Development of acquired arteriovenous fistulas in rats due to venous hypertension

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Dural sinus thrombosis has been hypothesized as a possible cause of dural arteriovenous fistulas (AVF's). The pathogenesis and evolution from thrombosis to actual development of an AVF are still unknown. To study dural fistula formation, a surgically induced venous hypertension model in rats was created by producing an arteriovenous shunt between the carotid artery and the external jugular vein. The external jugular vein beyond the anastomosis was ligated 2 to 3 months after surgery and angiography was performed to identify any new acquired AVF's.

Forty-six male Sprague-Dawley rats, each weighing approximately 300 gm, were used for this study. In Group I, 22 rats underwent a common carotid artery anastomosis to the external jugular vein, which is the largest draining vein from the transverse sinus via the posterior facial vein, followed by proximal external jugular vein ligation. In Group II, 13 rats underwent the same surgical procedure, followed by contralateral posterior facial vein occlusion. Group III served as the control group, in which 11 rats underwent only unilateral external jugular vein occlusion with or without contralateral posterior facial vein occlusion. The shunts in Groups I and II were ligated at 2 to 3 months following surgery, and transfemoral angiography was performed immediately before and after occlusion.

New acquired AVF's had developed in three rats (13.6%) in Group I, three rats (23.1%) in Group II, and no rats (0%) in Group III. One of these newly formed fistulas was located at the dural sinus, analogous to the human dural AVF. The other five were located in the subcutaneous tissue, including the face and neck. The dural AVF in the rat was present on follow-up angiography at 1 week after the bypass occlusion. It is concluded that chronic venous hypertension of 2 to 3 months' duration, without associated venous or sinus thrombosis, can induce new AVF's affecting the dural sinuses or the subcutaneous tissue.

Key Words: arteriovenous fistula · angiogenesis · chronic venous hypertension · acquired dural arteriovenous fistula · rat

Dural sinus thrombosis has been described as a precipitating cause of dural arteriovenous fistulas (AVF's). However, the pathogenesis of evolution from thrombosis to development of an AVF is still unknown. In addition, there are many examples of AVF's in which pre-existing venous thrombosis has not been documented. These cases frequently show stenosis or irregularity of the dural sinuses. Several authors have also reported an association between dural AVF's and vascular anomalies such as aneurysms and vascular malformations involving the brain, skin, and bone. These findings suggest that dural AVF's develop in the presence of structural weakness in the dura which is activated by a trigger factor.

Venous sinus obstruction may also have a hemodynamic impact upon the development of dural AVF's by encouraging alternative venous drainage, although other components, such as angiogenic factors, activated in the process of sinus thrombosis may play a role in the development of dural AVF's. It is of interest that most posttraumatic dural AVF's do not develop at the site of dural injury but may be distant from the site of trauma. This may support the possible role of hemodynamic changes as the etiology of dural...
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AVF's. From these clinical findings, we speculated that venous hypertension derived from sinus abnormalities may be a trigger factor for the development of acquired AVF's.

To study this hypothesis of venous hypertension inducing formation of an AVF, an animal model using rats was designed. Arteriovenous shunts were surgically created to direct blood flow from the common carotid artery to the dural sinuses. The shunt was subsequently ligated at 2 to 3 months after the surgery. Angiography was performed to identify any new acquired AVF's that had developed by sustained venous hypertension.

Materials and Methods

This study conformed to the guidelines of the animal experimentation committee at the University of California, San Francisco. Forty-six male Sprague-Dawley rats, each weighing approximately 300 gm, were used for this study.

Surgical Protocol

All animals were maintained on a commercial stock pellet diet throughout the experimental period. Venous hypertension in the dural sinus of all rats was induced in the following manner. Each rat was anesthetized with an intraperitoneal injection of sodium pentobarbital (40 mg/kg). In 22 Group I rats, the left common carotid artery and external jugular vein were exposed via a midline linear skin incision. All branches from the external jugular vein, such as the anterior facial vein and the proximal portion of the external jugular veins, were obliterated by a bipolar coagulator except for the posterior facial vein, the largest draining vein from the dural sinus in the rat.\(^\text{11}\) The external jugular vein was then cut and anastomosed to the common carotid artery in an end-to-side fashion, using 10–0 microsutures (Fig. 1).

