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Adventitial Inflammation of the Coronary Arteries in Patients, with and without Diabetes Mellitus, Who Died of Acute Coronary Disease: A Reliable Marker of Active, Progressive, Atherosclerotic Disease

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Abstract

Background: Atherosclerosis is a progressive, chronic inflammatory disease, but it is not yet possible to identify specific plaques with active, progressive, disease. Adventitial inflammation (AI) is a component of the chronic inflammatory response and may be useful in identifying the actively growing, vulnerable plaque, with impending disruption.

Methods: The hearts of 61 patients who died of acute coronary disease (ACD), 18 diabetic and 43 non-diabetic, and 22 control patients were obtained fresh and uncut at the autopsy table. The coronary arteries were injected with a colored barium-gelatin mass and the heart fixed in formalin. After fixation, the coronary arteries were dissected intact, decalcified, cut at 2-3 mm intervals, and all segments mounted for microscopic study to determine the frequency of AI and its relationship to the overall plaque burden (PB), the PB in the proximal and distal segments of each coronary artery, and all plaque disruptions (PD).

Results: Al was present in 50% of 5,466 coronary segments in these 61 patients compared to 16% in the control patients. Patients with diabetes had a greater PB, P=<0.02, and more extensive AI than non-diabetics, p<0.001, in both proximal and distal segments. There was a direct relationship between PB and AI in both diabetic and non-diabetic patients, but was significantly greater in diabetic patients, p=<0.001. Multiple PD's, 148, were present in these 61 patients and 95% were associated with AI, but there was no significant difference in the frequency of PD's in diabetic compared to non-diabetic patients.

Conclusions: Al appears to be a reliable histologic marker of active, progressive, atherosclerotic disease and may be helpful in identifying the vulnerable plaque with impending disruption. Diabetes accelerates atherosclerotic disease, but does not accelerate PD.

Keywords: Diabetes; Inflammation; Plaque burden; Acute coronary disease

Introduction

Atherosclerosis is a chronic inflammatory disease believed to be initiated by an injury to the arterial wall [1]. The intimal inflammatory response in atherosclerosis is well known, but relatively little emphasis has been placed on the frequency or significance of the adventitial inflammatory response in patients with atherosclerosis. Recent reports indicate the adventitia is an "injury sensing" tissue, and that the adventitial inflammatory response is an important component of the overall inflammatory response in atherosclerosis [2-5]. Our aim is to extend our previous studies of AI by comparing the PB and the adventitial inflammatory response, determined histologically, in diabetic and non-diabetic patients [6-8]. These findings may prove to be helpful in identifying the actively growing, vulnerable plaque with impending PD.

Materials and Methods

The demographic features and the different clinical syndromes responsible for death in the patients included in this study are presented in Table 1. The study group consists of 61 patients and included 42 men and 19 women, 18 diabetic and 43 patients without diabetes, randomly selected for death caused by ACD. There were no significant differences in age or the frequency of the different acute coronary syndromes responsible for death, including cardiogenic shock, sudden cardiac death with acute myocardial infarction, sudden cardiac death without acute infarction, and cardiac rupture associated with acute

	Diabetic (%)		Non-diabetic (%)		Total	P Values	
Number	18	30	43	70	61		
Mean Age	63		63			NS	
Males	11	26	31	74	42	NS	2.13
Age Range	33-84	57	32-60	60	60	NS	
Females	7	37	12	63	19	NS	2.14
Age Range	54-86	71	49-93	71	71	NS	
Syndrome							
C Shock	10	38	16	62	26	NS	1.07
SCD + AMI	4	27	11	73	15	NS	0.002
SCD - AMI	2	20	8	80	10	NS	0.12
C Rupture	2	20	8	80	10	NS	0.12

C Shock = Cardiogenic shock; SCD + AMI = Sudden cardiac death with acute myocardial infarction; SCD - AMI = Sudden cardiac death without AMI; C Rupture = Cardiac rupture associated with AMI; NS = No significant difference

 Table 1: Presents the demographic features of diabetic and non-diabetic patients included in this study and the clinical syndrome responsible for death.

