

Clinical Pathologic Correlations

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Coronary Artery and Saphenous Vein Graft Remodeling: A Review of Histologic Findings after Various Interventional Procedures—Part V

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Summary: Catheter balloon angioplasty is a well accepted form of nonsurgical treatment of acutely and chronically obstructed coronary artery vessels. It is also the centerpiece for various new intervention techniques. Their morphologic effect on the site of obstruction has been termed "remodeling." Part V of this six-part series focuses on remodeling effects of balloon angioplasty on obstructed young (≤ 1 year) and old (> 1 year) saphenous vein bypass grafts.

Key words: vessel remodeling, coronary angioplasty, restenosis, coronary artery bypass, saphenous vein bypass graft angioplasty, saphenous vein bypass graft

Balloon Angioplasty of Aortocoronary Saphenous Vein Bypass Grafts

Coronary embolization as a complication of balloon angioplasty of saphenous vein grafts has been emphasized by several investigators.¹⁻⁴ Its frequency, which is higher than that in balloon angioplasty of native coronary arteries, accounts for 2 (1.9%) of 103 cases reported by Saber *et al.*³ who recently submitted pathologic documentation of coronary embolization after balloon angioplasty of aortocoronary saphenous vein bypass grafts.

In one of their 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.

Embolization of thrombotic or atheromatous material probably occurs more frequently after balloon angioplasty than has been recognized since it is clinically asymptomatic in most cases because of the small size and number of emboli. Balloon dilatation of saphenous vein grafts, however, is probably more likely to produce symptomatic embolization because vein grafts and their atheromatous plaques generally are larger than the coronary arteries to which they are anastomosed. In addition, atherosclerosis in vein grafts tends to be more friable and less fibrocalcific than its counterpart in the native coronary arteries.¹ Saber *et al.*³ recommended that balloon angioplasty of aortocoronary saphenous vein bypass grafts over 1 year of age be performed with the realization that involvement by friable atherosclerosis is likely and that atheroembolization represents a risk.³

Balloon Angioplasty of Aortocoronary Saphenous Vein Bypass Grafts

Morphologic changes in aortocoronary saphenous vein bypass grafts following balloon angioplasty have been reported.^{3,5} This section summarizes clinical and morphologic observations in two patients undergoing percutaneous transluminal coronary angioplasty (PTCA) of saphenous vein bypass grafts early and late after graft insertion.⁵ Operatively excised segments of saphenous vein bypass grafts from two patients undergoing balloon angioplasty of the bypass graft early (young) (≤ 1 year) and late (old) (> 1 year) after aortocoronary bypass surgery was the basis of this study.

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Angioplasty of Saphenous Vein Graft Early after Bypass Surgery

Morphologic Features

The operatively excised portion of saphenous vein graft (Fig. 1) measured 40 mm in length and was free of calcific deposits. The excised segment included the site of maximal balloon inflation and a short distal portion through which the catheter and guide wire had passed but in which balloon inflation did not occur. The external diameter (about 7 mm) of the proximal 30 mm of graft (the portion subjected to angioplasty) was slightly wider compared with the external diameter (about 5 mm of the distal nondilated segment). The entire specimen was cut transversely into eight 5 mm segments numbered 1 to 8. Segments 1 to 6 were from areas of previous balloon angioplasty, and segments 7 and 8 were from nondilated areas.

Angioplasty of Saphenous Vein Graft Late after Bypass Surgery

Morphologic Features

The operatively excised portion of saphenous graft (Fig. 2) measured 42 mm in length and had foci of calcific deposits in the area of dilation. The entire specimen was cut transversely into eight 5 mm long segments numbered 1 to 8. Segments 4 to 6 were from the site of maximal balloon inflation. The area of the angioplasty dissection noted angiographically was specifically localized on the excised saphenous vein specimen.

