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Original Article

Hemodynamic and Anatomical Factors in Arteriovenous Malformation Clinical Presentation: 45 Case Studies

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Abstract: ***Background:*** Hemodynamic factors have been implicated in hemorrhage from cerebral arteriovenous malformations (AVMs). The goal of this endovascular study is to analyze the hemodynamic variability in AVM feeders in a balanced group of ruptured and unruptured AVMs of various sizes and at both superficial and deep locations. ***Methods:*** We monitored feeder artery pressure (FP) using microcatheters in 45 patients with AVMs (16 with hemorrhage, 29 without) during superselective angiography and AVM embolization. ***Results:*** Mean FP was 49 mm Hg. Significant determinants of FP were the systemic pressure ($p < 0.001$), AVM size ($p = 0.03$), and the distance of the microcatheter tip from the Circle of Willis ($p = 0.06$), but not the presence of hemorrhage, patient age, or feeder artery diameter. The FP in ruptured AVMs was 7 mm Hg higher than in unruptured ones (53.8 mm Hg vs. 47.1 mm Hg, $p = 0.032$). The presence or absence of venous outflow stenosis and the position of the AVM nidus (superficial or deep to the cortical surface) were important anatomical predictors of AVM presentation. ***Conclusion:*** The pressure in the feeding artery supplying an AVM is the result of factors which include the systemic arterial pressure, the size of the AVM nidus, and the distance of the AVM from the Circle of Willis. The correlation between these variables makes it difficult to study the risk of hemorrhage as a function of a single factor, which may account for the variation in the conclusions of previous studies.

RÉSUMÉ : Facteurs hémodynamiques et anatomiques liés à des malformations artério-veineuses observées cliniquement : 45 études de cas. ***Contexte :*** On estime que des facteurs hémodynamiques peuvent être impliqués dans des cas d'hémorragie attribuables à des malformations artério-veineuses (MAV) cérébrales. L'objectif de cette étude endovasculaire est donc d'analyser la variabilité hémodynamique des artères nourricières en lien avec des MAV. Pour ce faire, nous avons compté sur un échantillon également réparti de MAV rompues et non rompues, de tailles diverses et situées à la fois en surface et en profondeur. ***Méthodes :*** Au moyen de micro-cathéters, nous avons surveillé la pression des artères nourricières (PAN) de 45 patients donnant à voir des MAV (16 avec hémorragies, 29 sans hémorragies) pendant des examens d'angiographie supersélectifs et lors de l'embolisation de ces MAV. ***Résultats :*** La PAN moyenne était de 49 mm Hg. Les déterminants significatifs de cette PAN ont été la pression systémique ($p < 0{,}001$), la taille des MAV ($p = 0{,}03$), la distance entre l'extrémité du micro-cathéter et le cercle de Willis ($p = 0{,}06$) mais pas la présence d'une hémorragie, l'âge des patients ou le diamètre des artères nourricières. La PAN dans des cas de MAV rompues s'est avérée plus élevée de 7 mm Hg que dans des cas de MAV non rompues (53,8 mm Hg contre 47,1 mm Hg ; $p = 0{,}032$). À noter que la présence ou l'absence d'une sténose affectant le débit sanguin de même que la position du foyer (*nidus*) de la MAV (superficielle ou profonde par rapport à la surface corticale) sont apparues comme des facteurs anatomiques prédictifs importants d'une MAV. ***Conclusion :*** La PAN d'une MAV est donc le résultat de facteurs tels que la pression artérielle systémique, la taille du foyer des MAV et la distance entre les MAV et le cercle de Willis. La corrélation entre ces facteurs rend difficile l'étude des risques d'hémorragie en fonction d'un seul d'entre eux, ce qui peut expliquer la variabilité des conclusions contenues dans des études précédentes.

