Histopathologic Insight into Saphenous Vein Bypass Graft Disease

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Key Words

Coronary artery bypass grafting • Atherosclerosis • Vein graft • Stenosis

Abstract

Objectives: Vein graft disease is a major drawback of coronary artery bypass grafting. However, histopathologic studies of old human aortocoronary grafts are scarce. **Methods:** We screened patients undergoing redo coronary artery bypass grafting at three university hospitals and selected those with at least one excisable old vein graft. Native non-grafted saphenous veins were also obtained as controls. Clinical and angiographic data were separately documented. **Results:** We evaluated 117 segments from 29 veins. All but 4 old graft segments showed degrees of luminal narrowing and fibro-intimal proliferation. Moreover, 61 segments demonstrated atherosclerotic plaques. Such plaques were typically concentric and, compared with other segments, more frequently represented necrosis, calcification and giant cells ($p < 0.001$ for all comparisons) and had a higher inflammatory cell count, predominantly of lymphocytic origin. Native saphenous veins frequently showed fibrosis, but no calcification or

active inflammation. Angiographic findings showed moderate correlation with the histological degree of luminal stenosis (Spearman's $\rho = 0.564$, $p < 0.001$). **Conclusions:** Human vein graft atherosclerosis and arterial atherosclerosis share many features; however, we found lymphocytes to be the dominant inflammatory cells within plaques. Conventional angiography underestimated the atherosclerosis burden in vein grafts. Improved understanding of disease pathophysiology could lead to the development of novel interventions that reduce costly and suboptimal repeat revascularizations.

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Introduction

Coronary artery bypass grafting (CABG) is a major revascularization option for patients with ischemic heart disease [1]. Arterial conduits are biologically superior and have high short- and long-term patency rates and a low

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risk of graft atherosclerosis. On the other hand, vein grafts are plentiful and easily harvested and comprise the majority of bypass conduits for CABG. However, such grafts may be compromised postoperatively or due to early thrombosis or fibrointimal hyperplasia. The 10-year patency rate of vein grafts is no more than 50–60%, for which atherosclerosis is considered the main cause. Such graft failure leads to recurrence of ischemic symptoms and clinical deterioration, mandating costly, riskier and less effective repeat revascularization procedures [2–5].

Therefore, it is important to investigate the histopathologic aspects of late vein graft failure, so that improved therapeutic interventions can be introduced for patients undergoing CABG. However, few histopathologic studies exist on human saphenous vein bypass graft disease, partly because of difficulties in obtaining old vein grafts and the preference of some surgeons for keeping the old bypass grafts during the redo surgery [5–10]. Because of this, animal models have served as the conventional means of conducting research on aortocoronary vein graft stenosis and atherosclerosis [11–13]. Animal models are helpful for hypothesis generation, but the biological cascades of atherosclerosis are not identical in humans and other species such as mice (especially with regard to lipid metabolism pathways), and findings from animal studies cannot be fully extrapolated to humans [14, 15]. For example, in humans it is unclear whether the proximal, middle and distal parts of vein grafts are similarly diseased.

Intravascular ultrasonography (IVUS) has broadened our understanding of atherosclerosis burden and its underestimation by conventional angiography in coronary arteries and in aortocoronary vein grafts [16, 17]. However, IVUS provides less detail for pathophysiological investigation compared with microscopic evaluation. Moreover, it is unclear how the angiographic and histological findings correlate in old human vein grafts [18].

In this study, we investigated the histopathological characteristics of old human vein grafts and assessed the correlation between angiographic and histological findings.

Methods

Patients undergoing redo CABG in three university hospitals in Tehran (Modarres Hospital, Tehran Heart Center and Rajaei Heart Center) were screened prospectively from January 2007 to November 2008. Patients were eligible to enter the study if they met these three criteria: (1) a previous history of CABG, with at least one aortocoronary vein bypass graft; (2) at least one excisable

aortocoronary vein bypass graft during the redo operation that had not undergone complete occlusive cord-like changes [19]; (3) an interval of at least 1 year between the first CABG and the redo operation.

