Are the Culprit Lesions Severely Stenotic?

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Section Editor: Gregg W. Stone, MD
New York, New York

AT THE END OF THE 1980S, DATA OF RETROSPECTIVE ANGIOGRAPHIC studies suggested that in more than two-thirds of patients, acute myocardial infarction (AMI) evolves from mild to moderate (<70%) stenosis. This observation has been a paradigm for many years, suggesting that unexpected thrombus formation was the main preventive target for acute coronary events. Yet, published data challenge this paradigm. Indeed, both angiographic studies as well as studies performed using intravascular imaging show that stenosis severity underlying an AMI is variable and often severe. The information provided by intracoronary imaging also suggests qualitative and quantitative heterogeneity of infarct-related plaques. The knowledge of this heterogeneity is likely to have major clinical implications.

Yes!

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Although important advancements have been pursued in the knowledge of mechanisms of coronary instability, severity of the underlying coronary stenosis leading to AMI is still debated. In particular, at the end of the 1980s a paradigm emerged from data of retrospective angiographic studies suggesting that in more than two-thirds of patients AMI evolves from mild to moderate (<70%) stenosis (1–3). However, data provided by pathologists have been contradictory. In particular, in a post-mortem study in 162 patients who died of AMI, mean percent luminal area reduction at sites of coronary thrombus was 91% (4). In another study by Davies and Thomas (5), 74 of 100 subjects who died within 6 h of an ischemic cardiac arrest had coronary thrombus; percent luminal area reduction at sites of coronary thrombus was ≥75% in 65% of cases. Finally, Narula et al. (6) found that mean percent vascular area involvement at sites of coronary thrombus was almost always more than 50%. Furthermore, the paradigm arising from angiographic studies is challenged by the wide range of time intervals between the first angiogram and AMI, and that a long time interval does not take into account the possibility of plaque progression between the two coronary angiograms as suggested by the frequent observation of angina onset some months before AMI (7). It is important to consider prospective angiographic studies: 1) focused on the progression to occlusive disease of coronary atherosclerosis; 2) performed in patients treated by thrombolysis or primary percutaneous coronary intervention (PCI) (8–18); and 3) pertaining to culprit lesion evaluation by intravascular imaging in the setting of AMI.

Early angiographic and post-fibrinolysis studies. Little et al. (1) in a study enrolling 42 patients demonstrated that in 66% of patients the artery that subsequently occluded had <50% stenosis on the initial angiogram. Of note, the first
angiogram was performed 706 ± 685 days before AMI. Similar observations were reported by Ambrose et al. (2). Indeed, Dacanay et al. (3) showed that among patients with Q-wave and a first angiogram <18 months before AMI, 82% had stenosis severity >50% as compared with only 33% when the first angiogram was >18 months from AMI. Similar findings have been reported by Ojio et al. (19). More recently, Zaman et al. (20), in a population of 41 patients with ST-segment elevation myocardial infarction (STEMI) and a previous coronary angiography showed that lesions leading to STEMI ≤3 months after evaluation were more severe than those leading to STEMI in >3 months before MI (59 ± 31% vs. 36 ± 21%, p = 0.02). Interestingly, Ojio et al. (19) and Zaman et al. (20) observed angiographic features of complex lesions in a variable proportion of patients (60% and 20%, respectively) at the angiogram preceding AMI, and may suggest that changes in plaque activity might have contributed to progression of lesion severity, in keeping with pathological studies showing that both multiple plaque ruptures and intraplate hemorrhage may cause lesion progression even in the absence of an acute coronary syndrome (ACS) (21).

