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PART 2
Pathology

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2 CHAPTER 2

The pathology of vulnerable plaque

Renu Virmani, Allen P Burke, James T Willerson, Andrew Farb, Jagat Narula & Frank D Kolodgie

Although cellular and molecular biology studies have greatly advanced our knowledge of the pathophysiology of cardiovascular disease, our laboratory has gathered insight into the mechanisms responsible for coronary thrombosis by meticulous analysis of the underlying plaque morphology in autopsy specimens from sudden coronary death victims with severe coronary artery atherosclerosis.[1,2] In approximately 50–60% of these cases, the culprit lesion (fatal plaque) exhibits an acute coronary thrombus whereas the remainder include stable coronary plaques with >75% cross-sectional area luminal narrowing.[3] More than half of patients without acute coronary thrombi have healed myocardial infarcts that could be responsible for sudden death, and in 15–20% of cases there is no myocardial pathology to point to a terminal arrhythmia.[4] In this overview, we will discuss what characterizes an arterial plaque that is vulnerable to rupture in addition to how plaque progression leads to severe stenosis. These critical issues may help define the causes of sudden coronary death and assist in the development of treatment options targeting the unstable plaque.

Luminal thrombosis and acute coronary syndromes

Patients with acute coronary syndromes typically present with unstable angina, acute myocardial infarction, and sudden coronary death. Most acute coronary syndromes are precipitated by luminal thrombi, which arise from three different plaque morphologies: rupture, erosion, and calcified nodules.[4] Plaque rupture is defined as a lesion consisting of a necrotic core with an overlying thin disrupted fibrous cap heavily infiltrated by macrophages and T-lymphocytes; a luminal thrombus develops because of physical contact between platelets and the thrombogenic necrotic core. By contrast, erosions present with a luminal thrombus superimposed on a smooth muscle cell and proteoglycan-rich plaque with few inflammatory cells. Most eroded lesions are devoid of a necrotic core, but when present, there is no communication of the thrombus with the necrotic core because of a thick intact fibrous cap. Finally, the calcified nodule is the least common of all lesions that cause coronary thrombi. These lesions typically contain calcified plates along with bony nodules that erupt into a lumen devoid of endothelial cells.

The frequency of the coronary lesions with thrombi is 55–60% for ruptures, 30–35% for erosions, and 3–7% along with calcified nodules. Both ruptured and eroded lesions appear similar by angiography (Figure 2.1).[5] Although lesions with rupture occur in men of all ages (this is consistent for all plaque morphologies with thrombi), the frequency of sudden coronary death decreases with advancing age. Approximately 80% of coronary thrombi in women greater than 50 years old occur from plaque rupture and there is a strong association with circulating cholesterol. In acute myocardial infarction or sudden coronary death, plaque erosion occurs primarily in patients under the age of 50 years, and represents the majority of acute coronary thrombi in premenopausal women.[6] Further, 20–25% of acute myocardial infarcts occurring in hospitalized patients are due to plaque erosion.[7] In elderly patients, nonthrombotic substrates for sudden

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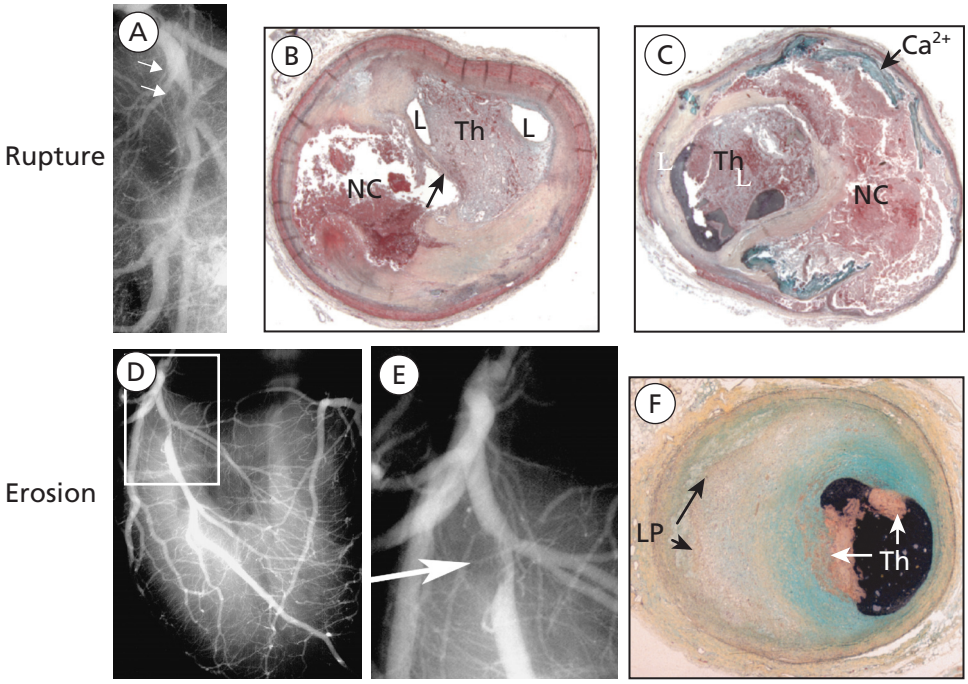

Figure 2.1 Angiographic and histologic representation of plaque rupture and erosion. A 43-year-old white male with no known history of risk factors was found unresponsive in the bathroom where he was last seen alive 20 minutes earlier. A, Postmortem angiogram shows the LAD at the origin of the left diagonal with a near total occlusion. Sections taken from these sites show a plaque rupture (arrow, B) with an underlying necrotic core (NC). The occluded artery shows an organizing thrombus with small lumens (L). In C, the fibrous cap is intact with a large underlying necrotic core with peripheral calcification (Ca^{2+}) and the lumen shows organizing thrombus (Th) with small lumens (L). At autopsy there was a healing transmural myocardial infarction present in the distribution of the LAD. Postmortem angiogram (D, E) and corresponding photomicrograph (F) from a 38-year-old man who was last seen alive 8 hours antemortem, who died from sudden coronary death. A focal stenosis is present in the left anterior coronary artery (boxed area), which is highlighted in E and an arrow points to the area of narrowing at the take off of the left diagonal. F, Acute nonocclusive luminal thrombus (Th) is present on the surface of an erosive plaque rich in proteoglycans (green), and the underlying plaque shows pathologic intimal thickening with lipid pools (LP). (Reproduced in part from figure 4, Farb A, et al., Circulation 1995;92:1701–1709.)

cardiac death, such as cardiomegaly and myocardial scarring, are more frequent.

Plaque rupture and its precursor lesion – the thin cap fibroatheroma

The morphology of plaque rupture consists of a relatively large necrotic core with an overlying thin disrupted fibrous cap infiltrated by macrophages. The smooth muscle cells component within the cap is absent or sparse. The thickness of the fibrous cap near the rupture site is 23 ± 19 μm, with 95% of the caps measuring less than 64 μm.[1] Those plaques that closely resemble ruptures but lack a luminal thrombus have been designated by our laboratory as thin-cap fibroatheromas (TCFA), or more traditionally, vulnerable plaques (Figures 2.2, 2.3).[4] In a more conservative sense, however, the term "vulnerable" should be reserved for lesions that underlie all causes of coronary thrombi, including pathologic intimal thickening, thick- and thin-cap fibroatheromas, and calcified plaques with nodules.

