Neovascularization in acute venous thrombosis

Nicos Labropoulos, PhD, DIC, RVT, Ahmad F Bhatti, MD, RVT, Salomon Amaral, MD, Luis Leon, MD, RVT, Marc Borge, MD, Heron Rodriguez, MD and Peter Kalman, MD, Maywood, Ill

Objective: The aim of this study was to describe the phenomenon of arteriovenous fistula (AVF) formation in venous thrombus.

Methods: Patients referred to the vascular laboratory for evaluation for deep venous thrombosis were included. Duplex ultrasound scanning was used to detect flow within the thrombus. The flow patterns and the resistivity index were obtained in the veins above/proximal and below/distal to the thrombus, in the adjacent arteries, and within the perivenous vessels. Patients with trauma, hemodialysis access, endovenous ablation, known AVF, or inflammatory conditions were excluded.

Results: There were 22 patients with AVF flow in thrombosed veins. Deep veins were involved in 15 cases and superficial veins in the remainder. Perivenous vessels feeding the AVF in the thrombus could be clearly identified in 16 patients (19 vein segments). In 21 of 22 patients, multiple flow channels were present throughout the involved thrombosed vein segment. These flow channels were isolated to a single vein segment. They measured <4 cm in length in 19 cases and were more extensive in the remaining three. Reflux within the vein segment was identified in 13 cases. Local symptoms that could be attributed to the arterIALIZED thrombosed veins occurred in four cases, and none of the patients manifested systemic symptoms. The flow within the thrombus had high end-diastolic velocities with a mean resistivity index of 0.48 (SD, 0.08), which is typical of a fistula flow pattern. The flow in the main arteries was unaffected.

Conclusion: Neovessels were found with AVF flow in thrombi of superficial and deep veins. They had variable length and multiple flow channels, with inflow from perivenous arteries. The flow in the adjacent main arteries was not affected, and no systemic symptoms were detected. The exact etiology and natural history of this phenomenon are not known, and its clinical significance is unclear. (J Vasc Surg 2005;42:515-8.)

Few reports exist regarding vascular remodeling of venous thrombi, and the available data are largely from animal studies. Spontaneous arterial flow in veins with recanalized thrombosis has been described in only one report. These events occur in the acute setting of venous thrombosis has been described in only one report. These events occur in the acute setting of venous thrombosis, and the exact etiology and natural history of these spontaneous arterialized venous thrombi are not known. This process is likely secondary to an inflammatory mediated response that occurs with venous thrombosis. Neovascularization has been shown to occur in thrombus remodeling; however, arteriovenous fistulae (AVF) have not been previously described in such thrombi. This study describes the clinical presentation and development of AVF within venous thrombi and their effects on the adjacent blood vessels.

PATIENTS AND METHODS

Patients with signs or symptoms of acute deep venous thrombosis (DVT) were sent to the vascular laboratory for duplex ultrasound (DU) evaluation. Linear array multifrequency transducers 4 to 7 MHz, 4 to 8 MHz, and 5 to 12 MHz were used with HDI 5000 and 122 scanners (Philips Medical Systems, Bothell, Wash). Our protocol for assessing DVT includes vein compression, color flow imaging, and Doppler examination of the superficial and deep veins. Those patients in whom arterial flow in thrombosed venous segments was identified were evaluated for the source of arterial flow, the extent and location of this flow, the appearance of arteries, and flow direction in proximal and distal vein segments.

The diameter of the flow channels was measured, and when the wall was not visible on B-mode, color flow was used to determine the caliber. The peak systolic (PSV) and end-diastolic velocities (EDV) were recorded, and the resistivity index (RI) was used to characterize the flow pattern by using the formula (PSV–EDV)/PSV. Excluded from the study were patients with lower-extremity catheterization, penetrating trauma, hemodialysis access, a history of endovenous ablation, known AVF, or inflammatory conditions.

All patients with DVT were anticoagulated with unfractionated heparin or low-molecular-weight heparin and warfarin. Those with superficial thrombosis were treated with nonsteroidal anti-inflammatory drugs or aspirin. Compres- sion was prescribed in both groups of patients. The prevalence of the AVF among patients with lower-extremity DVT was not calculated, as not all the patients were looked at in detail for this condition. No follow-up studies were performed. Descriptive statistics were used for the analysis of patient and AVF characteristics.

RESULTS

There were 22 patients (13 men, 9 women) with AVF in thrombosed veins, and their mean age was 60 years (range, 27 to 99). All patients had acute or acute-on-chronic thrombosis (days to weeks). Thirteen were identified in the right lower extremity and nine in the left. The
distribution and location of the AVF in the different veins is summarized in the Table. Most AVF (17 of 25) were found in the proximal veins. Feeder vessels, small perivenous arteries supplying blood through the venous wall (vasa vasorum) into the thrombus, could be identified in 16 cases (Fig 1). The flow in these arteries was enhanced, and the reverse flow was absent.

There were 25 involved vein segments in 22 patients. One of the patients with great saphenous vein AVF had also involvement of the posterior arch vein in the upper medial calf. This was in continuity with the AVF in the great saphenous vein. Another case involved the common femoral, deep femoral, and femoral veins.

