MORPHOLOGIC STUDIES

Balloon Angioplasty of Aortocoronary Saphenous Vein Bypass Grafts: A Histopathologic Study of Six Grafts From Five Patients, With Emphasis on Restenosis and Embolic Complications

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Among 103 patients undergoing percutaneous transluminal balloon angioplasty of obstructed aortocoronary saphenous vein bypass grafts at the Mayo Clinic, six grafts from five patients were available for histopathologic examination. The interval from graft insertion to angioplasty ranged from 5 to 105 months and that from angioplasty to graft excision ranged from 6 h to 24 months.

Angioplasty produced intimal fissures in three grafts initially obstructed by intimal fibromuscular proliferation. Healing and restenosis resulted from filling of lacerations with fibrocellular tissue and apparently also from restitution of muscular tone.

In two of three grafts initially narrowed by atherosclerosis, balloon angioplasty caused extensive plaque rupture and restenosis resulted from extrusion of plaque debris and secondary luminal thrombosis. In the third graft, angioplasty produced no distinct lesions and late restenosis was due to progressive atherosclerosis of the vein graft. Atheroembolization was observed in both patients with plaque rupture and was associated with reoperation in one and death in the other.

In conclusion, the results derived from six saphenous vein bypass grafts subjected to balloon angioplasty indicate that restenosis may result from intimal fibrocellular proliferation, thrombosis, restitution of muscular tone and progressive atherosclerosis. Symptomatic atheroembolization may occur in grafts >1 year old.

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The usefulness of percutaneous transluminal balloon angioplasty for the relief of coronary artery obstructions has been well documented clinically (1-6), and various microscopic alterations have been reported to account for the observed luminal expansion (7-22). Less well established, however, is the efficacy of balloon angioplasty for the treatment of stenotic lesions of aortocoronary saphenous vein bypass grafts. Although balloon dilation of vein grafts has been reported in ≥431 cases (23-35), the corresponding histopathologic lesions, to our knowledge, have been documented in only three grafts from three patients (14,25). With these considerations in mind, the present study was undertaken to investigate the microscopic alterations after balloon angioplasty of six stenotic vein grafts.

Methods

Study patients. Between January 1980 and December 1987, 103 patients underwent balloon angioplasty of obstructed saphenous vein bypass grafts at our institution. Among these, six segments of dilated grafts from five patients were available for histopathologic examination (four from operation and two from autopsy). The interval between angioplasty and graft removal ranged from 6 h to 24 months.

Pathologic preparation. In the pathology laboratory, all specimens were handled carefully to prevent induction of artifactual lesions. Specimens were fixed in 10% neutral buffered formalin and then placed into decalcification solution. After decalcification was completed, the grafts were step-sectioned at 3 mm intervals, including the regions subjected to angioplasty, and processed routinely. Paraffin blocks were cut at several levels and slides were stained with hematoxylin-eosin, elastic-Van Gieson and Masson’s tri-
Table 1. Clinical and Pathologic Features of Aortocoronary Saphenous Vein Bypass Grafts Subjected to Percutaneous Transluminal Balloon Angioplasty

<table>
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<td>5</td>
<td>12</td>
<td>42</td>
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<td>Graft stenosis (%)</td>
<td></td>
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<td>12</td>
<td>7</td>
<td>5,5</td>
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<td>Muscular tone + FCP</td>
<td>Progressive Plaque + extrusion &amp; thrombosis</td>
<td>Muscular tone + FCP</td>
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Ath = atherosclerosis; Avg = average; cath = cardiac catheterization; F = female; FCP = fibrocellular proliferation; IFP = intimal fibromuscular proliferation; M = male; PTBA = percutaneous transluminal balloon angioplasty.

The sites of angioplasty were identified in autopsy specimens by written records from the cardiac catheterization laboratory and in surgical specimens by written descriptions from the surgeons. Although it is possible that the observed abnormalities at these sites could have occurred spontaneously, the fact that similar changes were not present elsewhere in the vein grafts or coronary arteries (in the two autopsy cases) indicates that this is a remote possibility and supports our interpretation that the lesions are related to the balloon angioplasty procedure.

