(RESEARCH ARTICLE)

Smoking, ulcerated coronary plaques, and smoker's paradox: A new hypothesis

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Abstract

Smoking accelerates the onset of acute coronary disease. *Smoker's paradox* is the term applied to the observations that the short-term prognosis following an acute myocardial infarction is better in the smoker than in the nonsmoker. Efforts to explain these surprising observations have not been successful.

The approach used in this study was to compare the pathologic findings in the coronary arteries following a complete histologic examination of the major branches of the epicardial coronary tree in smokers and nonsmokers. I found many ulcerated plaques in both smokers and nonsmokers, often without associated luminal stenosis or luminal thrombosis. These ulcerated plaques were discovered only on histologic examination and were consistently associated with dense foci of adventitial inflammatory cells.

Based on these findings, the following hypothesis is proposed: Smoking injures the coronary artery endothelium, causing erosions, ulcerations, and a chronic inflammatory response in the arterial adventitia. These ulcerated plaques persist as chronically active, open ulcerations, constantly exposed to flowing blood, leading to increasing luminal stenosis as long as smoking continues. These ulcerated plaques eventually form the substrate for occlusive thrombosis and acute coronary events and are components of active, progressive, inflammatory, atherosclerotic disease. Premature acute coronary disease in the young smoker is due to accelerated plaque ulceration, luminal stenosis, and occlusive thrombosis. Smoker's paradox can be explained by rapid resolution and healing of these potentially unstable ulcerated plaques when the patient is required to stop smoking during hospitalization for the acute myocardial infarction event.

Keywords: Smokers Paradox; Ulcerated Plaques; Inflammation

1. Introduction

Smoking accelerates the risk and promotes the early onset of acute coronary disease (ACD), [1,2] but the mechanism responsible is still not completely understood. [3,4] Smoker's paradox refers to the observation that the short-term prognosis is better in the smoker than the nonsmoker following an acute myocardial infarction. Smoker's paradox, despite a number of thorough, comprehensive studies, is also unexplained. [1,5,6] Are there any structural changes taking place within the artery wall that could reverse so rapidly, as suggested by McGill? [3] A number of theories have been advanced, such as the younger age of the smokers, confounding, or differences in the character of the occlusive thrombus, but none has been proven. The smoker's paradox persists even with thrombolytic therapy or percutaneous coronary intervention. [6,7] Previous pathologic studies from this laboratory of patients who died of ACD have identified a large number of ulcerated plaques (UPs) that were not associated with either significant luminal stenosis or luminal thrombosis, [8,9] but were consistently associated with dense foci of adventitial inflammation. The possibility exists that these UPs are sites of active, progressive, inflammatory, atherosclerotic disease and play an important role in the onset of ACD in the young smoker as well as the older nonsmoker. [10]

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I propose these UPs are focal sites of and a component of active, progressive, inflammatory atherosclerotic disease, resulting in increasing luminal stenosis, but without resolution, healing and closure of the UPs. The aim of this report is to gain further insight into smoker's paradox and to evaluate the role of these UPs and their possible contribution to the premature coronary disease in smokers. This study contributes to the knowledge base by showing there are significant similarities as well as differences in the two groups that provide insight into smoker's paradox as well as ACD in general.

2. Methods

2.1. Clinical characteristics and smoking history

The 59 patients included in this report were part of a previously reported autopsy study of 83 patients who died of ACD. [11] This report includes only those patients whose medical records clearly stated the smoking history. The initial selection of all hearts was based on proven or strongly suspected ACD. Most of the hearts were obtained from Mercy General Hospital, Sacramento, California, or from the Sacramento County Coroner's office. The causes of death included cardiogenic shock, sudden cardiac death with and without associated acute myocardial infarction, and myocardial rupture associated with acute infarction. Males made up 61% of the patient population studied. A smoking history was available for 7 of 22 control patients who died of non-coronary causes: 5 smokers and 2 nonsmokers, all males.

