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High-Flow, Aortocaval Fistulae: Radiologic and Histopathologic Evaluation in a Rat Model

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An animal model for a high-flow, aorta-to-vena cava fistula has been developed using microsurgical techniques in the rat. This model provides a means for histopathologic and angiographic evaluation of the natural evolution of major vessel, artery to vein fistulae. Data obtained from such a model may have relevance to the successful treatment of high-flow, head and neck fistulae using detachable intraarterial occlusive balloons. This microsurgical technique is unique, since it requires no intervening sutures or graft material that would alter the histopathologic process. After a series of such aortocaval fistulae were created, serial histologic and angiographic features were elucidated for intervals between 1 day and 6 months. Three stages of evolution are noted including: an initial hemorrhagic dissection phase; a subacute phase where organization of the thrombus and actual formation of a fistulous tract occurs; and a chronic phase characterized by pseudoaneurysm formation, arterialization of the vena cava, and proximal vasodilatation of the aorta.

Significant advance in the treatment of high-flow arteriovenous fistulae has been made by the introduction of detachable intravascular balloons [1–7]. These occlusive balloon systems have made nonoperative treatment of carotid and vertebral artery fistulae possible. Such occlusive techniques have been used for arteriovenous fistulae in both acute and chronic circumstances. To date, however, a radiologic-histopathologic study has not been performed to clarify the natural history of direct, major vessel, arterial-to-venous fistulae. To this end, a model has been devised in the rat in which a fistula is created between the abdominal aorta and adjacent vena cava. The purpose of this project is to correlate to angiographic and histopathologic changes associated with the formation and maturation of a high-flow, arteriovenous fistula.

Materials and Methods

Aortocaval fistulae were created with clean, semisterile conditions using microsurgical techniques reported by Mickle et al. [8]. The methodology for this procedure involves retroperitoneal dissection until the vena cava is identified. After cross-clamping the vena cava and aorta, a venotomy is created through which a needle puncture is made through the opposing cava and aortic walls. The venotomy is then closed. After removing the clamps, an aortocaval fistula develops through the puncture site without requiring the use of sutures or graft material to either attach the vessels or hold them in proximity [9–11]. Serial histopathologic sections and transfemoral angiograms were obtained at intervals between 1 day and 6 months. For pathologic evaluation, the region of the fistula was excised and embedded in plastic with thin sectioning to minimize artifacts. Only hematoxylin-eosin stains were used for the pathologic analysis. The angiographic evaluation was obtained via transfemoral catheterization and rapid, single-plane angiography. Postangiographic subtraction techniques were employed using standard Dupont subtraction methods. No angiographic complications, particularly arterial or venous dissection, were observed.

Results

Day 1

Animals studied within the first day had fistulae of 90 min to 24 hr in age. Histologic changes during this interval were essentially the same. The fistulae were clinically patent in all cases. The cut margins of both the aorta and cava had retracted and the intervening space was filled by blood clot. The hemorrhage had dissected between the adventitia of the vessels for a varying distance (fig. 1). Extensive thrombus had become attached to the endothelial surface of the vena cava, but little was noted in the aorta. This presumably is accounted for partly by the pattern of blood flow and partly by the presence of the surgical venotomy.

1 Week

At 1 week, the dissecting hemorrhage had become organized, and there was early evidence of endothelium covering the surface of the fistula site. Organized blood clot was evident within the fistula and along the wall of the vena cava. No intrinsic inflammatory or degenerative arterial or vein transmural changes were present. Angiography (fig. 2) demonstrated rapid arteriovenous shunting, but the exact margins of the fistulae were indistinct. Compared with normal control animals, the lumen size of the aorta was not appreciably enlarged, while the lumen size of the vena cava was near normal or at best mildly dilated. Heart size remained normal.

