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Research Article

ACUTE PHASE REACTANCTS IN PERICARDIAL FLUID ARE INDICATORS OF CORONARY ARTERY DISEASE

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ABSTRACT

Inflammation in formation of atherosclerosis, and acute phase reactants in the site of inflammation have major functions. Thus, do the acute phase reactants constitute the biggest risk factor for coronary artery disease? 55 patients are included in the study. Patients with coronary artery bypass surgery are included in Group I (38 patients) and patients with valve operation are included in Group II (17 patients). CABG patients are further divided into two sub-groups as on-pump and off-pump. In both groups, homocystein, high sensitivity C reactive protein, ceruloplasmin, lipoprotein A and serum amyloid A protein levels are analyzed from blood and pericardial fluid. In patients with coronary artery disease, the measured high specific C- reactive protein levels from blood and pericardial fluid are found to be significantly high compared to patients with valve operation.

Homocystein levels of pericardial fluids of patients with CABG are found to be higher than patients with valve operation and it is confirmed that the situation is correlated with blood homocystein levels. Although there are lots studies expressing the relation between coronary artery disease and lipoprotein A, ceruloplasmin and serum amyloid A protein levels; no significant difference for those parameters was obtained in our study. We determined that other phase reactants are higher in patients with coronary artery disease, in accordance with the literature. We aimed to state that acute phase reactants not only increase as a result of disease, but their levels are also elevated beforehand, as an indicator of the disease.

Key words: Acute Phase Reactants, Pericardial Fluid, Coronary Artery Disease

INTRODUCTION

Coronary artery disease (CAD) is the most important mortality and morbidity reason in all countries. According to World Health Organization, in 1998, deaths due to CAD constitute 13.7% of annual deaths worldwide.

It is proved for the first time that inflammation plays an important role in the formation of coronary atherosclerosis by Constantinides in 1996.

Normal endothelium resists against attachment of blood elements. Endothelial dysfunction is known to be the first major step for the pathogenesis of atherosclerosis. Dysfunction is formed due to damage caused by oxidized LDL (low density lipoprotein) on endothelium. 3 molecules are responsible from this situation. Selectins play a role in attachment of cells to endothelium with weak interactions in the early steps. Leucocytes attach firmly to endothelium with vascular cell adhesion molecule-1 (VCAM-1), intracellular adhesion molecule (ICAM-1) and platelet endothelial cell adhesion molecule-1 (PECAM-1), which are found on the endothelium. Adhesion molecules that provide attachment of leucocytes to ICAM-1 and VCAM-1 are integrins found on the leucocytes. It is known that cytokines are important in complication of atherome plaque.

Atherosclerosis is a complex, inflammatory, fibroproliferative response to lipoprotein accumulation within the artery intima. According to classical atherosclerosis classification, fatty line mainly consists of macrophages loaded with fat droplets that accumulated within the intima. Common intima thickness is a structure within intima that is made of large number of smooth muscle cells (SMC). Macrophages, T-lymphocytes and extra cellular lipid debris are other components. Fibrous plaque is white in color macroscopically and generally raised from the surface of the vein. Lipid nucleus constitutes more than 40% of the plaque volume. Plaques with low risk of complication are characterized as stable plaques. Plaques that could have been damaged easily, in other words plaques with high complication risk are characterized as unstable plaques. Small plaques that do not cause to myocardial ischemia may cause to acute coronary syndrome (ACS) after damaged if they are unstable.

Major risk factors for atherosclerosis are; age, sex, smoking, family history, hypertension, hypercholesteremia, diabetes mellitus and low level of high density lipoprotein (HDL). Factors that enhance coagulation (fibrinogen, hyperhomocysteinemia, increase lipoprotein A, increased factor VII, factor VIII and Von Willebrand factors) and inflammation indicators (fibrinogen, C-reactive protein, Cu^{++}, Fe^{++}, interleukin-6, Tumor necrosis factor) are also risk factors for CAD.

Although content of the pericardial liquid resembles the content of plasma, it is considered to be ultrafiltrated form plasma and concentrations of lots of molecules are close to their concentrations at plasma. Systemic diseases, coronary artery diseases, malignant diseases, connective tissue diseases, infections and idiopathic reasons may alter the composition of pericardial liquid.

