Pathologic Changes in Aortic-Coronary Arterial Saphenous Vein Grafts

By Zeev Vlodaver, M.D., and Jesse E. Edwards, M.D.

SUMMARY
This is a pathologic study of segments of saphenous vein used as a graft between the aorta and a coronary artery in the surgical treatment of coronary atherosclerosis. Except for an occasional case with thrombotic occlusion of the graft, no lesions were observed in grafts which had been in place for less than 1 month. In each of two grafts in place for 1 month, mild fibrous thickening of the intima was present. Eight grafts which had been in place for 3½ months or longer consistently showed lesions, either organized thrombi (two grafts) or intimal fibrotic proliferative lesion (six grafts). In this group, five of the six grafts with intimal fibrous proliferation showed near or complete occlusion of the lumen.

The intimal fibrous proliferative lesion appears primarily to be a response to arterial pressure within the segment of vein. Obstructive atherosclerosis in the artery beyond the anastomosis with the graft may favor the development of the intimal lesion. The intimal lesion may progress rapidly according to the data in one of the cases. In this, patency of the graft demonstrated angiographically 3½ months after the operation was followed by near-complete occlusion of the lumen by the proliferative lesion 3 weeks following demonstration of patency.

Additional Indexing Words:
Coronary surgery
Angina pectoris
Myocardial infarction
Coronary atherosclerosis

RECENT INTEREST in the use of saphenous veins as grafts between the aorta and coronary arteries in the treatment of atherosclerosis makes the long-range character of the vein graft of considerable practical importance.¹⁻⁷ With this in mind, a pathologic study was done on 21 patients who had had this operation, yielding a total of 29 vein grafts. The operations had been done in various hospitals in the Twin Cities of Minnesota, but most of the cases were either from the Charles T. Miller or University of Minnesota hospital.

Among the cases studied, each was a classic example of coronary atherosclerosis, often with involvement of each of the three coronary arteries. In each instance, healed myocardial infarction in one or more than one area of the left ventricle was present.

Method
Each case was placed into one of four groups according to length of survival after operation as follows. Group I consisted of 15 grafts from 10 patients who died either during the operation or in the early postoperative hours. In group II, there were four grafts from three patients. The patients lived 1 day, 4 days, and 7 days, respectively. Group III consisted of two grafts from two patients, each patient living 1 month. Group IV consisted of eight grafts from six patients who survived from 3½ to 9 months after the operation. In each instance, except one, the entire specimen of heart and graft (or grafts) was

From the Departments of Pathology of the Charles T. Miller Hospital, St. Paul, Minnesota and of the University of Minnesota, Minneapolis, Minnesota.

Supported by U. S. Public Health Service Research Grant 5 R01 HE05694 and Research Training Grant 5T01 HE05570 from the National Heart and Lung Institute and by the Otto Bremer Foundation.

Address for reprints: Jesse E. Edwards, M.D., Department of Pathology, The Charles T. Miller Hospital, 125 West College Avenue, Saint Paul, Minnesota 55102.

Received June 8, 1971; accepted for publication July 1, 1971.

Circulation, Volume XLIV, October 1971 719
available for study. In one case (6½ months) only histologic segments of the vein grafts were available to us.* Each of the patients in group IV had died suddenly.

Obstructive lesions were observed in seven of the eight grafts which had been in place for 3½ months or longer. These consisted either of intimal fibrous proliferation or organized thrombi. Before describing the details of these changes, a review will be made of the histologic character of the normal greater saphenous vein in the adult and the observations made among the four groups representing different time intervals after insertion of the grafts.

*We are indebted to Dr. Allen S. Judd of St. Mary's Hospital, Minneapolis, Minnesota, for material from this case.

The Normal Saphenous Vein

The normal greater saphenous vein exhibits a thin, relatively acellular, fibrous intima which may show irregular minimal dense collagenous thickening. The media is relatively thick and varies in structure depending upon the relationship to the venous valves. In segments between valves, the muscle of the media is oriented, for the most part, in a circular fashion (fig. 1a). In contrast to arteries in which the circular medial muscle is a continuous layer, the circular muscle of the saphenous vein, as in other veins, is made up of interlacing bundles of smooth muscle, on the one hand, and of collagen and elastic tissue, on the other. In the vicinity of the

Figure 1

Photomicrographs of normal saphenous veins. (a.) A segment between valves shows a circular medial layer. (Elastic tissue stain, X 25.) (b.) A segment at the level of a valve shows a thick media in which the fibers are, for the most part, oriented in longitudinal fashion. (Elastic tissue stain, X 20.)