Diseased vein grafts were harvested during the redo CABG procedure. Although the removal of angiographically patent aortocoronary saphenous vein bypass grafts during the redo operation has been widely debated, there is evidence to support changing all vein grafts from the first operation during the redo operation, especially if the redo operation is performed 5 years or more after initial surgery [6, 7, 20]. Accordingly, angiographically patent bypass grafts were also removed when harvesting such veins was feasible and deemed justified by the surgeon. Where possible, a few segments of newly harvested native saphenous veins (intended for the redo bypass) were also collected as controls. At least one of the study investigators witnessed the redo surgical procedure of each patient studied. Excised vein grafts and native saphenous veins were immediately handed to the study team, with the proximal end demarcated. Each vein graft was then divided into three parts: proximal, mid-portion and distal. Each of the recently harvested native saphenous vein segments was kept as a single sample. Each specimen was given a specific 3-character code to demarcate the patient being evaluated, the anatomic location from which the vein graft was harvested [e.g. right coronary artery (RCA) vs. left anterior descending artery], and the graft segment being evaluated (i.e. proximal, mid-portion or distal). Specimens were immediately preserved in 10% buffered formalin solution and transferred to the pathology laboratory for further submission, processing and paraffin embedding. To preclude bias, the pathologists were blinded to the coding system and the clinical and angiographic data. After appropriate processing, 3- to 4- μ m sectioning and hematoxylin and eosin staining were performed.

To record the vessel wall diameter of each segment (in millimeters), the mean of vessel wall diameter in three separate locations was calculated. Luminal narrowing of all segments was evaluated by a 5-level scale (with 0 representing complete patency and 4 denoting total occlusion). Similarly, a 5-step scale was used to assess fibrointimal proliferation (with 0 signifying no fibrointimal proliferation and 4 denoting very severe fibrosis). The presence or absence of calcium deposits in each segment was also considered. The inflammatory cell count in each segment was calculated as the mean number of inflammatory cells in 10 separate high-power fields of each segment. The existence or absence of vasa vasorum in harvested bypass grafts was also checked. A morphologic criterion was used to assess the presence or absence of necrosis. Each segment was reviewed by two pathologists. Where there was a discrepancy in any of the microscopic analyses, the issue was discussed and, if it was unresolved, a third opinion was requested from another pathologist. Microscopic evaluations were performed at the Pathology Department of the National Research Institute of Tuberculosis and Lung Disease, a WHO-colaborating university-affiliated tertiary care center for cardiopulmonary disease.

Demographic data and cardiovascular risk factor profiles were recorded in separate data sheets. Pre-redo CABG angiograms were also assessed by two separate experts, who were kept blinded to the microscopic data. Again, where there was a discrepancy, a third opinion was requested. In the analysis of angiograms, if a portion of a bypass graft was totally cut off, no data were entered

about the angiographic condition of the segments distal to the totally occlusive part of the graft. For instance, if proximal RCA was cut off angiographically, only proximal RCA data were considered for the angiographic variables, though proximal, mid-portion and distal parts were evaluated microscopically. Otherwise, each of the three parts of each bypass graft was separately rated angiographically, using a similar 5-step scale to that used for microscopic assessment (0 denoting complete patency and 4 representing total occlusion).

Patients provided informed consent to the use of excised grafts and medical data for research purposes. The study protocol was approved by Shahid Beheshti University of Medical Sciences High Research Council and Shahid Beheshti University of Medical Sciences Ethics Committee. All patient data remained confidential and were not shared with any third party.

We used a statistical software package for statistical analysis (STATA 8.0, StataCorp LP, College Station, Tex., USA). Continuous data were reported as mean $\pm$ standard error of the mean. Correlation between categorical variables was assessed using the χ^2 test with exact correction when necessary. We used the Student t test and the analysis of variances for comparison of the means between two groups and between more than two groups, respectively. For similar analyses with non-parametric data, we used the Mann-Whitney U test and the Kruskal-Wallis test. Concordance between the angiographic and microscopic degrees of luminal narrowing was assessed using the Spearman coefficient. A p value <0.05 was considered as significant.

