Dynamics of intracoronary thrombosis in STEMI and sudden death patients
Kramer, M.C.A.

Citation for published version (APA):

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Download date: 13 Dec 2018
Summary and conclusions of the thesis

Acute myocardial infarction (AMI) is one of the most common causes of morbidity and mortality worldwide. Each year about 85,000 people in the Netherlands experience an acute myocardial infarction. ST-elevation myocardial infarction (STEMI) predominantly results from atherosclerotic plaque disruption with superimposed occlusive coronary thrombus formation. Primary percutaneous coronary intervention (PPCI) is the preferred treatment in STEMI patients in order to restore coronary artery patency and blood flow. In adjunct to standard PPCI, thrombus aspiration has been performed at the Academic Medical Center in Amsterdam since August 2001, when thrombus aspiration catheters became available. Initially, the decision to perform thrombus aspiration was taken when deemed technically feasible as determined by the operator and subsequently on routine basis when thrombus aspiration was included in the ESC guidelines as recommended therapy. At that point at time, the composition of aspirated intracoronary atherothrombotic material was largely unknown. This thesis comprises several studies on the histopathological features and clinical significance of thrombus aspirate from patients with STEMI undergoing PPCI as well as several morphological studies on atherosclerosis in sudden (cardiac) death victims.

Part I Thrombus aspiration and histopathology in ST-segment elevation myocardial infarction

In the first part of the thesis (Chapter 2 to 4), the histopathological features of thrombus aspirates obtained from STEMI patients undergoing PPCI are discussed. As mentioned above, AMI is primarily caused by rupture of a nonocclusive atherosclerotic plaque with subsequent formation of an occlusive thrombus. The first histopathological observations in STEMI patients with symptoms less or equal than 6 hours, by Rittersma et al., showed that in approximately 50% of STEMI patients, coronary thrombi were days to even weeks old suggesting an important discrepancy between time of onset of the thrombotic event and the occurrence of overt acute clinical symptoms. Thrombus age was determined without knowledge of the clinical scenario and was based on accepted histomorphological criteria. In Chapter 2, the histopathological features of thrombi aspirated during PPCI in a large consecutive STEMI population were described to confirm the concept that there is a variable and unpredictable time span between the onset of plaque disruption and the onset of clinical symptoms. We could obtain histopathologically confirmed material in 74% of patients and we found features of older thrombus (lytic and/or organized, >1 day) in 40% of the aspirated material. These results continued to support the concept of atherosclerosis as a dynamic disease and the fact that there is a heterogeneous time course of different processes leading to the occlusive event. Interestingly, we also demonstrated in this study that there may be a
time window of several days after plaque disruption in which thrombus embolization is most likely.

Although, the role of calcification on plaque instability is still controversial, the concept that inflammation plays a crucial role in destabilization of a plaque is widely accepted. The relationship between inflammation and coronary calcification is unknown. In Chapter 3 we demonstrated that (micro)calcifications in aspirated thrombi are strongly related to the intraplaque inflammatory biomarkers, C-reactive protein (CRP) and osteopontin (OPN), in culprit lesions. In addition, macrophages with intracellular CRP and OPN were significantly more often observed in thrombi with (micro)calcifications compared with the thrombi without (micro)calcifications. Coronary calcification is an excellent marker for diverse invasive and non-invasive imaging techniques and may therefore be helpful in the identification of intra-plaque inflammation as indicator for high-risk vulnerability to rupture and acute cardiovascular events.

The presence of older thrombus in 40-50% of STEMI patient treated with PPCI showed that an acute coronary occlusion might be due to the failure of a disrupted plaque to heal, however, the dynamics and timing of the healing process remain poorly understood. Therefore, the temporal changes in neo-vessel formation (angiogenesis) in aspirated coronary thrombi were investigated in the study described in Chapter 4. With the use of thrombus age as a time scale we visualized survival, activation, and proliferation of endothelial cells (ECs). Although it progresses slowly during the first 5 days, we found that angiogenesis in the coronary thrombi begins as early as within the first day after thrombus formation following plaque disruption. Interestingly though, while bone marrow derived primitive cells appear the play an important role in the formation of neovessels, their role seems to be limited in the process of thrombus organization.