Circulation, Volume XLIV, October 1971
**Pathologic Changes in Vein Grafts**

**Observations in Vein Grafts**

**Groups I and II**

In the 19 grafts which had been in place for a short time (up to 7 days) no significant differences were noted compared to the normal.

**Group III**

Each of two grafts had been in place for 1 month. Each showed minimal thickening with avascular mucoid connective tissue (fig. 2). The changes which had caused no significant narrowing of the lumen qualitatively were like the lesions of greater severity observed in group IV. These will be described in greater detail in the next section.

**Group IV**

Eight grafts which had been in place for periods varying from 3½ to 9 months were obtained from six patients. The findings are summarized in Table 1. In four patients (cases 1, 3, 4, and 6) solitary grafts had been

---

**Table 1**

**Summary of Findings in Group IV**

<table>
<thead>
<tr>
<th>Case</th>
<th>Time in place (months)</th>
<th>Graft</th>
<th>Lesion*</th>
<th>Lumen</th>
<th>Atherosclerosis of artery distal to graft (grade)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>RC</td>
<td>3½</td>
<td>Organized thrombus; (FIP)</td>
<td>Ocluded</td>
<td>III</td>
</tr>
<tr>
<td>2 a</td>
<td>T-shaped, vertical to RC</td>
<td>3½</td>
<td>FIP</td>
<td>Severe obstruction</td>
<td>III</td>
</tr>
<tr>
<td>b</td>
<td>Horizontal to LAD</td>
<td>3½</td>
<td>FIP</td>
<td>Proximal occlusion</td>
<td>II</td>
</tr>
<tr>
<td>3</td>
<td>LAD</td>
<td>4½</td>
<td>FIP; (organizing thrombus)</td>
<td>Occlusion</td>
<td>III</td>
</tr>
<tr>
<td>4</td>
<td>RC</td>
<td>6½</td>
<td>FIP; (intramural thrombus)</td>
<td>Severe obstruction</td>
<td>Unknown</td>
</tr>
<tr>
<td>5 a</td>
<td>RC</td>
<td>7</td>
<td>FIP</td>
<td>Moderate obstruction</td>
<td>II</td>
</tr>
<tr>
<td>b</td>
<td>Lt cir</td>
<td></td>
<td>Organized thrombus</td>
<td>Severe obstruction</td>
<td>III</td>
</tr>
<tr>
<td>6</td>
<td>RC</td>
<td>9</td>
<td>FIP</td>
<td>Severe obstruction</td>
<td>III</td>
</tr>
</tbody>
</table>

*Lesion listed in parentheses present but of little importance in causing luminal narrowing.

Abbreviations: RC = right coronary artery; LAD = left anterior descending artery; Lt cir = left circumflex coronary artery; FIP = fibrous intimal proliferation.

*Circulation, Volume XLIV, October 1971*
inserted. In one patient (case 5) two independent grafts had been inserted: (1) one to the right coronary artery and (2) the other to the left circumflex artery.

In case 2, a "T"-shaped graft was used. The "vertical" (main) channel ran from the aorta to the right coronary artery, while a right-angle branch ("horizontal") of this graft had been inserted into the anterior descending coronary artery. In our tabulation, the main part of this graft is considered one graft (case 2a), while the right-angle branch is considered a second graft (case 2b). In each of the eight grafts in group IV, significant lesions were found (table 1).

In each of two grafts (cases 1 and 5b) organized thrombosis caused complete occlusion of the lumen (fig. 3a). In one of these cases (case 1) the organized thrombus was superimposed upon minimal intimal fibrous thickening essentially like that observed in group III (fig. 3b).

Each of the remaining six grafts showed easily recognizable fibrous intimal proliferation. In one of these (case 5a) moderate narrowing of the lumen was present diffusely (fig. 4). In three grafts (cases 3, 4, and 6), intimal fibrous proliferation caused uniformly severe narrowing of the lumen (fig. 5).