Although there are similarities, TCFAs differ from ruptured plaques based on a trend towards a smaller necrotic core, fewer macrophages within the fibrous cap, and generally less calcification (Table 2.1). We have quantified several morphologic

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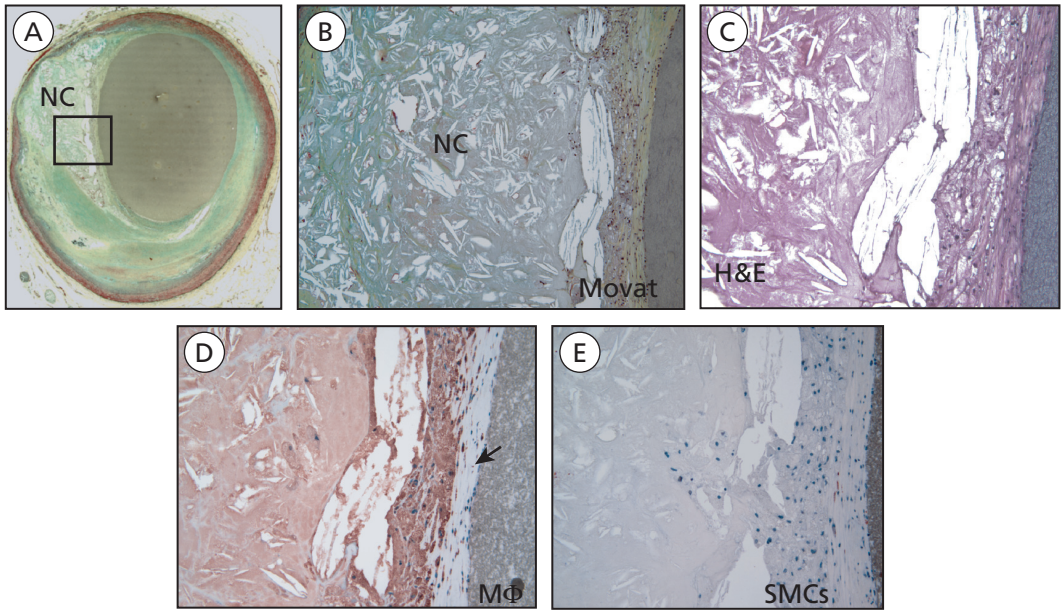

Figure 2.2 A nonhemodynamically limiting thin-cap fibroatheroma. A thin-cap fibroatheroma having a necrotic core (NC) and an overlying thin fibrous cap (<65 μm) is shown in A. B, High-power view of the boxed area in A. Note an advanced necrotic core with a large number of cholesterol clefts with surrounding loss of matrix, and no cellular infiltration is seen. The fibrous cap is infiltrated by macrophages, better seen in C when stained by H&E. D and E show macrophage infiltration (CD68+) and rare staining of smooth muscle cells (α-actin positive) in the fibrous cap. (Reproduced with permission from Kolodgie F, et al., Heart 2004;90:1385–1391.)

Table 2.1 Morphologic characteristics of plaque rupture and thin-cap fibroatheroma. (Reproduced with permission from Kolodgie FD et al., Curr Opin Cardiol 2001;16:286–290.)

Plaque type	*Necrotic core (%)*	*Fibrous cap thickness (μm)*	*Mϕs (%)*	*SMCs (%)*	*T-lymph*	*Calcification score*
Rupture	34 ± 17	23 ± 19	26 ± 20	0.002 ± 0.004	4.9 ± 4.3	1.53 ± 1.03
TCFA	23 ± 17	<65	14 ± 10	6.6 ± 10.4	6.6 ± 10.4	0.97 ± 1.1
P value	NS		0.005		NS	0.014

Mean values ± standard deviation are given. Abbreviations: Mϕs = macrophages; SMCs = smooth muscle cells; T-lymph = T-lymphocytes; TCFA = thin-cap fibroatheroma.

parameters in various human coronary plaque types, including culprit lesions (Table 2.2). The number of cholesterol clefts in the necrotic core, vasa vasorum, and hemosiderin-laden macrophages are significantly greater in ruptured plaques than in erosions or stable plaques with >75% cross-sectional-luminal narrowing. Significant differences in cellular infiltration between TCFAs and ruptures were found only for macrophages as well as a greater accumulation of hemosiderin. Hemorrhagic events at other sites of the coronary vasculature are more common in rupture cases than in those with severe coronary disease without luminal thrombi. The mean number of hemorrhages in lesions from patients with plaque rupture was 2.5 ± 1.3 versus zero in erosion ($P = 0.0001$) and 0.05 ± 0.6 in stable plaques ($P = 0.04$).[4] Evidence of prior hemorrhages in TCFAs, when analyzed by anti-glycophorin

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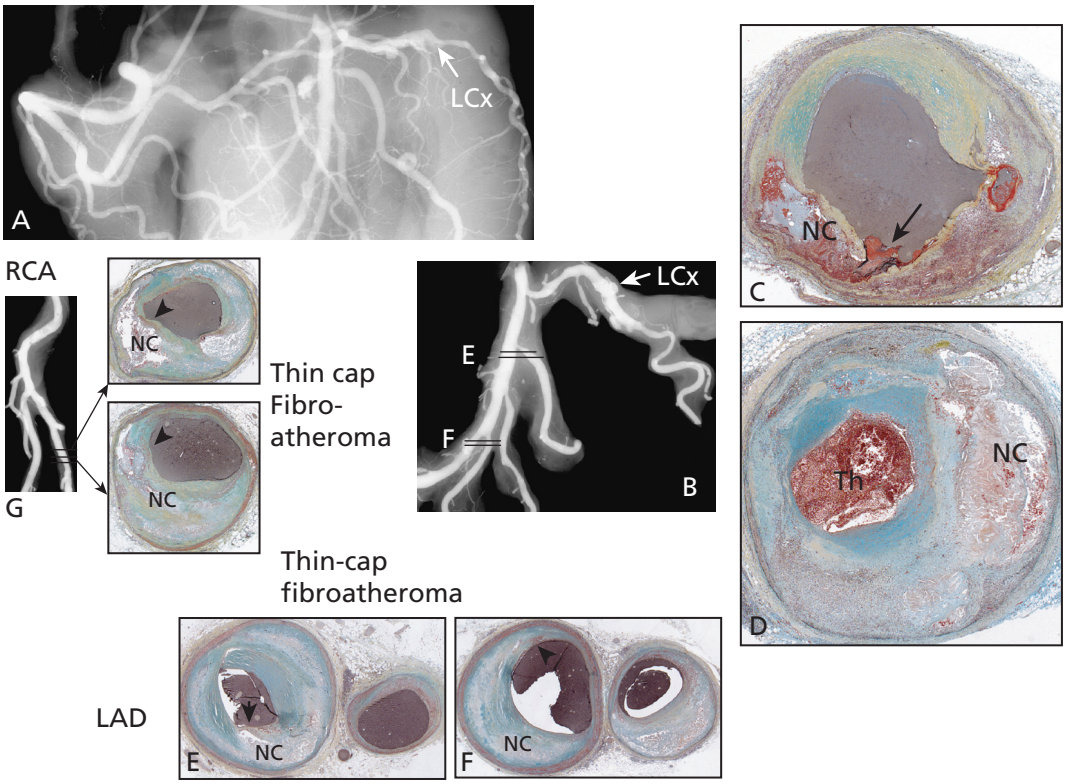

Figure 2.3 Plaque rupture in a 43-year-old white male who collapsed at work and could not be resuscitated. Patient had recent complaints of shoulder pain and headache but no known medical history or risk factor. At autopsy there was hemopericardium with 500 ml of blood and a long vertical tear on the posterolateral surface of the left ventricle. There was an acute transmural myocardial infarction lateral wall of the left ventricle and a hemorrhagic tract in the area of the rupture, which was located in the middle of the infarct. Coagulation necrosis with prominent neutrophilic inflammatory infiltrate was noted, consistent with a 2–3-day-old infarct. A postmortem angiogram showed total occlusion of the left circumflex (LCx) artery (arrow in A and B) and the sections showed the site of fibrous cap rupture (arrow in C) and an underlying hemorrhagic necrosis (NC), just distal to the site of rupture the coronary artery showed underlying atherosclerosis with a 70% diameter stenosis and an overlying occlusive thrombus (Th) (D). Sections taken from the first diagonal and left anterior descending (LAD) (E) and another from the third diagonal and LAD (F) show areas of thin cap fibroatheroma (vulnerable plaque) with mild insignificant luminal narrowing of the LAD with positive remodeling. G, Angiogram of the distal right coronary artery (RCA) and the PDA, shows mild irregularities and at the site of sectioning, shown in white lines. Note in these two sections the sites of thin cap fibroatheroma (vulnerable plaque; arrow) with thin fibrous cap and underlying necrotic core (NC). (Reproduced with permission from Kolodgie F. et al., Heart 2004;90:1385–1391.)