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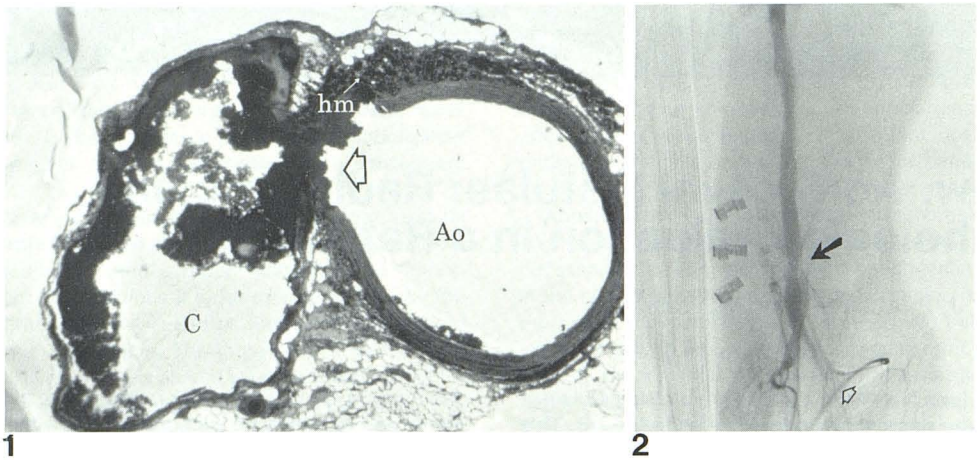


Fig. 1.—Day 1. Histopathologic cross section of region of aortocaval fistula after microsurgical creation shows features of acute dissecting hemorrhage (hm). Margins of aorta (Ao) and vena cava (C) have retracted; intervening space is occupied by thrombus and periadventitial connective tissue. Blood clot attached to nearly entire venous wall. Clinically, fistula was widely patent (*arrow*), although margins and central lumen are distorted by thrombus. Transmural thickness of aorta and vena cava are normal and no dilation of veins is noted within surrounding regions.

Fig. 2.—1 week. Anteroposterior (AP), subtracted, transfemoral aortogram shows patent aortocaval fistula (*solid arrow*). Margins of fistula are unsharp, which is related to irregular thrombus within fistula and along venous wall adjacent to fistula. Catheter (*open arrow*) has been inserted within left femoral artery and distal tip is distal to fistula site. With injection of contrast media, none refluxes into more proximal aorta, while all passes through aortocaval fistula. No reflux of contrast is present into those veins normally flowing into vena cava. Subsequent films demonstrated rapid opacification of heart, pulmonary circuit, and proximal aorta, all of which appeared to be of normal size and configuration.

2–3 Weeks

By this time the dissecting thrombus had become well organized (fig. 3). Little or no inflammatory change was evident either within the vessel walls or within the thrombus. Endothelium covered most of the luminal surface of the fistula. Angiographically (fig. 4), the margins of the fistula had become more precise. The vena cava showed signs of mild generalized dilatation, but no retrograde opacification of its venous tributaries. Portions of the aorta above and below the aortocaval fistula remained unchanged. Organized thrombi attached to the endothelium were imaged as luminal filling defects. The vena cava distal to the aortocaval fistula showed focal dilatation, stasis of contrast media, and poor contrast washout.

4 Weeks

By 4 weeks there had been continued retraction and fibrosis of the dissecting hemorrhage. The fistula began to form a finite tract, which included some degree of aneurysmal dilation. Actual pseudoaneurysm formation was present in some cases. The intima and media of the vena cava had significantly thickened such that the transmural thickness of the vein had approached that of the aorta. Radiographically, the fistula tract had become well defined. Pseudoaneurysm formation was identified as focal accumulation of contrast media within the fistula region. The aortic lumen had begun to dilate proximal to the aortocaval fistula. Retrograde filling was present into veins previously draining antegrade into the vena cava. This finding correlated with the development of a pericaval venous plexus.