In Group II, 13 rats underwent the same surgical procedure as the Group I rats, followed by contralateral posterior facial vein occlusion, so as to increase the venous pressure above that of Group I. In this group, facial swelling usually appeared after surgery and in severe cases, the rats died from respiratory difficulties. The mortality rate was over 50% in Group II; therefore, no further investigation was conducted in this group.

In Group III, 11 rats underwent unilateral external jugular vein occlusion, with contralateral posterior facial vein occlusion in nine and without contralateral posterior facial vein occlusion in two. These animals served as a control group.

Following surgery, the rats were fed with the same pellet diet as previously. Two to 3 months after surgery, the wound was reopened and the surgical shunt was ligated in Group I and II rats. Angiography was performed immediately before and after ligation of the surgical shunt in Group I and II rats and also in the Group III rats without any treatment.

Angiographic Protocol

A Tracker-10 microcatheter, 40 cm long, was used for angiography. A No. 23 elastic tube was inserted into the proximal portion of the catheter to assist in guidewire insertion. The rat was anesthetized as described above. The right femoral artery was exposed, the distal portion of the artery ligated, and the proximal portion temporarily clipped.

A small incision was made in the exposed femoral artery, and the Tracker-10 catheter was introduced using an operative microscope. The rat was then moved into the angiography suite. The catheter was navigated into the right and left common carotid arteries under fluoroscopic guidance. A Seeker Lite or Terumo 0.010-in. guidewire was used to navigate the catheter.* Right and left common carotid angiography was performed before and immediately after surgical shunt ligation, with rapid sequence digital subtraction angiography at 8 frames/sec, using 0.1 to 0.15 ml of contrast material (iomecol, 300 mg/ml) for each angiogram.

In three of the six rats that developed new AVF's, long-term follow-up angiography was also performed at 1 week, 4 weeks, and 3 months, respectively, after ligation of the surgical shunt.

Histological Examination

Seven rats in Group I and five rats in Group II were perfused with saline, followed by 4% buffered paraformaldehyde transcardially using a perfusion pump.
after 100 mg/kg of sodium pentobarbital was given by intraperitoneal injection. The dural sinuses were removed and their sections stained by hematoxylin and eosin and examined by light microscopy. The dural sinus of one rat with a dural AVF was not perfused because the rat died several hours following the second angiogram.

**Results**

New acquired AVF's developed in three (13.6%) of the 22 rats in Group I, three (23.1%) of the 13 rats in Group II, and none (0%) of the 11 Group III rats. The appearance rate of AVF between Groups I and II was not statistically significant (using chi-squared analysis).

**Group I Rats**

In the 22 Group I rats with a carotid artery-jugular vein shunt with unilateral proximal external jugular vein occlusion, left common carotid angiography prior to shunt occlusion demonstrated a high-flow arteriovenous (AV) shunt. The major draining veins were as follows: left sigmoid-to-transverse sinus to the right transverse-to-sigmoid sinus to the vein from the transverse sinus to the posterior facial vein and down to the right external jugular vein. Branches of the common carotid artery were not well opacified due to the steal phenomenon by the high-flow AV shunt in this group (Fig. 2). Right common carotid angiography prior to shunt occlusion demonstrated opacification of the left AV shunt via the circle of Willis in a retrograde fashion.

Following surgical AV shunt ligation, new acquired AVF's were demonstrated in three rats on angiography. The three AVF's were located on the dural sinus, face, and neck, respectively. Angiography of the rat with the dural sinus AVF demonstrated the following appearance. The right common carotid injection showed early opacification of the torcular herophili on the arterial and early capillary phases (Fig. 3). The left common carotid artery injection did not show the dural AVF but did reveal a patent superior sagittal sinus. Follow-up right common carotid angiography showed persistence of the patent dural AVF 1 week after ligation of the surgical shunt. Histopathological findings of the dural AVF showed thickening of the sinus walls with formation of many small vessels present within the sinus wall itself (Fig. 4). Sinus walls without angiographically proved dural AVF showed findings similar to those of dural AVF.