Keywords: Arteriovenous malformation; Feeding pressure; Hemodynamics; Intracranial hemorrhage; Seizure

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Introduction

Since 1980, neurosurgeons have measured intraoperative feeder artery pressure (FP) in cerebral arteriovenous malformations (AVMs) to correlate hemodynamics with clinical presentation, particularly with respect to hemorrhage.[1–4] Early studies used small needles inserted into cortical feeders. It was found that FP is usually well below systemic pressure (SP) and that the lowest FP is in feeders ≥ 8 cm from the Circle of Willis.[1] In one early study, 2 ruptured AVMs had FPs of 70 and 71 mm Hg, while 3 unruptured ones had FPs of 30, 34, and 42 mm Hg.[5] Another study found the same pattern, but small AVMs were also found to have higher FPs than large ones.[4] These studies done at craniotomy had an important

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caveat, in that the only feeders needled were longer ones supplying superficial AVMs.[6] Sampling bias thus remains a concern in open craniotomy studies that cannot control for location and the potential interplay of size and clinical presentation.[7]

Endovascular measurement of FP became possible during the late 1980s.[8] Microcatheter technology allows physiologically valid data to be obtained during awake endovascular procedures in AVMs of different locations and sizes.[8] The goal of this endovascular study is to analyze the hemodynamic variability in AVM feeders in a balanced group of ruptured and unruptured AVMs of various sizes and at both superficial and deep locations.

Methods

Data were obtained from clinical records and imaging studies in 45 consecutive patients with cerebral AVMs treated at the University of California at Los Angeles. All patients who were evaluated at our center underwent cerebral angiography with superselective catheterization of one or more AVM feeders. Hemodynamic monitoring was performed under local anesthesia using methods previously described,[8] with measurements of mean FP and simultaneous mean systemic arterial pressure (SP) to gauge the completeness of embolization. Pressure measurements were obtained on Hewlett-Packard 78205D pressure monitors (Hewlett-Packard Co., Waltham, MA, USA) with Spectramed TNF-R pressure transducers (Spectramed Inc., Oxnard, CA, USA).[8] Cases excluded from analysis included two who had undergone previous surgery, one who had undergone previous embolization, and three in whom only postembolization pressure measurements were available. Patients with single-holed pial arteriovenous fistulas or dural arteriovenous fistulas were also excluded.

Data were collected according to the Canadian Tri-Council policy statement on ethical conduct for research involving the secondary use of data originally collected for health care purposes.

Data included age, gender, and clinical presentation with hemorrhage or seizures. Imaging data were collected by consensus between a neurosurgeon (SPL) and a neuroradiologist (EFR) and included the AVM diameter (in cm), location (superficial or deep based on proximity to the cortex), laterality (left or right), associated aneurysm (absent or present), pattern of venous drainage (superficial or deep/mixed), and venous outflow stenosis (present or absent).[9,10] Measurement of AVM size was based on the maximum diameter of the AVM nidus on MRI, CT, or angiographic images.[11] Venous stenosis was defined as >50% narrowing of a major draining vein.

The same caliber microcatheter was used in all patients (standard microcatheters; internal diameter 0.53 mm[12]). For each AVM feeder, the presence of an aneurysm on the feeder or in the nidus was noted. The diameter of the feeder was measured in millimeters. In embolizing the AVM, the microcatheter is navigated close to the nidus to prevent reflux of glue into normal arterial branches. The distance both from the tip of the microcatheter to the AVM nidus and from the catheter tip back to the Circle of Willis was measured using orthogonal angiographic projections (Figure 1). Only data from the first catheterized AVM feeder were used since embolization could alter the hemodynamics of a subsequent feeder. In five cases, two hemodynamic measurements were made in the same feeder and the arithmetic mean was used. The FP was only considered valid if it exhibited a waveform like the mean SP waveform.

