of insulin resistance (HOMA-IR). Odds ratios were given as two-tailed 95% CIs. All analyses were performed using Jump version 5.0.1 J software (SAS Institute, Cary, NC). Probability was considered to be significant if it was <0.05.

RESULTS

General characteristics

The general characteristics of the studied subjects are shown in Table 1. Sex distribution was not different among the five classes of glucose tolerance (NGT, IFG, IGT, newly detected diabetes, and known diabetes). IGT consisted of isolated IGT (n = 10) and the combined IGT/IFG (n = 42) group. Age was higher in the group of subjects with known diabetes than in the other four groups. Body weight, waist circumference, and BMI were higher in the IGT and newly detected diabetes groups. Systolic blood pressure was higher in the group of subjects with known diabetes than in the other four groups.

As shown in Table 2, plasma glucose levels in the group with IFG were higher at 0, 30, and 60 min but not at 90 and 120 min, whereas those levels were higher at any point in the groups with IGT and newly detected diabetes than in the group with NGT. HOMA-IR was higher in those with IGT, newly detected diabetes, and known diabetes but not in those with IFG. HOMA of β-cell function (HOMA-B) was lower in those with IFG, newly detected diabetes, and known diabetes but not in those with IGT. Total and LDL cholesterol levels were comparable among the five groups. Triglycerides were higher in those with IGT, newly detected diabetes, and known diabetes.

LV systolic and diastolic function

There were no subjects excluded for having an LV ejection fraction <50%. As shown in Table 3, the thickness of the interventricular septum and LV posterior wall as well as relative wall thickness were higher in the group with known diabetes than in the group with NGT. LV mass index and LV systolic function indices, such as the LV ejection fraction and cardiac index, were comparable between groups.

As shown in Table 3, peak early (E) transmitral Doppler velocity was lower, but late (A) velocity tended to be higher, and thus the E-to-A ratio was lower in

Table 1—*Main demographic and clinical characteristics*

	NGT	IFG	IGT	Newly detected diabetes	Known diabetes
n	104	18	52	72	41
Male/female	48/56	10/8	27/25	39/33	18/23
Age (years)	51 ± 14	53 ± 12	55 ± 14	58 ± 13*	61 ± 9*
Body weight (kg)	61 ± 12	64 ± 12	68 ± 13*	68 ± 13*	61 ± 12
Waist (cm)	85 ± 11	89 ± 10	94 ± 10*	93 ± 11*	91 ± 9*
Hip (cm)	95 ± 7	97 ± 6	98 ± 9	97 ± 10	94 ± 7
BMI (kg/m^2)	24.2 ± 3.9	25.8 ± 3.1	27.1 ± 4.4*	27.1 ± 5.0*	25.1 ± 3.5
Systolic blood pressure (mmHg)	128 ± 20	128 ± 14	134 ± 20	135 ± 19	139 ± 25*
Diastolic blood pressure (mmHg)	74 ± 13	75 ± 11	78 ± 11	78 ± 12	76 ± 11
Heart rate (mmHg)	66 ± 12	67 ± 11	68 ± 12	72 ± 12*	69 ± 10

Data are means ± SD. *$P < 0.05$ vs. NGT by Tukey-Kramer HSD post hoc test.

