BIG ENDOTHELIN-1 LEVEL AS A PREDICTIVE MARKER FOR THE PRESENCE OF ISOLATED CORONARY ARTERY ECTASIA IN PATIENTS PRESENTED WITH CHEST PAIN

Thesis

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List of abbreviations

Abbreviation	Full term
ACE	Angiotensin converting enzyme
ACS	Acute coronary syndrome
ANOVA	Analysis of variance
CA	Coronary angiography
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CAE	Coronary artery ectasia
CASS	Coronary Artery Surgery Study registry
CLM	Cardiac lactate metabolism
CRP	C-reactive protein
CT	Computed tomography
CV	Coefficient variation
DM	Diabetes Mellitus
EC	Endothelial cell
ECG	Electrocardiogram
ECM	Extracellular matrix
EDTA	Ethylenediaminetetraacetic acid
EF	Ejection fraction
ET-1	Endothelin-1
ETA	Endothelin A receptor
ETB	Endothelin B receptor
ICAE	Isolated coronary artery ectasia
ICAM-1	Intercellular adhesion molecule-1

Abbreviation	Full term
IL-6	Interleukin-6
IVUS	Intravascular ultrasound
LAD	Left anterior descending
LCX	Left circumflex coronary artery
LIMA	Left internal mammary artery
LMCA	Left main coronary artery
MI	Myocardial infarction
MMP	Matrix metalloproteinase
MR	Magnetic resonance
MRA	Magnetic resonance angiography
Ng/ml	Nano gram per millilitre
NO	Nitric oxide
NTG	Nitro-glycerine
PCI	Percutaneous coronary intervention
PDA	Posterior descending artery
PTFE	Polytetrafluoroethylene
RCA	Right coronary artery
ROC	Receiver operating characteristic
RPM	Revolutions per minute
SVG	Saphenous venous graft
Tid	ter in die (Three times a day)
TIMP	Tissue inhibitor of metalloproteinase
TNF	Tumor necrosis factor
VCAM-1	Vascular adhesion molecule-1

Abbreviation	Full term
VEGF	Vascular endothelial growth factor
VSMC	Vascular smooth muscle cell

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Introduction

Coronary artery ectasia (CAE) is a common finding of coronary angiography, which is diagnosed when the diameter of the dilated coronary artery segments are greater than 1.5 times the diameter of adjacent normal segment **(Swaye et al., 1983, Hartnell et al., 1985, Giannoglou et al., 2006)**.

The incidence of CAE is in the range of 0.3–5.3% in angiographic examination and is observed in 1–5% of patients with angiographic evidence of coronary artery disease (CAD) (**Giannoglou et al., 2006, Satran et al., 2005**). The dilation of the coronary artery can be localized or diffused.

CAE is associated with increased coronary morbidity such as coronary spasm, dissection and thrombus formation and could cause angina pectoris, positive stress tests, or acute coronary syndromes (ACS) even without significant coronary stenosis (**Gunduz et al., 2012, Sayin et al., 2001**).

Regardless of the severity and extent of CAE, the etiology, prognosis, morbidity and mortality related to this vascular abnormality are still a matter of debate.

Several investigations have suggested that congenital, inflammatory, and connective tissue disorders are possible etiologies and the atherosclerotic lesion might be a potential cause for the development of CAE because it is frequently coincident with CAD in some patients (**Swanton et al., 1978, Kruger et al., 1999, Giannoglou et al., 2006**). However, a few observations have also suggested that CAE can be found in a number of patients without the apparent atherosclerotic stenosis, called as the isolated CAE (**Li et al., 2009**).

Therefore, to find the biomarkers to discriminate isolated CAE from CAD may be important for clinical implication.

Endothelin-1 (ET-1) has been implicated in atherosclerotic and ischemic heart Disease (**Thorin and Clozel, 2010**). It is released continuously mostly from endothelial cells (EC) (**Russell and Davenport, 1999**) and is one of the most potent vasoconstrictors identified so far (**Yanagisawa et al., 1988 and Brunner et al., 2006**).

In addition to EC, ET-1 is also produced by vascular smooth muscle cells(VSMC), cardiomyocytes, leukocytes, macrophages, various neurons and other cells (**Kedzierski and Yanagisawa, 2001**).

It has been reported that ET-1 modulates the expression of extracellular matrix (ECM) and matrix metalloproteinase (MMP) which is the main enzyme that degrades ECM molecules (**Abraham and Dashwood, 2008 and Hathaway et al., 2015**).

This makes ET-1 an important role in the vascular remodeling which is unusually associated with endothelial dysfunction and vascular disease.

Recently, several investigations reported that the elevation of circulation levels of ET-1 had an association with CAD, vascular injury and atherosclerosis (**Ruschitzka et al., 2000, Ivey et al., 2008 and Hathaway et al., 2015**). The imbalance between MMPs and tissue inhibitor of metalloproteinase (TIMPs) may be the molecular mechanisms contributing to CAE (**Li et al., 2007, Turhan et al., 2005b**).

Recently, some reports suggested that serum total MMP activity was significantly higher in the CAE groups than the patients with normal coronary arteries (**Liu et al., 2015**).

Even though ET-1 is a useful biomarker in various disease states, it has been reported to be rapidly cleared from the circulation. However, big ET-1, the biological precursor of ET-1, has a longer half-life and easier to be detected. Therefore, it has been more widely used in clinical researches.

Aim of the study

The aim of this work is to study the relationship between big ET-1 level and isolated CAE in patients presented with chest pain, undergoing coronary angiogram.