A staining (a protein specific to the erythrocyte membrane), is significantly greater than in fibroatheromas with early or late necrosis or lesions with pathologic intimal thickening and correlates with both necrotic core size and extent of macrophage infiltration.[8]

Healed plaque ruptures

Morphologic studies suggest that plaque progression beyond 40–50% cross-sectional-luminal narrowing occurs secondary to repeated ruptures, which may or may not be clinically silent. Ruptured lesions with healed repair sites are called healed plaque ruptures (HPR) and as shown by Davies et al., these plaques are easily detected microscopically by the identification of breaks in the fibrous cap with an overlying repair reaction consisting of a proteoglycan-rich mass or a collagen-rich scar tissue, depending on the duration of healing (Figure 2.4).[9]

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Table 2.2 Comparison of necrotic core size, number of cholesterol clefts, macrophage infiltration, number of vasa vasorum, and hemosiderin-laden macrophages in culprit plaques. (Reproduced with permission from Virmani R et al., Arterioscler Thromb Vasc Biol 2000;20:1262–1275.)

Plaque type	*Necrotic core (%)*	*Cholesterol clefts (%)*	*Macrophage infiltration of fibrous cap (%)*	*Mean no. vasa vasorum*	*Mean no. hemosiderin-laden macrophages*
Rupture	$34 \pm 17^{\Omega,\ni}$	$12 \pm 12^{*,\wedge}$	$26 \pm 20^{\Psi,\tau,\varpi}$	$44 \pm 22^{\varphi,\perp,\partial}$	$18.9 \pm 11^{\delta,\lambda,\notin}$
TCFA	24 ± 17	8 ± 9	$14 \pm 10^{\Psi}$	$26 \pm 23^{\varphi}$	$4.4 \pm 3.6^{\sigma}$
Erosion	$14 \pm 14^{\Omega}$	$2 \pm 5^{*}$	$10 \pm 12^{\tau}$	$28 \pm 18^{\perp}$	$4.3 \pm 4.7^{\lambda}$
Stable	$12 \pm 25^{\ni}$	$4 \pm 6^{\wedge}$	$3 \pm 0.7^{\varpi}$	$13 \pm 9^{\partial}$	$5.0 \pm 9.3^{\notin}$
P value	Ω 0.003	*0.002	Ψ 0.005	φ 0.07	δ 0.001
	$\ni$ 0.01	^0.04	$\tau < 0.0001$	$\perp$ 0.02	$\lambda < 0.0001$
			ϖ 0.0001	∂ 0.01	$\notin$ 0.03

Abbreviation: TCFA = thin-cap fibroatheroma.
The Greek notations are for comparison.

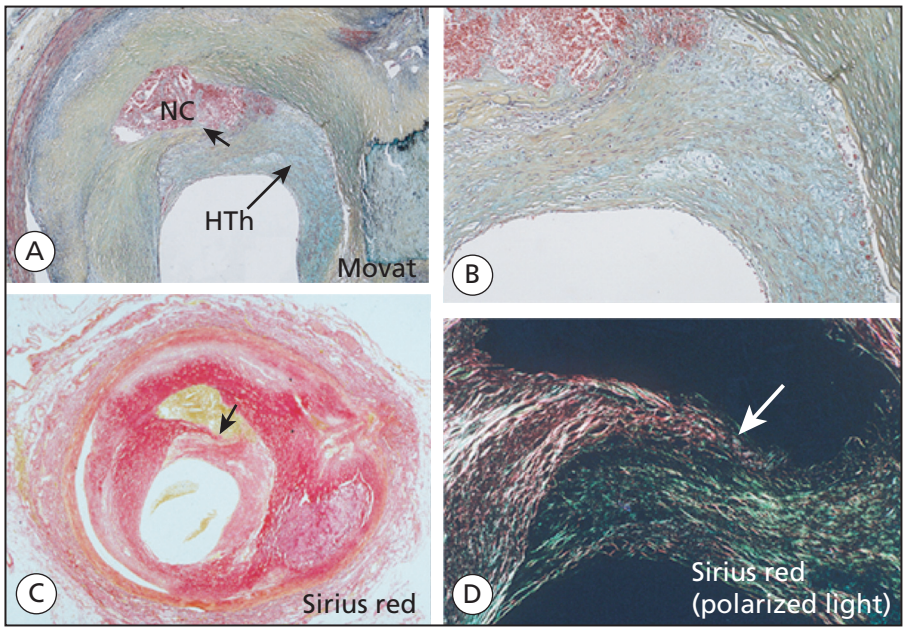

Figure 2.4 Healed plaque rupture. A and B, Movat pentachrome. A, Areas of intraintimal lipid-rich core with hemorrhage and cholesterol clefts; an old area of necrosis (NC) is seen underlying a healed thrombus (HTh). B, Higher magnification showing extensive smooth muscle cells within a collagenous proteoglycan-rich neointima (healed thrombus) with clear demarcation from the fibrous region of old plaque to right. C and D, Layers of collagen by Sirius red staining. C, Note area of dense, dark-red collagen surrounding lipid hemorrhagic cores seen in corresponding view in A. D, Image taken with polarized light. Dense collagen (type 1) that forms fibrous cap is reddish-yellow and is disrupted (arrow), with newer greenish type III collagen on right and above rupture site. (Reproduced with permission from Burke et al., Circulation 2001;103:934–940.)

Early-healed lesions are rich in proteoglycans, which is eventually replaced by type I collagen.

The prevalence of silent ruptures in the clinical population is unknown. Few angiographic studies have demonstrated plaque progression and short-term studies have suggested that thrombosis is the likely cause. Davies showed that the frequency of HPRs increases along with lumen narrowing.[9] In

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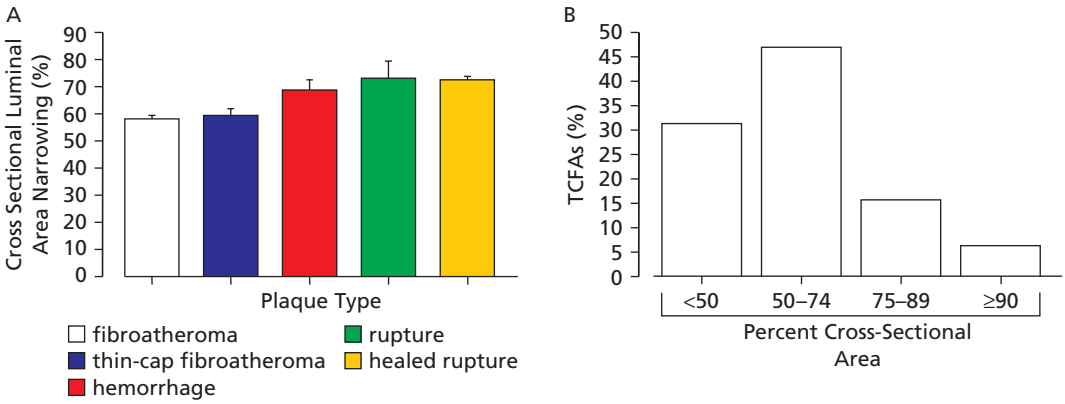

Figure 2.5 Morphometric analysis of thin-cap fibroatheromas. A, The percentage cross-sectional area luminal narrowing by type of plaque. The thin-cap fibroatheromas and fibroatheromas are less narrowed than plaque rupture and healed plaque rupture. B, Over 80% of thin-cap atheromas have <75% cross-sectional area luminal narrowing.

plaques with 0–20% diameter stenosis, the incidence of HPRs was 16%, and in lesions with 21–50% stenosis the incidence was 19% and in plaques with >50% narrowing, the incidence was 73%. In our laboratory, 61% of hearts from sudden coronary death victims show HRPs; this incidence is highest in stable plaques (80% HPRs), followed by acute plaque rupture (75% HPRs) and plaque erosions (9% HPRs).[10] Multiple healed ruptures with layering were common in segments with acute and healed ruptures and the percent cross-sectional-luminal narrowing was dependent on the number of healed repair sites. The underlying percent luminal narrowing for acute ruptures exceeds that for healed ruptures (79 ± 15% vs. 66 ± 14%, $P = 0.0001$).