Morphologic Observations in the Early (Young) Saphenous Vein Graft

The lumen of each of the eight 5 mm saphenous vein segments was narrowed > 75% in cross-sectional area by intimal thickening (Fig. 2). Histologically, the diffuse intimal thickening of both dilated and nondilated segments consisted of cellular fibrocollagenous tissue without foam cells or cholesterol clefts (intimal "fibrous hyperplasia," "fibrous proliferation"). Segments 1 to 6 were serially sectioned at 10 μ intervals to search for sites of splits, tears, or cracks, or other morphologic evidence of previous balloon angioplasty. Control segments 7 and 8 were also sectioned in a similar fashion. Histologic assessment by light microscopy did not disclose any distinctive morphologic lesion(s) in the intimal, medial, or adventitial layers of dilated or nondilated segments of the saphenous vein graft.

Ultrastructural evaluation of segments 2 (dilated) and 6 (nondilated) disclosed the absence of endothelial luminal cells in the dilated segment compared with their presence in the nondilated segment. Cells lining the graft lumen in the dilated segment had features of myofibroblasts (cytoplasmic filaments with focal condensations and abundant rough endoplasmic reticulum). Fibrin-like extracellular material (possibly representing residual basement membrane) condensed along the luminal border of these myofibroblasts. The endothelial

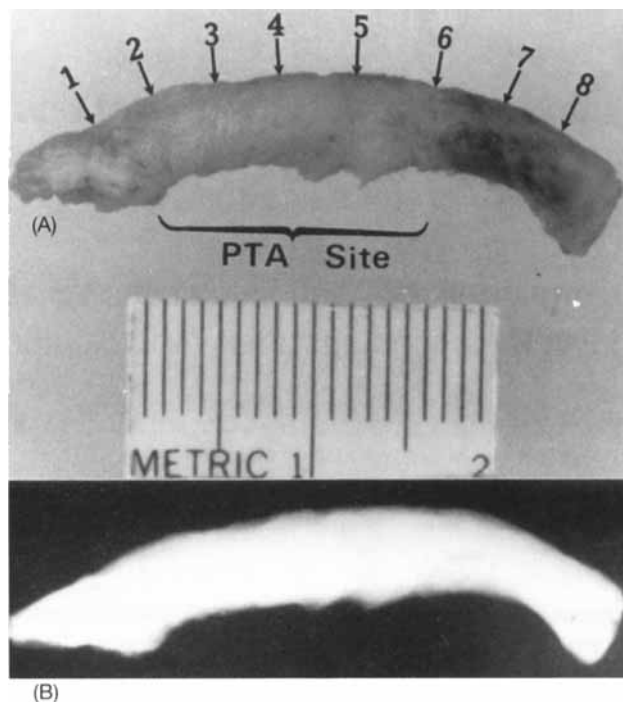


FIG. 1 Excised saphenous vein conduit following transluminal balloon angioplasty (PTA). (A) Sites of transverse sectioning. The numbers correspond to serial sections seen in Figure 2. (B) Radiograph showing no calcific deposits. From Ref. 5 with permission.

cells lining the lumen of the distal nondilated segment had luminal and abluminal micropinocytotic vesicles and well-formed intercellular junctions. No distinctive differences in myofibroblasts or collagen fibrils were noted between segments 2 and 8.

Morphologic Observations in the Late (Old) Saphenous Vein Graft

The lumen of each of the eight 5 mm saphenous vein segments had diffuse but variable degrees of intimal thickening (Fig. 3). The maximum cross-sectional area luminal reduction by intimal thickening occurred in segments 3, 4, and 6. Histologically, the intimal thickening in segments 4 to 6 consisted of foam cells, cholesterol clefts, fibrocollagenous tissue, foci of myofibroblasts, and calcific deposits characteristic of atherosclerotic plaque (Figs. 3, 4). Intimal thickening of segments 1 to 3 and 7 and 8 was predominantly fibrocollagenous in nature except for occasional foci of foam cells, cholesterol clefts, and calcium. The site of angioplasty dissection (segments 4 to 6) (Figs. 4, 5) had partial separation of the intima from the media. This intimal flap had begun to reattach to the wall of the graft, representing healing of a localized plaque tear or fracture.⁵

Clinical Morphologic Correlations

Each of the patients just described had one or more clinically successful PTCA dilations of a stenotic saphenous vein bypass graft early (2 months) or late (52 and 54 months) after

