Editorial Comment

Plaque Size, Vessel Size and Plaque Vulnerability: Bigger May Not Be Better

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Coronary thrombosis is now generally accepted as the proximate cause of acute coronary syndromes (1). Nearly 70% to 80% of coronary thrombi occur as a consequence of fissure or rupture of the fibrous cap of the plaque, with the remaining thrombi occurring from superficial endothelial erosions without a frank rupture or fissure (2–5). Plaques that have ruptured are generally characterized by a large, eccentric, lipid-rich atheromatous core, thinned-out fibrous caps with reduced smooth muscle cell and collagen content, increased inflammatory cell infiltration with mostly activated macrophages and, to a lesser extent, activated T-lymphocytes and mast cells, and increased neovascularization (6–8). Undisrupted plaques with similar compositional characteristics have, by inference, been considered vulnerable for disruption (the vulnerable plaque).

While the histomorphometric features of ruptured plaques (and by inference vulnerable but unruptured plaques) are reasonably well accepted, the relationship of such features to the size of the plaque and the severity of luminal obstruction is not as clear. Angiographic studies have suggested that 60% to 70% of acute coronary syndromes evolve from coronary lesions that in the weeks to months prior to the acute event were only mildly or moderately obstructive of the lumen (1,9–11). Similarly, it has been shown that in 30% to 40% of cases of acute myocardial infarction, myocardial stress perfusion scintigraphy, performed weeks to months before the index infarction, failed to reveal evidence for reversible ischemia in the corresponding myocardial segments (12). These studies have led to the popular concept that a significant number of acute coronary events attributed to plaque rupture and thrombosis result from “less obstructive” plaques often erroneously thought of as “small plaques.” On the other hand, prospective studies have also suggested that the risk of progression to total occlusion is greater in severe stenoses than in milder stenoses (13) and that at autopsy, coronary thrombosis is more prevalent in severely stenotic plaques (2,14). These observations raise the following questions: 1) how do we reconcile the seemingly paradoxical angiographic vs. autopsy results; 2) if true, why are less obstructive plaques more often responsible for acute coronary events; 3) are less obstructive plaques small or big; 4) does the plaque size or luminal stenosis correlate with histomorphometric and immunocytochemical determinants of plaque vulnerability?

Several potential explanations can account for the apparent angiographic–pathology paradox (Table 1). Angiographic, intravascular ultrasound and autopsy studies support question 1 and angiographic studies support question 2. Question 3 appears reasonable based on clinical experience and the known physiology of coronary collaterals. However, there has been little real data in support of questions 3 and 4. Loree et al. (15) have used in vitro models of stenoses with variable thickness of the fibrous cap, lumen size and lipid-core and demonstrated, with computer modeling, that circumferential stress is more in less obstructive plaques because of larger lumen size and higher wall stress (LaPlace’s Law). However, the clinical relevance of these data from in vitro models remains to be defined. The question of whether plaques that are less obstructive of the lumen are intrinsically more vulnerable because of compositional characteristics remains an intriguing but unsubstantiated possibility.

In this issue of the journal, Pasterkamp et al. (16) examined 254 of 1,521 cross-sections from 50 femoral arteries of 28 elderly patients (mean age of 79 years) dying of noncardiac causes to determine the relationship between vessel size, plaque area and lumen area on one hand and histomorphometric indices of plaque vulnerability (lipid-atheromatous size, collagen content, extent of smooth muscle cell and inflammatory cell immunoreactivity in the fibrous cap and shoulder regions of the plaque) on the other. The markers of vulnerability were observed significantly more often in cross-sections with the largest plaque area and vessel size, whereas there was no relationship between lumen area and the markers of vulnerability. Large plaque size despite less luminal encroachment suggested centrifugal arterial enlargement consistent with positive remodeling. These observations are in agreement with previous autopsy studies that have demonstrated that coronary plaques that result in acute thrombosis and myocardial infarction are often large (14,17). The authors speculate that positive remodeling and plaque rupture may share common pathophysiologic underpinnings, both reflecting extracellular matrix dysregulation at the base of the plaque (for positive remodeling) or in the cap (for plaque rupture).

Several limitations of the study by Pasterkamp et al. (16) must be pointed out. First, it is important to recognize that the concept of histomorphometric markers of vulnerability represents an extrapolation from data derived from already rupt-
Table 1. Why Do Most Acute Coronary Syndromes Evolve From Angiographically Determined Mild to Moderate Stenoses?

1. Angiography underestimates the severity of atherosclerosis and luminal narrowing, whereas pathological studies overestimate the severity of luminal stenosis.
2. Mildly stenotic plaques outnumber severely stenotic plaques by a factor of 5 to 10; therefore, even if severely stenotic plaques progress to occlusion from plaque disruption and thrombosis more frequently than mildly stenotic plaques, more total occlusions evolve from mildly stenotic plaques than from severely stenotic plaques.
3. Severely stenotic plaques are more likely to recruit collaterals than mildly stenotic plaques; therefore, progression from mild stenosis to total occlusion is more likely to result in an overt clinical event than progression from a tight stenosis to total occlusion.
4. Mildly stenotic plaques may be subject to greater circumferential hemodynamic stress because of larger luminal radius (LaPlace’s Law) than severely stenotic plaques, making them more susceptible to plaque rupture.
5. Mildly stenotic plaques may be intrinsically more vulnerable because of compositional characteristics.

Thus, bigger may not always be better.

References