Association between serum γ-glutamyltransferase levels and coronary microvascular function in hypertensive patients

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Objective **Serum γ-glutamyltransferase (GGT) level is an independent risk factor for cardiovascular (CV) disease, and there is a strong association between serum GGT levels and most CV risk factors, including hypertension; however, the role of serum GGT level as an independent risk factor for target organ damage in hypertension remains controversial. Accordingly, we aimed to determine whether serum GGT level is independently and specifically associated with coronary flow reserve (CFR) impairment in hypertensive patients.**

Methods **We examined 100 never-treated and newly diagnosed hypertensive individuals, and CFR was achieved in 97 (97%) of them. They were divided into two groups based on serum GGT levels.**

Results **Subjects with higher GGT had significantly impaired CFR as compared to those with lower GGT (2.10 ± 0.36 versus 2.57 ± 0.54, $P < 0.0001$). After adjusting for potential confounders, including age, sex, body mass index, blood pressure, lipids and glucose, we found that serum GGT levels were independently associated with CFR impairment ($\beta = -0.62$, $P < 0.0001$). We also found that GGT level was a good predictor of low CFR at the receiver-operating characteristic curve. Area under the curve was 79% [95% confidence interval: 0.70–0.88], and GGT level was significantly predictive of low CFR ($P < 0.0001$).**

Conclusion **These results support a role for serum GGT level as an independent marker of target organ damage in hypertensive subjects without concomitant risk factors.** *J Hypertens* **25:2497–2503 © 2007 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

Recent epidemiological and clinical studies have shown that γ-glutamyltransferase (GGT) is an independent risk factor for the mortality and morbidity of cardiovascular (CV) disease [1,2]. There is a strong association between serum GGT levels and many CV risk factors, including hypertension [3–5]. In addition, several prospective studies reported that baseline serum GGT concentration was an independent risk factor for the development of coronary artery disease (CAD), diabetes mellitus, stroke and hypertension [5–9].

Patients with hypertension may have symptoms and signs of myocardial ischemia despite angiographically normal coronary arteries, which may be related to impaired coronary microvascular function [10]. In the absence of epicardial coronary artery stenosis, coronary flow reserve (CFR) may be considered a marker of coronary microvascular function, and attenuated CFR is mostly the result of minimal changes in coronary resistance that are independent of vascular tone [11–13]. Therefore, structural changes in the coronary vasculature are most likely to be the major contributors to altered CFR. Quantitative histological studies performed on septal biopsy tissue showed that reduced coronary dilatory capacity was associated with increased arteriolar media area, and perivascular and interstitial fibrosis in patients with arterial hypertension and angina pectoris in the absence of relevant coronary artery stenosis [12]. These conditions are sensitive indicators of hypertensive target-organ damage [12,13]. Furthermore, it has been suggested that impairment of CFR may occur very early in hypertension before hypertrophy is apparent, and may cause subsequent ischemia and fibrosis [11]. Thus, the search for impaired CFR may be recommended as part of global risk assessment. Accordingly, the present study was performed to evaluate the association between serum GGT concentrations and impaired CFR in a group of middle-aged never-treated and newly diagnosed patients with essential hypertension without concomitant risk factors.

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Methods

Study population

The overall study population included 100 never-treated and newly diagnosed essential hypertensive subjects. In each subject, blood pressure was measured on three separate days in a week, after 15 min of sitting comfortably, and these three values were averaged. Individuals who had diastolic blood pressure (BP) $\geq$ 90 mmHg and/or systolic BP $\geq$ 140 mmHg in the office setting were diagnosed as hypertensive. A complete physical examination was performed, with particular attention to peripheral arterial pulses and carotid bruits. Each subject was questioned about major CV risk factors, including family history of CAD, current smoking status, alcohol consumption and diabetes mellitus. Family history of CAD was obtained by questioning the subjects about CAD in first-degree male relatives before 55 years and in female relatives before 65 years of age. Age, gender and body mass index (BMI) were recorded. Fasting blood glucose, total cholesterol, high-density lipoprotein (HDL)-cholesterol, low-density lipoprotein (LDL)-cholesterol and triglyceride levels, which were measured with original kits using an Abbott-Aeroset autoanalyzer (Chicago, Illinois, USA), were noted. Plasma levels of C-reactive protein were measured by use of a highly sensitive sandwich enzyme-linked immunosorbent assay (ELISA) using the Abbott-Aeroset autoanalyzer. Serum GGT levels were measured at 37°C by enzymatic calorimetric test using a Roche/Hitachi analyzer (Mannheim, Germany) [2]. The normal reference value of the GGT level for a healthy individual was 8–61 U/l in our laboratory. The hypertensive subjects were divided into two groups based on median value of serum GGT levels (21 U/l for women, 30 U/l for men): 49 subjects with lower GGT (group I) and 48 subjects with higher GGT level (group II). Tests for interaction between GGT and gender were significant; therefore, all analyses were conducted with stratifying for gender.

