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Atheromas that cause fatal thrombosis are usually large and frequently accompanied by vessel enlargement☆

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Abstract

Several lines of clinical evidence show that AMI frequently occurs at sites with mild to moderate degree of coronary stenosis. The degree of luminal stenosis depends on plaque deposition and degree of vessel remodeling, features poorly assessed by coronary angiography. This postmortem study tested the hypothesis that the size of coronary atheroma and the type of remodeling distinguish culprit lesion responsible for fatal AMI from equi-stenotic nonculprit lesion in the same coronary tree. The main coronary branches from 36 consecutive patients with fatal AMI were studied. The culprit lesion (Group 1) and an equi-stenotic nonculprit segment (Group 2) obtained in measurements of another coronary branch from the same patient were compared. Morphometry and plaque composition was assessed in both groups. Compared to Group 2, Group 1 had larger areas of: plaque 9.6 vs. 4.7 mm^2, vessel 12.7 vs. 7.4 mm^2 and lumen 1.7 vs. 1.2 mm^2; ($P < .01$). Positive remodeling was more frequent in Group 1 than Group 2: 21/30 (70%) vs. 8/26 (31%). Plaque area correlated positively with lipid core and macrophages and negatively with fibrosis and smooth muscle cells. Atherosclerotic plaques that cause fatal thrombosis are more frequently positively remodeled and tend to be larger than nonculprit plaques with the same degree of cross-sectional stenosis. We tested whether arterial remodeling and plaque size vary between segments containing a fatal thrombosed plaque versus an equi-stenotic nonculprit plaque. Culprit vessel segments had higher cross-sectional areas of intimal plaque and of vessel wall than equi-stenotic nonculprit plaques. The cross-sectional area of the vessel correlated positively with both the lipid core area and $CD68^+$ macrophage content, and negatively with fibrosis area and smooth muscle cell content. These results add elements explaining limitations of angiography in identifying plaques and provide new insights into the role of remodeling in plaque instability.

Keywords: Atherosclerosis; Remodeling; Plaque; Myocardial infarction; Pathology

1. Introduction

As long appreciated by pathologists [1,2], compensatory enlargement of human arteries tends to maintain lumen area despite growth of atheromas. Recent coronary intravascular ultrasound (IVUS) [3–5] and histopathological [6] studies have documented different types and degrees of coronary remodeling in human coronary arteries. By IVUS, coronary shrinkage can contribute up to 39% of lumen reduction [7–10]. Despite consistent data relating stable angina and lumen loss with negative coronary remodeling

Table 1
Distribution of lesions

	Group 1	Group 2	*P* value
% stenosis[a]	84 ± 13	79 ± 11	NS
Coronary branch[b]			
LAD	14	17	
LCX	6	7	NS
RCA	16	12	
Distance from the ostium[c]	3.7 ± 2.1	2.9 ± 1.6	NS

[a] Mean ± S.D. of degree of stenosis.
[b] Number of coronary artery; LDA, left anterior descending; LCX, circumflex; RCA, right coronary artery.
[c] Value expressed in centimeters, mean ± S.D.

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Table 2
Morphometric and composition differences between groups

	Culprit lesions (Group 1)	Nonculprit lesions (Group 2)	*P*
Plaque area[a]	9.6 ± 4.7	4.7 ± 2.3	.01
Lumen area[a]	1.7 ± 1.5	1.2 ± 0.9	.01
Vessel area[a]	12.7 ± 5.0	7.4 ± 3.0	.01
% lipid core[b]	33.8 ± 22.0	6.5 ± 11.4	.01
% fibrosis[b]	39.9 ± 19.5	64.4 ± 16.3	.01
% muscle cells[b]	2.2 ± 3.3	9.2 ± 9.2	.01
% macrophages[b]	4.6 ± 3.9	0.8 ± 0.9	.01

[a] Value expressed in mm^2, mean ± S.D.
[b] Percent of plaque area.