C-Reactive Protein (CRP)

CRP is protein that is synthesized in liver under the control of IL-6. It is a non-specific indicator of inflammation[1, 2, 3]. There is a need of more sensitive methods to quantify CRP if it is to be used in diagnosis and for determination of risks in cardiovascular diseases. For this reason, high sensitivity CRP quantification methods (hs-CRP) are developed.

CRP binds to plasma membrane of damaged cell and forms a complex with plasma LDL and VLDL cholesterol. Formed

complex activates classical complement system and shows proinflammatory effect.

Clinical and laboratory evidences indicate that atherosclerosis has a systemic inflammation extension other than being a simple lipid accumulation disease[4]. Levels of circulating CRP can increase up to 1000 fold and can return to basal level within 7-12 days.

Hs-CRP appears to be the most powerful indicator to detect myocardial infarction and ischemia. It is promising that statins and aspirin are reported to have CRP lowering effects[5,6].

Homocystein and Atherosclerosis

Homocytein (hcyt) is a sulfur containing amino acid, which is formed by demethylation of an essential amino acid methionine.

With increased homocystein level, antithrombotic and fibrinolytic effects of endothelium are disrupted and endothelium gains prothrombotic feature. Homocystein increases the activities of factor XII and factor V, whereas it suppresses the activities of antithrombin III, protein C and thrombomodulin thus alters the antithrombotic properties of healthy endothelium[7].

When the results of case-controlled and prospective studies are investigated, it is shown that there is a distinct and strong relation between homocystein level and cardiovascular risk[8]. Mild hyperhomocysteinemia is reported to be around 5-7% in general population and 13-47% in patients with asemptomatic vascular diseases[9]. It is thought that the role of hyperhomocysteinemia in atherosclerosis is due to endothelial dysfunction and damage. It is determined in various in vitro and animal studies that homocytein has a direct toxic effect on endothelium[10,11]. Homocystein also increases the intensity and speed of the atherosclerosis by inducing the endothelium dysfunction[12,13]. In case control studies on patients with CAD, ischemia or peripheral vascular disease, serum homocystein level is found to be higher compared to control group[14,15]. It is determined that 4µm/L increase in homocystein level, increases the risk of coronary heart disease by 1.4 fold[16].

Nygard et al.[17] found a strong and gradual relation between homocystein level and all cause mortality on 587 patients, who has angiographically proven CAD. They also determined that patients with homocystein concentration 15µm/L and above have the highest risk.

Results of 12 prospective and 18 retrospective studies are investigated by homocystein study group and it is stated that providing a 25% (3µmol/L) decrease in serum homocystein concentration causes a 11% decrease in risk of ischemic heart diseases and 19% decrease in risk of a stroke[18].

Lipoprotein A (Lp A)

Lp A is a variant of LDL. It is formed upon binding of Apoprotein B 100 and Apoprotein A to each other via a disulfide bond. Lp A is also an acute phase reactant and it is synthesized in liver. It behaves as a positive acute phase reactant in cases of infection and inflammation[19].

It increases the tendency to endothelial dysfunction and atherosclerosis and it causes to acceleration of atherosclerosis. It accelerates both the formation of foam cells within plaques and plaque progression[20].

High Lp A level causes to a 3-122 fold increase in the cardiovascular incidences in different series when combined with other risk factors, depending on the number of present risk factors[21,22]. The incidence correlation is highest up to age 45, correlation decreases after age 55 and after age 65, correlation is completely lost[20,23].

In a prospective study which 1216 patients with angiographically determined coronary artery disease are examined, it is determined that high Lp A is an independent predictor of mortality within 6.7 years of study [24].

In an intense study, the threshold level for Lp A is found to be >30mg/dl. In this study frozen serum samples are used. But in studies done with fresh serum samples, Lp A levels above 20 mg/dl indicated patients with high risk[21,22].

Ceruloplasmin

Ceruloplasmin is an enzyme protein synthesized in liver. Being an acute phase protein, it is one of the main factors of organism's natural defense.