Thin-cap fibroatheroma – location, extent of luminal narrowing, length and percent area of the plaque occupied by necrotic core

The extent of luminal narrowing varies with lesion morphology (Figure 2.5A). TCFAs and fibroatheromas have the least luminal narrowing while lesions with acute plaque rupture, hemorrhage, or healed repair sites show the most stenosis. The vast majority of TCFAs (over 80%) have <75% cross-sectional-area luminal narrowing (i.e. <50% diameter stenosis, Figure 2.5B). Healed and acute plaque ruptures show the severest narrowing with 46% and 43%, respectively showing less than 70% cross-sectional-area narrowing. By contrast, only 27% of TCFAs show severe luminal narrowing (Figure 2.6). In a population whose first manifestation of coronary disease is sudden death, these findings are consistent with the hypothesis that TCFAs are precursor lesions to ruptures and that healed plaque ruptures are mostly clinically silent.[10]

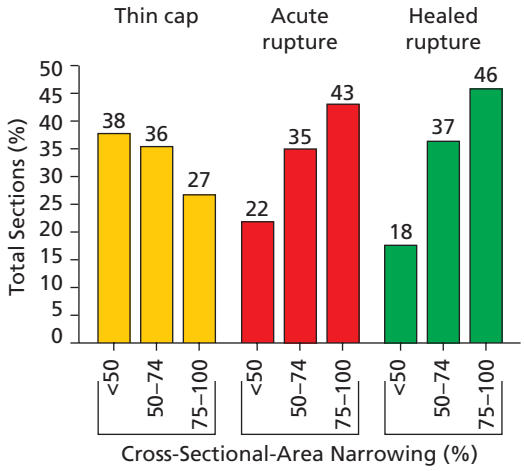

Figure 2.6 Percent cross-sectional area narrowing by plaque morphology. Severe narrowing (>75% cross-sectional area luminal narrowing) was more frequently seen in plaque ruptures and healed plaque ruptures than thin-cap fibroatheroma. Note 74% of thin-cap fibroatheromas were ≤74% narrowed in cross-sectional area. (Reproduced with permission from Virmani R, et al., J Interv Cardiol 2002;15:439–446.)

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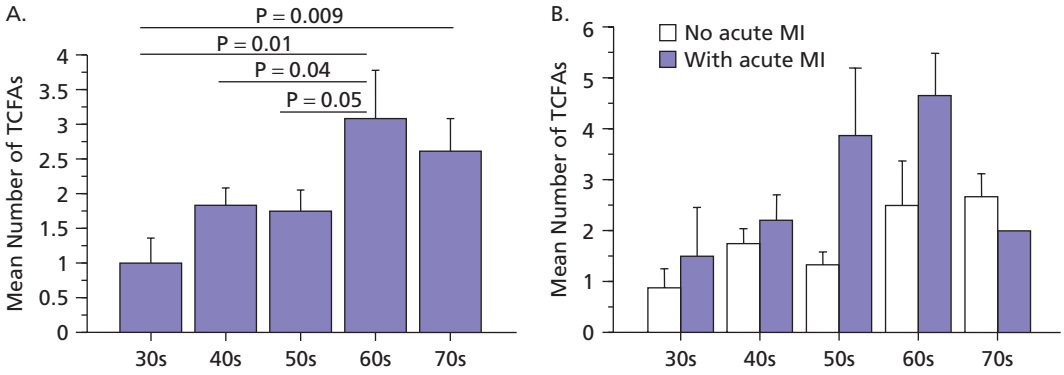

Figure 2.7 Frequency of thin-cap fibroatheromas by decades. A, Bar graph shows the mean number of thin-cap fibroatheromas (TCFAs) in individuals with sudden coronary death stratified by decades. Note, the majority of TCFAs are found in individuals in their sixties and seventies. B, Bar plot illustrating the mean number of TCFA (purple bars) in individuals with or without acute myocardial infarction (AMI). Patients with an AMI have a greater frequency of TCFA then those without and the difference are greater in those in their fifties and sixties.

Table 2.3 Approximate size of the necrotic core in advanced plaques. (Reproduced with permission from Virmani R et al., J Interv Cardiol 2002;15:439–46.)

	Plaque type		
Dimension	*Fibrous cap atheroma*	*Thin-cap fibroatheroma*	*Acute plaque rupture*
Length (mm)			
Mean	6	8 mm	9 mm
Range	1–18 mm	2–17 mm	2.5–22 mm
Necrotic core area (mm^2)	1.2 ± 2.2	1.7 ± 1.1	3.8 ± 5.5
Necrotic core (%)	15 ± 20	23 ± 17	34 ± 17

Values of the necrotic core represent mean ± SD.

In sudden coronary deaths, the number of TCFAs is least in individuals dying in their thirties versus their sixties or seventies. Although the incidence of TCFAs occurring in the thirties, forties or fifties is similar, there is a sudden rise in the sixties and seventies (Figure 2.7A). Moreover, the incidence in each decade is highest in individuals dying with an acute myocardial infarction versus those without a history of infarction (Figure 2.7B).

The mean necrotic core size in lesions from sudden coronary death victims is independent of luminal narrowing and greatest in plaque ruptures, followed by TCFAs, and is least in fibroatheromas (Table 2.3). In a detailed morphometric analysis of ruptured plaques, 80% of necrotic cores were larger than 1.0 mm^2 and comprised >10% of the plaque area in nearly 90% of lesions (Figure 2.8). In 65% of ruptures, the necrotic core occupies >25% of the plaque. By contrast, only 75% of TCFAs have necrotic cores >10% of the plaque area. The mean cross-section-luminal narrowing in TCFAs is 71% with the necrotic core representing 10–25% of the lesion. On the other hand, the length of the necrotic core in ruptures and TCFAs is similar, varying from 2 to 22.5 mm, with a mean of 8 and 9 mm, respectively (Table 2.3).[11] In plaque vulnerability, it may be critical whether the necrotic core is circumferential and what percentage of the artery is affected. We have measured the circumference of necrotic cores in cross-sections of coronary arteries and

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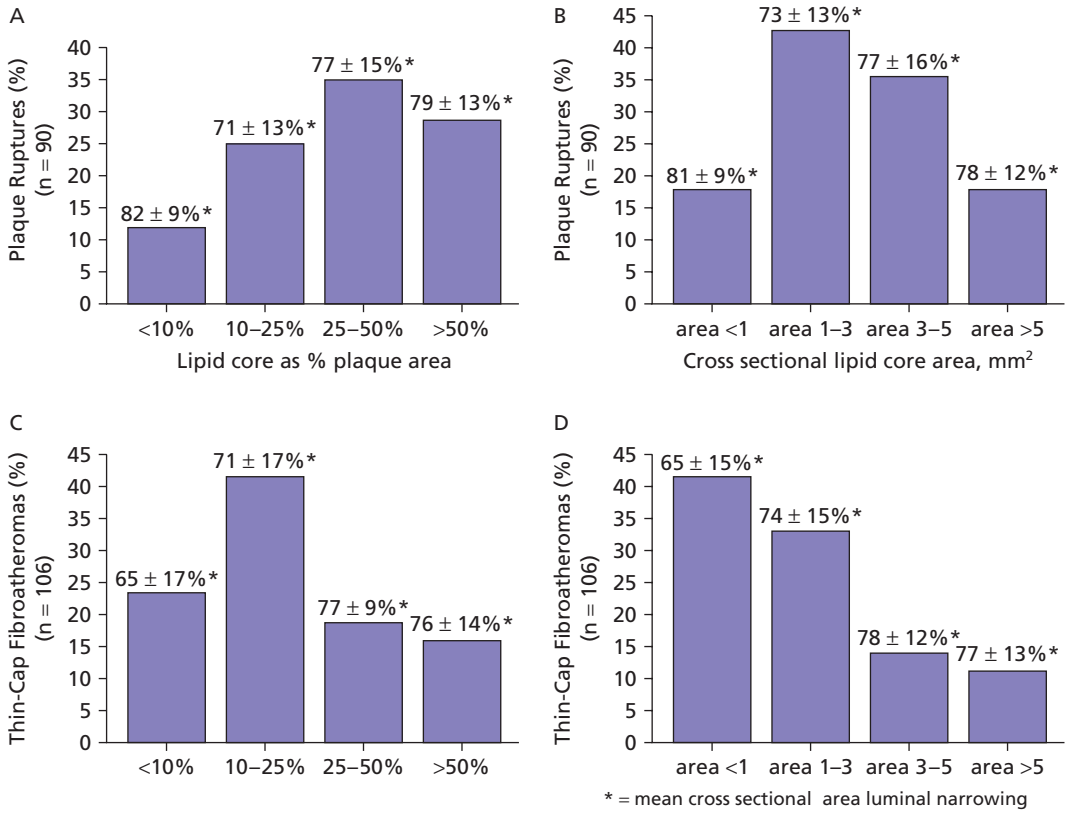