6 Weeks

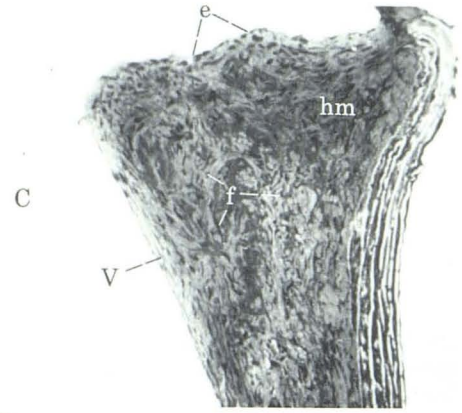
By 6 weeks (fig. 5) the aortocaval fistulous tract was well developed. The lumen of the vena cava had dilated, and its wall had become arterialized with evidence of smooth muscle hypertrophy and intimal proliferation. Intimal thickening first became evident in the aorta at this time. The aortic intimal thickening occurred only adjacent to the aortocaval fistula, whereas the vein changes occurred throughout the vena cava. An extensive pericaval venous plexus had developed. Endothelium completely covered the surface of the fistula tract. The physiologic effects of the elevated venous pressure became apparent on the 6 week angiogram. The vena cava had substantially dilated and exhibited retrograde opacification of veins formerly draining into the inferior vena cava. While the fistula tract had formed it also continued to expand in cross-sectional diameter to the point of actual aneurysmal proportions in many of the cases (fig. 6).

4–6 Months

Between 4 and 6 months the fistula had fully matured histologically. A single fistula tract was often replaced by multiple tracts or septa within the fistula. Calcification occurred in some cases along the margins of the aortocaval fistula. Smooth muscle bundles were readily identified in the caval wall. The luminal surface of the vena cava was ridged, which was evident histologically and angiographically (fig. 7). The proximal aorta had substantially dilated to nearly the size of the vena cava. Blood flow was preferentially directed into the aortocaval fistula accounting for the decreased size of the aorta and iliac vessels distal to the fistula (fig. 8).

Discussion

This sequence of histologic changes associated with the maturation of an aortocaval fistula are highly reproducible. In general, they represent: an acute phase of hemorrhagic dissection lasting 2 weeks; a subacute phase characterized by organization of the



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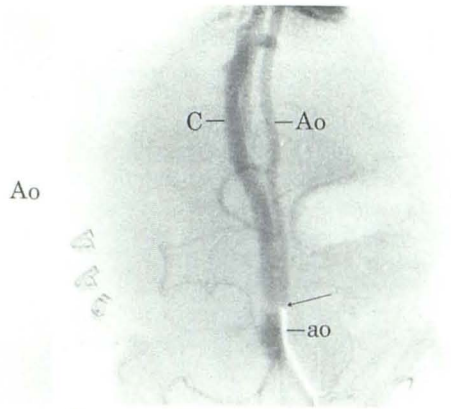

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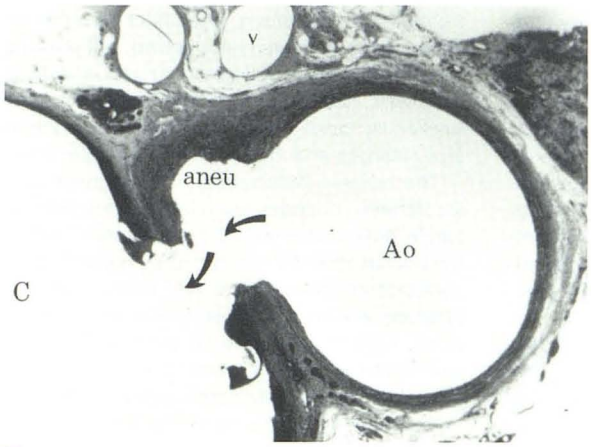
Fig. 3.—2 weeks. Moderately high-power histologic section from fistula. Whereas initial thrombus (cf. fig. 1) was ragged and irregular, by 2 weeks there have been substantial reparative processes. Tissue is sampled in cross section from inferior margin of fistula such that aorta (Ao) and vena cava (C) have same orientation as less magnified histologic section of fig. 1. Dissecting hemorrhage (hm) has become organized and replaced in large part by fibrosis (f). Early thickening of endothelium of venous (V) wall. Early endothelium (e) partly covers fistula margins. Aortic and vena cava margins remain widely separated.

