Intimal Fibromuscular Hyperplasia at the Venous Anastomosis of PTFE Grafts in Hemodialysis Patients

Clinical, Immunocytochemical, Light and Electron Microscopic Assessment

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Failure of arteriovenous communications used for chronic hemodialysis was studied during sequential 5-year periods after placement of either endogenous Brescia-Cimino (B-C) fistulas (50 patients) or polytetrafluoroethylene (PTFE, Gore-Tex) grafts (66 patients). Venous stenosis near the anastomosis was the reason for failure in 45% of PTFE grafts compared with 16% of B-C fistulas (p<0.001). Failure occurred, on average, 16 months after PTFE graft placement compared with 22 for B-C fistulas (p=NS). Proximal vein segments removed from five failed and two functioning PTFE graft communications were studied using light and electron microscopy and immunocytochemical techniques. All venous segments removed during surgical shunt repair exhibited a marked intimal hyperplasia. The intimal cellular component was almost exclusively smooth muscle. Accumulation of intracellular lipid droplets was not seen. Foam cells as well as extracellular lipid deposits were absent; macrophages and lymphocytes were absent from the zone of proliferation. Ultrastructural examination revealed a large proportion of extracellular matrix surrounding smooth muscle cells in the neointima. Collagen and elastin were present in the extracellular matrix, in greatest concentration deeper in the intima. Closer to the lumen, most of the extracellular volume consisted of proteoglycan. Hemosiderin was absent from the lesions as were consistent signs of luminal and intimal fibrin. Uniform intimal gradients of actin, collagen, and proteoglycan suggest that this is a steadily progressive, rather than episodic, proliferative response. These clinical and histologic observations and an analysis of hemodynamic stresses support the postulate that upstream release of platelet-derived growth factor, and possibly, shear-induced intimal injury stimulate this response. This myointimal proliferative process provides a readily accessible model of fibromuscular hyperplasia in humans; its understanding may lead to effective methods for its prevention and may provide clues to the pathogenesis of arteriosclerosis. (Circulation 1989;80:1726–1736)

As a general rule, chronic hemodialysis patients require hospitalization 1 month each year; half of that time is for placement or surgical revision of their arteriovenous communication. Brescia-Cimino (B-C) arteriovenous fistulas or polytetrafluoroethylene (PTFE) grafts are the two most commonly used arteriovenous communications. Progressive venous stenosis, occurring just downstream of the B-C fistula or the PTFE-to-vein anastomosis, is the most common reason for failure of B-C fistulas and grafts.1–10 In many dialysis patients, it is a recurrent problem. Hunter8 found that venous stenoses occur commonly between 1 and 6 months after creation of B-C fistulas, most often within 1–5 cm of the anastomosis. Mennes et al9 observed that patients return for repair of venous stenoses in an average time of 9±3 months. Giaccchino et al10 has found B-C fistulas to require surgical revision 0.6 times per year per patient with an average access life of 1.6 years. Clinically, high dialysis pressures and inadequate flows result, often

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requiring operative repair before complete occlusion occurs. Although there is a general perception that venous stenosis occurs more frequently with PTFE grafts, this has not been documented in the literature.

This process of accelerated venous stenosis could be a maladaptive response to new stresses, including mechanical injury at surgery, exposure to arterial pressure, compliance mismatch, or to the high shear stresses of rapid flow and turbulence. It may be a response aggravated by the altered biochemical state(s) associated with renal failure. It may result from formation and organization of thrombus and its release of mitogenic substances at the site of stenosis or upstream in the PTFE graft. Clues to the role of these and other mechanisms may come from a detailed evaluation of the histology of the occlusive lesion, which has not been completely described previously.

In this report, we compare, clinically, the frequency of venous stenosis in B-C fistulas and PTFE grafts. Furthermore, we describe the intimal cellular and extracellular matrix response of native venous segments exposed to the rapid flow of blood emerging at arterial pressure from the PTFE conduit. We discuss the implications of these observations for the pathogenesis of this lesion.