Apart from the large time interval between the 2 coronary angiograms, early studies were limited by a retrospective design that may have introduced selection biases, while prospective studies indeed provided different information. In particular, the largest available prospective evidence comes from the CASS (Coronary Artery Surgery Study) study (8). In a cohort of 314 patients treated either medically or by coronary artery bypass graft surgery (CABG) that underwent a repeat coronary angiography within a 42- to 66-month period, the authors were able to show that the most important predictor of new segment occlusion both in patients treated medically and by CABG was the initial severity of lesion. In particular, in patients treated medically only 2.3% of stenosis <50% showed occlusion as compared with 13.5% of stenosis 50% to 95% and to 23.6% of stenosis 81% to 95%.

Other information that challenged initial studies focused on the angiographic severity of underlying stenosis leading to AMI were provided by the use of early thrombolysis in STEMI. Mathey et al. (9) showed that in patients presenting with STEMI the existence of high-grade fixed coronary stenosis prompted CABG. This should be taken into account as the presence of residual thrombus may overestimate lesion severity by angiography. However, independently of time of the repeat angiography, from 2 weeks in the study by Van Lierde et al. (11) to 5 weeks in that by Brown et al. (12), mean percent diameter stenosis in recanalized culprit vessels was around 60% by quantitative coronary analysis (QCA), suggesting that severe lesions may underlie coronary thrombosis at least in a subset of patients.

**Figure 1. Severity of Coronary Stenosis According to the Time Interval Between Angiography and Subsequent Acute MI**

Shorter time intervals are associated with greater stenosis severity. MI = myocardial infarction.
of thrombus were independent predictors of ACS. IVUS has helped in the clarification of the frequent dissociation between post-mortem data and angiographic severity of coronary stenosis due to expansive (positive) vessel remodeling.

Finally, data from the PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) study have suggested that a small luminal area (i.e., minimal luminal area ≤4 mm²) is independently associated with the 3-year risk of acute coronary events (27). In a substudy of the PROSPECT study, increasing baseline angiographic diameter stenosis was associated with an increased risk of major cardiovascular events (28), and that one-third of non–culprit lesion-related events showed a diameter stenosis >50% at baseline (29). Regarding the evaluation of lesion severity by OCT, it is worth mentioning a recent OCT study that showed in patients with ACS a mean area stenosis of about 80% (30).

Conclusions. The extent of stenosis underlying an AMI is heterogeneous, ranging from mild to severe. This heterogeneity suggests that either stenosis severity is a pure epiphenomenon not related to thrombus formation or that different pathogenetic mechanisms of coronary thrombosis may operate according to stenosis severity, a concept that needs to be further explored. Thus, some patients may have a moderate stenosis associated with strong thrombogenic stimuli, while others may have a severe stenosis causing an acute coronary syndrome, possibly in the absence of a strong thrombogenic stimulus.

Patients with severe stenosis indeed may develop an acute coronary syndrome due to shear stress–related thrombus formation (31). Furthermore, especially when a history of progressive recent angina is present, rapid plaque progression may lead to acute coronary syndrome due to intraplaque hemorrhage that is strictly linked to plaque inflammation (21). A recent OCT study showed that plaque progression was associated with the presence of TCFA and microchannels (32).

In contrast, patients with a moderate to mild stenosis presenting an ACS may be characterized by a potent thrombogenic stimulus. Some of the cases might be related to coronary erosion which is more often observed in women and smokers and characterized by less severe stenosis as compared with fissured plaques in post-mortem studies (33). Other patients may, however, have sustained vasoconstriction leading to thrombosis because of blood stagnation (34).

No!
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Acute thrombosis on a disrupted or eroded atherosclerotic plaque is responsible for acute myocardial infarction (AMI) in nearly all cases of type 1 infarction by the universal definition (35). In the 1980s and early 1990s, several small, retrospective angiographic studies in which patients had prior angiograms available revealed a surprising finding. In most patients, the culprit site responsible for subsequent AMI was usually <50% diameter stenotic on the first study. In many cases, the culprit site appeared normal (1,2,36–38). Additional data from other angiographic studies, intravascular ultrasound (IVUS) analyses, and pathologic studies at autopsy supported the concept that angiography underestimated plaque size, that angiographic results might appear normal even with large plaque burden related to positive remodeling (39), and that plaque was often nonobstructive before the acute event. Over time, this concept became accepted by cardiologists and was even incorporated into the characteristics of vulnerable plaque (40).