The case with the right-angle graft (case 2) deserves special mention. The vertical segment of the graft (aorta to right coronary artery) showed moderate degrees of luminal narrowing in the proximal half and severe degrees in its distal half. The proximal half of the right-angle graft showed complete obliteration of the lumen while the distal half was moderately narrowed by the intimal change (figs. 6 and 7).

Another case was of special interest (case 3). Three and one-half months after a graft was connected with the anterior descending coronary artery, angiography revealed wide patency of the graft (fig. 8a). The patient suffered sudden death 23 days later. At necropsy, the ostium and proximal segment of the graft were occluded by intimal fibrous proliferation (fig. 8b and c). Distally, including the site of anastomosis to the artery, the lumen of the graft was narrowed severely by

Figure 3
(a.) Case 5b, with graft in place for 7 months. The lumen is occluded by an organized thrombus (T.). (Elastic tissue stain, × 57.) (b.) Case 1, with graft in place for 3½ months. Longitudinal section of saphenous vein graft. The intima shows fibrous proliferation (F.I.P.). In addition, luminal occlusion results from a superimposed organized thrombus (T.). (Elastic tissue stain, × 25.)

Circulation, Volume XLIV, October 1971
intimal fibrous proliferation. The narrow remaining lumen was entirely compromised by an organizing thrombus (fig. 8b). The latter was continuous with a recent thrombus in the coronary artery.

Fibrous intimal proliferation was characterized by thickening of the intima with fibroplastic cells (fig. 9a and b) lying in a basophilic, mucoid matrix. Foamlike cells surrounded the lumen. With stains for fat, negative reactions were obtained. With stains for acid mucopolysaccharides, the mucoid matrix gave a strongly positive reaction (fig. 9c). Blood vessels were either absent or few in number. Blood pigment was absent. The fibrous thickening was usually pure, although in one case the process was complex (case 4). This showed a basal layer of fibrous intimal thickening, an intermediate layer of organized
thrombosis, and a superficial layer of intimal fibrous thickening. In two cases, superficial thrombosis, either recent or organizing, was present on the surface of the thickened intima (fig. 9d). No significant alterations in the media were recognized in any of the grafts.

Since severely obstructive lesions, either thrombotic or proliferative, were common in group IV, it was of interest to determine whether obstructive atherosclerosis was present in the related arteries distal to the insertion of the graft. This opportunity was afforded us in the case of seven grafts. In five of the seven instances, obstructive atherosclerosis of severe degree (grade III) was found in the artery distal to the graft.

Such arterial lesions were found in each of the two cases with organized thrombi and in three cases with obstructive intimal fibrous proliferation. In one of the cases with organized thrombi (case 5b) an additional factor was a narrow aortic ostium of the graft. In one of the two exceptions, in which the artery was devoid to significant obstruction distal to the anastomosis, the graft showed only moderate degrees of intimal fibrous proliferation (case 5a), while in the other (case 2b) occlusion of a right-angled graft by intimal proliferation was observed.

Comment

This study on saphenous veins used as aortocoronary arterial communications revealed significantly obstructive lesion in the grafts to be common among grafts in place 3% months or longer. It is to be admitted that the material is selected only from patients who failed to survive and, in this way, may not be entirely representative of all patients with such grafts in place. Nevertheless, the lesions observed have reasonable explanations.

It will be recalled that, in two of the eight long-range grafts, the lumen was occluded by organized thrombi. In each of these, significant atherosclerosis was present beyond the site of graft to the coronary artery. The latter phenomenon may explain thrombosis on the basis of restricted flow through the graft. The phenomenon of thrombosis may perhaps not be a natural phenomenon if the anastomosis is made beyond obstructive arterial lesions. An additional factor favoring thrombosis may be a narrow aortic ostium of the graft, as observed in one of our cases. The problem of thrombosis, therefore, appears mainly to be one in identifying unobstructed segments in the coronary arteries.

