MATRIX METALLOPROTEINASES AND INFLAMMATORY MARKERS IN CORONARY ARTERY ECTASIA THEIR RELATIONSHIP TO SEVERITY OF CORONARY ARTERY ECTASIA

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Matrix metalloproteinases and inflammatory markers in coronary artery ectasia: their relationship to severity of coronary artery ectasia.

Abstract

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OBJECTIVE: Although underlying mechanisms of coronary artery ectasia (CAE) are clearly unknown, destruction of extracellular matrix may be responsible for the ectasia formation. Thus, we investigated the role of matrix metalloproteinases (MMP-9) and inflammatory markers (hs-CRP)

METHODS: This study consisted of 30 consecutive CAE patients, 30 obstructive coronary artery disease (CAD) patients, and 20 controls with normal coronary arteries undergoing cardiac catheterization. Plasma levels of MMP-9 and hs-CRP were measured.

RESULTS: hs-CRP level was significantly higher in the CAE group than both in CAD and control groups (2.3 ± 0.5, 1.19 ± 0.54, 0.8 ± 0.3 mg/l, respectively , both p =0.00), while , MMP-9 level was significantly higher in both CAE group and CAD than control groups (27.71 ± 4.7, 25.2 ± 4.1 , 18.6 ± 3.3 ng/ml, respectively , both p =0.00). In subgroup analyses, MMP-9 level was significantly higher in CAE patients with multivessels involvement compared with those with single-vessel ectasia (29.4 ± 3.1 vs. 25.2 ± 5.5 ng/ml, P=0.01).while, hs CRP level was comparable in both groups (2.3 ± 0.52 vs. 2.4 ± 0.45 ng/ml, P=0.82).

CONCLUSION: Our results suggest that the increased level of MMP-9, hs-CRP may be responsible for ectasia formation in patients with CAE and their plasma levels is correlated with the severty of CAE.

Key word: cap-cas- coronary artery- inflammatory-cardiology

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LIST OF ABBREVIATIONS

ACEI : Angiotensin converting enzyme inhibitors.

ACS : Acute coronary syndrome.

ATP : Adenosine triphosphate.

CAE : Coronary artery ectasia.

CAD : Coronary artery disease.

CCBs : Calcium-channel blockers.

CABG : Coronary artery bypass graft

DM : Diabetes Mellitus.

EDRF : Endothelium derived relaxing factor

HTN : Hypertension.

HDL : High density lipoprotein.

hs-CRP : High sensitive C-reactive protein.

IHD : Ischemic heart disease.

IL-6 : Interleukin 6.

IL-8 : Interleukin 8.

IL-18 : Interleukin 18.

IFN-γ : Interferon-γ

IVUS : Intravascular Ultrasonography.

LAD : left anterior descending artery.

LCX : Left circumflex artery.

LDL : Low density lipoprotein.

LMCA : Left main coronary artery.

MCP-1 : Monocyte chemotactic protein-1

MMP-3 : Matrix metalloproteinase 3.

MMP-8 : Matrix metalloproteinase 8.

MMP-9 : Matrix metalloproteinase 9.

MRI : Magnetic Resonance Imaging.

Mvo2 : Myocardial oxygen consumption.

NO : Nitric oxide.

NOS : Nitric oxide synthase.

O-CAD : Obstructive coronary artery disease.

PCI : Percutaneous coronary intervention.

PGI2 : Prostacyclin.

RCA : Right coronary artery.

TIMP : Tissue inhibitor of matrix metalloproteinase

TNF-α : Tumour necrosis factor-α

VCAM-1: Vascular cell adhesion molecule-1.

INTRODUCTION

Coronary artery ectasia or aneurysms (CAE) is characterized by an abnormal dilatation of the coronary arteries,which is a variant of coronary artery disease (CAD) [1,2].

Coronary ectasia was defined as a dilation exceeding the 1.5 fold of normal diameters in major coronary arteries [1,2].

RCA is the most commonly involved vessel followed by the LCX and later the LAD[3,4].

Its incidence seems to rise in recent years. In general,CAE is considered to be a different form of vascular remodeling in response to atherosclerosis; however, the underlying mechanisms responsible for ectasia formation are clearly unknown [1,2].

Earlier studies have reported that CAE is associated with concomitant aneurysms in other vascular beds such as aorta and its major branches possibly because of a common underlying mechanism [5,6].

Some of the mechanisms postulated to explain ectatic transformation include arteriosclerotic disease resulting in weakening of media [7,8] and post - stenotic dilatation with post - stenosis flow velocity augmentation[9-10].