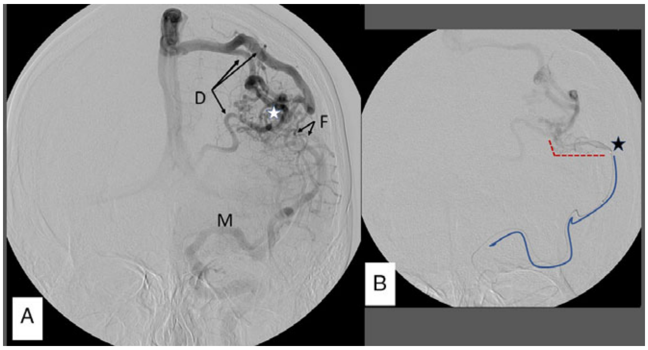

Figure 1: Representative microcatheter image. (A) (left). Anteroposterior left internal carotid angiogram, late arterial phase, Towne projection. Left middle cerebral M1 segment (**M**) provides arterial blood supply to AVM located at white star (☆) via feeders (**F**). Blood flow passes through AVM into three venous drainers (**D**). (B) (right). Microcatheter angiogram, identical projection as in (A). Microcatheter tip is located at black star (★). Distance from microcatheter to AVM is indicated by **dashed line**. Distance from microcatheter tip to Circle of Willis is indicated by **solid line** extending to proximal M1.

Data analysis was performed with commercially available software (InStat, GraphPad software, San Diego, CA, USA) for unpaired *t*-tests, 2×2 contingency tables, and correlation. Descriptive statistics included means and standard deviation for continuous variables and frequencies and proportions for categorical variables. Logistic and multivariable linear regression analyses were completed by an independent biostatistician using R 3.6.3.[13] To evaluate the factors associated with increased risk of a hemorrhage, modified Poisson regression[14] was used to obtain estimates of relative risk and 95% confidence intervals (CI). Given the small sample of patients with a hemorrhage, multivariable analyses were not conducted. Linear regression was used to evaluate the factors associated with FP. Variables entered in the multivariable regression model were selected using backward stepwise selection with the Akaike information criterion.

Results

All Patients

Of the 45 patients included, 16 (36%) had hemorrhage while 28 presented with seizures. One was discovered incidentally. All underwent cerebral angiography with superselective catheterization of one or more feeders. The mean AVM nidus diameter was 3.2 cm (range 1.8–6.2 cm). Nidus size was well distributed with 14 AVMs having a diameter less than 2.5 cm, 29 ranging from 2.5 to 5.0 cm, and 2 greater than 5.0 cm. Mean feeder pressure was 49 mm Hg (range 30–90 mm Hg), with a mean SP of 90 mm Hg.

FP and Anatomical Factors in AVMs with and without Hemorrhage

Baseline demographics, AVM size, and laterality and catheter distance factors were compared (Tables 1 and 2). Those with and without hemorrhage showed no significant differences in mean age, gender distribution, AVM size, or laterality. In terms of catheter position, there was no difference in the distance from the tip of the microcatheter to the AVM nidus, nor proximally to the level of the Circle of Willis.

Table 1 presents the characteristics of patients who did and did not experience a hemorrhage. Results showed that a 1 mm Hg increase in FP was associated with a 2% increased risk of hemorrhage (95% CI 0.2%, 5%). Inspection of the data (Figures 1 and 2)

Table 1: Gender distribution, laterality of the AVM nidus, presence of aneurysm, position of nidus, and nature of venous drainage in all patients and in patients with and without hemorrhage

	All Patients	Patients with hemorrhage	Patients without hemorrhage	*p*
N	45	16	29	
Gender distribution (male/female)	21/24	6/10	15/14	0.53 (NS)
Lateralization (right/left)	18/26	6/9	12/17	1.00 (NS)
Aneurysm present	6	2	4	1.00 (NS)
Nidus position (superficial/deep)	40/4	11/4	29/0	0.01 (significant)
Venous drainage (superficial/deep or mixed)	26/19	5/11	21/8	0.01 (significant)
Venous stenosis (present/absent)	4/39	4/10	0/29	0.008 (significant)

Analysis of 2 × 2 contingency tables using Fisher's exact test.
NS = not significant.

