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Biomarkers and Coronary Atherosclerotic Burden and Activity as Assessed by Coronary Angiography and Intra-Coronary Imaging Modalities

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1. Introduction

Coronary artery disease (CAD) is one of the leading causes of death worldwide and it is expected that the rate of CAD will accelerate in the next decade due to overall aging of population and increases in the prevalence of cardiovascular risk factors (type 2 diabetes, obesity, metabolic syndrome) in younger generations (Amborsioni et al., 2003). The mortality associated with atherosclerotic disease is mainly related to the acute coronary syndromes (ACS), including acute myocardial infarction (AMI), unstable angina (UA) pectoris and sudden cardiac death. Inflammation plays a central role throughout the entire disease progression, and it lies at the root of atherosclerosis initiation, progression and its complications (Bonow et al., 2002).

However, recent data support the notion that plaques within the coronary circulation become "more severe" or at "high-risk" (vulnerable plaque) in response to a wide array of local and systemic influences, both inflammatory and non-inflammatory (Alsheikh-Ali et al., 2010; Finn AV et al., 2010). Indeed, plaques may have similar structural features and morphologic assessment, but may differ in their biology, their activity, and thus their likelihood of advancing toward clinical complications. Advances in the understanding of the pathogenesis of coronary atheroslcerosis have stimulated development of novel biomarkers, and expanded their role in the different spectra of their underlying pathophysiology (Hochholzer et al., 2010). In this regard, an emerging approach is represented by the assessment of plaque burden, morphology, and remodeling with in vivo atherosclerosis imaging and its correlation to novel biomarkers (Prati & Zimarino, 2010).

In the past, invasive coronary angiography (CAG) has been the only diagnostic procedure for identifying coronary atherosclerosis. However, newer intracoronary imaging modalities have been developed allowing a more accurate and precise evaluation of coronary atherosclerotic lesions, with regard to specific morphologic criteria, especially concerning vulnerability. Intravascular ultrasound (IVUS) is a catheter-based technology that allows for assessment of vessel wall thickness and structure while coronary angioscopy also allows to visualize the vessel lumen (Kaneda et al., 2010). More recently, optical coherence

tomography (OCT) has been introduced as an invasive technique that provides images of vessel wall morphology and plaque characteristics (Prati et al., 2009; Bezerra et al., 2009).
By using these novel techniques, an array of biomarkers assessing plaque growth and destabilization, myocardial stress and ischemia, along with inflammatory processes, has been developed, including cellular adhesion molecules, cytokines, and proatherogenic enzymes. Importantly, different biomarkers may look at different phases of coronary atherosclerotic disease and CAG, along with IVUS, angioscopy and OCT, may be of great clinical utility in assessing the role of these new biomarkers in coronary atherosclerosis pathophysiology (Libby & Theroux, 2005; Hansson, 2005).
The present chapter will summarize our current understanding of inflammatory and non-inflammatory biomarkers, validated with intracoronary imaging modalities, their presumed pathophysiological role in coronary atherosclerosis and the clinical evidence that supports their prognostic importance.

2. Soluble biomarkers

A dynamic inflammation model has supplanted the previously held view of atherosclerosis as a passive deposition of debris in the arterial wall (Libby, 1995a, 1995b; 2001; 2002; Libby & Theroux, 2005). Numerous mediators contribute to atherogenesis, including chemokines, cytokines, growth factors, proteases, adhesion molecules, hemostasis regulators, and receptors, and their interactions may regulate plaque progression and instability (Blake & Ridker, 2002;).
A biomarker is defined as a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes or pathogenic processes or as a physiologic response to a therapeutic intervention. In clinical medicine, biomarkers are routinely used in disease diagnosis, prognosis, ongoing clinical decision-making, and follow-up to assess effects of therapy. A framework for the validation of biomarkers was proposed by Boissel et al. (Boisell et al., 1992) and subsequently adapted by Espeland et al. (Espeland et al., 2005) in a discussion of the usefulness of carotid ultrasound to measure the clinical efficacy of lipid-lowering medications. Espeland et al. (Espeland et al., 2005), in modifying the terminology of Boissel et al. (Boisell et al., 1992), described clinical and statistical characteristics that a biomarker should have to be considered a surrogate marker of efficacy in atherosclerotic disease. Importantly, the clinical criteria outlined for validating surrogate markers are efficiency, linkage, and congruence. Taken together, these data suggest that four main factors are related to the development of effective biomarkers (Fry, 2010): 1. Analytical validity: the accuracy and precision with which a particular biomarker is identified by the Proposed test; 2. Clinical validity: the accuracy with which a test identifies or predicts a patient's clinical status; 3. Clinical utility: assessment of the risks and benefits, such as cost or patient outcome, resulting from the test; 4. Ethical, legal or social implications.
Several inflammatory and non-inflammatory soluble biomarkers have been widely investigated during the last two decades in the setting of CAD, including both stable and unstable pattern of clinical presentation. On the one hand, many of these biomarkers have been associated with the presence of CAD; on the other hand, they have been associated with the presence of "vulnerable" plaque, thus with an increased risk of cardiac death and non-fatal AMI, eventually stressing both their diagnostic and prognostic role. In this regard, intracoronary imaging modalities may help to understand the pathological role exerted by soluble biomarkers in the pathogenesis of CAD.

3. Inflammation

Recent research has shown that inflammation plays a key role in CAD and other manifestations of atherosclerosis. Immune cells dominate early atherosclerotic lesions, their effector molecules accelerate progression of the lesions, and activation of inflammation can elicit ACS.

3.1 C-reactive protein

C-reactive protein (CRP) was identified more than five decades ago as an acute-phase reactant that was capable of activating the complement system (Tillet & Francis, 1930; Abernathy & Avery, 1941). It was subsequently noted to be one of a number of acute-phase biomarkers, along with the erythrocyte sedimentation rate and complement, which was elevated in AMI (Boltax & Fischel, 1956). After the development of more sensitive, reliable, and readily available assays for CRP, a number of epidemiologic studies were conducted to assess the value of CRP in predicting cardiovascular risk (Ridker et al., 1997, 2001, 2002, 2005a, 2005b; Danesh et al., 2004; Koenig et al., 2004; Cushman et al., 2005). In a post-mortem study of 302 autopsies of men and women with atherosclerosis, median CRP levels were higher with acute plaque rupture than in stable plaques or controls (Burke et al., 2002). The levels correlated with the staining intensity for CRP in macrophages and the lipid core of plaques, and it increased with the number of thin cap atheromas found in coronary arteries. Moreover, plasma CRP levels at the upper end of the reference range in apparently healthy men and women, in the absence of other sources of inflammation, has been previously correlated with increased risk of future cardiovascular events, including MI, peripheral vascular disease with intermittent claudication and stroke (Ridker, 2001). These data support the view that systemic CRP accurately reflects the number of vulnerable atherosclerotic plaques. Liuzzo et al. (Liuzzo et al., 1994) reported that patients with UA and elevated levels of CRP (>3 mg/dl) had higher rates of death, AMI and need for revascularization compared to patients without elevated levels. Of note, this increased risk may be evident as early as 14 days after presentation (Morrow et al., 1998). Importantly, the U.S. Centers for Disease Control and Prevention and the American Heart Association have both advocated the use of CRP as an adjunct to global risk prediction among those at intermediate risk for CAD (Pearson et al., 2003). Thus, among non-specific markers of inflammation, CRP is the most investigated and has widely been associated with an increased risk of future cardiovascular events both in primary and secondary prevention studies (Willerson et al., 2004; Ridker et al., 1997, 2001, 2005a, 2005b; Haverkate et al., 1997). However, the association of CRP levels with angiographic coronary atherosclerotic burden is controversial, whereas its association with coronary instability has consistently been reported in several studies.

More than 15 years ago, Mori et al. (Mori et al., 1995) reported that baseline CRP levels were associated with the severity of CAD, as determined by the Gensini score and this association remained significant even after adjustment for body-mass index, smoking history, hypertension, and total cholesterol. Subsequently, Tataru et al. (Tataru et al., 2000) found a correlation between CRP levels and the number of diseased vessels in patients with a previous history of MI. Zebrack et al. (Zebrack et al., 2002) enrolled 2.554 patients with angina but without AMI who underwent CAG (1.848 patients had CAD and 706 patients did not). CAD was quantified in 5 ways and combined for a CAD score and CRP was measured in all patients who were followed for up to 5 years for death or MI. Interestingly,

CRP correlated with the extent of CAD, but correlation coefficients were low (0.02 to 0.08). Of angiographic measures, the CAD score best predicted future events. CRP retained predictive value within each quintile of CAD score. CRP and CAD independently and additively contributed to the risk prediction: low CRP and lowest CAD score were associated with lowest risk, and high CRP and highest CAD score were associated with the highest risk, with a 10-fold difference between extremes (2.5% vs. 24%). In conclusion, they demonstrated that CRP correlated with extent of CAD, but the degree of correlation was low, however, both severity/extent of CAD and CRP were independent and additive predictors of risk. Azar et al. measured CRP levels in 98 patients with stable angina or an abnormal stress test who were referred for diagnostic CAG. They showed that the CRP level did not correlate with the extent and severity of coronary narrowing measured by angiography (Azar et al., 2000). In the acute setting of CAD, Niccoli et al. (Niccoli et al., 2008) studied 97 consecutive patients with UA undergoing CAG and CRP was measured by an ultrasensitive nephelometric method. Atherosclerotic disease severity and extent were assessed by angiography using the Bogaty score. No significant correlation was found between baseline CRP serum levels and angiographic measures of atherosclerotic disease severity and extent. In this study, the authors demonstrated that in patients with UA, CRP serum levels and coronary atherosclerosis are not correlated, but they were both independently associated with a worse outcome at 6-month follow-up. In UA patients, the association between atherosclerotic background and CRP may be altered by the increase in CRP associated with the acute phase response. On the other hand, in vitro studies suggest that the proatherogenic role of CRP is associated with very high levels of serum CRP (up to 50 mg/L), much higher than that observed in patients with CAD or ACS (Devaraj et al., 2003).