The studies about aortic aneurysms have provided that development of aneurysm is associated with destruction of

extracellular matrix by matrix metalloproteinases (MMPs) such as MMP-3 and MMP-9 [11-16].

They have suggested that increased activity or level of MMPs and/or decreased level of tissue inhibitors of MMPs (TIMPs) have an important role both in development and enlargement of aortic neurysms. The circulating levels of these enzymes may reflect their activity in the vessel wall [17].

As in the aortic aneurysms, MMPs especially MMP-3 and MMP-9 and/or TIMPs may serve as potential contributors for CAE. A few studies investigating the proteolytic role of MMPs in CAE patients are found [18-21].

These studies have shown divergent results. Similarly, studies evaluating the role of inflammatory markers including C-reactive protein (CRP) and interleukins (ILs) have also demonstrated different results [19-23].

AIM OF THE WORK

To investigate the role of, MMP-9, and inflammatory markers such as high-sensitive CRP (hs-CRP) in patients with CAE and the relationship between these markers and severity of CAE.

CORONARY ANATOMY

From the right and left aortic sinuses arise the right and left coronary arteries, respectively, and their ostia normally originate about two thirds the distance from the aortic annulus to the sinotubular junction and about midway between the aortic commissures [24,25].

Whereas right coronary artery arises nearly perpendicularly from the aorta, the left arises at an acute angle [24]. Rarely, the anterior descending and circumflex arteries arise separately from a double-barrel left coronary ostium[24,25].

The right coronary artery (RCA) is embedded in adipose tissue throughout its course within the right atrioventricular groove. In 50 to 60 percent of persons, its first branch is the conus artery, which supplies the right ventricular outflow tract and forms an important collateral anastomosis (circle of vieussens), just below the pulmonary valve, with an analogous branch from the left anterior descending coronary artery[24,25].

In about a third of patients, the conus artery arises independently from the aorta[25]. The infundibular septum is supplied by the descending septal artery, which usually originates from the proximal right or conus coronary artery[24,25].

Among the numerous marginal branches of the right coronary artery that supply the remainder of the right ventricular free wall, the largest branch travels along the acute margin from base to apex[24,25]. In at least 70 percent of human hearts, the posterior descending artery arises from the distal right coronary artery supply the basal and middle inferior wall, basal (inlet) inferior septum, right bundle branch, AV node,

AV (His) bundle, posterior portion of the left bundle branch, and posteromedial mitral papillary muscle [25].

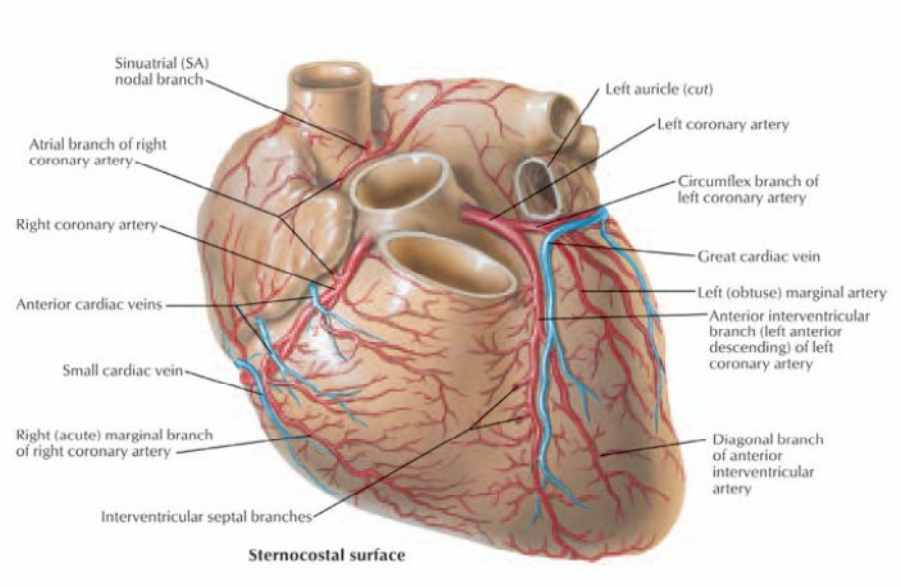
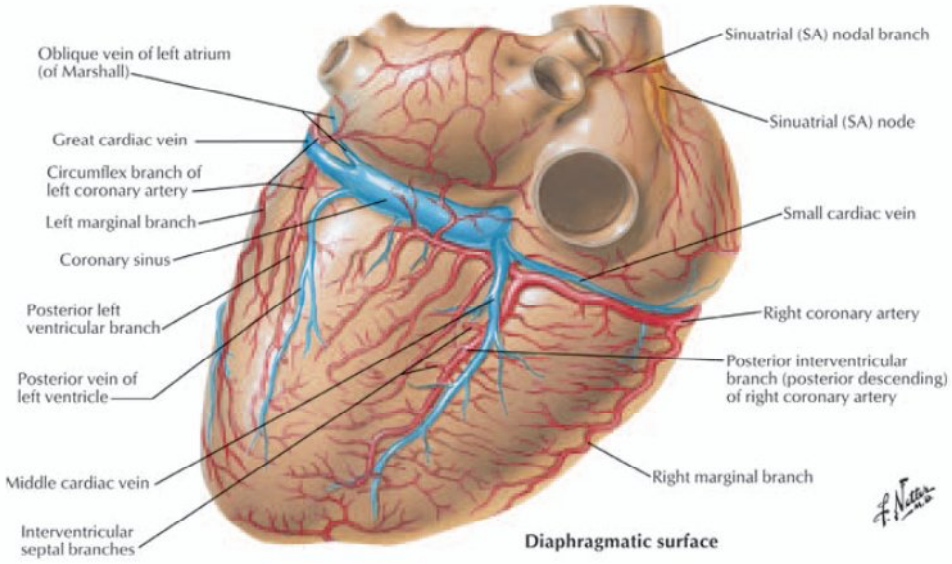