Inclusion criteria included 18–55 years of age, and a regular menstrual cycle for women. Exclusion criteria included the presence of any systemic disease such as hemolytic, hepatic, and renal diseases or any disease that could impair CFR [e.g. diabetes mellitus: fasting plasma glucose level measured on three separate days in a week $>$ 126 mg/dl (7.0 mmol/l); or impaired oral glucose tolerance test: fasting plasma glucose $<$ 126 mg/dl (7.0 mmol/l) but 2-h plasma glucose after a 75-g oral glucose challenge $>$ 140 mg/dl (7.8 mmol/l)], family history of CAD and excessive alcohol consumption ($>$ 50 g/day). Subjects were excluded from the study if they used any vasoactive drug, had undergone previous antihypertensive therapy, were current smokers and had ST-segment or T-wave changes specific for myocardial ischemia (including strain pattern), Q waves and incidental left bundle branch block on ECG. Individuals were also excluded if they had severe dyslipidemia and/or excessive obesity (HDL cholesterol levels $<$ 30 mg/dl, LDL cholesterol levels $>$ 160 mg/dl, triglyceride levels $>$ 400 mg/dl, BMI greater than 35 kg/m^2), elevated other liver enzymes, or left ventricular mass index (LVMI) $>$ 126 g/m ($>$ 48 g/m$^{2.7}$) in men and $>$ 99 g/m ($>$ 44 g/m$^{2.7}$) in women [14] (to avoid the confounding effects of LVH on CFR). Written informed consent was obtained from each subject. The institutional ethics committee approved the study protocol.

Echocardiographic examination

Each subject was examined using an Acuson Sequoia C256 Echocardiography System equipped with 3V2c and 5V2c broadband transducers with second harmonic capability (Acuson Corp., Mountain View, California, USA). Two-dimensional, M-mode and subsequent transthoracic Doppler echocardiographic examinations were performed on each subject.

Left ventricular mass determination

Left ventricular mass (LVM) was calculated from M-mode records taken on parasternal long-axis images according to the formula below (corrected American Society of Echocardiography cube method) [14,15].

$$\mathrm{LVM} = 0.8 \times (1.04[(\mathrm{IVSd} + \mathrm{PWd} + \mathrm{LVDD})^3 - (\mathrm{LVDD})^3]) + 0.6\,\mathrm{g}.$$

where IVSd is the interventricular septum thickness at diastole; PWd, the posterior wall thickness at diastole; and LVDD, the left ventricular diastolic diameter. To take into account differences in body size that might influence cardiac size, left ventricular mass was divided by height and height$^{2.7}$ to create an LVMI.

Coronary flow reserve measurement

The visualization of the distal left anterior descending coronary artery (LAD) was performed using a modified, foreshortened, two-chamber view obtained by sliding the transducer on the upper part and medially from an apical two-chamber view, to reach the best alignment to the interventricular sulcus. Coronary flow in the distal LAD was examined by color Doppler flow mapping over the epicardial part of the anterior wall, with the color Doppler velocity set in the range of 8.9–24.0 cm/s [16]. The left ventricle was imaged on the long-axis cross-section, and the ultrasound beam was then inclined laterally. Next, coronary blood flow in the LAD (middle to distal) was searched by color Doppler flow mapping (Fig. 1). All subjects had Doppler recordings of the LAD with dipyridamole infusion at a rate of 0.56 mg/kg over 4 min. By placing the sample volume on the color signal, spectral Doppler of the LAD showed the characteristic biphasic flow pattern with larger diastolic and smaller systolic components (Fig. 1). Coronary diastolic peak velocities were measured at baseline and after dipyridamole by

