Microvascular Obstruction Is Caused by Atherothrombosis in Patients With Acute Coronary Syndrome Undergoing Percutaneous Coronary Intervention

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The diagnosis of acute coronary syndrome (ACS) is primarily based on the mode of clinical presentation and is a term used for any conditions suggesting the acute induction of myocardial ischemia. The precise molecular and cellular triggers that lead to ACS remain poorly understood; however, histopathologic studies have illustrated several mechanisms that may explain the sudden onset of symptoms in ACS patients. The most common substrate underlying ACS is thought to be rupture of a vulnerable plaque that contains a necrotic core covered by a fibrous cap. The term, thin-cap fibroatheroma (TCFA) is used to describe vulnerable plaque because histomorphometric analysis of ruptured plaques revealed fibrous cap thickness to be <65 μm in 95% of the lesions. Once the disruption of the fibrous cap occurs, the lesion is no longer classified as a TCFA. In morphological measurement, plaque ruptures have the largest necrotic core, 3.8±5.5 mm², followed by TCFA, 1.7±1.1 mm², with 75% of the lesions involving >120 degree of circumferential arc; whereas thick cap fibroatheromas have the smallest necrotic core (1.2±2.2 mm²). The highest positive remodeling index is seen in plaque ruptures, followed by plaque hemorrhage, TCFA, healed plaque rupture, and fibroatheroma. Also, plaque rupture and TCFA are located predominantly in the proximal portions of the coronary tree.

Following the rupture of plaque, the exposure of necrotic core material to blood flow leads to thrombotic luminal obstruction with or without distal embolization of platelet-rich thrombus, or less commonly, atherosclerotic debris.

The main causes of coronary thrombosis include plaque erosion as well as rupture, with erosion accounting for 25% to 35%, and rupture for 65% to 75%, of patients presenting with ACS in pathology series. Erosions are found more frequently in younger individuals and especially in women age <50 years. There are clear morphological differences between ruptured and eroded lesions, with plaque erosion lesions being rich in proteoglycans, such as versican and hyaluronan. Conversely, ruptures have a thin ruptured cap made of type I collagen and an underlying large necrotic core. The incidence of intramyocardial microemboli is significantly higher in erosion (71%) as compared with rupture (42%) without previous intervention (Figure 1).

The concept of microvascular obstruction (MVO) of the myocardium was first described by Kloner et al, who documented a link between angiographic no-reflow phenomenon and severely damaged intramural microvessels with endothelial cell swelling, protrusions, and decreased pinocytic vesicles in a canine epicardial coronary artery occlusion and reperfusion model. Other studies have reported details of histological changes of MVO with production of reactive oxygen species that lead to disruption of endothelial cells, fibrin and platelet deposition, neutrophil activation, and red cell extravasation following reperfusion. In addition, the reperfusion-related response may be exaggerated from distal embolization of atherosclerotic debris or thromboemboli, especially following invasive coronary interventions.

The study by Ozaki et al presented in this issue of Circulation: Cardiovascular Imaging involved 70 ACS patients, who were separated on the basis of presence of TCFA (n=32) and non-TCFA (n=38), identified by optical coherence tomography (OCT). The definition used for TCFA was a fibrous cap <70 μm and a lipid-rich plaque involving >90 degree of circumferential arc; this is somewhat different from the histopathologic characteristics because of the inability of OCT to determine the area of the necrotic core. MVO was assessed by late gadolinium enhancement cardiovascular MRI and was more frequently observed in patients with TCFA (38%) as compared with those without TCFA (8%) following percutaneous coronary intervention with stenting. Although it is logical that following balloon dilatation and stent placement, necrotic materials behind the fibrous cap of TCFA would be released and cause distal embolization, why only the presence of TCFA made such a big difference in the development of MVO is unclear. There were no differences in the prevalence of thrombus (TCFA, 81%, versus non-TCFA, 63%; P=0.12) or plaque rupture (TCFA, 59%,
versus non-TCFA, 37%; \( P=0.09 \) in their study. How can we reconcile this result with our current understanding of differences between rupture, TCFA, and erosion? Ozaki et al used the term TCFA for plaques that had ruptures; to us, this is not an appropriate, as the 2 are not interchangeable, given that the ruptured plaques have a disrupted cap rather than an intact cap. A more appropriate classification would have been lesions with rupture, TCFA without rupture, and thick cap fibroatheroma (presumably corresponding to plaque erosion), and further stratification by thrombus burden. By using this classification schema, the mechanisms of MVO would likely have been made clearer. Therefore, we remain at a loss for comprehending fully the findings of this study, except that presence of necrotic core of \( >90 \) degrees and thin fibrous cap are associated with greater MVO.