2.2. The postmortem technique

The postmortem technique, developed in this laboratory, has been previously described in detail. [8,9,11,12] In brief, all hearts, including controls, were obtained fresh and uncut at the autopsy table. The coronary arteries were cannulated and injected with a colored barium gelatin mass, with red color injected in the left coronary artery and blue in the right. The pressure within the perfusion system was elevated to 80 mmHg for 2 minutes and then 140 mmHg for 8 minutes. The heart was then fixed in 10% buffered formalin. The coronary arteries were then dissected free from the external surface, decalcified, and cut at 2–3 mm intervals. All coronary cross sections, approximately 90 from each heart, were mounted and stained with hematoxylin and eosin for histologic study. Selected sections were also stained with Martius scarlet blue stain, and phosphotungstic acid stain. Subserial sections were performed on many cross sections, particularly those found to have UPs. Radiographs and photographs were taken of the specimens at all stages of the examination process. The coloring material withstands histologic processing and was essential in identifying UPs. A UP was identified when the colored injection mass penetrated the endothelial barrier and mixed with plaque contents within the intima (Figure 1D). Minor superficial erosions of the endothelium with little or no penetration of the intima were not included in this study.

2.3. Determination of luminal stenosis

The percentage of cross-sectional luminal narrowing of each segment was measured by projecting the microscopic slide, measuring the planimetered area of the lumen, and then by dividing the luminal area by the area of the wall inside the internal elastic lamina. These measurements were made by a technician. Initially, such measurements were taken on all sections but, with experience, the percentage of stenosis was subsequently judged by gross inspection of the slide through the microscope.

2.4. Determining the overall plaque burden

The plaque burden in patients with ACD generally refers to the frequency and severity of only luminal stenosis. I have expanded this definition of *plaque burden* to include not only the frequency and severity of luminal stenosis, but also the frequency of adventitial inflammation, the presence of calcification in the artery wall, and the presence of a necrotic plaque core, for each segment examined.

2.5. UPs and luminal thrombosis

This report makes a clear distinction between UPs with and without associated intraluminal thrombosis. The term *UP* includes ulcerations and plaque rupture associated with penetration of colored injection mass into the plaque. *Thrombosis* is defined as a thrombus encroaching on or extending into the lumen of the artery.

2.6. Statistical analysis

Statistical analysis of the data presented in this report utilized chi-square and Fisher's exact probability tests. P values <0.05 were considered significant.

3. Results

Table 1 compares the mean age and gender of smokers and nonsmokers who died of ACD. Smokers were significantly younger than nonsmokers, and male smokers, but not female smokers, died at a significantly younger age than nonsmokers. There was no significant difference in the frequency of different clinical syndromes responsible for death between smokers and nonsmokers.

Table 1 The mean age of smokers and nonsmokers who died of acute coronary disease by gender.

	Smokers		Nonsmokers		Total		p Value
Category	#	%	#	%	#	%	p
All Patients	36	61	23	39	59	100	
Mean Age	56		73		62		p=<0.05
Males	31	74	11	26	42	71	p=<0.05
Mean Age	55		69		59		
Females	5	29	12	71	17	29	
Mean Age	60		75		70		p=NS

NS = Not significant.

Table 2 compares the frequency of UPs associated with and without luminal thrombosis in relation to the severity of luminal stenosis in smokers and nonsmokers. There was no significant difference in the overall frequency of UP with or without luminal thrombosis in the two groups. However, in both smokers and nonsmokers, thrombosis was consistently associated with luminal stenosis of >80%, but rarely present when the stenosis was <80%. There was no significant difference between smokers and nonsmokers in the frequency of UPs, thrombosis, and 80% luminal stenosis at each level of luminal stenosis. The overall frequency of UPs averages 2.49 per patient, ranging from 1 to 7 per patient, with 71% of patients showing more than 1 UP.

Table 2 Comparing the frequency of ulcerated plaques with and without luminal thrombosis and of coronary thrombosis with percentage of luminal stenosis in smokers and nonsmokers.

