

New Insights into Mechanisms of Acute Myocardial Infarction: A Journey of 100 Years

Huay Cheem Tan,^{1,2}*FAMS, FRCP, FACC*, Kian Keong Poh,^{1,2}*FAMS, FRCP, FACC*

In Singapore, there were 7813 patients who suffered from acute myocardial infarction (AMI) in the Year 2011, among whom 2100 (26.9%) had ST-segment elevation myocardial infarction (STEMI). Much knowledge has been gained since the early description of the mechanism of AMI by Dr James Bryan Herrick who published in 1912 that thrombosis in the coronary artery led to the symptoms and consequences of heart attack and that this was not inevitably fatal.¹ Interestingly, he also said that, “the hope for the damaged myocardium lies in the direction of securing a supply of blood through friendly neighbouring vessels so as to restore so far as possible its functional integrity”—a concept which we now called collaterals formation.

There have been many revisions of the definition of AMI with the latest 3rd Universal Definition of Myocardial Infarction emphasising that the term ‘AMI’ should be used when there is evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischaemia.² For that, a detection of a rise and/or fall of cardiac biomarker values (preferably cardiac troponin) with at least one value above the 99th percentile upper reference limit, and with at least one of the following: symptom of ischaemia, new or presumed new significant ST-segment-T wave (ST-T) changes or new left bundle branch block (LBBB), development of pathological Q wave in electrocardiogram, imaging evidence of new loss of viable myocardium or new regional wall motion abnormality or identification of an intracoronary thrombus by angiography or autopsy. The mere rise of troponin is inadequate in establishing the diagnosis of AMI without the supporting evidence of other clinical or imaging evidence. This is because besides myocyte necrosis, apoptosis, normal myocyte turnover, increased cellular wall permeability may also result in elevation of cardiac troponins.³ Diseased skeletal muscle may also cause increases in circulating cardiac troponin T, but not cardiac troponin I.

The classification of AMI has also undergone revision

such that it is now divided into Type 1 (the common spontaneous MI caused by plaque erosion or rupture), Type 2 (MI resulting from either increased oxygen demand or decreased supply, for example, anaemia, arrhythmias, or hypotension), Type 3 (sudden unexpected death), Type 4a (MI associated with percutaneous coronary intervention, PCI), Type 4b (MI associated with stent thrombosis) and Type 5 (MI associated with coronary artery bypass grafting, CABG).

Formation of Coronary Plaques

Acute coronary syndrome (ACS) arises from the erosion or rupture of atherosclerotic plaque. Most adult human lesions originate as pre-existing intimal masses with accumulation of fat subjacent to it. When this early adaptive intimal thickening progresses to become pathologic intimal thickening, the atherosclerotic process enters into a more dynamic stage with the subsequent formation of fibroatheroma.⁴ Pathological intimal thickening typically shows incompletely coalesced extracellular lipid, with most of it located deep within the plaque, underneath a layer of macrophages and smooth muscle cells. The smooth muscle cells may contain lipid droplets with a poorly formed fibrous cap (due to the absence of a necrotic core).

In contrast, fibrous cap atheroma classically shows a distinct layer of connective tissue completely covering the lipid core. The fibrous cap consists purely of smooth muscle cells in a collagenous-proteoglycan matrix, with varying degrees of infiltration by macrophages and lymphocytes. A fibrous cap atheroma may have a thick or thin cap, overlying a lipid-rich core. It has a “true” necrotic core (NC) which contains cholesterol esters, free cholesterol, phospholipids, and triglycerides. Early NC formation is a result of macrophage infiltration and apoptosis, whereas late NC is likely the result of defective efferocytosis as well as plaque haemorrhage which contribute to free cholesterol within the NC.

¹Cardiac Department, National University Heart Center, National University Health System, Singapore

²Yong Loo Lin School of Medicine, National University of Singapore, Singapore

Address for correspondence: A/Prof Tan Huay Cheem, Yong Loo Lin School of Medicine, National University of Singapore, 1E Kent Ridge Road, NUHS Tower Block, Level 9, Singapore 119228.