Erren et al. (Erren et al., 1999) previously evaluated 147 patients undergoing semiquantitative CAG and they measured CRP, serum amyloid A (SAA), and the proinflammatory cytokine IL-6; the active and total fractions of the anti-inflammatory cytokine transforming growth factor-b (TGF-b); the macrophage activation marker neopterin; and the infection marker procalcitonin. Compared with 62 patients without either CAD or peripheral artery disease, 57 patients with CAD but no peripheral artery disease showed greater median CRP and IL-6 levels and a lower level of active-TGF-b. Moreover, CRP, IL-6, and neopterin levels showed a positive and the active TGF-b level a negative correlation with the extent of coronary atherosclerosis. Compared with these 57 patients with CAD alone, 15 patients with peripheral artery disease and CAD had higher median levels of SAA, IL-6, neopterin, and total TGF-b. However, these strong univariate associations of markers of inflammation and atherosclerosis were lost in multivariate analysis once age, sex, and HDL cholesterol or fibrinogen were taken into account. Taken together, these data suggest that increased plasma levels of CRP, SAA, IL-6, TGF-b, neopterin, and procalcitonin constitute an inflammatory signature of advanced atherosclerosis and are correlated with the extent of disease but do not provide discriminatory diagnostic power over and above established risk factors. Indeed, as previously mentioned, Lee et al. (Lee et al., 2006) reported on the associations between 3 plasma markers of low-gade inflammation, such as CRP, IL-6 and SAA protein and total homocysteine with CAD and death in a Canadian angiography cohort of 1.117 patients followed for 8.5 years. They found no significant association between elevated levels of these biomarkers and CAD (defined as the presence of any lesion with stenosis greater than 10%), but they did find significant independent associations of

elevated IL-6 (a key pro-inflammatory cytokine) and homocysteine levels with both CAD-related and all-cause death. These findings do not support the hypotheses that these biomarkers play a causal role in atherogenesis. The importance of this study is that no previous studies have examined such associations in a large, prospective angiographic cohort in which CAD was defined using sensitive criteria. However, it is worth noting that when Lee et al. used the definition of CAD as the presence of any lesion of 50% stenosis (which was developed for assessing suitability for cardiac surgery or angioplasty), they observed significantly higher CRP and IL-6 levels in the CAD group (Lowe et al., 2005).

On the other hand, several data suggest that CRP may be a marker of plaque activity (Liuzzo et al., 1994). In a previous report, Arroyo-Espliguero et al (Arroyo-Espliguero et al., 2004) sought to assess whether CRP was an independent predictor of future cardiovascular events after adjustment for CAD severity and whether CRP levels correlate with number of angiographically complex coronary artery stenosis. They studied 825 consecutive anginal patients (700 with chronic stable angina and 125 with ACS without ST-segment elevation). The composite endpoint of non-fatal AMI, hospital admission with class IIIb UA and cardiac death was assessed at 1 year follow-up. CRP levels were higher in chronic stable angina patients with the combined end-point ($p=0.03$) after adjustment for number of diseased coronary arteries. CRP was also significantly higher in patients with ACS compared to stable patients ($p=0.004$) and correlated with number of complex angiographic stenoses ($p=0.01$). Interestingly, in this report, CRP levels predicted future cardiovascular events independently of CAD severity and correlated with number of angiographically complex coronary artery stenosis in patients with ACS, thus suggesting that CRP levels may be a marker of atheromatous plaque vulnerability and CAD activity. This concept was endorsed by studies showing that CRP levels correlate with cardiovascular risk in ACS patients, thus giving further support to the increasingly accepted hypothesis that CRP is not merely a marker of systemic inflammation but may also be a pathogenic mechanism in ACS (Yeh et al., 2001; Pasceri et al., 2000; Zwaka et al., 2001). Additionally, the relation of serum CRP concentrations with adverse cardiovascular events during follow-up in patients with stable angina also suggests that clinical "stability" does not always indicate atheromatous plaque stability (van der Wal et al., 1999). Geluk et al. (Geluk et al., 2008) recently evaluated the population based on the Prevention of Renal and Vascular Endstage Disease (PREVEND) study. Of note, 8.139 subjects without previous documented CAD were followed for the incidence of CAD and coronary events from 1997 to 2003. In the prospective PREVEND study of subjects without previous documented CAD, CRP levels at baseline were associated with angiographic characteristics and clinical consequences of plaque instability during follow-up. Because CRP was weakly correlated with angiographic plaque burden, it was suggested that CRP is stimulated not only by the extent of atherosclerosis but, importantly, by other factors. Indeed, they postulated that CRP is a measure of inflammed, unstable atherosclerotic plaque (both angiographically visible and occult), whereas angiography indicates the extent of visible stable and unstable occlusive plaque. The value of CRP in predicting future death or MI was apparent in all ranges of CAD severity. Those with extensive CAD were at relatively high risk of death or MI regardless of CRP levels. However, in the presence of a low to moderate risk angiogram (or even a normal angiogram), CRP became particularly useful in distinguishing patients at substantially lower versus higher risk for death or MI. A particularly high risk was observed in subjects with lower CAD scores but highly elevated CRP despite a lower prevalence of all traditional

risk factors in these patients with low/moderate CAD scores (i.e., lower cholesterol levels, absence of diabetes, hypertension). Because these patients may be considered to have insignificant CAD and hence to be at low risk for MI, less aggressive medical therapy may be offered to them in comparison to patients with more extensive CAD, thus possibly underestimating their cardiovascular risk (Pearson et al., 2003; Lowe, 2005; Beaglehole & Magnus, 2002; Greenland & O'Malley, 2005).

With the introduction of IVUS, new important data regarding CRP levels and CAD burden and, especially, plaque morphology have been provided, shedding some lights on CRP diagnostic and prognostic role in CAD patients. Sano et al. (Sano et al., 2003) investigated the relation between lesion morphology as seen under pre-intervention IVUS and CRP in 90 consecutive patients presenting with AMI. Patients were divided into an elevated CRP group (≥3 mg/L) or a normal CRP group on the basis of serum CRP levels. There were no differences in patient characteristics or angiographic findings. Interestingly, they observed significantly more plaque rupture in the elevated CRP group than in the normal CRP group (70% versus 43%, p=0.01). A multivariate logistic regression model revealed that the presence of ruptured plaque alone correlated with elevation of serum CRP (p=0.02; odds ratio, 3.35; 95% CI, 1.22 to 9.18). These data further suggest that in the setting of AMI, elevated CRP levels may reflect the inflammatory activity of a ruptured plaque. Additionally, Sano et al. (Sano et al., 2003) found that in the normal CRP group, 44% of analyzed lesions were non–rupture-type lesions. Indeed, several pathological reports showed that AMI may be caused not only by plaque rupture but also by plaque erosion, which is a major substrate for coronary thrombosis in AMI (van der Wal et al., 1994; Farb et al., 1996; Arbustini et al., 1999). A more recent IVUS study (Otake et al., 2008) investigated the relation between plasma CRP and adiponectin and coronary plaque components in patients with ACS. Ninety-three culprit plaques (ACS n=50, non-ACS n=43) and 56 nonculprit plaques (ACS n=28, non-ACS n=28) were analyzed using virtual histology (VH)-IVUS to examine relations among plasma CRP, adiponectin, and ratios of each coronary plaque component. Plasma adiponectin was significantly lower and plasma CRP was significantly higher in patients with than without ACS. Notably, culprit plaques in patients with ACS had greater amounts of necrotic core plaque than those in patients without ACS. There was an inverse relation between CRP and adiponectin with regard to necrotic core ratio in both culprit and nonculprit lesions in patients with ACS, but not those without ACS. Thus, once again, increased plasma CRP levels might be related to the progression of ACS. Zhang et al. (Zhang et al., 2006) performed IVUS examination in 152 patients with confirmed CAD before percutaneous coronary intervention and measured CRP levels in all patients. Unstable and ruptured plaque were found more frequently in patients with AMI and UA. The levels of plasma CRP were higher in ruptured plaque group. CRP >8.94 mg/L was used to predict ruptured plaque with a ROC curve area of 0.76 (95% confidence interval, 67.0%-85.8%), sensitivity of 71.8%, specificity of 77.0% and accuracy of 69.2% (p<0.01). Chen et al. (Chen et al., 2007) aimed at investigating whether combined IVUS and measurements of serum inflammatory biomarkers could predict coronary plaque ruptures in patients with angina pectoris. The study population consisted of 20 patients with stable angina and 40 patients with UA. IVUS was performed in the 2 groups to measure intima-media thickness, the plaque acoustic density of the common carotid arteries, and the flow-mediated dilation of the brachial arteries. Serum lipid profile and inflammatory biomarkers were measured in all patients. Of 139 coronary artery plaques identified by IVUS, 48

plaques (9 in stable angina and 39 in UA) developed ruptures. Among measured parameters, they found that the values of carotid intima-media thickness, coronary external elastic membrane area, plaque area, plaque burden, plaque eccentric index and remodeling index, and serum CRP were significantly higher in UA patients than in stable angina patients ($p<0.05$ to 0.01). Additionally, they found that soluble intercellular adhesion molecule-1, and soluble vascular cell adhesion molecule-1 were significantly higher in UA patients ($p<0.05$). However, of these parameters, carotid intima-media thickness, serum CRP, and the coronary remodeling index, only, were found to be significant predictors of coronary plaque rupture, with odds ratios of 9.51 (95% confidence interval 1.29 to 21.81), 3.02 (95% confidence interval 1.01 to 7.65), and 0.01 (95% confidence interval 0.00 to 0.34), respectively. Taken together, these data suggest the intriguing possibility that the association between CRP and risk of cardiovascular events is mediated by unstable plaque phenotype, raising the possibility that CRP is not only a marker of vascular inflammation but also of plaque disruption. However, Park et al. (Park et al., 2010) recently enrolled 188 patients who underwent 3-vessel VH-IVUS with peripheral blood sampling, including CRP levels measurements. VH-TCFA was defined as a necrotic core >10% of plaque area in the presence of >40% plaque burden. There were 38 patients with ruptured plaque and 150 patients without (107 patients with VH-TCFA, 43 patients without VH-TCFA) in culprit/target lesions. In the present study there were no significant differences in the CRP level between patients with and without VH-TCFA in the culprit/target lesions. However, it is worth mentioning that when lesions are analyzed post-rupture, after the necrotic core may have embolized, they most often appear "dark-green" and will be classified as fibrotic plaque rather than necrotic core in VH-IVUS analysis, and have a reduced calculated relative size of the necrotic core. Therefore, when the relationships between each plaque characteristic and plasma biomarker levels, including CRP, were evaluated in the study performed by Park et al. (Park et al., 2010), ruptured plaques were excluded to avoid the possibility of incorrect VH-IVUS interpretation and this may partially explain the different results between studies.