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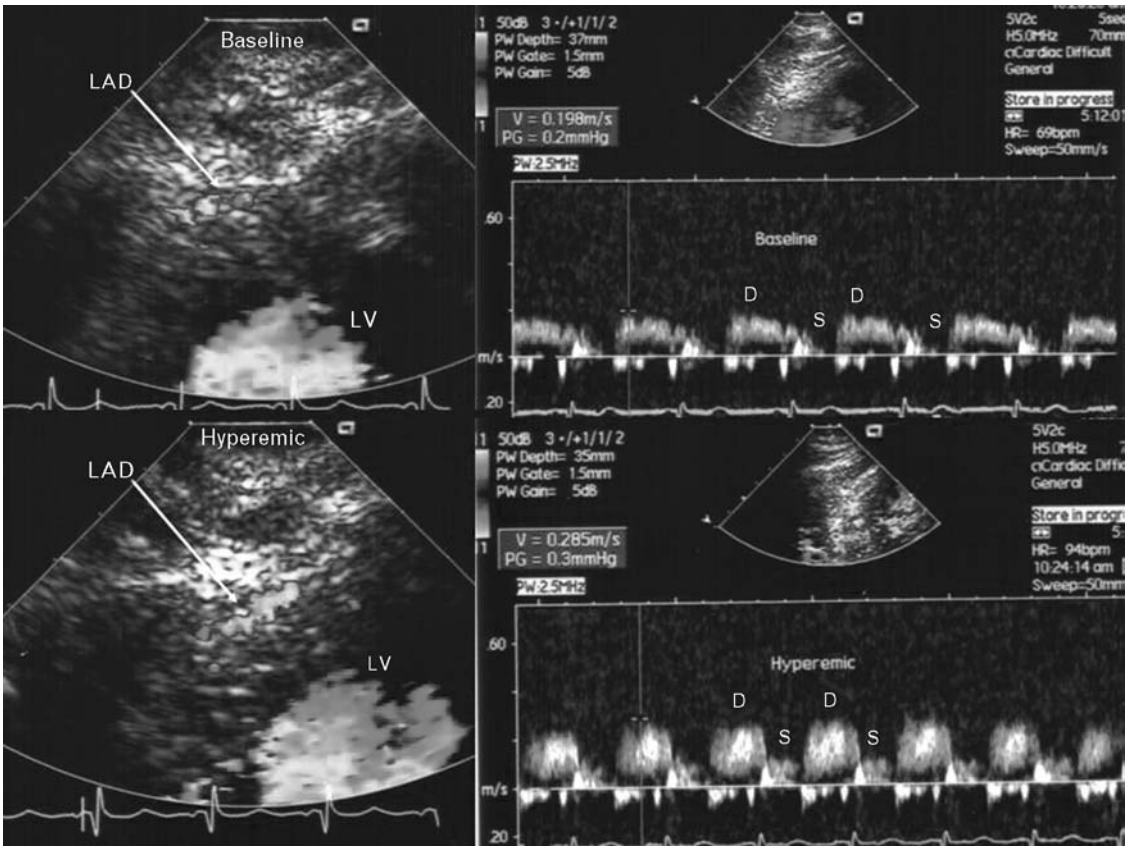
Fig. 1



Mid to distal segment of the left anterior descending coronary artery (LAD) in color-coded transthoracic Doppler echocardiography (arrows): spectral Doppler coronary blood flow by sampling in the mid to distal segment of the LAD. LV, left ventricle; S, systole; D, diastole.

averaging the highest three Doppler signals for each measurement. CFR was defined as the ratio of hyperemic to baseline diastolic peak velocities [16]. CFR $\geq$ 2.0 was considered normal [16–18]. CFR measurement was achieved in 97 of 100 subjects (97%). To test the coefficient of repeatability of the CFR measurement, the measurement was repeated in 10 subjects 2 days later. Intra-observer intra-class correlation coefficients for coronary flow measurements were 0.902 and 0.852 (baseline and hyperemic diastolic peak velocities, respectively), and for CFR value it was 0.886.

Statistical analyses

All analyses were conducted using SPSS 9.0 (SPSS Inc., Chicago, Illinois, USA). The groups were compared using the Student *t*-test for continuous variables and chi-squared for categorical variables. Participants were also divided into quartiles of GGT concentration (25th, 50th and 75th percentiles), and the cut-off points were 19, 30 and 49 U/l among men and 15, 21 and 30 U/l among women for the categories of GGT used, respectively. Pearson's correlation analysis was used to test univariate relations. Prediction of variables was obtained by stepwise, forward, multiple regression including potential confounders (age, sex, BMI, BPs, lipids, glucose and LVMI). The receiver-operating characteristic (ROC) curve was determined to evaluate the predictive performance of GGT to detect low CFR. The area under the ROC curve (AUC) and its standard error were calculated. A P value of < 0.05 was considered significant.

Results

Clinical characteristics of the study population

The general characteristics and risk factors of the groups are presented in Table 1. The following were similar within the lower and higher GGT groups: age, gender, BMI, systolic and diastolic BP, heart rate, lipid profiles except triglyceride, and hemoglobin. Uric acid and fasting glucose levels were slightly higher, and triglyceride and hsCRP levels were significantly higher in the higher GGT group than in the lower GGT group (Table 1).

