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ANGIOLOGY 2013 64: 15 originally published online 21 September 2012
DOI: 10.1177/0003319712459799

The online version of this article can be found at:
http://ang.sagepub.com/content/64/1/15
Association of Serum Gamma-Glutamyltransferase With Arterial Stiffness in Established Coronary Artery Disease

Cansheng Zhu, PhD¹, Zhaojun Xiong, PhD², Zhenda Zheng, MD², Yanming Chen, PhD³, Xiaoxian Qian, PhD², and Xiaohong Chen, PhD¹

Abstract
Serum gamma-glutamyltransferase (GGT) has been reported to predict vascular risk. We enrolled 978 patients (507 men and 471 women) with established coronary artery disease (CAD). The GGT, brachial–ankle pulse wave velocity (baPWV) to assess arterial stiffness, and conventional risk factors were evaluated. The means of baPWV tend to increase in both genders according to GGT tertiles. Body mass index, GGT, logarithmical (systolic blood pressure [LnSBP]), uric acid (UA), total bilirubin, Ln (cholinesterase), and Ln (total cholesterol) were correlated with baPWV in men in a multivariate model. However, only GGT, LnSBP, UA, and Ln (high-density lipoprotein cholesterol) were correlated with baPWV in women. The GGT was a significant determinant for increased baPWV both in men (β = 0.017; P < .001) and in women (β = 0.015; P < .001). In conclusion, GGT was independently associated with increased arterial stiffness both in men and in women with established CAD.

Keywords
brachial–ankle pulse wave velocity, arterial stiffness, coronary artery disease, gamma-glutamyltransferase

Introduction
Serum gamma-glutamyltransferase (GGT) activity is used as a marker of alcohol consumption or hepatobiliary disease. However, in patients with a history of myocardial infarction (MI) and coronary artery disease (CAD), it has been found that GGT activity has an independent predictive value for mortality and the incidence of nonfatal MI. In a large study of middle-aged men, GGT activity had a prognostic significance for overall and cardiac-related mortality. A meta-analysis showed a relation between GGT activity and the incidence of cardiovascular events independent of alcohol intake. One unit per liter higher GGT activity (on a log scale) was associated with a 20% increase in the risk of CAD, a 54% increase in the risk of stroke, and a 34% increase in the risk of CAD and stroke combined. The role of GGT in cardiovascular disease is partly explained by the correlation of GGT with several metabolic risk factors, including obesity, dyslipidemia, hypertension, diabetes, and metabolic syndrome. However, the exact mechanisms behind the association between GGT and cardiovascular disease are still unknown.

Arterial stiffness represents vascular damage and is a measure of the degree of atherosclerosis. Increased arterial stiffness, determined invasively, has been shown to predict a higher risk of coronary atherosclerosis. Recent studies have shown that brachial–ankle pulse wave velocity (baPWV), which can be measured fairly reproducibly by an automated device, correlates well with aortic stiffness determined by an invasive method. Previous studies showed that increased baPWV is associated with metabolic syndrome, cardiovascular diseases, stroke, and renal disease, as well as elevated total mortality.

There are a few studies on the relationship between serum GGT activity and baPWV in relatively large numbers of participants; however, this relationship has not been well studied. Previous studies have shown that increased serum GGT activity was associated with increased baPWV in men but not in women. One study has shown that the relationship between serum GGT activity and baPWV was very weak;
whether serum GGT activity is associated with baPWV in established CAD is still unknown. Therefore, we investigated whether serum GGT activity is independently associated with baPWV in established CAD.

Materials and Methods

Study Patients

During the period from October 2010 to May 2012, 978 patients (507 men and 471 women) from the department of cardiovascular diseases, the Third Affiliated Hospital of Sun Yat-Sen University were analyzed. The inclusion criteria were an established angiographic CAD diagnosis, characterized by coronary angiography or elective myocardial revascularization procedures, as decided by an assisting physician. A lesion was defined as significant if it caused a 50% reduction in the luminal diameter by visual estimation in vessels ≥1.5 mm. All procedures were approved by the ethics committee of The Third Affiliated Hospital of Sun Yat-Sen University.