Nevertheless, if the preceding plaque was not angiographically severe, angiography at the onset of AMI usually depicted total occlusion. How could this occur? A contrary opinion to the idea of a mild angiographic lesion suggested that the lesion preceding myocardial infarction (MI) is not mild but usually severe, on the basis of several other data presented in the following discussion. In this report, we revisit the concept of the “mild diameter stenosis lesion” before MI and suggest how the contrary opinion does not contradict the concept of the mild lesion.

To examine the relationship between angiography and AMI pathogenesis,
time intervals should be assessed: 1) remote from AMI, when the responsible plaque is quiescent; 2) just before AMI; and 3) immediately after successful thrombolytic therapy or thrombectomy (Fig. 3). This discussion is limited for the most part to ST-segment elevation myocardial infarction (STEMI), previously defined as transmural or Q-wave AMI.

**Angiographic narrowing remote from AMI.** Other recent studies have supported the concept of the mild lesion, although not all cases were in patients with STEMI. These are presented to indicate a pattern seen in most studies related to acute coronary syndrome (ACS) and AMI pathogenesis.

In 2005, Glaser et al. (41) reported on 216 patients who required additional angiography for clinical progression at 1 year of a nontarget lesion. Fifty-nine percent presented with unstable angina and 9% with nonfatal MI. A majority of lesions (60.5% [95 of 157]) were <50% initially, and only 13% were >70%. These Percents were similar to those seen in the studies of the 1980s. Furthermore, in the PROSPECT study, nonculprit events represented nearly 50% of all repeat events at 3 years. IVUS in a subgroup with visual angiographic narrowing on the repeat study (71% [52 of 73]), while only 29% were >80% initially. Subsequently, Ellis et al. (43) found that the highest risk for subsequent anterior MI (either transmural or nontransmural) from CASS was a severe stenosis (90% to 98%) in the left anterior descending coronary artery. However, angiographic follow-up after the infarction was not available to confirm the severe stenosis as the culprit lesion (43). Similarly, Buchwald et al. (44) concluded that severe lesions preceded most transmural or Q-wave infarcts. Again, follow-up angiography was not available (44).

The last study of import comes from Mancini et al. (45), who analyzed 61 of 119 patients (56%) with optimal medical therapy who subsequently had AMIs and subsequent angiographic studies, as well as other patients with ACS without AMI or just more angina. Lesions with <50% diameter stenosis at baseline were responsible for only one-third of events. Patients with AMIs were not analyzed separately, and particularly in those with STEMIs, baseline angiographic data were not reported. Thus, of the 3 studies above, 2 (Ellis et al. [43] and Buchwald et al. [44]) did not have follow-up angiograms to document infarct site location, and 2 (Ellis et al. [43] and Mancini et al. [45]) included both STEMI and non-STEMI in their analyses. Because of these discrepancies, these data do not undermine the mild lesion argument.

**Angiographic narrowing in the days to weeks before AMI.** Two studies assessed angiographic narrowing immediately before STEMI. Ojio et al. (19) retrospectively assessed 40 patients with MI. Five-year angiographic follow-up from participants in CASS (Coronary Artery Surgical Study) indicated, on the basis of qualitative analysis of the angiograms, that severe lesions (>80% diameter narrowing on the first angiogram) were most likely to totally occlude on follow-up (8). However, no clinical data were available to assess their symptoms. Furthermore, there were many more lesions that were milder or <80% narrowed that occluded on the repeat study (71% [52 of 73]), while only 29% were >80% initially. Subsequently, Ellis et al. (43) found that the highest risk for subsequent anterior MI (either transmural or nontransmural) from CASS was a severe stenosis (90% to 98%) in the left anterior descending coronary artery. However, angiographic follow-up after the infarction was not available to confirm the severe stenosis as the culprit lesion (43). Similarly, Buchwald et al. (44) concluded that severe lesions preceded most transmural or Q-wave infarcts. Again, follow-up angiography was not available (44).

