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Thrombin Activatable Fibrinolysis Inhibitor (TAFI) Activity In Patients with Isolated Coronary Artery Ectasia

İzole Koroner Arter Ektazisi Olan Hastalarda Trombin ile Aktive Olan Fibrinoliz Inhibitör (TAFI) Aktivitesi

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Abstract

Thrombin activatable fibrinolysis inhibitor (TAFI) forms the molecular link between the coagulation and the fibrinolytic systems with a strong anti-fibrinolytic activity. Isolated coronary artery ectasia (CAE) is a clinical entity characterized by localized or diffuse dilatation greater than 1.5 times diameter of adjacent segments, of coronary arteries, without concomitant stenosis. Previous studies demonstrated increased frequency of acute coronary events in patients with isolated CAE compared to patients with normal coronary arteries (NCA). The goal of the present study was to investigate whether TAFI activity is increased in patients with isolated CAE compared to normal subjects. Thirty patients with isolated CAE, 30 age- and gender-matched control participants with NCA, were included in the study. There was no difference in TAFI activity between CAE and NCA groups (130±42% vs. 124±35%, p=NS). The findings of the current study indicate that TAFI activity is not associated with CAE. To our knowledge, this is the first report investigating the relation of CAE with TAFI activity. We believe that further studies are required to define the precise role of TAFI in patients with isolated CAE.

Key words: Coronary artery ectasia, thrombin activatable fibrinolysis inhibitor, coronary angiography, TAFI activity.

Özet

Trombin ile aktive olan fibrinoliz inhibitörü (TAFI) güçlü bir antifibrinolitik aktivite ile koagülasyon ile fibrinolitik sistem arasındaki moleküler bağlantıyı oluşturur. Izole koroner arter ektazisi (KAE) birlikte koroner arter hastalığının yokluğunda koroner arterlerin komşu segmentlerine göre 1.5 kattan fazla lokalize ya da düffüz genişleme ile karakterize bir klinik bulgudur. Daha önceki çalışmalar normal koroner arterli (NKA) bireyler ile karşılaştırıldığında izole KAE'li hastalarda akut koroner olayların sıklığında bir artışı ortaya koydu. Bu çalışmanın amacı NKA ile karşılaştırıldığında izole KAE'li hastalarda TAFI aktivitesinde artış olup olmadığını araştırmaktı. Bu çalışmaya izole KAE'li 30 hasta ile yaş ve cinsiyet uyumlu NKA'li 30 kişi (kontrol grubu) alındı. KAE ve NKA grupları arasında TAFI aktivitesinde anlamlı bir fark izlenmedi (%130±42 ve %124±35, p=AD). Bu çalışmanın bulguları TAFI aktivitesinin CAE ile ilişkili olmadığını göstermektedir. Bilgilerimize göre bu çalışma TAFI aktivitesi ile CAE'nin ilişkisini araştıran ilk yayındır. Daha ileri çalışmaların izole KAE'li hastalarda TAFI'nin kesin rolünü tanımlamada gerekli olduğuna inanıyoruz.

Anahtar kelimeler: Koroner arter ektazisi, trombin ile aktive olan fibrinoliz inhibitörü, koroner anjiyografi, TAFI aktivitesi.

Introduction

Coronary artery ectasia (CAE) is a clinical entity characterized by localized or diffuse dilatation greater than 1.5 times diameter of adjacent segments of coronary arteries. The prevalence of isolated CAE has been reported as 1.2 to 4.9% in various studies [1,2]. Although the etiopathogenesis of CAE is not clearly understood; some studies have revealed that CAE may be a form of atherosclerosis that has greater inflammatory aspects than atherosclerosis alone [3].

Previous studies demonstrated an increased frequency of acute coronary events such as thrombus formation, coronary micro-emboli, vasospasm, and slow flow in patients with isolated CAE compared to subjects with normal coronary angiograms.

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Thrombin activatable fibrinolysis inhibitor (TAFI) forms the molecular link between the coagulation and the fibrinolytic systems [4] with a strong anti-fibrinolytic activity. Since higher levels of TAFI activation may have a role in increasing thrombotic events, we investigated TAFI activity in patients with isolated CAE compared to normal subjects.

Material and Methods

Patients and Study Protocol

The present study was cross-sectional and observational study, consisting of sixty participants who underwent coronary angiography due to suspected coronary artery disease, between January 2011 and December 2011, at Rize Education and Research Hospital. The patients had normal coronary arteries (NCA) or CAE without any atherosclerotic lesion by visual assessment. Coronary angiograms were evaluated by two experienced interventional cardiologists for isolated coronary ectasia. Those patients with concomitant CAD were excluded. The control group was selected in a consecutive manner from the recently catheterized patients during the study period.