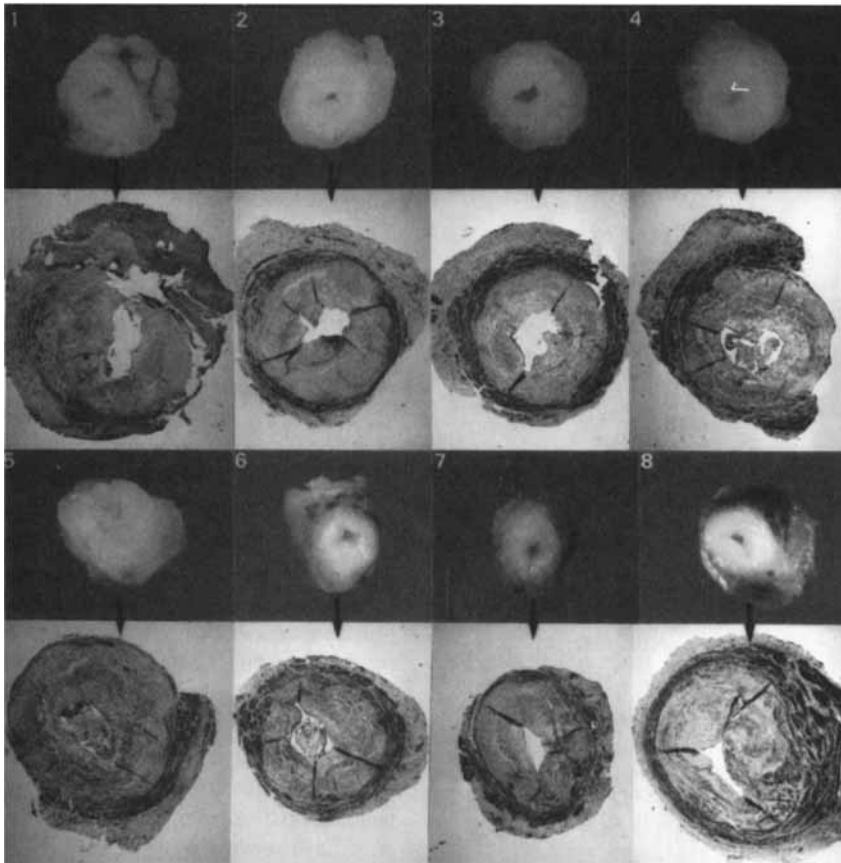


FIG. 2 Morphologic and histologic photographs of the eight segments of saphenous vein graft, corresponding to the sites labeled in Figure 18. Segments 1 through 6 are from the area of balloon inflation and dilatation, and segments 7 and 8 are from nondilated portions of the graft ("controls"). Each of the eight segments had diffuse and severe cross-sectional area luminal narrowing by intimal thickening consisting of fibrocollagenous tissue. No segments contained atherosclerotic plaque or calcium deposits. No distinctive histologic changes were observed in the segments subjected to transluminal balloon angioplasty compared with control segments. Elastic stains; magnification $\times 6$. From Ref. 5 with permission.

graft insertion. Angiographic similarities between the early and late saphenous vein grafts included an increase in luminal diameter associated with a decrease in mean transstenotic pressure gradient following angioplasty, and restenosis of the graft at the site of previous dilation 1 or 2 months later. Angiographic differences between the grafts included the absence of cracks, breaks, or splits following dilation in the early graft, but the presence of an intimal split following the second angioplasty procedure in the late graft. An additional angiographic difference between the grafts was the location of stenosis. The site of stenosis in the early graft was at the proximal end of the graft (aortic anastomosis), whereas the site of stenosis in the late graft was in the graft body (mid-portion). Morphologic similarities between the grafts included diffuse intimal thickening by fibrocollagenous tissue with fibrotic medial and adventitial layers. Morphologic differences between the grafts were distinctive: the early graft had thickened intima without atherosclerotic plaque changes or calcific deposits and no morphologic evidence of previous dilations, whereas the late graft had thickened intima typical of atherosclerotic plaque with focal calcific deposits and morphologic evidence of angioplasty injury.⁵