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infarction. The diagnosis of diabetes mellitus was obtained from the medical record.

The hearts were obtained fresh and uncut from the department of pathology of Mercy General Hospital, Sacramento, CA, while the hearts of the control patients were obtained primarily from the Sacramento County Coroner's office. The coronary arteries were cannulated and injected with a colored barium-gelatin mass, and after formalin fixation, the arteries were dissected intact, decalcified, and then cut at 2-3 mm intervals and all segments mounted for histologic study. On average, 90 segments were examined for each heart in the study, totaling 5466 segments from these 61 patients, and, in addition, 3-5 subserial sections were examined for each coronary segment. All diagonal branches of the coronary arteries were excluded from the study. All PD's, including erosions, fissures and plaque ruptures, with and without significant luminal stenosis or luminal thrombosis were tabulated, and their location, in the proximal or distal segment determined. PD's were defined as any breach of endothelial integrity



Figure 1: Coronary section from the mid right coronary artery in a 38 yearold man who died sudden cardiac death out-of-hospital. Narrow black arrows = Dense focus of adventitial lymphocytes. Fat black arrows = Intimal calcification involving ¾ of the artery circumference. Luminal stenosis estimated to be less than 50%. Open black arrows = Small, focal endothelial erosion. White asterisk = Injection mass in lumen.



Figure 2: Mid right coronary artery section in 82 year-old woman who died sudden cardiac death in-hospital. Luminal stenosis estimated to be 70%. Narrow black arrows = Dense foci of adventitial lymphocytes. Fat black arrows = Intimal calcification at 2 sites. PR = Plaque rupture without luminal thrombus. White asterisk = Injection mass in lumen.



Figure 3: Coronary section from the mid right coronary artery in 56 year-old man who died sudden cardiac death in-hospital following an acute inferior myocardial infarction. Narrow black arrows = Multiple foci of adventitial lymphocytes. T = Occluding thrombus superimposed on a ruptured plaque [RP]. Fat black arrows = Intimal calcification



Figure 4: Coronary section from the proximal right coronary artery in a 50 year-old woman who died sudden cardiac death in-hospital. Luminal stenosis estimated to be 80%. Narrow black arrows = Dense foci of adventitial lymphocytes, suggesting this segment is the site of active, progressive disease. Fat black arrow = Tiny focus of intimal calcification. Note no evidence of lymphocytes within the atheroma. ATH = Atheroma. White asterisk = Injection mass in lumen.

with penetration of colored injection mass into the underlying tissue, with or without associated luminal thrombosis (Figures 1-4). Any PD extending into adjacent segments was counted as one PD. Control patients included 3 women, age range 15-67, mean 47, and 19 men age range 19-74, mean 43. Five control patients died as a result of accident or trauma, 5 of non-coronary cardiomyopathy, 3 of cancer, 2 of suicide, 2 of stroke and 5 of miscellaneous causes. None of the control patients were known to have diabetes.

The PB of each of the three main coronary arteries left anterior descending (LAD), circumflex and right coronary artery was determined in the following manner. The midpoint of each artery was determined by counting the total number of segments in that artery and dividing that number in half to form the proximal and distal segment groups. This method was used because the length of each coronary artery can vary from patient to patient. Two patients had a Citation: Frink RJ (2012) Adventitial Inflammation of the Coronary Arteries in Patients, with and without Diabetes Mellitus, Who Died of Acute Coronary Disease: A Reliable Marker of Active, Progressive, Atherosclerotic Disease. J Clin Exp Cardiolog S12:001. doi:10.4172/2155-9880.S12-001

left dominant system. The findings in the left main coronary artery were included with the LAD, and if there were an odd number of segments, the odd segment was added to the proximal group. The PB was determined by recording the number of segments with >50% or <50% luminal stenosis. The degree of cross sectional luminal stenosis of each segment was measured, using the microscope slide, by dividing the area of the lumen by the area of the wall inside the internal elastic lamina. Initially all segments were measured by this method, but after experience was gained, the degree of narrowing was estimated by gross inspection of the microscope slide [6].