Table 2: Patient age, AVM size, feeder diameter, catheter distances, and hemodynamic data in all patients and in patients with/without hemorrhage

	All patients	Patients with hemorrhage	Patients without hemorrhage	*p*
N	45	16	29	
Age	33.9 ± 14.3	37.3 ± 15.2	31.6 ± 13.5	0.13
AVM size (cm)	3.17 ± 1.09	3.02 ± 1.09	3.26 ± 1.10	0.49
Feeder diameter (mm)	2.30 ± 0.66	2.06 ± 0.68	2.43 ± 0.62	0.07
Distance from catheter to AVM (cm)	3.21 ± 2.32	3.69 ± 2.18	2.98 ± 2.38	0.35
Distance from catheter to circle of Willis (cm)	7.01 ± 3.65	5.96 ± 3.36	7.58 ± 3.73	0.16
Feeder pressure (mm Hg)	49.5 ± 12.6	53.8 ± 15.3	47.0 ± 10.4	0.13
Systemic pressure (mm Hg)	90.9 ± 14.3	92.6 ± 16.8	90.0 ± 12.9	0.57
Pressure drop (mm Hg)	41.5 ± 11.9	38.8 ± 13.5	43.0 ± 10.9	0.26
FP/SP ratio	0.55 ± 0.11	0.59 ± 0.13	0.52 ± 0.09	0.1

Values given as mean ± standard deviation. Means compared in patients with and without hemorrhage using unpaired Student's *t*-test, assuming equal standard deviations from the two populations (assumption tested) or alternate (Welch) *t*-test if the difference between the two standard deviations was significant. Two-tailed *p*-value <0.05 considered significant.

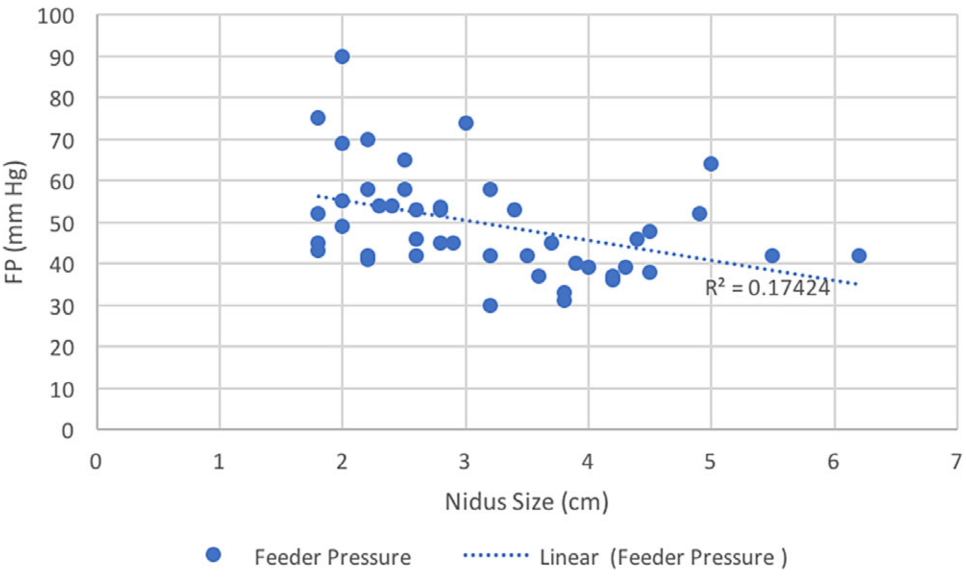

Figure 2: Arteriovenous malformations feeder artery pressure (FP) vs. size.