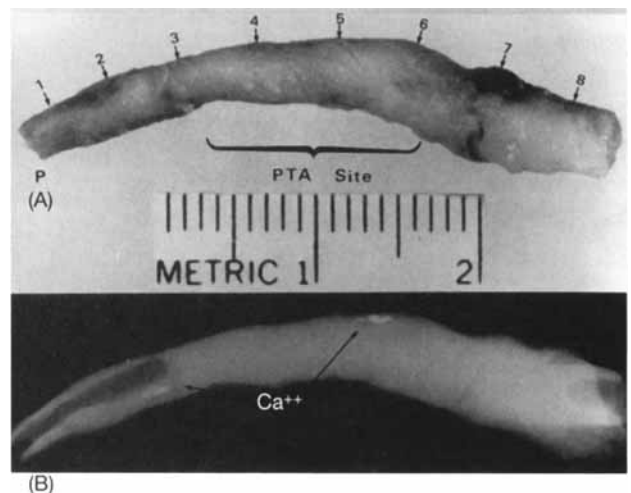


FIG. 3 Operatively excised portion of a 56-month-old saphenous vein graft. (A) The brackets indicate the site of two transluminal balloon angioplasty (PTA) procedures located in the midportion of the graft (P = proximal end). The numbers represent sites of transverse sections appearing in Figure 4. (B) Radiograph of transverse section discloses foci of calcific (Ca^{++}) deposits. From Ref. 5 with permission.

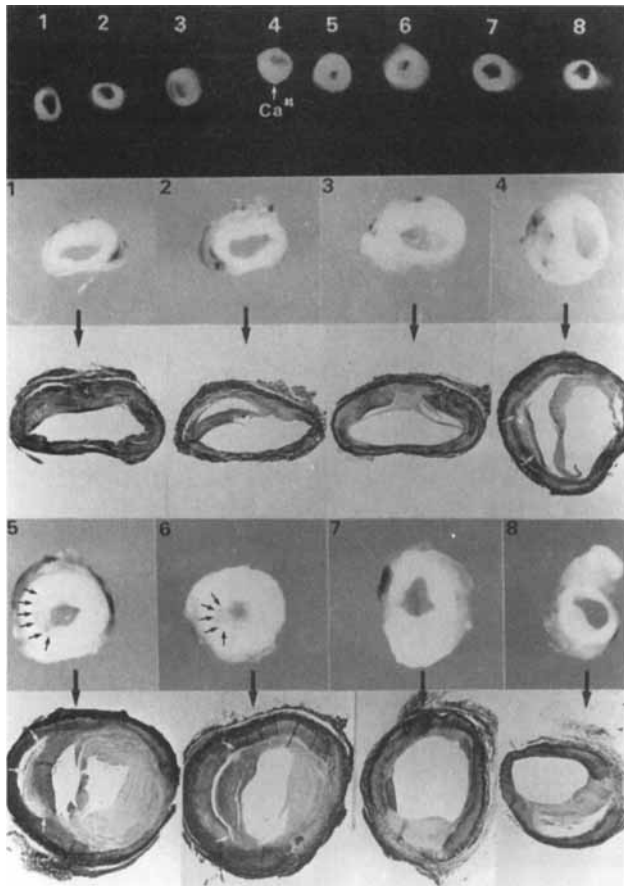


FIG. 4 Photographs of morphologic and histologic segments of saphenous vein graft corresponding to the sites labeled in Figure 3. Each of the segments shows diffuse but variable degrees of intimal thickening composed of atherosclerotic plaque. The segment with the most severe luminal narrowing (5) corresponds to the area of previous transluminal balloon angioplasty procedures (small arrows). The top panel represents radiographs of the individual cross sections (#1-8) showing calcific deposits Ca#. From Ref. 5 with permission.