Clinical Examination

Clinical data including medical history, smoking status, and medications used were recorded for each participant. All the patients had clinical examination which included anthropometric and blood pressure (BP) measurements. Height and weight were measured while the patients were wearing light clothing without shoes. Body mass index (BMI) was calculated as kg/m². The BP was measured by doctors in the right arm, which was placed at the heart level, with a standard mercury sphygmomanometer after the participant had been sitting quietly for more than 5 minutes; 3 BP measurements, taken 60 seconds apart, were recorded. The average of the 3 systolic BP (SBP) and diastolic BP (DBP) values was used in our analyses.

Laboratory Data

After overnight fasting, early morning blood samples were drawn from the antecubital vein into vacuum tubes and then analyzed using standard methods at the Laboratory of Analytical Biochemistry at The Third Affiliated Hospital, Sun Yat-Sen University, Guangzhou, with a biochemical analyzer (Hitachi 7180, Japan). Measurements included serum total bilirubin (TB) concentrations, aspartate aminotransferase (AST), alanine aminotransferase (ALT), GGT, alkaline phosphatase (ALP), cholinesterase (Cho), blood urea nitrogen (BUN), creatinine (Cr), uric acid (UA), total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and fasting plasma glucose.

Measurement of baPWV

The baPWV was assessed by using a fully automatic device (Omron Healthcare, Kyoto, Japan). The patients rested in the supine position for 5 minutes. The baPWV was automatically calculated according to the formula (L/PTT); L is the difference between the length from heart to ankle and the length from heart to brachium. The PTT was the pulse transit time between the brachial and tibial arterial waveforms. Mean right and left baPWV value was calculated. All measurements were conducted by a single examiner who was blinded to the clinical data.

Statistical Analysis

SPSS 17.0 software was used to perform the statistical analysis. The clinical and chemical parameters were compared according to GGT quartiles. Data were expressed as means ± SD or median (interquartile range [IQR]) or percentage. The chi-square statistical test or Fisher exact test was used for all categorical variables, while one-way analysis of variance (ANOVA) was used for all continuous variables. Simple and multiple linear regression analyses were used to assess the correlation between baPWV and GGT activity. Variables such as AST, ALT, TB, ALP, Cho, SPB, DBP, BUN, Cr, TC, TG, HDL-C, and LDL-C were logarithmically (Ln) transformed before statistical analysis to approximate normal distribution. A P < .05 (2-sided) was considered significant.

Results

The clinical and laboratory characteristics of the patients according to GGT tertiles are summarized in Table 1. The age of the enrolled patients ranged from 25 to 86 years (women, 25-81; men, 34-86) with a mean age of 64.6 ± 10.5 years (women, 67.3 ± 8.3; men, 62.9 ± 11.4). The mean age did not significantly differ among each GGT tertile group in men and women. The BMI, AST, ALT, TB, ALP, SBP, DBP, fasting glucose, and LCL-C increased gradually as GGT increased in both genders. For women, we also observed positive relationships between GGT tertiles and diabetes and TG.

The means and SD of baPWV according to GGT tertiles are shown in Figure 1. The means of baPWV tend to increase in men according to GGT tertiles: tertile 1 = 1776.8 (1419.6-2086.9), tertile 2 = 1974.0 (1732.0-2125.0), and tertile 3 = 2016.3 (1892.5-2364.0) cm/s (Figure 1A). The means of baPWV tend to increase in women according to GGT tertiles: tertile 1 = 1635.0 (1523.0-2022.5), tertile 2 = 1804.5 (1670.5-2260.4), and tertile 3 = 1858.8 (1795.1-2209.5) cm/s (Figure 1B). The GGT tertiles were tertile 1 (<25 U/L), tertile 2 (25-42 U/L), and tertile 3 (>42 U/L) for men and tertile 1 (<20 U/L), tertile 2 (20-28 U/L), and tertile 3 (>28 U/L) for women.

Univariate analysis showed that age, BMI, TB, ALT, GGT, Cho, SBP, DBP, UA, TC, and HDL-C were significantly associated with baPWV in men. In women, age, BMI, current smoker, Cho, GGT, SBP, DBP, UA, TC, TG, HDL-C, and LDL-C were significantly associated with baPWV (Table 2).

