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Gamma-glutamyl transferase and atrial fibrillation in patients with coronary artery disease

Gjin Ndrepepa [a,*], Erion Xhepa [a], Roisin Colleran [a], Siegmund Braun [b], Salvatore Cassese [a], Massimiliano Fusaro [a], Karl-Ludwig Laugwitz [c], Adnan Kastrati [a,d]

[a] Department of Adult Cardiology, Deutsches Herzzentrum München, Technische Universität, Munich, Germany
[b] Department of Laboratory Medicine, Deutsches Herzzentrum München, Technische Universität, Munich, Germany
[c] 1 Medizinische Klinik, Klinikum rechts der Isar, Technische Universität, Munich, Germany
[d] DZHK (German Centre for Cardiovascular Research), Partner Site Munich Heart Alliance, Munich, Germany

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ABSTRACT

Background: The association between gamma-glutamyl transferase (GGT) and atrial fibrillation (AF) in patients with coronary artery disease (CAD) is uncertain.
Methods: This study included 5501 consecutive patients with CAD, all of whom had baseline GGT measurements available. The primary endpoint was presence of AF.
Results: Overall 809 patients (14.7%) had AF on hospital admission. Patients with AF had significantly higher GGT activity compared with patients in sinus rhythm (median [25th–75th percentile]: 52.0 [32.9–96.0] U/L versus 34.8 [23.8–55.9] U/L, $P < 0.001$). The prevalence of AF increased from 8.6% of patients in the first GGT decile to 30.3% of patients in the tenth decile ($P < 0.001$). After multivariable adjustment, GGT activity remained independently associated with the probability of the presence of AF (adjusted adds ratio = 1.66, 95% confidence interval 1.53–1.81, $P < 0.001$ for each standard deviation increment in the GGT logarithmic scale). GGT predicted the probability of AF with an area under the receiver operating characteristic (ROC) curve of 0.6496, 95% confidence interval 0.6287 to 0.6705, $P < 0.001$ indicating moderate strength to discriminate between patients with and without AF.
Conclusions: In patients with CAD, elevated GGT activity is independently associated with the presence of AF. GGT may be a circulating marker of the risk for AF.

1. Introduction

Atrial fibrillation (AF) is a leading cause of morbidity and mortality, with an estimated worldwide prevalence of 33.5 million cases in 2010 [1]. A recent meta-analysis of 104 cohort studies with 9,686,513 participants and 587,867 cases of AF showed that AF is associated with an increased risk of all-cause and cardiovascular mortality, sudden cardiac death, major cardiovascular adverse events, ischemic heart disease, heart failure, ischemic stroke, chronic kidney disease and peripheral arterial disease [2]. Although numerous cardiac and noncardiac predisposing factors and risk markers for AF have been identified [3], AF occurrence remains poorly predictable. Gamma-glutamyl transferase (GGT) – an enzyme involved in glutathione metabolism – is routinely used as a highly sensitive marker of hepatobiliary disease and alcohol consumption [4]. There is strong evidence to suggest an association between elevated GGT activity and both the metabolic syndrome and cardiovascular disease [5]. Furthermore, elevated GGT activity is a predictor of cardiovascular mortality in population-based studies [6,7] and studies involving patients with coronary artery disease (CAD) [8–10]. Both population-based and clinical studies suggest that higher values of liver enzymes, particularly GGT, are associated with an increased risk of developing AF [11–14]. However, evidence regarding an association between elevated GGT and AF remains limited and no study has investigated such an association in patients with CAD. The rationale for investigating the association between GGT and AF stems from the association between GGT with a number of well-defined factors predisposing to AF, including cardiovascular risk factors [7], liver disease [15], alcohol consumption [4], systemic inflammation [16] and increased oxidative stress [17]. The aim of current study was to assess whether there is an association between circulating GGT activity and presence of AF in patients with CAD.

2. Methods

2.1. Patients

The current study is a retrospective analysis of 5501 patients with angiography-proven CAD who underwent percutaneous coronary intervention between January 2000 and January 2011 in 2 German

* Corresponding author at: Deutsches Herzzentrum, Lazarettstrasse 36, 80636 München, Germany.
E-mail address: ndrepepa@dhm.mhn.de (G. Ndrepepa).

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university hospitals. The characteristics of included patients and the source sample have been previously reported [10]. In brief, all patients had angiographically-confirmed CAD and baseline (admission) measurements of GGT available. Exclusion criteria included: known hepatobiliary disease, cancer, alcohol abuse, cardiogenic shock, valvular AF or acute infection. Patients who developed AF during the hospital course were also excluded. The study conforms to the Declaration of Helsinki.

2.2. Study definitions

AF was defined based on electrocardiographic documentation of absence of discrete P waves and their replacement with irregular chaotic oscillatory atrial activity (F waves) in the setting of irregular QRS complexes. All included patients had either persistent (AF lasting >7 days and/or requiring electrical or pharmacological cardioversion for termination) or permanent AF (AF not successfully terminated by cardioversion, longstanding [>1 year] AF or AF where cardioversion was not indicated or attempted). Cardiovascular risk factors (arterial hypertension, diabetes, hypercholesterolemia and current smoking) were defined using accepted criteria. Obesity was assessed by calculating body mass index using the patient's weight and height measured during the hospital course. Renal function was assessed by calculating the creatinine clearance according to the Cockcroft-Gault formula [18]. Global left ventricular ejection fraction was calculated on the left ventricular angiograms using the area-length method [19]. Angiographic diagnosis of CAD was based on documentation of coronary stenosis with ≥50% lumen obstruction in at least one major coronary artery. Angiographic analysis was performed in the core laboratory using an automated edge detection system (CMS; Medis Medical Imaging Systems, Neuen, the Netherlands) by personnel blinded to the clinical or laboratory data of the patients.

