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Inflammatory mediators of coronary artery ectasia

Os mediadores inflamatórios de ectasia coronária

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Abstract
The exact mechanisms underlying coronary artery ectasia (CAE) remain uncertain. This study aims to investigate whether and how inflammatory mediators play a role in the pathogenesis of CAE. The data sources of this study were located by literature searches on MEDLINE, Highwire Press and Google search engine for the year range 2000-2013. The most sensitive of the four types of plasma inflammatory mediators were cell adhesion molecules and systemic inflammatory markers followed by cytokines, while proteolytic substances were the least sensitive indicators of CAE. Hypersensitive C-reaction protein, homocysteine, intercellular adhesion molecule 1, vascular cell adhesion molecule 1, matrix metalloproteinase-9, tissue inhibitor of metalloproteinase-2, vascular endothelial growth factor and neopterin levels were significantly higher in CAE and coronary artery disease (CAD) patients than in controls without CAE. The percentage of granulocytes was higher in CAE, in comparison with individuals with normal coronary arteries. Polymerase chain reaction determination of angiotensin converting enzyme genotypes showed that the DD genotype was more prevalent in CAE patients than in CAD patients, while prevalence of the I allele was higher in CAD than in CAE patients. CAE is more a result of inflammatory processes than of extracellular matrix degradation, as demonstrated by investigations of plasma inflammatory mediators, activation markers and angiotensin converting enzyme genotypes. Contemporary theories are unable to explain CAE's predilection for the right coronary artery or the occurrence of multi-vessel and multi-segment involvement.

Keywords: coronary aneurysm; extracellular matrix; inflammation mediators.

Resumo
Os mecanismos exatos da ectasia de artérias coronárias (EAC) não são completamente compreendidos. Este estudo busca verificar, em detalhes, se e como os mediadores inflamatórios funcionam na pathogenesis de EAC. A fonte de dados do presente estudo veio da recuperação de literatura das investigações relevantes em MEDLINE, na Prensa de Highwire e na ativação de pesquisa do Google, do ano 2000 para 2013. Dos quatro tipos de mediadores inflamatórios do plasma, as moléculas de adesão de célula e os marcadores inflamatórios sistêmicos foram os mais sensíveis, sendo que cytokines foram mais sensíveis e substâncias de protease foram menos sensíveis na indicação da presença de EAC. A proteína C reativa hipersensível, o homocysteine, a molécula de adesão intercelular 1, a molécula de adesão de célula vascular 1, a matriz metalloproteinase-9, o nervo inibidor de tecido de metalloproteinase-2, o fator de crescimento endotelial vascular e os níveis de neopterin foram mais altos nos pacientes com EAC do que nos controles sem EAC. A porcentagem de granulocytes foi maia em grupo EAC, comparando-se com os indivíduos com a artéria coronária normal. A determinação de genótipo do enzima do angiotensin-conversão utilizando-se a técnica de reação em cadeia da polimerase revelou que o genótipo DD foi prevalente na EAC, mas não nos pacientes de DAC, enquanto a presença do alelo I foi maior na DAC do que no EAC. O EAC é mais um resultado do processo inflamatório do que da degradação da matriz extracelular, como evidenciado por investigações dos mediadores inflamatórios de plasma, marcadores de ativação e genótipos de enzima do angiotensin a conversão. A predileção de EAC na artéria coronária direita e nos envolvimentos de multinavio e de multissegmento não é apurada por teorias contemporâneas.

Palavras-chave: aneurisma coronário; matriz extracelular; mediadores de inflamação.

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INTRODUCTION

Coronary artery ectasia (CAE) has been defined as localized or diffuse dilation of the coronary arteries seen on coronary angiography and exceeding by 1.5 times the diameter of an adjacent and normal segment.1,2 Prevalence of CAE among patients who underwent angiographic studies was 0.3-5.3%.3 Coronary artery ectasia may be the result of etiologies that are atherosclerotic (50%), congenital (20-30%), related to inflammatory or connective tissue diseases (10-20%), or iatrogenic following coronary interventions (3-4%).4 Inflammatory processes play important roles in innate host defenses against infections, and therefore elevated inflammatory cytokine and C-reactive protein (CRP) levels are associated with systemic inflammatory response.5

