Transdural arterial recruitment to brain arteriovenous malformation: clinical and management implications in a prospective cohort series

David Bervini, MD, MAdvSurg,1,2 Michael Kerin Morgan, MD,2 Marcus Andrew Stoodley, PhD,2 and Gillian Ziona Heller, PhD3

1Department of Neurosurgery, Inselspital, Bern University Hospital, Bern, Switzerland; and Departments of 2Clinical Medicine and 3Statistics, Macquarie University, Sydney, New South Wales, Australia

OBJECTIVE The occurrence of transdural arterial recruitment (TDAR) in association with brain arteriovenous malformation (bAVM) is uncommon, and the reason for TDAR is not understood. The aim of this cohort study was to examine patient and bAVM characteristics associated with TDAR and the implications of TDAR on management.

METHODS A prospective surgical database of bAVMs was examined. Cases previously treated elsewhere or incompletely examined by digital subtraction angiography (DSA) assessment were excluded. Three studies of this cohort were performed, as follows: characteristics associated with TDAR, the relationship between TDAR and neurological deficits unassociated with hemorrhage (NDUH), and the impact of TDAR on outcome from surgery. Regression models were performed.

RESULTS Of 769 patients with complete DSA who had no previous treatment, 51 (6.6%) were found to have TDAR. The presence of TDAR was associated with increasing age (p < 0.01; OR 1.05; 95% CI 1.02–1.07); presentation with NDUH (p < 0.01; OR 2.71; 95% CI 1.29–5.71); increasing size of the bAVM (p < 0.01; OR 1.57; 95% CI 1.29–1.91); and combined supply from both anterior and posterior circulations (p = 0.02; OR 2.37; 95% CI 1.17–4.78). Further analysis of TDAR cases comparing those with and without NDUH found an association of larger size (6.6 cm [2.9 SD] compared with 4.7 cm [1.8 SD]; p < 0.01) and combined supply from both anterior and posterior circulations (relative risk 2.5; 95% CI 1.0–6.2; p = 0.04) to be associated with an NDUH presentation.

For the 632 patients undergoing surgery there was an increased risk of complications (where this produced a new permanent neurological deficit at 12 months represented by a modified Rankin Scale score of > 1) with the following variables: size; location in eloquent brain; deep venous drainage; increasing age; and no presentation with hemorrhage. The presence of TDAR was not associated with an increased risk of complications from surgery.

CONCLUSIONS The authors found that TDAR occurs in older patients with larger bAVMs, and that TDAR is also more likely to be associated with bAVMs presenting with NDUH. The likely explanation for the presence of TDAR is a secondary recruitment arising as a consequence of shear stress, rather than a primary vascular supply present from the earliest development of the bAVM.

https://thejns.org/doi/abs/10.3171/2016.5.JNS16730

KEY WORDS brain; arteriovenous malformation; AVM; prospective cohort; artery; dura mater; vascular disorders
moya disease. Because meningeal arteries do not supply the brain under normal conditions, it cannot be assumed that TDAR in association with a bAVM is due to the same mechanisms responsible for recruitment by the bAVM of arteries normally supplying the brain. It has yet to be established whether TDAR arises as a primary development with the bAVM, or as a secondary development in response to stimuli created by the bAVM.

The aim of this study was to examine cases of bAVM in patients with a complete digital subtraction angiography (DSA) assessment who had received no previous potentially effective treatment. These cases were drawn from a consecutively enrolled, prospectively collected database and examined for evidence that may shed light on the association of TDAR and bAVM.

**Methods**

**Patient Population**

The study was approved by the institutional ethics committee and was performed in accordance with the committee’s guidelines. A consecutive database of 802 cases of bAVM enrolled between 1989 and 2015 was retrospectively analyzed. The senior author (M.K.M.) prospectively collected data on all consecutively enrolled patients with bAVM in a specifically designed bAVM database that included clinical and radiological data. All patients presenting with complete DSA studies prior to any treatment and patients with no prior intervention for bAVM were analyzed. Cases were prospectively allocated into 1 of 3 reasons for presentation: 1) hemorrhage; 2) bAVM-related neurological deficit unassociated with hemorrhage (NDUH); and 3) neither hemorrhage nor neurological deficit. The NDUH group excluded patients presenting with hemorrhage (past or present), seizures, migraine, or other causes of neurological deficits unassociated with bAVM (e.g., previous head injury). A neurological deficit was said not to exist, for the purpose of this analysis, if neurological symptoms occurred in the absence of confirmatory evidence of a deficit on clinical examination, or when neurological deficits were present only during seizures or migraines. The neurological deficit and the presumed cause of the NDUH were recorded prospectively. The cause of NDUH was recorded to be due to the following: raised intracranial pressure (papilledema associated with visual loss); focal venous hypertension (neurological deficit relevant to brain, with CT brain or MRI changes consistent with venous occlusion); or no definite cause identified. The modified Rankin Scale (mRS) score was reported at the time of first visit and at last follow-up.