Report of Cases

Case 1

Graft 1. In March 1985, a 66 year old man with ischemic heart disease and a history of hypertension and smoking underwent placement of an aortocoronary circular sequential saphenous vein bypass graft to the right, obtuse marginal, first and second diagonal and left anterior descending coronary arteries. Five months later, during evaluation for unstable angina, an angiogram showed 99% obstruction along the proximal portion of the graft. Balloon angioplasty was performed, but angiography showed 70% residual stenosis (Table 1). Accordingly, the patient underwent operative excision of the stenotic proximal segment of the old graft and placement of a new interposition saphenous vein graft.

Morphology (Fig. 1). Grossly, the resected portion of vein graft was characterized by aneurysmal dilation. Microscopically, the proximal region was the site of 95% obstruction by extensive intimal proliferation. In general, the media was hypertrophied in nonstenotic areas and was fibrotic and atrophic in the area of severe stenosis. Additional lesions were considered to represent the aftermath of balloon dilation and included complex intimal tears that extended focally to the level of the internal elastic lamina (Fig. 1A and B). Leukocytes and shallow fresh thrombus were also observed focally along the fissure tracts.

Graft 2. In March 1986, unstable angina again developed. At angiography, the interposition graft showed 90% obstruction just distal to its ostium. Balloon angioplasty was completed satisfactorily, and a subsequent angiogram showed only 20% residual stenosis (Table 1). Five months later, however, the graft again showed 90% obstruction. At oper-
ation, a new interposition graft was inserted and the old one was resected.

Morphology (Fig. 1). Microscopically, the graft was involved by 90% narrowing due to intimal fibromuscular proliferation. Moreover, phlebosclerotic medial hypertrophy and fibrosis, which presumably were present preoperatively, resulted in a vessel of small caliber. Evidence of previous angioplasty included healing by fibrosis along the intimal lacerations (Fig. 1C and D). Despite the intimal tears, the lumen remained severely narrowed.

Case 2

In September 1982, a 64 year old man with ischemic heart disease and hypertriglyceridemia underwent insertion of an aortocoronary sequential saphenous vein bypass graft to the first obtuse marginal, first diagonal and left anterior descending arteries. During an evaluation for angina in February 1984, coronary angiography demonstrated 99% obstruction of the graft at its anastomosis to the first obtuse marginal branch. Balloon angioplasty reduced the obstruction to 70% (Table 1). In March 1986, the patient was evaluated for progressive angina and was scheduled for coronary bypass surgery but died suddenly before the operation.

Figure 1. Case I: A and B (graft 1). Low power photomicrograph of cross section of vein graft (A) shows severe luminal obstruction by intimal fibromuscular proliferation and narrow slitlike lumen (arrows). High power view (B) demonstrates complex intimal tears (arrowheads) attributable to balloon angioplasty, with minimal relief of luminal obstruction. C and D (graft 2). Fissure tracts (arrowheads) are the result of balloon angioplasty and are not associated with luminal widening (C) or are filled by loose fibrocellular tissue (D). L = lumen. (A and B, Masson’s trichrome stain; C, hematoxylin-eosin stain; D, elastic-Van Gieson stain; A, original magnification x36 and B through D, x90; all reduced by 35%.)

Morphology. At autopsy, the heart weighed 560 g (expected, 330 g) and was the site of critical three-vessel coronary atherosclerosis, biventricular hypertrophy, four chamber dilation and an old transmural inferior myocardial infarction. Microscopically, extensive atherosclerosis produced 95% obstruction of the vein graft, including the region subjected to angioplasty; medial atrophy and fibrosis were also identified. Plaques in the vein graft, however, were larger and contained a more extensive component of necrotic friable debris than did their counterparts in the native coronary arteries. No distinct lesions were observed that could be directly attributed to the angioplasty procedure, and in multiple sections of ventricular myocardium there was no evidence of coronary embolization.
Figure 2. (Case 3): A and B (vein graft). Low power view (A) shows rupture (arrowheads) of atheromatous plaque due to balloon angioplasty and secondary thrombosis (Thr). Sections taken at adjacent sites were involved by such extensive disruption that luminal boundaries were obliterated. High power photomicrograph (B) demonstrates nature of plaque with foam cells, cholesterol clefts, blood elements and necrotic debris. C and D, Intramural coronary artery branches. Atheromatous emboli obstruct vessels in anterolateral (C) and inferoseptal (D) walls of left ventricle (compare with B). (A, elastic-Van Gieson stain, original magnification ×13; B through D, hematoxylin-eosin stain, original magnification ×180; all reduced by 35%).