Methods

Clinical Studies

To define the clinical impact of dialysis shunt venous stenosis and to compare its occurrence in the two most commonly used types of dialysis accesses, we evaluated the follow-up of 116 chronic hemodialysis patients whose accesses were placed by the principal surgical group doing this procedure in Seattle. B-C fistulas were placed in 50 patients (mean age, 38 years; 74% male) and PTFE grafts were placed in 66 patients (mean age, 45 years; 48% male) using standard indications and technique. The operations were performed between September 1975 and November 1979. The medical records for these two consecutive and prospectively defined patient groups have been maintained for the purposes of comparison. Patients were scheduled for routine follow-up every 6 months. At each readmission for operative access repair, the surgeons clearly documented the clinical features of its failure, the pathologic findings at operation (venous stenosis, thrombosis, graft aneurysm, infection, etc.), and the technique of revision. Sixteen patients required more than one revision. Because the surgeons constructed most of the chronic hemodialysis accesses in Seattle during this period, nearly all patients with access failure returned to them for revision. Exceptions include those dying, moving out of town, or seeking another surgeon (uncommon).

Thus, the frequency of venous stenosis and of access revision may be underestimated because of the above reasons for failing to return, but the comparison between the two types of fistulas and the proportion of access failures due to venous stenosis is undoubtedly accurate.

Vein Samples

Five occluded or severely narrowed vein segments just distal to the anastomosis with a PTFE hemodialysis shunt were obtained at the time of operative repair in four patients (one had two revisions). The reason for removal was thrombosis in three patients and sub-total occlusion resulting in high venous pressures during dialysis in two patients. Two normally patent PTFE-to-vein anastomoses were also examined. One patient died of coronary heart disease with a normally functioning graft. One patient recovered renal function and had his patent graft removed. The PTFE grafts ranged in age from 2 to 31 months; patients ranged in age from 25 to 83 years. Five of the six patients were men. Samples from shunts revised because of infection were excluded from this analysis. These specimens were fixed without distending pressure for 24 hours or more in 10% phosphate buffered formalin (for light microscopy), methanol-Carnoy’s (60% methanol, 30% chloroform, and 10% glacial acetic acid, for immunocytochemistry and light microscopy), or Karnovsky’s fixative (phosphate buffered paraformaldehyde (2%) and gluteraldehyde (2.5%), for electron microscopy). Some samples in Karnovsky’s fixative were processed with 0.2% ruthenium red to visualize the proteoglycan content. The samples were then cut into cross-sectional segments and embedded in paraffin or epon. We examined vein sections cut 0.5–1.0 cm downstream from the anastomosis in an effort to minimize histologic changes associated with suture reaction and healing at the anastomosis.

Light Microscopy and Immunocytochemistry

Venous sections cut for light microscopic examination were stained with hematoxylin-eosin, Mason’s trichrome, and alcian blue. Monoclonal antibodies were used to determine cell type. Antibodies to vimentin (intermediate filament/mesenchymal cells), smooth muscle actin (CGA-7), nonspecific muscle actins (HHF-35), macrophages (HAM-56), lymphocytes and monocytes (T-200), T-cell lymphocytes (UCHL-1), endothelium (Ulex europaeus agglutinin, UEA), and fibrinogen/fibrin were used, with an avidin-biotin immunoperoxidase procedure and a nickel chloride color intensification and color modification scheme developed by Hsu and Soban and modified by Gown and Vogel.

Electron Microscopy

Selected venous sections were fixed overnight at 4°C as described above, routinely dehydrated, and embedded in epoxy resin. Representative areas of each lesion were sectioned at approximately 1 μm and were stained with a combination
TABLE 1. Comparison of Brescia-Cimino Fistulas and PTFE Grafts During 5 Years After Placement

<table>
<thead>
<tr>
<th>Failure due to venous stenosis</th>
<th>Number of failures</th>
<th>Mean time to failure</th>
<th>Fraction of all revisions</th>
<th>No revision performed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n)</td>
<td>(%)</td>
<td>(mo±SD)</td>
<td>n</td>
</tr>
<tr>
<td>Brescia-Cimino fistula (n=50)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>16</td>
<td>22±13</td>
<td>8/21</td>
</tr>
<tr>
<td>PTFE graft (n=66)</td>
<td>30*</td>
<td>45</td>
<td>16±15</td>
<td>32†/69</td>
</tr>
</tbody>
</table>

PTFE, polytetrafluoroethylene (Gore-Tex).