Over the years the number of investigations into CAE has been increasing, with similar metrological but different morphological interpretations presented by many authors. The topographical extent of CAE has been classified into four types: type I, diffuse ectasia of two or three vessels; type II, diffuse disease in one vessel and localized disease in another vessel; type III, diffuse ectasia in one vessel; and type IV, localized or segmental ectasia.6 The average diameter of ectatic segments has been reported as 5.87±0.78 mm;7 and the maximum diameters of ectatic segments were 5.51±1.83 mm for the left anterior descending coronary artery (LAD), 4.82±1.13 mm for the circumflex artery (Cx) and left anterior descending coronary artery (LAD), of ectatic segments were 5.51±1.83 mm for the left main coronary artery (8.8%) was the least often involved arteries are the RCA (67.6%) and LAD (64.7%), followed by the Cx (35.3%), while the left main coronary artery (8.8%) was the least often involved. Ozbay et al.8 reported an ectasia distribution of 60% in RCA, 57% in Cx and 50% in LAD, with 1-, 2- and 3-vessel ectasia accounting for 42.5%, 45% and 12.5%, respectively. Turhan et al.7 reported CAE distribution of 81% in RCA, 78% in LAD and 75% in Cx, with 1-, 2- and 3-vessel ectasia proportions of 19%, 28% and 53%, while rates of 1- to 6-segmental ectasia were 3%, 9%, 41%, 16%, 22% and 9%, respectively, with a mean of 3.4±1.2 ectatic segments per case. In general, ectasia often presents in 3-vessel and 3-segment forms and is most commonly found in the RCA.

It is well-known that atherosclerosis is an inflammatory process, as confirmed by recent studies of atherosclerosis focusing in particular on the role of chemokines in atherosclerotic leukocyte accumulation.9 The coronary slow flow phenomenon has been observed angiographically in patients with CAE, potentially indicating that endothelial dysfunction is involved and that there is a link to subclinical atherosclerosis or inflammation.10 However, the exact links between inflammatory mediators and CAE remain to be clarified.

MATERIALS AND METHODS

A comprehensive literature search was conducted on MEDLINE, Highwire Press and Google search engine for the year range 2000-2013. Search terms included “coronary artery ectasia”, “inflammatory mediators”, “tumor necrosis factor (TNF)-α”, “interleukins (ILs)”, “selectin”, “homocysteine”, “intercellular adhesion molecule 1 (ICAM-1)”, “vascular cell adhesion molecule 1 (VCAM-1)”, “hypersensitive C-reactive protein (hsCRP)”, “matrix metalloproteinases (MMPs)”, “tissue inhibitors of metalloproteinases (TIMPs)”, “vascular endothelial growth factor (VEGF)”, “neopterin”, “cathepsins” and “cystatin C.” Additionally, articles describing “activation markers”, “percentages of leukocyte members” and “angiotensin converting enzyme (ACE) genotype” in connection to ACE were also identified and retrieved. The search yielded 22 potentially relevant nonrandomized and retrospective studies published from 2000 to 2013.5,8,11-29 Exclusion criteria described in the articles selected included the following: recent or current myocardial infarction, acute coronary syndromes, left ventricular dysfunction, left ventricular hypertrophy, cardiomyopathies, congenital heart disease, valvular heart disease, inflammatory arrhythmias or immunologic diseases, active infection, hepatic, renal or thyroid functional abnormalities, immunosuppressive therapy and statin use.

Data were extracted from the text, figures and/or tables, with details of the study population, demographics, causative coronary artery disorders, types of mediators investigated, investigation methods and relationships between nature of the coronary artery disorders and types of mediators. Patients with isolated CAE were the main study subjects and were defined as the CAE group. Patients with coronary artery disease (CAD) and individuals with normal coronary arteries (NCA) according to angiography were taken as controls, and were defined as CAD and NCA groups, respectively.
Quantitative data were collected, calculated and compared across CAE, CAD and NCA patients. Results were illustrated in bar graphs. Linear correlations between plasma levels of biomarkers and CAE morphology were summarized. Results for expression of activation markers and ACE genotypes were also compiled.