Email: huay_cheem_tan@nuhs.edu.sg

Vulnerable Plaques

The concept of 'vulnerable plaque' was first introduced by Muller et al in an attempt to understand why certain lesions are likely to rupture resulting in coronary thrombosis.⁵ Subsequently, Libby et al defined 'vulnerable plaque' as thin cap fibroatheroma (TCFA) which are composed of a lipid-rich core in the central portion of an eccentric plaque lined by thin, friable fibrous cap.⁶ Burke et al further defined 'vulnerable plaque' as lesion with a fibrous cap of $<65\mu\text{m}$ thick.⁷ The consensus clinical definition of vulnerable plaque now is any thrombosis-prone plaque or plaque at a risk of rapid progression, with potential of becoming a culprit lesion and triggering an acute coronary syndrome (ACS) independent of its specific morphology (although TCFA is still believed to be the most prevalent lesion type in 60% to 70% of cases).⁸ The presence of TCFA is the focal manifestation of an underlying systemic disease. Along with ruptured plaques, TCFA accounted for only 1.2% to 1.6% of the total length of coronary tree examined in patients dying from cardiovascular cause.⁹ The majority of these lesions occurred in the proximal third of arteries with 92% of them clustered within 2 or fewer non-overlapping 20-mm segment. While TCFA is more prone to rupture than thick-cap fibroatheroma, the activity at the onset of the ACS is also important. Plaque rupture causing thrombosis may occur in thick fibrous cap (up to $140\mu\text{m}$) depending on the exertion level. Tanaka et al showed that the median thickness of broken fibrous cap at rest is $50\mu\text{m}$ whereas that of broken plaque during exertion is $90\mu\text{m}$.¹⁰

The rupture of an atheromatous plaque with superimposed thrombosis is the accepted cause of most ACS and sudden coronary death. There are 3 types of lesions that cause coronary thrombosis: (i) plaque rupture, (ii) plaque erosion, and (iii) calcified nodules. Plaque ruptures are found in 60% of individuals dying suddenly with luminal thrombi and are the most frequent cause of death in young men (<50 years) and older women (>50 years).¹¹ It is defined by an area of fibrous cap disruption whereby the overlying thrombus is in continuity with the underlying necrotic core. Ruptured lesions typically have a large necrotic core and a disrupted fibrous cap infiltrated by macrophages and lymphocytes. The smooth muscle cell content within the fibrous cap at the rupture site may be quite sparse. The plaque is usually positively remodelled and critically occlusive.

Plaque erosions constitute about 40% of cases of thrombotic sudden coronary death, more common in young women and men <50 years of age, and are associated with smoking, especially in premenopausal women. Plaque erosion is identified when the thrombosed arterial segment fails to reveal fibrous cap rupture and typically, the endothelium is absent at the erosion site. The exposed intima consists predominantly of smooth muscle

and proteoglycans, and surprisingly, contains minimal inflammation. The lesions are usually sub-critically stenosed and do not show any positive modelling.

Calcified nodule refers to a lesion with fibrous cap disruption and thrombi associated with eruptive, dense, calcific nodules. It accounts for 2% to 7% of thrombi in sudden coronary death. The lesions typically showed calcific nodules protruding into the lumen through a disrupted thin fibrous cap. There is absence of an endothelium at the site of the thrombus. Instead, there are inflammatory cells including macrophages and T lymphocytes. It occurs in older individuals, usually men; patients with type 2 diabetes mellitus, metabolic syndrome, hypertension and smoking. The calcified nodules are equally common in tortuous right and left coronary arteries.