[7–10], little is known about coronary remodeling in lesions causing acute coronary syndromes. Pasterkamp et al. [11] demonstrated in femoral arteries association of histologic markers for plaque vulnerability with vessel enlargement. Recent angioscopic and IVUS studies [12,13] correlated lesions responsible for acute coronary syndromes with large plaques and vessel segment enlargement. No histopathological studies have focused on the size of atheromas and markers of plaque stability and instability in the light of these new concepts of coronary remodeling. Therefore, this study tested the hypothesis that

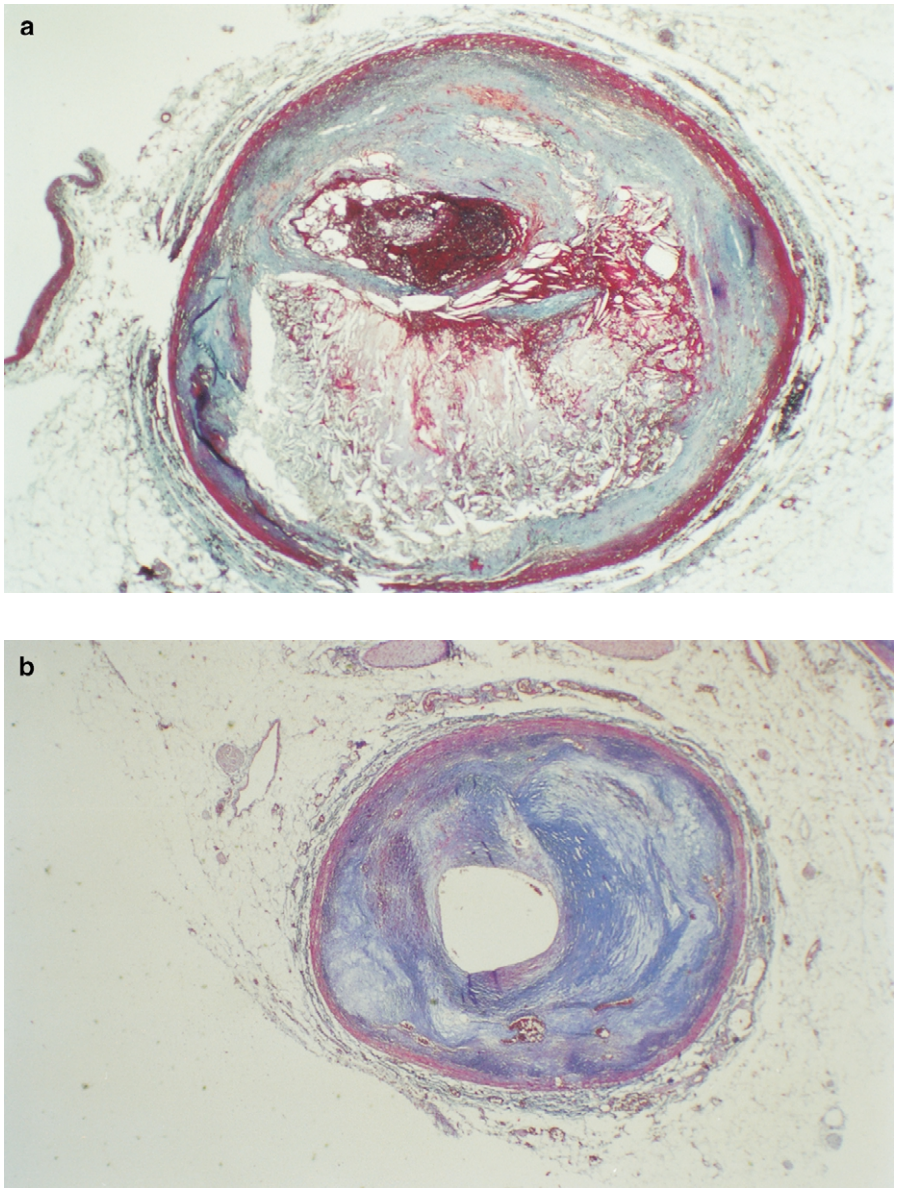

Fig. 1. An example of disparate remodeling and histological composition in a ruptured and equi-stenotic nondisrupted plaque in the same patient. The photomicrographs were taken at the same magnification (1.25 × — Masson's thichrome stain). Despite right coronary artery (RCA) was the dominant artery (which emitted the posterior-descending branch), the left circumflex coronary artery (LCX) was an important artery, irrigating all the lateral wall of left ventricle. (a) Shows the third centimeter of the RCA, which had positive vessel remodeling: vessel area of 16.2 mm^2, plaque area of 13.6 mm^2 and stenosis of 92.6%; the plaque has a large lipid core (49.8% of the plaque area). (b) Shows the third centimeter of the LCX, which did not show vessel remodeling: vessel area of 6.9 mm^2, plaque area of 5.5 mm^2 and stenosis of 90.6%; there is no discernable lipid core.

coronary lesions responsible for fatal AMI are large and characterized by vessel enlargement.