Table 2—*Biochemical parameters of studied patients*

	NGT	IFG	IGT	Newly detected diabetes	Known diabetes
n	104	18	52	72	41
Glucose (mmol/L)					
0 min	5.0 ± 0.4	6.3 ± 0.3*	5.4 ± 0.7*	7.4 ± 1.5*	9.8 ± 3.6*
30 min	7.7 ± 1.7	10.9 ± 0.2*	9.4 ± 1.6*	12.7 ± 2.5*	
60 min	7.4 ± 2.2	10.4 ± 0.6*	10.9 ± 1.8*	14.9 ± 3.4*	
90 min	6.6 ± 1.2	7.9 ± 0.7	9.8 ± 1.6*	15.8 ± 3.2*	
120 min	5.9 ± 0.9	4.7 ± 0.9	8.8 ± 1.1*	15.2 ± 3.3*	
Insulin (pmol/L)					
0 min	44 ± 28	55 ± 21	67 ± 31*	78 ± 42*	50 ± 38
30 min	408 ± 357	611 ± 371	415 ± 232	313 ± 199	
60 min	408 ± 251	791 ± 92*	573 ± 356*	400 ± 274	
90 min	362 ± 295	687 ± 127*	622 ± 381*	478 ± 353	
120 min	280 ± 201	249 ± 126	660 ± 512*	543 ± 404*	
HbA_{1c} (%) [NGSP]	5.48 ± 0.33	5.88 ± 0.42	5.86 ± 0.50	7.68 ± 1.39*	9.31 ± 1.52*
HOMA-IR	1.45 ± 0.99	2.18 ± 0.83	2.38 ± 1.23*	3.75 ± 2.24*	3.58 ± 2.26*
HOMA-B	88 ± 52	59 ± 25*	105 ± 53	65 ± 45*	46 ± 63*
Total cholesterol (mmol/L)	5.21 ± 0.99	5.04 ± 0.77	5.58 ± 0.98	5.54 ± 1.04	5.56 ± 0.92
Triglycerides (mmol/L)	1.24 ± 0.76	1.71 ± 0.92	1.93 ± 1.06*	1.89 ± 1.14*	1.78 ± 1.09*
HDL cholesterol (mmol/L)	1.56 ± 0.43	1.34 ± 0.32*	1.34 ± 0.27*	1.35 ± 0.36*	1.35 ± 0.28*
LDL cholesterol (mmol/L)	3.08 ± 0.83	2.89 ± 0.61	3.33 ± 0.89	3.30 ± 0.82	3.39 ± 0.79

Data are means ± SD. *$P < 0.05$ vs. NGT by Tukey-Kramer honestly significant difference post hoc test.

those with IFG, IGT, newly detected diabetes, and known diabetes (Table 4). The early transmitral FPV measured by color M-mode Doppler echocardiography was lower in those with IGT, newly detected diabetes, and known diabetes. The categorical class of LV diastolic function was shown in Fig. 1. The frequencies of LV diastolic dysfunction (mildly impaired relaxation plus pseudonormal plus severely restrictive pattern) in NGT, IFG, IGT, newly detected diabetes, and known diabetes were 13, 22, 50, 51, and 61%, respectively ($\chi^2 = 54.2$, $P < 0.0001$).

As shown in Table 4, IGT was a significant predictor for LV diastolic dysfunction after adjusting for age, sex, systolic blood pressure, and heart rate, but

Table 3—*Echocardiographic parameters of LV systolic and diastolic function*

	NGT	IFG	IGT	Newly detected diabetes	Known diabetes
n	104	18	52	72	41
Systolic function					
Intraventricular septum (cm)	0.93 ± 0.19	0.86 ± 0.19	1.00 ± 0.21	1.03 ± 0.26*	1.06 ± 0.19*
LV posterior wall (cm)	0.92 ± 0.19	0.86 ± 0.17	1.05 ± 0.20*	1.05 ± 0.26*	1.02 ± 0.21*
Diastolic LV dimention (cm)	4.49 ± 0.51	4.61 ± 0.38	4.47 ± 0.56	4.58 ± 0.58	4.44 ± 0.45
Systolic LV dimention (cm)	2.74 ± 0.46	2.90 ± 0.37	2.82 ± 0.47	2.81 ± 0.54	2.63 ± 0.37
Relative wall thickness	0.42 ± 0.10	0.37 ± 0.07	0.47 ± 0.11*	0.46 ± 0.14*	0.48 ± 0.12*
LV end-diastolic volume (mL)	94 ± 24	99 ± 20	93 ± 27	99 ± 29	91 ± 21
LV end-systolic volume (mL)	29 ± 12	33 ± 11	31 ± 13	32 ± 15	26 ± 9
LV ejection fraction (%)	69 ± 7	67 ± 7	67 ± 8	69 ± 10	71 ± 7
LV mass (g)	161 ± 58	152 ± 56	186 ± 70	200 ± 79	185 ± 43
LV mass index (g/m^2)	101 ± 33	91 ± 25	112 ± 35	119 ± 45	118 ± 27
Cardiac output (L/min)	4.25 ± 1.11	4.15 ± 0.99	4.23 ± 1.49	4.59 ± 1.27	4.43 ± 1.08
Cardiac index ($L/min/m^2$)	2.68 ± 0.73	2.53 ± 0.61	2.54 ± 0.78	2.74 ± 0.74	2.83 ± 0.68
Diastolic function					
Left atrial dimension (cm)	3.49 ± 0.49	3.58 ± 0.40	3.62 ± 0.39	3.63 ± 0.50	3.60 ± 0.54
E peak flow (cm/s)	71 ± 24	65 ± 14	54 ± 15*	53 ± 15*	52 ± 13*
A peak flow (cm/s)	69 ± 22	66 ± 11	74 ± 17	71 ± 20	80 ± 20
E/A peak flow	1.12 ± 0.44	1.01 ± 0.26*	0.77 ± 0.30*	0.80 ± 0.32*	0.68 ± 0.19*
Isovolumic relaxation time (ms)	75 ± 26	98 ± 23*	95 ± 29*	93 ± 20*	102 ± 29*
Acceleration time (ms)	100 ± 17	98 ± 19	102 ± 18	100 ± 19	95 ± 21
Deceleration time (ms)	161 ± 36	173 ± 50	206 ± 43*	153 ± 36	172 ± 39
FPV (cm/s)	53 ± 11	51 ± 7	44 ± 9*	47 ± 12*	43 ± 11*