Takano et al. (Takano et al., 2005) have evaluated, using coronary angioscopy, changes of ruptured plaques in non culprit lesions in living patients and ability of CRP to predict disease activity of the plaque ruptures, also shown in other previous studies (Ishibashi et al., 2002). They have identified by angioscopy 48 thrombi in 50 ruptured coronary plaques in nonculprit lesions in 30 patients with mean angioscopic follow-up period was 13 +/- 9 months. They have shown that ruptured plaques in nonculprit lesions tend to heal slowly with a progression of angiographic stenosis and the serum CRP level in patients with healed plaques was lower than that in those without healed plaques, although in patients with healed plaques did not significantly decrease from baseline to follow-up. Of note, at univariate logistic regression, serum CRP levels at follow-up were predictors of healing in nonculprit ruptured plaques, while, a multivariate logistic regression analysis, the authors showed that serum CRP levels at follow-up were not independent predictors of plaque healing. Thus, the power of serum levels of CRP in predicting disease activity should also be confirmed. Furthermore, the same authors have previously reported that statin therapy reduces the serum CRP level and angioscopic complexity of the plaques (the existence of the thrombus and the irregularity of the plaque) in nonculprit lesions (Takano et al., 2003). In this study, data from univariate logistic regression analyses indicated that both statin therapy and serum CRP level at follow-up are considered predictors of healing in nonculprit ruptured plaques. However, a multivariate logistic regression analysis showed

that neither statin therapy nor serum CRP level at follow-up is an independent predictor of plaque healing. These findings, however, should be confirmed in larger study populations.

A study by Tanaka et al. (Tanaka et al., 2008) enrolled 43 consecutive ACS patients (with or without ST-segment elevation) undergoing OCT assessment and presenting with a ruptured plaque at the culprit site. Patients were divided into a rest group and an exertion group on the basis of their activities at the onset of ACS. Of interest, the thickness of the broken fibrous cap correlated positively with activity at the onset of ACS. The culprit plaque ruptured at the shoulder more frequently in the exertion group than in the rest group (rest 57% versus exertion 93%, $p=0.014$). The thickness of the broken fibrous cap in the exertion group was significantly higher than in the rest-onset group (rest onset: 50 μm [interquartile median 15 μm]; exertion: 90 μm [interquartile median 65 μm], $p<0.01$). These data suggest a thin-cap fibroatheroma (TCFA) is a lesion predisposed to rupture both at rest and during the patient's day-to day activity, and some plaque rupture may occur in thick fibrous caps depending on exertion levels. Moreover, this study demonstrated also an inverse relationship between fibrous cap thickness and serum levels of CRP ($r=-0.31$, $p<0.01$). Li et al. (Li et al., 2010) investigated in stable and unstable patients the relationship between plaque morphology assessed by OCT and serum levels of several inflammatory biomarkers, such as CRP, IL-18, TNF-α, white blood cell count. This study demonstrated that the plasma levels of inflammatory factors and white blood cell count were correlated inversely with fibrous cap thickness ($r=0.775$ for CRP, $r=-0.593$ for IL-18, $r=-0.60$ for TNF-α, and $r=-0.356$ for white blood cell count). Patients with TCFA (cap thickness less than 65 micron) had higher plasma levels of inflammatory factors as well as WBC counts than those with thicker fibrous caps. ROC curves for CRP, IL-18, TNF-α and white blood cell count, which displayed the capability of prediction about TCFA, showed the area under the curves were 0.95, 0.86, 0.79 and 0.70 ($p<0.05$), respectively. Meanwhile, in multivariate logistic regression analysis, CRP was the only significant independent predictor of TCFA. Therefore, although IL-18, TNF-α and white blood cell count could also show similar characteristics, their predictive value was weak compared with CRP.

Kashiwagi et al. (Kashiwagi et al., 2009) evaluated the relationship between coronary arterial remodelling assessed by IVUS, fibrous cap thickness assessed by OCT and CRP concentrations in patients with ACS. Positive remodelling was defined as remodelling>1.05, intermediate remodelling as remodelling=0.95–1.05, and negative remodelling as remodelling<0.95. On the basis of the IVUS findings, patients were divided into 2 groups (positive remodelling group, intermediate remodelling/negative remodelling group). Lipid-rich plaques and TCFA were more frequent in the positive remodelling group than in the other group and intermediate remodelling inversely correlated with the thickness of fibrous cap. Levels of CRP were higher in the positive remodelling group than in the other group and were higher in patients with a thin fibrous cap, suggesting that the inflammatory process may simultaneously contribute to both plaque growth and plaque instability.

Kitabata et al. (Kitabata et al., 2010) investigated in stable and ACS patients the relationship between the presence of microchannels in coronary plaque assessed by OCT and serum CRP levels. Microchannel was defined as a no-signal tubuloluminal structure on the cross-sectional OCT image. Microchannels were found in 24 (38%) of the 63 enrolled patients and patients were divided into 2 groups according to the presence or absence of microchannels. The frequency of plaque rupture tended to be greater in the microchannel group (50% vs

28%, p=0.11). The thickness of the fibrous cap (median 60 vs 100 micron, p=0.001) was significantly lower in the patients with microchannels, and significant differences were found in the frequency of thin-cap fibroatheroma (54% vs 21%, p=0.012) and positive remodeling (67% vs 36%, p=0.02) between the 2 groups. CRP levels in the microchannel group were significantly greater than those in the no-microchannel group (median 0.27 vs 0.13 mg/dl, p=0.015). Moreover, increased microchannel counts were associated with greater high-sensitivity CRP levels (p=0.01). Takarada et al. (Takarada et al., 2010) enrolled 82 Non-ST-elevation-ACS patients undergoing OCT assessment of culprit lesion at baseline and after 9 months, evaluating morphological changes of coronary plaque and changes in serum levels of CRP. Of interest, the change in fibrous cap thickness had a significant positive correlation with changes in CRP levels (r=0.44, p<0.01). A recently published study by Ferrante et al. (Ferrante et al., 2010) enrolled 25 consecutive ACS patients undergoing percutaneous coronary intervention and OCT assessment, evaluating the relationship between plaque morphology and serum levels of myeloperoxidase (MPO) and CRP. OCT classified the culprit lesion as ruptured in 18 (72%) or eroded in 7 patients (28%) and detected intraluminal thrombus in 89% of ruptured plaques and 100% of eroded plaques. CRP levels did not differ significantly between patients with an eroded plaque and those with a ruptured plaque (median, 11.3 mg/L; 25th to 75th percentile, 1.3 to 28.5 versus median, 3.9 mg/L; 25th to 75th percentile, 1.3 to 17.8; p=0.76, respectively). On the contrary, a study by Bouki et al. (Bouki et al., 2010) showed that higher levels of serum CRP and IL-18 were found in patients with plaque rupture vs. those with no plaque rupture (median value: 19.2mg/L vs. 1.6mg/L, p<0.001 and 219.5pg/ml versus 127.5pg/ml, p=0.001 respectively), and TCFA versus those without TCFA (median value: 15.2mg/L versus 1.6mg/L, p=0.004 and 209.0pg/ml versus 153.2pg/ml, p=0.03, respectively). Moreover, serum CRP was the only independent predictor of plaque rupture (p=0.02, odds ratio 1.1, 95% confidence interval 1.0 to 1.2), and a cut-off value of CRP>4.5mg/L could detect ruptured plaque with a sensitivity of 91.7% and a specificity of 77.8%. Taken together, these data show that the association of CRP levels with coronary atherosclerotic burden is still controversial, whereas its association with coronary instability has consistently been reported in several studies, by using different intracoronary imaging modalities. Although initially considered only a marker of inflammation, CRP itself has been shown to possess proinflammatory and pro-atherogenic properties. It stimulates endothelial cells to express adhesion molecules and secrete cytokines (Pasceri et al., 2000, 2001) and it decreases the expression of endothelial nitric oxide synthase (Verma et al., 2002; Venugopal et al, 2002). CRP accumulates in macrophage-rich regions of nascent atherosclerotic lesions and activates the macrophages to express cytokines and tissue factor, while enhancing macrophage uptake of LDL (Zwaka et al., 2001). It also amplifies pro-inflammatory effects of several other mediators including endotoxin (Nakogomi et al., 2000; Burke et al., 2002). These biological properties exerted by CRP may be held responsible for the detrimental role of this acute-phase reactant which may participate in the unstable patter of CAD.

To date, there are no widely accepted and established markers of inflammation for cardiovascular disease and no known therapeutic measures to modulate coronary inflammation. CRP is currently the best marker of inflammation, and in addition to weight loss, exercise, and smoking cessation, statins are the best therapeutic option to modulate inflammation. New avenues for diagnosing and treating coronary inflammation should be investigated in larger and randomized trials.