Definition

Coronary artery ectasia (CAE) is a common finding of coronary angiography, which is diagnosed when the diameter of the dilated coronary artery segments are greater than 1.5 times the diameter of adjacent normal segment **(Swaye et al., 1983, Hartnell et al., 1985 and Giannoglou et al., 2006)**.

CAE is associated with increased coronary morbidity such as coronary spasm, dissection and thrombus formation and could cause angina pectoris, positive stress tests, or acute coronary syndromes even without significant coronary stenosis **(Gunduz et al., 2012 and Sayin et al., 2001)**.

Regardless of the severity and extent of CAE, the etiology, prognosis, morbidity and mortality related to this vascular abnormality are still a matter of debate.

Several investigations have suggested that congenital, inflammatory, and connective tissue disorders are possible etiologies and the atherosclerotic lesion might be a potential cause for the development of CAE because it is frequently coincident with coronary artery disease (CAD) in some patients **(Swanton et al., 1978, Kruger et al., 1999 and Giannoglou et al., 2006)**. However, a few observations have also suggested that CAE can be found in a number of patients without the apparent atherosclerotic stenosis, called as the isolated CAE **(Li et al., 2009)**.

Epidemiology and classification

Incidence of CAE detected by means of coronary arteriogram has been found to vary between 0.3% and 4.9% **(Hartnell et al., 1985, Swaye et al., 1983)**. In the largest series from the CASS registry, **Swaye et al.** found CAE in 4.9% of coronary angiograms and the incidence is higher in men than in women (2.2% vs. 0.5% respectively) and postmortem incidence is given 1.4%. Advent of new noninvasive technologies such as computed tomography (CT) and magnetic resonance (MR) coronary angiography, may increase the rate of recognition **(Diaz-Zamudio et al., 2009)**. **Zeina et al.** found the prevalence of CAE 8% by coronary CT angiography **(Zeina et al., 2007)**.

Markis et al. suggested a classification of CAE according to the number and diffuseness of involved coronary vessels (Table 1) **(Zeina et al., 2007, Markis et al., 1976)**. According to the diameter of the vessel lumen CAE is classified as small (<5mm), medium (5–8mm) or giant (>8mm).

Types of CAE	Definition
Type 1	Diffuse ectasia of two or three vessels.
Type 2	Diffuse ectasia in one vessel and localized disease in another.
Type 3	Diffuse ectasia in one vessel only.
Type 4	Localized or segmental involvement.

Table 1 – Markis classification of coronary artery ectasia **(Markis et al., 1976)**.

Etiology and pathophysiology

Atherosclerosis is considered as the main etiologic factor responsible for more than 50% of cases in adults **(Hartnell et al., 1985**, **Swaye et al., 1983**, **Syed et al., 1997**, **Zeina et al., 2007**, **Gziut and Gill, 2008)** while Kawasaki disease is the most common cause in children or young adults **(Diaz-Zamudio et al., 2009**, **Zeina et al., 2007 and Markis et al., 1976)**.

Coronary aneurysms develop in 15–25% of untreated children with Kawasaki disease **(Kato et al., 1996, Rowley and Shulman, 1999)**, but after the introduction of the aspirin and intravenous gamma globulin therapy, resolution occurs at least 50% of the cases **(Newburger et al., 1986)**.

There are marked histopathological similarities between ectasia and atherosclerosis. Arterial lumen may be narrowed, preserved or dilated with progression of atherosclerosis. The exact mechanism of luminal dilation in some atherosclerotic vessels is unclear while atherosclerosis predominantly causes narrowing of the vessel lumen.

Certain plaques, as a result of a phenomenon so called 'arterial remodeling', do not reduce luminal size, presumably because of expansion of the media and external elastic membrane **(Schoenhagen et al., 2001)**. This finding also may be operative in the case of ectasia or aneurysm of other vessels. Observations with the use of intravascular ultrasound demonstrated that arterial remodeling may be bidirectional according to the expansion or shrinkage of external elastic membrane (i.e. positive and negative remodeling respectively) **(Schoenhagen et al., 2001)**. Positive (or expansive) remodeling is principally a compensatory mechanism to preserve luminal size during the progression of atherosclerosis. CAE is thought to be a result of

exaggerated expansive remodeling in which both external elastic membrane and luminal size increase **(Antoniadis et al., 2008 and Chatzizisis et al., 2007)**.

Enzymatic degradation of the extracellular matrix by matrix metalloproteinases and other lytic enzymes and thinning of the tunica media associated with severe chronic inflammation is suggested as the key pathogenetic mechanism of the exaggerated expansive remodeling.

Endothelin-1 (ET-1) has been implicated in atherosclerotic and ischemic heart Disease **(Thorin and Clozel, 2010)**. It is released continuously mostly from endothelial cells (EC) **(Russell and Davenport, 1999)** and is one of the most potent vasoconstrictors identified so far **(Yanagisawa et al., 1988 and Brunner et al., 2006)**.

In addition to EC, ET-1 is also produced by vascular smooth muscle cells(VSMC), cardiomyocytes, leukocytes, macrophages, various neurons and other cells **(Kedzierski and Yanagisawa, 2001)**.

It has been reported that ET-1 modulates the expression of extracellular matrix (ECM) and matrix metalloproteinase (MMP) which is the main enzyme that degrades ECM molecules **(Abraham and Dashwood, 2008 and Hathaway et al., 2015)**.

The severity of the changes in the media correlates positively with the diameter of ectasia. No evidence of ectasia is observed in cases with intact and uninvolved media layer **(Antoniadis et al., 2008)**.

Genetic predisposition of coronary ectasia could be suggested from its association with angiotensin-converting enzyme DD genotype **(Gulec et al., 2003)**