Arteriovenous Malformation in the Brain: a Theoretical Study Explaining the Behavior of Liquid Embolic Agents during Endovascular Treatment

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SUMMARY – *There is no theoretical study on blood flow in brain arteriovenous malformation (AVM). We present a numerical theory on AVM and liquid embolic agent AVM embolization. Darcy's law was used to compute flow relations for brain AVMs. Maag's formula was used to explain the diffuse patterns of N-butyl-2-cyanoacrylate (NBCA) and ethylene-vinyl alcohol copolymer (EVOH) in brain AVMs. According to Darcy's law, the instantaneous blood flow rate through an AVM is directly proportional to the pressure drop between two places in the AVM and indirectly proportional to the distance between them. The greater the pressure gradient (through the AVM), the greater the discharge rate, and the discharge rate of blood will often differ through different AVM (or even through the same AVM, in a different direction) even if the same pressure gradient exists in both cases. Subsequent to Darcy's initial discovery, Maag found that the radius of NBCA or EVOH diffusion is inversely proportional to their viscosity. Darcy's Law and Maag's formula could be used to analyze flow patterns of brain AVM and liquid embolic agent behavior in AVM near ideal.*

Introduction

Intracranial arteriovenous malformations (AVMs) have been described as lesions of the cerebral vasculature for 160 years since Luschka and Virchow¹. Brain AVM is a conglomeration of abnormal arteriovenous shunts that may be connected to each other by one or more fistulas, with feeding arteries and draining veins within brain parenchyma^{2,3}. This direct connection of arteries and veins (a lack of a capillary bed) causes pulsatile low resistance and turbulent high-velocity blood flow, high-pressure vascular channels, which can often lead to rupture of vessels^{2,3} (Figure 1). Understanding AVM embolization is very emotional and only based on our experiences, such as the fact that NBCA diffuses in AVM in a blood flow direction and Onyx could diffuse inversing the pressure gradient in AVM. There is a lack of rational understanding of the factors affect-

ing embolic agent diffusion in AVM. Embolic agents diffuse well in some AVM but not in others. This theoretical study will explain the behavior of liquid embolic agents during endovascular AVM embolization. We hope to present this as a breakthrough to open the gateway for a liquid embolic agent diffusion theory in AVM.

Methods

Darcy's Law

The basic law governing the flow of fluids through porous media is Darcy's law, formulated by the French civil engineer Henry Darcy in 1856 on the basis of his experiments on vertical water filtration through sand beds (Figure 2)⁴. In his experiments on unidirectional flow in a uniform medium, Henry Darcy revealed a linear proportionality between the flow velocity

Figure 1 A,B) T2-weighted MR images of AVM. C-E) Angiograms of brain AVMs.

and the applied pressure difference. When the outflow is stable, Q is the flow volume through the sample content over time t . Darcy's law is:

$$Q = \frac{kA \Delta p t}{\mu L} \quad (1)$$

where: Δp = pressure [cmH₂O], L = length of sample [cm], Q = volumetric flow [cm³], A = cross-sectional area of sample [cm²], k = permeability (cm/s), μ = incompressible fluid of viscosity (cp or mPa·s), t = time [s].

Since its discovery, Darcy's law has been found valid for any linear flow of Newtonian fluid in consistent units. Likewise, while it was established under saturated flow conditions, it may be adjusted to account for unsaturated and multiphase flow.

The flow rate is $q=Q/t$, according to Eqn. (1), the flow rate is related to other factors by

$$q = \frac{kA \Delta p}{\mu L} \quad (2)$$

The superficial velocity is $v = \frac{q}{A}$. Also, we recognize that the limit of the quotient of the pressure difference and the length of flow is minus the pressure gradient (or its derivative with respect to length, $\lim_{\Delta x \rightarrow 0} \frac{p(x+\Delta x) - p(x)}{\Delta x} = -\frac{dp}{dx}$). For transient processes in which the flux varies from point to point, we need a differential form of Darcy's law. The differential form of Darcy's law for one-dimensional, horizontal flow is:

$$u = v_{\text{sup}} = -\frac{k}{\mu} \frac{dp}{dx} \quad (3)$$

The change in sign is necessary because the direction of flow is opposite to the direction of pressure change. Eqn. (3) can be integrated to compute forms of Darcy's law for various flow geometries and fluid types. A generalization of Darcy's law for anisotropic permeability should be considered first because the blood flow in AVM is a turbulent flow. In AVMs, the permeability is assumed to be a horizontal permeability.