Results

During the study period, 18 patients underwent redo CABG, and for 2 of these, none of the previously grafted veins were excised. Two further patients were excluded because their harvested bypass grafts had undergone cord-like remodeling. One patient was excluded because the excised vein grafts were improperly processed and the prepared segments had suboptimal quality for microscopic evaluation. Finally, 117 segments from 29 grafts harvested from 13 patients were evaluated (7 old bypass grafts harvested from the RCA location, 7 bypass grafts from the obtuse marginal artery location, 3 bypass grafts from the left circumflex artery location, 3 bypass grafts from the left anterior descending artery location, and 9 native recently harvested saphenous veins). The median time from the first operation was 10 years. Table 1 summarizes the background information.

In the old bypass graft segments (n = 100), 4 had no evidence of luminal narrowing, whereas minimal, moderate and severe luminal narrowing were evident in 17, 18 and 34 segments, respectively, and 27 segments demonstrated complete luminal obstruction. Fibrointimal proliferation on the other side was found in all but 4 segments (minimal, moderate, severe and very severe fibro-

Table 1. Background information

Age, years	58.25 $\pm$ 2.29
Body mass index	28.68 $\pm$ 0.98
Time from previous operation, years	11.81 $\pm$ 1.55
Gender	
Male	12
Female	1
History of smoking	
Present	6
Absent	7
History of hypertension	
Present	3
Absent	10
History of diabetes mellitus	
Present	5
Absent	8
History of dyslipidemia	
Present	8
Absent	5
Severity of previous CAD	
1VD	0
2VD	0
3VD	13

Of note, even though only 5 patients had a previous history of diabetes mellitus, all patients had a fasting plasma glucose level >90 mg/dl, and the majority (n = 11) had a fasting plasma glucose level >105 mg/dl. CAD = Coronary artery disease; 1VD = single-vessel disease; 2VD = two-vessel disease; 3VD = three-vessel disease.

sis in 23, 40, 30 and 3 segments, respectively). Sixty-one segments demonstrated luminal atherosclerotic plaques. The majority of such plaques (68%) were concentric. Angiographic findings were moderately correlated with histological data for luminal narrowing and weakly correlated with the presence or absence of luminal atherosclerotic plaques in light microscopic analysis (Spearman's $\rho = 0.564$, $p < 0.001$, and Spearman's $\rho = 0.331$, $p = 0.007$, respectively).

Areas of necrosis and the existence of giant cells were also more frequent in segments with luminal atherosclerotic plaques ($p < 0.001$ for both comparisons; fig. 1; table 2). Inflammatory cells were more abundant within segments with luminal atherosclerotic plaques ($p < 0.001$). Even though lymphocytes were the dominant inflammatory cells both in segments with and without luminal plaques, histiocytes were more plentiful in segments containing luminal plaques, compared to segments without luminal plaques ($p = 0.031$). The mean and maximal vessel wall diameters were greater in segments

Fig. 1. Severe inflammatory response in a vein graft atheromatous plaque. Notice the formation of giant cells (arrowheads). **a** $\times 40$. **b** $\times 100$.

containing luminal atherosclerotic plaques (1.08 ± 0.07 vs. 0.75 ± 0.04 mm, $p < 0.001$, and 1.58 ± 0.11 vs. 1.02 ± 0.06 mm, $p < 0.001$, respectively). Interestingly, luminal narrowing and fibrointimal proliferation were correlated with each other (Spearman's $\rho = 0.539$, $p < 0.001$) but not with the presence of luminal atherosclerotic plaques ($p = 0.49$ and 0.48 , respectively).