Ceruloplasmin decreases intoxication, enables the continuation of cardiac functions, strengthens hematopoietic and immune systems[25]. Ceruloplasmin levels are shown to be elevated in acute myocardial infarction and besides old infarction.

Serum Amyloid A Protein

Serum amyloid A protein (SAA) is a protein that is synthesized mainly in liver and rest is synthesized extrahepatically from macrophages, endothelial cells, adipocytes, smooth muscle cells and atherosclerotic lesions.

SAA levels increase in a number of inflammatory diseases and malign tumors. SAA is studied in cardiovascular diseases, especially in myocardial infarction, atherogenic composition and angina forms[26].

MATERIALS AND METHODS

38 patients who had a coronary artery bypass operation and as a control group 17 patients with valve operation are included in our study, who had their operations between years 2008-2009 in our clinic. 19 of patients with coronary artery bypass patients were operated off-pump and other 19 were operated on-pump. Patients with valve operation are not divided into sub groups. Study was carried out as per guidelines of ethical committee with ethical clearance number: 09.10.2008/ 23-3.

Standardized anesthesia technique (propofol in induction, pentotal agents and pancuronium bromide or vecuronium for neuromuscular blockage) is used. As a continuation, narcotics like phentanyl and remiphentanyl and inhalation agents are used in combination and balanced.

In on-pump patients, aorta unicaval cannulation is done. Cross clamp is used for the first time in all cases. First cold crystalloid cardioplegia (plejisol, St. Thomas II, Minnesota, USA) is given from anterograde way. Continuation of myocardium protection is provided by cold blood cardioplegia from retrograde cannula. During operation, moderate hypothermia at 28 ^{0}C is applied. Before the cross clamp is removed, to prevent reperfusion damage and to provide a controlled reperfusion, warm blood cardioplegia is administered for the last time. Membrane oxygenator is used in all cases. Pump flow is adjusted to be between 2-3 lt/min/m^2 and nonpulsatile, and average artery pressure is adjusted to stay at the level of 50-60mmHg during cross clamp.

In off-pump patients, before opening the pericardium, 1 ampoule of Mg sulfate and 1 ampoule of aritmal (2%) is administered. ACT (active coagulation time) is aimed to be kept below 200-250 seconds. During the anastomose, bulldog clamps are placed to artery. Average blood pressure of patients are kept around 40-50 mmHg.

Blood samples are taken from patients after anesthetic induction following 12-hour starvation. After sternotomy, pericardium is cut open with 3-4 cm incision and pericardial liquid samples are taken via syringe. Taken blood and pericardial fluid samples are transferred to tubes containing Ethylene Daimine Tetraacetic Acid (EDTA) just after the operation and plasma is separated by centrifugation for 5 minutes at 4000 rpm. Plasma samples are kept at -80^{0}C to be studied.

All plasma samples gathered for homocystein are tested with homocystein kit (96-sample quantite L homocystein) biochemically with Immulate 2000 Homocystein chemiluminescence technique (Reference interval is taken as 5-14µmol/L).

Lp A is studied from serum of venous blood that is taken to dry tube and separated by centrifugation. Nefelometric measurements are done with Dade Behring device form Siemens company using the kits of the same brand. Reference interval is taken as 0-30mg/dl.

CRP (Dade Behring, CardioPhase hsCRP) and SAA (Dade Behring, N Latex SAA) serum levels are studied with immunofelometry (Dade Behring, Marburg Gmbh, Germany) method. Normal level for CRP is taken as <3.19 mg/dl and normal level for SAA is taken as <3.03 mg/dl.