**Figure 3. Theoretic Cross Sections of a Coronary Artery at Different Stages in the Evolution to STEMI.**

The left panel demonstrates a thin-capped fibroatheroma (TCFA) with positive remodeling and only mild luminal narrowing. The second panel from the left depicts an artery with some progression and an asymptomatic plaque rupture with intraluminal thrombus formation. The lumen begins to narrow. This asymptomatic progression to ST-segment elevation myocardial infarction (STEMI) is accelerated in the days to weeks before the event. The third panel depicts the thrombosed plaque of an acute STEMI that has completely obliterated the lumen with acute thrombus over layered thrombus. After thrombolytic therapy or mechanical thrombectomy, the last panel depicts an open but still significantly narrowed arterial cross-section with both plaque and residual thrombus occluding the lumen. Illustration by Dr. Fridolin Sy.
2 angiograms before and after AMI onset, similar to the analyses reported previously. However, when they analyzed the angiographic narrowing in 20 patients, obtained 3 ± 3 days before Q-wave (n = 12) or non-Q-wave (n = 8) AMI, the narrowing averaged 71 ± 12% at the culprit site, while it was 30 ± 18% in the 20 control subjects with first angiographic studies 6 to 18 months before their subsequent AMI events. Likewise, Zaman et al. (20) found that lesions leading to STEMI were more often narrowed on the first angiogram if the clinical event was ≥3 months after the initial angiogram (n = 7) compared with >3 months (n = 34) (59 ± 31% vs. 36 ± 21% diameter stenosis, respectively, p = 0.02).

However, why were these patients studied right before AMI? The likely answer is that they were either symptomatic with new-onset unstable angina and/or a lesion had asymptptomatically destabilized but had not totally occluded before AMI. In support of that hypothesis, 70% of patients with an angiogram 3 days before AMI had angiographic evidence of acute, complex culprit lesions (19), as described originally by Ambrose et al. (46), while these lesions were infrequent in controls (10%). These complex lesions indicate plaque disruption and/or intracoronary thrombus. Thus, this group with more than mild lesions just happened to be studied immediately before the onset of either Q-wave or non-Q-wave MI. Growth of the plaque and narrowing of the lumen must occur at some point prior to the onset of AMI as the lesion progresses to total or near total occlusion at the time of AMI. Pathologically, autopsy studies indicate that the thrombosed lesion responsible for fatal MI or sudden coronary death contains both acute and healed thrombus (47,48). Multiple episodes of asymptomatic thrombus formation usually precede the fatal event. Pathologic analysis of thrombectomy specimens at the time of primary percutaneous coronary intervention in patients with STEMI have also indicated that organized thrombus can be extracted in more than 50% of patients (49). This also suggests some chronicity to the process. Finally, if one considers unstable angina to be the forerunner to AMI, particularly if untreated, plaque disruption and/or thrombus (a complex plaque) with a severe stenosis will be seen in >70% of cases in the culprit on angiography, while total occlusion is unusual (46,50). These processes help explain the findings of Ojio et al. (19) and Zaman et al. (20).

**Angiographic narrowing immediately after thrombolytics or thrombectomy.** After the successful opening of a totally occluded vessel with thrombolytic therapy or after mechanical thrombectomy, the culprit lesion is generally severely narrowed. This has been used to support the concept that a severe lesion usually precedes MI. Thus, in 151 patients with STEMI with spontaneous reflow or with immediate reflow after uncomplicated wiring of the lesion but before primary percutaneous coronary intervention, the underlying diameter stenosis was >50% in 96%, and in 66%, it was >70% (22). Similar findings were also reported by Manoharan et al. (23). The underlying culprit lesion after mechanical thrombectomy was severe in nearly all and was <50% in only 11%.