Table. Distribution of AVF in the different veins in the lower extremity

<table>
<thead>
<tr>
<th>Vein segment</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common femoral</td>
<td>8</td>
<td>32</td>
</tr>
<tr>
<td>Popliteal</td>
<td>5</td>
<td>20</td>
</tr>
<tr>
<td>Great saphenous</td>
<td>4</td>
<td>16</td>
</tr>
<tr>
<td>Femoral</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>Posterior arch</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Deep femoral</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Lateral thigh</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Small saphenous</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>25</td>
<td>100%</td>
</tr>
</tbody>
</table>

Local symptoms such as tenderness, pain, or swelling could be attributed to the AVF in thrombosed veins in four cases, and systemic manifestations were absent in all patients.

The flow within the thrombus had high end-diastolic velocities, with an average RI of 0.48 (SD, 0.08), which is typical of a fistula flow pattern. The flow in the involved vein immediately above and proximal to the fistula was pulsatile and dissipated more proximally (Fig 3). The flow in the adjacent main arteries was unaffected (Fig 4). In the veins immediately proximal to the AVF, the flow was high enough to keep the venous valves continuously open. Reflux was found in 13 cases. It was localized in one, distal to the AVF in three, and both proximal and distal to the AVF in nine cases. Flow in the AVF within the thrombus could be cephalad, retrograde, or both, because multiple channels were formed in either direction.

The flow characteristics of the AVF within superficial vein thrombi were similar to those identified in the deep veins. The sequence of events leading to the AVF development became more evident in a patient with superficial venous thrombosis (SVT) who had one DU examination before the thrombus and three after. The details of this are explained in Fig 5. Findings were not verified by any histologic, surgical, or contrast-imaging modalities.

**DISCUSSION**

Spontaneous AVF formation with recanalized DVT or SVT has not been previously described, and therefore, the etiology of this process has not been investigated. We theorize that inflammation and neovascularization play predominant roles in the development of AVF. Inflammation in association with venous thrombosis has been shown to be reproducible in animal models.8,9 The important role of inflammatory mediators and the immune system in DVT formation have also been well described.2,3
Neovascularization is part of thrombus remodeling and involves monocytes, neutrophils, and other immunologic cells that are recruited in the inflammatory process. Ani- mal models of venous thrombosis have revealed positive staining of various endothelial markers in recanalized thrombus. Wakefield et al first related recanalization to angiogenesis and hypothesized that it is neovascularization and not thrombus retraction, absorption, or lysis that results in recanalization. However, all of these mechanisms may be involved in the remodeling process. Additionally, an increase in vascular endothelial growth factor has also been identified as constituent of normal venous thrombus remodeling.

In our patients, multiple small vessels with arterial signals were found directly adjacent to the involved vein segments, forming multiple small AVF within the thrombus. Vessels that were outside the thrombus could be differentiated from those traversing it. Vasodilation and local hyperdynamic flow created by inflammatory mediators may contribute to this process of vasa vasorum recruitment, enlargement, and growth.

Neovascularization may also play an important role in the creation or growth of these vessels. Arterial and venous vasa vasorum exist in veins, arise at several levels from adjacent perforating arteries (arterial vasa), and undergo alterations with thrombosis. Other vessels, such as peri- venous capillaries or venules, may also undergo transformation and participate in the phenomenon. Cavernous transformation of portal vein thrombosis (CTPVT) is well described. Gross pathology and histopathology studies have revealed numerous dilated thin vessels that form with this process. Although AVF have not been described in CTPVT, the underlying remodeling process may be similar.

Isolated arterial signals with DU scanning in recana- lized thrombus were described in a report by Kroger et al. In an attempt to study the process of revascularization of thrombosed veins, they prospectively followed 15 newly diagnosed DVT with DU scans every second or third day for 4 weeks. They found arterial signals in 53% of DVT between days 11 and 25. All signals were transient, had no apparent source or arterial vessels outside the vein, and occurred only at the periphery of the thrombi.

Our cases differ in that the intrathrombus flow was characterized as AVF and the feeding source was found to be small perivenous arteries. Additionally, these AVF were found throughout the thrombus and not only in the periphery. Kroger et al postulated that the origin of the inflow might be the vasa vasorum or capillaries, but they did not believe these small vessels could provide enough flow to produce the arterial signals they had observed.

In our patients, AVF occurred with both DVT and SVT. AVF are most commonly found in the common femoral vein and popliteal vein. Feeder vessels were identified in most cases, and flow occurred through several channels in the thrombus in all but one case. None of the patients manifested systemic symptoms, and most were asymptomatic with respect to this specific entity. This observation is evidence that the AVF must consist of relatively...
low flow because they have no apparent impact on the adjacent systemic arteries. On DU examination, the arterial signals in the thrombus had a high diastolic flow and low RI consistent with the low outflow resistance that one would expect in the venous segment of an AVF. Such enhanced flow has been described in patients with acute and chronic inflammation.16,17

CONCLUSION

Because the formation of AVF after DVT or SVT has not been previously described, all occurrences of this phenomenon may not have been recorded. Additionally, only larger AVF were likely to have been identified as a pathologic finding. Furthermore, with the advancement of DU technology and our recent focus on this phenomenon, we were able to find most of the cases recently. This has likely led to a significant underestimation of the actual incidence of this phenomenon. A prospective study with close follow-up on the remodeling of the thrombus and the evolution of flow characteristics is warranted to further evaluate and better understand this process and its impact on venous disease.

REFERENCES


Submitted Mar 15, 2005; accepted May 15, 2005.