Luminal narrowing, fibrointimal proliferation and distribution of inflammatory cells were comparable in proximal, mid-portion and distal segments ($p = 0.912$, 0.617 and 0.373). Presence of luminal plaques and evidence of calcification were similar between proximal and distal segments ($p = 0.339$ and 0.811 , respectively). Compared with distal and proximal segments, mid-portion segments had luminal plaques less frequently (52.94 vs. 65.15%), though the difference did not reach statistical significance ($p = 0.23$). However, mid-portion segments were less frequently calcified ($p = 0.05$). The mean vessel wall diameter was smaller in mid-portion segments, albeit nonsignificantly ($p = 0.17$). However, the maximal vessel wall diameter was significantly lower in mid-portion segments (1.10 ± 0.08 vs. 1.50 ± 0.11 mm; $p = 0.005$). Table 3 presents the data based on the vascular territories from which bypassed saphenous vein grafts were harvested.

Calcium deposits were more commonly seen in segments containing luminal atherosclerotic plaques ($p < 0.001$). Whereas the presence of calcium deposits had an excellent specificity of luminal atherosclerotic plaques (96.42%), the majority of atherosclerotic plaques were not calcified, and hence, sensitivity was much lower (36.06%). Although we had not stained the internal elastic lamina,

Table 2. Histopathologic findings in old bypass graft segments with versus without luminal atherosclerosis

	Luminal atherosclerotic plaques		p value
	yes	no	
Fibrointimal proliferation			
Yes	61	35	0.02
No	0	4	
Necrosis			
Yes	29	1	<0.001
No	32	38	
Calcification			
Yes	22	2	<0.001
No	39	37	
Giant cells			
Yes	18	1	<0.001
No	43	38	
Vessel wall, mm			
Mean $\pm$ SEM	1.08 ± 0.07	0.75 ± 0.04	<0.001
Maximal $\pm$ SEM	1.58 ± 0.11	1.02 ± 0.06	<0.001

SEM = Standard error of the mean.

because of extreme superficiality of the calcified areas, we supposed that most of them were intimal in location. Two segments without any atherosclerotic plaques also demonstrated calcium deposits. These segments showed moderate luminal narrowing and mild fibrointimal proliferation. Figure 2 displays various stages of atherosclerotic lesions in old bypass grafts.

Fig. 2. Various stages of atherosclerosis in saphenous vein grafts. **a** An early atherosclerotic plaque with fibro-intimal hyperplasia. The fatty streak (FS) is remarkable. **b** Severe atherosclerosis leading to luminal obstruction (arrow). **c** Calcification within an atheromatous lesion (asterisk). Hematoxylin and eosin staining.

Table 3. Microscopic and angiographic findings based on the harvesting location of old bypass grafts

a Microscopy findings

Harvesting location of bypass SVGs	Segments	Intraluminal plaques, n	
		calcified	non-calcified
RCA	40	7	17
LCX	16	1	9
LAD	16	7	5
OM	28	5	10
Total	100	20	41

b Coronary angiography findings

Harvesting location of bypass SVGs	Severity of stenosis in each segment					Total
	complete patency	intimal irregularity	stenosis up to 70%	severe stenosis (70–99%)	complete occlusion	
RCA	0	11	2	1	10	24
LCX	0	1	0	0	4	5
LAD	6	8	0	2	0	16
OM	1	6	0	3	10	20
Total	7	26	2	6	24	65

Contrary to other bypass saphenous vein grafts, the majority of luminal plaques in the left anterior descending region were calcified, although the difference did not reach statistical significance ($p = 0.109$). As described in further detail in the Methods section, if any segment had complete obstructive lesions in angiographic evaluation, angiographic data were not entered for segments distal to the totally occlusive part. Therefore, the angiographic segments are lower in number, compared to the microscopic segments. SVG = Saphenous vein graft; LCX = left circumflex artery; LAD = left anterior descending artery; OM = obtuse marginal artery.