2. Methods

The present work was approved by the Scientific and Ethic Committee of the Heart Institute (InCor) of São Paulo University Medical School.

2.1. Population and coronary segments

The major coronary artery branches (right, left main, left anterior descending, left circumflex) from 36 consecutive patients who died due to AMI, in the period of 1985 and 1986, were studied retrospectively. Men comprised 61% ($n=22$) and women 39% ($n=14$). The mean age was 64.4 years. Patients died from 1 h to 29 days after beginning of symptoms. Autopsy was performed <12 h postmortem. Paraffin embedded coronary arteries were studied histologically in cross-section at 3-mm intervals. The culprit lesions (Group 1) were identified by reviewing all sections and detecting the acute vascular occlusion that correlated with the area of myocardial infarction found at autopsy. Plaque rupture was a more frequent cause of vascular occlusion 30/36 (83.3%) than plaque erosion 6/36 (17.7%) in accord with prior studies [14]. Tissue blocks containing the culprit lesions were sectioned serially to define the exact site of plaque rupture or erosion. At each interval of 30 μm, we reserved 5-μm thickness sections for future microscopic studies. After the analysis of percent area stenosis in the culprit lesion, we searched in the other major coronary branches of the same patient a corresponding nonthrombosed lesion with the most similar degree of stenosis. All segments were reviewed and diseased segments were measured to determine an equi-stenotic segment. These nonculprit lesions constituted Group 2. Chronically occluded arteries were excluded. Morphometric analysis showed similar mean percent of stenosis between the Groups 1 ($84\% \pm 13$) and 2 (79 ± 11), $P=$ NS. There was no significant difference between these two groups in the distribution of segments regarding the coronary artery branch and the mean distance from the coronary ostium (Table 1).

2.2. Histological procedures

For histomorphology and morphometry, the sections were stained with Movat, Masson and hematoxylin–eosin stain. Immunohistochemistry with mouse anti-human antibodies (Dako Patts) was used to visualize the presence of macrophages (CD 68) and smooth muscle cells (HHF 35). For CD68-epitope recovery, the sections were boiled in sodium citrate buffer (10 mM, pH 6.0) for 15 min before reactions. Indirect horseradish peroxidase or alkaline phosphatase technique was used for immunohistochemical detection of the epitopes.

2.3. Analysis

A Leica image analysis Quantimet 500 system was used for morphometry.

2.4. Morphometry

Movat-stain was used for morphometry of lumen area, vessel area encompassed by the elastic external lamina and plaque area (area encompassed by elastic internal membrane – lumen area). Measures were expressed in squared millimeter.

2.5. Cellular composition

Masson-stained slides were used for quantifying the fibrous component of plaque using color image analysis. Areas not stained with Masson were taken as representing lipid cores. Areas occupied by fibrous component and also positive areas of CD 68 and HHF 35 were automatic detected by difference of color and intensity. The results were expressed in percent area of plaque.

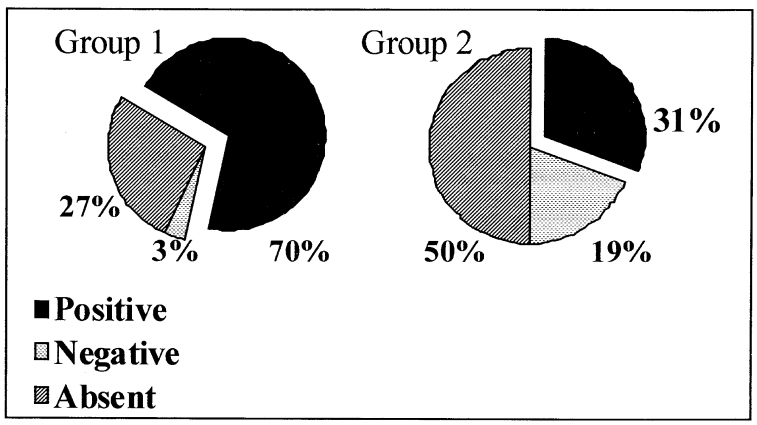

Fig. 2. In Group 1, predominate positive vessel remodeling (70%), oppositely to Group 2 in which predominate negative remodeling or no remodeling (69%).