	Luminal Stenosis (%)				
	<50	50–80	>80	Total	%
Smokers #36					
UP with LT	0	6	39	45*	53
UP without LT	10	26	4	40*	47
Total	10	32	43	85	100
Nonsmokers #23					
UP with LT	0	7	22	29*	47
UP without LT	8	21	4	33*	53
Total	8	28	26	62	100

LT = Luminal thrombosis; UP = Ulcerated plaque; * = p=Not significant

Table 3 compares the frequency of all the components included in the overall plaque burden plus the number of segments with <50% and >80% luminal stenosis. The nonsmoker had more frequent inflammation, calcification, plaques with a necrotic core, and more segments with >80% luminal stenosis. These results show it is the older nonsmoker with the greater overall plaque burden, showing age is a powerful risk factor in plaque growth. Table 3 also illustrates the similarity in the evolutionary growth sequence of each of the four lesions making up the overall plaque burden. Adventitial inflammation is the most common and presumably the first to develop, followed next by calcification, plaques with a necrotic core, and finally luminal stenosis of >80%. The consistent sequential development of these lesions illustrates atherosclerotic lesions develop similarly in smokers and nonsmokers, suggesting the atherosclerotic disease process is the same, not different, in both groups.

Table 3 Comparison of the frequency of adventitial inflammatory cell infiltrates, calcification, plaques containing a necrotic lipid core, and luminal stenosis in all coronary segments in smokers and nonsmokers.

	# of Sections Examined	Inflammatory Cell Infiltrates		Calcification		Lipid Core		Luminal Stenosis			
								<50%		>80%	
		#	%	#	%	#	%	#	%	#	%
Smokers (#36)	3275	1526	47	1106	34	819	25	1527	47	614	19
Nonsmokers (#23)	2021	1161	57	961	48	706	35	799	40	478	24
	5296	p=<0.001		p=<0.001		p=<0.001		p=<0.001		p=<0.001	
Controls											
Smokers (#5)	515	71	14	122	24	19	4	324	63	51	10
Nonsmokers (#2)	202	23	11	19	9	19	9	189	98	1	0.5
	717										
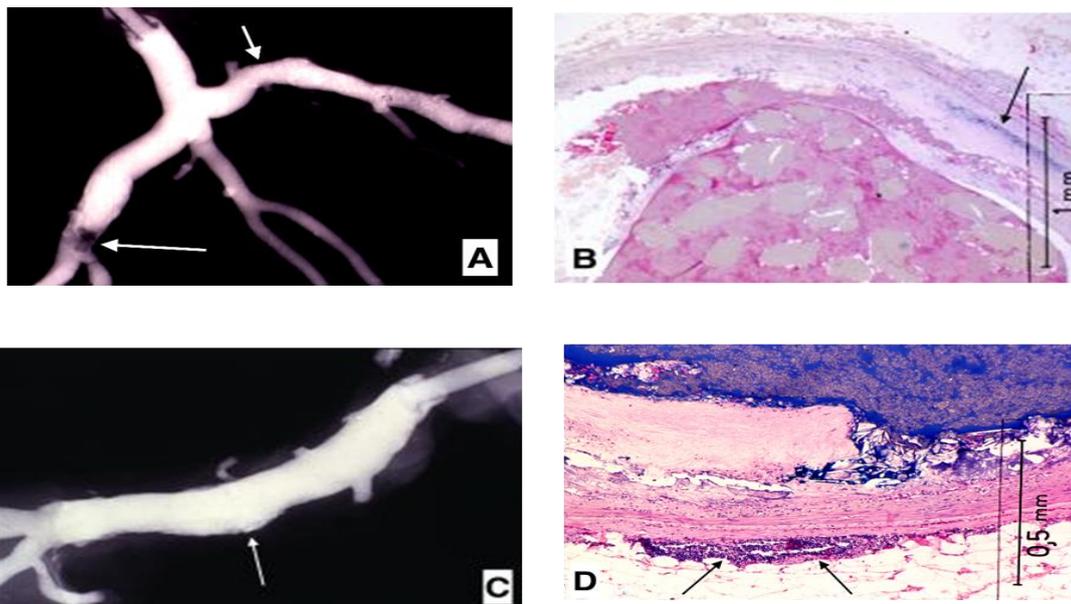
**Figures 1** A–1D are photos from a 38-year-old male smoker who died of sudden cardiac death out of the hospital.