A segment was considered to be inflamed if there were dense foci of lymphocytes localized in the adventitia overlying plaques (Figures 1-4) [6,8,9]. No attempt was made to determine the frequency of lymphocytes or other inflammatory cells in the intima, but adventitial lymphocytes were believed to reflect the inflammatory response occurring in the intima [10,11]. Prior reports have shown these adventitial lymphocytes are primarily T lymphocytes with some B lymphocytes [2-10]. All slides were stained with hematoxylin and Eosin. Statistical analysis utilized Chi-Square and Fisher Exact Probability test, using 2×2 contingency table for two independent variables. P values <0.05 were considered significant.

Results

Table 2 presents the overall PB and frequency of AI in both diabetic and non-diabetic patients and their occurrence in the proximal and distal segments. Diabetic patients had a greater overall PB than nondiabetics with 47% of all segments showing >50% luminal stenosis, compared to 44% in non-diabetics, p=<0.02, supporting prior studies that show diabetics have "accelerated" atherosclerosis [12-14]. Diabetic patients had more extensive AI, with 56% of segments showing AI compared to 47% in non-diabetics, p=<0.001. The frequency of AI was also greater in those segments with >50% stenosis in diabetics compared to those in non-diabetics, p=<0.001. Table 2 also shows diabetics have a greater PB in the proximal segments, but this did not reach the level of statistical significance. However, there was significantly more AI in the proximal segments in diabetics, particularly those with >50% stenosis, p=<0.001. The proximal segments are the most common site of active disease in both diabetic and non-diabetic patients with both groups having a greater PB than the distal segments. The greater PB and AI in the distal segments in diabetic patients compared to non-diabetics illustrate a more diffuse involvement of the coronary tree in patients with diabetes.

Table 3 compares the PB and the frequency of AI in the proximal and distal segments of the control patients. The proximal segments have the greatest PB and the more extensive inflammation, similar to the patients with ACD, but with significantly less PB and AI than in patients with ACD. These results suggest there are common pathogenetic factors, such as hemodynamic stress [15], that are present in all persons that tend to promote atherosclerotic-type injury and subsequent AI in the proximal segments of the coronary tree.

Table 4 compares the frequency of PD's and associated luminal stenosis in the proximal and distal segments, in patients with and without diabetes. The vast majority, 93%, of all PD's presented here were associated with AI supporting the view that PD's are the site of "active" disease [7,8,16]. Multiple PD's, 148, were found in these 61 patients, or 2.43 PD's per patient on average. The majority of PD's, 80%, were found in the proximal segments, with 90% associated with greater than 50% luminal stenosis, but there was no significant difference in the frequency of PD's between diabetic and non-diabetic patients, or

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between the proximal and distal segments. Although multiple PD's are common in patients with ACD, only 56% were associated with the presence of luminal thrombosis, illustrated in Figure 3, with no significant difference in the frequency of thrombosis between diabetic and non-diabetic patients.

Discussion

The vulnerable plaque

Acute coronary events, such as acute myocardial infarction, often develop suddenly without warning, usually due to sudden and spontaneous rupture of a vulnerable plaque [17,18]. A vulnerable plaque is a plaque with a soft center composed of necrotic plaque tissue, similar to an abscess [19], covered with a thin cap of fibrous tissue,

	Diabetic		Non-diabetic		Total		P value	
Total Segs	1665	%	3801	%	5466			
Segs >50%	785	47	1659	47	2444	45	<0.02	
Segs with AI	927	56	1787	56	2714	50	<0.001	
Segs >50% with AI	623	79	1122	79	1745	71	<0.001	32.8
Proximal Segment	s							
Total Segs	845	%	1933	%	2778			
Segs >50%	448	53	981	51	1429	51	NS	
Segs with AI	574	68	1134	57	1708	61	<0.001	
Segs >50% with AI	385	86	742	76	1127	66	<0.001	
Distal Segments								
Total Segs	820	%	1868	%	2688			
Segs >50%	338	41	678	36	1016	38	<0.02	
Segs with AI	353	43	553	30	906	34	<0.001	
Segs >50% with AI	238	70	380	56	618	61	<0.001	

Total Segs = Total number of segments; Segs >50% = Segments greater than 50% Stenosis; Segs with AI = Segments with adventitial inflammation; Segs >50% with AI = Segments greater than 50% stenosis with adventitial inflammation; NS = No significant difference

Table 2: Compares the plaque burden and the frequency of adventitial inflammation in the epicardial coronary tree and in the proximal and distal segments of the three main coronary arteries.

