Sequential morphological changes at the site of carotid endarterectomy

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Nineteen carotid arteries were examined post mortem after endarterectomy had been performed from 1 hour to 11 years previously. The sequential morphological changes at the endarterectomy site were divided into acute, reparative, and mature phases. All nine occluded arteries thrombosed during the acute phase postoperatively. The degree of medial necrosis, acute inflammation and adventitial exposure was more marked in these thrombosed acute phase arteries. By 30 days new intima covered the endarterectomy site and thereafter thrombosis was not seen. Avoidable technical errors led to thrombosis of three arteries. Anticoagulation after surgery may reduce the incidence of postoperative thrombosis. Recurrent symptomatic atheroma occurred in two cases at the original endarterectomy site 16 months and 11 years after operation.

Key Words - carotid endarterectomy • postoperative thrombosis • intimal hyperplasia • prophylactic anticoagulation • recurrent atheroma

The efficacy of surgical treatment of extracranial carotid atheromatous occlusive disease was first reported by Eastcott, et al., in 1954. The initial surgical procedures involved resection of the diseased carotid bifurcation followed by direct reanastomosis or grafting. Although the technique of arterial endarterectomy for the treatment of atherosclerotic occlusive disease of the aortoiliac system was first described in 1947, it was not until 1953 that Strully, et al., suggested its application to the carotid bifurcation. In 1956, Cooley, et al., first reported a case in which this technique was used with apparent success. During 17 years of application of this technique in the carotid artery little attention has been focused upon the morphological appearance of the endarterectomy site. No attempt has been made to date to correlate the observed features and the postoperative patency of the endarterectomized segment either in the carotid or aortoiliac systems.

This report describes the sequential morphological changes that occurred at the endarterectomy site in 19 carotid arteries obtained post mortem 1 hour to 11 years after operation. The value of prophylactic postoperative anticoagulation, the factors which contribute to postoperative thrombosis and recurrent symptomatic atheromatous occlusive disease at the original endarterectomy site will be discussed.

Material and Methods

Nineteen operated carotid arteries were obtained post mortem from 18 patients who had
died 1 hour to 11 years after endarterectomy. Ten patients died from neurological causes (three from intracerebral hemorrhage, seven from massive cerebral infarction) and eight from non-neurological causes (five from cardiac arrest, two from ruptured abdominal aortic aneurysm, and one from hypovolemic shock as a result of a ruptured carotid artery). The carotid arteries were fixed in formalin, decalcified if necessary, and the endarterectomy site sectioned transversely at several levels or serially. Tissue sections were stained for light microscopy with hematoxylin and eosin, Gomori connective tissue stain and Weigert's or Verhoeff's elastic tissue stains.

The operations were performed in several University of Toronto teaching hospitals by various neurosurgeons, cardiovascular surgeons, and their residents in the years 1959 to 1972. Standard longitudinal arteriotomy, endarterectomy and direct closure were performed in 15 arteries. One arteriotomy was transverse; two arteries were closed with an autogenous vein patch, and one with a Teflon patch. Choice of anesthesia, prophylactic anticoagulation, and shunt was varied. A second endarterectomy had been performed on two of the 19 arteries for recurrent symptomatic atheromatous occlusive disease at the original endarterectomy site, making a total of 21 endarterectomies.

Surgical specimens from all cases were examined to determine plaque morphology and thickness of intima and media removed.

**Results**

The media of normal extracranial carotid artery contains smooth muscle cells and fibrocytes interspersed with a variable amount of elastic tissue depending upon the portion of the artery examined (Fig. 1, left). A change in elastic content occurs in the vicinity of the bifurcation of the common carotid artery into internal and external branches. The proximal common carotid contains elastic tissue throughout the full thickness of the media. Distally, the internal carotid artery changes to a muscular type of artery with elastic tissue confined to an internal and external elastic lamina.