3.2 Fibrinogen

With improved understanding of the critical role of inflammation in atherothrombosis, attention has been focused on the circulating markers of inflammation, including fibrinogen (Ross, 1993; 1999; Lind, 2003). Evidence has been accumulated from several prospective studies that showed that high levels of fibrinogen were associated with an increased risk of coronary, cerebral and peripheral disease (Maresca et al., 1999; Danesh et al., 2004; Tamam et al., 2005). In a prospective study, Espinola-Klein et al. (Espinola-Klein et al. 2007) enrolled 720 patients preceding CAG. Patients were compared with regard to atherosclerotic burden and classified as follows: no clinically significant stenosis (n=57, 7.9%), CAD only (n=362, 50.3%), CAD with peripheral atherosclerosis (=multi-vascular atherosclerosis, n=301, 41.8%). They found a significant association between elevation of CRP and atherosclerotic burden (control: 2.6 (1.4–6.8) mg/l; CAD: 4.5 (2.1–12.1) mg/l; multi-vascular: 5.2 (2.0–15.6) mg/l, $p<0.001$). Results were similar with regard to IL-6 according to the extent of atherosclerosis (control: 7.8 (4.0–13.2) ng/ml; CAD: 11.4 (5.2–22.8) ng/ml; multi-vascular: 12.5 (5.8–24.5) ng/ml, $p<0.001$). The strongest association was registered, indeed, between elevation of fibrinogen and extent of atherosclerosis (control: 296.0 (256.0–326.5) mg/dl; CAD: 329.0 (281.8–399.3) mg/dl; multi-vascular: 351.0 (289.5–434.5) mg/dl, $p<0.0001$). Additionally, follow-up data after a median of 6.5 years were available in 719 patients (99.9%), and 75 patients (10.4%) died from cardiovascular causes. Presence of multi-vascular atherosclerosis, elevation of IL-18 and elevation of fibrinogen were independently related to cardiovascular death in a fully adjusted model Hazard ratio (95% confidence interval) 2.0 (1.2-3.5) for presence of multi-vascular atherosclerosis ($p<0.01$), 2.2 (1.2-3.9) for high fibrinogen ($p<0.01$) and 2.8 (1.6-4.9) for high IL-18 ($p<0.0001$). Fibrinogen was achieved as independent predictor for both, mortality and atherosclerotic burden, whereas IL-18 was not related to atherosclerotic burden. These data suggest that fibrinogen was the only inflammatory marker with an independent association to the extent of atherosclerosis in the arterial vessel three. Previous investigations found also a strong interdependence between high serum fibrinogen levels and severe peripheral occlusive disease, indicating advanced atherosclerosis (Wattanakit et al., 2005). Presumably, the predictive value of high fibrinogen level is caused by the association to high atherosclerotic burden which is predictive for a worse prognosis itself. Concordantly, Hoffmeister et al. (Hoffmeister et al., 2001) previously conducted a case-control study to assess the association between various markers of inflammation and the presence and severity of chronic stable CAD. They included 312 clinically stable patients with angiographically documented CAD, and the severity of CAD was evaluated by 3 coronary scoring systems: the clinical 1- to 3-vessel disease score, the American Heart Association extension score (1 to 15 segments), and the Gensini score. Fibrinogen levels were highly significantly elevated ($p<0.005$) in patients with stable CAD compared with controls. After multivariable adjustment by means of logistic regression analysis, the association between CAD and fibrinogen remained substantial. However, no association between fibrinogen levels and any of the coronary scores applied was found. Finally, Memon et al. (Memon et al., 2006) measured plasma fibrinogen levels in 138 patients with angiographically assessed CAD and in 183 healthy subjects matched according to age and gender. According to the number of significantly stenosed (>or=50%) vessels, the patients were classified in four groups: those without stenosis (0-vessel disease) and those with 1, 2 or 3-vessel disease. Fibrinogen levels were significantly higher in patients than in controls ($p<0.001$). Although fibrinogen levels tended to increase with the number of stenotic vessels, the differences were not statistical significant.

Taken together these data suggest that fibrinogen can be discussed as a serological marker of high atherosclerotic burden within arterial vessel tree and may be a screening marker to identify patients that should be evaluated carefully for atherosclerotic manifestations.

3.3 Eosinophil cationic protein

Leukocyte recruitment and expression of proinflammatory cytokines characterize all steps of atherothrombosis (Libby & Theroux, 2005). Recent observations suggest that eosinophils may play a role in coronary atherosclerosis. Indeed, prospective studies have consistently shown an association between eosinophil count and increased risk for future cardiovascular events (Prentice et al., 1982; Lee et al., 2001). Furthermore, eotaxin, an eosinophil-specific chemoattractant, is overexpressed in human atherosclerotic lesions (Haley et al., 2000) and patients with CAD show higher circulating levels of eotaxin as compared to healthy controls (Economou et al., 2001; Emanuele et al., 2006). Accordingly, a nonconservative polymorphism in the eotaxin gene (Zee et al., 2004) together with sequence variants affecting eosinophil count (Gudbjartsson et al., 2009) have recently been associated with an increased risk of myocardial infarction. Eosinophil cationic protein (ECP) is a zinc-containing, highly cationic protein, stored in the peroxidase-positive and negative eosinophil granules which is secreted through priming by various triggers, such as immunoglobulins and complement components (Venge et al., 1999). Several studies have shown that the measurement of ECP in most biological fluids may be used as a marker of eosinophil activity and turnover, and that increased ECP serum levels are related to the presence, activity and severity of asthma, atopic disorders, and other immune diseases, such as rheumatoid arthritis, psoriasis, and adult celiac disease (Hällgren et al., 1991). In this regard, the role of ECP in CAD has been recently assessed (Niccoli et al., 2010). One-hundred and ninety-eight consecutive anginal patients with angiographic evidence of CAD (stable angina or non-ST-elevation-ACS), or with angiographically normal coronary arteries were enrolled. The severity of CAD was graded according to Bogaty's score and coronary lesion morphology was defined as smooth or complex. Baseline ECP and high sensitivity CRP were measured in all patients. ECP levels were significantly higher in stable angina patients ($p<0.001$) and non-ST elevation-ACS ($p=0.016$) compared to patients with normal coronary arteries, without significant difference between stable and unstable patients ($p=0.45$). Additionally, CRP levels were significantly higher in unstable patients compared to stable patients ($p=0.03$) and normal coronary arteries patients ($p<0.001$), without significant difference between stable and normal coronary arteries patients ($p=0.20$). The addition of ECP to main cardiovascular risk factors improved the area under the curve from 0.88 to 0.92, $p=0.007$ for the angiographic diagnosis of CAD; further addition of CRP increased the area to 0.94, $p=0.014$. At multiple linear regression analysis, ECP levels independently predicted CAD severity ($p=0.001$), whereas CRP levels independently predicted lesion complexity ($p=0.01$). Taken together, these data suggest that ECP is a marker of CAD and that different inflammatory biomarkers reflect different phases of atherosclerotic plaque evolution (Niccoli et al., 2010). Further studies should address the role of ECP in CAD on larger study populations.

3.4 Myeloperoxidase

MPO is a member of the peroxidise superfamily that is predominantly found in neutrophils, monocytes and tissue macrophages and is released upon their activation as a response to

various stimuli (Nicholls et al., 2005). The enzyme is part of an innate host defence that acts on its substrate hydrogen peroxide of various sources augmenting its oxidative potential by producing potent oxidative species capable of modifying various cellular components by chlorination, nitration and cross-linking (Podrez et al., 2000; Heinecke et al., 2003). Demonstrations that MPO and its oxidation products are enriched within human atheroma (Daugherty et al., 2004) has increased interest in this enzyme in directions such as its participation in the promotion of atherosclerosis (Hazen et al., 1997), destabilization of atherosclerotic plaque (Sugiyama et al., 2001, 2004; Naruko et al., 2002) and in the possibility that MPO can serve as a biomarker to predict future adverse events in patients with CAD (Baldus et al., 2003; Brennan et al., 2003). Clinical studies have shown that plasma levels of MPO are increased in patients with stable CAD (Zhang et al., 2001) , ACS (Baldus et al., 2003; Brennan et al., 2003), and ST-segment elevation AMI (Mocatta et al., 2007; Khan et al., 2007). Other studies have proven that neutrophils, the main source of MPO release, are activated in ACS; however, their activation has not been linked with ischaemia/reperfusion per se (Biasucci et al., 1996). Furthermore, some observational studies have shown that baseline MPO plasma levels are predictive of future adverse coronary events in patients with acute chest pain (Brennan et al., 2003) or ACS (Baldus et al., 2003; Cavusoglu et al., 2007) regardless of troponin levels.

Ndrepepa et al. (Ndrepepa et al., 2008) recently conducted a case–control study in which 874 patients with angiographically proven CAD were included. Cases included 680 patients with CAD (382 patients with stable CAD, 107 patients with non-ST-segment elevation-ACS and 191 patients with ST-segment elevation AMI), while controls included 194 subjects with normal coronary angiograms. MPO was measured using an enzyme immunoassay before angiography and heparin administration. MPO levels were significantly higher in cases as compared to controls ($p<0.001$). MPO levels were significantly higher in patients with AMI as compared to patients with stable CAD and with non-ST-segment elevation-ACS ($p<0.0001$). Elevated MPO level was associated with ACS with an area under receiver operating characteristic curve of 0.731 (95% confidence interval 0.692–0.770; $p<0.001$). Independent correlates of MPO level were ACS ($p<0.001$), CRP ($p=0.007$), creatinine ($p=0.026$), left ventricular ejection fraction ($p=0.027$, negative association) and smoking ($p=0.028$). Taken together, these data suggest that MPO level is elevated in patients with CAD and higher levels of MPO may be found with progression of CAD from stable CAD to non-ST-segment elevation ACS and to AMI. In a recent study, Wainstein et al. (Wainstein et al., 2010) have demonstrated that, in stable CAD, there was no association between MPO polymorphism and CAD severity, although a relationship was observed between plasma MPO levels and extent of CAD. de Azevedo et al. (de Azevedo et al., 2011) recently tested the hypothesis that MPO levels are higher in ACS patients with a greater extent of angiographic coronary involvement, by performing a cross-sectional study, examining high risk ACS patients who underwent CAG within 72 hours of the onset of symptoms and measuring their plasma MPO levels after sheath insertion. Gensini score was used to evaluate angiographic severity of CAD in 48 patients. Spearman's correlation coefficient did not show a significant association between MPO levels and Gensini scores ($r=0.2$; $p=0.177$). There was no correlation between MPO and age, hypertension, diabetes, leukocyte count, troponin I, CK-MB, TIMI risk score C4 and Gensini score in the multivariate analysis. These findings indicate that MPO expression may not be associated with anatomical severity of