However, does the residual stenosis represent only plaque? Brown et al. (12) showed that residual thrombus is present following thrombolytic reopening of a vessel and that the underlying plaque was only moderate. Follow-up angiography in 2 different studies performed hours to weeks after thrombolytic therapy to allow endogenous thrombolysis showed that the residual diameter narrowing was moderate (50% to 57%) on follow-up (10,11). Pathologic studies after fatal MI also support the concept that the underlying culprit plaque (excluding acute thrombus) may not be severely narrowed. However, unless postmortem preparations pressure fix arteries, the degree of stenosis will be overestimated.

Such was the case in the study of Qiao and Fishbein (4), who found thrombosis on plaques that had a mean stenosis of 91%. With pressure fixation, Davies and Thomas (5) showed that the average area stenosis was 79%, corresponding to a diameter stenosis of 52%. Furthermore, heightened vaso-motion in epicardial arteries and in the microvasculature is common in STEMI and could increase residual diameter narrowing acutely (51).

Optical coherence tomography (OCT) and IVUS studies after thrombectomy are flawed and have added little concerning the degree of underlying area stenosis. IVUS cannot reliably distinguish between plaque and thrombus (52). Therefore, unless complete thrombectomy is done, the measured IVUS stenosis area is prone to significant overestimation. Hong et al. (53) assessed IVUS images in 125 patients with STEMI. Thrombus at the culprit lesion was not completely removed even after thrombectomy.

Although OCT has better resolution than IVUS (54), the yellow-orange color scale typically used in current Fourier transformation OCT may not easily distinguish it from surrounding plaque (55). Furthermore, lipid-rich plaque or thrombus causes OCT signal attenuation, which confounds accurate area measurements behind plaque and thrombus. Other studies using OCT in AMI (2,24) are also flawed in quantifying luminal narrowing by the lack of complete thrombus aspiration.

In conclusion, these data in total strongly support that in a majority but not in all cases, mild angiographic lesions usually precede STEMI in the months before AMI. These lesions are quiescent and usually are TCFAs on pathologic or intravascular analysis, in which positive remodeling has maintained luminal area despite being large plaques. However, in the days to weeks before STEMI, some are transformed through rapid progression from intraluminal thrombus formation or intra-plaque hemorrhage into truly vulnerable plaques that subsequently progress to symptomatic, total coronary occlusion. Most patients who subsequently develop STEMI are not fortunate to undergo angiography in time to detect
this rapid progression and eventual occlusion, as they are either asymptomatic beforehand or misinterpret their symptomatology. Finally, this concept of whether or not a lesion is mild or severe should not be considered frivolous. STEMI still accounts for hundreds of thousands of events each year. The demonstration of coronary atherosclerosis either through invasive angiography or otherwise is a premonitory sign that can occasionally progress to an acute and sometimes fatal event. Obviously, invasive angiography is insensitive to plaque size and atherosclerotic plaque burden. Nevertheless, the demonstration of atherosclerosis without severe diameter narrowing must be treated as aggressively medically as when severe disease is demonstrated. Otherwise, we perform a great disservice to our patients by reinventing the past!

However, we also do not want to assume that only mild stenoses have vulnerable potential and to not worry about fixing severe lesions. Although a majority of lesions leading to STEMI are not severely narrowed before the event, there are still some, as noted even in the earlier angiographic studies, that do have moderate or severe stenosis beforehand. Furthermore, as mentioned earlier, some severe stenoses are in the active process of transformation from prior mildly stenotic vulnerable plaques and require consideration for invasive management.

Author Disclosures
All authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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**Key Words:** acute myocardial infarction, angiographic stenosis, angiography, intracoronary imaging, stenosis severity.