The primary outcome measure of this study was presence of AF and the association of interest was that between GGT activity and the probability of presence of AF at the time of patient admission.

2.3. Laboratory measurements

Blood for GGT measurement was taken on admission (before angiographic examination) in all patients. The catalytic activity of gamma-glutamyl transferase (EC 2.3.2.2; γ glutamyl peptide: amino acid γ glutamyltransferase) in plasma was measured at 37 °C with an enzymatic colorimetric assay using a Roche/Hitachi cobas c 501 analyser. The assay is standardized against the IFCC method [20]. The measuring range in plasma is 3–1200 U/L (0.05–20 μkat/L) and the lower detection limit of the test is 3 U/L (0.05 μkat/L). The consensus value is <60 U/L (<1 μkat/L) for healthy men and <40 U/L (<0.67 μkat/L) for healthy women. C-reactive protein (CRP) was measured using a fully automated latex-enhanced immunoturbidimetric assay on a Cobas Integra analyser (Roche Diagnostics, Mannheim, Germany). The assay has an analytic sensitivity of 0.085 mg/L and a measuring range of up to 160 mg/L. The upper limit of the reference range in healthy adults is 5 mg/L. Creatinine was measured in serum using a kinetic colorimetric assay based on the compensated Jaffe method. All laboratory measurements were performed by personnel blinded to patient clinical data.

2.4. Statistical analysis

Data are presented as medians (with 25th–75th percentiles) or counts and proportions (%). The distribution of continuous data was tested using the 1-sample Kolmogorov-Smirnov test. As all continuous data showed a non-Gaussian distribution pattern, the Kruskal-Wallis rank-sum test was used for intergroup comparisons. Categorical variables were compared with chi-square test. Multiple logistic regression was used to test the association between GGT and the probability of presence of AF. The following variables were entered into the model: GGT, age, sex, body mass index, diabetes, arterial hypertension, hypercholesterolemia, smoking status, previous myocardial infarction, previous coronary artery bypass surgery, clinical presentation (stable CAD vs. acute coronary syndrome), multivessel disease, creatinine clearance, C-reactive protein, and left ventricular ejection fraction. Due to non-Gaussian distribution, GGT was entered into the model after logarithmic transformation and the risk estimate associated with this variable was calculated per standard deviation increment in the GGT logarithmic scale. The receiver operating characteristic (ROC) curve analysis was performed to calculate the area under the ROC curve and 95% confidence limits to show the discriminatory power of GGT to predict the probability of presence of AF. The best GGT cutoff value for prediction of the probability of AF, whilst maximizing sensitivity and specificity through minimizing the square root of $(1 - \text{sensitivity})^2 + (1 - \text{specificity})^2$ was calculated. All analyses were performed with the R 2.15.1 Statistical Package (the R foundation for Statistical Computing, Vienna, Austria). A two-sided $P < 0.05$ was considered statistically significant.

3. Results

3.1. Baseline data

AF was present on admission in 809 patients (14.7%). Baseline clinical characteristics of patients in AF compared with those in sinus rhythm at the time of hospital admission are shown in Table 1. Patients with AF were older, had higher rates of prior myocardial infarction and coronary artery bypass surgery, and presented more often with stable CAD. They had higher GGT, C-reactive protein and serum creatinine values compared with patients presenting in sinus rhythm. Furthermore, patients with AF had less hypercholesterolemia, were less likely to be current smokers and had lower creatinine clearance and left

Table 1
Baseline data.

Variable	Atrial fibrillation (n = 809)	Sinus rhythm (n = 4692)	P value
Age (years)	73.5 [67.0–80.2]	66.5 [58.0–73.8]	<0.001
Women	206 (25.5)	1140 (24.3)	0.475
Arterial hypertension	557 (68.8)	3169 (67.5)	0.462
Hypercholesterolemia	539 (66.6)	3297 (70.3)	0.037
Diabetes	223 (27.6)	1225 (26.1)	0.385
On insulin treatment	73 (9.0)	368 (7.8)	0.254
Body mass index (kg/m^2)	27.0 [24.6–30.0]	27.0 [24.6–29.8]	0.800
Current smoker	79 (9.8)	947 (20.2)	<0.001
History of MI	196 (24.2)	975 (20.8)	0.027
History of CABG	133 (16.4)	569 (12.1)	<0.001
Clinical presentation			<0.001
Stable CAD	495 (61.2)	2472 (52.7)	
ACS	314 (38.8)	2220 (47.3)	
Extent of CAD			0.349
One-vessel disease	170 (21.0)	1061 (22.6)	
Two-vessel disease	227 (28.1)	1368 (29.2)	
Three-vessel disease	412 (50.9)	2263 (48.2)	
Multivessel disease	639 (79.0)	3631 (77.4)	0.313
C-reactive protein (mg/L)	3.69 [1.47–11.0]	2.33 [1.00–5.88]	<0.001
GGT (U/L)	52.0 [32.90–96.0]	34.8 [23.8–55.9]	<0.001
Serum creatinine (mg/dL)	1.04 [0.88–1.30]	0.90 [0.80–1.10]	<0.001
Creatinine clearance (mL/min)	66.9 [48.4–90.4]	88.3 [66.9–110.1]	<0.001
LVEF (%)	53.0 [39.0–60.0]	58.0 [48.0–62.0]	<0.001

Data are shown as median [25th; 75th percentiles] or number of patients (%).
ACS = acute coronary syndrome; CABG = coronary artery bypass graft surgery; CAD = coronary artery disease; GGT = gamma glutamyl transferase; LVEF = left ventricular ejection fraction; MI = myocardial infarction.