Figure 2.8 The distribution frequency of plaque ruptures (A, B) and thin-cap fibroatheromas (C, D) by size of lipid core or lipid core as a percent of plaque area. The majority of plaque ruptures occur when the lipid core area forms 25–50% of plaque area, or 1–3 mm^2 lipid core area. In the case of thin-cap fibroatheromas, the degree of cross-sectional area luminal narrowing and area of necrotic core is shifted to the left (lesser or smaller) as compared to plaque ruptures. (Reproduced with permission from Burke AP, et al., J Am Cardiol 2003;41:1874–1886.)

have determined that on average 75% of TCFAs have >120 degrees of the intima affected by necrosis (Figures 2.9, 2.10).

In 38 hearts with severe stenosis, in which the coronary arteries had been serially cut from the ostium to a distal intramyocardial location, the mean cross-sectional narrowing was least in lesions with TCFAs (59.6%), intermediate for those lesions with hemorrhage into a plaque (68.8%), and greatest in ruptures (73.3%) or healed plaque rupture (72.8%).[11] Overall, approximately 80% of TCFAs show <75% cross-sectional-luminal narrowing (Figure 2.5A), indicating that sites with <50% diameter stenosis are the most useful for the detection of vulnerable plaque. Moreover, acute and healed ruptures, lesions with intramural hemorrhage, and TCFAs

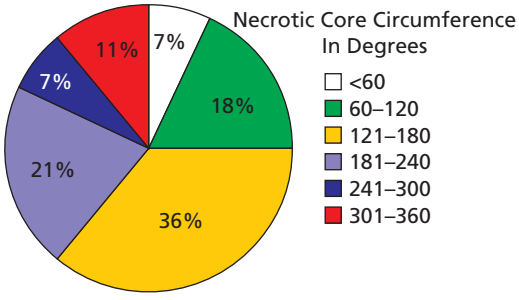

Figure 2.9 Circumferential presence of the necrotic core in each section measured in degrees. The majority of necrotic cores in thin-cap fibroatheromas are between 121 and 180 degrees in circumference; approximately 75% of these lesions have necrotic cores >120 degrees in circumference.

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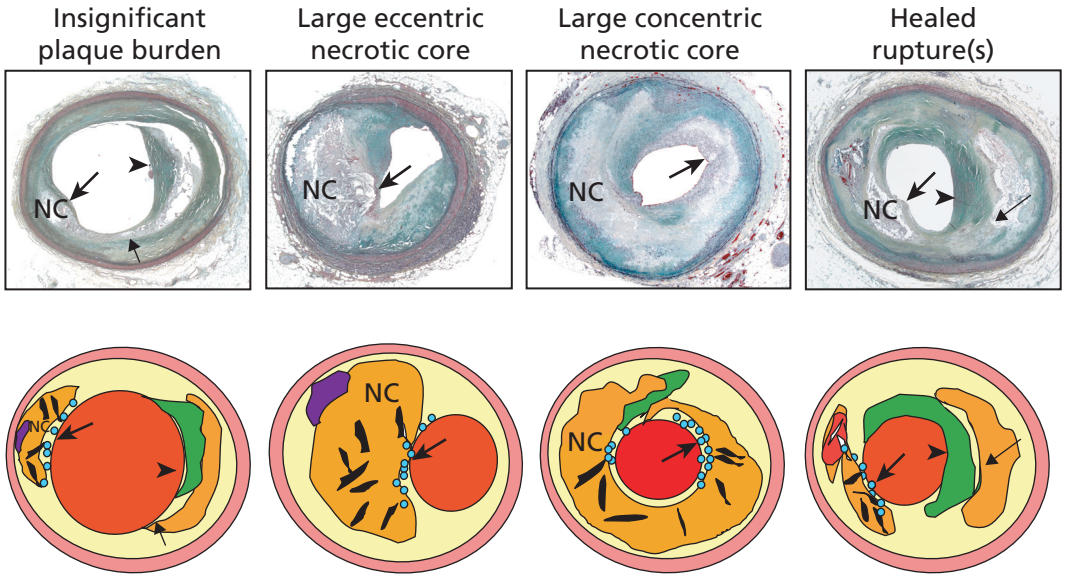

Figure 2.10 Photomicrographs with corresponding cartoon illustrations demonstrating morphologic variants of the thin-cap fibroatheroma. An attenuated fibrous cap infiltrated by macrophages, and sparsely populated by α-actin positive smooth muscle cells, characterizes this lesion. The underlying necrotic core may be calcified with areas of hemorrhage. The lesion in the left panel is an example of insignificant plaque burden; there is marked fibrous cap thinning (arrow) with a relatively small necrotic core (NC). A healed plaque rupture repair site is seen on the right (arrowhead) and the small arrow highlights the suspected point of rupture. The lesion on the extreme right shows a previous site of plaque rupture and an area of fibrous cap thinning (arrow) in a plaque with severe luminal narrowing. Stenotic lesions with previous healed repair sites and cap thinning are the most common variant of the thin-cap fibroatheroma. The two lesions in the middle panels are examples of plaques containing large eccentric or concentric necrotic cores with fibrous cap thinning (arrows). Note these lesions are an uncommon cause of sudden death in the presence of plaque rupture. In a large series of 142 cases only 11% of acute ruptures show rupture of a virgin plaque without evidence of prior rupture. Key: yellow = collagen; red = lumen/hemorrhage; green = new collagen; purple = calcification, orange = necrotic core, blue = macrophages, and white = cholesterol crystals. (Reproduced with permission from Kolodgie FD, et al., Curr Opin Cardiol 2001;16:286–290.)

are associated with positive remodeling, while stable plaques (fibrous-rich lesions), total occlusions, and erosions all show negative remodeling.

Incidence of thin-cap fibroatheroma in various coronary syndromes and its distribution in the coronary arteries

In patients with an acute myocardial infarction, the incidence of TCFAs is highest in males with a mean of three per heart with half as many in women (Figure 2.11). In patients dying suddenly, however, the incidence is similar between both sexes. Incidental deaths or those from plaque erosion show the fewest number of TCFAs. The number of TCFAs by plaque morphology shows the highest

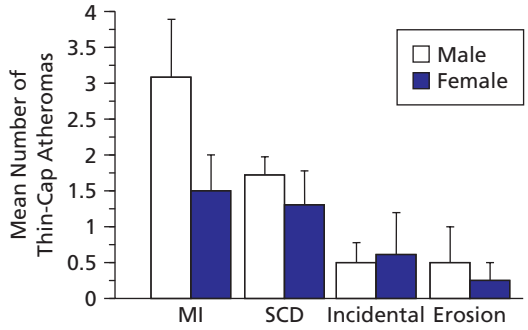

Figure 2.11 Thin-cap fibroatheromas are most frequent in patients dying with acute myocardial infarction (MI), followed by sudden coronary death (SCD) victims and incidental disease. Fibroatheromas and thin-cap fibroatheromas are uncommon in patients dying with plaque erosion. (Reproduced with permission from Burke AP, et al., J Am Coll Cardiol 2003;41:1874–86.)