Table 3
Morphometric and composition differences between ruptured and eroded plaques

	Ruptured	Eroded	*P*
Plaque area[a]	10.3 ± 4.9	5.9 ± 2	.01
Lumen area[a]	1.6 ± 1.7	2.2 ± 0.6	NS
Vessel area[a]	13.3 ± 5.1	9.7 ± 2.5	.02
% lipid core[b]	37.7 ± 21.4	14.3 ± 9.4	NS
% fibrosis[b]	35.3 ± 16	63.2 ± 14.9	.02
% muscle cells[b]	1.6 ± 2.6	5.2 ± 4.9	NS
% macrophages[b]	5.2 ± 3.9	1.7 ± 2.4	.05

[a] Value expressed in mm^2, mean ± S.D.
[b] Percent of plaque area.

2.6. Coronary remodeling

We assessed this variable in both groups when it was possible to identify a reference segment. For each group, two reference segments (proximal and distal) were selected with the smallest plaque burden and < 50% cross-section stenosis. Reference segment must be spaced at most 2 cm proximally or distally from the main lesion. Among 36 segments from Groups 1 and 2, the proximal or distal references were obtained in 30/36 and 26/36 segments, respectively. Remodeling was determined by the relative cross-sectional vessel area (lesion vessel area/reference vessel area) × 100%. The studied lesions showed three kinds of remodeling: positive remodeling (relative vessel area > 105% of the proximal reference or >125% of the distal reference), negative remodeling (relative vessel area < 95% of distal reference or < 75% of the proximal reference) and no remodeling when the relative vessel area was in-between these boundaries.

2.7. Statistical methods

All data were expressed as mean and standard deviation. Qualitative data were presented as frequencies. Comparison of data was performed using a one-tailed paired Student's *t* test. Differences were considered significant when *P* value was < .05. Pearson correlation was used to assess the relation between vessel size and plaque composition.

3. Results

The mean area of plaque was significantly higher in culprit lesions (Group 1) than in nonculprit lesions (Group 2) (Table 2 and Fig. 1). Despite Group 1 presented a mean area