Analyses of echocardiographic measurements

Interventricular septum thickness, left ventricle posterior wall thickness, left ventricular diastolic diameter, left ventricular systolic diameter, left atrium diameter and

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Table 1 Demographic and biochemical characteristics of the two γ-glutamyltransferase (GGT) groups

	Patients with lower GGT ($n=49$)	Patients with higher GGT ($n=48$)	P
Age (year)	46.6 ± 7.4	45.0 ± 6.9	0.26
Male/female (*n*/*n*)	27/22	24/24	0.68
Body mass index (kg/m^2)	28.3 ± 2.6	27.6 ± 3.0	0.36
Systolic BP (mmHg)	145.4 ± 7.1	146.4 ± 6.9	0.49
Diastolic BP (mmHg)	92.2 ± 5.7	92.2 ± 3.9	0.97
Heart rate (bpm)	73.4 ± 9.1	71.4 ± 8.1	0.27
Total cholesterol (mg/dl)	192.3 ± 30.6	203.5 ± 32.6	0.09
HDL cholesterol (mg/dl)	46.3 ± 8.4	47.4 ± 10.2	0.20
LDL cholesterol (mg/dl)	121.7 ± 24.6	121.3 ± 26.5	0.95
Triglyceride (mg/dl)	127.2 ± 47.0	153.0 ± 65.2	0.03
Hemoglobin (g/dl)	15.1 ± 1.2	14.9 ± 0.8	0.62
hsCRP (mg/l)	2.4 ± 2.2	4.2 ± 2.3	< 0.001
Glucose (mg/dl)	94.4 ± 6.6	96.7 ± 8.0	0.14
Uric acid (mg/dl)	4.8 ± 1.6	5.2 ± 1.6	0.10
GGT (U/l)	17.6 ± 6.6	40.3 ± 12.7	< 0.001

BP, blood pressure; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein.

left ventricular ejection fraction were similar between the lower and higher GGT groups, but LVMI was borderline greater in the higher GGT group than in the lower group. Mitral A_{max} and mitral E/A ratio were slightly different between the groups (Table 2).

Analysis of coronary flow reserve measurements

Baseline and peak heart rate and BPs were similar between the two groups. Baseline diastolic peak flow velocity (DPFV) did not significantly differ between the lower and higher GGT groups. However, hyperemic DPFV and CFR were significantly higher in the lower GGT group than in the higher GGT group (Table 2).

Relationship between serum γ-glutamyltransferase levels and coronary flow reserve

GGT levels were inversely and significantly correlated with CFR (Fig. 2). In addition, after dividing the patients into quartile-based GGT concentrations (25th, 50th and 75th percentiles), we showed that CFR decreased progressively with higher GGT levels (2.66 ± 0.53, 2.53 ± 0.54, 2.21 ± 0.34 and 1.98 ± 0.37; from quartiles 1 to 4, respectively) (Fig. 3). Furthermore, in stepwise linear regression analysis, when CFR was taken as dependent, and GGT and other study variables including age, sex, systolic and diastolic BP, LVMI, heart rate, hsCRP and lipids (total cholesterol, HDL-cholesterol, LDL-cholesterol and triglyceride) as independent, we found that only GGT level ($\beta = -0.62$, $P < 0.0001$) and mitral E/A ratio ($\beta = 0.22$, $P < 0.05$) were independently correlated with CFR. We also demonstrated that GGT level was an accurate predictor of low CFR on the receiver-operating characteristic (ROC) curve. The area under the curve (AUC) was 79% (95% confidence interval 0.70–0.88), and GGT levels were significantly predictive of low CFR ($P < 0.0001$) (Fig. 4).