The second lesion observed was more common, being seen in six of the eight long-range grafts. This lesion is characterized by intimal thickening with avascular highly cellular connective tissue, a lesion which we have chosen to call intimal fibrous proliferation. Similar lesions in saphenous vein aortocoronary arterial grafts have been described recently by Johnson and associates\(^8\) and by Grondin and associates.\(^9\)
The intimal fibrous proliferative lesion appears to be a natural consequence of subjecting a vein to arterial pressure. Similar lesions are present in veins associated with arteriovenous fistulae. Such lesions have been used to support the concept of "arterializa-
Figure 8

Case 3, with graft in place for 4½ months. (a.) Angiogram made 3½ months after insertion of graft between aorta and anterior descending coronary artery (L.A.D.) Patency of the graft (V.G.) is indicated. (b. and c.) Photomicrographs of graft taken at the time of death about 3 weeks after the angiogram shown in a. (b.) Segment of the saphenous vein graft showing almost complete occlusion of the lumen by intimal fibrous proliferation. The narrowed lumen shows complete occlusion by a small amount of organizing thrombotic material (T.). (c.) Longitudinal section through aorta and anastomosis with vein. The latter shows severe intimal proliferation (F.I.P.) including involvement of the aortic ostium. (Elastic tissue stain, × 4.)

The "vulsion" of veins. We prefer not to use this term, since the venous structure of the media remains essentially unchanged and normal arteries do not show an intimal structure comparable to the intimal proliferative changes in veins. Rather, we would consider the intimal fibrous proliferation of veins subjected to arterial pressure as a reparative phenomenon responding to unusual hemodynamic stress. It is appropriate to consider factors which, in addition to the arterial pressure in the graft, may favor the development of the intimal fibrous lesion.

Among the five grafts with intimal fibrous proliferation and in which the nature of the coronary artery beyond the graft was known,
Characteristics of fibrous intimal proliferation. (a.) Surrounding a narrowed lumen, intimal fibrous proliferation is characterized by the presence of fibroblastic cells lying in a basophilic matrix. (Hematoxylin and eosin, × 80.) (b.) High-power magnification of intimal fibrous proliferation in relation to the lumen. Large cells with clear cytoplasm are present. These stain negatively for fat. (Hematoxylin and eosin, × 400.) (c.) Severe thickening of the intima by intimal fibrous proliferation showing heavily positive reaction for acid mucopolysaccharides. (Acid mucopolysaccharide stain, × 20.) (d.) Encasement of organized thrombotic material within intimal fibrous proliferation. In a longitudinal section of the vein the organized thrombotic material (T.) lies superimposed on a zone of intimal fibrous proliferation (F.I.P.) and secondarily capped by similar tissue. (Elastic tissue stain, × 24.)
the venous lesion was severe in three cases with distal severely obstructive atherosclerosis. In two grafts, the arterial lesion was only moderate in degree. Obstructive atherosclerosis beyond the level of anastomosis may have represented the basis for additional mechanical stress to the graft in the form of a water-hammer effect.

In the case of two grafts, the artery beyond the site of anastomosis showed only grade II atherosclerosis. In one of these, the graft had been in place for 7 months and the intimal lesion was only moderate in extent. The case may support the water-hammer concept as being in effect when obstructive atherosclerosis is present downstream from the graft.

In the second case without significantly obstructive atherosclerosis beyond the graft (anterior descending artery), complete occlusion of the graft was present near the right-angle anastomosis of the graft to a vertical graft running between the aorta and the right coronary artery. This case may perhaps represent the phenomenon that at right-angled branching there are mechanical stresses peculiar to this phenomenon.

The nature of the intimal fibrous proliferative lesions suggests that it is made up of young connective tissue. The presence of tissue rich in fibroblasts and in acid mucopolysaccharides may support this concept. That the proliferative lesion may progress rapidly is supported by one of our cases (case 3). In this case, it will be recalled, the graft was demonstrated to be widely patent 3 months after being in place, while 3 weeks later, at the time of death, pathologic examination showed severe restriction in the caliber of the lumen of the graft by the proliferative lesion. In this case, although an organizing thrombus occluded the remaining lumen, the lumen had been severely narrowed by the proliferative lesion.

References
Pathologic Changes in Aortic-Coronary Arterial Saphenous Vein Grafts
ZEEV VLODAVER and JESSE E. EDWARDS

_Circulation_. 1971;44:719-728
doi: 10.1161/01.CIR.44.4.719

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1971 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/44/4/719

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/