Data are means ± SD. *$P < 0.05$ vs. NGT by Tukey-Kramer honestly significant difference post hoc test.

Table 4—*Logistic regression models for LV diastolic dysfunction*

Odds ratio	NGT	IFG	95% CI	*P*	IGT	95% CI	*P*	Newly detected diabetes	95% CI	*P*	Known diabetes	95% CI	*P*
Unadjusted	1.00	0.24	0.03–1.32	NS	2.94	1.03–8.53	0.044	3.29	1.28–8.68	0.014	7.18	2.30–23.6	<0.001
Adjusted for age and sex	1.00	0.31	0.04–1.77	NS	3.23	1.08–9.86	0.037	3.02	1.13–8.24	0.029	4.66	1.43–15.81	0.012
Adjusted for age, sex, systolic blood pressure, and heart rate	1.00	0.49	0.06–3.08	NS	3.43	1.09–11.16	0.037	2.29	0.81–6.61	NS	3.40	0.96–12.46	0.060
Adjusted for age, sex, systolic blood pressure, smoking, and total cholesterol	1.00	0.83	0.09–6.13	NS	3.80	1.10–13.5	0.036	2.02	0.64.6.44	NS	3.26	0.89–12.25	0.075
Adjusted for age, sex, BMI, and HOMA-IR	1.00	0.39	0.04–2.69	NS	2.86	0.86–9.70	0.087	1.58	0.48–5.19	NS	4.08	1.06–16.22	0.042

The adjusted odds ratio was calculated by multiple logistic regression analysis with confounding variables. NS, not significant.

IFG was not. IGT still was a predictor after adjusting for established CHF risk factors but was no longer a significant predictor of LV diastolic dysfunction after adjusting for BMI and HOMA-IR.

CONCLUSIONS—In this hospital-based registry of subjects free of CHF and other cardiovascular complications, the prevalence of LV diastolic dysfunction was higher in those with IGT as well as in those with newly detected and known diabetes but not in those with IFG. After adjusting for established risk factors, IGT, but not IFG, was a predictor of LV diastolic dysfunction.

LV diastolic dysfunction and CHF in glucose intolerance

Diabetes is recognized as a predictor of CHF (5–7). Postprandial, but not fasting, hyperglycemia is known to be a better predictor of major cardiovascular events or total mortality, but the impact of postprandial or fasting glucose levels on LV diastolic function has not been elucidated (1,2).

This is, to our knowledge, the first report demonstrating that IGT, but not IFG, predicts LV diastolic dysfunction independently of known risk factors such as diabetes, hypertension, LVH, smoking, and serum cholesterol level.

The association of insulin resistance to LV geometry and function has been previously described (16,17). Sundström et al. (16) reported that oral glucose tolerance test 2-h glucose levels, but not fasting plasma glucose, was significantly related to LV relative wall thickness and LV concentric remodeling but less related to LVH in a population-based sample of elderly men. Rutter et al. (17) reported that LV mass (adjusted for age, height, heart rate, and systolic blood pressure) increased across categories of worsening glucose tolerance.