Table 2 Data from echocardiographic examinations of the study subjects

	Patients with lower GGT ($n=49$)	Patients with higher GGT ($n=48$)	P
IVS (cm)	1.07 ± 0.11	1.07 ± 0.12	0.78
PW (cm)	1.01 ± 0.11	1.01 ± 0.11	0.95
LVDD (cm)	4.59 ± 0.36	4.58 ± 0.43	0.82
LVSD (cm)	2.89 ± 0.26	2.89 ± 0.30	0.58
LAD (cm)	3.32 ± 0.30	3.33 ± 0.28	0.76
EF (%)	66.8 ± 2.9	66.6 ± 2.5	0.70
LVMI (g/m)	66.3 ± 13.6	69.5 ± 16.8	0.11
LVMI (g/m)$^{2.7}$	33.9 ± 6.2	35.7 ± 5.0	0.12
Mitral E_{max} (cm/s)	71.1 ± 16.2	70.0 ± 15.5	0.74
Mitral A_{max} (cm/s)	68.0 ± 13.9	73.3 ± 14.7	0.07
E/A	1.07 ± 0.25	0.98 ± 0.25	0.09
Mitral E deceleration time (s)	207.4 ± 44.2	217.6 ± 34.9	0.21
Baseline heart rate (bpm)	73.2 ± 6.9	72.1 ± 11.2	0.78
Baseline systolic BP (mmHg)	148.9 ± 8.4	150.1 ± 7.3	0.24
Baseline diastolic BP (mmHg)	91.8 ± 4.3	90.1 ± 4.9	0.63
Peak heart rate (bpm)	95.2 ± 12.5	94.9 ± 12.2	0.90
Peak systolic BP (mmHg)	138.1 ± 6.1	142.9 ± 8.8	0.12
Peak diastolic BP (mmHg)	89.7 ± 3.4	90.6 ± 3.8	0.32
Baseline DPFV (cm/s)	24.5 ± 4.3	26.5 ± 6.6	0.08
Hyperemic DPFV (cm/s)	63.1 ± 17.2	55.2 ± 14.7	< 0.01
CFR	2.57 ± 0.54	2.10 ± 0.36	< 0.001

BP, blood pressure; CFR, coronary flow reserve; DPFV, diastolic peak flow velocity of left anterior descending coronary artery; EF, ejection fraction; GGT, γ-glutamyltransferase; IVS, interventricular septum; LAD, left anterior descending coronary artery; LVMI, left ventricular mass index; LVDD, left ventricular diastolic diameter; LVSD, left ventricular systolic diameter; PW, posterior wall.

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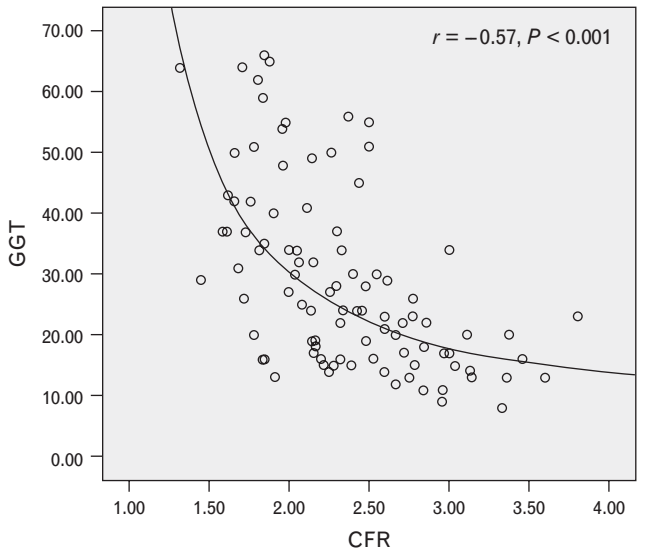
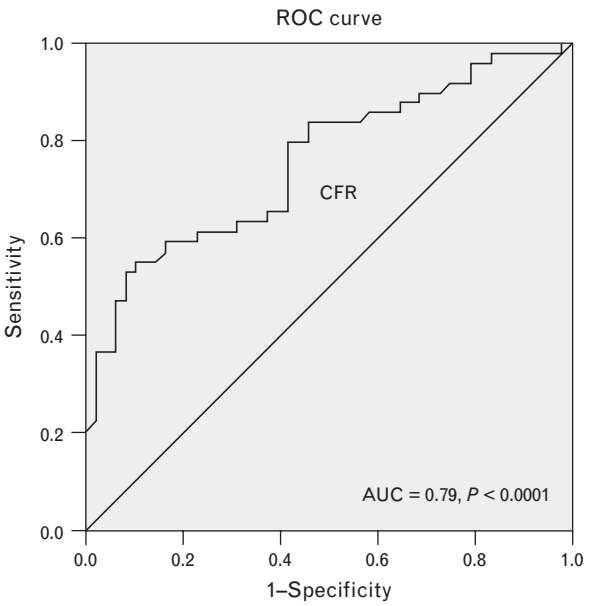
Fig. 2



Relationship between serum γ-glutamyltransferase (GGT) levels and coronary flow reserve (CFR).