The permeability may vary horizontally because of compact or diffuse AVM type; plexiform, fistulous, or mixed shunts. The result is that we must consider different permeabilities for blood flows in these different directions. In a three-dimensional system, the components of velocity are

Figure 2 Simple column.

$$\begin{aligned} u_x &= -\frac{1}{\mu} \left(k_{xx} \frac{\partial p}{\partial x} + k_{xy} \frac{\partial p}{\partial y} + k_{xz} \frac{\partial p}{\partial z} \right) \\ u_y &= -\frac{1}{\mu} \left(k_{yx} \frac{\partial p}{\partial x} + k_{yy} \frac{\partial p}{\partial y} + k_{yz} \frac{\partial p}{\partial z} \right) \\ u_z &= -\frac{1}{\mu} \left(k_{zx} \frac{\partial p}{\partial x} + k_{zy} \frac{\partial p}{\partial y} + k_{zz} \frac{\partial p}{\partial z} \right) \end{aligned} \quad (4)$$

In anisotropic systems, permeability is a tensor. Physically, elements like k_{xy} give the flow that occurs in the x -direction due to pressure gradients in the y -direction. Anisotropic porous media can act like "louvers", with flow being "shunted" toward the direction of highest permeability (parallel to the louvers) even if the pressure gradient is not in that direction. For porous media, $k_{ij} = k_{ji}$, and one can always define a coordinate system in which the off-diagonal terms are zero. This is the principal coordinate space, which is defined in exactly the same way the principal stress space was defined in statics. In the principal coordinate space (X, Y, Z), $u_X = -\frac{k_X}{\mu} \frac{\partial p}{\partial X}$, and so on. The

negative sign is needed because fluid flows from high pressure to low pressure. If the change in pressure is negative, then the flow will be in the positive ' x ' direction.

Permeation Grouting Theory

N-butyl-2-cyanoacrylate (NBCA) and ethylene-vinyl alcohol copolymer (EVOH) have been used frequently in the endovascular treatment of intracranial AVMs^{5,6}. If the mixture comes into contact with aqueous solutions, precipitation of the polymer is initiated by diffusion of DMSO. This process begins on the surface while the core is still liquid, resulting in a soft non-adherent mass. Therefore, Onyx has a lava-

A

B

C

Figure 3 A) Left carotid artery angiogram showing an AVM of the left frontal lobe. B) Onyx18 permeation patterns in the AVM. C) A Marathon microcatheter was accessed to a previously embolized AVM.

like flow pattern within blood vessels without any fragmentation during its injection. Due to these properties and because Onyx is not absorbable, it is capable of producing permanent vascular occlusion. (Figure 3). Figure 4 shows the Onyx dispersion pattern in AVM. The

spherical diffusion formula is the most widely used, Maag's formula, to explain the penetrating grouting calculation formula⁷. Based on the generalized Darcy's law and theory for spherical diffusion model, Maag's formula was used for calculating the effective diffusion radius of

Newton fluid injected into homogeneous sandy stratum. Maag's slurry penetration formula ⁷, derived from Darcy's law, is as follows:

$$R = \sqrt[3]{\frac{3kpr_0t}{n\beta}} \quad (5)$$

where: R = Diffusion radius (cm), k = permeability (cm/s), β = viscosity (cp or mPa·s), p = pressure (cmH₂O), r_0 = the grouting pipe radius (cm), n = porosity, t = time (s).

Results

Darcy's law is a simple mathematical statement which neatly summarizes several properties of blood flow in AVMs. If there is no pressure gradient over a distance, no flow occurs (these are hydrostatic conditions). If there is a pressure gradient, flow will occur from high pressure towards low pressure (opposite the direction of increasing gradient, hence the negative sign in Darcy's law). The greater the pressure gradient (through the same formation material), the greater the discharge rate, and the discharge rate of fluid will often be different through different formation materials (or even through the same material, in a different direction) even if the same pressure gradient exists in both cases.

Subsequent to Darcy's initial discovery, Maag found that, all other factors being equal, R is inversely proportional to the fluid viscosity [β (cp or mPa·s)] and AVM porosity (n). The viscosity of NBCA in centipoise (cp or mPa·s) is 2~5 (25°C). EVOH is now commercially available as a non-adhesive liquid embolic system under the names Onyx 18, Onyx 20, and Onyx 34 (ev3, Irvine, CA, USA). The numbers 18, 20, and 34 quantify the viscosity of Onyx in centipoise (cp or mPa·s) ⁸. Therefore, their penetration properties are NBCA > Onyx 18 > Onyx 20 > Onyx 34.