Patients were excluded from analysis if they had been partially treated by surgery, endovascular treatment, or focused irradiation prior to enrollment in the database (Fig. 1). The second author had responsibility for the patients’ assessment and entry into the database. The database was accessible to residents, fellows, and occupational therapists at the time of assessment and follow-up.

**Characteristics Examined**

In the current study, the following bAVM morphological and patient characteristics were assessed: sex; age of patient; eloquent location (as per the Spetzler-Martin [SM] grading system—i.e., located in primary sensory cortex, motor cortex, language cortex, internal capsule, diencephalon, brainstem, deep cerebellar nuclei, or cerebellar peduncle); maximum diameter (measured as maximum...
nidus diameter in centimeters on pretreatment MRI, CT angiography, or DSA); deep venous drainage; infratentorial location; presence of TDAR between the meningeal arteries and the bAVM (e.g., Fig. 2); presence of posterior circulation arterial feeders; and presence of anterior circulation arterial feeders.

Outcome Assessments
Outcome assessment was performed using the mRS, which was administered preoperatively and at follow-up visits. A complication of surgery was considered to be a new permanent neurological deficit assigned within 6 weeks of surgery and an mRS score of >1 at 12 months.

Statistical Analysis
For comparisons between any 2 groups, the Fisher exact test, Mann-Whitney test, and t-test were performed when appropriate. Relative risks were computed. From the outcome of these tests, the variables identified as significant were further analyzed by multiple logistic regression (backward Wald) to identify characteristics associated with presentation with TDAR. In addition, a variable identified in previous studies as significant (i.e., age$^1$) was also included in the multiple logistic regression.

Due to the large number of comparisons, a statistical significance level of 1% was used throughout. The modified Wald method was used to calculate the 95% confidence interval for a proportion (www.graphpad.com/quickcalcs/) for the outcome data. Statistical analysis was performed using Prism (version 6, GraphPad Software, Inc.) and IBM SPSS Statistics (version 22, IBM Corp.) software.

Results
Univariate Analysis of Characteristics Associated With the Presence of TDAR
Of the 802 bAVMs in the database, 33 were excluded from analysis due to either incomplete DSA studies or previous partial treatment by surgery, radiosurgery, or embolization. Of the 769 patients with complete DSA who had no previous treatment, 51 (6.6%) were found to have TDAR. The characteristics examined when comparing those with TDAR and those without it are reported in Table 1.

The risk of TDAR was found to be significantly associated (at the 1% significance level) with the following personal characteristics: no hemorrhage (relative risk [RR] 0.4, 95% CI 0.2–0.8); NDUH (RR 6.0, 95% CI 3.6–9.9); and a history of 3 or more seizures (RR 2.9, 95% CI 1.7–5.1).

With regard to bAVM characteristics, those with TDAR had a larger size (5.5 cm [SD 2.5 cm] versus 3.3 cm [SD

FIG. 2. Neuroimages obtained in a 50-year-old woman presenting with neurological deficit from brainstem compression caused by a proximal feeding artery aneurysm. Axial T2-weighted MRI study (A), left lateral vertebral (B), and anteroposterior vertebral (C) DSA studies with early (D) and late (E) lateral left external carotid artery DSA studies demonstrating meningeal feeding arterial contribution to an occipital bAVM.
1.6 cm], p < 0.01), and TDAR was significantly associated with having deep venous drainage (RR 2.6, 95% CI 1.5–4.5); posterior circulation (RR 3.1, 95% CI 1.8–5.3); simultaneously both an anterior and posterior circulation supply (RR 3.0, 95% CI 1.8–5.1); and not being classified as an SM Grade I or II bAVM (RR 0.2, 95% CI 0.1–0.4).

The mean age of patients with TDAR was 43 years (SD 14 years), which was significantly older than the mean age of those without TDAR (37 years; SD 16 years) (p = 0.02). No patient with TDAR was younger than 16 years of age.