Thirty patients with isolated CAE (mean age 61±10 years) and 30 age and gender matched control participants with NCA, but without CAE (mean age 57±11 years), were included in the study; the relationship between TAFI activity, C-reactive protein (CRP), and CAE was investigated.

Isolated CAE is defined as localized or diffuse dilatation of the epicardial coronary arteries with luminal diameter exceeding 1.5 times of normal adjacent segment without any concomitant atherosclerotic lesion through visual assessment. When there was no identifiable adjacent normal segment, the mean diameter of the corresponding coronary segment in the control group served as normal values.

All patients had chest pain or angina equivalent symptoms with either positive treadmill test or myocardial perfusion study. Clinical characteristics, which consisted of multiple descriptors from each patient's history and physical examination, were collected by physicians from the cardiology clinic, of each patient at the time of cardiac catheterization and were stored in the database of coronary angiography laboratory at our institution. Standard selective coronary angiography with at least four views of the left coronary system and two views of the right coronary artery were performed using the Judkins technique and 6-French right and left heart catheters without the use of nitroglycerin.

Laboratory measurements

Blood samples were drawn by venipuncture to perform routine blood chemistry after fasting for at least 8 hours before coronary angiography. Fasting blood glucose, serum creatinine, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglyceride levels were recorded. Glucose, creatinine, and lipid profile were determined by standard methods. Serum CRP levels were determined by nephelometric method.

To measure TAFI activity, blood was collected into tubes containing 0.109 mmol/L trisodium citrate from an antecubital vein under fasting conditions in the morning. Plasma samples, prepared by centrifugation at 2000g for 15 minutes, were stored at −80 °C for two months. Plasma TAFI levels were measured by an enzyme-linked immunosorbent assay (ELISA) (Imuclone TAFI, American Diagnostica) according to the manufacturer's instructions, and expressed as percent of normal. For the TAFI assay, 100% concentration corresponds to normal pool human plasma diluted 1:50, which is the standard assay dilution.

Statistical analysis

Continuous variables were given as mean±SD and categorical variables as percentage. Data were tested for normal distribution using the *Kolmogorov-Smirnov* test. The $\chi 2$ test was used for the univariate analysis of the categorical variables. All tests of significance were two-tailed. Statistical significance was defined as $p<0.05$. The SPSS statistical software (SPSS for windows, version 15.0, Inc., Chicago, IL, USA) was used for all statistical calculations.

Results

The clinical characteristics of the study population are demonstrated in Table 1. There were no statistically significant differences between the two groups with regard to age, gender, presence of hypertension or diabetes mellitus, and smoking habit ($p>0.05$).

While CRP was poorly associated with TAFI activity ($r=0.309$, $p=0.014$), neither TAFI nor CRP were related to isolated CAE (Table 1).

Discussion

Since TAFI activation may have a role in increasing thrombotic events in CAE patients, the hypothesis that TAFI activity may be increased in these patients compared to normal subjects were investigated in the current study. We found a non-significant increase of TAFI activity in patients with isolated CAE compared to patients with angiographically normal coronary arteries. To our knowledge, this is the first report investigating the relation of CEA with TAFI activity.

There is still controversy regarding the mechanisms and reasons in pathogenesis of CAE. The frequent coexistence of CAE with CAD and histopathological findings resembling those of atherosclerosis have led to the conclusion that atherosclerosis may play a role in the pathogenesis, and CAE is a variant of atherosclerosis related to positive remodeling described as the enlargement of the area within the external elastic membrane. However, there are several unknown aspects, such as why only some of the patients with CAD have CAE while most of the

Table 1. TAFI levels in patients with isolated CAE and NCA.

	NCA, n=30	Isolated CAE, n=30	p
Age, years	57±11	61±10	NS
Male, %	43%	65%	NS
BMI, kg/m2	28±5	30±5	NS
Hypertension, %	69%	45%	NS
Diabetes mellitus, %	12%	20%	NS
Smoking, %	30%	50%	NS
Hyperlipidemia, %	40%	60%	NS
FH, %	27%	10%	NS
FGL, mg/dl	110±50	102±16	NS
Creatinine, mg/dl	0.8±0.2	0.9±0.2	NS
Total cholesterol, mg/dl	184±29	176±40	NS
LDL, mg/dl	115±23	108±32	NS
HDL, mg/dl	42±9	39±12	NS
Triglycerides, mg/dl	136±103	146±71	NS
CRP, mg/dl	0.73±1.29	0.72±1.05	NS
LVEF (%)	64±4	66±5	NS
TAFI activity (%)	124±35	130±42	NS