	Proximal		Distal		Total		P value	
Total Segs	911	%	875	%	1786	%		
Segs >50%	144	16	75	9	219	12	<0.001	
Segs with AI	171	19	123	14	294	16	<0.001	
Segs >50% with AI	71	49	19	25	90	41	<0.001	

Total Segs = Total number of segments; Segs >50% = Segments greater than 50% Stenosis; Segs with AI = Segments with adventitial inflammation; Segs >50% with AI = Segments greater than 50% stenosis with adventitial inflammation; NS = No significant difference

 Table 3: Compares the plaque burden and adventitial inflammation in 22 control patients without acute coronary disease or diabetes.

	Diabetic		Non-diabetic		Total		P value	
Total PD	51	%	97	%	148	%		
Proximal	40	78	79	81	119	80	NS NS	
>50%	37	93	70	89	107	90		
Distal	11	22	18	19	29	20	NS	
>50%	9	82	9	50	18	62		
Thrombosis	25	49	58	60	83	56		
					1.16			

Total PD = Total number of plaque disruptions; NS = No significant difference >50% = Number of segments greater than 50% stenosis

 Table 4: Compares the frequency of plaque disruptions in diabetic and nondiabetic patients, their location in either the proximal or distal segments and the frequency of associated luminal thrombosis.
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often called a Thin Cap Fibro Atheroma (TCFA), most frequently located in the proximal segments of the coronary tree [19,20]. When the thin cap ruptures, coronary thrombosis often occurs, resulting in acute coronary events. The current challenge facing cardiologists and other physicians is to identify these TCFA's before rupture occurs and develop strategies to either prevent rupture with medical treatments and/or intervene with treatments such as percutaneous coronary intervention to treat the plaque before rupture occurs [21,22]. The first task is to have a reliable technique to identify the TCFA and the second to identify those characteristics that indicate the plaque is actively growing and may soon rupture. There are many TCFA's in patients with coronary disease, but only a very few go on to rupture, emphasizing the need to ID those features that indicate impending PD.

Injury and inflammation

Atherosclerosis is a chronic inflammatory disease believed to be caused by injury to the inner lining of the artery wall, the intima [1]. This injury often occurs at multiple sites within the coronary tree, allowing cholesterol and other blood constituents to enter and be retained within the intima, initiating plaque formation. The retained cholesterol stimulates an inflammatory response, first in the intima and then later in the adventitia, the outer layer of the artery wall. This adventitial inflammatory response is composed of lymphocytes (Figures 1-4), is primarily defensive in nature, aimed at neutralizing the injurious agent or process and removing the retained cholesterol and other lipids. The IA or process responsible for causing the injury is apparently not neutralized by this inflammatory response because injury continues, the inflammation persists, plaques continue to grow, and the disease continues to progress. Atherosclerosis injury is a diffuse process with many plaques in various stages of development spread throughout the coronary tree.

The adventitial inflammatory response begins to appear after the plaque is well established, particularly when the plaque has grown to occupy about 50% of the cross sectional area of the artery lumen. AI is found only over plaques and never over normal wall indicating it is related in some way to the injurious activity taking place within the underlying plaque [9]. Prior studies show antigens generated in the intima migrate to the adventitia and are presented to adventitial lymphocytes by dendritic cells [23]. These dense foci of adventitial lymphocytes resemble germinal centers of secondary lymph organs, suggesting an immunologic response [11].