χ² Statistical comparison, *p<0.001, †Two PTFE grafts each had two repairs due to venous stenosis, ‡p<0.005.

of azure A and methylene blue. Selected areas were trimmed further for thin sectioning and were examined by transmission electron microscopy (TEM). Thin-sections for TEM were stained with uranyl acetate and lead citrate and were examined in a Japan Electron Optics Laboratory 100-B electron microscope.

Results

Access Patency

Fifty B-C fistulas and 66 patent PTFE grafts were placed. As shown in Table 1, eight B-C fistulas (16%) and 30 grafts (45%) failed because of venous stenosis and required revision or abandonment (one PTFE graft; two B-C fistulae) (p<0.001) within 5 years. For B-C fistulas, failure due to venous stenosis occurred at an average of 22.3±13.1 months after placement, and for grafts, failure occurred at 16.0±15.0 months (p<0.25, NS). For various reasons, revision was required for 11 B-C fistulas and 34 grafts (primarily for graft thrombosis); six B-C fistulas and seven grafts were abandoned in favor of a new access. Thirty-three patients with B-C fistulas (66%) and 25 patients with grafts (38%) did not return for repair of a failed access during the 5-year observation period (p<0.005). Thus, venous stenosis occurred significantly more frequently and somewhat earlier in PTFE grafts than in B-C fistulas, and patients with the latter required significantly fewer repair procedures.

Light Microscopy and Immunocytochemistry

In all shunts requiring surgical revision, a marked proliferative thickening of the intimal layer was
observed in the vein segment just downstream of the anastomosis (Figure 1a and c). In these cases, the original lumen was nearly completely occluded by this process. This was in striking contrast to the vein removed downstream of a normally functioning graft placed 3 months earlier (Figure 1b and d). A 2-year-old functional graft (not shown) removed post-mortem also displayed little intimal thickening. The degree of intimal thickening and the age of the graft at the time of its repair showed no obvious correlation.

Identification of neointimal cell type was facilitated by specific immunocytochemical staining. The intimal hyperplasia appeared to consist almost entirely of smooth muscle cells as demonstrated by monoclonal antibody stains to nonspecific muscle and smooth muscle actins (Figure 2a and b). Antibodies to other cell types showed very little binding in the neointima (Figure 3a, b, and c). Macrophages were absent from the hyperplastic zone except in limited numbers near the neovascular channels near the base of the intima and, perhaps also, under the central luminal endothelium (Figure 3a). (Note that antimacrophage antibody HAM-56 also shows variable cross reactivity with endothelial cells.) Lymphocytes and monocytes were also found predominantly in the media and adventitia and rarely in the intima (Figure 3b). Most of the lymphocytes exhibited positive staining as T-cells (data not shown). In some cases, a limited number of infiltrating vessels were identified at the base of the intima (Figure 3c); this was much more pronounced in the veins of older accesses (8–24 months) than in newer ones. An identical section stained with Masson’s trichrome (Figure 3d) shows the structural components of this section.

There were smooth gradients, from media to lumen, of certain intimal histologic features suggesting that the hyperplastic response was steadily progressive rather than episodic. These features include cell density, cell orientation, smooth muscle actin staining, proteoglycan staining by alcan blue, and intimal collagen distribution as detected by the Masson’s trichrome stain. The cell density was often nonuniform and slightly decreased nearer to the lumen (Figures 1a, 4a, 5, and 7). The orientation of the intimal smooth muscle cells was generally very disorganized, which was in contrast with the more orderly circumferential and longitudinal orientation of cells from the outer and inner venous media, respectively (Figures 1a and 2a vs. 1b). The gradient of actin staining by CGA-7 (Figure 2b) suggested that actin was less concentrated in cells nearer the lumen, which is consistent with the interpretation that these are younger, less well differentiated proliferating cells, functioning principally in the synthetic mode.

Collagenous appearing material, as assayed by the blue staining material in the Masson’s trichrome stain, was present in normal density in the vein media, and was comparatively sparse in the intima, particularly near the lumen (Figure 4a). The internal elastica, when present, was found just inside the band of medial collagen. These observations were confirmed by TEM (see below).