coronary lesions in ACS. However, in a previous study (Düzgünçinar et al., 2008), 48 stable CAD patients with angiographically documented coronary lesions were enrolled and the authors demonstrated a weak, but statistically significant association between MPO levels and Gensini score (r=0.228; p=0.04). Of note, they found a stronger association between MPO levels and calcium scores by multislice computed tomography in 30 patients (p=0.02). In another study, MPO levels were considered independent predictors of multivessel disease in 389 unselected stable and unstable patients referred for CAG (Cavusoglu et al., 2006). On the other hand, Kubala et al. (Kubala et al., 2008) evaluated 557 clinically stable patients submitted to CAG and did not find a significant difference in MPO levels between patients with documented CAD (at least 1 vessel with 50% stenosis) and patients without CAD. Finally, in a recently published cross-sectional study, after evaluating 118 stable CAD patients, a lack of association between MPO promoter polymorphism and angiographic severity of coronary atherosclerosis was observed (Wainstein et al., 2010). Nevertheless, as a secondary objective, that study revealed a trend toward greater angiographic severity of CAD among patients with plasma MPO levels in the upper range (Wainstein et al., 2010). The lack of association might be attributed to the fact that angiography-based Gensini scores provide information on anatomical severity, hindering a functional and morphological analysis of the atherosclerotic plaque. A recently published study by Ferrante et al. (Ferrante et al., 2010) enrolled 25 consecutive ACS patients undergoing PCI and OCT assessment, evaluating the relationship between plaque morphology and serum levels of myeloperoxidase (MPO) and CRP. OCT classified the culprit lesion as ruptured in 18 (72%) or eroded in 7 patients (28%) and detected intraluminal thrombus in 89% of ruptured plaques and 100% of eroded plaques. Baseline systemic levels of serum MPO were significantly higher in patients with an eroded plaque than in those with a ruptured plaque (median, 2500 ng/mL; 25th to 75th percentile, 1415 to 2920 versus median, 707 ng/mL; 25th to 75th percentile, 312 to 943; p=0.001), whereas CRP levels did not differ significantly (median, 11.3 mg/L; 25th to 75th percentile, 1.3 to 28.5 versus median, 3.9 mg/L; 25th to 75th percentile, 1.3 to 17.8; p=0.76, respectively). In addition, the same study showed that the density of MPO-positive cells within thrombi overlying plaques in postmortem coronary specimens retrieved from sudden coronary death victims was significantly higher in lesions with erosion (n=11) than ruptures (n=11) (median, 1584; 25th to 75th percentile, 1088 to 2135 cells/mm2 versus median, 579; 25th to 75th percentile, 442 to 760 cells/mm2; p=0.0012). Of importance, this study supports the concept that elevations in specific inflammatory biomarkers reflect different morphologies of complications of coronary atherosclerosis and highlights the heterogeneity of coronary mechanisms of ACS.

Taken together, these data suggest a controversial role of MPO for CAD burden, while an involvement in disease activity seems to be clear. However, this issue should be investigated in larger studies and, again, IVUS and OCT may play a crucial role in the accurate assessment of plaque vulnerability.

3.5 Matrix metalloproteinases

In human atherosclerosis, unstable atherosclerotic plaque is an important event that triggers ACS. Plaque rupture frequently correlates with loss of the extracellular matrix at certain locations, often in the shoulder areas of the plaque. Focal destruction of the extracellular matrix renders the plaque less resistant to mechanical stresses imposed

during systole and therefore vulnerable to rupture. Recent findings have revealed enhanced expression of matrix metalloproteinases (MMPs) in the vulnerable region of plaques and this contributes to the weakening of plaque caps by degrading the extracellular matrix.

MMPs are a family of zinc-containing endoproteinases that share structural domains but differ in substrate specificity, cellular sources, and inducibility. The list of MMPs has grown rapidly in the past several years, and by now >20 mammalian members have been cloned and identified. The members of the MMP family can degrade all of the components of the blood vessel wall and therefore play a major role in both physiologic and pathologic events that involve the degradation of extracellular matrix components.

In recent studies using knockout mice, electrical injury of femoral arteries in mice which stimulates intimal thickening, caused enhanced expression of MMP-2 and MMP-9 (Lijnen et al., 1998). In TIMP-1-deficient mice intimal thickening was significantly higher compared with that in wild-type controls (Lijnen et al., 1999) Together, these observations support a role for MMP involvement in intimal thickening, particularly in migration of vascular smooth muscle cells. Previous studies demonstrated that lipid-laden macrophages from human atherosclerotic plaque elaborate MMP-1 and MMP-3 (Galis et al., 1995) and culture of macrophages with fibrous caps of human atherosclerotic plaque induces MMP-dependent collagen breakdown (Shah et al., 1995). Other researchers have also detected the expression of several other MMPs including MMP-1, MMP-2, MMP-7, MMP-9, and MMP-12 in the shoulder areas of plaque (Shu et al., 1998). Brown et al. (Brown et al., 1995) reported that MMP-9 was commonly expressed in coronary atherectomy specimens from patients with recent plaque rupture. Kai et al. (Kai et al., 1998) reported that circulating MMP-2 and MMP-9 levels on admission were elevated in patients with AMI and UA. Inokubo et al. (Inokubo et al., 2001) also reported that plasma levels of MMP-9 were significantly increased in the coronary circulation in patients with AMI and UA compared with those in control subjects, suggesting a process of active plaque rupture in ACS. Hirohata et al. (Hirohata et al., 1997) also observed increased plasma MMP-1 and MMP-2 levels, respectively, in patients with AMI. Thus, increased MMP expression may modulate vascular and ventricular remodeling in ACS.

Wang et al. (Wang et al., 2008) evaluated the vulnerability of coronary artery plaque with CAG, IVUS and the levels of plasma inflammatory markers in 58 consecutive patients with lesion of a single blood vessel demonstrated by CAG. Patients were randomly divided into 3 groups based on the angiographic morphology of the lesions: type I lesion group (n=16), type II lesion group (n=25), type III lesion group (n=17). A control group of stable angina (n=17) was established. A subgroup of 28 patients (including 18 ACS patients and 10 stable angina control patients) who underwent IVUS study were analyzed. Then the plasma levels of MMP, including MMP-2 and MMP-9, CD40L and PAPP-A were measured with ELISA, along with CRP levels. The plasma levels of MMP-2, MMP-9 and PAPP-A in type II lesion group were significantly higher than the other groups ($p< 0.05, 0.05, 0.001$, respectively). In type II lesion group, linear correlation analysis manifested significantly positive correlation between levels of CRP and MMP-2 ($r=0.508$); MMP-2 and MMP-9, CD40L, PAPP-A ($r=0.647$, 0.704, 0.751, respectively); MMP-9 and CD40L, PAPP-A ($r=0.491$, 0.639, respectively); CD40L and PAPP-A ($r=0.896$). IVUS subgroup analysis showed that the area of plaques and plaques burden in culprit lesion, the incidence of high-risk plaques, remodeling index and positive remodeling percentage in ACS patients were significantly greater than those in the

control group (p=0.0001, 0.037, 0.028, 0.015, 0.040, respectively). Compared with the control group, the plasma levels of CRP, MMP-2, MMP-9 and PAPP-A were markedly elevated (p=0.033, 0.0001, 0.0001, 0.027, respectively).

Park et al. (Park et al., 2010) recently enrolled 188 patients who underwent 3-vessel VH-IVUS with peripheral blood sampling, including plasma levels of MMP-2,-9, tissue inhibitor of metalloproteinase-1, adiponectin, macrophage migration inhibitory factor, along with CRP levels measurements. Among the biomarkers, only the MMP-9 level was significantly higher in patients with ruptured plaque (p=0.002). In the subgroup without ruptured plaque, significant differences in the levels of several biomarkers were not observed between patients with and without VH-TCFA. In both culprit/target and nonculprit/non-target vessels, the MMP-9 level showed a weak correlation with the total number of ruptured plaques (r=0.231, p=0.002). Among the biomarkers tested in this study, the MMP-9 level was significantly higher in patients with ruptured plaque. However, measurement of several biomarkers, including MMP-9, was incapable of predicting the presence of VH-TCFA. This 3-vessel VH-IVUS study of 188 patients showed that the plasma level of MMP-9 might increase in patients with multiple ruptured plaques, as well as in patients with ruptured plaque in the culprit/target lesions. Both acute coronary syndrome and the MMP-9 level were independent predictors of ruptured plaque in the culprit/target lesions. However, the presence of VH-TCFA in the culprit/target lesions or multiple VH-TCFAs detected by 3-vessel VH-IVUS study were not be predictive with the use of several biomarker assays, including MMP-9, in this study. The clinical presentation of ACS, not the level of the biomarkers, was the only independent predictor of VH-TCFA in the culprit/target lesions. MMPs belong to a family of multidomain zinc-dependent endopeptidases that promote degradation of all protein and proteoglycan–core-protein components of the extracellular matrix (Galis et al., 2002). Among the family of MMPs, MMP-2 and MMP-9 are found in the macrophages and smooth muscle cells covering the shoulder region of atherosclerotic plaque (Galis et al., 1994). MMP-9 and MMP-2 are highly expressed in the vulnerable regions of atherosclerotic plaque and it has been suggested that they are causally involved in plaque rupture (Lijnen et al., 2003). Other studies have shown that the level of MMP-2 activity is higher in stable lesions of carotid artery plaque (Sluijter et al., 2006) and that the level of MMP-9 is increased in more unstable plaque (Sluijter et al., 2006, Lotus et al., 2000). Blakenberg and collegues reported that a higher level of plasma MMP-9 was a predictor of cardiovascular mortality: the patients in the highest quartile of MMP-9 level (>72 ng/ml) had the highest probability of cardiovascular death (Blankenberg et al., 2003). Taken together, these data suggest that MMP-9 has a more significant role in plaque vulnerability than MMP-2, but more clinical studies are required to evaluate the exact role of MMP-2 in plaque vulnerability. Thus, CAG and IVUS combined with the study on plasma levels of inflammation mediators were helpful in judging the vulnerability of coronary artery plaques.

Matrix metalloproteinases play a crucial role in initiating ACS by degrading extracellular matrix components, which leads to vulnerability of the plaque as well as formation of atherosclerotic lesions. Although the use of MMP inhibitors may have unforeseen adverse effects if used in the wrong setting, development of therapeutic drugs specifically targeted against MMPs may be useful in the prevention of atherosclerotic lesion development and cardiac events.

4. Lipidics

Inflammation, neovascularisation, imbalance between coagulation and anticoagulation system are interesting aspects (Ross et al.,1993; Katagiri et al., 2007; Glass et al., 2001), but another one is that of lipid system and coronary plaque.

4.1 Lipid profile

One of the major predisposing factors to atherosclerosis is an abnormal lipoprotein metabolism and it may be present in over 70% of patients with premature CAD (Genest et al., 2005).