Measurement data were expressed as mean ± standard deviation and compared using the *t* test; while enumerative data were expressed as frequencies and compared using Fisher’s exact test. Two-tailed *p*<0.05 values were considered statistically significant.

**RESULTS**

**Patient data**

A total of 22 relevant research articles on inflammatory mediators of CAE were identified and analyzed, with an overall population of 1743 patients, breaking down as 759 (43.5%), 504 (28.9%) and 480 (27.5%) patients recruited into CAE, CAD and NCA groups respectively. All patients were adults aged over 50. No gender difference between groups was noted. Plasma inflammatory mediators related to CAEs were discussed in 17 articles, and could be categorized into 4 types: cytokines (TNF-α, IL-6, IL-18), proteolytic substances (cathepsins, cystatin, MMP-2, MMP-3, MMP-9, TIMP-1 and TIMP-2), cell adhesion molecules (selectins, ICAM-1, VCAM-1 and VEGF) and systemic inflammatory markers (homocysteine, hs-CRP and soluble neopterin). Additionally, there were 5 articles that studied expression of activation markers in peripheral blood and expression of ACE genotypes. Where methods used to test for plasma biomarkers were reported, enzyme-linked immunosorbent assay was used in 20 groups of patients (71.4%), immunonephelometry in 4 (14.3%), florescence polarization immunoassay (FPIA) in 2 (7.1%) and particle enhanced turbidimetric assay (for hsCRP) and sequential immunometric assay (for IL-6) were each used in 1 (3.6%) patient group (*χ²*=59.196, *p*<0.0001).

**Plasma Inflammatory Mediators**

**Cytokines**

Plasma TNF-α and IL-6 levels were significantly higher in CAE than in NCA groups; whereas IL-18 levels did not differ significantly between the two groups (Figure 1).

**Proteolytic substances**

There were no intergroup differences in cathepsins L and K or in cystatin C (Figure 2), MMP-2 or -3 (Figure 3), or TIMP-1 (Figure 4). MMP-9 levels were higher in CAE than in CAD and NCA groups, and were much higher in CAD than in the NCA group (Figure 3). TIMP-2 was significantly reduced in CAE patients compared with NCA subjects (Figure 4).

**Cell adhesion molecules**

E-selectin was significantly elevated in CAE patients compared with CAD and NCA groups (*p*<0.001 for CAE vs. CAD; and *p*<0.001 for CAE vs. NCA) (Figure 5). Patients with CAE were associated...
with significantly higher levels of P-selectin compared with NCA (Figure 5). Moreover, patients with CAE had much higher ICAM-1, VCAM-1 and VEGF levels than patients with NCA. Furthermore, a significant difference in ICAM-1 was detected between CAD and NCA groups (Figure 6).

**Systemic inflammatory markers**

Homocysteine levels were much higher in CAE than in NCA groups (Figure 7). Both hs-CRP and neopterin tapered off in all three groups, and were highest in CAE, higher in CAD and lowest in NCA groups, with all differences between groups significant (Figure 7).

**Correlations between plasma inflammatory mediators and CAEs**

Different ectatic morphologies, in terms of length, diameter, number, location and extent, exhibited...
different relationships to plasma inflammatory mediator levels. Positive relationships were revealed between length of CAE and hsCRP, E-selectin, ICAM-1 and VCAM-1 levels, between maximum diameter of CAE and cathepsin L and P-selectin levels, between the number of CAE and homocysteine levels, between the location (in the LAD) and cathepsin L levels, and between the extent (localized or diffuse) and IL-6 levels, the cathepsin L to cystatin C ratio, and hs-CRP, MMP-3 and neopterin levels. Cystatin C and TIMP-1 exhibited an inverse relationship with extent (localized or diffuse) of CAE (Table 1).

Activation markers in peripheral blood

The percentage of granulocytes was higher in CAE than in the NCA group, whereas the percentage of monocytes was higher in NCA than in the CAE group. Mean flow cytometry fluorescence intensities for cluster of differentiation (CD)11a on granulocytes, monocytes and lymphocytes and for CD45 on granulocytes and monocytes were both significantly higher in CAE than in NCA group. In CAE group patients, TNF-α levels significantly correlated with mean fluorescence intensity levels of CD45+ on granulocytes, monocytes and lymphocytes. Most of the CAE patients had multivessel CAEs, and the CAD patients with CAE had significantly elevated activation markers including CD11b, CD11c, CD54, CD83 and CD86, and major histocompatibility complex (MHC) class II molecules on the surface of mature dendritic cells, in comparison with CAD patients without CAE and with NCA subjects. Mean fluorescence intensities of CD45 and CD11b on monocyte and lymphocyte surfaces were significantly higher in CAE patients than in NCA subjects.