Therapeutic Implications for Saphenous Vein Angioplasty Derived from Morphologic Observations

The fate of an aortocoronary saphenous vein bypass graft appears to be dependent on several factors relevant to the time interval from bypass grafting to graft obstruction. Graft occlusion developing within 1 month of bypass graft insertion is almost invariably secondary to graft thrombosis related to technical factors such as stenosis at aortic or coronary anastomotic site, intraoperative vein trauma, or poor distal runoff secondary to severe atherosclerosis or reduced caliber of the distal native vessel.⁵ These technical factors and the nature of the obstructing material (thrombus) appear to limit the role of balloon angioplasty in successfully relieving saphenous vein graft obstruction occurring within 1 month of bypass operation.⁵

Functionally significant graft stenoses developing between 1 month and 1 year following graft insertion nearly always are characterized by intimal thickening histologically composed of cellular or acellular fibrocollagenous tissue. The venous medial and adventitial layers become fibrotic, and the graft resembles a thick, fibrous tube. Focally stenotic lesions produced by this intimal thickening appear amenable to dilation by balloon angioplasty, as illustrated in the first patient described earlier. However, in view of the histologic composition of the intima, the dilating mechanism is probably not intimal compression⁵ but rather graft stretching (Fig. 6). Depending on the degree of graft stretching, the dilating procedure may have limited therapeutic success (weeks to months) with graft restenosis representing gradual restitution of tone of an overstretched graft segment.⁵

Saphenous vein graft stenoses occurring beyond 1 year and generally after 3 years following graft insertion usually consist of atherosclerotic plaque in addition to intimal fibrous thickening.⁶⁻¹⁰ The atherosclerotic plaque in saphenous vein grafts appears morphologically similar to that observed in native coronary arteries: foam cells, cholesterol clefts, blood product debris, fibrocollagenous tissue, and calcific de-

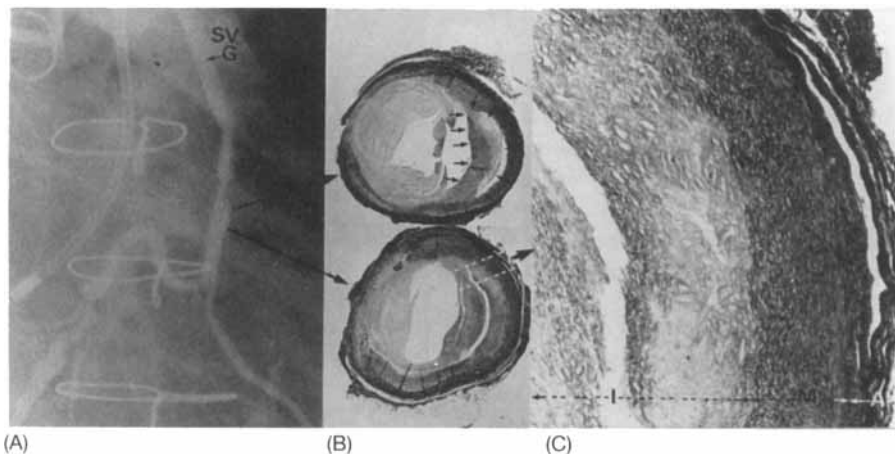


FIG. 5 Angiographic morphologic-histologic correlation at the site of angioplasty dissection 2 months before graft excision. (A) Angiographic frame of saphenous vein bypass graft (SVG) after transluminal balloon angioplasty showing a line of dissection. (B) Corresponding morphologic segments (large arrows) of SVG in area of angiographic dissection showing severe luminal cross-sectional area narrowing with an intimal flap (small arrows) and a partially healed intimal fracture. (C) Higher magnification ($\times 80$) of boxed area in (B) showing the intimal (I) fracture site. The intimal thickening is composed of fibrocollagenous tissue, foam cells, and cholesterol clefts. M = media, A = adventitia. Elastic stains. From Ref. 5 with permission.

posits.^{9,11} Focal stenoses produced by this type of lesion also appear amenable to dilation by balloon angioplasty, as illustrated in the second patient described earlier. The mechanism(s) of conduit dilation in this setting appears similar to that proposed for coronary artery angioplasty: plaque splitting, cracking, or breaking with or without localized intimal-medial dissection (Fig. 7).⁵ Therapeutic limitations in dilating saphenous vein grafts narrowed by atherosclerotic plaque should be similar to those observed in atherosclerotic coronary arteries subjected to balloon angioplasty.