Proteoglycan staining with alcian blue was most intense in the extracellular matrix (ECM) surrounding the intimal cells nearest the lumen (Figure 4b). Staining was moderate around cells at the base of the intima, and only faint around cells of the vein media. Thrombus totally occluded the lumen in three cases; it appeared fresh and relatively uniform in age, without obvious layering suggestive of episodic or protracted thrombus formation. In one case (Figure 5) a 1–2-day-old central plug of thrombus (possibly embolic) appeared to terminally occlude a vein lined with 4–5-day-old formed mural thrombus. At the interface between intimal cells and thrombus, we observed a less intense extension of the alcian blue staining into the bordering thrombus (Figure 6), which is consistent with an ingrowth of these cells into the thrombus.

A hyaline monolayer intermittently covered the luminal surface in arcs totaling about 10% of the circumference in the two sections that were severely
narrowed, but not occluded, before surgery. This material had the morphological (Figure 7a) and immunocytochemical (Figure 7b) appearance of fibrin; it was adherent only at sites of endothelial disruption. It was not possible to determine whether this was a morphological feature of the developing lesion or was an artifact of its surgical removal. The limited presence of fibrin in the ECM, confirmed by TEM (see below), is more supportive of the latter possibility. Platelets were not visualized in the two sections without thrombotic occlusion and were typically present in all formed thrombus.

Neither extracellular lipid deposits nor lipid laden foam cells were observed in the paraffin sections; this was confirmed by TEM (see below). Hemosiderin, potentially a clue that this intimal fibromuscular lesion may represent organization of an original thrombus, was absent.
FIGURE 5. Hematoxylin and eosin–stained cross section of vein removed at the time of its total occlusion by thrombus (age, 9 months); bar, 300 μm. Note what appears to be a 2-day-old central plug of thrombus (arrows) in the midst of approximately 4–6-day-old formed mural thrombus (T). Thrombosis appears to be the terminal occlusive event; underlying intimal fibromuscular hyperplasia (I) is similar to that of Figures 1–4.

FIGURE 6. Alcian blue (0.3 M MgCl₂)–stained cross section of Figure 5; bar, 100 μm. Note the region of overlap (arrows) in proteoglycan staining between the intimal cellular region (I) and the thrombus (T).
Electron Microscopy

Ultrastructural examination of the lesion revealed an unusually large proportion of ECM separating the smooth muscle cells (Figures 8 and 9). This was especially evident near the lumen where the matrix was strikingly rich in proteoglycan (Figure 8a, b) as demonstrated by ruthenium red staining. Relatively little collagen and elastin were seen in this zone. Deeper in the intima, collagen fibrils were more abundant (Figure 9a, b) as were elastin bundles. Although the composition of the matrix changed progressively from inner to outer intima, the cell type remained the same; smooth muscle cells, exhibiting characteristic dense bodies and peripheral cytoskeletal filaments, were the dominant cell type in each region. Many smooth muscle cells appeared to be of the synthetic phenotype with large nuclei, extensive rough endoplasmic reticulum, and Golgi complexes (Figure 8a).

The determination that the lesion was made up almost exclusively of smooth muscle cells was supported by the electron microscope observations. Macrophages and lymphocytes were not seen in the neointima. In contrast to the typical atherosclerotic plaque, lipid vacuoles were scanty; foam cells and extracellular lipid deposits were not observed. Fibrin was sometimes found in the intimal extracellular matrix, but neither in a consistent nor significant amount.

Discussion

Although veno-occlusive disease of arteriovenous communications was recognized as a complication soon after the development of hemodialysis, detailed histologic studies of this lesion are lacking. Glashan and Walker first examined veins used in “Quinton/Scribner” external A-V shunts placed for hemodialysis access. The age of the shunts varied from 24 hours to 6 months. Endothelial damage and loss near the tip of the dialysis cannulas were observed in all specimens. In earlier specimens, thin deposits of fibrin covered the damaged intima. Later specimens showed thick laminated deposits of fibrin with progressive organization through cellular ingrowth. According to the investigators, the fibrin thrombus became organized by cellular ingrowth, with slow accumulations of fresh fibrin which, in turn, become organized, eventually occluding the lumen. Later, Stehbens and Karmody reported two cases of “venous atherosclerosis” downstream of saphenous vein grafts placed for hemodialysis. In contrast to the present study, Stehbens and Karmody observed the characteristics of a more classic atherosclerotic plaque. Deposits of amorphous and granular material were found as well as necrotic muscle cells and cellular debris. Large cells without myofibrils were frequent, many of these cells containing lipid (foam cells). Extracellular lipid with a “few small foci of calcification” was also observed.

