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Assessment of Coronary Plaque Composition with Dual Source Computed Tomography and Virtual Histology Intravascular Ultrasoundin Patients with Acute Non-ST Elevation Myocardial Infarction and Patients with Stable Coronary Artery Disease: A Comparison with Blood Levels of Five Possible Biomarker Candidates of Plaque Vulnerability

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The propensity of a coronary atherosclerotic plaque to rupture – its so-called vulnerability - is known to be largely dependent on inflammatory processes at the site of the plaque leading to an instable microanatomy.In case of rupture, sudden vessel obstruction leads to ischemia and subsequent myocardial necrosis. The clinical manifestation is the acute coronary syndrome (ACS), which is a life-threatining acute manifestation of coronary artery disease (CAD). Strong efforts are made to reliably risk-stratify plaques and patients suffering from CAD.
The reference standard for the assessment of coronary plaque composition is virtual histology intravascular ultrasound (VH-IVUS), performed in the course of invasive coronary angiography. However, due to its invasiveness, the search for accurate non-invasive plaque imaging modalities is ongoing.Coronary CT angiography (cCTA) is increasingly used not only to reliably rule out CAD but also to diagnose CAD and further characterize atherosclerotic plaques. One objective of this study was therefore to quantitatively assess coronary atherosclerotic plaque composition in patients presenting with ACS,in more detail, in patients with acute non-ST elevation myocardial infarction (NSTEMI) andto compare plaque composition with that of patients with stable CAD by means ofcCTAandVH-IVUS. Another approach to determine presence of vulnerable plaques in patients with CAD is the assessment of chemical biomarkers circulating in the patient's blood, associated with plaque destabilization, inflammation and rupture. Consequently, we also assessed in our patient cohort concentrations of matrixmetalloproteinase-9 (MMP-9), myeloperoxidase (MPO), pregnancy associated plasma protein A (PAPP-A), placental growth factor (PlGF) and soluable CD 40 ligand (sCD40L) by performing conventionally available enzyme-linked immunoassays and investigated for possible differences between patients with NSTEMI and patients with stable CAD.
60 patients (35 with NSTEMI) were enrolled in the course of the study. 40 corresponding plaques (22 of NSTEMI patients) of 28 patients (15 with NSTEMI) were finally assessed bya first-generation dual source CT scanner and 20-MHz VH-IVUS performed in the course of invasive coronary angiography (ICA)regarding volumes and percentages of fatty, fibrous and calcified component, overall plaque burden and maximal percent area stenosis. cCTA plaque analysis revealed no significant differences between plaques of patients with NSTEMI and stable CAD regarding absolute and relative amounts of any plaque component, neither did VH-IVUS plaque analysis. The only difference with regard to plaque morphology observed in this study was higher area stenosis in NSTEMI patients compared to patients with stable CAD as measured with VH-IVUS. Volumes of fatty component were measured systematically lower in cCTA, whereas calcified and fibrous volumes were measured higher. No significant bias was observed comparing volumes of overall non-calcified component and overall plaque burden.
Regarding the analysis of biomarker levels, in total, 47 blood samples (28 of NSTEMI patients) were collected. NSTEMI patients had higher MMP-9, MPO and sCD40L levels and lower PAPP-A and PlGF levels than the group of patients with stable CAD, yet only concentrations of sCD40L were significantly differing between NSTEMI patients and patients with stable CAD. Levels of sCD40l were negatively and significantly correlated with PAPP-A and PlGF levels.PAPP-A and PlGF concentrations were

positively correlated with each other and these two biomarkers were also both significantly elevated after ICA procedure independent of patient group and the performance of percutaneous interventions in the course of ICA. Concentrations of the study biomarkers did not correlate with concentrations of hsTnI, CRP, HDL, LDL, total cholesterol and triglycerides.The only correlation observed between study biomarker concentrations and plaque components was a weak positive correlation between percentage of fatty component and sCD40L levels.

In summary, these data suggest that plaques of patients with NSTEMI and of patients with stable CAD cannot be differentiated by mere quantification of plaque components, neither by dual source cCTA nor with VH-IVUS. The most promising biomarker candidate observed in this study was sCD40L, which showed significantly higher concentrations in NSTEMI patients than in patients with stable CAD, suggesting usefulness todetermine patients at risk and blood levels were positively correlated with fatty plaque component, which is a surrogate for plaque vulnerability.

Longitudinal studies are warranted to evaluate to which extentcoronary plaque composition imaging can add to proper risk stratification of plaques and patients and prompt treatment strategies, and to determine specific biomarkers of coronary plaque vulnerability. Assumed that a reliable diagnostic approach applicable in clinical routine will be established and vulnerable plaques could be accurately distinguished from stable plaques, proof of the usefulness of “preventive” conservative or even interventional treatment strategies of vulnerable plaques with regard to short-term and long-term survival and morbidity of patients with CAD is still to be made.