Bilateral carotid angiography in the remaining 21 rats showed normal arterial structures with the main veins draining into the right external jugular vein. Sinus thrombosis was not present angiographically.

**Group II Rats**

In the 13 Group II rats with a carotid artery-jugular vein shunt with proximal external jugular and contralateral posterior facial vein occlusion, left common carotid angiography prior to shunt ligation demonstrated a high-flow AV shunt. Opacification of the venous system was more marked than in Group I rats. Veins in the facial region were more prominently demonstrated and accounted for intense facial swelling in this group. The venous drainage pattern was also different from Group I. The dural sinuses as well as veins of the anterior section of the head, such as the superficial temporal vein, drained to the vertebral veins or via the anterior facial vein to the external jugular vein. Left common carotid angiography showed opacification of the arterial system, and right common carotid angiog-
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A relatively large number of animals were necessary for this study since the rate of developing dural AVFs was thought to be quite low, judging from the fact that not all patients with venous hypertension or sinus thrombosis develop dural fistulas. Only male rats were used in this study in order to exclude any potential effects of hormones, such as estrogen, that may also be a major factor contributing to the formation of a dural AVF.\(^\text{18}\)

In this study, we concluded that only venous hypertension without thrombosis could cause development of these new acquired AVFs. This was demonstrated in our model since there was no pre-existing thrombosis in the area where the AVF developed on angiography. However, our results do not refute the fact that sinus thrombosis may be a predisposing factor of dural AVFs. This experiment was designed only to investigate whether venous hypertension can cause AVFs.

Acquired AVFs were located in the face, neck, or dural sinus in the rats in our series. The reason for the development of AVF’s due to venous hypertension in multiple areas, including the dural sinus and soft tissue, is because venous hypertension was not restricted to the dural sinus only but also included the entire rat’s head, the brain, and soft tissues of the face. Therefore, development of the various fistulas was not specific for dural sinuses but included many of the areas in which venous hypertension was induced.

Follow-up studies of the acquired AVFs were examined in three rats. One of the dural AVFs remained open at least 1 week after ligation of the surgical shunt. The other two AVFs were shown to have spontaneously closed on follow-up angiography performed 3 weeks and 3 months, respectively, after ligation of the surgical shunt. The appearance of AVF’s was not thought to be an immediate phenomenon just after reversal of the venous hypertension, since patency of an acquired AVF for at least 1 week was confirmed angiographically in one case.

The spontaneous cure of dural AVFs is also well known in reported clinical series of fistulas, and as also shown in two AVF rats we examined.\(^\text{15}\) Further studies will be necessary to examine the natural course of these newly formed AVFs for the purpose of demonstrating whether they enlarge and cause clinical signs or whether they spontaneously thrombose.\(^\text{1,9,13,14,21}\)

The Group II rats demonstrated that the appearance rate of dural AVFs increased according to the elevation in venous pressure. Bederson, et al.,\(^\text{7}\) reported that mean torcular pressure was increased from 13.5 ± 1.1 to 34.8 ± 2.1 mm Hg by occluding venous outflow in rats in a carotid artery-jugular vein anastomosis study, although the common carotid artery and external jugular vein were anastomosed end-to-end in their model. However, statistical differences were not proved between Group I and II animals in our series, although the rate of development for AVF’s was higher in Group II than in Group I rats. We speculated that the venous pressure is already high enough even in Group I rats to develop AVF’s, judging from the angiographic find-

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Fig. 4. Histopathological findings of the superior sagittal sinus in the Group I rat with a dural arteriovenous fistula. An enlarged superior sagittal sinus and marked thickening of the sinus wall are seen. There are numerous dilated vessels located within the sinus wall. H & E, × 118.

raphy did not demonstrate the apparent steal phenomenon as revealed in Group I animals.