Table 1. Correlations between plasma inflammatory mediators and morphology of coronary artery ectasia.

| Biomarkers                          | Length | Diameter | Number | Location                        | Extent                |
|------------------------------------|--------|----------|--------|---------------------------------|-----------------------|
| Cytokines                          |        |          |        |                                 |                       |
| Tumor necrosis factor-α            | No     |          |        |                                 |                       |
| Interleukin-6                      | No     |          |        |                                 |                       |
| Proteolytic substances             |        |          |        |                                 |                       |
| Cathepsin L                        | Positive |          | Positive | Positive (for the left anterior descending coronary artery) |                       |
| Cystatin C                         | Positive |          | Inverse |                       |                       |
| Cathepsin L to Cystatin C ratio    | Positive |          | Positive |                       |                       |
| Matrix metalloproteinase-3         | Positive |          | Inverse |                       |                       |
| Tissue inhibitor of metalloproteinase-1 | Positive |          | Inverse |                       |                       |
| Cell adhesion molecules            |        |          |        |                                 |                       |
| E-selectin                         | Positive |          | Positive |                       |                       |
| P-selectin                         | No      |          | Positive |                       |                       |
| Inter cellular adhesion molecule 1 | Positive |          | Positive |                       |                       |
| Vascular cell adhesion molecule 1  | Positive |          | No      |                       |                       |
| Systemic inflammatory markers      |        |          |        |                                 |                       |
| Homocysteine                       | Positive |          | Positive |                       |                       |
| Hypersensitive C-reactive protein  | Positive |          | No      |                       |                       |
| Neopterin                          | Positive |          | Positive |                       |                       |
TNF-α levels were significantly correlated with mean fluorescence intensities of CD45+ on granulocytes, monocytes and lymphocytes. Additionally, CAE patients exhibited increased platelet activation, with higher levels of plasma P-selectin, β-thromboglobulin and platelet factor 4, in comparison with NCA subjects. C. pneumoniae IgG levels were the only marker of infection, among those that were studied, that were significantly higher in CAE patients than in NCA subjects. C. pneumoniae IgG tests were positive in 98.9% of CAD and 98.5% of CAE patients, compared to 83.5% in NCA subjects.

**ACE genotype**

Determination of ACE genotypes by polymerase chain reaction revealed that the DD genotype was more prevalent in CAE than in CAD patients, while prevalence of the I allele was higher in the CAD than in CAE group.

**DISCUSSION**

Inflammatory mediators are substances, which can be endogenous or exogenous, that are released by immune cells when harmful agents impact on the human body, leading to inflammatory reactions through specific receptors. There are various inflammatory mediators covered by a range of different classification systems, but members of the class of mediators of acute inflammation mainly include vasoactive amines, plasma protein systems, prostaglandins and leukotrienes (eicosanoids), acetyl glycerol ether phosphocholine (PAF), cytokines, phagocyte products and nitric oxide. Nonetheless, chronic inflammation is often caused by persistent infections, prolonged exposure to toxic agents, or autoimmunity, and it is often pathologically present with infiltration of mononuclear cells due to persistent reaction to injury. Therefore, in chronic inflammation, inflammatory mediators prevail with T-lymphocyte and macrophage products including cytokines, growth factors, proteases, oxygen free radicals, complements and lipid mediators, etc.

CAE is more likely to be involved in a chronic inflammation. Nowadays, there is increasing evidence to support this hypothesis. It has become obvious that chronic inflammatory mediators are associated with development of CAE, including cytokines, proteolytic substances, cellular adhesion molecules and systemic inflammatory mediators, in addition to the activation markers in peripheral blood and ACE genotypes, as indicated in the present study.