The sequential morphological changes found at the endarterectomy site are arbitrarily divided into three merging phases: acute, reparative, and mature. The distribution of patent and thrombosed arteries and the length of time from operation to death is given in Table 1.

**Acute Phase**

Three constant features of the acute phase were seen in five thrombosed and five patent arteries obtained from 1 hour to 6 days after operation: 1) acute inflammatory reaction; 2)

**TABLE 1**

<table>
<thead>
<tr>
<th>Phase</th>
<th>Number of Arteries</th>
<th>Time Range Operation to Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>active</td>
<td>5</td>
<td>1 hr to 6 days</td>
</tr>
<tr>
<td>reparative</td>
<td>0</td>
<td>18 days</td>
</tr>
<tr>
<td>mature</td>
<td>5</td>
<td>32 days to 11 yrs</td>
</tr>
</tbody>
</table>

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necrosis of media; and 3) mural thrombus deposition. Each feature varied considerably in severity in different areas of the same endarterectomy site, as well as between different specimens. In addition, the severity of the changes was not strictly related to the time elapsed from operation but appeared to be an individual reaction of that particular vessel and patient to the procedure.

Some degree of adventitial acute inflammatory cell infiltration was seen at all endarterectomy sites. Similarly, some medial necrosis was present in most specimens, particularly in areas where the residual media was thinnest (Fig. 1, right). Infiltration of the media by polymorphs occurred only in those areas where the media was necrotic (Fig. 2) and was sometimes associated with the deposition of mural thrombus. Thicker deposition of mural thrombus occurred at sites where the residual media was thin and necrotic and where adventitia was exposed directly to the lumen and where the acute inflammatory response was greatest (Fig. 3). Both medial necrosis and the acute inflammatory response were greater at the arteriotomy site.

There was a tendency for the medial necrosis and the inflammatory response to be more prominent in the walls of thrombosed arteries. The acute inflammatory cell infiltration and the medial necrosis was marked in two and moderate in three of the five thrombosed vessels. On the other hand, the same changes were judged moderate in three and mild in one of four patent vessels. The fifth patent vessel was obtained only 1 hour after operation and showed no necrosis or inflammation.

Reparative Phase

The essential features of the reparative phase are: 1) resolution of the inflammatory response; and 2) organization of mural thrombus to form new intima. Evaluation of

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**Fig. 2.** Acute phase, 38 hours postoperative. The surgically thinned media (between arrows) is necrotic and infiltrated by polymorphonuclear leucocytes extending in from the marked adventitial reaction. H & E, × 260.

**Fig. 3.** Acute phase, 40 hours postoperative; bifurcation of the common carotid. Mural thrombus is deposited on the internal carotid endarterectomy site where adventitia is exposed to lumen (arrows). ECA = external carotid artery; ICA = internal carotid artery. Verhoeff’s stain, × 15.
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this phase was restricted to examination of one thrombosed 18-day artery. No inflammatory response was present in the wall. A patent portion of the endarterectomy site revealed organization of the mural thrombus to form the new, highly cellular intima (Fig. 4). Re-endothelialization could not properly be assessed because of the thrombus adherent to the surface of the hyperplastic intima.

Mature Phase

The features of the mature phase seen at the endarterectomy site of the five patent arteries obtained 32, 34, and 51 days, and 5 and 11 years after operation consisted of: 1) maturation of new intima over incorporated surface irregularities; 2) re-endothelialization; and 3) formation of new elastic tissue.

New intima completely covered one endarterectomy site as early as 32 days postoperatively (Fig. 5). In another specimen an autogenous vein patch graft was covered with a thick layer of new intima after 51 days (Fig. 6). The elastic component of the vein graft and the cellularity of its media was preserved.