Figure 1A is the dissected, decalcified, proximal left coronary artery showing an occlusive thrombosis, the culprit lesion (long white arrow). Figure 1B shows an UP in the proximal circumflex coronary artery (short white arrow in Figure 1A) without significant luminal stenosis or thrombosis. The black arrow indicates a focus of inflammation. Figure 1C is the X-ray of the proximal segment of the dissected, decalcified right coronary artery showing no evidence of luminal

stenosis but also showing indistinct margins to the X-ray. Figure 1D is taken from this part of the artery (the white arrow in Figure 1C), showing a small UP with a dense focus of adventitial inflammation (the black arrows) without evidence of luminal thrombosis. The patient had a UP in many segments taken from the first 3 cm of this right coronary artery.
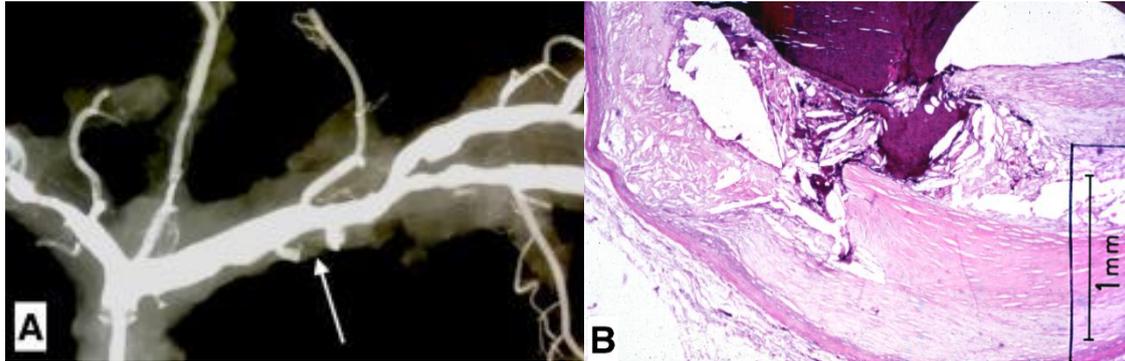
Figures 2 A and 2B are taken from a 53-year-old female smoker who died sudden cardiac death 6 weeks after an acute myocardial infarction. Figure 2A is the dissected, decalcified

Proximal/mid left anterior descending artery showing irregular disease but no significant stenosis. Figure 2B is a photo of a deep ulceration taken from the area of the white arrow in Figure 2A, without evidence of thrombosis. The patient had an occlusive thrombosis of the proximal circumflex coronary artery.
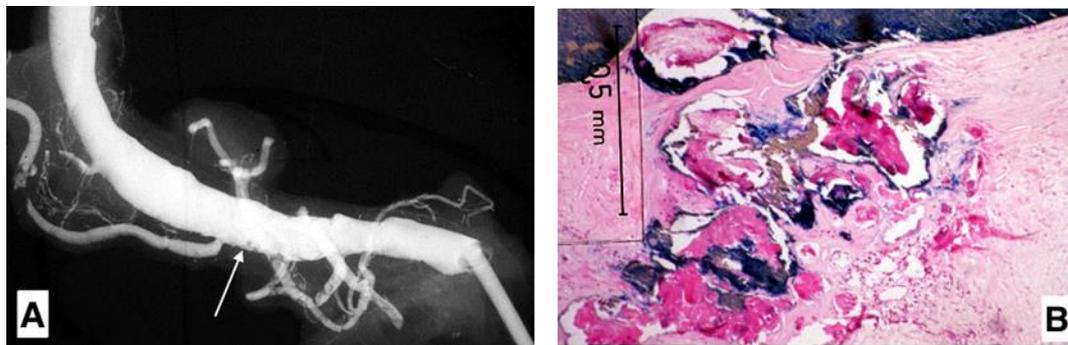
Figures 3 A and 3B are photos from an 86-year-old female nonsmoker who died of myocardial rupture following an infusion of streptokinase for an acute myocardial infarction.

Figure 3A is an X-ray of the dissected, decalcified proximal right coronary artery showing no evidence of luminal stenosis. Figure 3B is a microscopic view taken from the area of the white arrow in Figure 3A, showing an intra-intimal thrombus mixed with blue injection mass indicating connection to the lumen. Resolution of such lesions, as seen here, could add to plaque size and increasing luminal stenosis.