The observations of the present study provide certain insights about the nature of these proliferative lesions, especially the role played by smooth muscle cells. Although the composition of the ECM differed substantially across the thickened intima, the dominant cell-type throughout was the smooth muscle cell. At this point, it is unclear why proteoglycans tend to dominate the ECM in the inner intima, whereas collagen dominates deeper in the intima, near the internal elastic lamina. Smooth muscle cells in these two regions appear to differ somewhat in phenotypic expression. Differences in cell maturation are reflected in the antibody staining discrepancy between CGA-7 and HHF-35, demonstrating a decline in smooth muscle actin-specific (CGA-7) staining in the intimal region nearest the lumen. Gown et al have previously found CGA-7 to have a reduced reactivity with actively proliferating smooth muscle cells, whereas HHF-35 appeared to react in a more uniform manner independent of cell state. They also found a similar gradient of smooth muscle cell staining by CGA-7 in
FIGURE 8. Electron micrographs of the proteoglycan rich zone in the neointima. The tissue was fixed in Karnovsky’s fixative with ruthenium red added. Panel a: A large proportion of the volume was taken up by extracellular space filled with proteoglycan. Smooth muscle cells tended to have an extensive rough endoplasmic reticulum (arrow) and Golgi complexes in addition to characteristic dense bodies and peripheral cytoskeletal filaments. Bar, 1 μm. Panel b: Detail of the ruthenium red stained proteoglycan granules adjacent to smooth muscle cell. Bar, 0.2 μm.

the human atherosclerotic lesion. Presumably, the smooth muscle cells nearest the lumen are in the earliest phase of the proliferative phenotype and as such would secrete matrix proteins made up primarily of proteoglycans. The smooth muscle cells deeper in the intima are in a later stage of connective tissue synthesis, secreting primarily collagen into the ECM, and with a more fully developed contractile capacity.

Several hypotheses have been offered for the pathogenesis of this lesion. In addition to the organization of mural thrombus suggested by Glashan and Walker, mechanical stress to the vein wall, differences in circumferential compliance of the vein and graft materials, platelet activation, immunologic factors, and hemodynamic factors, such as shear stress, high arterial pressure in the venous system, and nonlaminar flow have all been proposed. An explanation for the development of this lesion must be consistent with the following observations: 1) Obstruction occurs at the downstream venous anastomosis of this high-flow shunt, and rarely at the arterial anastomosis; 2) obstruction is significantly more frequent for the PTFE grafts than the B-C fistulas; 3) the intimal cell population is almost exclusively smooth muscle; 4) there are generally uniform intimal gradients in smooth muscle cell actin content and ECM composition; 5) consistent signs of luminal fibrin or macroscopic thrombus formation, and of intimal fibrin, or hemosiderin accumulation are absent; and 6) extracellular and intracellular lipid, foam cells, and intimal macrophages are absent. These findings suggest a steadily progressive (rather than episodic) smooth muscle hyperplasia that is stimulated by conditions present near the PTFE-to-vein anastomosis and is
One pathogenic hypothesis that is consistent with these observations is that the lesion represents a variant of the "response-to-injury" model proposed by Ross and Glomset. In this respect, the dynamics of flow through the shunt may be relevant. Typically, 1,000–1,500 ml blood flow per minute through the 3–4 mm diameter feeder artery, the 6-mm PTFE graft, and 3–4-mm proximal vein segment. The state of flow at various points in this course may be smooth (laminar) or turbulent, depending on the Reynold’s number. Given blood’s viscosity of 0.04 poise and density of 1.0 g/ml, Reynold’s number is 32×Q/D, where Q is flow in milliliters per second, and D is lumen diameter in cm. Flow remains, or tends to become, laminar for Reynold’s numbers 2,000 or less and turbulent above 2,000. In the feeder artery and proximal vein segment, the Reynold’s number is in the range 1,700–2,000, close to turbulent transition but probably laminar in these vessels when lumen diameter is uniform and normal. Turbulence generated by eddy formation beyond the diameter mismatch at the arterial anastomosis would be suppressed because of the relatively low graft Reynold’s number in the range 800–1,300. Predictably, these eddies would dampen out over the “inlet length”: \[ L_i = 0.03 \times \text{Reynold’s number} \times D, \] about 16–24 cm. For laminar flow, shear stress is estimated as \[ \tau_L = 0.4 \times Q/D^3. \] Thus, in the PTFE graft, shear stress is 30–45 dynes/cm²; in the 4-mm artery and vein, it is 100–150 dynes/cm²; and in a moderate 2-mm vein stenosis, it is 800–1,200 dynes/cm². This latter value greatly exceeds the value of 379±85 dynes/cm² determined by Fry to be acutely destructive to dog endothelial cells. When flow is turbulent, the intimal shear stress is even greater and is estimated as...
\[ \tau = 0.027 \times Q^{1.75}/D^{3.75} \]. If eddies generated at the arterial anastomosis were to persist, incompletely damped, along the entire graft, the entry of this turbulent flow into a normal vein segment would generate intimal stresses of 120–240 dynes/cm², and flow entering a 2-mm venous stenosis would generate a stress of 1,600–3,200 dynes/cm². Thus, the generation and persistence of turbulence, as suggested by the palpable thrill commonly felt over the PTFE grafts, would provide a mechanism for localized intimal injury in the region of the venous anastomosis and for accelerated luminal narrowing as a response to injury.