Seventeen variables including age, current smoker, BMI, SBP, DBP, AST, ALT, GGT, ALP, Cho, UA, TC, TG, HDL-C, LDL-C, and TB were entered into the model. The results showed that BMI, GGT, LnSBP, UA, TB, LnCho, and...
LnTC were correlated with baPWV in men in the multivariate model. However, only GGT, LnSBP, UA, and LnHDL-C were correlated with baPWV in women. The GGT was found to be a significant determinant for increased baPWV both in men ($\beta = .017; P < .001$) and in women ($\beta = .015; P < .001$; Table 3).

### Discussion

We found that a positive association between serum GGT activity and increased baPWV in CAD is independent of the conventional cardiovascular risk factors in both genders. Multiple regression analysis further identified GGT activity...
as an independent and significant determinant for increased baPWV.

The GGT is an enzyme responsible for the extracellular cat-
abolism of antioxidant glutathione and act as a prooxidant in
the extracellular space. The GGT is expressed in the liver,
kidney, cerebrovascular endothelium, and pericytes. As a
potential mechanism it has been proposed that GGT reduces
Fe^{3+} to its bivalent form and releases a free thyl radical that
oxidizes LDL in the extracellular space. Moreover, some
evidence suggests that human platelets may be a source of
GGT. Therefore, increased platelet turnover at the sites
of atheromatous plaques may contribute to an increase in serum

Figure 1. A. Mean brachial–ankle pulse wave velocity (baPWV) according to serum gamma-glutamyltransferase tertiles in men (bars represent
the mean and standard deviation, *P < .01). B. Means of baPWV according to serum gamma-glutamyltransferase tertiles in women (bars rep-
resent the mean and standard deviation, *P < .01). P values were calculated by 1-way analysis of variance (ANOVA). Log transformation was
performed to normally distribute the data before the ANOVA.

Table 2. Univariate Regression Analysis With Brachial–Ankle Pulse Wave Velocity (baPWV) as the Dependent Variable in Different Sexes

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β ± SEb</td>
<td>P</td>
</tr>
<tr>
<td>Age, years</td>
<td>0.075 ± 0.012</td>
<td>.001</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>0.115 ± 0.063</td>
<td>.001</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>0.071 ± 0.041</td>
<td>.12</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>0.085 ± 0.056</td>
<td>.14</td>
</tr>
<tr>
<td>Beta-blocker, %</td>
<td>-0.074 ± 0.047</td>
<td>.11</td>
</tr>
<tr>
<td>Statins, %</td>
<td>-0.062 ± 0.055</td>
<td>.26</td>
</tr>
<tr>
<td>TB, µmol/La</td>
<td>-0.178 ± 0.038</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>AST, U/La</td>
<td>0.003 ± 0.026</td>
<td>.91</td>
</tr>
<tr>
<td>ALT, U/La</td>
<td>0.062 ± 0.031</td>
<td>.038</td>
</tr>
<tr>
<td>GGT, U/La</td>
<td>0.138 ± 0.051</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ALP, U/La</td>
<td>0.005 ± 0.067</td>
<td>.41</td>
</tr>
<tr>
<td>Choa</td>
<td>0.184 ± 0.059</td>
<td>.003</td>
</tr>
<tr>
<td>SBP, mm Hg*</td>
<td>2.512 ± 0.083</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>DBP, mm Hg*</td>
<td>1.873 ± 0.133</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>BUN, mg/dL*</td>
<td>0.026 ± 0.065</td>
<td>.73</td>
</tr>
<tr>
<td>Cr, mg/L*</td>
<td>0.013 ± 0.067</td>
<td>.86</td>
</tr>
<tr>
<td>UA, mg/L</td>
<td>0.108 ± 0.010</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>TC, mg/dL*</td>
<td>0.317 ± 0.064</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>TG, mg/dL*</td>
<td>0.052 ± 0.042</td>
<td>.25</td>
</tr>
<tr>
<td>HDL-C, mg/dL*</td>
<td>-0.109 ± 0.043</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>LDL-C, mg/dL*</td>
<td>0.132 ± 0.078</td>
<td>.02</td>
</tr>
</tbody>
</table>