Diabetes and active disease

We chose to study the issue of active disease by comparing the PB and AI in patients with and without diabetes because patients with diabetes have accelerated atherosclerosis and therefore more extensive active disease than non-diabetics [12-14,18]. Although unselected, the patients included were well matched for age and sex and clinical syndrome between diabetic and non-diabetic patients. The results show diabetic patients have a greater PB and more extensive AI than non-diabetics, (Table 2), suggesting accelerated injury is the underlying mechanism, related in some way to the lipid and metabolic abnormalities associated with diabetes [12,18,24]. The accelerating effects of diabetes are added to those factors that promote atherosclerosis in the proximal segments, resulting in a greater PB and more extensive inflammation in the proximal segments of the coronary tree, (Table 2).

These results suggest a direct cause and effect relationship exists between injury, PB and AI. If AI could be identified in vivo this would

help to identify the plaque with currently active disease, and the potential for impending rupture. Physicians could focus on specific plaques to anticipate and possibly predict impending PD, particularly in high risk patients.

Diabetes and plaque disruptions

We expected to find more PD's in diabetic patients because of the most extensive AI and greater PB in these patients, but Table 4 showed no differences in the frequency of PD's nor in the frequency of luminal thrombosis. These results are in contrast to reports by other investigators [3,18], and may be explained in part by the differences in technique to identify PD's. The results presented here are based strictly on the microscopic findings in the entire epicardial coronary tree and do not support the view that diabetic patients have a greater tendency to develop thrombosis than nondiabetic patients. There may be other factors beyond PB and AI that determine whether PD will or will not develop.

Inactive disease

If AI is a marker of active disease, is the absence of AI overlying a plaque a reliable sign of inactive, non-progressive disease? Atherosclerosis is not necessarily a steadily progressive disease, because the course can be altered by instituting preventive measures and controlling risk factors. The Jupiter trial showed plaques can be reversed and inflammation decreased by administering statin drugs [25]. Approximately 30% of all plaques with >50% stenosis do not have AI, (Table 2). Does this mean these plaques never developed AI at any time during development, or does it mean the active process in that particular plaque has subsided and the plaque has gone into remission?

Table 2 also shows approximately 30% of segments with <50% stenoses do have AI, showing the adventitial inflammatory response can develop early in plaque development. We speculate that all actively growing plaques, causing >50% luminal stenosis, are associated with AI, and the absence of AI is a sign the disease in that particular plaque has become inactive, stabilized and stopped growing.

If this reasoning is correct, large plaques causing significant luminal stenosis but without AI, may not require intervention, and can be safely observed and left alone.

Evolving techniques to identify active disease

A variety of scanning techniques are being developed to evaluate the vulnerable plaque and plaque inflammation in vivo [21-24,26-28]. These techniques will soon evolve to the point of being able to identify inflammation without invasive techniques and be able to thoroughly characterize the vulnerable plaque and those features that indicate impending disruption. Recent reports by Abela have pointed to the potential significance of cholesterol crystals in the pathogenesis of PD [29-31]. Cholesterol crystals are a common component of the atheromatous core, have very sharp ends and are usually randomly scattered throughout the necrotic core. Abela showed these cholesterol crystals, when formed in a closed beaker, and expand in a manner similar to the conversion of water to ice, assume a parallel configuration, and disrupt an overlying membrane with their sharp ends. In addition, these crystals form quickly resulting in a sudden increase in pressure within the enclosed space. A sudden increase in intra plaque pressure due to the rapid formation of cholesterol crystals could be sufficient to cause a sudden and spontaneous disruption of a TCFA without warning. We have also observed these cholesterol crystals frequently are aligned in a parallel configuration at the site of PD's and speculated

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that this particular configuration could, in an actively expanding TCFA, act like a battering ram, to disrupt the fibrous cap and promote PD [32]. Cholesterol crystals can be identified using OCT and may be one additional methods of evaluating and predicting impending PD [26].

Summary

AI appears to be a reliable marker of active atherosclerotic disease and may be useful in identifying the vulnerable TCFA with impending disruption. Diabetes accelerates atherosclerosis, but does not accelerate PD nor promote luminal thrombosis. The absence of AI overlying a plaque may identify a stable, non-progressive plaque that could be safely left alone in certain circumstances regardless of plaque size. Parallel CC may be a sign of impending PD.

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