In conclusion, intraluminal thrombus and fragments of atherosclerotic plaques obtained by thrombus aspiration during PPCI in STEMI patients provide an unique opportunity for the histopathological investigation of culprit lesions and gains further insight in the pathogenesis of acute myocardial infarction. Acute coronary occlusion might represent the final phase in a series of nonocclusive atherothrombotic events transpiring in the foregoing days or even weeks. The demonstration of the slow progression of angiogenesis in coronary thrombi following plaque disruption attests to new therapeutic options in the treatment of unstable coronary artery disease. Further, the association between (micro)calcifications and intraplaque inflammation may have important consequences for in vivo coronary plaque imaging.
Part II Histopathology of thrombus aspirate and prognosis after ST-segment elevation myocardial infarction

We have previously shown that in approximately 40% to 50% of STEMI patients treated with PPCI within 12 hours after onset of symptoms the coronary thrombi were days to even weeks old. However, both the prognostic consequence of the presence of older thrombus was unclear as was the association between thrombus age and e.g. serum biomarkers and ST-segment recovery. Therefore, we performed several studies in which the relationships between thrombus aspiration and thrombus age were assessed with serum biomarkers, ST-segment recovery, and with clinical outcome. These studies are described in the second part of the thesis (Chapter 5 to 9).

In Chapter 5 we demonstrated that thrombus age is a strong independent predictor of long-term mortality in STEMI patients treated with thrombus aspiration in adjunct to PPCI. In the patients with older thrombus the rate of death was 2-fold higher as compared with patients with only fresh thrombus. The difference in mortality occurred primarily in the first 14 days after PPCI and is sustained over time. The presence of older thrombus is most likely a biomarker for mortality unrelated to causality. A possible explanation for the strong association between thrombus age and long-term mortality may be that patients with older thrombus have experienced temporary occlusive thrombosis with spontaneous lysis, resulting in less effective reperfusion.

To further investigate the pathophysiological mechanism(s) responsible for the association between thrombus composition and clinical outcome, we evaluated the predictive power of thrombus age for 1-year mortality in STEMI patients treated with PPCI in relation to 5 serum biomarkers (cardiac troponin T [cTnT], N-terminal pro-brain natriuretic peptide [NT-proBNP], C-reactive protein [CRP], glucose, and estimated glomerular filtration rate [eGFR]) and established clinical risk factors in Chapter 6. We included all patients in whom aspirated thrombus material could histopathologically be classified according to thrombus age, laboratory measurements of one biomarker or more were available, and whom were treated with PPCI between 2005 and 2011. We showed that thrombus age was a strong predictor of mortality independently of serum biomarkers cTnT, glucose, NT-pro-BNP, eGFR, CRP, and established clinical risk factors. Moreover, thrombus age provided complementary and independent information to a previously published multimarker model including established clinical risk factors and multiple biomarkers for predicting 1-year mortality.

Chapter 7 described a study covering the association between ST-segment recovery, the histopathology of aspirated thrombus, and subsequent outcome in unselected STEMI patients. There was a trend toward better ST-segment recovery in patients with only fresh thrombus as compared with patients with older thrombus. Furthermore, incomplete ST-segment recovery was significantly more often seen in patients in whom no material could be aspirated as compared to patients in whom only fresh thrombus was present. Independent
of the histopathology of aspirated thrombus, the presence of ST-segment recovery was a strong predictor of long-term mortality. At present, reports describing thrombus aspiration alone as the definitive treatment of STEMI are limited and the outcome of patients undergoing such treatment is largely unknown. Additional balloon angioplasty and stent implantation may be unnecessary in patients, in whom thrombus aspiration results in removal of most thrombotic material, leaving the culprit lesion without angiographic signs of (significant) residual stenosis. In Chapter 8, we describe the safety and feasibility of thrombus aspiration without additional balloon angioplasty and stent implantation in a selected group of STEMI patients. In the majority of the patients, an acceptable angiographic result was obtained after thrombus aspiration with minimal, non-significant residual stenosis, angiographic normal flow, and no need to for additional balloon angioplasty and stent implantation. In addition, long-term clinical follow-up was excellent with a low risk of recurrent ischemic events and a low cardiac mortality. Thus far, previous reports on thrombus aspiration in the setting of PPCI did not provide information on the success or failure of the thrombus aspiration device in reaching the culprit lesion and obtaining macroscopic atherothrombotic material. Therefore, in Chapter 9 we focused on the factors associated with the failure in reaching the culprit lesion and to remove thrombus with the various thrombus aspiration devices and determined the potential prognostic implications. The angiographic analysis in 1399 unselected STEMI patients showed the presence of a calcified lesion, marked proximal tortuosity of the infarct-related artery, and the presence of a bifurcation lesion as independent predictors of failure of the aspiration device to reach and/or cross through the culprit lesion. We found that neither the failure to reach and/or cross through the culprit lesion nor the failure to aspirate material were associated with the successful restoration of coronary flow, and more importantly, with 1-year mortality. Therefore, the presence of older thrombus has important prognostic implications on the long-term mortality. The predictive power for 1-year mortality is independently of serum biomarkers and established clinical risk factors. The patients with older thrombus have a significant higher death rate in the first days to weeks after the index STEMI and this difference in mortality is sustained over time. Our findings emphasize the necessity for further research into invasive and non-invasive imaging modalities for thrombus age detection during PPCI. It is conceivable that knowledge of the composition and age of the thrombus at the time of PPCI could help to identify patients at the highest risk for recurrent events. Although many interventional cardiologists believe that it is unsafe to leave thrombotic lesions untreated (no balloon angioplasty or stent implantation) during PPCI, we showed thrombus aspiration alone during PPCI is feasible and safe in selected STEMI patients. Our study can be considered as a “proof of principle” and this needs to be further investigated.
Part III Atherosclerosis in sudden cardiac death victims