A second pathogenic hypothesis is that the platelet activation associated with turbulent shear stresses or with repeated thrombus formation after needle puncture in the PTFE graft could release sufficient platelet-derived growth factor (PDGF) to promote downstream smooth muscle proliferation. A compelling argument favoring this idea is the greater frequency of venous stenosis with the PTFE grafts compared with the B-C fistulas (45% vs. 16% during 5 years; \( p < 0.001 \)) despite comparable shunt flows, venous pressures, and dialysis frequency. The PTFE graft is punctured three times weekly upstream of the venous anastomosis; by comparison, the venous limb of the fistula is punctured at a downstream point. Platelet release products from thrombus at the PTFE puncture site would bathe the anastomosis, but not so for the B-C fistula. Indeed, Reidy has described increased arterial smooth muscle cell mitotic activity well downstream of a thrombogenic site in the thoracic aorta, possibly stimulated by upstream release of PDGF. This hypothesis may, at first, seem less compelling because the smooth muscle proliferation is localized to the anastomotic region rather than distributed diffusely along the proximal vein. This discrepancy may be explained by postulating that hemodynamic injury at the downstream anastomosis locally increases endothelial permeability to blood products, including growth factors. Thus, injury to the vein plus PDGF release in the graft may combine to provoke this lesion.

An accelerated rate of atherosclerosis has been described among dialysis patients. However, a risk contribution due to dialysis, independent of hypertension, and lipid abnormality has never been conclusively shown. Abnormal lipid levels have been found in the uremic state. The most common lipid abnormality is hypertriglyceridemia and the predominant pattern is type IV according to the classification scheme of Fredrickson et al. Because of the absence of lipid deposits, macrophages, and foam cells, we believe our results do not support a major role for lipids in the formation of this lesion.

There are several reasons for studying this venous obstructive process of the vascular accesses. First, a better understanding of its pathogenesis may lead to therapy to increase the lifetime of the access. Second, the problem occurs not only at the venous anastomosis of prosthetic dialysis shunts but also at the downstream anastomosis in coronary bypass and peripheral arterial reconstructive grafts. Concepts developed from study of the shunt disease may apply to these other clinical situations. Third, this process is uniquely accessible; fresh tissue specimens for histochemical analysis are frequently available from dialysis patients after surgical repair. Flows may be measured by Doppler techniques, and pressures and blood samples may be obtained by direct puncture. Contrast radiographic fistulograms are easily performed, making quantitative angiographic assessment of progressive narrowing quite feasible. Platelet thrombus formation in accesses is readily studied using radionuclide techniques.

In conclusion, this postanastomotic occlusive process in humans affords a readily accessible potential model for the fibromuscular hyperplasia of atherosclerosis and for certain other clinically important anastomotic vascular obstructive processes.

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