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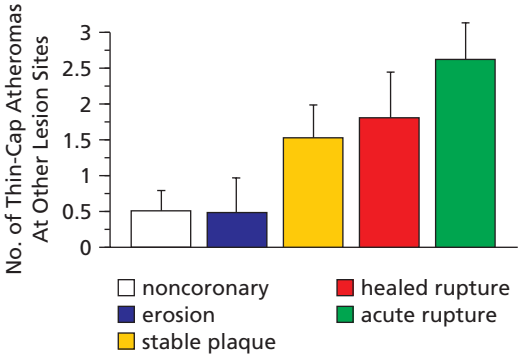

Figure 2.12 Number of thin-cap atheromas by cause of sudden coronary death. Bar graph showing the number of thin-cap fibroatheromas by cause of sudden coronary death. On average, each case of acute rupture shows at least two thin-cap fibroatheromas at other sites of coronary tree.

in cases of plaque rupture followed by healed plaque rupture, and stable plaques; the incidence is least in erosion and noncoronary deaths (Figure 2.12).[12]

Location and distribution of thin-cap fibroatheromas

The majority of TCFAs, acute and healed ruptures, lesion with intraplaque hemorrhage, and fibroatheromas occur predominantly in the proximal portion of the three major coronary arteries and about half arise in the mid-portion of these arteries (Figure 2.13). These lesions are few in the distal coronary circulation. By far the proximal portion of the left anterior descending coronary artery is the most frequent location with sites in the proximal right and left circumflex coronary arteries about half as common. Other locations of significant lesion development are infrequent (Figure 2.14).

Inflammation and causation of occlusive thrombi

We have shown that fibrous cap thickness is dependent on the amount of macrophage infiltrate; the thicker the fibrous cap the fewer the macrophages (Figure 2.15). Serial sections of TCFAs have show that necrotic cores may begin deep within the plaque but over a relatively short distance of <1.4 cm the lipid core may approach the lumen, and therefore serial sectioning may help identify the presence of TCFAs (Figure 2.16).

Many investigators believe that inflammation is predominantly responsible for acute coronary syndromes, in particular ruptured plaques.[13] Fibrous cap rupture allows platelets and inflammatory cells to come into contact with the thrombogenic necrotic core. Before the innovative studies of Nemerson et al., demonstrating circulating tissue factor, the necrotic core was thought to be its major source.[14] It is now thought that circulating monocytes rather than plaque macrophages support the development of acute thrombi in unstable coronary plaques.

In a preliminary study, monocyte infiltration of the thrombus correlated with the severity of

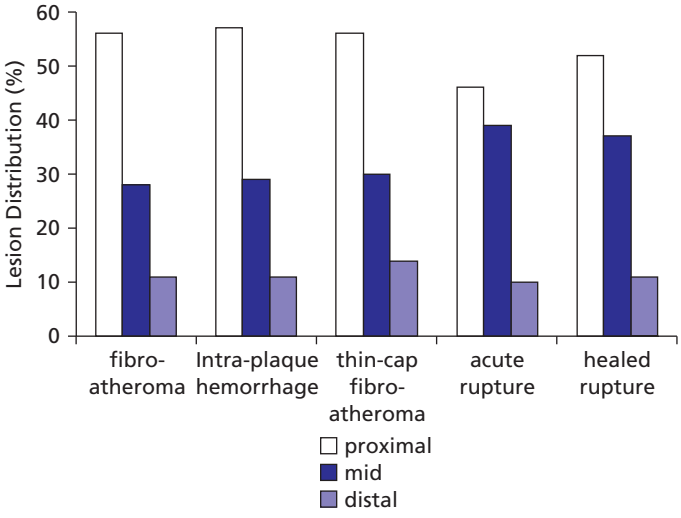

Figure 2.13 Distribution of various unstable plaques from the coronary ostium. Coronary locations were divided into proximal, middle, and distal.

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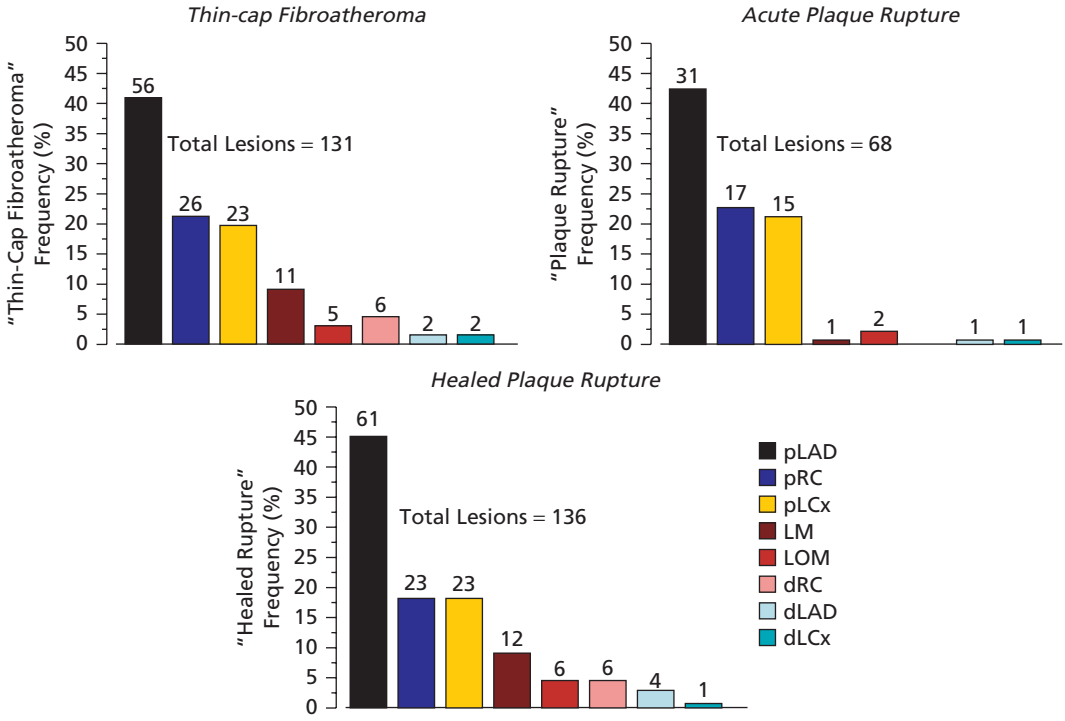

Figure 2.14 Bar graphs illustrating the frequency and location of thin-cap fibroatheromas. The proximal left anterior descending coronary artery (pLAD) represents the first 0.5 cm of the artery measured to the second diagonal branch. The proximal right coronary artery (pRC) includes the distance to the right marginal branch of the right coronary artery (first 5 cm). The proximal left circumflex (pLCx) is the level to the first left obtuse marginal (LOM) origin and is the most variable in length. LM = left main; dRC = distal right coronary; dLAD = distal left anterior descending; dLCx = distal left circumflex artery. Note, the majority of thin-cap fibroatheromas, ruptures, and healed ruptures occur in the pLAD. (Reproduced with permission from Kolodgie FD, et al., Curr Opin Cardiol 2001;16:286–290.)