The DMSO-compatible microcatheters (Coviden) currently used in endovascular embolization of AVMs are summarized in Table 1. R is positively proportional to the radius of the microcatheter (r_0), injection time (t) and AVM permeability (k), which is associated with nidus (compact or diffuse) and shunt (plexiform, fistulous, or mixed) types ^{9,10}. Depending on the morphologic features of the superselective contrast injection, the appropriate NBCA or Onyx type for embolization should be selected. Diffuse or fistulous AVMs should be treated with Onyx 20 or 34 (due to their higher viscosity).

Compact or plexiform AVMs should be embolized with NBCA or Onyx 18 (with lower viscosity) for easy penetration to obtain a better penetration into the nidus.

Table 1 The radius of currently used DMSO-compatible microcatheters

Catheters	Distal I.D. (in)	r_0 (mm)
UltraFlow™ HPC	0.012	0.15
Marathon™	0.013	0.17
Rebar™ 10	0.015	0.19
Headway Duo	0.0165	0.21
Rebar™14	0.017	0.22
Echelon™	0.017	0.22
Rebar™ 18	0.021	0.27
Rebar™ 27	0.027	0.34

Although higher pressure is associated with a larger diffusion radius, the embolization procedure should be stopped immediately when the injection resistance increases significantly to prevent rupture of the microcatheter or vessels. This phenomenon may be an indicator of the complete filling of the embolized nidus compartment.

Discussion

Darcy's law and Maag's formula were initially used for theoretical research on industrial permeation grouting. We think that the model of dynamic principle of AVM and its embolization is consistent with Darcy's law. The fluid mechanics of blood seepage in AVM and diffusion of liquid embolic agent permeation in AVM are consistent sets of units that can be used in Darcy's law. Darcy's law is mathematically analogous to incompressible linear phenomenological transport laws. Applications of Darcy's model to blood flow in an AVM nidus where u , P , L and k are the Darcy velocity (the average of the blood flow velocity over the AVM cross section), blood pressure, dynamic viscosity of the blood and the permeability of the AVM porous medium, respectively. Our work has applied this law in the field of the mechanics of blood perfusion through soft tissues.

At low pressure, flow of liquid embolic agents in AVM is much like laminar flow of liquids – the flow rate is proportional to the difference in pressure. The Onyx injection started at a rate of 0.1 mL/min. The embolic agent released the tip of the microcatheter under free-flow

A

B

Figure 4 A,B) Onyx dispersion pattern in AVM.

Figure 5 Non-linear regression resulted in a cubic curve ($R^2=0.572$).

conditions and filled the directly dependent nidus compartment antegradely and later retrogradely until it flowed to the tip of the microcatheter. Thus, Eqn. (4) could be used for accurate analysis of liquid embolic agent behavior in AVM near ideal.

The Darcy model has been utilized successfully in several biomedical applications leading to a number of developments in the areas⁹. Huyghe and van Campen⁵ presented a constitutive formulation for finite deformation of porous solids in order to model flow through different hierarchical arrangements. They de-

veloped an extended Darcy model utilizing an averaging method which transformed the network of pores into a continuum. They considered the pores a network of cylindrical vessels in which Poiseuille-type pressure-flow relationships are valid. In three dimensions, Eq. (3) can be generalized to

$$\mathbf{v} = \frac{k}{\mu} \nabla p \quad (6)$$

where the permeability k is a general second-order tensor. The terms $\mathbf{v}$ and ∇p are Darcy

velocity and pressure gradient vector. For isotropic porous medium, the permeability is scalar and Eq. (6) reduces to

$$\nabla p = -\frac{k}{\mu} \nabla p \quad (7)$$

Later, Vankan et al.¹¹ compared a hierarchical mixture model of blood perfusion in biological tissue that utilizes an extended Darcy equation for blood flow with a network analysis of the biological tissue. A good correspondence is achieved between both methods if the hierarchical quantification is based on the network fluid pressure. Vankan et al.¹² also performed a simulation for blood flow through a contracting muscle, with a hierarchical structure of pores (the hierarchy corresponds to the tree-like vascular structure). The fluid flow was described by a Darcy model for deformable porous media with a second-order permeability tensor while fluid pressure and hydrostatic solid pressures were related through an elastic fluid solid interface. The state of the fluid, the Darcy permeability tensor and the elastic interface were taken to be functions of space as well as the hierarchical level. They found that their calculated blood pressures approximately corresponded to blood pressures measured in skeletal muscles. Butler et al.¹³ studied interstitial fluid flow in axisymmetric soft connective tissues such as ligaments or tendons (fibrous tissue connecting bones and cartilage and connective tissue that connects muscle to bone, respectively) when they are in tension. The flow in these tissues were modeled as Darcian flow through a porous medium having the pressure and velocity of the interstitial fluid as the unknown variables. A parametric study was conducted by varying the fluid viscosity and the permeability of the solid matrix where they were found to strongly affect the resulting fluid flow behavior. Baish et al.¹⁴ considered a simple network model to model the important fea-

