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The relation between plasma concentration of osteopontin and matrix metalloproteinase-2 and severity of chronic heart failure.

Thesis submitted in partial fulfillment for the Degree of M.D. Medical Biochemistry.

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قَالُوا سُبْحَانَكَ لا عِلْمَ لَنَا إِلَّا مَا عَلَّمْتَنَا إِنَّكَ أَنْتَ الْعَلِيمُ الْحَكِيمُ

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Abstract

Background—Extracellular matrix remodeling is thought to play an important role in the progression of heart failure (HF). Matrix metalloproteinases-2 (MMPs) havebeen demonstrated to influence left ventricular properties and serve as targets of potential anti-remodeling agents. Osteopontin, a glycoprotein that can be detected in plasma, was found to be up regulated in several animal models of cardiac failure and may thus represent a new biomarker that facilitates risk stratification in patients with heart failure.

Aim— We therefore tested whether osteopontin and MMP-2 plasma levels are elevated in patients with chronic heart failure and whether they are related to the severity of (CHF) speculating it may assume prognostic value.

Subjects and Methods— We analyzed osteopontin and matrix metalloproteinase-2 plasma levels using sandwich ELISA technique in fifty one patients suffering from chronic heart failure (group C).Seventeen with asymptomatic left ventricular systolic dysfunction (group B) (E.F=40%-55%) were enrolled in this study.Sixteen age and sex matched healthy controls(group A)(E.F>55%) were also included in the present study.

Results—We found that osteopontin plasma levels were significantly elevated in patients with heart failure as compared with healthy control subjects (72.0±20versus 25.4±5.3ng/mL, *P*=0.001), irrespective of heart failure origin (ischemic ,valvular and idiopathic).

Also, metalloproteinase-2 plasma levels were significantly elevated in patients with heart failure as compared with healthy control subjects (416.6versus 194ng/mL, *P*=0.001), irrespective of heart failure origin (ischemic , valvular and idiopathic).

Furthermore, osteopontin and metalloproteinase-2 levels were higher in patients with moderate to severe heart failure than in patients with no or mild symptoms. For OPN(76.8±17 and 95.2±11.9 ng/mL for New York Heart Association class III/IV respectively, versus 53.4±7.7ng/mL for class I/II, *P*<0.0001), and for MMP-2 (420±110 and502±100ng/mL for New York Heart Association class III/IV respectively, versus 361±59ng/mL for class II,*P*<0.0001).

Conclusion—Ourfindings suggest that osteopontin and matrix metalloproteinase-2 plasma levels are directly related toseverity of chronic heart failure.

Key Words: heart failure**,** metalloproteinase-2**,**osteopontin.

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Abbreviations

6.WT	6 walk minute test
ACC	American College of Cardiology
ACF	AortoCaval Fistula.
ACEIs	Angiotensine converting enzyme Inhibitors
AF	Atrial fibrillation.
AHA	American Heart Association.
ANG II	angiotensin II
ARB	Angiotensine receptor blocker
AP-1	functional activating protein-1
BMP	Body mass Index
CABG	Coronary artery bypass grafting
CKD	Chronic kidney disease
CMR	Cardio magnetic resonance image
COP	Cardiac Output
COPD	Chronic obstructive pulmonary disease
CRP	C-Reactive protein
CRT	Cardiac resynchronization therapy
cTnT	Cardiac troponin T
CVD	Cardiovascular disease
DHF	Diastolic Heart failure
DM	Diabetes mellitus
ECM	Extra-cellular matrix
EMB	Endomyocardial biopsy
Et-1	Endothelin -1
Eta-1	Early t-lymphocyte activating protein-1
ESRD	End Stage Renal Disease
GFR	Glomerular filtration rate
HF	Heart failure

HFNEF	Heart failure normal ejection fraction
HFPEF	Heart failure preserved ejection fraction
HFPSF	Heart failure preserved systolic frunction
IMA	Ischaemic modified albumin
I/R	Ischemia/ Reoxygenation.
LCF	Liver cell failure
LV	Left ventricle
LVAD	Left ventricular assist devices
LVEF	Left ventricular ejection fraction
MR	Mitral regurge
MMPs	Matrix Metalloproteinases
MT-MMPs	Mnebrane Type Matrix Metalloproteinases
NICP	non-ischaemic chest pain.
NYHA	New York Heart Association.
PAWP	Pulmonary Artery Wedge Pressure
PCI	Percutaneous Coronary Intervention
PDGF	platelet-derived growth factor
PLE	Protein loosing enteropathy
PRCGVPD sequence	
RCTs	Randomized Clinical Trial
SHF	Systolic Heart Failure.
SIBLING	Small Integrin Binding Ligand N-linked Glycoprotein.
STEMI	ST elevated myocardial infarction
TNFα	Tumor Necrosis Factor-α
UA	Unstable Angina
VHD	ValvularHeart Disease

Introduction

Heart failure is a common severe disease which affects about 1% of population after the age of 65. The prognosis of patients with HF is poor with an annual mortality about 20%, and they display a six to nine folds higher risk of dying from sudden cardiac death ***(Rosamond et al., 2007)***. Thus in patients with heart failure an accurate diagnosis and prognostic evaluation are critical to identify those at great risk for cardiac decompensation and death among these patients.