The etiology of CAE can vary, from congenital to inflammatory, but since it is most frequently seen in relation to atherosclerosis, a predominantly inflammatory process is implied. Atherosclerotic changes were observed to be more common among patients with aneurysms of the thoracic and abdominal aorta, popliteal arteries and pulmonary artery. Increased lumen and also circumferential intimal thickening of ectatic coronary artery segments suggests that CAE and CAD share a common pathogenesis. Carotid intimal-medial thickness was significantly higher in both CAE and CAD patients with histological changes compatible with atherosclerosis than in NCA subjects. CAE can also be associated with various conditions, such as exposure to herbicides, inflammatory disorders (such as Kawasaki disease, Behçet’s disease, Takayasu aortitis, polyarteritis nodosa and Mediterranean fever), connective tissue disorders (such as Ehler-Danlos syndrome) and genetic disorders like Noonan syndrome. Coronary vasculitis can even be present in the acute phase of acute renal failure and rheumatic heart disease, and may also be associated with CAE.

Aydin et al. reported elevated plasma TNF-α levels, whereas Adiloglu et al. recorded lower TNF-α levels in CAE patients in comparison with NCA subjects. The lower TNF-α levels were explained as predominance of TH2 and lack of TH1 type immunity in CAE patients, similar to aortic aneurysm patients. The absence of any significant correlation between the dimensions of ectatic segments and IL-6 levels might be due to the narrower range of the diameters of the coronary arteries, compared with the abdominal aorta. One-vessel, 2-vessel and diffuse CAE had different IL-6 levels but statistical significance was not attained.

Proteolytic enzymes, such as cathepsins K and L, participate in the non-caspase pathway involved in apoptosis and atherosclerotic lesions. Apoptotic pathways may be activated in the mitochondria by cathepsins, which cleave Bcl-2 interacting protein Bid and degrade the anti-apoptotic members of the Bcl-2 family, including Bcl-2, Bcl-xL and Mcl-1. Cathepsins also contribute to monocyte and macrophage differentiation and migration. CAE is characterized by irregular, diffuse, saccular, or fusiform dilation of the coronary arteries, and the major pathophysiologic process involved in ectasia is most likely vascular remodeling in response to atherosclerosis. Experimental data show increased inflammatory response and activation of MMPs in the vessel wall, mediated by activation...
of the renin-angiotensin system. Additionally, an insertion/deletion polymorphism of ACE is closely correlated with coronary vascular tone and development of aneurysms. It was also found that CAE patients had an increased prevalence of the 5A/5A polymorphism of MMP-3, compared with CAD patients, implying overexpression of MMP-3 with increased extracellular matrix degradation. Overexpression of MMPs and imbalanced MMP/TIMP in CAE patients, as well as significant correlations between pro-brain natriuretic peptide and MMP-2, TIMP-1 and MMP-2/TIMP-1 in CAE but not in CAD and NCA groups, indicates that matrix remodeling is involved in pathogenesis of CAE. The concurrence of decreased MMP inhibition and increased angiogenic activity suggests accelerated and persistent extracellular matrix remodeling predisposing to aneurysm formation and increased risks of thrombosis formation.

Patients with isolated CAE have elevated levels of plasma soluble ICAM-1, VCAM-1 and E-selectin in comparison with patients with obstructive CAD but without CAE and in comparison with NCA subjects, with ICAM-1 being the only independent variable associated with isolated CAE, suggesting that ectasia develops in an intensively inflammatory vascular wall that predisposes to plaque instability. VEGF is a key regulator of physiological angiogenesis during embryogenesis, skeletal growth and reproductive functions. VEGF, which increases in response to inflammation, may play a role in the pathogenesis of coronary artery lesions. Furthermore, transforming growth factor-β, overexpression in patients with CAE and CAD in addition to significant correlation between plasma cystatin C levels and transforming growth factor-β, strongly support this hypothesis. Thus, CAE may be a destructive inflammatory lesion of the vascular wall. However, it is not clear why some patients with coronary atherosclerosis develop CAE while most do not.