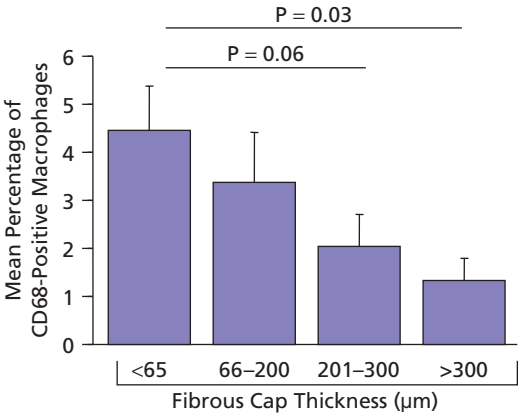

Figure 2.15 The relationship of fibrous cap thickness to macrophage infiltration. Bar graphs plotting the percentage of CD68-positive macrophages with fibrous cap thickness stratified into caps <65 μm, 66–200 μm, 201–300 μm, and >300 μm in thickness. The amount of macrophage infiltrate increases with decreased fibrous cap thickness.

thrombosis.[15] Occlusive thrombi showed a greater density of CD68-positive macrophage (15.7 ± 12.5% vs. 3.0 ± 2.7%, $P = 0.05$) and myeloperoxidase (MPO)-positive monocytes (12.2 ± 7.5% vs. 5.0 ± 2.7%, $P = 0.006$) and neutrophils (2.9 ± 3.4% vs. 0.36 ± 0.50, $P = 0.03$) than nonocclusive thrombi. Similarly, the length of the thrombus showed a positive correlation with the density of macrophages ($P = 0.004$) and MPO positive cells ($P = 0.04$) within the thrombus. In the disrupted fibrous cap, the density of MPO-positive cells was greater in occlusive (5.5%) than nonocclusive (0.9%) thrombi; although this association was similar for neutrophils (0.7% vs. 0.4%), this was not apparent for macrophages (13% vs. 20%). The precise role of MPO in triggering acute coronary thrombosis is unclear, in addition to providing a pro-oxidant milieu, the production of hypochlorous acid may cause breakdown of the fibrous cap.[16–18]

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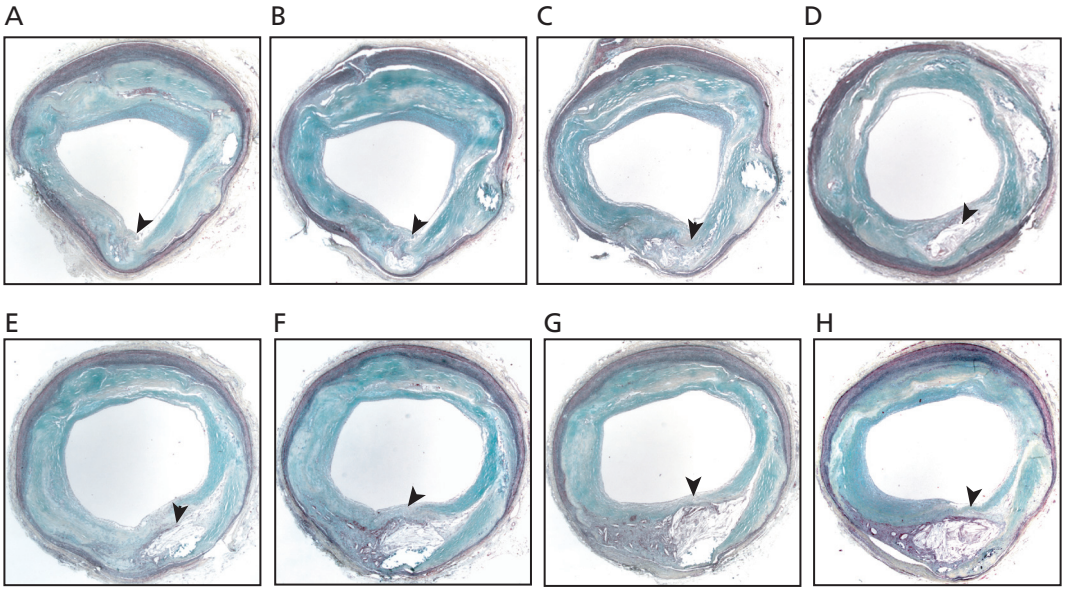

Figure 2.16 Serial sections of a thin-cap fibroatheroma. Photomicrographs to show a vulnerable plaque with sections taken at every 200-μm interval in the coronary artery of a patient dying suddenly with acute thrombus with underlying plaque rupture. Note the gradual increase in the necrotic core size (arrowhead) from A to E and thereafter the necrotic core is large with a thin fibrous cap that is infiltrated with macrophages. The necrotic core is rich in free cholesterol and there is extensive inflammatory reaction with giant cell formation. (Reproduced with permission from Virmani R, et al., J Interv Cardiol 2002;15:439–446.)

Plaque erosion

Plaque erosion is defined as an acute thrombus in direct contact with the intima in an area of absent endothelium. The underlying plaque in erosion is rich in smooth muscle cells and proteoglycan matrix.[6] We speculate that coronary vasospasm may be involved in its pathophysiology since macrophages and lymphocytes are typically absent. Further, eroded lesions tend to be eccentric and are infrequently calcified. The underlying lesion morphology tends to be that of pathologic intimal thickening or fibroatheroma. As with rupture, the most frequent location for erosion is the proximal left anterior descending (LAD; 66%) followed by the right (18%) and the left circumflex (14%) coronary arteries. Single vessel disease is approximately twice as frequent (56%) as double vessel (26%) disease. Finally, in comparison to ruptures, preliminary data suggests that erosions tend to embolize more frequently (74% vs. 40%), respectively.[19]

Plaque erosion accounts for 20% of all sudden deaths or 40% of coronary thrombi in patients dying suddenly with coronary artery thrombosis.[1,4,6] The risk factors for erosion are poorly understood and are different from those of rupture. Consistently plaque erosion is associated with smoking, especially in women; plaque erosions account for over 80% of thrombi occurring in women less than 50 years old. On average, individuals with erosion are younger than those with rupture, and there is less severe narrowing at the thrombus site.

Calcified nodules

The least frequent lesion associated with coronary thrombosis is the calcified nodule. These lesions consist of heavily calcified plates and fibrous tissue in lesions with or without a necrotic core. The luminal surface of the plaque shows fractured calcified plates with nodules of calcium and/or bone formation. Calcified nodules appear to erupt from the plaque into a lumen obstructed by a superimposed thrombus. There is often fibrin surrounding bony spicules along with osteoblasts and

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osteoclasts, and inflammatory cells.[4] Calcified nodules are more common in older male individuals than women. These lesions are more frequent in carotid than coronary arteries and may be related to repeated intraplaque hemorrhage.

Role of calcification in the detection of the thin-cap atheroma

Coronary calcification correlates highly with plaque burden, but its effect on plaque instability is less obvious. The earliest calcification in coronary lesions occurs in apoptotic smooth muscle cells in lesions with pathologic intimal thickening where the formation of remnant membrane vesicles shows active calcification. The coalescence of microscopic calcium deposits forms larger granules and plates that can be visualized by standard imaging techniques. In a series of sudden death cases, over 50% of TCFAs showed an absence or only speckled calcification on postmortem radiographs.[20] In the remaining segments, calcification was almost equally divided into fragmented or diffuse patterns, suggesting a large variation in the degree of calcification within these lesions. By contrast, 65% of acute ruptures show speckled calcification, with the remainder showing a fragmented or diffuse pattern. Plaque erosions are almost devoid of calcification or, when present, it is only speckled. Calcified nodules contain massive amounts of calcium relative to plaque area and in some instances even show bone formation. This type of lesion, however, only rarely triggers thrombosis and tends to occur in the right or left anterior descending coronary artery of older individuals.[4] It has been reported that calcification is greatest in sudden coronary death victims than those dying with acute myocardial infarction or unstable angina in arteries with 76–100% cross-sectional luminal narrowing.[21,22] However, in our experience in sudden coronary death victims, calcification is dependent on the age of the patient; radiographic coronary calcification is present in 46% of men and women under the age of 40 years, 79% of men and women aged 50–60 years, and 100% in individuals older than 60 years.[12] The amount of calcification within a coronary artery increases with age; however, women generally show a 10-year lag compared to men, with equalization by the eighth decade.