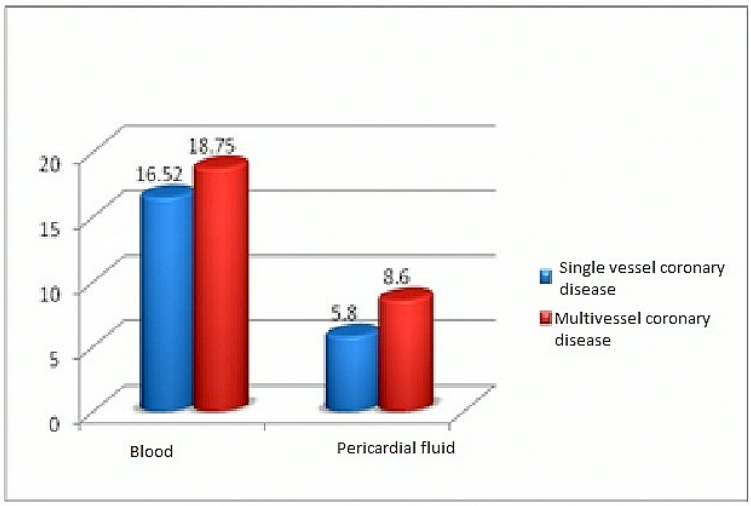
Ceruloplasmin is studied with immunofelometry (Dade Behring, Marburg Gmbh, Germany) method. Normal level for ceruloplasmin is taken as 0.2 mg/dl.

There is no determined range of values for patients' acute phase reactants from pericardial fluids. Levels of acute phase reactants from pericardial fluids of valve patients from control group are taken as reference range of values and study is planned accordingly.

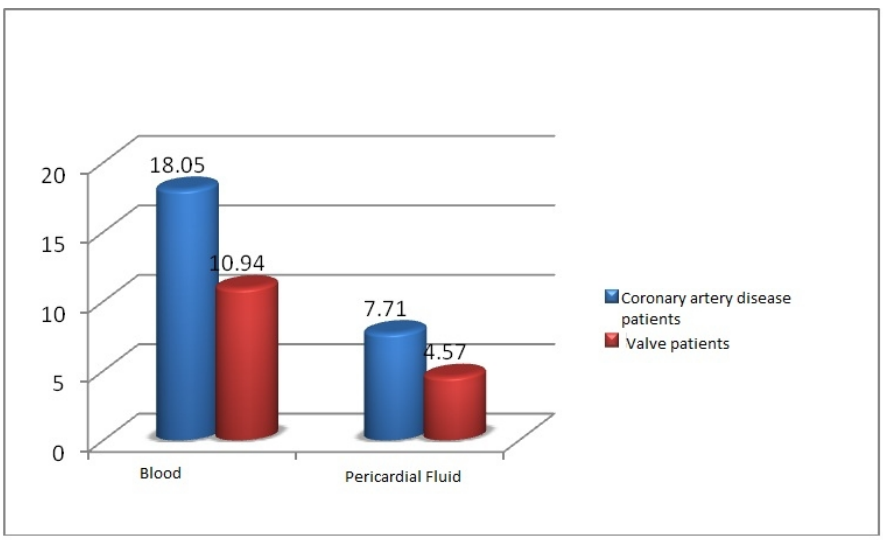
Statistical Analysis

Homocystein (hcyt), Hs-CRP, ceruloplasmin, lipoprotein A and SAA levels from blood and pericardial fluid samples of both groups are analyzed with various criteria. One sample t test is used for determination of significance of ceruloplasmin, lipoprotein and SAA levels. In comparison of averages of homocystein and Hs-CRP levels between coronary and valve patients, student t test is used. In CAD group, for comparison of homocystein levels from blood and pericardium and for determination of significance of relation between blood SAA levels and kidney functions, Pearson Correlation Test is used.