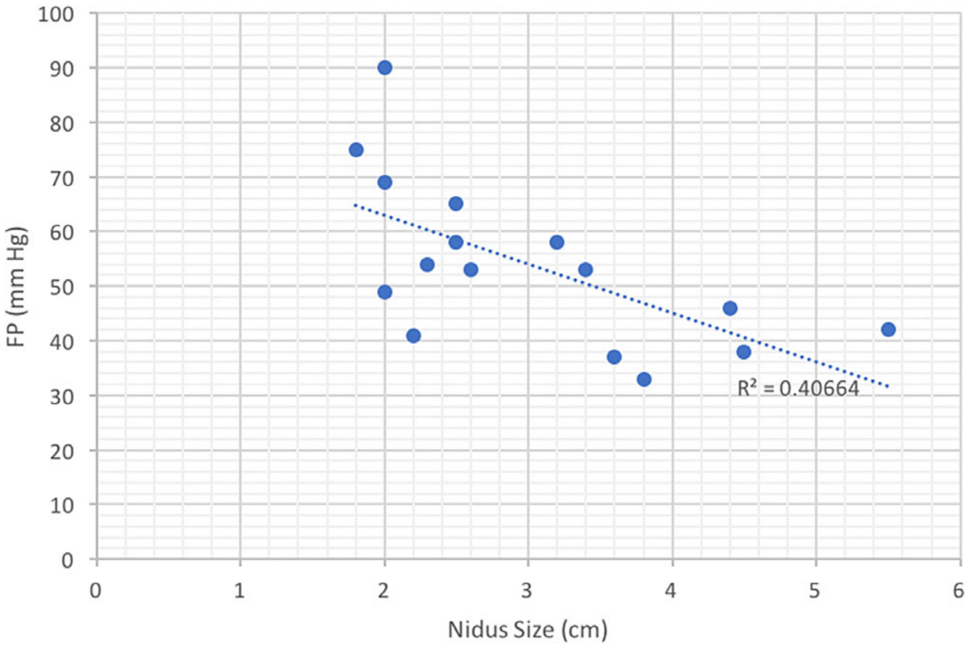

Figure 3: Arteriovenous malformations presenting with hemorrhage: Feeder pressure vs. AVM size.

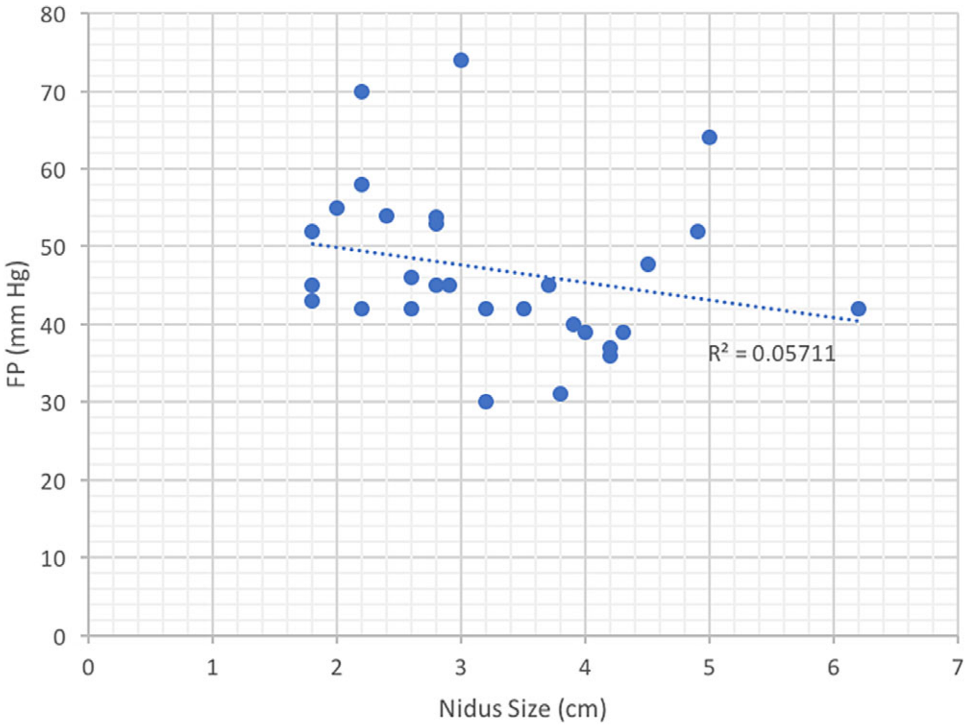

Figure 4: Arteriovenous malformations presenting with no hemorrhage: Feeder pressure vs. AVM size.

