**Impact of NAD(P)H Oxidase-Derived Reactive Oxygen Species on Plaque Formation and Vascular Remodeling: Comparison of Histochemical Characteristics and Intravascular Ultrasound Finding of Atherosclerotic Lesions**

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**Background:** Oxidative stress induced by reactive oxygen species (ROS) in the vessel wall plays an essential role in atherogenesis. Recently, we demonstrated that the generation of ROS via NAD(P)H oxidase was correlated with plaque instability by using coronary specimens obtained by directional coronary atherectomy (DCA). In this study, the relation of ROS generation and vessel remodeling was studied using a combination of preintervention intravascular ultrasound (IVUS) and measurement of ROS corresponding to DCA specimens.

**Methods:** On the pre-DCA IVUS images of 30 patients, lesions and reference segments were analyzed for vessel area (VA) and plaque area (PA). Positive remodeling was defined as lesion VA > proximal and distal reference VAs, and remodeling index was calculated as lesion VA / average of proximal and distal reference VA. The degree of ROS generation and expression of NAD(P)H oxidase p22phox in DCA specimens were evaluated by the dithionitroreducing method and immunohistochemistry as the ratio of positive area to total surface area in each segment.

**Results:** ROS generation in coronary specimens was closely associated with expression of p22phox, and it was significantly correlated with lesion PA and remodeling index (r=0.60, p<0.001, r=0.79, p<0.001, respectively). Positive remodeling was observed more frequently in patients with high ROS generation, compared to those with low ROS generation (75.0% vs 11.1%, p=0.001).

**Conclusions:** ROS generation is correlated with both plaque volume and vascular positive remodeling. NAD(P)H oxidase-derived ROS may have a significant role in the progression of atherogenesis and the associated remodeling process.

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**Compensatory Enlargement Delay Vascular Healing of the Culprit Lesion Following Acute Myocardial Infarction**

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**Background:** Although there have been many reports on the mechanism of plaque disruption leading to acute myocardial infarction (MI), the process by which the culprit lesion subsequently heals has not been well described. We hypothesized that positive remodeling of the culprit lesion at the onset of acute MI may retard the healing of the vessel 6 months later.

**Methods:** We studied 28 acute MI patients (26 men, 60.8±9.2 years) within 24 hours after onset. In all cases, both angiography (Clinical Supply Co.; Vecmova) and intravascular ultrasound were performed immediately before percutaneous coronary stenting (Multi-Link or S670/S660). The extent of atheromatous burden of the vessels, the severity-score and the Gensini-score were assessed. In all cases, both angiography and intravascular ultrasound were performed immediately before percutaneous coronary stenting (Multi-Link or S670/S660). We also assessed the role of the C242T p22phox polymorphism, which has been hypothesized to affect NADPH-oxidase dependent ROS release. Methods: In 154 male patients who underwent coronary angiography because of suspected coronary heart disease (CHD) the coronary arteries were assessed using the extent-score, which reflects the total atherosclerotic burden of the vessels, the severity-score and the Gensini-score. In all patients, NADPH-oxidase dependent ROS release from mononuclear cells, isolated by Ficoll separation, was quantified by luminal enhanced chemiluminescence after phosphoester stimulation. The C242T polymorphism was assessed by restriction fragment length polymorphism. p22phox-mRNA from mononuclear cells was measured by quantitative PCR.

**Results:** Peak ROS release in mononuclear cells was significantly different (p<0.001) between patients with (n=123) and without (n=31) ROS release was largely dependent on NADPH oxidase as indicated by inhibition with diphenylene iodonium. The extent-score, but not the severity- and the Gensini-score, showed a positive significant correlation with peak ROS-release from mononuclear cells (p<0.001). Multivariate analysis, correcting for effects of lipid-levels, age, concomitant medication, blood pressure and diabetes confirmed the independent correlation. The amount of p22phox-mRNA from mononuclear cells significantly correlated with ROS release (p<0.01). No correlation was found for the distribution of the p22phox 242C- and the 242T-polymorphism and CHD or ROS release.

**Conclusion:** These data demonstrate a correlation between coronary atherosclerotic burden and NADPH-oxidase dependent ROS-production. The present findings support the concept of oxygen-radicals as important risk factors for atherogenesis.