Fig. 4

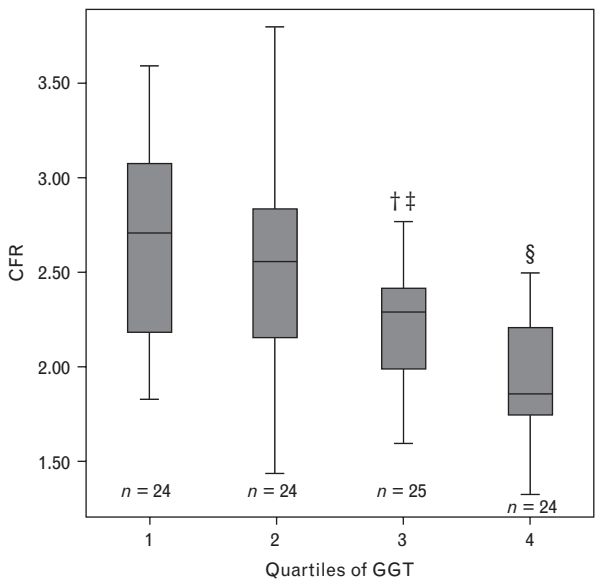


Receiver-operating characteristic (ROC) curve analysis of serum γ-glutamyltransferase (GGT) levels for low coronary flow reserve (CFR). Diagonal segments are produced by ties. AUC, area under the curve.

Relationships of serum γ-glutamyltransferase levels and coronary flow reserve with other study variables

Serum GGT level correlated significantly with glucose level ($r=0.29$, $P=0.004$), triglyceride level ($r=0.37$, $P<0.001$), hsCRP level ($r=0.34$, $P=0.001$), LVMI ($r=0.23$, $P=0.02$), and mitral E/A ratio ($r=-0.20$, $P=0.04$). CFR correlated significantly with glucose level ($r=-0.19$, $P=0.04$), triglyceride level ($r=-0.25$, $P=0.02$), hsCRP level ($r=-0.37$, $P<0.001$), mitral A ($r=-0.21$, $P=0.02$), and mitral E/A ratio ($r=0.32$, $P=0.002$).

Fig. 3



Coronary flow reserve (CFR) decreased progressively with higher γ-glutamyltransferase (GGT) levels. †$P<0.01$ versus quartile 1; ‡$P<0.05$ versus quartile 2; §$P<0.001$ versus quartiles 1 and 2.

Discussion

The present study used second harmonic transthoracic Doppler echocardiography (TTDE) for CFR determination to evaluate the possible association between serum GGT levels and CFR in arterial hypertension where changes in afterload, renal and LV structure may influence coronary blood flow supply. Hypertensive subjects were divided into two groups based on the median value of GGT, with the cut-off point 30 for men and 21 for women. The main findings of the study were that hypertensive subjects with higher GGT had altered CFR, and that an independent association between serum GGT levels and CFR was evident in essential hypertensive individuals, who were newly diagnosed, had never taken any antihypertensive therapy (including diuretics) and did not have any systemic disease except hypertension. To our knowledge, this is the first study showing an independent association between GGT levels and CFR. Accordingly, CFR was significantly different in our hypertensive subjects with lower and higher GGT.

GGT has a protective function in the antioxidant system with maintaining appropriate hepatic glutathione levels,

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which is a crucial antioxidant defense for the cells [19,20]. In addition, it is well known that substantial oxidative stress exists in hypertension [21]. In line with these suggestions, recent studies have reported that there is a positive association between serum GGT levels and BP [22,23]. In addition, it has recently been shown that there is a relationship between serum GGT levels and microalbuminuria, a marker of hypertensive target organ damage [9].

Coronary endothelial dysfunction resulting in an ineffective vasodilator function is common in hypertensive individuals. Reduced CFR is largely the result of minimal changes in coronary resistance that are independent of vascular tone [11–13]. Hypertensive pressure overload of the left ventricle and coronary circulation has several consequences for the coronary circulation: capillaries and myocytes are likely to suffer damage if perfusion pressure in this part of the coronary circulation is increased, and myocyte hypertrophy leads to an increased distance between arterioles oriented in parallel. The thickening of the wall of resistance vessels can be caused by an increase in the number or diameter of the single smooth muscle cells in the media, leading to an increase in the cross-sectional area of the vessel wall (hypertrophy), or by a reorganization of smooth muscle cells without an increase in the vascular wall area (remodeling) [24–26]. A relative or absolute decrease in the number of resistance vessels per myocardial volume in the presence of chronic increased coronary perfusion pressure may also lead to a normalized terminal perfusion pressure. Otherwise, a diminished number of parallel resistance vessels may reduce vasodilator capacity [26,27]. Taken together, these findings imply that structural changes in the coronary vasculature are most likely to be the major contributors to impaired CFR. These structural changes may be qualitatively similar to the well-described effects of hypertension on the peripheral circulation [28]. Accordingly, it has been reported that reduced coronary dilatory capacity was associated with increased arteriolar media area, and with perivascular and interstitial fibrosis in patients with arterial hypertension in the absence of relevant coronary artery stenosis [12]. These findings are surrogate markers of hypertensive target organ damage [12].