The third part (Chapter 10 to 12) of the thesis comprises several morphological studies on the process of atherosclerosis and complications in sudden (cardiac) death victims. Autopsy studies on large series of sudden cardiac death victims play a pivotal role in the understanding of the pathophysiology of atherosclerosis; plaque progression, plaque instability, and the pathogenesis of acute myocardial infarction. Although there are many detailed autopsy studies describing the various plaque morphologies, little is known about how atherosclerosis progresses from early to more advanced plaques, marked by the formation of a necrotic core. The progression of human coronary plaques from pathological intimal thickening (PIT) to late fibroatheroma in human coronary artery lesions is described in Chapter 10. We found that the progress of atherosclerosis is associated with increased macrophage infiltration, increased apoptotic cell density, and a defective clearance of apoptotic bodies by macrophages. Further, we observed increase in Lp-PLA2 expression and decrease in proteoglycans and hyaluronan expression with the progression of atherosclerosis for PIT macrophage poor to late fibroatheroma. These findings show that these molecules and their interplay with macrophages contribute to the progression of atherosclerosis even in its early phases.

Although, the histopathologic analyses of atherothrombotic material obtained by aspiration is informative, there is still limited understanding of the healing properties of coronary thrombi in relation to the underlying plaque morphology. It is unclear why some of thrombi smolder with a subsequent ‘secondary’ occlusive event with later presentation of acute MI and whether the rate of thrombus maturation differs between events caused by plaque rupture or plaque erosion. In Chapter 11 we studied coronary thrombi in 111 sudden cardiac death victims (death presumably within 24 hours from first symptoms) and explored whether thrombus maturation in fatal lesions was depending on the etiology of the underlying culprit plaque. We found that in plaque ruptures, nearly one-half of thrombi showed a lack of healing, where more than 85% of the thrombi in erosions exhibited late stages of healing. Parameters of macrophage infiltration, thrombus length, and occlusive versus nonocclusive morphology showed no association with thrombus healing. We concluded that these data support our previous finding that thrombus initiation, in a substantial number of patients, occurs before the onset of clinical symptoms. Considering erosions predominantly occur in women and younger men and STEMI patients with healing thrombi have poorer prognosis indicate that women and younger men might require different strategies of treatment.

In the last chapter of the thesis, Chapter 12, we emphasize that the management of patients with an indication for oral anticoagulation (OAC), who undergo PCI with (drug-eluting) stent implantation, is challenging because of the need to balance between the risk of bleeding against the ongoing risk of stent thrombosis. The combined use of antiplatelet and anticoagulation agents is associated with an increased risk for (gastrointestinal) bleeding, however, the optimum management of a patient with a major bleeding, who has recently
undergone coronary stent implantation, is unclear and therefore has to be avoided. We describe a case of fatal very late stent thrombosis in a patient presented with hematemesis, while taken aspirin and OAC.

In conclusion, elucidating the role of the pivotal processes of atherosclerotic progression, through which lipid pool convert to the necrotic core, is practically important to prevent the development of more advanced lesions. By showing that proteoglycans, hyaluronan and Lp-PLA2 contribute to the progress of atherosclerosis in relation to increased macrophage presence, apoptotic bodies and defective clearance by macrophages we provide further insight in early atherosclerotic plaque progression. However, further studies are required to clarify the implications of these findings as mechanism of plaque progression and eventually to the prevention of cardiovascular events. The results from our morphological studies continued to support the concept of atherosclerosis as a dynamic disease and the fact that there may be a large discrepancy between the time of onset of the thrombotic event and the occurrence of overt acute clinical symptoms in a considerable proportion of the patients with STEMI. The demonstration that the etiology of the underlying culprit plaque influences thrombus maturation shows that the best treatment strategy may be different in STEMI patients with plaque rupture and plaque erosion. Finally, the combination of (drug-eluting) stent implantation followed by dual antiplatelet therapy and the requirement of oral anticoagulation may signify an increased risk of bleeding, whereas discontinuation of antiplatelet therapy in such situations may increase the risk of stent thrombosis.