revealed that one patient with a hemorrhage had a very high feeder pressure (90 mm Hg). As a sensitivity analysis, this individual was removed, and analyses were re-run. The results were similar, though there were no factors that were significantly associated with hemorrhage. A 1 mm Hg increase in FP was associated with a 2% increased risk of hemorrhage (95% CI −1%, 6%); however, this association was not significant ($p = 0.20$). Although the relationship was not statistically significant, what was consistent was that the CIs from original and sensitivity analyses both suggested that there is an association between feeder pressure and hemorrhage; the lack of statistical significance may be associated with the small sample size.

Among the anatomical factors, there were significant differences in AVM nidus position and venous drainage (Table 2). All the deeply located AVMs presented with hemorrhage, while all of those without hemorrhage had a nidus which came to the cortical surface. Most of those presenting with hemorrhage had deep venous drainage (11 out of 16). This was less

Table 3: Results of unadjusted and multivariable (adjusted) linear regressions, predicting feeder artery mean pressure

	Unadjusted model		Adjusted model	
	B (95% CI)	*p*-value	B (95% CI)	*p*-value
Had hemorrhage	6.76 (−0.97, 14.5)	0.08	–	–
Age, years	0.23 (−0.04, 0.49)	0.09	–	–
Size of AVM	−4.82 (−8.04, −1.59)	0.004	−3.08 (−5.85, −0.31)	0.030
Feeder artery diameter	−4.46 (−10.27, 1.35)	0.13	–	–
Systemic mean arterial pressure	0.54 (0.33, 0.76)	<0.001	0.49 (0.28, 0.71)	<0.001
Distance catheter to COW	−0.39 (−1.43, 0.65)	0.45	−0.74 (−1.52, 0.04)	0.06
Distance COW to AVM	0.08 (−0.76, 0.91)	0.85	–	–
Distance catheter to AVM	1.31 (−0.31, 2.94)	0.11	–	–

AVM = arteriovenous malformation; B = unstandardized regression coefficient; CI = confidence interval; COW = circle of Willis.

Table 4: Hemodynamic data obtained from previous studies of cerebral AVMs

		Presentation: hemorrhage/No hemorrhage (relative to AVM diameter)						
Author (year)	Number of patients	<2.5 cm	2.5–5.0 cm	>5.0 cm	Mean FP	Mean SP	Mean PD	Mean FP/SP
Nornes and Grip[1]*	8	–	–	–	56	103	46	0.54
Hassler and Steinmetz[6]**	6	0	4	2	43	80	37	0.54
Barnett et al.[5]	6	1/1	0/2	1/1	53	73	20	0.73
Leblanc and Little[7]	13	3	5	5	50	71	21	0.70
Spetzler et al.[4]	24	7/0	3/2	0/12	48	74	26	0.65
Handa et al.[15]***	21	3/1	3/9	1/4	56	–	–	–
Miyasaka et al.[3]****	15	–	–	–	50	75	75	0.66
Kader et al.[2]*****	52	0/0	←17/35→		37	74	37	0.51
Duong et al.[16]	62	48/14	←not provided→		39	79	40	0.49
Henkes et al.[17]	139	←58/90→			54.5	99.5	45.0	0.55
Present study	45	6/8	9/20	1/1	49	90	41	0.55
Average [mean ± S.E.M.]	–	–	–	–	49 ± 2.0	82 ± 3.7	39 ± 5	0.59 ± 0.03

In most instances, mean pressure values were calculated from results tabulated in each report. All pressure data are in mm Hg.
FP = feeder pressure; SP = systemic pressure; PD = pressure drop; *=size of AVMs not indicated; **=clinical presentation not indicated in report; ***=no systemic pressure in report; ****=AVM size given by volume in this study; *****=no pressure measurements in AVMs≤ 2.5 cm diameter.

common in cases without hemorrhage (8 out of 29, $p = 0.01$). Stenosis of the venous drainage was seen in four cases. All presented with hemorrhage.