4. Discussion

4.1. Ulcerated plaques in the coronary arteries

Multiple UPs, often located at sites without significant coronary artery luminal stenosis and not associated with luminal thrombosis, are a common finding in patients who died of ACD. [8,9,11]

What is the significance of these ulcerations and what role do they play in plaque growth and acute coronary events? Why is thrombosis absent when they are exposed to flowing blood? There was no significant difference in the frequency of these UPs between smokers and nonsmokers (Table 2), except the male smokers were significantly younger (Table 1). If these UPs were caused by or related to smoking, they may then persist as chronic ulcerations as long as smoking continues. These UPs are often not visible as such, even on postmortem coronary angiograms. Previous studies by De Weert et al., [13] show plaque ulcerations, similar to those illustrated in this report, are present in the carotid arteries on carotid angiograms, and on postmortem examination of the abdominal aorta in smokers. [14] The natural history of these UPs is unknown, especially whether they can resolve, heal, and reestablish endothelial integrity with smoking

cessation. Insignificant lesions have been shown to accelerate rapidly and cause acute coronary events in some reports, but the pathogenesis of these lesions has also not been determined. [15,16] If some insignificant coronary lesions can accelerate rapidly then they may also reverse and heal rapidly.

Previous studies from this laboratory showed these UPs are consistently associated with dense infiltrates of lymphocytes in the arterial wall adventitia. [8,9,11] Reports from other laboratories have shown these lymphocytes are in an "activated" state, suggesting they are sites of active, progressive, inflammatory, atherosclerotic disease. [10,17,18] If these UPs are sites of active disease, then they may play a role in accelerating plaque growth and increasing luminal stenosis. One mechanism that could contribute to increasing stenosis could be the fibroproliferation associated with chronic inflammatory diseases like atherosclerosis. [18,19] Acute coronary events are often believed to be caused by an occlusive thrombus superimposed on the sudden disruption of a vulnerable, unstable plaque, obstructing coronary blood flow. [20] However, the sudden onset of an acute event does not prove that the UP was a sudden or recent event. The UP could have been present for an indefinite length of time as a chronic ulceration, unrecognized, without causing any symptoms before the acute event. I have found many UPs at all levels of luminal stenosis without thrombosis in both smokers and nonsmokers (Table 2). I propose UPs are sites of active atherosclerotic disease and their formation is accelerated by smoking. These UPs are consistently associated with foci of lymphocytes in the adventitia of the artery wall and serve as a marker of active atherosclerotic disease. They may persist as chronic UPs as long as smoking continues. These chronically active UPs may promote plaque enlargement and increasing luminal stenosis. Significant luminal stenosis, approaching 80%, is a necessary requirement for the formation of occlusive luminal thrombosis, whether the stenosis occurs as result of a sudden disruption of a vulnerable plaque, or slowly and gradually as a result of chronic, progressive atherosclerotic disease. I speculate the premature onset of ACD in the young smoker is due to acceleration of luminal stenosis followed by occlusive thrombosis at the site of one or more chronic UPs. The UP would be a component, not a complication, of increasing luminal stenosis. Smoking appears to accelerate the formation of UPs selectively without accelerating any of the other components of the overall plaque burden such as inflammation, calcification, or plaques with a necrotic core and 80% luminal stenosis (Table 3). This evidence suggests smoking does not accelerate atherosclerosis per se, but only the UPs. [21] These observations may also explain why angina pectoris is not commonly observed in the young smoker with ACD and why risk factors for acute coronary heart disease are not the same as for atherosclerosis. [22]

4.2. What is the pathogenesis of UPs in the nonsmoker?

Other known cardiovascular risk factors that may be present in the older nonsmokers may be producing very similar ongoing endothelial injury and UPs as we see in the young smoker. These risk factors include high cholesterol, high blood pressure, diabetes, etc., and could be one explanation for the similar frequency of UPs in the nonsmoker. These traditional risk factors in the nonsmoker may be less toxic than cigarette smoke and act more slowly in the older patient. Otherwise the acceleration and progression to luminal stenosis and acute coronary events, as outlined above, would be the same as in the smoker, but at a later age, producing the results seen in Table 3. Presumably, control of these other risk factors could reduce the risk of acute coronary events in the nonsmoker similar to smoking cessation.