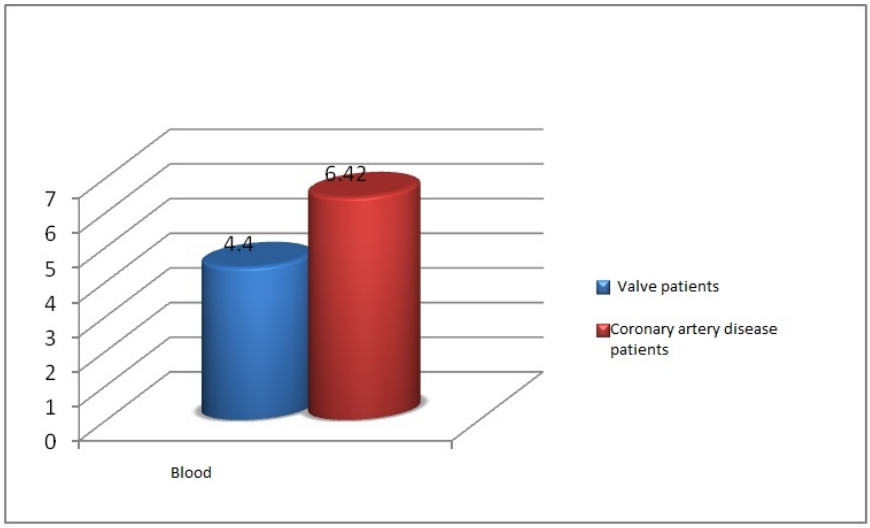
In this study, statistical analysis is done using SPSS 16.0 statistical package program. P values obtained after test are evaluated at $\alpha = 0.05$ significance level.



Graph 1: Average homocystein levels from blood and pericardial fluid of single vessel and multivessel coronary disease patients.



Graph 2: Average homocystein levels from blood and pericardial fluid of coronary artery disease patients and valve patients.



Graph 3: Average Hs-CRP levels from blood of coronary artery disease patients and valve patients

RESULTS

In CAD, there is positive and moderate relation between blood homocystein levels and homocystein levels from pericardial fluid (p= 0.009, ρ=0.421).

No statistically significant difference found between homocystein levels from blood (p=0.616) and pericardial fluids (p=0.562) of female and male patients.

Homocystein levels from both blood (t=-2.414) and pericardial fluid (t=-7.881) of multivessel CAD patients are found to be higher than single vessel CAD patients.

Homocystein levels from both blood (t=8.485) and pericardial fluid (t=8.981) of CAD patients are found to be higher than valve patients (Graphic 2).

Hs-CRP levels from both blood (t=4.337) and pericardial fluid (t=2.955) of CAD patients are found to be higher than valve patients (Graphic 3).

No statistically significant difference found between ceruloplasmin levels from blood and pericardial fluid of CAD patients (p=0.086).

In comparison between Lp A levels from blood and pericardial fluid of CAD patients, no significant difference is determined.

In comparison between SAA levels from blood (p=0.131) and pericardial fluid (p=0.096) of CAD patients, no significant difference is determined.

There is no statistically significant relation between SAA levels measured from blood and kidney functions before (p=0.400) and after (p=0.553) the operation.

In diabetic CAD patients, Hs-CRP levels measured from both from blood and pericardial fluid are higher compared to non diabetic patients.

DISCUSSION

Increasing evidences indicate that other than representing an ordinary lipid accumulation on the artery wall, atherosclerosis is an inflammatory disease.

It is understood for the first time that inflammation plays an important role in the formation of coronary atherosclerosis with the study of Constantinides in 1996.

C-reactive protein, one of the acute phase reactants, is an indicator of fibrinolytic activity and subclinic atherosclerosis. Plasma levels of CRP are regulated by proinflammatory cytokines like IL-6[27].

Systemic indicators of inflammation like C-reactive protein, serum amyloid A and fibrinogen (which are acute phase reactants) are revealed to be strong parameters in prediction of coronary events on asymptomatic males[28] and females[29], in patients with stable[30] and unstable[31,32,33] angina and following the infarction[34,35].

Proinflammatory cytokines may accelerate atherogenesis and/or its results. But it is not known whether it is a risk factor that can alter the inflammation or not[36]. In 1997, Ridker *et al*. reported in their study that high CRP levels in healthy males may be indicating the first myocardial infarction and ischemia[28].

As a result of their study, Toshihisa *et al*. reported that high CRP levels in acute myocardial infarction is an indicator of cardiac rupture, left ventricular aneurysm and one-year mortality[37].

In the cohort study conducted by Haverkate *et al*. by following 2121 patients with angina for two years, it is determined that coronary event risk increases 2 folds when CRP level is above 3.6 mg/dl. Lots of studies support that cardiovascular event risk increases 2-4 folds in patients with high CRP levels[38,39].