No recognizable mural thrombus, residual or new, was present at any of the endarterectomy sites. A variable thick layer of mature hyperplastic intima incorporated and smoothed over surface irregularities. Areas of adventitial exposure, large and small medial tags, unevenly approximated arteriotomy edges, luminal sutures, and healed intimal and medial dissections were innocently buried beneath thick smooth intima in the walls of patent vessels (Fig. 7 left). One arteriotomy developed a small diastasis recognized as an asymptomatic diverticulum on postoperative arteriograms at 5 months, 11 months, and 5 years after endarterectomy. Thick intima covered the endarterectomy site and the connective tissue exposed by the diastasis.

The lining layer of cells that covered the new intima was indistinguishable from normal endothelium by light microscopy. The earliest evidence of new elastic deposition was

![Fig. 4. Reparative phase, 18 days postoperative. New highly cellular intima covers the surgically thinned media (stained black). Verhoeff's stain, X 130.](image1)

![Fig. 5. Mature phase, 32 days postoperative. The surface irregularity of the residual media (black arrows) is covered by new smooth hyperplastic intima. H & E, X 33.](image2)
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seen in the deeper portion of the new intima in a patent area of a 104-day thrombosed artery, but a distinct lamina was seen only in the 11-year patent artery (Fig. 7 right).

Postoperative Thrombosis

Nine thrombosed arteries were examined for factors that might have contributed to the postoperative thrombosis. The following features were judged unavoidable: 1) thin residual media with marked necrosis and inflammatory response; 2) exposure of adventitia directly to the lumen (Fig. 8); 3) medial tags and flaps; and 4) small intimal and medial dissections (Fig. 9). Each of these features was seen in patent acute, and mature phase arteries, and more than one feature might be seen in any one specimen.

Three cases seemed to demonstrate avoidable or correctable technical errors. One stenosed artery in which backflow was obtained at the time of arteriotomy became occluded distally after endarterectomy and flow could not be restored. A temporary bypass shunt had been used in this case. The second stenosed artery was subjected to incomplete endarterectomy; its lumen was found to be occluded by atheromatous debris admixed with thrombus. In the third stenosed artery a distal intimal flap was demonstrated in the internal carotid artery just beyond the arteriotomy site (Fig. 10). Neither of these last two features was seen in any of the patent arteries.

The lumen of the thrombosed segment of a reparative phase endarterectomy site (18 days) contained organizing thrombus and that of thrombosed mature phase endarterectomy sites (3 months, 3 years, remote) mature, collagenous connective tissue (Fig. 8). In each, the endarterectomized surface was in continuity with tissue occluding the lumen, without any evidence of intervening new intima. On the other hand, proximal patent segments of these same endarterectomy sites acquired endothelial linings. These observations indicate that the occluded segments of all nine arteries became thrombosed during the acute phase postoperatively before new intima could form.

Prophylactic Anticoagulation

Complete clinical records were available for 20 of the 21 endarterectomy procedures. After 12 of the procedures the artery remained patent, and after eight the artery became thrombosed. Eight of the 12 patients with patent arteries received a therapeutic level of orally administered anticoagulation pre- and postoperatively. None of the eight patients with thrombosed arteries received therapeutic anticoagulation. In three cases, however, thrombosis was felt to be due to technical errors.

The remaining five cases with thrombosed arteries could be distinguished from those that were patent by such recognized contribution factors as preoperative occlusion of the vessel, the presence of intracranial disease or hematological abnormalities, differences in basic surgical technique, and postoperative complications. The only feature that set them apart was the accentuated acute inflammatory response and medial necrosis in four of the vessels obtained within 6 days of operation.
Two of the three patients who died of intracerebral hemorrhage were receiving anticoagulation therapy at the time of death. One patient died 6 days after operation from a massive intracerebral hemorrhage into an area of recent infarction; the second died 51 days after operation from an occipital lobe intracerebral hemorrhage associated with amyloid angiopathy.