The association between CAD and levels of total cholesterol, LDL and low HDL has been proven and widely accepted in diagnostic practice. As a consequence the National Cholesterol Education Program III (NCEP III) recommended the analysis of Tc in combination with LDL and HDL-c as a basis for the screening and treatment of patients with CAD. High concentration of LDL cholesterol and lipoprotein (a) or low levels of HDL cholesterol are able to promote atheroma formation and are recognised as particularly important risk factors for atherosclerosis and CAD (Rosenson, 1996; . Grundy et al., 1989; LaRosa et al., 1990; v et al., 1994). Of note, randomised trials showed that LDL reduction decreases mortality and coronary events both in a primary and in a secondary prevention (Shepherd et al., 1995, Sacks et al., 1996). It was found that the reduction in non-fatal MI and CAD death was strongly correlated with the small incremented serum HDL-cholesterol level (Robins et al., 2001). An independent association of triglycerides (TG) with atherosclerosis and/or CAD remains uncertain. Some studies suggest that TG level does not influence the CAD risk whereas others provide some proofs that it does (Avins & Neuhaus, 2000). Ten years ago it was suggested that there is an inverse association between HDL level and the number of diseased coronary vessels (Romm et al., 1991). However, some other studies manifested that there is no association of CAD severity with lipid concentration (Lekakis et al., 2000; Cerne et al., 2000). This conflicting data persuaded Tarchalski et al. (Tarchalski et al., 2003) to perform a prospective study for evaluation of the relationship between serum lipid levels and the extent of atherosclerosis within coronary arteries in patients with suspected CAD and no previous MI, and who were not treated with lipids lowering therapy before entering the study. The study was conducted in 141 patients (53.6 ± 7.8 years old; 32 female) who underwent a routine CAG for CAD diagnosis. A modified angiographic Gensini Score was used to reflect the extent of coronary atherosclerosis. Fasting serum lipid concentrations were determined using cholesterol esterase/peroxidase (CHOD/PAP) enzymatic method for total cholesterol and its fractions and lipase glycerol kinase (GPO/PAP) enzymatic method TG evaluation. Gensini score was positively correlated with total cholesterol ($r=0.404$; $p<0.001$), LDL cholesterol ($r=0.484$; $p<0.001$) and TG ($r=0.235$; $p=0.005$). There was a negative correlation between Gensini Score and HDL cholesterol ($r=-0.396$; $p<0.001$). This study clearly showed that in angina pectoris patients with no previous MI, the extent of coronary atherosclerosis is positively correlated with pro-atherogenic lipids, i.e. total cholesterol, LDL cholesterol and TG and negatively correlated with antiatherogenic HDL cholesterol. Cabin and Roberts (Cabin & Roberts, 1982) previously assessed the amount of cross-sectional area narrowing by atherosclerotic plaques histologically in each 5 mm segment of the entire lengths of the right, left main, left anterior descending, and left circumflex coronary arteries in 40 patients with fatal CAD and known fasting serum total cholesterol and TG levels. The number of 5 mm segments of coronary

artery narrowed severely (76 to 100% in cross-sectional area) by atherosclerotic plaques in each group was as follows: 172 of 505 (34%) 5 mm segments from group I; 242 of 353 (69%) segments from group II; 120 of 295 (41%) from group III and 425 of 884 (48%) segments from group IV. The mean percentage of 5 mm segments narrowed severely was significantly greater in group II than in group I ($p<0.005$) or group III ($p<0.01$). Additionally, the mean number of four coronary arteries per subject severely narrowed and the number of subjects with severe narrowing of the left main coronary artery were significantly greater in groups II and III than in group I. The percentages of 5 mm segments narrowed severely correlated significantly with the serum triglyceride level ($p<0.03$). Although it correlated with the number of severely narrowed coronary arteries per subject, the serum total cholesterol level, however, did not correlate with the percentage of 5 mm segments of coronary artery with severe narrowing. In 1994, Ladeia et al. (Ladeia et al., 1994) correlated lipid profile with CAD. One hundred patients with symptoms of CAD were studied by CAG. Coronary artery stenotic and normal proximal lumen were measured with a pachymeter, and the percent degree of obstruction calculated. CAD was documented in 74 patients, (56-75.6% men), with > or = 50% stenosis in 67 (90.5%), 54 (79.1%) men. The lesions were univessel in 24 (33.4%), bivessel in 29 (39.7%), and trivessel in 20 (27.4%). Seventy patients had total cholesterol > or =200 mg/dl, 29 (41.4%) > or =240 mg/dl); 69 (71.9%) LDL > or =130 mg/dl, 37 (38.5%) > or =160 mg/dl; 35 (36.5%) HDL <35 mg/dl and 10 TG > or =200 mg/dl. CAD patients had lower HDL values (38.8 +/- 10 mg/dl vs 48.2 +/- 13.6 mg/dl, p=0.01) and higher Castelli risk indexes (total cholesterol/HDL =5.9 +/- 1.7 vs 5.1 +/- 1.4 and LDL/HDL =4.1 +/- 1.5 vs 3.4 +/- 1.2, p=0.04). Patients with > or =50% stenosis and multivessel disease showed higher Castelli risk indexes (p=0.01 and p=0.04 for total cholesterol/HDL, and p=0.01 and p=0.02 for LDL/HDL, respectively). Twenty one (70%) of the 30 patients with total cholesterol<200 mg/dl had CAD (28% of the patients with CAD), in whom there was a high frequency of patients with a low HDL level (11/21, 52.4% vs 3/9, 33%, p=0.06). Thus, lower HDL and higher Castelli risk indexes values were associated with more severe and intensive CAD. Additionally, total cholesterol <200 mg/dl is compatible with CAD, especially if there is a low HDL level. These findings further strengthen the need of HDL measurement for CAD risk assessment.

Several mechanisms may explain these associations. The observed positive association of the extent of coronary atherosclerosis with total cholesterol seems to be caused by cholesterol present in LDL particles. Circulating LDL can enter cells via apo B/E receptors or through an unregulated scavenger receptor (Brown & Goldstein, 1986). The latest mechanism, present in smooth muscle cells and macrophages, can result in excess accumulation of intracellular cholesterol and the formation of foam cells. The unregulated scavenger receptors are able to uptake both native and modified LDL particles. The most common form of LDL modification is its oxidation, which can occur in any of the cells within the artery, including the endothelial cells, T lymphocytes, smooth muscle cells and macrophages (Hiltunen et al., 1998; Kloiche et al., 2000). Foam cells can rupture leading to the release of oxidized LDL, proteolytic enzymes and toxic oxygen derivatives that can altogether damage the vessel wall (Hiltunen et al., 1998; Kloiche et al., 2000, Dimmeler et al., 1997). Oxidized (Oxy) LDL particles can promote atherosclerotic changes by several mechanisms, such as acting as a monocyte chemoattractant, inducing endothelial cells dysfunction and apoptosis, and reducing nitric oxide release and endothelium-dependent vasodilatation (Li & Mehta, 2000; Mathew et al., 1997; Anderson et al., 1996). Oxy LDL may increase platelet aggregation and thromboxane release what causes vasoconstriction and

thrombus formation (Chen et al., 1996). Cytokines released from activated platelets and injured endothelial cells can stimulate smooth muscle proliferation and the formation of atherosclerotic plaque (Ross, 1993). Thus, the increased LDL cholesterol is related to the development of atherosclerotic changes within arteries. The inverse association of Gensini score with HDL cholesterol observed in the study performed by Tarchalski et al. (Tarchalski et al., 2003) can be explained by antiatherogenic properties of HDL particles. HDL is engaged in reverse cholesterol transport from cells and atherosclerotic plaques into the liver or to other tissues (Tall, 1990). The uptake of cellular cholesterol by HDL is controlled by apolipoprotein A-I and cholesterol efflux regulatory protein. Apolipoprotein A-I serves as a signal transduction protein to mobilize cholesterol esters from intracellular pools and also activates lecithin-cholesterol acyltransferase dependent cholesterol esterification. Cholesterol efflux regulatory protein promotes the transfer of intracellular cholesterol to the cell membrane and surface (Marcil et al., 1999). Further, cholesterol is removed from HDL particles by direct liver uptake or it is transferred to apolipoprotein B-containing lipoproteins, i.e. very low density lipoprotein, intermediate density lipoproteins and LDL (Tall, 1990; Marcil et al, 1989). In addition to reverse cholesterol transport, HDL has a variety of vascular actions that can counteract atherogenesis. HDL contains paraoxonase, an enzyme that protects lipoproteins from oxidative modification and it is able to destroy oxidized lipids present in oxy-LDL and to hydrolyze lipid peroxides in human atherosclerotic lesions. It was observed that lower serum paraoxonase is linked to more severe CAD (Aviram et al., 2000; James et al., 2000; Shih et al., 1998). HDL is thought to maintain endothelial function and a low blood viscosity through a permissive action on red cell deformability (Kuhn et al., 1991; Epand et al., 1994). It is speculated that HDL may downregulate thrombin generation and in this way limit its influence on atherosclerosis (Griffin et al., 1999). As regards TG serum levels and CAD burden, according to literature it remains uncertain if there is an independent association of TG with coronary atherosclerosis. Lipoproteins rich in TG, i.e. very-low density lipoprotein and intermediate density lipoprotein (lipoprotein remnants) have been identified in human atherosclerotic plaques (Rosenson, 2001). Moreover, hypertriglyceridemia is associated with other abnormalities predisposing to the development of atherosclerosis.

Taken together, these data suggest the role of lipid prophile both in coronary initiation, progression and instability.

4.2 Adiponectin

Obesity is one of the most common causes of cardiovascular morbidity and mortality (Matsuzawa et al., 1995). Abdominal visceral fat accumulation is accompanied by impaired glucose tolerance, dyslipidemia, and hypertension, and finally leads to atherosclerotic vascular disease. As important molecules linking these diseases and the inflammatory response, previous studies have shown the dynamic function of adipose tissue as an endocrine organ, releasing various cytokines, adipokines and inflammatory markers, which are involved in the development of atherosclerosis (Fortuno et al., 2003). Notably, adipose tissue secretes a variety of bioactive molecules that directly contribute to the development of cardiovascular disease (Matsuzawa et al., 1999). Adiponectin is an adipose-specific plasma protein, with antiatherogenic and anti-inflammatory properties (Ouchi et al., 1999; 2001). and low plasma adiponectin was observed in patients with CAD (Ouchi et al. 2001).