Considering the fact that impaired CFR is a surrogate marker of hypertensive target organ damage, and GGT is possibly a marker of oxidative stress and is associated with target organ damage in hypertension, we performed the present study to examine whether GGT is a predictor of impaired CFR among those with newly diagnosed hypertension.

In this study we excluded hypertensive subjects with confounding factors, which are commonly encountered in normal population, such as left ventricular hypertrophy, diabetes mellitus, obesity, dyslipidemia and CAD, to investigate the independent association between GGT levels and CFR. Therefore, the study does not provide information about the association between serum GGT levels and CFR in the hypertensive population overall.

In the present study, a relatively low dose of dipyridamole was used for hyperemic stimulus. In addition, dipyridamole mildly dilates epicardial coronary vessels. The standardized pharmacologic protocol of dipyridamole to measure hyperemic coronary flow, and thus the CFR, is still controversial, and a 0.56 mg/kg dose has generally been used in most previous studies [16,29,30]. Thus, we used low-dose dipyridamole (0.56 mg/kg over 4 min) for CFR assessment.

In conclusion, the present study demonstrated an independent association between serum GGT levels and CFR impairment in untreated essential hypertensive subjects, even in the absence of known CV risk factors. These results support a role for GGT level as an independent marker of target organ damage in hypertension.

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References

1 Emdin M, Passino C, Michelassi C, Titta F, L'Abbate A, Donato L, *et al.* Prognostic value of serum gamma-glutamyl transferase activity after myocardial infarction. *Eur Heart J* 2001; **22**:1802–1807.
2 Ruttmann E, Brant LJ, Concin H, Diem G, Rapp K, Ulmer H, Vorarlberg Health Monitoring and Promotion Program Study Group. Gamma-glutamyltransferase as a risk factor for cardiovascular disease mortality: an epidemiological investigation in a cohort of 163,944 Austrian adults. *Circulation* 2005; **112**:2130–2137.
3 Van Barneveld T, Seidell JC, Traag N, Hautvast JG. Fat distribution and gamma-glutamyl transferase in relation to serum lipids and blood pressure in 38-year-old Dutch males. *Eur J Clin Nutr* 1989; **43**:809–818.
4 Lee DH, Silventoinen K, Jacobs DR Jr, Jousilahti P, Tuomileto J. γ-Glutamyltransferase, obesity, and the risk of type 2 diabetes: observational cohort study among 20,158 middle-aged men and women. *J Clin Endocrinol Metab* 2004; **89**:5410–5414.
5 Lee DH, Jacobs DR Jr, Gross M, Kiefe CI, Roseman J, Lewis CE, Steffes M. Gamma-glutamyltransferase is a predictor of incident diabetes and hypertension: the Coronary Artery Risk Development in Young Adults (CARDIA) Study. *Clin Chem* 2003; **49**:1358–1366.
6 Wannamethee G, Ebrahim S, Shaper AG. γ-Glutamyltransferase: determinants and association with mortality from ischemic heart disease and all causes. *Am J Epidemiol* 1995; **142**:699–708.
7 Perry IJ, Wannamethee SG, Shaper AG. Prospective study of serum γ-glutamyltransferase and risk of NIDDM. *Diabetes Care* 1998; **21**: 732–737.
8 Jousilahti P, Rastenyte D, Tuomilehto J. Serum γ-glutamyl transferase, self-reported alcohol drinking, and the risk of stroke. *Stroke* 2000; **31**:1851–1855.

