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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 correlate 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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This finding leads to the formation of collateral vessels, including veins, which can 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 venousplexus 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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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.

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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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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 dilatation (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 dilatation of formerly small periadventitial veins (v).

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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.
Elevated pressure within the vena cava results in both retropericaval venous network, which presumably functions as a collateral and diminishes. 

Diameter of the vena cava enlarges earlier than the aorta. Even-grade filling of caval tributaries and the development of an extensive same size as the vena cava, while the aorta distal to the fistula 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 histopathologic changes associated with a direct arterial-to-venous 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.

REFERENCES

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