Figure (1): *sternocostal surface of the heart*

The left main coronary artery (LMCA) travels for a very short distance along the epicardium between the pulmonary trunk and the left atrium. It then divides into anterior descending and circumflex arteries. An intermediate artery also may arise at this division, thus forming a trifurcation rather than a bifurcation, and follows the course of a circumflex marginal branch[24,25] figure (1).

The left anterior descending coronary artery (LAD) courses within the epicardial fat of the anterior interventricular groove, wraps around the cardiac apex, and travel a variable distance along the inferior interventricular groove toward the cardiac base. Its septal perforating branches supply the anterior and apical septum. The first septal perforating branch supplies the AV (His) bundle and proximal left bundle branch[25].

The epicardial diagonal branches of the LAD supply the anterior left ventricular free wall, part of the anterolateral mitral papillary muscle, and the medial one third of the anterior right ventricular free wall.[24,25]



Figure(2): *diaphragmatic surface of the heart*

Although short segments of the LAD may travel within the myocardium (covered by a so called myocardial bridge), the resulting systolic luminal narrowing is probably benign in the vast majority of people. [25]

The left circumflex coronary (LCX) artery courses within the adipose tissue of the left atrioventricular groove and commonly terminates just beyond its large obtuse marginal branch. It supplies the lateral left free wall and a portion of the anterolateral mitral papillary muscle. [24,25]

Along the inferior surface of the heart, the length of the right coronary artery varies inversely with that of the circumflex artery. The artery that crosses the cardiac crux and gives rise to the posterior descending branch represents the dominant coronary artery. figure(2) Dominance is the right in 70 percent of human hearts, left in 10 percent, and shared in 20 percent.[24,25]

CORONARY CIRCULATION PHYSIOLOGY

Regulation of coronary blood flow:

The task of coronary circulation is to supply the myocardium with oxygen and substrates and remove metabolic waste products. Contractile cardiac function relies on aerobic metabolism and as basal oxygen extraction is about 60 percent; an adequate increase of coronary blood flow is required to meet increased myocardial oxygen consumption (MVo2) [26].

During strenuous exercise coronary blood flow can increase about five times. The maximal increase in coronary flow above resting levels is defined coronary flow reserve and is expressed as the ratio between the flow during maximal vasodilatation and basal flow. Low Mvo2 at rest requires a low coronary flow; therefore it is associated with a larger coronary flow reserve than a high resting Mvo2 [27].

Physiologic control of myocardial perfusion:

The in-series distribution of resistance as well as total vascular resistance are largely determined by changes of coronary vasomotor tone, while the transmural distribution of perfusion across the left ventricular wall is largely determined by extravascular compressive forces.

Extravascular mechanical forces:

At variance with all other organs, the heart generates its own perfusion pressure, and extravascular forces squeeze the vessels closed when extravascular pressure is higher than intravascular distending pressure. [28]