Additionally, several reports showed an inverse relation between serum CRP and adiponectin (Engeli et al., 2003; Yudkin et al., 1999). Otake et al. (Otake et al., 2008)

investigated the relation between plasma adiponectin and CRP and coronary plaque components in 93 patients with ACS, using VH-IVUS to examine relations among plasma CRP, adiponectin, and ratios of each coronary plaque component. They interestingly found that plasma adiponectin was significantly lower and plasma CRP was significantly higher in patients with than without ACS. There was an inverse relation between serum CRP and adiponectin with regard to necrotic core ratio in both culprit and nonculprit lesions in patients with ACS. The authors concluded that increased plasma CRP and hypoadiponectinemia might be related to the progression of ACS. Additionally, Sawada et al. (Sawada et al., 2010) enrolled 50 patients with stable CAD, showing that patients with TCFA had significantly lower plasma adiponectin levels than patients without TCFA ($p<0.0001$). Furthermore, the plasma adiponectin levels in patients with multi-vessel TCFA were significantly lower than those in patients with single-vessel TCFA ($p=0.049$). Multivariate logistic regression analysis revealed that plasma adiponectin was the strongest predictive factor of the presence of TCFA ($p=0.0007$). Of importance, these data suggest that in patients with stable CAD, adiponectin may be a useful biomarker to stratify "vulnerable patients" into risk categories. These findings suggest that adiponectin affected plaque components, and low plasma adiponectin, a well-known independent risk factor for CAD, might enhance the vulnerability of atherosclerotic plaques and vessels, which could lead to ACS.

5. Coagulative/fibrinolysis state

Coronary thrombosis occurs in most patients with AMI (De Wood et al., 1980) and there is also epidemiological evidence indicating the pathogenetic importance of haemostatic function in CAD (Meade et al., 1986). The precise role of haemostatic factors in the presence of coronary atherosclerosis, however, has not been fully elicited yet.

5.1 Platelets

Platelets are actively involved in the inflammatory cascade leading to vascular atherosclerosis (Libby & Simon, 2001;; Davi & Patrono, 2007). Platelets are enucleate cells of 1-2 μm length with average life span of 7–8 days, generated by bone-marrow derived megakaryocytes after cytoplasmic fragmentation, and play a pivotal role in the process of atherosclerosis. Large interest has been directed towards an improved understanding of platelet physiology, the assessment of platelet function and the development of improved antiplatelet treatment with faster and stronger activity. Patients with stable CAD have increased platelet reactivity and circulating monocyte-platelet aggregates (Furman et al., 1998), which also have been demonstrated early markers of AMI (Furmam et al, 2001). In addition, platelet reactivity is progressively increased as a function of the number of vascular districts involved by atherosclerosis (cerebral, cardiac, peripheral) (Keating et al., 2004). Although the platelet count does not appear to predict cardiovascular outcomes (Pizzulli et al., 1998) and a larger platelet size may correlate with CAD (Pizzulli et al., 1998) and MI. It has been observed a large variability in baseline platelet reactivity and effects of antiplatelet therapies, that may potentially due to the variability in platelet size. In fact, larger platelets have a greater mass and are both metabolically and enzymatically more active than smaller platelets. Indeed, they have a greater prothrombotic potential, with higher levels of intracellular thromboxane A2, and TG levels, as well as increased levels of procoagulant surface proteins (e.g. P selectin, GpIIb/IIIa). Hemostatically reactive platelets,

larger platelets, have more granules and adhesion receptors that have resulted in decreased bleeding time showing increased activation. Indeed, platelet aggregability has been directly related with systemic atherosclerotic disease (Keating et al., 2004). In addition, the most detrimental manifestation of coronary atherosclerotic disease (i.e., myocardial infarction) is mediated by platelet activation (Fitzgerald et al., 1986). On this basis, numerous therapeutic options, targeting platelet aggregability, have been proposed.

5.1.1 Mean platelet volume

Mean platelet volume (MPV) has been shown to be an indicator of platelet activation, that plays a pivotal role in the pathophysiology of atherosclerotic disease (Tsiara et al., 2003; Broadley et al., 2003). It has been reported that elevated values of MPV are associated with cardiovascular diseases (Pizzulli et al., 1998; Jagroop & Mikhailidis, 2003). Few and small reports have investigated so far the relationship between MPV and the extent of CAD, with contrasting results. Also an increase in MPV may be due to the usage of small platelets during acute ischemia (Pizzulli et al., 1998). On these grounds, MPV could be accepted as a parameter of platelet activity and has become a prognostic factor in CAD. Confirming the importance of MPV, several additional reports have demonstrated that MPV was associated with impaired myocardial perfusion and clinical outcome after primary angioplasty. De Luca et al. (De Luca et al., 2009) measured MPV in 1411 consecutive patients undergoing coronary angiography. Significant CAD was defined as stenosis >50% in at least 1 coronary vessel. They additionally measured carotid intima-media thickness in 359 patients. The relationship between MPV and platelet aggregation was valuated by PFA-100 in 50 consecutive patients who were not taken any antiplatelet therapy, and in a cohort of patients who were on aspirin by PFA-100 (n=161) and Multiplate (n=94). Patients were divided into three groups according to tertiles of MPV. Patients with higher MPV were slightly older ($p=0.038$), with larger prevalence of diabetes ($p<0.0001$), hypertension ($p=0.008$), previous CAD ($p=0.041$), less often with stable angina ($p=0.043$) and family history of CAD ($p=0.011$), more often on statins ($p=0.012$), and diuretics ($p=0.007$). MPV was associated with baseline glycaemia ($p<0.0001$) and red blood cell count ($p=0.056$), but inversely related to platelet count ($p<0.0001$). MPV was not associated with the extent of coronary artery disease ($p=0.71$) and carotid intima-media thickness ($p=0.9$). No relationship was found between MPV and platelet aggregation. This study showed that MPV was not related to platelet aggregation, the extent of CAD and carotid intima-media thickness. Thus, according to this study (De Luca et al., 2009) this parameter cannot be considered as a marker of platelet reactivity or a risk factor for CAD. This is the largest study so far conducted to investigate the relationship between MPV and CAD.

Several factors may contribute to explain these findings. The increase in MPV may be a process driven by increased production of bone-marrow derived larger circulating reticulated platelets within the blood stream (26). Indeed, the MPV has been shown to correlate with both megakaryocyte ploidy and with the percentage of circulating reticulated platelets (Smith et al., 2002). Furthermore, a positive correlation between thrombopoietin (a key thrombopoietic hormone) levels and MPV values has been demonstrated in CAD (Senaran et al., 2001). Thus, larger MPV may not imply higher platelet reactivity, that has been shown to be related to the extent and complexity of CAD (Korovesis S, et al., 2000) but may be associated with even reduced aggregation since larger platelets may be precursor and not fully mature platelets. In fact, De Luca et al. (De Luca et al., 2009) did not observe any impact of MPV on platelet aggregation or aspirin resistance. Supporting these data, van

der Planken et al. (van der Planken et al., 2000) did not find any relationship between platelet prothrombinase activity, a final pathway platelet procoagulant activity of type 1 diabetic platelets, and MPV. Furthermore, as shown by previous reports, MPV may be associated with other prognostic factors, such as smoking, diabetes, obesity, hypertension, that may primarily affect the extent of CAD and clinical outcome.

5.2 Coagulative and fibrinolysis markers

Previously clinical data support the proposition that activation of the coagulation and the platelet system is closely associated with myocardial ischaemia there is little information on the relation between the development of coronary atherosclerosis and the haemostatic system.

Nichols et al. (Nichols et al., 1982) did not detect increased concentrations of platelet factor 4, B thromboglobulin, and fibrinopeptide A in a group of patients with abnormal coronary angiograms without previous MI. Furthermore, Schmitz-Huebner et al. (Schmitz-Huebner et al., 1988) analysed blood samples for haemostatic assessment from 225 patients with angina pectoris who were admitted to hospital for CAG. Thromboglobulin, platelet factor 3, platelet factor 4, factor VII:C, factor VIII:C, von Willebrand factor antigen, activated partial thromboplastin time, fibrinogen, antithrombin III, protein C:Ag, plasminogen, and antiplasmin were measured before angiography. Of note, patients who had had a MI in the two months before the investigation were excluded from the study. Multiple linear regression analysis showed that none of the haemostatic variables contributed independently to the prediction of an angiographic score that indicated the extent of coronary atherosclerosis. There were some significant correlations between haemostatic variables and conventional risk factors for CAD. However, the importance of the coagulation/fibrinolytic system is highlighted by several autopsic studies that show a high prevalence of old plaque disruptions without infarctions. A transient shift in the coagulation and anticoagulation balance is likely to result in an acute event. The prolonged presence of residual thrombus over a disrupted or eroded plaque will induce smooth muscle migration and produce new intima, leading to plaque expansion (Hoffmesister et al., 1995). Autopsic studies show that plaque growth is induced by episodic plaque disruption and thrombus formation (Holvoet et al., 1997). Therefore, an active fibrinolytic system may be able to prevent luminal thrombosis in some cases of plaque disruption (Hoffmeister et al, 1999). t-PA, as a crucial factor in fibrinolytic system, plays an important role in the balance between coagulative system and fibrinolytic system, which is mainly responsible for the dissolution of fibrin clots in the circulation, by converting inactive plasminogen to active plasmin. A rapid decline in release of active t-PA is associated with an increasing plaque burden and vulnerability. The reduction in acute fibrinolytic capacity reflects impairment of acute t-PA release that is likely to involve endothelial cell injury (Munkvad et al., 1990; Gyongyosi et al., 2004; Hoffmeister et al., 1998). In the study performed by Wang et al. (Wang et al., 2008), the authors aimed at assessing the association between vulnerability of plaque assessed with IVUS and plasma levels of fibrinolytic biomarkers in patients with ACS. Eighty-nine patients with ACS were enrolled in the study. Blood was collected to measure t-PA levels by liquid phase bead flow cytometry. Eighty-nine non-bifurcated lesions (identified by coronary angiography) were investigated using IVUS before catheterization. The areas of plaque and media were calculated and lesions were classified into two groups: VH-IVUS derived VH-TCFA and non-VH-TCFA plaque. Plasma t-PA level in patients with TCFA was significantly lower than that with non-TCFA (1489 ± 715) pg/ml vs (2163 ± 1004) pg/ml).