4.3. The overall plaque burden in acute coronary disease

Table 2 shows there is no significant difference in the frequency of UPs in the smoker and nonsmoker, but it is the older nonsmoker with the greater overall plaque burden (Table 3). What role, if any, does the overall plaque burden play in the pathogenesis of UPs in the nonsmoker? Table 3 illustrates the evolutionary sequence of each individual lesion composing the overall plaque burden and shows the sequence is the same in both smokers and nonsmokers even though the plaque burden is significantly different. The nonsmokers have the same number of UPs as the smokers, suggesting the number of UPs is not related to the greater plaque burden in the nonsmokers. Likewise, the lesser overall plaque burden in the smoker suggests the plaque burden did not play a role in accelerating the pathogenesis of UPs in the smoker. I conclude the overall plaque burden, per se, is not a major factor in causing or promoting the development of UPs in either the smoker or nonsmoker.

4.4. Smoker's paradox

How do these findings relate to smoker's paradox? [1,5,6] I speculate the following: I assume the attending physician, family, and all interested parties will require and urge the patient to stop smoking during the hospitalization for the acute event and hopefully in the ensuing months. [23] Discontinuing smoking, even for a relatively brief hospital stay may be sufficient for the many unrecognized UPs in the coronary tree to resolve, heal, and reendothelialize quickly, removing the substrate for recurrent acute thrombosis and thus improving the immediate prognosis. It is unlikely there could be any quick reduction in size of established coronary plaques associated with fibrosis and calcification that could

reverse so quickly. [3,4] The improved immediate short-term prognosis in smoker's paradox can be explained by a relatively rapid resolution of potentially unstable, unrecognized UPs at multiple sites in the smoker.

4.5. Smoking cessation in the asymptomatic patient

The medical literature is replete with many articles showing smoking cessation, at any age and with virtually all risk factors, is associated with a rapid and dramatic decrease in the risk of cardiovascular disease. [24,25,26] The decrease in risk occurs no matter how long or how much the patient has smoked, nor the presence or the number of associated traditional risk factors, nor the presence of previous known ACD. As in smoker's paradox, the rapid decrease in risk may be due to resolution and healing of multiple, potentially unstable, unrecognized UPs in the asymptomatic smoker when smoking is discontinued.

5. Conclusion

Smoker's paradox is unexplained. The evidence presented here shows there are many unrecognized UPs throughout the coronary tree in both smokers and nonsmokers who died of ACD. The natural history of these UPs has not been determined. I am advancing the hypothesis that the UP is a component, not a complication, of active, progressive, atherosclerotic disease; is caused by smoking; and persists as long as smoking continues. The sudden onset of acute coronary events does not prove the UP or the plaque disruption is an acute event. The improved short-term prognosis in smokers following an acute coronary event, smoker's paradox, may be due to the rapid resolution and healing of unrecognized, potentially unstable UPs when the patient is required to stop smoking during hospitalization. The rapid decrease in cardiovascular risk when *any* person stops smoking may be explained on the same basis. The development of techniques to identify and treat UPs could open new approaches to the prevention of ACD.

Limitations

I do not have a detailed smoking history of the patients in this study, and no information on secondary smoke exposure or how many of the nonsmokers were ex-smokers. Because of the variability in the smoking history records, quantification of the amount smoked or number of years the patient smoked was not possible. Information regarding other cardiovascular risk factors, including cholesterol levels, history of high blood pressure, diabetes mellitus, and family history of heart disease, etc., was available for the majority of patients, but not for all. Therefore, the possible role of these risk factors is not considered in this report.

Compliance with ethical standards

Acknowledgments

Disclosure of conflict of interest

The author states the following: He has complied with all ethical standards. He has no conflicts of interest to disclose.

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Author's short biography
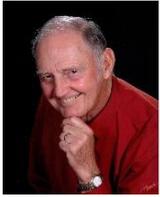
Dr. Richard Frink is a retired cardiologist and independent investigator in Sacramento, CA with a long-standing interest in the pathologic substrate of acute coronary disease, particularly the inflammatory response associated with ulcerated plaques and their role in the onset of acute coronary disease in all patients.