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ABSTRACT OF PHD THESIS

Assesment of coronary plaque vulnerability in acute coronary syndromes – from biomarkers to three-dimensional imaging

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The leading cause of mortality and morbidity in industrialized world is represented by coronary artery disease, and the majority of the deaths in these patients are caused by an acute coronary syndrome. One of the major factors that influence the prognosis after an AMI is represented by the amplitude of the inflammatory reactions in the postinfarction period, which in turn influence the amplitude of the left ventricular remodeling process and is directly correlated with the vulnerability degree of coronary plaques. Recent studies suggested several new markers that are associated with the degree of the inflammatory response in the post-infarction phase, such as circulating levels of high-sensitive C-Reactive Protein, or epicardial fat thickness. Epicardial adipose tissue is a metabolically active visceral adipose tissue, which has been proved to be involved in the pathogenesis of coronary artery diseases progression through secretion of proinflammatory cytokines. It has been recently demonstrated that the inflammatory cytokines released by this epicardial fat surrounding coronary arteries may modulate the coronary artery function and promote atherosclerosis progression.

This thesis aims to assess the role of different markers in evaluation of coronary plaque vulnerability in patients with acute coronary syndromes, from biomarkers that express an increased inflamatory status to complex three-dimensional imagistic markers such as epicardial fat thickness assessed by Coronary CT or CT analysis of plaque composition and density.

The research is structured in 3 studies:

Study 1 aimed to **a**ssess the correlation between the amplitude of the left ventricular (LV) remodeling at 6 months post-acute myocardial infarction (AMI) and several markers expressing an increased inflammatory status, such as epicardial fat thickness (EFT) and persistence of elevated circulating levels of highly sensitive C-Reactive Protein (hs-CRP). The study included 92 patients with revascularized AMI: group 1 (n=49) - hsCRP <3.0 mg/l, and group 2 (n= 43) -hs-CRP >3.0 mg/l; left ventricular end-diastolic (LVED) and end-systolic (LVES) volumes were determined at baseline and at 6 months, together with EFT, ejection fraction (EF) and remodeling index (RI).

Study 2 aimed to demonstrate the association between the severity of coronary atherosclerosis (as expressed by the Syntax score, the presence of multivascular disease and the total number of coronary arterieswith significant stenoses) and increased levels of hsCRP at 30 days after an acute myocardial infarction. Eighty-three consecutive patients 30 days post AMI, who were subjected to coronary angiography and primary PCI, were divided into: group 1 - 35 low-risk patients, with hsCRP levels <2 mg/l, and group 2 - 48 high-risk patients, with hsCRP levels >2 mg/l.

Study 3 aimed to demonstrate the relationship between the presence and the amount of a low-density core (LDC) with a CT density < 30 Hounsfield units (HU) by coronary computed tomography

angiography (CCTA) and IVUS-derived markers of vulnerability in the culprit lesions (CL) of patients with acute coronary syndromes (ACS). In 43 patients with acute coronary syndromes, 105 coronary plaques were scanned and analyzed.

Results:

In study 1, six-month EF significantly correlated with hs-CRP circulating levels at baseline (r=-0.57, p<0.0001) and with the EFT (r=-0.61, p<0.0001). Linear regression demonstrated a good correlation between hsCRP level and EFT (r=0.6251, p<0.0001) and multivariate analysis revealed that hs-CRP values >3.0 mg/dl (Odds ratio [OR] 2.8, p=0.02), an EFT > 7.0 mm (OR: 6.3, p=0.001) and the anterior location of the infarction (OR: 2.6, p=0.03) were independent predictors for deleterious left ventricular remodeling after an AMI.

In study 2, angiographic analysis revealed the presence of a multivascular disease in 48.5% of the patients in group 1 versus 72.9% of the patients in group 2 (p=0.037). The Syntax scores for groups 1 and 2 were 22.2 +/- 6.6 and 27.07+/-0.94, respectively (p=0.001), and these values were significantly correlated with the hsCRP values (r=0.56, p<0.0001). The ejection fraction at 30 days was significantly lower in the patients with elevated levels of hsCRP (52.91+/-4.03 vs 49.04+/-5.74, p=0.001), showing an inverse correlation with hsCRP levels (r=-0.52, p<0.0001).

In study 3, the presence of a low attenuation plaque (LAP) was identified in 67.4% of the CL and 29.03% of the non-CL (*P*= 0.0001). The presence of a LDC > 6.0 mm^3 was significantly correlated with the percentage of the necrotic core (NC) (22.08% versus 7.97%, *P* = 0.001) and the fibro-fatty tissue by IVUS (18.68% versus 15.87%, *P* = 0.02). LDC volumes showed a good correlation with the percentage of the NC (*r* = 0.7303, *P* < 0.0001) and the fibro-fatty tissue in the CL (*r* = 0.4928, *P* < 0.0008).

Conclusions:

Our study demonstrates that a larger amount of epicardial adipose tissue and the persistence of a marked inflammation at seven days post-infarction are associated with a more severe impairment of ventricular function in patients with AMI. The patients with increased epicardial fat volumes and persistently high levels of hs-CRP at seven days post-infarction have a poorer outcome, as reflected by lower EF, marked enlargement of the ventricular cavities and the development of ventricular remodeling at six months. hsCRP is an inflammatory marker which can aid the risk stratification in post myocardial infarction patients, identifying subsets of patients at risk based on persistently elevated levels of circulating hsCRP at 30 days postinfarction.

In the same time, the amount of low-density atheroma within the plaque, as determined with CCTA correlated well with VH-IVUS-derived markers of vulnerable plaques. Therefore, the identification of a significant low-density core within a coronary plaque on CCTA may provide a method to predict the risk associated with coronary lesions via a noninvasive method.

Given the current necessity for a cost-effective approach and justification of expensive imaging tests, together with the high degree of accuracy of information provided by CCTA using non-invasive plaque quantification, CCTA could in the future replace invasive techniques for the complex evaluation of intracoronary plaque vulnerability. In the same time, assessment of epicardial fat thickness by routine echocardiography, associated with determination of hs-CRP levels, could play a considerable role in risk stratification in patients post AMI, and may help to identify subsets of patients at increased risk for ventricular remodeling and heart failure.