tures of flow through a network of permeable and compliant vessels embedded in an isotropic porous medium. They used the Darcy model to represent the flow through the porous medium. Weber et al.¹⁵ reported their experiences in the treatment of intracranial AVMs with Onyx embolization focusing on the embolization technique with Onyx. Non-linear regression for Onyx volume and injection time was performed and resulted in a cubic curve ($R^2=0.572$) (Figure 5), which is consistent with Maag's formula. In this non-linear regression analysis, the relationship between the perfusion radius (R) and injection time (t) was only considered, besides the factors of Onyx viscosity (18 and 20), pushing pressure (p) and AVM type, which is associated with k and n .

Limitations

Darcy's law and Maag's formula may be too simple to elucidate the natural state of properties of blood flowing in AVMs and liquid embolic agent AVM embolization. In this theoretical consideration only a steady flow is taken into account, but in the brain the pulsatile low resistance flow still prevails in many AVMs. And there is a major difference between industrial permeation grouting and the biological tissue. But we think that this may provide a simple and understandable method for explanation of AVM and AVM embolization. This theory needs further investigation to make it more precise.

Conclusions

Darcy's Law and Maag's formula could be used to analyze flow patterns of brain AVM and liquid embolic agent behavior in AVM near ideal. This theory needs further investigation to make it more precise.

References

- 1 Perret G, Nishioka H. Report on the cooperative study of intracranial aneurysms and subarachnoid hemorrhage: Section VI. Arteriovenous malformations. An analysis of 545 cases of craniocerebral arteriovenous malformations and fistulae reported to the cooperative study. *J Neurosurg.* 1966; 25: 467-490.
- 2 Friedlander RM. Clinical practice. Arteriovenous malformations of the brain. *N Engl J Med.* 2007; 356: 2704-2712.
- 3 Fleetwood IG, Steinberg GK. Arteriovenous malformations. *Lancet.* 2002; 359: 863-873.
- 4 Darcy HRP. *Les Fontaines Publiques de la ville de Dijon*, Paris. Vector Dalmont; 1856.
- 5 Lv X, Wu Z, Li Y, et al. Hemorrhage risk after partial endovascular NBCA and ONYX embolization for brain arteriovenous malformation. *Neurol Res.* 2012; 34: 552-556.
- 6 Lv X, Wu Z, Jiang C, et al. Endovascular treatment accounts for a change in brain arteriovenous malformation natural history risk. *Interv Neuroradiol.* 2010; 16: 127-132.
- 7 Schmertmann JH, Henry JF. A design theory for compaction grouting. In: Borden RH, Holtz RD, Juran I, Editors. *Proceedings of grouting. Soil improvement and geosynthetics*. New York. ASCE 1992.
- 8 Lv X, Jiang C, Li Y, et al. Embolization of intracranial dural arteriovenous fistulas with Onyx-18. *Eur J Radiol.* 2010; 73: 664-671.
- 9 Huyghe JM, Vancampen DH. Finite deformation-theory of hierarchically arranged porous solids. 2. Constitutive behavior, *Int J Eng Sci.* 1995; 33: 1873-886.
- 10 Khaled ARA, Vafai K. The role of porous media in modeling flow and heat transfer in biological tissues. *International Journal of Heat and Mass Transfer.* 2003; 46: 4989-5003.
- 11 Vankan WJ, Huyghe JM, Janssen JD, et al. Finite element analysis of blood flow through biological tissue. *Int J Eng Sci.* 1997; 35: 375-385.
- 12 Vankan WJ, Huyghe JM, Drost MR, et al. A finite element mixture model for hierarchical porousmedia. *Int J Numer Meth Eng.* 1997; 40: 193-210.
- 13 Bulter SL, Kohles SS, Thielke RJ, et al. Interstitial fluid flow in tendons or ligaments: a porous medium finite element simulation. *Med Biol Eng Comput.* 1997; 35: 742-746.
- 14 Baish JW, Netti PA, Jain PK. Transmural coupling of fluid flow in microcirculatory network and interstitium in tumors, *Microvasc Res.* 1997; 53: 128-141.
- 15 Weber W, Kis B, Siekmann R, et al. Endovascular treatment of intracranial arteriovenous malformations with onyx: technical aspects. *Am J Neuroradiol.* 2007; 28: 371-377.

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