Case 3

A 59 year old woman with hypercholesterolemia and ischemic heart disease underwent placement of an aortocoronary sequential saphenous vein bypass graft to the first diagonal and left anterior descending arteries in March 1981. She had an acute myocardial infarction 5 months later and a second infarction 6 years later (March 1987). At the latter time, the graft was totally occluded angiographically. Treatment with streptokinase and balloon angioplasty of the distal anastomosis reduced the obstruction from 100 to 50% (Table 1). Furthermore, balloon dilation of a proximal 90% obstruction was also associated with reduction to 50% stenosis. Soon thereafter, however, the patient had a sudden and profound drop in cardiac output and systemic blood pressure and died despite resuscitative efforts. An autopsy was performed.

Morphology (Fig. 2). The heart weighed 510 g (expected, 275 g) and was involved by biventricular hypertrophy, four-chamber dilation, an old transmural inferior myocardial infarction and three-vessel critical coronary atherosclerosis. The saphenous vein graft was aneurysmally dilated and was involved by severe atherosclerosis, with 95% stenosis, and focal medial fibrosis. Atheromas within the vein graft were composed predominantly of cholesterol crystals and necrotic debris; in contrast, those in the smaller native coronary arteries generally exhibited a greater fibrous component. Lesions attributable to balloon angioplasty included extensive disruption of the friable atheromatous plaques and secondary luminal obstruction due to extruded atheromatous debris and acute thrombosis (Fig. 2A and B). Moreover, multiple small intramural coronary artery branches were obstructed by embolic thromboatheromatous debris (Fig. 2C and D). Embolic involvement of both the anterior and the inferior aspects of the left ventricle was considered to be due
to enlarged collateral channels between the left and right coronary circulations.

**Case 4**

In 1980, a 52 year old man with ischemic heart disease and a history of hyperlipidemia and smoking underwent coronary bypass surgery with the placement of two saphenous vein grafts, one to the left anterior descending artery and one sequentially to the right posterior descending and posterolateral arteries. Angiography performed at the time of an acute myocardial infarction in April 1986 (6 years later) demonstrated total occlusion of the right graft and 50% obstruction of the left graft. Medical therapy included streptokinase and dipyridamole.

In June 1986, the patient had another myocardial infarction and angiographically both grafts were completely occluded. Emergency balloon dilation of the left graft was performed and the extent of stenosis was reduced to 30% (Table 1). In July 1986, the patient had recurrent angina and underwent coronary revascularization surgery. At operation, thrombus was removed from the left anterior descending artery at the origin of its first diagonal branch, and the old left and right bypass grafts were excised and replaced with new grafts.

**Morphology (Fig. 3).** The left vein graft was aneurysmally dilated and microscopically was the site of 95% obstruction due to atherosclerosis and medial atrophy and fibrosis. The plaque was fractured, presumably as a result of balloon angioplasty, and extrusion of atheromatous debris within embolus removed surgically from left anterior descending coronary artery (compare with A and B). (Hematoxylin-eosin stain; A, original magnification ×18; B and C, ×90; D, ×180; all reduced by 35%).
was considered to represent an embolus from the ruptured plaque in the vein graft, a result of previous balloon angioplasty.

**Case 5**

In June 1977, a 15 year old boy underwent operative repair of tetralogy of Fallot and anomalous origin of the left coronary artery from the pulmonary artery in which a segment of saphenous vein was used. Nine years later, in October 1986, the patient was evaluated for ventricular arrhythmia and ischemia, and 95% obstruction of the vein graft near its aortic anastomosis was demonstrated angiographically. Angioplasty was performed, and the severity of obstruction was reduced to 60% (Table 1). One month later, however, 95% stenosis was again documented, and the patient underwent excision and revision of the aortic anastomosis site.

**Morphology.** Microscopically, the resected tissue represented the graft at its aortic anastomosis site and was involved by intimal and medial fibrosis. Intimal fissuring and disruption were observed and were considered to be the result of balloon angioplasty. The fissures were partially filled with shallow, loose fibrocellular tissue.