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; Cho, cholinesterase; Cr, creatinine; DBP, diastolic blood pressure; Fhp, family history of premature coronary artery disease; GGT, gamma-glutamyl transpeptidase; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; SE, standard error; TB, total bilirubin; TC, total cholesterol; TG, triglyceride; UA, uric acid.

a Log transformation was performed to normally distribute the data prior to analysis.
b Standardized regression coefficients.
GGT activity. The GGT activity has been detected in atheroma-
tous plaques in carotid and coronary arteries where it co-
localizes with oxidized LDL. Although additional studies are
needed to determine the origin of GGT activity in ather-
sclerotic plaques, GGT may participate directly in atherogen-
esis and plaque progression. Recently, emerging evidence has
shown that increased serum GGT is strongly associated with
development of cardiovascular disease. Furthermore, sev-
eral prospective cohort studies have reported that baseline
serum GGT activity is an independent risk factor for the de-
velopment of cardiovascular disease, hypertension, stroke, and
type 2 diabetes, after adjusting for alcohol consumption.4,27,28
In our study, serum LDL-C increased as GGT increased in
both genders. Additionally, BMI, AST, ALT, TB, ALP, SBP, DBP,
and fasting glucose were also related to serum GGT in both
genders. This result was consistent with the previous reports.29

Noninvasive aortic stiffness is postulated to be a surrogate
marker of early atherosclerosis. An automated computer-
asisted baPWV measurement facilitates a valid and reproduc-
ible assessment of arterial stiffness that is closely associated
with invasive measurements.11 The baPWV reflects the stiff-
ness of both the central and peripheral muscular arteries and
serves as a simple index of the severity of arterial stiffness and
atherosclerosis.30 Recent reports have shown an association
between cardiovascular disease and baPWV.31 Another study
reported that an increased baPWV is associated with a poor
prognosis in patients with CAD and heart failure.32 Two
cross-sectional studies have investigated the association
between serum GGT activity and baPWV with both
reporting gender difference. Our study showed that increased
serum GGT activity is associated with increased baPWV in
both genders. Our results are inconsistent with previous results
because of the population selected. The participants of the pre-
sent study are the patients with established CAD. In another
study of large population (>10,000 participants), no gender dif-
ference in the association between serum GGT activity and
baPWV was observed, which is consistent with our findings.

Age was significantly associated with baPWV in men by the
univariate analysis, but it was excluded from the significant
determinants by the multivariate analysis in this study. This
result might be due to the particularity of this population. All
patients enrolled in this study were diagnosed with estab-
lished CAD. Additionally, the number of patients was rela-
tively small and the results of this study need to be assessed
in larger sample size.

The limitations of this study are, first, because it is a cross-
sectional study, we could not determine whether there was a
causal relationship between serum GGT activity and arterial
stiffness. We have no data to determine whether pharmacologi-
cal interventions, including antihypertensive agents and statins,
have beneficial effects on arterial stiffness. Previous study has
revealed that decreased arterial stiffness with time, as assessed
by baPWV, was observed in elderly patients treated with ator-
vastatin after 6 months of therapy.35 Follow-up studies are
needed to observe the effect of statins on arterial stiffness in
patients with established CAD. Second, we could not obtain
details about alcohol consumption. Despite these limitations,
our study demonstrates no gender difference in the association
between serum GGT activity and baPWV in patients with
established CAD.

In conclusion, our findings show that GGT activity is inde-
pendently associated with an increased level of arterial stiffness
measured by baPWV in both males and females with estab-
lished CAD. Given that GGT is easily measured and is exten-
sively used in clinical practice, further studies are needed to
elucidate the causal relationship between GGT and baPWV in
patients with established CAD.

Authors’ Note
Cansheng Zhu and Zhaojun Xiong contributed equally to this work.

Declaration of Conflicting Interests
The authors declared no potential conflicts of interest with respect to
the research, authorship, and/or publication of this article.

Funding
The authors received no financial support for the research, authorship,
and/or publication of this article.

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