Fig. 4.—2 weeks. Late phase, AP subtracted, transfemoral aortogram, shows size relation between dilated vena cava (C) and the aorta. There is no disproportion in size between aorta proximal (Ao) to fistula and part distal (ao) to fistula. Fistula (*arrow*) is better defined than at 1 week (cf. fig. 2). No reflux of contrast media into venous tributaries has occurred.



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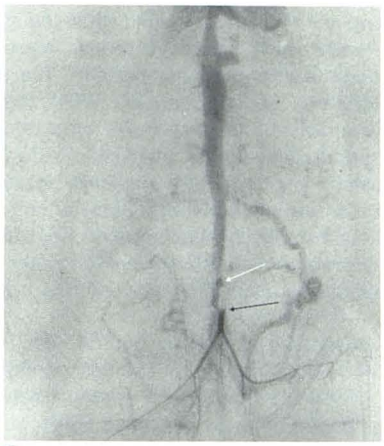

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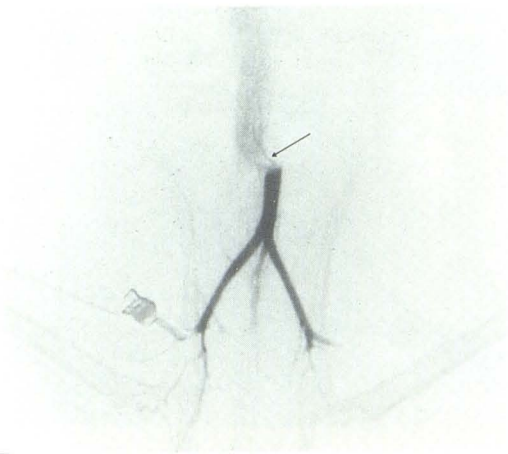
Fig. 5.—6 weeks. Aortocaval fistula has matured histologically. Chronic phase is characterized by elongation of fistula from space to fistula tract. In addition, aneurysmal dilation (aneu) or pseudoaneurysm formation has occurred to a varying degree in region of previous dissection. Luminal surface of fistula is completely covered by endothelium and subintimal region is fibrotic. Two other changes have also occurred. First, thickening of vena cava (C) wall. Although intima had begun to thicken by 2 weeks, by 6 weeks there is both intimal and medial hypertrophy with increasing tunica media musculature. Vena cava transmural thickness has approached that of aorta. Second, pericaval venous plexus has developed characterized by marked dilation of formerly small periadventitial veins (v).

Fig. 6.—6 weeks. Angiography correlates well with histologic picture in fig. 5. Fistula has now formed distinct tract (*black arrow*). In addition, focal contrast accumulation is present, representing pseudoaneurysm (*white arrow*). Persistent rapid arterial-to-venous circulation is evident, however, there is now reflux of contrast media into venous tributaries to vena cava. Presumably, appearance of such reflux implies inability of venous system to accept additional blood flow. Histologically, prominent pericaval vein plexus is an attempt to deal with substantial increase in venous blood volume.

hematoma and formation of the fistula tract occurring at 2–4 weeks; and a more chronic phase associated with pseudoaneurysm formation, arterialization of the vena cava and dilatory vascular effects, which ultimately leads to cardiac decompensation about 4–6 months after fistula formation. The localized vessel wall changes and the maturation of the aortocaval fistulous tract were best defined by the histopathologic examination, while the physiologic changes associated with aberrant blood flow were most apparent on the angiographic studies.

The acute phase of fistula maturation was characterized by



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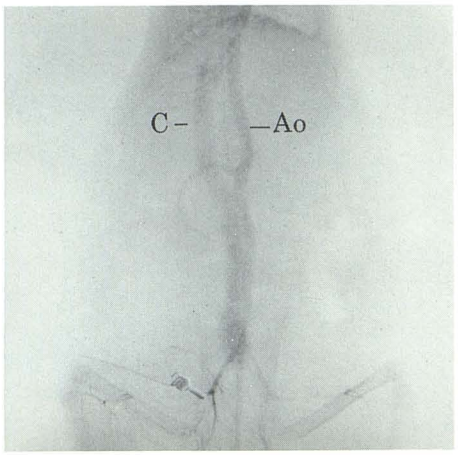

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Fig. 7.—4 months. Early arterial phase, transfemoral, rat aortography shows multiplicity of channels or tracts within aortocaval fistula, which occurs in chronic phase of fistula development. Luminal margin of vena cava appears ridged near fistula, reflecting marked intimal hyperplasia seen histologically.