Progression of Plaques to Cause Events

Studies have shown that lesion severity and morphology are dynamic and progressive before clinical expression. Myocardial infarction frequently develops from previously non-severe lesions that progress over time. Glaser et al found in a National Heart Lung & Blood Institute (NHLBI) Dynamic registry that 5.8% PCI patients underwent second PCI procedure at 1 year for clinical plaque progression. Among these, majority (86.9%) of lesions were $\leq 60\%$ in severity during original PCI.¹² At National University Heart Centre, Singapore (NUHCS), a total of 1043 consecutive patients with STEMI who presented to our centre, between June 2008 and August 2010, and underwent successful primary angioplasty were enrolled in a retrospective analysis.¹³ Lesion severity measurement was performed once successful restoration of coronary blood flow was achieved, either after wiring only, or follows thrombus aspiration or balloon inflation with low-calibred catheters. It was found that the majority (80%) of STEMI patients had diameter stenosis $>50\%$, suggesting that the risk of acute coronary events may be a function of coronary stenosis severity. An example of a coronary angiography of a patient presenting with acute ST elevation myocardial infarction is illustrated in Figure 1. After thrombus aspiration, there remained significant residual stenosis at the culprit site (Fig. 2). These findings were corroborated by Frobert et al who showed that among 250 patients with STEMI, 66% of patients had underlying stenosis of $>70\%$, and 96% of patients had stenoses of $>50\%$.¹⁴ There was no difference in stenosis severity between coronary arteries and gender. Furthermore, Manoharan et al demonstrated among 102 patients with STEMI with restoration of normal antegrade coronary flow after thrombus aspiration, that only 11% of culprit stenosis had lesions $<50\%$.¹⁵ Finally, the PROSPECT trial which studied the natural history of coronary atherosclerosis, found that the mean angiographic

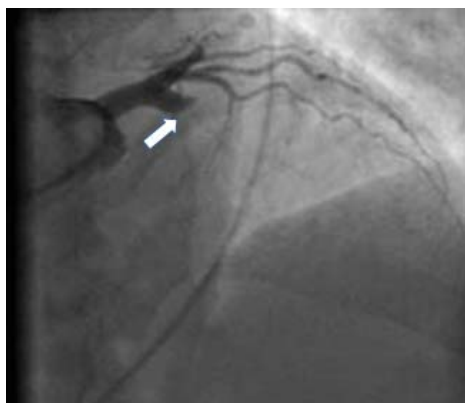


Fig. 1. Coronary angiogram showing an occluded left anterior descending artery (arrow) in a patient with ST elevation myocardial infarction.

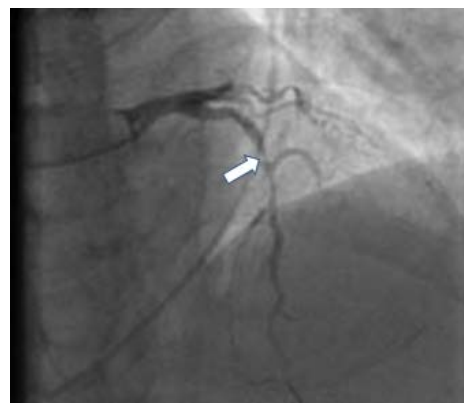


Fig. 2. This shows significant residual stenosis at the culprit site after thrombus aspiration (arrow).

diameter stenosis of 106 lesions which were subsequently responsible for major cardiovascular events was $32 \pm 21\%$ at baseline and $65 \pm 16\%$ at 3.4 years follow-up.¹⁶

Causes of Plaque Progression

Intraplaque haemorrhage is a major cause of plaque progression. The occurrence is due to ruptured vasa vasorum which are usually formed as a result of neovascularisation in response to hypoxia induced by growing plaque. The presence of red blood cells increases the risk of plaque destabilisation by provoking inflammation and enlargement of the necrotic core, and causing plaque rupture or erosion.¹⁷ Not all plaque rupture leads to thrombotic occlusion of the coronary artery. In fact, many may remain silent. In the course of healing, the thrombi may organise, remodel and be incorporated into the atherosclerotic plaque itself, resulting in plaque size growth. Burke et al showed in among the plaques of 142 men who died of sudden cardiac death, with increased numbers of healed rupture sites, there is an increase in mean percent luminal narrowing in both acute and healed rupture (stable plaque) sites.¹⁸ Indeed, 80% of plaques that cause $>50\%$ diameter stenosis have evidence of old healed plaque rupture with incorporation of thrombus into the atheroma.¹⁹ This process contributes to the progression of coronary atherosclerosis and may explain the first appearance, or step change in severity, of angina pectoris.

Conclusion

Coronary atherosclerosis with resultant atherothrombosis contributes to clinical manifestation of coronary occlusion and acute myocardial infarction. Although often times silent, recurrent atherothrombotic events lead to increase the plaque size and coronary luminal narrowing. Greater

understanding and better clinical detection of thin cap fibroatheroma, especially by non-invasive imaging, may help prevent development of future coronary syndromes.