It is also interesting that aspiration of the thrombus, which results in intensive negative pressure that may change lesion morphology, was applied in 78% of TCFA group and 53% of non-TCFA group. From histological examination of ACS patients, it has been shown that 70% of the aspirates contain atherothrombotic materials; thus, the results of low MVO presence in TCFA groups in this study may have been because of aspiration. In patients undergoing percutaneous coronary intervention, it has been reported that atheroemboli are a frequent phenomenon, especially in atherosclerotic vein grafts (\( >90 \)% of cases); and we illustrate 1 such case with distal embolization following stenting in native coronary artery (Figure 2). This not only holds true for aspiration devices, but also for other distal protection devices, such as filter wire or other methods, and pharmacological vasodilators, such as verapamil or adenosine in the prevention of no-reflow. Additional investigations are needed in those in whom OCT has been performed to determine plaque morphology to understand and attenuate MVO in ACS patients.

Last, as demonstrated in the study, the use of multiple modalities may provide more detailed information compared with situations where only a single modality is used. Further, in vivo clinical studies are essential to determine what we can only infer from autopsy studies. However, in this era of ample noninvasive and catheter-based new technologies, it is essential to use the right terminology and to interpret results with great caution, because interventions themselves induce changes in plaque characteristics. Furthermore, we should be aware of limitations of each technology. For example, the ability of OCT to detect TCFA wanes in the presence of foamy macrophages on the luminal surface, which exhibit bright signals on OCT and may mimic TCFA; therefore, it may be ideal to combine OCT with intravascular ultrasound. Similarly, cardiovascular MRI may underestimate or fail to identify the area of MVO caused by slow penetration of contrast over time.

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**Figure 1.** A sudden death case with acute thrombosis by plaque erosion. Thirty-seven-year-old woman with history of hypertension and diabetes mellitus, complained of chest pain of 1 week duration. Subject had a witnessed arrest and could not be resuscitated. Postmortem angiogram showed focal severe stenosis limited to the proximal LAD (left column). Histology identified presence of plaque erosion with nonocclusive thrombus (Thr) overlying a plaque that showed 75% cross-sectional area narrowing and an early necrotic core (fibroatheroma with a thick fibrous cap; mid column, Movat's Pentachrome). Histological examination of the myocardium revealed intramural platelet rich thromboemboli (red arrows) and acute myocardial infarction with acute inflammatory infiltrate (black arrowheads; right column, H&E). LAD indicates left anterior descending coronary artery; LCx, left circumferential coronary artery; LM, left main coronary artery; NC, necrotic core; RCA, right coronary artery.
Figure 2. An autopsy case with atheroembolization in intramyocardial arteries. Sixty-eight-year-old man who underwent stent placement for the treatment of unstable angina 1 week previous to sudden death. Postmortem angiography (upper-left images) and OFDI (left middle) revealed nonocclusive thrombus within the stented segment of mid-LAD. Histological sections of the stented coronary artery (upper-right images, Movat’s Pentachrome) demonstrated disruption of a thin fibrous cap by stent strut (asterisks), which penetrated into the necrotic core (NC). Histological section of the myocardium revealed intramyocardial obstruction of microvessels by atheroemboli (black arrows; bottom images, H&E). Note presence of spindle-shaped cholesterol crystals within microvessels and necrotic core. LAD indicates left anterior descending coronary artery; LCx, left circumferential coronary artery; OFDI, optical frequency domain imaging; Thr, thrombus.

Disclosures

None.

References

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