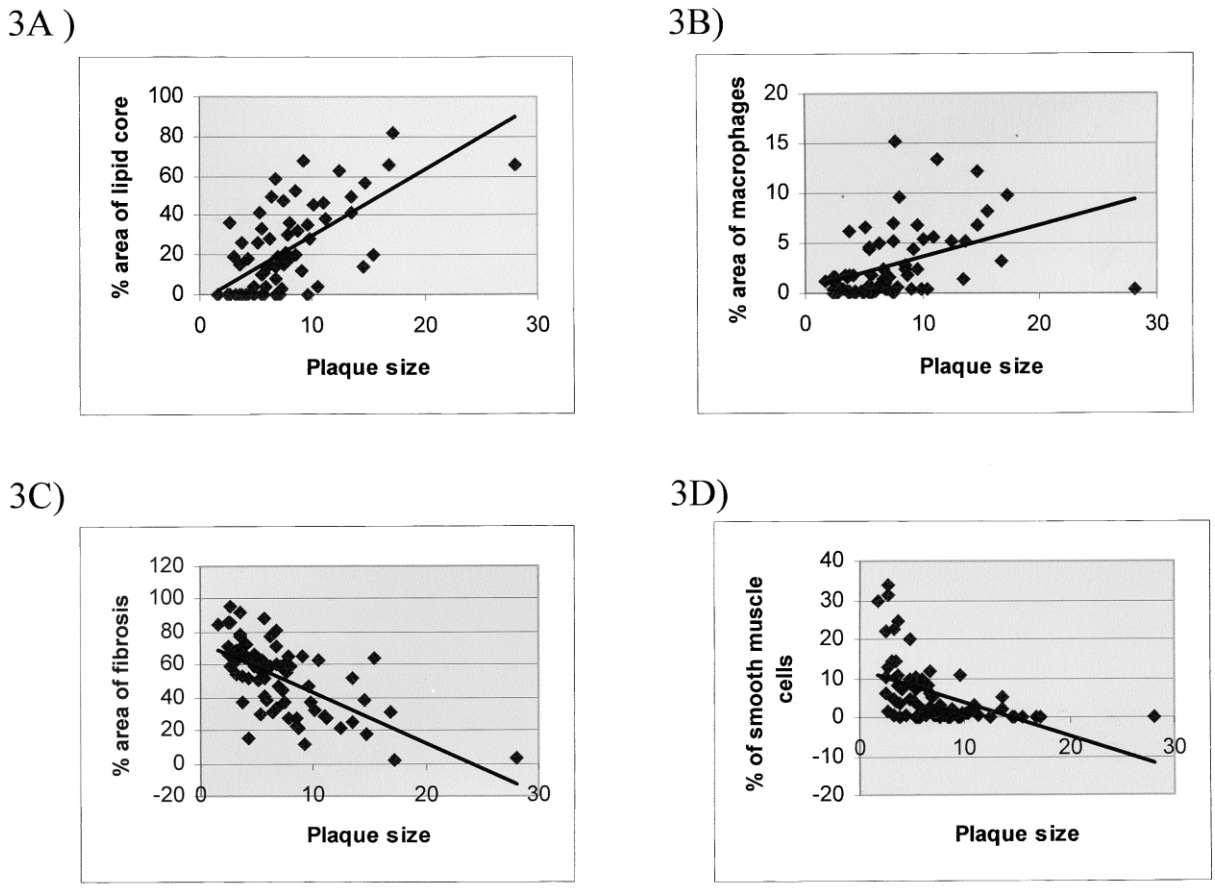

Fig. 3. (A, B) Represent the positive relation; between plaque size (values expressed in mm^2) and the percent area occupied by the lipid core and macrophages, $r = .68$ and .41, respectively ($P < .01$). (C, D) Show the negative relation between plaque size and percent area occupied by fibrosis and smooth muscle cells, $r = -.64$ and $-.48$, respectively ($P < .01$).