**Recurrent Atheromatous Disease**

A recurrent asymptomatic atheromatous deposit was found at the original endarterectomy site in one patent mature phase artery 11 years after operation (Fig. 11). Recurrent symptomatic atheromatous disease at the original endarterectomy site was confirmed both angiographically and operatively in two arteries. In one mildly hypertensive patient with diet-controlled diabetes and a mildly elevated serum cholesterol of 300 mg %, an angiographically normal artery was demonstrated 12 days after first endarterectomy. Sixteen months later a symptomatic stenosing atheromatous ulcer with mural thrombus was successfully removed from the original endarterectomy site. The surgeon felt that a severe cicatricial reaction around the vessel also contributed to the stenosis. The second patient, with normal serum cholesterol but with severe aortoiliac, peripheral vascular and coronary artery disease, had a slightly irregular but fully patent artery 5 years after first endarterectomy and Teflon patch graft. Six years later he developed an acute thrombotic occlusion superimposed upon recurrent stenosing atheroma. Endarterectomy successfully restored the flow. Detailed serum lipid studies were not performed in either patient. Both patients had received oral anticoagulation for 6 months after the initial endarterectomy.

**Discussion**

It appears that a variable degree of adventitial acute inflammatory infiltration and medial necrosis is a sequel to any endarterectomy procedure in the acute phase; this is the
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result of perivascular surgical dissection, arteriotomy and manipulation during dissection of the plaque. The accentuation of these features at the arteriotomy site supports this theory of mechanical etiology. Histological study of the fibrosis developing at the site of longitudinal versus circumferential arteriotomy in carotid and femoral arteries of cats indicates that the greater the surgical trauma, the greater the scar.14

Infiltration by polymorphs only occurs into necrotic media; both the necrosis and inflammatory response are more prominent where residual media is thinnest. It is at such sites of thin necrotic, inflamed media or direct adventitial exposure to the lumen that mural thrombus is deposited.

The exposure of adventitia to the lumen is not necessarily a technical error but may be a result of the pathogenesis of atheroma. The media becomes progressively thinned and may disappear completely where atheroma is thickest, leaving the atheroma in direct contact with the adventitia. The extent of atrophy of the media cannot be assessed at operation so that, in some cases, excision of the plaque will inevitably expose the adventitia directly to the lumen of the artery. Similarly, small medial tags and flaps or small medial dissections are not apparent to unmagnified vision and may be left behind after the most carefully performed endarterectomy.

These features are unavoidable sequels to any endarterectomy. They are seen commonly in both patent and thrombosed acute phase arteries, and in a healed, incorporated form in patent mature phase arteries. However, the incomplete endarterectomy or the distal intimal flap are technical errors which should be avoided or corrected when they occur.

All nine thrombosed arteries in this series became occluded in the acute phase postoperatively. The deposition of mural thrombus on the endarterectomy site depends upon the exposure of subendothelial collagen22 and the presence of an acute inflammatory reaction17 which induces platelet

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Fig. 8. Thrombosed internal carotid artery, 3 years postoperative. The lumen is filled with collagenous connective tissue and is in direct apposition to the previously exposed adventitia (arrows). No new intima has formed. Weigert's stain, x 33.

Fig. 9. Thrombosed internal carotid artery, 38 hours postoperative. A large intimal and medial dissection (hollow arrows) is lifted into the occluded lumen by blood in the plane of dissection deep in the media (solid arrows). H & E, x 15.
aggregation as well as the release of tissue thromboplastin which initiates the clotting mechanism. In this series it appears that the more severe the medial necrosis, acute inflammation, adventitial exposure and surface irregularity, the greater the tendency to form exuberant mural thrombus which progressed to postoperative occlusion. The prominence of the acute inflammatory infiltration and medial necrosis in thrombosed acute phase arteries raises the question of excessive surgical dissection and manipulation of the artery as a potential contributing factor.

No complete layer of new intima was seen over an endarterectomy site where thrombosis had occurred; therefore, it appears that once coverage by new intima has been achieved (at approximately 30 days) the risk of acute total thrombosis is reduced. Gunning, et al., found new intima and cells resembling endothelial cells at the endarterectomy site as early as 23 days postoperatively in their Case 15. The mature phase endarterectomy site appears to be prone to the gradual development of recurrent atheroma rather than acute thrombosis.