In some patients, native non-grafted vein segments were not obtainable because of the long operation time, the physicians' preferences or the small size of the recently harvested native saphenous veins. Of the 17 segments of native non-grafted saphenous veins, 12 showed mild to moderate luminal narrowing. Only 2 non-grafted vein segments were free of fibrointimal proliferation (13 segments had mild fibrointimal proliferation, and in 2 segments, moderate fibrointimal proliferation was present; fig. 3). There was no evidence of calcium deposits, necrosis or giant cell formation within the non-grafted saphenous veins. The mean inflammatory cell count in all such segments was <10 /high-power fields. The mean and maximal vessel wall thickness in each segment was significantly lower in non-grafted saphenous veins compared with harvested old bypass grafts (0.43 ± 0.04 vs. 0.95 ± 0.04 and 0.57 ± 0.06 vs. 1.36 ± 0.08 mm, respectively; $p < 0.001$ for both comparisons).

Vasa vasorum was detectable in all but 10 segments from old bypass grafts and in all 17 segments from the recently harvested native saphenous veins. Even though we attempted to locate venous valves in bypassed vein segments, such structures were not detectable in the atheromatous lesions by light microscopy.

Discussion

Our study demonstrated some degree of fibrointimal proliferation and luminal narrowing in almost all excised old vein graft segments, and this accords with previous studies on human saphenous vein bypass grafts [3, 11, 18]. Interestingly, such findings were present even in segments deemed 'patent' by coronary angiography [18]. In our study, findings of conventional coronary angiogra-

Color version available online

Fig. 3. Recently harvested native saphenous veins. Note that some of the native recently harvested saphenous veins were intact (**a**), whereas some others had marked fibrointimal proliferation and luminal narrowing (**b**) even before being grafted. Hematoxylin and eosin staining.

phy had a moderate correlation with the presence and degree of luminal narrowing and a weak correlation with the presence or absence of luminal atherosclerotic plaques. Whereas the most notable shortcoming of conventional angiography was underestimation of the degree of luminal narrowing and missing some atherosclerotic plaques, in a minority of segments, the degree of luminal narrowing was overestimated by conventional angiography, an effect that might be due to the dynamic response of the vessels to vasoreactive substances rather than to the presence of a fixed anatomical obstruction [21].

A few existing studies have reported histopathological findings in human vein grafts. In an autopsy study, Lie et al. [5] reported atherosclerosis in 14 out of 40 vein grafts in patients who survived 13–75 months after aortocoronary bypass. In another autopsy study of patients with a history of CABG, Batayias et al. [22] reported fibrointimal proliferation in the vast majority of vein grafts that were implanted 1 year before or earlier. They also reported typical vein graft atherosclerosis in 3 out of 6 patients surviving more than 3 years after the operation, but no further details about the histopathological characteristics or clinicoangiographic correlates were provided.

In our study, an increased number of inflammatory cells, the presence of giant cells and areas of necrosis and calcification were more frequent in segments containing atherosclerotic plaques, consistent with findings from studies on atherosclerosis of native coronary arteries [3, 23]. Moreover, histiocytes were more abundant in

sections containing atherosclerotic plaques. However, contrary to what has been reported from the analysis of arterial plaques [23], in our study, lymphocytes were the predominant inflammatory cells in the majority of atherosclerotic plaques. The majority of studies on human aortocoronary bypass grafts did not describe the dominant inflammatory cell types in vein graft atherosclerotic lesions [8, 18]; however, the findings of a study by van der Wal et al. [24] also suggested a predominance of lymphocytes in venous compared with arterial plaques. Although the reasons for a predominance of lymphocytes in vein graft atherosclerotic lesions need further investigation, it has been suggested that dendritic cells and lymphocytes co-accumulate in atherosclerotic vein grafts, suggesting an immune-mediated antigen presentation to lymphocytes [25]. It might be the case that in human venous plaques, lymphocytes are dominant inflammatory cells that render the venous plaques more vulnerable to rupture or disruption because of interferon- γ production, which reduces the fibrous cap thickness [3, 9]. We detected vasa vasorum in the vast majority of the vein graft segments. This finding is notable, firstly because bypass grafts would need these small vessels to receive nutrients, and secondly, because such vessels might play a role in transferring the lipid material from red blood cells to atherosclerotic plaques [3, 26].