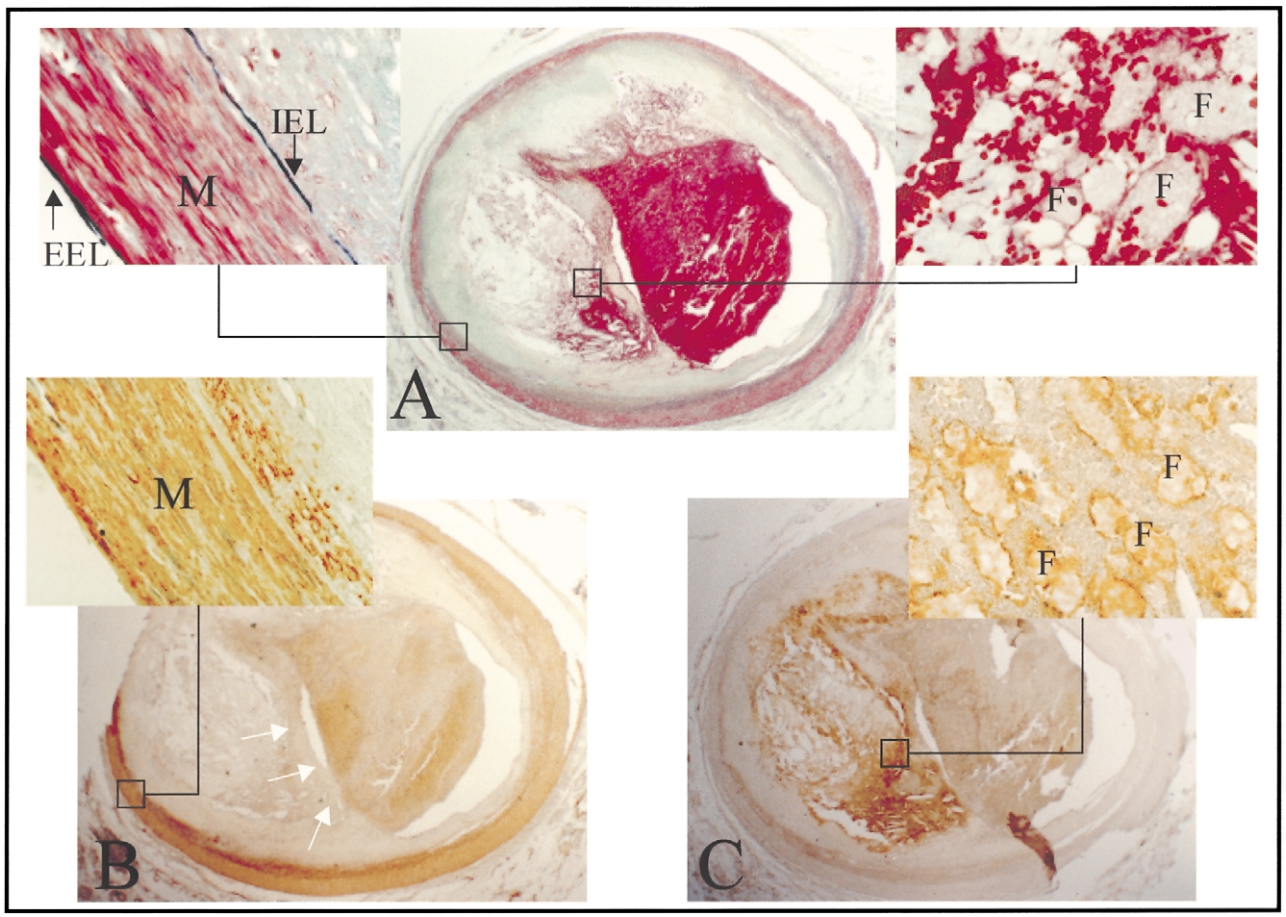

Fig. 4. An example of a thrombosed ruptured plaque that caused acute myocardial infarction with fatal outcome. (A) Movat stain. (B) The immunostaining for HHF 35 antigen shows that the fibrous cap does not have smooth muscle cells (white arrows), contrasting with the strong positivity of smooth muscle cells in the medial layer (insert). (C) Demonstrates that the plaque contains many macrophages immunostained for CD68 epitope concentrated near the cap (insert). IEL, internal elastic lamina; EEL, external elastic lamina; M, media layer; F, foam cell.

plaque larger than Group 2, the lumen area was more preserved in Group 1 (Table 2 and Fig. 1). The paradoxically finding of segments containing larger atheromas having a more preserved lumen than segments with smaller atheroma area was due to larger vessel area in Group 1 (Table 2 and Fig. 1). Culprit lesions more frequently had positive vessel remodeling, 21/30 (70%) than negative 1/30 (3.3%) or no remodeling, 8/30 (26.7%). In contrast, nonculprit lesions (Group 2) had predominantly negative 5/26 (19.2%) or no vessel remodeling 13/26 (50%) rather than positive remodeling 8/26 (30.8%) (Fig. 2). The evaluation of the type of vessel remodeling was precluded in 6 cases from Group 1 and in 10 cases from Group 2 because the lesions were too diffuse to permit selection of a reference segment.

In the culprit group, we searched for differences between segments containing an eroded plaque versus segments with ruptured plaque (Table 3). Plaque and vessel areas were significantly larger in ruptured plaques with significantly more area occupied by macrophages and a trend of presenting larger lipid core .In contrast, eroded plaque had more fibrotic component and tendency to have more area occupied by smooth muscle cells.

The vessel remodeling could only be assessed in three cases of eroded plaques, two of them showing lack of remodeling and the other positive vessel remodeling.

To further explore the role of larger plaques as culprits for acute coronary occlusion causing fatal AMI, we related the plaque size with the factors previously described as markers of vulnerability (macrophages and lipid core) and markers of stability. We found a positive correlation of plaque size with markers of instability and a negative correlation with markers of stability. The percent area of lipid core and macrophages correlated positively with plaque area: $r=.68$, $P<.001$ and $r=.41$, $P<.001$, respectively. The percent area of fibrosis and smooth muscle cells correlated negatively with plaque area: $r=-.64$, $P<.001$ and $r=-.48$, $P<.001$, respectively (Figs. 3 and 4).

4. Discussion

This postmortem study suggests a relationship between the size of atheroma and the type of vessel remodeling

present in patients with fatal AMI. Atheromas that caused fatal coronary occlusion were significantly larger and more frequently with positive vessel remodeling than equi-stenotic nonculprit lesions in the same patient (Figs. 1 and 2).

Many previous angiographic studies have shown that the degree of coronary stenosis correlates poorly with thrombotic complications causing acute coronary syndromes [15–20]. We have recently learned a great deal about the composition of vulnerable plaques [21,22]. The characterization of vulnerable plaques formerly was focused only on its composition. However, in contrast to angiographic studies, some postmortem studies have shown that coronary occlusion associates with high-grade stenosis [23,24]. Discrepancies between angiography and postmortem determination could be explained by some methodological differences [25–27] but mainly by the inability of angiography to assess vascular remodeling [28,29]. Despite the presence of a large atheroma, positive vessel remodeling can preserve totally or partially the lumen. Thus, the angiogram can show a low degree of stenosis in the face of considerable atherosclerotic burden.