**Multivariate Analysis of Characteristics Associated With the Presence of TDAR**

Multiple logistic regression found that the presence of TDAR was associated with increasing age (p < 0.01; OR 1.05, 95% CI 1.02–1.07); presentation with NDUH (p < 0.01; OR 2.37, 95% CI 1.17–4.78) (Table 2). Presentation with 3 or more seizures, deep venous drainage, and posterior circulation supply were not associated with the presence of TDAR.

**Univariate Analysis of Patients With TDAR for Characteristics Associated With NDUH**

Further analysis of all patients with TDAR identified that the presence of NDUH was associated with larger bAVM size (6.6 cm [2.9 cm SD] versus 4.7 cm [1.8 cm SD]; p < 0.01) and combined supply from both anterior and posterior circulations (RR 2.5, 95% CI 1.0–6.2; p = 0.04) (Table 3).

**Risk of Complications From Surgery**

Because the univariate analysis suggested an association between TDAR and new neurological deficit following surgery (or preoperative embolization with an intention to treat by surgery) (Table 1), this association was further explored by multiple logistic regression to ac-
count for the differing incidence of variables known to influence the complication incidence. This was done both for all 632 patients undergoing surgery (or preoperative embolization followed by an intention to treat with surgery) in whom complete preoperative DSA studies were available and who had undergone no previous treatment (by surgery, radiosurgery, or embolization) prior to entry into the database, as well as for the subset of patients with SM Grades I–III. Analysis of the subset of patients with SM Grades I–III was performed separately because this group was previously identified as being generalizable to all patients with SM Grades I–III, both those undergoing surgery and those not undergoing surgery. In contrast, in those patients with SM Grades IV and V bAVMs undergoing treatment, the selection is highly biased.

This second analysis by multiple logistic regression disclosed that TDAR was not associated with an increased risk of complications from surgery. Increased risk of complications from surgery (where this produced a new permanent neurological deficit at 12 months of either an mRS score of > 1 or > 2) was associated with the following: size; location in eloquent brain; deep venous drainage; increasing age; and the absence of presentation with hemorrhage. The details of this association are given in Table 4 for both complications leading to an mRS score of > 1 at 12 months. Diffuseness was not included in this analysis because it was not recorded prospectively in the database.

**Discussion**

We found TDAR present in approximately 7% of patients with a bAVM. Although reported as early as 1966, the difficulty in discriminating dural arteriovenous fistula (AVF) from bAVM before the advent of selective angiography almost certainly explains the high proportion (21%) of bAVMs with TDAR reported in early series. Our study found that TDAR was more likely to be present in older patients, those with a larger bAVM, presentation with NDUH, and supply from both anterior and posterior circulations (as opposed to either anterior or posterior circulation alone). This parallels Koo and colleagues’ report on 124 superficially located bAVMs (from 438 cases) in which 32 with TDAR were identified. This represents 7% of their entire cohort and agrees with our incidence. Similar to our findings, Koo and colleagues found older age and larger size were significantly associated with TDAR in the subgroup of superficial bAVMs.

**Hypothesis for Development of TDAR**

Three possible explanations for the occurrence of TDAR include 1) development of TDAR at the generation of the bAVM; 2) recruitment of the transdural arteries as collateral vessels to ischemic brain that subsequently enlarge to supply the bAVM—the driver for this process is bAVM-induced hypoxia inducing angiogenesis; and 3) recruitment of the transdural arteries, after bAVM establishment, to arteries directly supplying the bAVM—the driver for this process is bAVM-induced high wall shear stress (WSS) causing angiogenesis and arteriogenesis. Of these 3 explanations, we hypothesize that the third one, WSS-induced angiogenesis and arteriogenesis, best explains the

**TABLE 2. Summary of multivariate binary logistic regression for the presence of TDAR for 769 patients with bAVM, complete DSA, and no prior treatment**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Binary Logistic Regression for the Presence of TDAR (p value)</th>
<th>OR (95% CI) for Variables w/ p &lt;0.01 in Univariate Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in yrs</td>
<td>&lt;0.01</td>
<td>1.05 (1.02–1.07)</td>
</tr>
<tr>
<td>Preop &gt;2 seizures</td>
<td>0.74</td>
<td></td>
</tr>
<tr>
<td>Preop NDUH</td>
<td>&lt;0.01</td>
<td>2.71 (1.29–5.71)</td>
</tr>
<tr>
<td>Size in cm</td>
<td>&lt;0.01</td>
<td>1.57 (1.29–1.91)</td>
</tr>
<tr>
<td>Deep venous drainage</td>
<td>0.06</td>
<td>1.87 (0.96–3.64)</td>
</tr>
<tr>
<td>Pst circulation supply</td>
<td>0.40</td>
<td></td>
</tr>
<tr>
<td>Both ant &amp; pst circulation supply</td>
<td>0.02</td>
<td>2.37 (1.17–4.78)</td>
</tr>
</tbody>
</table>
findings in our series. The reasons for this include the following.