Homocysteine enhances production of several pro-inflammatory cytokines. Hyperhomocysteinemia is an important risk factor for atherosclerosis and thrombotic disease. Patients with isolated CAE had significantly higher levels of plasma homocysteine than controls and 59% of patients with isolated CAE had elevated plasma homocysteine, compared to 7% of NCA subjects. This phenomenon is evidence to support an inflammatory etiology of CAE. Plasma hs-CRP levels were significantly higher in CAE group than in CAD group at baseline, but had significantly decreased from baseline 3 months later in both CAE and CAD patients. There was a positive correlation between hs-CRP and low density lipoprotein cholesterol in both CAE and CAD groups. Neopterin is produced by activated macrophages performing immune and macrophage activities. Patients with isolated CAE had increased neopterin level compared with NCA subjects, indicating a possible role for neopterin in inflammatory processes in CAD patients.

The source and mechanism of immune activation in CAEs remain unknown. T-cells from patients with congestive heart failure had enhanced surface expression of the activation markers CD69 and CD25, while there was no upregulation of the monocyte activation marker CD32. Patients with elevated plasma thiols homocysteine and cysteine levels had increased risk of atherosclerosis. Total cysteine concentration, but not total homocysteine, CRP, or neopterin, was higher in CAD patients with stepwise increases relative to the extent of CAD. Mean serum neopterin levels were significantly higher in patients with adverse cardiac events than in those without. Multiple regression analysis revealed that neopterin levels, severity of CAD and a history of previous myocardial infarction were independent predictors of adverse cardiac events.

The first phase of inflammation is adhesion of leukocytes to the endothelium, mediated by several adhesive molecules. Elevated cellular adhesion molecule levels in CAE patients may be an indicator of endothelial activation and inflammatory processes. The neutrophil-lymphocyte ratio was significantly higher in the CAE group compared with control, and this ratio was also positively correlated with the number of ectatic segments. Furthermore, CAE patients had higher mean platelet and eosinophil volumes. Increased concentration of eosinophils might be explained by vascular destruction, endothelial dysfunction and thrombosis in CAE patients. Activated cells express “activation markers,” which is a class with many members, including immunoglobulins, T cells, natural killer cells, monocytes and other antigen-presenting cells that trigger immune reactions by entering cell cycles. Activated cells may also enter the cell cycle by means of T cell receptors encountering antigens or by “bystander” mechanisms via exposure to certain cytokines.

The ACE DD genotype was more prevalent in patients with CAE. Most patients with CAE have concurrent CAD, which indicates an internal connection between the DD genotype and presence of CAD. However, univariate methods detected no correlation between the DD genotype of the ACE
gene polymorphism and CAD. The D allele of an ID polymorphism was associated with higher plasma ACE concentrations. Therefore, the deleterious effect of the DD genotype might be attributable to overexpression of ACE. Angiotensin II may promote CAE formation by enhancing inflammatory reactions, promoting smooth muscle cell migration, inducing extracellular matrix remodeling and MMP generation, or by stimulating production of reactive oxygen species.

The etiology of CAE’s predilection for the RCA has not been well-described. An insertion/deletion polymorphism of the ACE was found to be associated with coronary vascular tone and the development of aneurysms. In contrast with discrete saccular CAE, diffuse fusiform CAE is often bilateral and is often associated with abdominal aortic aneurysms rather than with concurrent CAD. The absence of CAD in CAE patients did not preclude patients from having left ventricular function impairment. The ACE DD genotype might be a potential risk factor for CAE, and the role that the renin-angiotensin system might play in the genesis of CAE suggests use of ACE-modulating agents could reduce the risk of CAE.

To date there is no data on the anatomical changes that may occur over time in CAE, nor is there sufficient comparative research into the different anatomical forms of CAE involvement. In order to further clarify the underlying etiologies, experimental investigations designed to reveal the precise molecular mechanisms involved are needed.

In conclusion, the pathogenesis of CAE is more reliant on a strong inflammatory reaction than on extracellular matrix remodeling as has been demonstrated by investigation of inflammatory mediators. Activation markers and ACE genotypes may also play an important role in the development of CAE. However, contemporary theories are unable to explain CAE’s predilection for the RCA or the occurrence of multi-vessel and multi-segment involvements. Further investigations of different CAE morphologies designed to reveal the precise underlying pathogenesis are essential if effective antagonists of the causative mediators responsible for CAE formation are to be identified.

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