In fact, our study showed that although culprit plaques are usually larger than the corresponding equi-stenotic nonculprit lesions, they have better preserved lumen due to vessel enlargement. Despite same degree of histological stenosis, Group 1 had larger lumen area then Group 2, 1.7 ± 1.5 vs. 1.2 ± 0.9 mm^2, respectively (mean ± S.D.).

Pasterkamp et al. [11] have shown in femoral arteries an association of histological markers of plaque vulnerability with vessel enlargement. Recent intracoronary ultrasound studies [12,30] also demonstrated that acute coronary syndromes often involve sizable plaques at enlarged vessel segments. All patients in that study had been selected for PTCA, which presumably represents a selection of patients with flow-limiting stenosis. Lesions that cause AMI are frequently "silent" and, thus, the present study tested whether previous finding can be applied in fatal acute myocardial infarction. We found that patients who succumbed to AMI also had culprit lesions characterized by large atheromas frequently accompanied by positive vessel remodeling.

Our data show that fatal coronary thromboses occurred more frequently when the vessel had positive remodeling, despite the more preserved lumen, consistent with the "Remodeling Paradox" [11] as described by Pasterkamp et al. in femoral arteries.

The mechanism by which positive remodeling relates to acute coronary syndromes remains uncertain. We hypothesize two possible mechanisms.

1. Macrophage mediated extracellular matrix remodeling: The present study documented a positive relationship between size of the plaque and the percent area occupied by macrophages (Figs. 3 and 4). Metalloproteinases produced by macrophages may degrade extracellular matrix components in the media and adventitia permitting vessel enlargement, as well as weakening the lesion's fibrous cap [31,32]. In contrast, stable lesions tend to have a well-developed collagen skeleton [33].

2. Lipid accumulation and plaque burden: Most plaque ruptures do not cause arterial occlusion. Falk [23] demonstrated that the likelihood of vascular occlusion after rupture increases with plaque burden. The determinants of occlusive thrombosis following rupture are complex and include the thrombotic–thrombolytic equilibrium [34], hemodynamic variables and also the character and extent of exposed plaque components [35]. We showed a positive correlation between plaque size and lipid core. Tissue factor in free lipid core is considered a major prothrombotic stimulus in plaques. Indeed, tissue factor levels are higher in coronary atherectomy specimens from unstable vs. stable coronary syndromes [36]. Large lipid rich plaques may therefore be more likely to promote arterial occlusion when disrupted by exposing a great amount of tissue factor and others prothrombogenic plaque elements (Fig. 1).

5. Limitations

It is known that eroded plaques differ from ruptured plaques in their composition. Virmani and colleague's works [14,37,38] contributed to define plaque erosion as a particular entity. The sample size of eroded atheromas in this work was too small for any conclusions regarding this group.

This study used specimens collected serially in 1985 and 1986, some clinical aspects and risk factor profile are unknown. We chose this material because we had performed systematic histological study of the entire length of the main epicardial coronary arteries from all patients who had died after acute myocardial infarction at our institution. Also the use of this cohort obviated eliminating specimens submitted to thrombolysis or primary angioplasty. No reperfusion therapy was used in our institution in that period. Therefore, features such as intraplaque hemorrhage, erosion or rupture of the plaque present in this material resulted from natural evolution of the plaque rather than iatrogenic intervention. The equal treatment of tissues from both groups, internally controlled as they originated from the same hearts, supports the validity of the comparative data.

This postmortem study necessarily represents a selected subgroup of AMI patients with fatal outcome. Therefore, these results do not necessarily apply for all patients with AMI. However, the concordance of our results with those obtained in femoral arteries by Pasterkamp et al. and by intracoronary ultrasound, supports the generalizability of our findings.

6. Conclusions

Our results show that fatal acute myocardial infarction is related with large atheromas, frequently present in a vessel

segment with positive remodeling. The large atheroma does not necessarily cause important lumen loss because of compensatory enlargement of vessel. This study underscores the importance of focus on the lesion versus the lumen and the limitation of angiography in identifying vulnerable plaques. Moreover, these results provide insights into the composition features and biology of plaques associated with compensatory enlargement to vulnerability.

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