**Discussion**

The clinical utility of percutaneous transluminal balloon angioplasty for the treatment of stenotic lesions of aortocoronary saphenous vein bypass grafts depends not only on the immediate relief of obstruction but also on the frequency and rate of restenosis and the incidence of serious complications. Four topics warrant further comment: 1) causes of vein graft obstruction; 2) histopathologic counterparts of balloon angioplasty; 3) causes of vein graft restenosis after angioplasty; and 4) embolic complications after balloon dilation of vein grafts.

**Causes of vein graft stenosis.** Failure of aortocoronary saphenous vein bypass grafts is generally the result of either vein graft stenosis or progressive atherosclerotic narrowing of distal native coronary arteries. When the graft is stenotic, the most common causes are thrombosis, intimal fibromuscular proliferation and atherosclerosis (14, 36-45). The nature of the obstruction, however, tends to be related more to the postoperative interval than to the site of stenosis.

Stenosis within the 1st month is almost always due to thrombosis and is generally related to technical factors such as anastomotic narrowing, operative trauma to the vein graft and inadequate distal runoff. The thrombus may be localized or diffuse and may be occlusive or associated with only partial luminal obstruction.

Between 1 month and 1 year postoperatively, intimal fibromuscular proliferation is the most prevalent form of obstruction. The intima is characterized by an admixture of smooth muscle cells, fibroblasts, collagen and ground substance, and the media eventually undergoes atrophy and fibrosis.

Postoperatively, beyond 1 year and particularly after 3 years, atherosclerosis becomes an important cause of vein graft stenosis and may coexist with intimal fibromuscular proliferation. Plaques in vein grafts resemble those in native coronary arteries and tend to be rich in cholesterol crystals, necrotic debris, blood elements and foam cells. Accordingly, the plaques are generally soft and friable rather than densely fibrotic or calcific. Furthermore, because vein grafts tend to be larger than the native coronary arteries to which they are anastomosed, and because vein graft atherosclerosis often occurs in aneurysmally dilated segments, the plaques are generally quite large relative to the native coronary arteries.

**Histopathology of coronary angioplasty.** The alterations produced by balloon angioplasty of atherosclerotic plaques in coronary arteries have been examined microscopically in experimental animals (7-9), postmortem specimens of human coronary arteries subjected to angioplasty (10) and surgical and autopsy specimens angioplasty was performed in living patients (11-21). Various lesions have been observed to account for the relief of obstruction, although in some cases no alterations were recognized.

For soft atheromas, intimal tears may form tracts that extend into the necrotic core of the lesion and may be associated with extrusion and embolization of the atheromatous debris. In contrast, for fibrocalcific atheromas, the intimal tears tend to be peripheral, at the junction of the plaque and the uninvolved portion of the vessel wall, and may result in dissection of a portion of the plaque away from the underlying internal elastic lamina and in the formation of an intimal flap. Stretching of the vessel's wall opposite an eccentric atheroma may also result in luminal expansion.

Restenosis of coronary arteries subjected to balloon angioplasty occurs in 25 to 40% of patients (4, 5, 27). Intimal fibrocellular proliferation, a healing process, is the major histopathologic counterpart of obstruction (12, 17, 18), although thrombosis and progressive intimal atherosclerosis may also be important in some cases. Moreover, when relief of obstruction is due to medial stretching opposite an atheroma, restenosis may result from restitution of medial tone (22).

**Histopathology of vein graft angioplasty.** Within the 1st postoperative month, balloon angioplasty may be beneficial to relieve stenoses, particularly at distal anastomosis sites. Beyond the 1st postoperative month, lesions subjected to balloon dilation generally represent intimal fibromuscular proliferation and, in older grafts, atherosclerosis. The manner in which balloon angioplasty relieves obstructions in vein grafts appears to be similar to that described for native coronary arteries and is characterized primarily by intimal tears and plaque disruption (14).
Restenosis is also similar to that observed in native coronary arteries.