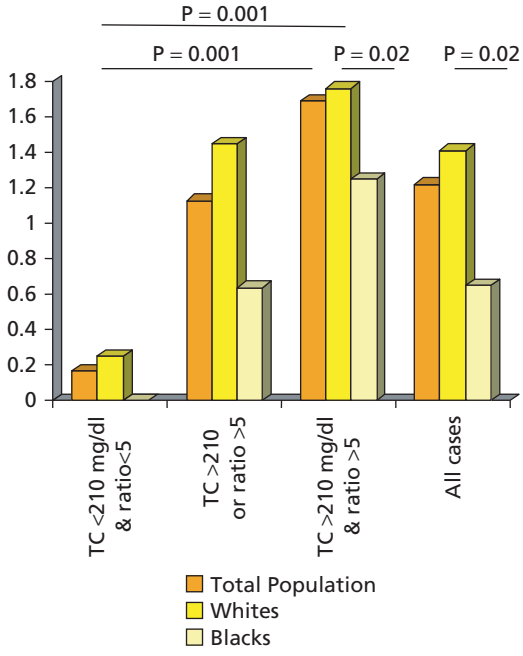

Figure 2.17 Mean number of thin-cap fibroatheromas and serum cholesterol in men. The bar plot is based on total population and race. The mean numbers of thin-cap fibroatheromas (TCFAs) are plotted against total cholesterol (TC) or total cholesterol/high-density lipoprotein cholesterol ratio (TC/HDL-C). The number of TCFAs are greatest in individuals with TC >210 and ratio >5. Whites generally demonstrated an increased incidence of TCFAs over blacks.

Role of risk factors in predicting thin-cap atheromas

Thin-cap fibroatheromas are a frequent finding in men dying suddenly with coronary thrombosis, in particular in individuals with a high total cholesterol (TC) and TC/high density lipoprotein (HDL) ratio (>210 mg/dl and TC/HDL-C ratio >5) (Figure 2.17).[1] The incidence of TCFAs in women is most frequent in those over 50 years with total cholesterol levels >210 mg/dl (Figure 2.18).[2] In sudden coronary deaths, smoking shows a positive correlation with thrombosis, and is more common in women with plaque erosion as compared to rupture.[2] Plaques of premenopausal women demonstrate relatively little necrotic core and calcification compared to those of postmenopausal status and men, possibly reflected by the high rate of plaque erosion in young women.[2] Another risk factor

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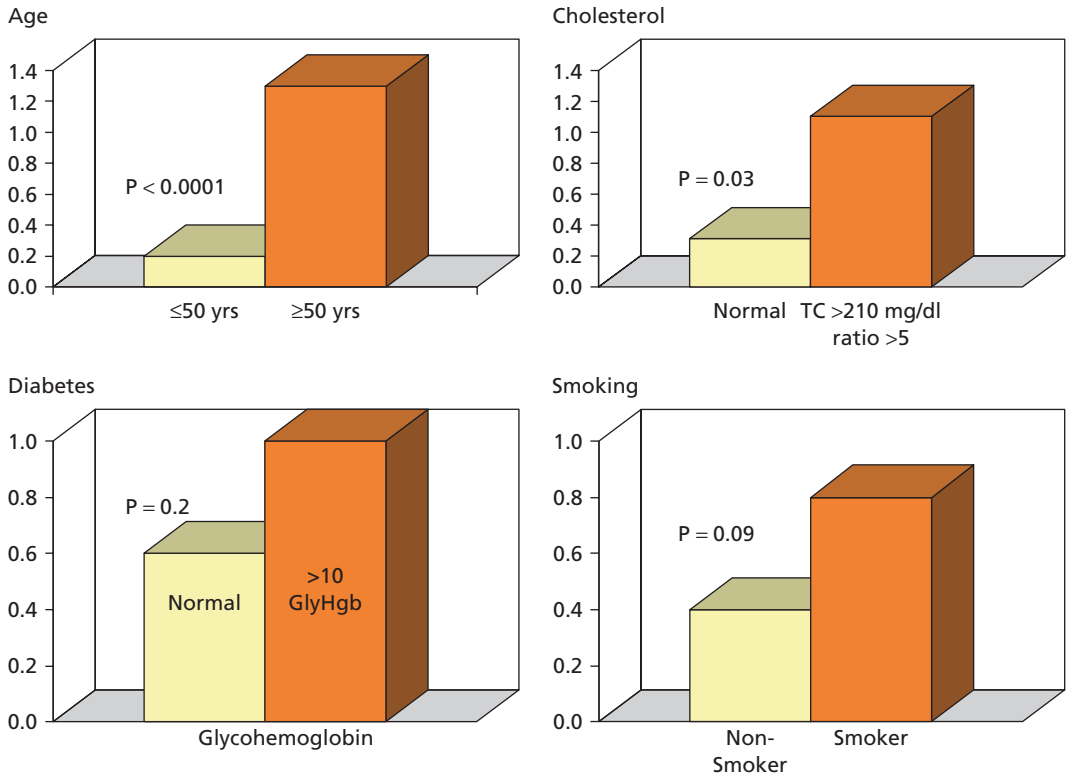

Figure 2.18 Mean number of thin-cap fibroatheromas in 51 women with sudden coronary death (SCD) and severe coronary disease. Traditional risk factors of age, cholesterol, diabetes, and smoking are plotted. In women, predictive factors of TCFAs include age, serum cholesterol, and smoking; diabetes as measured by glycohemoglobin was not. (Reproduced in part with permission from Burke AP, et al., Am Heart J 2001;141(2 Suppl):S58–62.)

reported to predict the development of acute coronary syndromes is high sensitivity C-reactive protein (hs-CRP, lower limit of normal is equal or less than 3 mg/ml).[23] The increased relative risk of sudden cardiac death associated with hs-CRP is seen only in the highest quartile, who were at a 2.78-fold increased risk of sudden cardiac death (95% CI 1.35–5.72) compared to men in the lowest quartile.[24] We have shown that the median hs-CRP was significantly higher in sudden coronary death victims dying of plaque rupture, erosion, or stable plaque than controls dying of noncoronary conditions (control hs-CRP 1.4 μg/dl versus sudden death 2.7 μg/dl, $P < 0.0001$).[25] By multivariate analysis, log-transformed hs-CRP levels were associated with greater plaque burden ($P = 0.03$), independent of age, gender, smoking, and body mass index. Antibody staining demonstrated hs-CRP localized to the necrotic core and surrounding macrophages and was strongest in patients with high serum hs-CRP levels. In addition, the mean number of TCFAs was most frequent in patients with high hs-CRP than in those with lower hs-CRP values (Table 2.4).[25]

Conclusions

The majority of acute coronary syndromes are the result of plaque rupture, followed by erosion, and least frequently eruptive calcified nodules. The lesion that mostly resembles acute rupture is the thin-cap fibroatheroma, which is characterized by a necrotic core with an overlying fibrous cap measuring <65 μm, containing rare smooth muscle cells and numerous macrophages. These lesions are mostly found in patients dying with acute

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Table 2.4 Correlation of serum hs-CRP with immunohistochemical staining intensity of plaques with thin-cap fibroatheromas. (Reproduced with permission from Burke AP et al., Circulation 2002;105:2019–23.)

CRP	*CRP staining intensity of plaques**	*Mean no. thin-cap fibroatheromas*
Low hs-CRP group (<1.0 mg/ml)	2.9 ± 0.5	0.95 ± 0.22
High hs-CRP group (>3.2 mg/ml)	6.2 ± 0.6	3.0 ± 0.3

*Staining intensity was assessed for macrophages and lipid core. A semiquantitative score of 0–4 was assigned to each section. A sum of the two scores resulted in an overall grading system of 0–8.
Abbreviation: hs-CRP = high sensitivity C-reactive protein.

myocardial infarction and are least common in plaque erosions or incidental noncoronary deaths. They are often located in the proximal coronary arteries, less frequent in the mid, and rarely present in the distal vessels. The average necrotic core length is ~2–17 mm (mean 8 mm) and the underlying cross-sectional area narrowing in the majority of lesions is <75%. The total necrotic core area in at least 75% of cases is 1 mm^2. Thin-cap fibroatheromas usually do not show severe luminal narrowing but are associated with positive remodeling and are generally less calcified than ruptures. Coronary risk factors such as high TC and high TC/HDL-C ratio, women >50 years, and patients with elevated levels of hs-CRP are predictive of thin-cap fibroatheromas. Because of its clinical significance, identification of the thin-cap fibroatheroma is a pivotal step towards reducing the morbidity and mortality of coronary artery disease. Newer imaging modalities and treatments are being developed, which will eventually play a significant role in the prevention and treatment of fatal cardiovascular events.

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