After ligation of the surgical AV shunt, three rats were found to have developed newly formed AVF’s, and follow-up angiography was performed in two of them. The fistulas were located in various parts of the face in the subcutaneous tissue. A left facial AVF was demonstrated by injection of the left common carotid artery showing early opacification of the dilated vein in the rat’s face. Follow-up angiography was performed on two rats; in one, an angiogram obtained 3 months after the first angiogram revealed spontaneous obliteration of the AVF. In the second rat, with a nose AVF, follow-up angiography 4 weeks after the first angiogram also demonstrated spontaneous obliteration of the fistula.

**Group III Rats**

The 11 Group III rats underwent unilateral external jugular vein occlusion, nine with and two without contralateral posterior facial vein occlusion. No new or acquired AV shunts were demonstrated in this control group.

**Discussion**

Chronic venous hypertension in a rat model was created by the surgical anastomosis of the carotid artery to the jugular vein with proximal jugular vein occlusion; the rat was then allowed to mature for 2 to 3 months. This period of chronic venous hypertension was based on our clinical experience that some patients with AVF developed their clinical symptoms a few months after an influenza-like inflammatory syndrome. Following anastomosis, angiography was performed to confirm the development of any new and acquired AVF’s after ligation of the surgical carotid artery-jugular vein shunt. Selective angiography was able to confirm the development of AVF’s in our model.
ings that demonstrated a tremendous amount of venous shunting in the rats’ head and face.

We propose that there may be several reasons for venous hypertension inducing formation of a dural fistula. The capillaries in the sinus or venous wall are similar to the vasa vasorum. Venules connect the capillaries to the sinus and are very short, judging from the anatomical structures of the dural sinuses. This anatomical structure is present in the usual venous system and vasa vasorum around the venous wall, and are believed to drain directly into the vein. Therefore, the elevated venous pressure in the dural sinus or vein would be transmitted directly to the capillaries and arterioles, while elevated arterial pressure would not be transmitted easily to these vessels by an arterial contraction mechanism, unless pressures were extremely high. Exposure of these vessels to venous hypertension via a retrograde route, in a sustained period, may result in the dilatation of the vessel caliber and loss of the sphincter control function in arterioles. These vasodilator changes are observed in the breakthrough phenomenon described in severe arterial hypertension. Vasodilatory changes caused by venous hypertension may not recover even after relief from hypertension; therefore, development of new AVF’s may occur.

A second possibility for formation of a dural AVF is that increased intraluminal pressure in the vessels stimulates angiogenesis and results in thickening of the vessel walls and appearance of new vessels around the vascular wall. This phenomenon is well known in arteries under long-standing hypertension. If new vessels were formed around the sinus or venous wall, there might also be formation of direct connections to the sinus or vein resulting in the development of a dural fistula.

A third factor is that the increase in venous pressure also causes reduction of perfusion pressure, resulting in tissue hypoxia. It is known that tissue hypoxia stimulates angiogenesis. Stimulated angiogenic factors, such as basic fibroblast growth factor, may develop new vessels in the sinus or venous wall and induce the AVF’s.

A fourth reason for venous hypertension inducing formation of a dural fistula is that microscopic communications exist between arteries and veins in normal dura mater at the level of the venous sinuses. These minute AV shunts, which are normally present within the dura mater, might enlarge in the presence of increased venous pressure leading to angiographically significant AV shunting. However, we do not know why these minute AV shunts are not normally demonstrated even on superselective angiography, nor do we understand their function under normal conditions.

In humans, fistulas of the dural AVF can be multiple and located within the sinus walls. There are many speculations as to why acquired dural AVF’s may occur; however, our animal model demonstrates that chronic venous hypertension can produce fistulas of the dural sinus as well as soft tissues of the head, neck, and face. Further detailed histological data using our model should help to clarify the exact mechanism for the development of dural AVF’s in future studies.

References

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