1. Is there evidence for TDAR developing after bAVM formation? Those diagnosed with TDAR were significantly older than those without TDAR, and no TDAR cases were identified in patients under the age of 16 years. Although bAVMs may develop after birth, the absence of TDAR in younger patients and the difference in age at diagnosis suggests that TDAR develops after the bAVM has been established.

2. Is there evidence that feeding arteries can contact the dura mater and be in a position to form anastomoses? Our experience of resecting bAVMs with dural attachment indicates that the point of vascular contact between bAVM and dura is directly over the bAVM, often in the center, rather than beyond the bAVM margins in adjacent, putatively ischemic brain. Contacts could either be due to enlargement of small bridging arteries that are known to exist and that are collateralized to the bAVM, or they could be due to the formation of new arteries from direct contact of the feeding arteries with the dura, which can arise as a consequence of their elongation and tortuosity. For existing collaterals to be of significance, one would expect no difference in patient age between parenchymal arteries and TDAR; however, measuring WSS is very difficult. In pulsating arteries, the precise identification of the wall with current radiological methods is extremely difficult. Such identification is critical when calculating WSS as well as the variation in WSS during the cardiac cycle. Normal WSS of approximately 11, 19, 21, and 22 dyne/cm² in the internal carotid artery, basilar and posterior cerebral arteries, anterior cerebral artery, and middle cerebral artery, respectively, has been reported. The WSS has been reported to be higher in arteries feeding and proximal to a bAVM than in the contralateral corresponding arteries. However, this is not found in all cases.

5. Is there evidence that AVMs can induce new vessel formation? Rat and mouse models of AVFs both induce sprouting angiogenesis related to a nonhypoxic increase in WSS unrelated to the pulsatile pressure. Furthermore, these new vessels have many of the histological findings of bAVM vessels. This mechanism may underpin the development of TDAR in bAVMs.

The association with NDUH may suggest an alternative hypothesis: that of recruitment of transdural arteries as collateral vessels in response to ischemic brain. This is likely to be the explanation for another TDAR disease state, moyamoya syndrome. Furthermore, the majority of cases of NDUH may be caused by hypoperfusion in our series. However, there may be significant differences in the mechanism of hypoperfusion caused by moyamoya and that associated with bAVMs. The hypoperfusion in brain adjacent to a bAVM is related to a combination of arterial hypotension and venous hypertension. The latter is not present in moyamoya. There is no evidence that venous hypertension-induced NDUH associated with dural AVF and retrograde parenchymal venous drainage can lead to TDAR. Therefore, it cannot be assumed that the bAVM can produce a similar driver for TDAR as is the case in moyamoya. The localization of the TDAR connection immediately over the center of most bAVMs, where there is no functioning brain or microcirculation to be responsive to hypoxia-induced angiogenesis, raises doubt as

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No Preop NDUH</th>
<th>Preop NDUH</th>
<th>p Value*</th>
<th>RR of Cases w/ NDUH for Characteristic; 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of pts</td>
<td>29</td>
<td>22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% female: 95% CI (no.)</td>
<td>55%; 38–72% (16)</td>
<td>41%; 23–61% (9)</td>
<td>0.40</td>
<td></td>
</tr>
<tr>
<td>Age in yrs: mean ± SD</td>
<td>43 ± 14</td>
<td>42 ± 14</td>
<td>0.74</td>
<td></td>
</tr>
<tr>
<td>Preop &gt;2 seizures: %; 95% CI (no.)</td>
<td>24%; 12–42% (7)</td>
<td>45%; 27–65% (10)</td>
<td>0.14</td>
<td></td>
</tr>
<tr>
<td>Size in cm: mean ± SD</td>
<td>4.7 ± 1.8</td>
<td>6.6 ± 2.9</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>Deep venous drainage: %; 95% CI (no.)</td>
<td>59%; 41–75% (17)</td>
<td>68%; 47–84% (15)</td>
<td>0.57</td>
<td></td>
</tr>
<tr>
<td>Elloquent: %; 95% CI (no.)</td>
<td>52%; 34–69% (15)</td>
<td>55%; 35–73% (12)</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>Infratentorial: %; 95% CI (no.)</td>
<td>21%; 9.5–39% (6)</td>
<td>36%; 20–57% (8)</td>
<td>0.44</td>
<td></td>
</tr>
<tr>
<td>SM Grades I &amp; II: %; 95% CI (no.)</td>
<td>24%; 12–42% (7)</td>
<td>14%; 3.9–34% (3)</td>
<td>0.48</td>
<td></td>
</tr>
<tr>
<td>Lt side: %; 95% CI (no.)</td>
<td>48%; 31–66% (14)</td>
<td>59%; 39–77% (13)</td>
<td>0.57</td>
<td></td>
</tr>
<tr>
<td>Both ant &amp; pst circulation supply: %; 95% CI (no.)</td>
<td>52%; 34–69% (15)</td>
<td>82%; 61–93% (18)</td>
<td>0.04</td>
<td></td>
</tr>
</tbody>
</table>