It is known that various segments of a bypass graft (i.e. the proximal, middle and distal segments) are subject to distinct shear forces and turbulent flows [3, 27]. We

did not observe a significant difference for any of the histopathological findings between proximal and distal segments of vein grafts; however, mid-portion segments (which are known to be subject to less turbulent flows) demonstrated stenosis, atherosclerotic plaques and plaque calcification less commonly.

The vast majority of recently harvested (non-grafted) native saphenous veins also demonstrated some degree of fibrointimal proliferation. This finding is in accordance with previous studies [3, 18].

The majority of patients undergoing redo CABG in this study were men (12:1). This ratio is markedly greater than that reported in patients undergoing native CABG in Iran [28, 29]; however, our sample size is too small to suggest a causal role for gender.

Bypass graft disease is the most common cause of unstable angina in patients with a history of CABG. Thrombus formation and refractoriness to medical therapy are also more frequent in such patients [30]. In addition, repeat revascularization procedures are more costly, riskier and less effective for patients with vein graft disease [3]. Furthermore, a recent study suggested that (radial) arterial grafts are no better than saphenous vein grafts for revascularization of target lesions other than those at the left anterior descending artery territory, at 1-year follow-up [31]. Therefore, a full understanding of vein graft atherosclerosis mechanisms is more important than ever to improve outcomes in venous bypass grafts. Compared with conventional angiography, strategies such as IVUS and near-infrared spectroscopy could be helpful in a better evaluation of the atherosclerosis burden, though their use is currently limited by their cost, as well as by complications such as vessel dissection and rupture [32, 33]. The usefulness of such techniques is being studied in randomized trials, with some impressive initial results [34].

Our study had several limitations, most of which could be exploited to devise future studies. Though we had planned to assess the venous valves in vein grafts with and without atherosclerotic plaques, venous valves were not detectable in old bypass grafts by light microscopy in our study. To the authors' knowledge, such a study has not been performed until now. Future studies using electron microscopy could determine if the presence of venous valves might have an effect on the evolvement of atherosclerotic plaques in vein grafts, due to possible alterations in hemodynamic flow patterns. We had also intended to correlate the angle of anastomosis of the first-operation bypass grafts with subsequent histopathological changes, but this was not feasible due to a lack of comprehensive data from the first operation of the enrolled patients and

unconvincing data from the redo operation regarding the angle of anastomosis. Due to financial constraints, we were unable to apply advanced supplementary staining techniques, and since we did not stain the internal elastic lamina, we could not proceed with separate analyses for each vessel wall layer. Finally, the number of evaluated old vein grafts in this study was greater than in the majority of previous histopathological studies on old human vein grafts [8–10, 18], but a further increase in the number of patients studied would allow a more thorough examination of the correlations of epidemiologic characteristics with clinicopathological data. Given the difficulties involved in obtaining old human bypass grafts, a multicentric multinational study might provide better resources for such detailed analyses.

Histopathological studies provide the most accurate clues to a better understanding of human aortocoronary vein graft disease. With better insight into disease pathophysiology, novel interventions could be introduced to improve care and future outcomes for patients undergoing CABG.

In conclusion, this study demonstrated the presence of atherosclerotic plaques in the majority of vein graft segments. Conventional coronary angiography underestimated the degree of luminal narrowing and the presence of atherosclerotic plaques in many vein segments. Segments containing atherosclerotic plaques had a higher mean inflammatory cell count and more frequently showed areas of necrosis, giant cells and calcification. Interestingly, lymphocytes were the predominant inflammatory cells in vein graft plaques. A clearer understanding of vein graft atherosclerosis pathophysiology will prepare the ground for the introduction of new interventions to improve the outcomes of patients undergoing CABG.

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Conflict of Interest

None.

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