FP and AVM Size

As AVM size increased, FP decreased (Pearson $r = -0.42$, $p = 0.0043$, Figure 2). Nonparametric Spearman's rank testing yielded the same results. At AVM sizes greater than 2.5 cm, no FP greater than 60 mm Hg was observed. In ruptured AVMs, although a wide range of FP was observed (Figure 3), the correlation between FP and size remained significant (Pearson's $r = -0.64$, $p = 0.0079$). In unruptured AVMs, FP also declined as AVM size increased (Pearson $r = -0.24$, $p = 0.21$; Spearman's rank correlation $r = -0.37$, $p = 0.048$) (Figure 4).

Correlation of Feeder Pressure with Other Variables

FP correlated strongly with SP ($r = 0.61$, $p < 0.0001$). This was noted in both the ruptured and unruptured groups ($r = 0.65$ and $r = 0.58$, respectively). No significant correlation existed between FP and feeder artery diameter ($r = -0.21$, $p = 0.16$). There was a slight trend towards an increase in FP as the distance from the tip of the catheter to the edge of the AVM nidus increased, but this was not significant ($r = 0.24$, $p = 0.096$).

Multiple Linear Regression

Table 3 presents the results of unadjusted and adjusted linear regressions evaluating the characteristics associated with FP. Results showed that the size of the AVM and the SP were independently associated with FP. Specifically, a 1 cm increase in the

Table 5: Literature review of similar studies correlating AVM hemodynamics and clinical presentation

Author (year)	N	FP (mean ± SD) in patients with hemorrhage	FP (mean ± SD) in patients without hemorrhage	Difference (mm Hg)	Significance	Correlation of FP and AVM size	Comments
Nornes and Grip[1]	8	61 ± 14	53 ± 12	8	N/A	N/A	N small
Barnett et al.[5]	6	70	44	26	N/A	N/A	N small
Leblanc and Little[7]	13	–	–	–	–	No	N small
Spetzler et al.[4]	24	64 ± 12	36 ± 17	28	Yes $p = 0.0002$	Yes $r = -0.64$ $p = 0.0008$	All small AVMs presented with hemorrhage; no large AVMs bled
Handa et al.[15]	21	61 ± 23	54 ± 14	7	No $p = 0.37$	No $p = 0.84$	Good balance of clinical presentation and AVM size
Miyasaka et al.[3]	15	57 ± 12	38 ± 5	19	Yes $p = 0.0011$	Yes $r = -0.68$ $p = 0.0057$	Small AVMs bled; larger ones did not
Kader et al.[2]	52	44 ± 13	34 ± 10	10	Yes $p = 0.0035$	No $r = 0.09$	No pressures measured in small AVMs
Duong et al.[16]	133	44 ± 18	35 ± 14	9	Yes $p = 0.0004$	N/A	Large N, but balance lacking re size, presentation
Henkes et al.[17]	139	57.5	52.6	4.9	No $p = 0.098$	Yes $r = 0.32$	Measurements were acquired over 6 weeks post-hemorrhage.
Present study	45	54 ± 15	47 ± 10	7	No $p = 0.13$	Yes $r = -0.42$ $p = 0.0043$	Good balance of clinical presentation and AVM size

The mean values for Nornes, Barnett, and Handa were obtained from the raw data available. Statistical results from Spetzler, Handa, Miyasaka, and Kader were repeated using the same methods used in the present study.
FP = feeder artery pressure; N = number of patients; SD = standard deviation.

AVM diameter was associated with a 3.1 mm Hg (95% CI 0.31, 5.85) decrease in the FP, whereas a 1 mm Hg increase in the SP was associated with a 0.49 mm Hg (95% CI 0.28, 0.71) increase in FP. In the adjusted model, significant predictors of FP were SP, AVM size, and distance of the microcatheter tip to the circle of Willis. AVM hemorrhage, feeder diameter, patient age, and the distance of the microcatheter tip from the AVM nidus did not enter the equation.