The current study focused on the LV diastolic function rather than LV geometry and remodeling. Patients with LV diastolic dysfunction, impaired relaxation, and elevated filling pressures would be expected to have a higher risk of CHF compared with systolic variables (18). LV filling indices on Doppler echocardiography has been applied to determine such diastolic dysfunction, although their accuracy is limited by the difficulties in distinguishing between the normal and the pseudonormal filling pattern and the influence of heart rate, age, and loading conditions (13). The early transmitral FPV measured by color M-mode Doppler

Figure 1—*Categorical class of LV diastolic function. LV diastolic function was defined as normal (□, FPV ≥45 cm/s), mild (⊡, FPV <45 and IRT <60), pseudonormal (▨, FPV <45 and 60 ≤IRT< 100 ms), or severe (■, FPV <45 and IRT <60 ms) in patients with NGT* (n = *104), IFG (18), IGT and/or IFG* (n = *52), newly detected diabetes (DM)* (n = *72), or known diabetes* (n = *41*). $\chi^2 = 87.6$, $P < 0.0001$.

echocardiography is a useful index to identify such pseudonormal filling patterns because FPV is solely correlated with the time constant of isovolumetric relaxation (τ), independently of other confounding conditions (13).

In the subjects without CHF and other cardiovascular complications, the prevalence of LV diastolic dysfunction, determined by FPV and IRT, was higher in those with IGT but not in those with IFG. After adjusting for established risk factors, such as diabetes, hypertension, smoking, and serum cholesterol level, IGT is a significant predictor of LV diastolic dysfunction. But IGT was no longer a significant predictor of LV diastolic dysfunction after adjusting for BMI and HOMA-IR.

Potential mechanisms of LV diastolic dysfunction

The prevalence of LV diastolic dysfunction in those with IGT, compared with those with IFG, might be explained by several potential mechanisms.

First, the association of insulin resistance with LV geometry could be linked to LV diastolic dysfunction. Postchallenge glucose levels are better predictors of relative wall thickness and LV concentric remodeling (17). LV hypertrophy and concentric remodeling can be largely accounted for by insulin resistance, a major underlying condition in IGT (17). This notion is supported by the fact that IGT was no longer a predictor of LV diastolic dysfunction after adjusting for BMI and HOMA-IR. Second, LV

relaxation of IGT and newly detected and known diabetes could be deteriorated by comorbid conditions, such as LV hypertrophy, hypertension, and obesity. In a categorical class of LV diastolic function (Fig. 1), the distribution of mildly impaired LV relaxation and pseudonormal and severely restrictive patterns were almost identical among those with IGT and newly detected and known diabetes. Third, endothelial dysfunction could be related to LV diastolic dysfunction in those with IGT as well as in those with diabetes. Impairments in LV diastolic function and forearm flow-mediated dilatation were functionally linked in diabetic patients (19). Inadequate vasodilation of coronary and peripheral arteries in response to stimuli that release nitric oxide (NO) is observed in those with IGT (20,21), and this abnormal efficiency of endothelial-derived NO can be linked to LV diastolic dysfunction in those with IGT (22).

Study limitations

First, the patient population is relatively small. Despite seemingly convincing results, this observation needs confirmation in a larger study. Second, LV function was made only by Doppler echocardiographic indices; therefore, this does not necessarily indicate real abnormalities of LV relaxation. We used relatively old-fashioned but commonly available methods because accurate tissue Doppler is expensive and is not always used in the clinical setting. Third, this study was conducted using a university hospital–based sample; therefore, the frequency of abnormal glucose tolerance, including IFG, IGT, and newly detected diabetes, could be biased compared with that in a community-based population.

Clinical implication

The prevalence of LV diastolic dysfunction was higher in those with IGT but not in those with IFG. Our results suggest that IGT, as well as newly detected and known diabetes, could be linked to an increased risk of cardiovascular events, partly through alteration of LV geometry and LV diastolic dysfunction.

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M.S. designed and researched data and wrote the manuscript. N.H., T.A., K.Y., and Y.O. researched data and discussed and reviewed the manuscript. M.H. and H.M. reviewed the manuscript.

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