In addition to the age of the bypass graft, at least two other anatomic factors appear to influence the therapeutic success of balloon angioplasty of saphenous vein grafts: (1) the *length of stenosis* and (2) the *location of stenosis*.⁵ Long stenotic segments of saphenous vein (>15–20 mm) are frequently technically more difficult to dilate and are associated with lower primary therapeutic success compared with short stenotic segments (<5 mm). Graft stenoses may be located at the anasto-

motoc sites (aorta-graft or coronary artery-graft) or within the body of the graft (Fig. 7).⁵ Angiographic studies^{12–15} have suggested that saphenous vein graft stenoses at the coronary artery-graft anastomotic site have the best therapeutic results, followed by lesions in the graft body and at the aorta-graft anastomotic site, respectively. An anatomic factor supporting the relatively high success rate at dilating stenotic coronary artery-graft anastomotic sites is the presence of atherosclerotic plaque in the coronary portion of the anastomosis.^{16–18} Stenoses in the graft body or aortic-graft anastomotic site are less likely to have the potential angioplasty advantage of associated atherosclerotic plaque unless the graft is over 3 years old.^{2–5, 8–10, 17, 18}

Clinical Results of Percutaneous Transluminal Angioplasty of Saphenous Vein Grafts

Gruntzig *et al.*¹⁹ reported as early as 1979 that vein graft angioplasty was successful in five of seven attempts. However, three of five grafts demonstrated restenosis during follow-up, prompting Gruntzig to suggest that there was a “different kind of disease”^{4, 17} in the bypass graft. Ford *et al.*^{14, 15} dilated nine saphenous vein grafts 4 to 84 months (mean = 46 months) after insertion. Primary angiographic success occurred in six of the nine grafts with only late success (>9 months) in two of the six initial successes. Of the two late successes, one graft was 18 months old at initial angioplasty and the second was 5 months old. Famularo *et al.*²⁰ recently reported morphologic observations in an unsuccessful dilation of a saphenous vein conduit with atherosclerotic plaque. Although the age of the graft was not provided, morphology of the angioplasty site showed intimal tears of atherosclerotic plaque. Douglas *et al.*¹³ reported their angioplasty results in 62 bypass grafts. Of 62 grafts, 40 (65%) were dilated early after insertion (≤ 1 year) and 22 (35%) were dilated late after insertion (>1 year). Of the early grafts, primary success occurred in 37 grafts (93%), with restenosis 6 months or later in 9 (24%). Of the 22 late grafts, primary success occurred in 21 grafts (95%), with the same restenosis rate as with the early grafts (24%).

De Feyter *et al.*⁴ have recently provided a clinical review of saphenous vein angioplasty studies of 1,571 patients undergoing saphenous vein angioplasty (mixed graft ages), with the initial success rate ranging from 75 to 94% (average 88%).⁴ Embolization rate ranged from 0 to 7% (average <3%).

As suggested first by Waller *et al.*,⁵ the site of balloon angioplasty in the aortocoronary bypass graft unit [aortic saphenous vein anastomotic site (proximal), body of graft, coronary-saphenous vein anastomotic site (distal)] influences the initial success and subsequent type and frequency of restenosis (Fig. 7).⁵

Breakdown of the early and late grafts according to stenosis location revealed that the distal graft stenoses (early and late) had a high initial dilation success and lower restenosis rate. Graft stenoses located in the body or proximal end had a slightly lower initial dilation success, but three times the restenosis frequency compared with the distal sites (39 vs. 13%).