* Fisher’s exact test, t-test, or Mann-Whitney test comparing groups with and without NDUH.
to whether hypoxic brain could be a catalyst in the case of bAVM. Chang and colleagues reported that symptomatic bAVMs were more likely than asymptomatic bAVMs to have an increased WSS in the feeding artery. This can be explained by the association between increased WSS and lower arterial pressure.

Continued angiogenesis and arteriogenesis subsequent to the formation of a bAVM from high WSS may allow an avenue of potential therapy for bAVM other than by anatomical extirpation. Such a dynamic process may facilitate therapeutic targets. A recent proposal targeting the production of vascular endothelial growth factor with miRNA-18a suggests the feasibility of such an approach.

### Presence of TDAR and the Risk of Surgery

Although we have previously reported our outcomes, we reexamined the cohort to exclude patients who had been partially treated by some other means previously. Transdural arterial recruitment was associated with a greater risk of surgery. However, when the presence of TDAR was adjusted for variables known to have an impact on surgical outcomes (variables associated with SM grade, age, and presentation with hemorrhage), there was no increased risk of surgery. In contrast to our previous report, age was found to be significant. These data reinforce the role of the Lawton-Young grading scale, with the exception of the variable “diffuseness” that was not ascribed in a prospective manner to the database interrogated. Although we found that TDAR was not a risk factor for adverse outcomes after surgery, this is not to say that adjustment to surgical technique is not necessary. The primary concern to the surgeon in the presence of TDAR is that retracting the dura from the surface of the bAVM can result in a tear of the lesion (or of the feeding arteries) that can lead to catastrophic hemorrhage. In cases of TDAR supply, a strategy to avoid this problem is to incise the dura containing the TDAR connection to the bAVM at a considerable distance from the lesion. This eliminates both the TDAR supply and the tension at the point of connection. For a bAVM deriving a contribution from the falx, an interhemispheric approach from the contralateral side allows a dural window to be cut, leaving an island of dura attached to the bAVM. A similar strategy of remote incision of the dura can be made in the tentorium and the convexity dura, as required for other locations.

The limitations of cohort studies are well known. There is the problem of whether the cohort treated by the authors reflects the general population of patients with a bAVM. In our study patients were likely to include those with entities more surgically complex than simple bAVMs, reflecting referral bias to a center with expertise in cerebrovascular surgery. Furthermore, there are limitations with regard to the conclusions related to WSS. We have presented no direct data on WSS and have hypothesized its role based on inferential data. However, calculations of WSS are extremely difficult to make accurately with current techniques and were impossible to make for much of the period over which the cohort data were collected. A source of particular difficulty in the calculation of WSS is the imprecision in identifying the wall of the artery as well as accounting for the arterial pulsatility. This may best be answered with computational fluid dynamics, with input data derived from a variety of sources. This will be a future avenue of our research.

### Conclusions

Transdural arterial recruitment occurs in older patients with larger bAVMs, and TDAR is also more likely to be associated with bAVMs presenting with NDUH. The likely explanation for the presence of TDAR is a secondary recruitment arising as a consequence of shear stress rather than a primary vascular supply present from the earliest development of the bAVM.
Acknowledgments

We thank Dr. Elizabeth Anne Ritson, MBBS, for editorial assistance.

References


Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Morgan, Bervini. Acquisition of data: Morgan. Analysis and interpretation of data: all authors. Drafting the article: Morgan, Bervini, Stoddley. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Morgan. Statistical analysis: Morgan, Bervini, Heller.

Correspondence

Michael Kerin Morgan, Department of Cerebrovascular Neurosurgery, Macquarie University, 2 Technology Pl., Macquarie University, NSW 2109, Australia. email: michael.morgan@mq.edu.au.