In a case report by Famularo et al. (25), balloon angioplasty of a vein graft that was obstructed by atherosclerosis resulted in plaque rupture, medial dissection and subsequent luminal occlusion by atheromatous debris (Table 1). Waller et al. (19) described their findings in a vein graft 56 months old that was subjected to two angioplasty procedures (Table 1). Obstruction was due to atherosclerosis, and balloon dilation caused plaque rupture and the development of an intimal flap. Healing by fibrosis resulted in reattachment of the intimal flap to the media. In a second case reported by Waller et al. (19), vein graft obstruction was caused by intimal fibromuscular proliferation (Table 1), and no alterations were observed by light microscopy that corresponded to the angioplasty procedure.

In the present study, six grafts from five patients were examined by light microscopy (Table 1). Among three grafts obstructed by intimal fibromuscular proliferation (Cases 1-1, 1-2 and 5) balloon angioplasty produced irregular intimal tears in each. Healing, occurring in two cases, was characterized by cellular fibrosis along the fissure tracts.

The other three grafts (Cases 2 to 4) had been implanted for 18 to 74 months at the time of angioplasty and were obstructed by atherosclerosis. Balloon dilation caused plaque rupture and atheromatous embolization in two cases and no apparent alterations in one. Healing was observed in one case and was associated with early fibrocellular proliferation along the rupture site.

**Restenosis of vein grafts after angioplasty.** In the case of Famularo et al. (25) and in two of the current patients (Cases 1-1 and 3), restenosis occurred almost immediately after the procedure, and the angioplasty may be considered to have failed. Graft obstruction resulted from extrusion of necrotic atheromatous debris from the ruptured plaque into the lumen in two of these three patients and was associated with secondary thrombosis in one (Case 3) of the two. In the third patient (Case 1-1) with severe intimal fibromuscular proliferation, restenosis may have occurred as a result of restitution of muscular tone in the media and intima (that is, the stretched portion of the vessel returned to its previous size) or as a result of inadequate balloon dilation.

**Late restenosis developing ≥1 month after balloon dilation** was observed in one patient reported by Waller et al. (19) and in four of the present cases. Lining of rupture tracts with proliferative fibrocellular tissue was the dominant histopathologic feature in four of the five cases, and progression of vein graft atherosclerosis apparently occurred in one (Case 2). It is also possible that restitution of muscular tone contributes to restenosis.

**Embolic complications of angioplasty.** Embolic complications after balloon angioplasty of coronary arteries have been observed in experimental animals (46) and in 0.06 to 1.0% of patients (4,47–50) but have been documented pathologically in only two patients (20,21). Although coronary embolization as a complication of balloon angioplasty of saphenous vein grafts has been emphasized by fewer investigators (28,35), its frequency is higher than that in native coronary arteries, and symptomatic instances accounted for 2 (2.4%) of 82 cases reported by Cote et al. (35) and for 2 (1.9%) of 103 cases at our institution.

In one of our two cases, a large thromboatheromatous embolus obstructed the proximal left anterior descending artery and was removed at the time of operation. In the second case, embolization of atheromatous and thrombotic debris resulted in obstruction of many intramural coronary artery branches and was considered contributory to the death of the patient. To our knowledge, histopathologic documentation of coronary embolization after balloon dilation of aortocoronary saphenous vein bypass grafts has not been previously reported.

**Embolization of thrombotic or atheromatous material** probably occurs more frequently after balloon angioplasty of coronary arteries than has been recognized but is clinically asymptomatic in most cases because of the small size and number of emboli. Balloon dilation of saphenous vein grafts, however, is probably more likely to produce symptomatic embolization because vein grafts and their atheromatous plaques are generally larger than the coronary arteries to which they are anastomosed and because atherosclerosis in vein grafts tends to involve dilated segments and to be more friable and less fibrocalcific than its counterpart in the native coronary arteries.

Accordingly, atherosclerotic plaques in vein grafts seem particularly vulnerable to disruption and to embolization of relatively large fragments. Keon et al. (51) reported that the incidence of perioperative myocardial infarction caused by atheroembolization during repeat coronary artery bypass surgery was 10 times greater than that during the initial operation and suggested clamping and minimal manipulation of old vein grafts in an attempt to prevent intraoperative embolization.

**Conclusions.** In light of the aforementioned observations, it seems prudent that percutaneous transluminal balloon angioplasty of aortocoronary saphenous vein bypass grafts >1 year of age be performed with the realization that involvement by friable atherosclerosis is likely and that atheroembolization represents a risk.

**References**