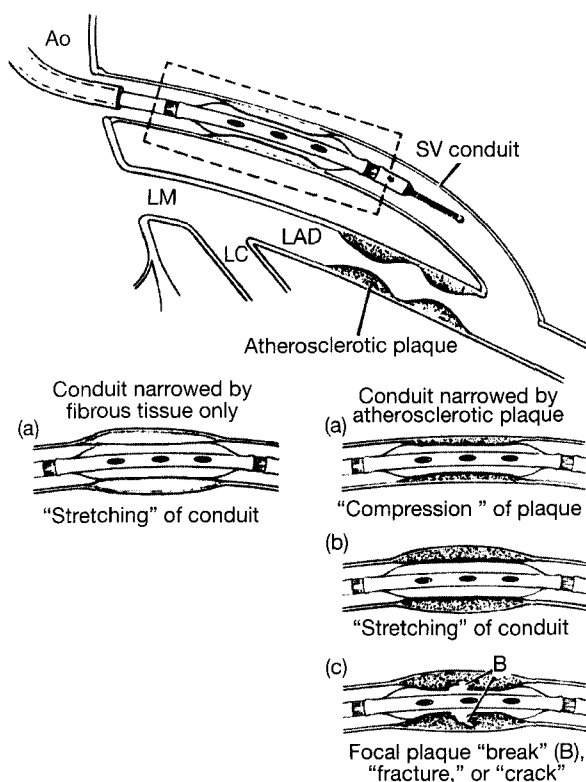


FIG. 6 Diagram illustrating possible mechanisms of luminal balloon angioplasty in stenotic aortocoronary saphenous vein (SV) bypass grafts. Two types of lesions characterize the SV stenoses depending on the interval from graft insertion to early obstruction. Early (≤ 1 year) graft (a, left) contains intimal thickening composed primarily of fibrocollagenous tissue without calcium, and dilatation is accomplished by conduit “stretching.” Late (>1 year) grafts (a, b, c right) contain intimal thickening composed of atherosclerotic plaque and calcium, and dilatation is accomplished by plaque compression (unlikely), graft stretching, or plaque fracture or break (most likely). Ao = aorta, LAD = left anterior descending coronary artery, LC = left circumflex coronary artery, LM = left main coronary artery. From Ref. 5 with permission.

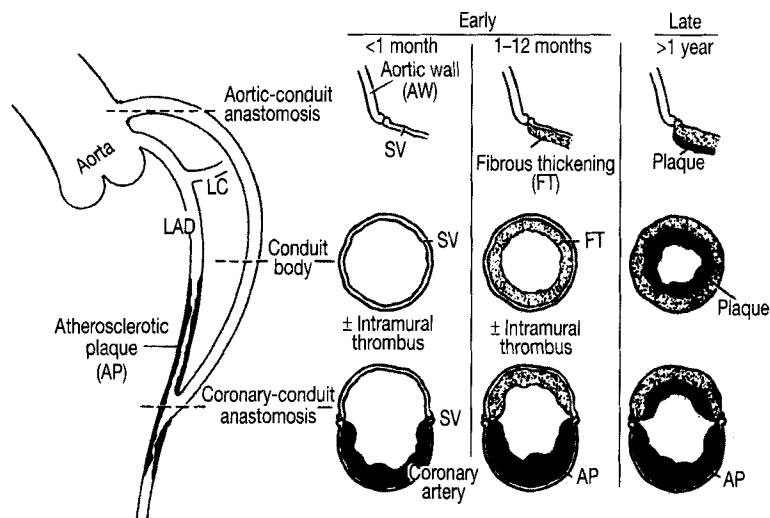


Fig. 7 Diagram shows the anatomic features of the saphenous vein (SV) bypass graft-native coronary artery unit with luminal changes developing with increasing graft age. Balloon angioplasty would be most successful in areas containing some element of atherosclerotic plaque (coronary-conduit anastomosis in the early and late grafts and the conduit body in the late grafts) and least successful in areas with primarily elastic tissue (aortic anastomotic sites). LAD = left anterior descending coronary artery, LC = left circumflex coronary artery. From Ref. 52 with permission.

A recent review⁴ of 15 studies,^{13, 21-34} reporting initial success rate of dilation and following restenosis rate according to site dilated, disclosed an average initial success rate of 93% (body), 90% (distal), and 86% (proximal). Restenosis rates according to site of dilation indicated the lowest restenosis rate in the body (28%), followed by distal (42%) and proximal (58%). Variability in definitions of "proximal," "body," and "distal" as well as considerable variability in ages of saphenous vein grafts account for the differences between morphologic studies^{3, 5} and clinical studies^{4, 13, 21-34}

New Interventional Techniques for Treatment of Obstructed Saphenous Vein Bypass Grafts

Several new interventional devices (stents, atherectomy, laser) have been used in the treatment of obstructed saphenous vein bypass grafts.