Discussion

This study is the fourth to establish that FP and AVM size have a significant relationship with each other (Tables 4 and 5).[3,4,17] Our study also found that the distance from the microcatheter tip to the circle of Willis is a contributor to feeder pressure. Thus, two independent factors (catheter distance and AVM size) would ideally be controlled in assessing the role of FP in AVM presentation.

AVM Presentation: Hemodynamic Factors

To be postulated as a major factor of AVM hemorrhage, elevated feeder pressure should be shown to be necessary for hemorrhage to occur and sufficient to cause it. In our study, AVM hemorrhage occurred in the presence of high, low, and average FP (Figure 2). Thus, elevated FP did not appear necessary for hemorrhage. Furthermore, FP as high as 74 mm Hg was seen in small unruptured AVMs (Figure 3), suggesting that elevated FP was not necessarily sufficient to cause hemorrhage.

Kader et al.[2] evaluated 52 AVMs and found FP to be higher in those AVMs which had bled than in those which had not bled. However, in that study FP measurements were only done in AVMs over 4 cm diameter, even though 90% of their ruptured AVMs were $\leq$2.5 cm.[2] Spetzler et al.[4] also found that elevated FP is a predictor of hemorrhage, but as with Kader there was potential selection bias (Table 5). Our study found a somewhat higher pressure (7 mm Hg) in ruptured AVMs, which was not statistically significant upon exclusion of one outlier ($p = 0.20$). Compared to prior studies, our study is better controlled in terms of clinical presentation and AVM size. The results demonstrate that FP correlates with but is probably insufficient on its own to cause AVM rupture.

AVM Presentation: Anatomical Factors

AVMs present with seizures in 17%–40% of cases.[18,19] Features such as AVM size, location (e.g., frontal lobe), venous ectasia, and superficial drainage have all been associated with seizure at presentation. Garcin et al.[20] found that 45 patients who presented with seizures had a cortically located AVM with a superficial draining vein. This is in line with our findings (Table 2). Our data also suggest that AVMs presenting with seizure have less likelihood of venous stenosis.

Recent studies suggest that a low number of draining veins plays a role in AVM rupture. Miyasaka et al.[21] demonstrated that small AVM size and a single draining vein carry an increased risk of hemorrhage. On the other hand, the series by Henkes et al. did not find a similar correlation.[17] Similarly, Duong et al. found that the number of draining veins was not significant, but that FP, size, and deep venous drainage were significant predictors of hemorrhage.[16] de Castro-Alfonso et al.[22] demonstrated that larger draining vein diameter carried an increased risk of hemorrhage. Although this may contradict the idea that venous stenosis increases hemorrhage risk, an increase in draining vein diameter could be due to outflow impairment or increased AVM flow. Finally, the risk of hemorrhage may also be influenced by cellular and even molecular factors.[23]

Conclusions

The pressure in the feeding artery supplying an AVM is the result of factors which include the systemic arterial pressure, the size of the AVM nidus, and the distance of the AVM from the circle of Willis. Determining whether FP is important in AVM hemorrhage would require that such factors be controlled in any comparative analysis of ruptured vs. unruptured AVMs. Previous studies have often compared small AVMs which bled to larger AVMs which had not bled. Our study suggests that feeder pressure is not as important as previously concluded and that anatomical factors also determine the natural history of AVMs. AVM size, SP, feeder pressure, and venous drainage features may all be part of a complex interplay that determines the risk of hemorrhage of a specific AVM. The correlation between these variables makes it difficult to study the risk of hemorrhage as a function of a single factor, which may account for the variation in the conclusions of previous studies.

Conflict of Interest. The authors have no conflicts of interest to be declared.

Statement of Authorship. AC: Contributed to data analysis and manuscript writing; ER: Data collection and analysis; GD: Data collection and analysis as well as manuscript editing; FV: Data collection and analysis as well as manuscript editing; SL: Data collection, analysis, and manuscript writing and editing.

Abbreviations. AVM = arteriovenous malformation; FP = feeder artery mean pressure; SP = systemic mean arterial pressure.

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