Decreased plasma levels of t-PA were associated with plaque vulnerability. Plasma levels of t-PA correlated negatively with plaque plus media and necrotic core in plaque in patients with acute coronary syndrome. Thus, t-PA may be considered an independent risk factor and a powerful predictor of vulnerable plaques. Decreased levels of t-PA may reflect instability of atherosclerotic plaques and might therefore serve as noninvasive determinants of those at high risk for consequent adverse events. Furthermore, in order to elucidate the causes of coronary instability in patients without systemic evidence of inflammation, Niccoli et al. (Niccoli et al., 2007) compared rate of episodic production of markers of thrombin generation [thrombin–antithrombin complexes (TAT)], of fibrinolysis [plasmin–antiplasmin complexes (PAP)], and angiographic severity and extent of coronary atherosclerosis in patients with severe UA and high or low systemic levels of CRP. They enrolled 40 consecutive patients (age 59.7±8.7, 76% males) admitted to coronary care unit with severe UA (Braunwald class IIIB. The authors assayed TAT and PAP using commercially available ELISA assays and CRP with high sensitivity nephelometry. The evaluation of atherosclerotic disease severity and extent was performed according to Bogaty's score. Patients were divided in two groups according to CRP levels: G1=CRP>3 mg/L and G2=CRP<3 mg/L. Number of diseased vessels and number of stenoses plus occlusion were similar between the two groups (1.8±0.9 in G1 vs 2.2±0.9 in G2, p=NS and 2.6±1.9 in G1 vs 2.7±1.3 in G2, p=NS, respectively), as well as extent score and index (8.4±4.5 in G1 vs 9.2±3.1 in G2, p=NS and 0.6±0.3 in G1 vs 0.6±0.27 in G2, p=NS, respectively). Episodic activation of thrombin generation, as assessed by TAT was more frequent in G1 than in G2 (85% vs 47%, p=0.03). Episodic activation of the fibrinolysis was more frequent in G1 than in G2 (80% vs 40%, p=0.01). This study demonstrated that patients with severe UA Who have on admission high serum levels of CRP are more prone to thrombin generation and fibrinolysis activation compared to patients with low admission CRP levels. Severity and extent of CAD was similar between patients with high or low CRP levels on admission. Furthermore, in this study performed by Niccoli et al. (Niccoli et al., 2007), in patients with systemic evidence of inflammation at baseline, episodes of thrombin and plasmin generation were observed more frequently than in patients without systemic evidence of inflammation. This is in keeping with results of studies (Levi et al., 2006) in the septic patients showing that severe systemic inflammation triggers blood coagulation. However, the authors (Niccoli et al., 2007) failed to find evidence of a hypercoagulable state or of a more severe coronary atherosclerosis in unstable patients without systemic evidence of inflammation. Future studies are warranted to investigate other mechanisms of destabilization in patients without systemic evidence of inflammation as for instance, mechanical rupture of a thin fibrous cap caused by greater mechanical stress.

5.3 Tissue factor

Atherosclerotic plaque rupture or fissuring is a key event in the pathogenesis of UA and MI (Fuster et al., 1992a,b). The exposure of blood to a procoagulant surface triggers thrombin generation, platelet aggregation, and fibrin deposition and leads to thrombus formation that can precipitate an acute coronary event. However, atherosclerotic plaques may rupture without triggering thrombosis. Necropsy data show that between 9% and 16% of people who die suddenly of non-cardiac causes have fissured plaques without thrombosis in their coronary arteries, but patients who die of cardiac causes have both thrombosed and non-thrombosed ruptured plaques (Falk, 1985; Davies et al., 1989). The reasons why some ruptured plaques develop thrombosis and others do not are still not known. Tissue factor is

a small transmembrane cell surface receptor that mediates cellular initiation of the coagulation serine protease cascades (Edgington et al., 1991). In vitro studies have shown that tissue factor expression was observed on various cultured and stimulated cell types such as monocytes (Jude et al., 1994; Leatham et al., 1995; Barstad et al., 1995). smooth muscle cells (Taubman et al., 1993; Maynard et al., 1977), endothelial cells and fibroblasts (Green et al., 1971). Tissue factor in the media or the adventitial layer of human normal arteries is localized to aid the body in the prevention of blood loss as an initiator of blood coagulation (Weiss et al., 1989; Drake et al., 1989; Fleck et al., 1990; Wilcox et al., 1989) Tissue factor has recently been shown to be expressed in human coronary atherosclerotic plaque from directional atherectomy specimens from patients with stable and unstable coronary syndromes (Annex et al., 1995). Therefore, when tissue factor expressed in the coronary atherosclerotic plaques is exposed to the blood by the plaque disruption, it may lead to the thrombus formation and the occlusion of the related coronary artery. The plaque rupture is closely associated with the soft extracellular lipids (Berliner et al., 1995), macrophages (van der Wal et al., 1994) matrix-degrading proteases (Libby, 1995) such as interstitial collagenase (MMP-1), which degrades two major plaque structural proteins, type I and III collagen, and activated mast cells in the shoulder region of the atherosclerotic plaques. Of note, Van der Wal et al. (van der Wal et al., 1994) have reported that the macrophages were the predominant cells at the immediate site of either rupture or superficial erosion of the fibrous cap that contained few smooth muscle cells. However, it is not clear whether the macrophages express tissue factor in vulnerable human coronary atherosclerotic plaques in patients with unstable angina.

Kaikita et al. (Kaikita et al., 1997) determined whether macrophages express tissue factor in human coronary atherosclerotic plaques. They examined directional coronary atherectomy specimens from 24 patients with UA and 23 with stable exertional angina. In these specimens, macrophages were detected in 22 (92%) of 24 patients with unstable angina versus 12 (52%) of 23 with stable exertional angina ($p=0.003$). The percentage of macrophage infiltration area was significantly larger in patients with unstable angina than in those with stable exertional angina (17±3% versus 6±2%, $p=0.008$). The immunohistochemical double staining revealed the expression of tissue factor on macrophages in 18 (75%) of 24 patients with unstable angina versus 3 (13%) of 23 with stable exertional angina ($p<0.0001$). Thrombus was identified in 20 (83%) of 24 patients with unstable angina versus 12 (52%) of 23 with stable exertional angina ($p=0.02$). Fibrin deposition was mainly observed around macrophages expressing tissue factor in the patients with unstable angina. Thus, in this study, the authors demonstrated that tissue factor expression on macrophages was more frequent in coronary atherosclerotic plaques in patients with UA. Tissue factor expressed on macrophages may play an important role in the thrombogenicity in coronary atherosclerotic plaques of these patients.

6. Conclusions and future perspectives

Cardiovascular disease remains one of the leading causes of morbidity and mortality in the developed countries, thus the development of novel therapeutic strategies to reduce cardiovascular burden and risk further than is currently possible is mandatory. Early detection of CAD is of paramount importance for initiating aggressive control of risk factors (smoking cessation, lipid lowering therapy, weight reduction therapy, aggressive therapy for hypertension) and establishing of pharmacologic therapy in order to reduce occurrence

of life threatening acute cardiovascular events (anti platelet agents, statins). The use of vascular imaging, combined with soluble molecular markers of disease burden, progression and activity, can provide crucial information that may help developing new pharmaceutical approaches. It is evident from the discussions now ongoing between industry, government regulators, and academia that there is a shared recognition of the need for the application of new tools in drug development. This general philosophy, applied to atherosclerosis treatment, is critical to addressing the epidemic of CAD. In this regard, the association between plaque burden, morphology and activity, as assessed by imaging modalities, and levels of circulating biomarkers, assessing lipid metabolism, inflammation, platelets and white blood cells activation, and endothelial activation, is an intriguing field. New imaging modalities in combination with the development of new biomarkers (bioimaging) may significantly improve our understanding and management of patients at risk of coronary artery disease and its harmful complications, proving valuable insights into atherosclerotic disease progression and the relation to disease activity. In the last decades, an ongoing and intense research by different groups and investigators trying to delineate the role of different biologically active substances in the pathogenesis of progression of atherosclerotic CAD has provided data of paramount importance. Indeed, cardiovascular biomarker research efforts have resulted in the identification of new risk factors and novel drug targets, as well as the establishment of treatment guidelines, thus recognizing the importance of biomarkers in advancing therapies. However, given the complex pathophysiology of cardiovascular disease, no single biomarker will likely prove able to provide a universal surrogate whereby change observed independently predicts benefit, increased risk, or no effect across all drugs and mechanistic targets but the integration of different biomarkers looking at different phases of the coronary atherosclerotic disease should be the way forward.

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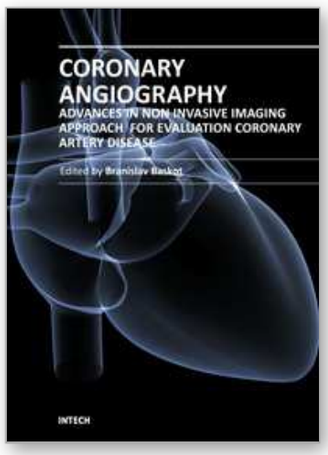

Coronary Angiography - Advances in Noninvasive Imaging Approach for Evaluation of Coronary Artery Disease

Edited by Prof. Baskot Branislav

ISBN 978-953-307-675-1
Hard cover, 414 pages
Publisher InTech
Published online 15, September, 2011
Published in print edition September, 2011

In the intervening 10 years tremendous advances in the field of cardiac computed tomography have occurred. We now can legitimately claim that computed tomography angiography (CTA) of the coronary arteries is available. In the evaluation of patients with suspected coronary artery disease (CAD), many guidelines today consider CTA an alternative to stress testing. The use of CTA in primary prevention patients is more controversial in considering diagnostic test interpretation in populations with a low prevalence to disease. However the nuclear technique most frequently used by cardiologists is myocardial perfusion imaging (MPI). The combination of a nuclear camera with CTA allows for the attainment of coronary anatomic, cardiac function and MPI from one piece of equipment. PET/SPECT cameras can now assess perfusion, function, and metabolism. Assessing cardiac viability is now fairly routine with these enhancements to cardiac imaging. This issue is full of important information that every cardiologist needs to now.

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