Stents

Intracoronary stents were applied to saphenous vein bypass graft treatment strategies as early as 1989.³⁵ Several studies³⁵⁻⁴⁰ indicated the success rate was high (>95%), but there was a high incidence of subacute thrombosis and bleeding complications from anticoagulation.⁴ In addition, the incidence of restenosis remained high, ranging from 21 to 47%, depending on the type of stent employed (Wall stent, Palmaz-Schatz stent, Cook stent). Restenosis was more frequent in the Wall stent studies (36%,³⁵ 47%³⁷), followed by the Cook stent (flexible coil stent) (35%³⁸), and least in the Palmaz-Schatz stent studies (21%,³⁹ 26%⁴⁰). In recent studies by Eeckhout *et al.*⁴¹ and Vaishnav *et al.*,⁴² the Wiktor (tantalum wire) stent has

been employed in treatment of obstructed saphenous vein bypass graft. Initial results indicate a high initial success rate and lower restenosis rate compared with other stents. One advantage of the Wiktor stent is its radiopaque nature. "Biliary" stents have also been used in large saphenous vein bypass grafts.^{43, 44} Initial results are encouraging.

Recently, van Beusekom *et al.*⁴⁵ studied histology after stenting by Wall stent of human saphenous vein bypass grafts excised surgically 3 to 320 days after stent implantation. In all, 21 stents from 10 patients were examined. Observations revealed that large amounts of platelets and leukocytes adhered to the stent wires during the first few days. At 3 months, the wires were embedded in a layered new intimal thickening, consisting of smooth muscle cells in a collagenous matrix. In addition, foam cells were abundant near the wires. Extracellular lipids and cholesterol crystals were found after 6 months. Smooth muscle cells and extracellular matrix formed the predominant component of restenosis. This new intimal thickening was lined with endothelium, in some cases showing defective intercellular junctions and abnormal adherence of leukocytes and platelets as late as 10 months after implantation. These authors concluded that this type of stent was potentially thrombogenic and seemed to be associated with extracellular lipid accumulation in venous aortocoronary bypass grafts.

Atherectomy: Directional and Extractional

Atherectomy devices have also been used in treatment of obstructed saphenous vein bypass grafts.^{39, 46-48} With directional atherectomy, the initial success rate was high (91 to 93%^{39, 46, 47}) but the restenosis rate was very high (31 to 63%).^{39, 46, 47} Embolization was also high ranging from 7^{39, 46} to 11.5%.⁴⁷ Extractional atherectomy was successful in 89%

of patients⁴⁸ but the restenosis rate was still high at 53%.⁴⁸ The embolization rate was about half (3.5%⁴⁸) of the directional atherectomy device, probably due to its mechanism of use: suction, extraction, and removal of material through the device.⁴⁸

Excimer Laser

Initial results with the use of excimer laser angioplasty in obstructed (old) saphenous vein grafts was favorable (97%)⁴⁹ but the restenosis rate was still very high (61%).⁴⁹ In a recent report of the Percutaneous Excimer Laser Coronary Angioplasty Registry,⁵⁰ 545 saphenous vein graft stenoses underwent excimer laser angioplasty. Ostial lesions (i.e., proximal aortic anastomotic sites) had a higher degree of success (95%) than lesions in the body of the graft. Lesions >10 mm had a lower success rate (84%) and higher complication rate (12%) compared with discrete lesions. Lesions in smaller vein grafts had higher success and lower complication rates compared with larger grafts.⁵⁰

Stenting of Internal Mammary Graft Stenosis

The major problem associated with long-term patency of internal mammary arteries used as bypass grafts is the early occurrence of stenosis at its distal coronary anastomotic site.⁵¹ Balloon angioplasty (as expected, given the anatomy at the site discussed earlier) has been highly successful. Recently, stent placement at this site for internal mammary graft stenosis has been reported.⁵¹

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