The development and prognosis of heart failure can be caused by a series of factors such as myocardial infarction , persisting hypertension induces among other effects , neuro-hormonal disorders ***(Zugc et al.,2003),*** local and systemic inflammation ***(Bristown, 1984)***,apoptosis of cardiomyocytes ***(Cohn,1996)***.As a consequence there is a deleterious extra cellular matrix turnover that proceeds and leads to heart hypertrophy and cardiac remodeling ***(Weber,1989)*** .

Heart failure (HF) pathophysiologic mechanisms include physiological, neurohormonal, molecular, and cellular changes that culminate in the activation of compensatory mechanisms aimed at maintaining heart function**.** When prolonged, these alterations can evolve into adverse accomodation processes. Hearts subjected to volume overload are challenged by distinct hemodynamic, and mechanical stress and neurohormonal activation resulting from increased preload, to accommodate the increased preload, the left ventricle (LV) undergoes structural and functional changes such as eccentric cardiac hypertrophy and extracellular matrix (ECM) remodeling ***(Spinale et al.,2007)*** .

Myocardial remodeling is structural changes occur within the myocardial wall that result in changes in LV geometry ***(Chen et al., 2000).***

Myocardial remodeling is the summation of both cellular and extracellular processes, ***(Brutsaert et al., 2003).*** While historically considered a static structure, it is nown recognized that the myocardial extracellular matrix (ECM) is a complex microenvironment containing a large portfolio of matrix proteins, signaling molecules, proteases, and cell types that play a fundamental role in the myocardial remodeling process ***(Coghlan and Coghlan, 2001),(Cohn et al.,2000).***

Expression and activity of MMP-1, MMP-2, MMP-9 and/or MMP-13 are increased in severe congestive HF and in human cardiomyopathic hearts ***(Peterson et al.,2001) &(Spinale et al.,2002)*** .

Increased matrix metalloproteinase (MMP) activity is associated with progressive LV dilatation and ECM degradation, contractile dysfunction, and neurohormonal activation in animal models of chronic pacing-induced tachycardia ***(Coker et al., 1998) & (King et al., 2003)***. This constant remodeling of the ECM is regulated by the activity of MMPs , which in turn are regulated by growth factors and cytokines. For example, the expression of TNFα and IL-1β is increased in patients with heart failure.

Osteopontin (OPN), also called cytokine Eta-1, is synthesized in a variety of tissues and cells and secreted into body fluids. Full-length human OPN protein consists of 314 amino acid residues with a predicted molecular mass of 32 kDa. Due to extensive post-translational modifications and negative charge resulting from the presence of acidic amino acids, apparent molecular weight of OPN can range from 45 to 75 kDa on SDS-PAGE. The functional domains of OPN are well conserved among species ***(Kazanecki et al., 2007)*** .

Osteopontin is an extracellular matrix protein that plays an important role in cardiac remodeling and fibrosis. In animal models, its expression is significantly upregulated after increased mechanical stress due to pressure overload ***(Xie et al., 2004).***

The aim of the present study is:

1- To assess appropriateness of plasma level of osteopontin and matrix metalloproteinase-2 to monitor disease progression and severity of heart failure.

2- Evaluation of the relation between osteopontin and matrix metalloproteinase-2 plasma levels and left ventricular dimensions (end-systolic and end-diastolic dimensions) and performance (ejection fraction) assessed by echocardiography.

3- Showing if there is difference in the change in plasma osteopontin and matrix metalloproteinase levels in chronic heart failure of different etiological origins whether ischemic or idiopathic.

Heart failure

Heart failure (HF) remains the only common cardiovascular syndrome increasing in prevalence and incidence. Despite significant advances in pharmacological and device therapies, morbidity and mortality for those afflicted with HF remains high ***(Adams, 2001) & (Hunt et al., 2001).***

Description of Heart Failure

Heart failure is a condition or process in which the heart is unable to pump enough blood to meet the needs of the body's tissues. Due to under-perfusion of organs, heart failure leads to reduced exercise capacity, fatigue, shortness of breath and may also lead to organ dysfunction (e.g., renal failure) in some patients ***(Shlipak et al., 2003).***

The heart doesn't "fail" in the sense of ceasing to beat (as occurs during a heart attack), it weakens, usually over the course of months or years, so that it is unable to pump out all the blood that enters its chambers ***(Radford et al., 2005).***

Mechanism of heart failure:

Heart failure can occur in several ways:

1. The muscles of the heart pumps (ventricles) become thin and weakened they stretch (dilate) to the extent that they cannot pump the blood with enough force to reach all the body tissues.
2. The heart muscles stiffen or thicken where; they lose elasticity and cannot relax.
3. Insufficient blood enters the chamber, so not enough blood is pumped out into the body to serve its needs.