CAD, Coronary artery disease; BMI, Body mass index; HDL, High-density lipoprotein; LDL, Low-density lipoprotein; CRP, C-reactive protein; LVEF, left ventricular ejection fraction; BMI, body mass index; NS, not significant

patients have not. Histopathological examination of ectatic vessels has revealed similar findings seen in atherosclerosis [5]. Furthermore it is not exactly known why connective tissue disorders [6,7], infections [8], and Kawasaki [9] disease are related with CAE [10,11]. Studies on CAE etiology have all focused on vascular endothelium and the biological properties of the arterial wall. However, the exact mechanism of abnormal luminal dilatation in CAE is still unknown. The histological examination of the ectatic segments revealed diffuse atherosclerotic alterations and disruption of the vascular media layer [12].

Compared to patients with CAD, higher levels of CRP [3], adhesion molecules [13,14], metalloproteinase-3 (MMP-3) [15], plasminogen activator inhibitor–1 [16], and phospholipase A2 [17] have been reported in patients with CAE.

Various animal models have demonstrated that TAFI regulates both venous and arterial fibrinolysis in vivo [18-21]. Upon activation with thrombin/thrombomodulin complex, TAFI becomes active (TAFI-a, 35.8 kDa), and modulates fibrinolysis in vivo by cleaving the C-terminal lysine residues from partially degraded fibrin [22,23]. The reduction of C-terminal lysine makes fibrin more resistant to cleavage by plasmin. Various pathological conditions, including tumors, disseminated intravascular coagulation, deep venous thrombosis (DVT) and CAD, induce changes in TAFI levels [24-27]. Elevated TAFI levels were observed in DVT and CAD caused by increased levels of coagulation factors and consequently increased fibrin clot formation [28,29].

Epidemiological data investigating the association between TAFI levels and risk of arterial disease are inconsistent. Higher TAFI levels have shown an association with increased risk of CAD in several case-control studies [30-32]. However, in another study, elevated TAFI levels or polymorphisms in the TAFI gene, associated with increased TAFI levels, have been related to a lower risk of myocardial infarction [33]. Higher TAFI antigen decreased the risk of myocardial infarction in young patients (aged < 51 yrs), whereas higher TAFI activity was associated with an increased risk [34]. Furthermore, in a prospective study, decreased TAFI levels were related with refractoriness to medical treatment in patients presenting with unstable angina pectoris [35]. Recently, biological functions of TAFI distinct from regulation of fibrinolysis have been demonstrated, including regulation of inflammation, blood pressure, cell migration, and wound healing [36]. These functions may depend on the substrates of TAFI other than fibrin, for instance bradykinin, the anaphylatoxins complement (C) 3a and C5a, annexin II, and osteopontin [37,38]. The two opposite effects of TAFI on the development of arterial thrombosis were proposed by epidemiological studies. While the association between high levels of TAFI and arterial thrombosis may be the result of a hypofibrinolytic state, the association between low TAFI levels and arterial thrombosis may be explained by the defective regulation of inflammation. Epidemio-

logical studies have also shown elevated TAFI levels to be a weak risk factor for the development of primary or recurrent venous thrombosis [24,39,40].

In the present study, while CRP was poorly related to TAFI activity, it was not related to CAE. In this aspect, the known relationship between CAD and CRP is different and the possible role of CRP on CAD appears to be invalid for CAE. Even though coronary ectasia has been related to inflammatory process, a recent study, comparing CAE patients with CAD and normal coronary angiograms also found similar CRP levels. In addition, former studies demonstrated conflicting results on CRP levels in patients with CAE [3,41,42].

Study limitations

In the current study, the patients did not undergo IVUS (intravascular ultrasound) to detect whether there was a positive atherosclerotic remodeling in ectatic arteries. Hence, the coexistence of non-obstructive CAD in patients with "isolated" CAE can not be proved absolutely. Nevertheless, in clinical practice, isolated CAE patients do not undergo IVUS routinely and coronary artery ectasia is usually diagnosed with visual assessment of coronary angiography.

Conclusion

In conclusion, to our knowledge, this is the first report investigating the relation of CAE with TAFI activity. The findings of the current study indicate that TAFI activity is not associated with CAE. We believe that further studies are required to define the precise role of TAFI in patients with isolated CAE.

Authors declare no conflict of interest.

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