Fig. 8.—6 months. Altered vascular status of rat circulation becomes apparent. Aorta (Ao) proximal to fistula has become dilated such that it approaches vena cava (C) in cross-sectional diameter. Disproportion in size has developed between dilated aorta proximal to fistula and diminutive aorta distal to fistula (note small size of iliac artery adjacent to vascular clip). These topographic changes correlate clinically with signs of water retention, weight gain, and congestive heart failure.

hemorrhage dissecting into the space created when the artery and vein walls retract. Perivascular connective tissues represent the only structures limiting the dissecting hemorrhage. The extent to which the hemorrhage developed was variable. While some cases exhibited dissections sufficient to compress the lumen of the aorta or vena cava, most cases demonstrate only limited extension and no luminal compression. Angiography during this phase reveals little detail of the fistula but only rapid arterial-to-venous shunting through the fistula. No substantial change in lumen size was evident either within the vena cava or in aortic segments proximal or distal to the fistula. Rat heart size and pulmonary contrast transit time were normal.

In the subacute phase the dissecting hemorrhage has been contained and the thrombus has rapidly become organized. The fistula itself, which initially was merely an aperture between the aorta and vena cava, has become a tract with a finite course. Just as the fistula thrombus organized, so did its luminal surface become endothelialized. Whereas the acute phase histologic sections demonstrate thrombus at the fistula and angiograms demonstrate indistinct fistula margins, by 2 weeks these studies reveal a well delineated fistulous tract. Early vena cava and heart size dilation occurs in the subacute phase.

Once the arteriovenous fistula has matured, the physiologic effects of altered circulation and elevated intravenous pressure dominate the histologic and angiographic features that characterize the chronic phase of fistula development. The fistula often changes from a single tract to one with intimal ridges or separate compartments. The tract may focally dilate, forming a pseudoaneurysm. The elevated pressure within the vena cava results in both retrograde filling of caval tributaries and the development of an extensive pericaval venous network, which presumably functions as an alternate venous drainage route. Angiographically, the cross-sectional diameter of the vena cava enlarges earlier than the aorta. Eventually, however, the aorta proximal to the fistula dilates to nearly the same size as the vena cava, while the aorta distal to the fistula diminishes. Of interest was the dilation of arterial branches arising from the proximal aorta. The effect on organ perfusion supplied by these dilated vessels is not known, but remains a subject of future evaluation. Late histologic changes include arterialization of the vein wall, calcification in the fistula margin, and intimal aortic thickening focally near the fistula site. In late phases the rat heart size enlarges and the pulmonary vascular transit time is slowed.

The biologic implications of this inevitable progression of histolopathologic changes associated with a direct arterial-to-venous rat fistula presumably would apply to most extracerebral portions of the human vascular system. They certainly should be applicable to vertebral artery–vertebral vein fistulae and it is likely that similar changes would occur with extradural carotid artery-to-cavernous sinus, high-flow, fistulae. A suitable animal model for this latter circumstance, however, has yet to be devised.

It is not clear whether detachable balloon occlusion is most likely to be successful and have the least risk or short- or long-term vascular complications if performed at specific periods during the fistula maturation process. This subject forms the basis for the next stage of high-flow fistula investigation using this model. Preliminary investigation has been performed, using an aortocaval fistula treated with a small Latex detachable balloon inserted through the femoral vein. Angiographically, the aortocaval fistula has been obliterated while preserving the aortic lumen. Some deformity in the course of the aorta occurred. Early histologic evidence suggests that the Latex balloon is infiltrated by macrophage cells and is resorbed by about 3–4 weeks. Long-term follow-up of the radiologic/histopathologic changes associated with balloon resorption are pending.

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