The retention of cellularity in the media of a vein patch graft after 51 days (Fig. 6) is likely due to the large size of the vein patch. Khodadad reviewed the confused literature describing the histological changes occurring in vein patch grafts and experimentally related the degree of fibrosis to the ratio between the unavoidable surgical trauma of anastomosis and the graft size. He found smaller grafts to be totally replaced by fibrous tissue in contrast to partial fibrosis in large grafts.

All five patients with patent acute phase arteries were under anticoagulation therapy...
Morphological changes at site of carotid endarterectomy at the time of death, in contrast to none of the five patients with thrombosed acute phase arteries. In one of the thrombosed arteries an incomplete endarterectomy may have accentuated occlusive mural thrombus deposition.

This suggests that anticoagulation could diminish the tendency to form exuberant mural thrombus. In this instance the prominence of the inflammation and necrosis in the thrombosed arteries raised the question of a "damping" effect of anticoagulants on the inflammatory reaction seen in the patent arteries.

From our findings we cannot state that prophylactic oral anticoagulation reduces the incidence of postoperative thrombosis. The true incidence of postoperative thrombosis is not known, since postoperative angiography at a 2- to 6-month interval is not routinely performed. Rather, only selected patients who develop symptoms after operation, or patients willing to submit to routine postoperative angiography are reported. Postoperative occlusions which are clinically silent or masked by some pre-existing neurological deficit, and those which occur in patients severely disabled after operation or in fatal cases, may all pass undetected.

Blaisdell, et al., performed early postoperative angiography 10 to 60 days after operation in 95 patients. Only one artery was thrombosed. This enviable result was obtained only by the use of intraoperative angiography which led to immediate revision in 25% of cases because of residual stenosis or acute intraoperative thrombosis. Rosental, et al., used intraoperative angiography and found 8% of 260 carotid endarterectomies unacceptable and in need of immediate revision. Intraoperative angiography is not a common technique; its wider adoption might result in a significantly higher rate of postoperative patency. Without controlled trials one cannot assess the effectiveness of pre- and postoperative oral anticoagulation in preventing thrombosis in the acute phase after endarterectomy. Until this information is available there can be no objection to the practice of anticoagulant administration in these cases as advocated by Lougheed, et al.

Edwards, et al., have noted the risk of fatal intracerebral hemorrhage with postoperative anticoagulation. In our series, two of three patients who died of intracerebral hemorrhage had been treated with anticoagulants. However, four who had not been so treated died of massive cerebral infarction related to postoperative thrombosis. Interestingly, our patients and those of Edwards, et al., who died of intracerebral hemorrhage while under the influence of anticoagulation had patent arteries at postmortem examination. The formation of new intima by approximately 30 days after surgery appears to reduce the chance of postoperative thrombosis. Anticoagulation for a longer period is probably unnecessary.

Recurrent stenosis after endarterectomy has been reported in 24 cases. In most instances no details were given or the stenosis was an asymptomatic angiographic demonstration. Only seven were reported symptomatic. Edwards, et al., reported three recurrent specimens to consist of "a tough thick fibrous lining" but did not mention atheroma. Heyman, et al., first reported recurrent atheroma in a surgical specimen but their case may resemble the description by Julian and Javid of residual atheroma at the distal end of the endarterectomy site left behind at the first procedure.

In our series, two patients with patent vessels at postoperative angiography later developed recurrent symptomatic atheroma 16 months and 11 years respectively after the first operation. The recurrent atheroma was found to be localized at the original endarterectomy site both angiographically and at operation. Both surgical specimens revealed typical atheromatous accumulations, one with an ulcer containing mural thrombus. One patient was diabetic and hypertensive and the other had severe systemic arteriosclerotic vascular disease. There have been no detailed reports of serum lipids in patients with recurrent symptomatic atherosclerotic disease.

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