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9 Lee DH, Jacobs DR Jr, Gross M, Steffes M. Serum gamma-glutamyltransferase was differently associated with microalbuminuria by status of hypertension or diabetes: the Coronary Artery Risk Development in Young Adults (CARDIA) Study. *Clin Chem* 2005; **51**:1185–1191.
10 Houghton JL, Frank MJ, Carr AA, von Dohlen TW, Prisant LM. Relations among impaired coronary flow reserve, left ventricular hypertrophy and thallium perfusion defects in hypertensive patients without obstructive coronary artery disease. *J Am Coll Cardiol* 1990; **15**:43–51.
11 Laine H, Raitakari OT, Niinikoski H, Pitkanen OP, Iida H, Viikari J, *et al.* Early impairment of coronary flow reserve in young men with borderline hypertension. *J Am Coll Cardiol* 1998; **32**:147–153.
12 Schwartzkopff B, Motz W, Frenzel H, Vogt M, Knauer S, Strauer BE. Structural and functional alterations of the intramyocardial coronary arterioles in patients with arterial hypertension. *Circulation* 1993; **88**:993–1003.
13 Brilla CG, Janicki JS, Weber KT. Impaired diastolic function and coronary reserve in genetic hypertension. Role of interstitial fibrosis and medial thickening of intramyocardial coronary arteries. *Circ Res* 1991; **69**:107–115.
14 Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, *et al.*, American Society of Echocardiography's Nomenclature and Standards Committee; Task Force on Chamber Quantification; American College of Cardiology Echocardiography Committee; American Heart Association; European Association of Echocardiography, European Society of Cardiology. Recommendations for chamber quantification. *Eur J Echocardiogr* 2006; **7**:79–108.
15 Devereux RB, Alonso DR, Lutas EM, Gottlieb GJ, Campo E, Sachs I, Reichek N. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. *Am J Cardiol* 1986; **57**:450–458.
16 Erdogan D, Yildirim I, Ciftci O, Ozer I, Caliskan M, Gullu H, Muderrisoglu H. Effects of normal blood pressure, prehypertension, and hypertension on coronary microvascular function. *Circulation* 2007; **115**:593–599.
17 Caiati C, Montaldo C, Zedda N, Bina A, Iliceto S. New noninvasive method for coronary flow reserve assessment: contrast-enhanced transthoracic second harmonic echo Doppler. *Circulation* 1999; **99**:771–778.
18 Galderisi M, Cicala S, Caso P, De Simone L, D'Errico A, Petrocelli A, de Divitiis O. Coronary flow reserve and myocardial diastolic dysfunction in arterial hypertension. *Am J Cardiol* 2002; **90**:860–864.
19 Whitfield JB. Gamma glutamyl transferase. *Crit Rev Clin Lab Sci* 2001; **38**:263–355.
20 Grundy SM. Gamma-glutamyl transferase: another biomarker for metabolic syndrome and cardiovascular risk. *Arterioscler Thromb Vasc Biol* 2007; **27**:4–7.
21 Hamilton C. Nitric oxide, oxidative stress and hypertension: a complex equation. *J Hypertens* 2002; **20**:1055–1056.
22 Yamada Y, Ishizaki M, Kido T, Honda R, Tsuritani I, Yamaya H. Relationship between serum gamma-glutamyl transpeptidase activity and blood pressure in middle-aged male and female nondrinkers. *J Hum Hypertens* 1990; **4**:609–614.
23 Ikai E, Noborizaka Y, Tsuritani I, Honda R, Ishizaki M, Yamada Y. Serum gamma-glutamyl transpeptidase levels and hypertension in nondrinkers: a possible role of fatty liver in the pathogenesis of obesity related hypertension. *Obes Res* 1993; **1**:469–474.
24 Kelm M, Schafer S, Mingers S, Heydthausen M, Vogt M, Motz W, Strauer BE. Left ventricular mass is linked to cardiac noradrenaline in normotensive and hypertensive patients. *J Hypertens* 1996; **14**:1357–1364.
25 Baumbach GL, Heistad DD. Remodelling of cerebral arterioles in chronic hypertension. *Hypertension* 1989; **13**:968–972.
26 Schiffrin EL, Hayoz D. How to access vascular remodelling in small and medium-sized muscular arteries in humans. *J Hypertens* 1997; **15**:571–584.
27 Strauer BE, Schwartzkopff B, Kelm M. Assessing the coronary circulation in hypertension. *J Hypertens* 1998; **16**:1221–1233.
28 Jennings GL, Dilley RJ. Left ventricular remodelling impacts on coronary flow reserve in hypertensive patients: is there a vascular mechanism? *J Hypertens* 2002; **20**:1291–1293.
29 Wilson RF, Laughlin DE, Ackell PH, Chilian WM, Holida MD, Hartley CJ, *et al.* Transluminal subselective measurement of coronary blood flow velocity and vasodilator reserve in man. *Circulation* 1985; **72**:82–92.
30 Galderisi M, Cicala S, D'Errico A, de Divitiis O, de Simone G. Nebivolol improves coronary flow reserve in hypertensive patients without coronary heart disease. *J Hypertens* 2004; **22**:2201–2208.

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