Limited number of studies that investigated the Hs-CRP level in pericardium has restricted our study. Thus we compared Hs-CRP levels from pericardial fluid of CAD patients with Hs-CRP levels from the valve patients of control group.

In our study, Hs-CRP levels of CAD patients from both blood (t=4.337) and pericardial fluid (t=2.955) is found to be higher than valve patients, in accordance with literature. This result reinforced its relation with atherosclerosis.

In studies on CAD, ischemia and peripheral vascular disease patients, serum homocystein levels are found to be higher compared to control group[13,40,41]. Increased homocystein level is thought to disrupt endothelial functions with direct cytotoxic effect. It also shown by laboratory studies that high homocystein concentration shows both thrombogenic and atherogenic effects[41]. In a meta analysis covering twenty prospective studies, each 5µmol/L increase in serum homocystein level is related to a 32% increase in CAD risk and a casual relation is stated[42].

In the study conducted by Tokgözoglu *et al*. in our country, it is shown that homocystein levels above 15micromol/L is found in the half of the CAD patients and this level increases the coronary risk 2.1 folds[43].

In our medline research, we did not encounter many studies on homocystein levels in the pericardium. In our study, CAD patients with elevated homocystein levels in their bloods also had elevated homocystein levels in their pericardial fluid. Both measured values are found to be higher compared to valve patients. Both from blood and pericardial fluid, measured homocystein levels are found to be higher in multivessel CAD patients compared to single vessel CAD patients. Relation between atherosclerosis and homocystein is apparent. There is a need for wide range and detailed studies to reveal the causation between hyperhomocysteinemia and CAD.

It is shown by studies that high Lp A levels go along with early-onset coronary artery disease[44]. But it is not known with which mechanism it causes to CAD. It is thought that Lp A causes to atherosclerosis by proatherogenic or protrombotic mechanism.

Lipoprotein A is added to NCEP ATP III guide as a new risk factor for CAD[45]. It interpreted that, high lipoprotein A has a relation with atherosclerotic events at coronary, cerebral and peripheral arteries[20,21,23]. In addition to that, publications that relate high lipoprotein A levels and occurrence of myocardial infarction and stroke at early ages are present[46].

In some studies, it is shown that relation between Lp A and coronary, carotis and peripheral artery diseases decrease with patients over age 65[20].

In an angiographic study, high liporpotein A is found to be related with vascular diseases with more vessels, more diffuse disease and more severe CAD[21,22].

In our study we could not find any statistically significant difference for continuation evaluations of Lp A levels from either blood or pericardial fluids of CAD patients.

Ceruloplasmin is the acute phase reactant that lasts elevated longest in the blood in stress cases. It is proposed that it reinforces formation of atherosclerosis by oxidizing LDL[47].

In their study *Mantari et al*. show that individuals with myocardial infarction has significantly higher (p=0.001) serum ceruloplasmin levels compared to control group[48].

Ceruloplasmin is reported to be high in patients with multiple cardiovascular defects like atherosclerosis, abdominal aortic aneurism[49], unstable angina[50], vasculitis and peripheral artery disease[51].

Increase in ceruloplasmin level can partially be explained as an acute phase response. But in our study, no statistically significant difference observed between blood and pericardial fluid samples of CAD patients and control group.

We investigated whether acute phase reactants in blood and pericardial fluid (Hs-CRP, Homocystein, lipoprotein A, ceruloplasmin, amyloid A) correlate with coronary artery disease.

Average blood homocystein level of CAD patients is evaluated as mild hyperhomocysteinemia. It is determined that homocystein level in pericardial fluid is higher compared to valve patients and it correlates with the homocystein level in blood for CAD patients. Homocystein levels from both blood and pericardial fluid of multivessel CAD patients are higher than single vessel CAD patients. Considering the effects of hyperhomocysteinemia, it is not known how long it lasts.

Blood and pericardial fluid levels of Hs-CRP are higher in CAD patients compared to valve patients. This study indicates that, it is beneficial to consider Hs-CRP levels alongside with known major risk factors while evaluating coronary artery disease risk of patients encountered clinically.

In our study, no relation determined between ceruloplasmin and lipoprotein A levels from blood and pericardial and coronary artery disease.

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