REFERENCES

1. Herrick JB. Landmark article (JAMA 1912). Clinical features of sudden obstruction of the coronary arteries. By James B. Herrick. *JAMA* 1983;250:1757-65.
2. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al. Third universal definition of myocardial infarction. *J Am Coll Cardiol* 2012;60:1581-98.
3. White HD. Pathobiology of troponin elevations: do elevations occur with myocardial ischemia as well as necrosis? *J Am Coll Cardiol* 2011;57:2406-8.
4. Virmani R, Kolodgie FD, Burke AP, Farb A, Schwartz SM. Lessons from sudden coronary death: a comprehensive morphological classification scheme for atherosclerotic lesions. *Arterioscler Thromb Vasc Biol* 2000;20:1262-75.
5. Muller JE, Tofler GH. Triggering and hourly variation of onset of arterial thrombosis. *Ann Epidemiol* 1992;2:393-405.
6. Libby P. Molecular bases of the acute coronary syndromes. *Circulation* 1995;91:2844-50.
7. Burke AP, Farb A, Malcom GT, Liang YH, Smialek J, Virmani R. Coronary risk factors and plaque morphology in men with coronary disease who died suddenly. *N Engl J Med* 1997;336:1276-82.
8. Naghavi M, Libby P, Falk E, Casscells SW, Litovsky S, Rumberger J, et al. From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: Part I. *Circulation* 2003;108:1664-72.
9. Cheruvu PK, Finn AV, Gardner C, Caplan J, Goldstein J, Stone GW, et al. Frequency and distribution of thin-cap fibroatheroma and ruptured plaques in human coronary arteries: a pathologic study. *J Am Coll Cardiol* 2007;50:940-9.
10. Tanaka A, Imanishi T, Kitabata H, Kubo T, Takarada S, Tanimoto T, et al. Morphology of exertion-triggered plaque rupture in patients with acute coronary syndrome: an optical coherence tomography study. *Circulation* 2008;118:2368-73.

11. Virmani R, Kolodgie FD, Burke AP, Farb A, Schwartz SM. Lessons from sudden coronary death: a comprehensive morphological classification scheme for atherosclerotic lesions. *Arterioscler Thromb Vasc Biol* 2000;20:1262-75.
 12. Glaser R, Selzer F, Faxon DP, Laskey WK, Cohen HA, Slater J, et al. Clinical progression of incidental, asymptomatic lesions discovered during culprit vessel coronary intervention. *Circulation* 2005;111:143-9.
 13. Kajiya T, Liang M, Tan HC. High grade culprit lesions are common cause of STEMI: A changing paradigm. *J Am Coll Cardiol* 2013;61 Suppl; Abstract 1171-216. doi:10.1016/S0735-1097(13)60101-1.
 14. Frøbert O, van't Veer M, Aarnoudse W, Simonsen U, Koolen JJ, Pijls NH. Acute myocardial infarction and underlying stenosis severity. *Catheter Cardiovasc Interv* 2007;70:958-65.
 15. Manoharan G, Ntalianis A, Muller O, Hamilos M, Sarno G, Melikian N, et al. Severity of coronary arterial stenoses responsible for acute coronary syndromes. *Am J Cardiol* 2009;103:1183-8.
 16. Stone GW, Maehara A, Lansky AJ, de Bruyne B, Cristea E, Mintz GS, et al. A prospective natural-history study of coronary atherosclerosis. *N Engl J Med* 2011;364:226-35.
 17. Kolodgie FD, Gold HK, Burke AP, Fowler DR, Kruth HS, Weber DK, et al. Intraplaque hemorrhage and progression of coronary atheroma. *N Engl J Med* 2003;349:2316-25.
 18. Burke AP, Kolodgie FD, Farb A, Weber DK, Malcom GT, Smialek J, et al. Healed plaque ruptures and sudden coronary death: evidence that subclinical rupture has a role in plaque progression. *Circulation* 2001;103:934-40.
 19. Mann J, Davies MJ. Mechanism of progression in native coronary artery disease: role of healed plaque disruption. *Heart* 1999;82:265-8.
-