

Vascular Malformations

Cerebral vascular pathology

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Learning outcomes

- Classify the four principal cerebral vascular malformations.
- Relate AVM and cavernous malformation architecture to blood flow.
- Recognize characteristic pathology and clinical consequences.
- Explain the contrasting endothelial molecular mechanisms.
- Use morphology and clinical context to distinguish major lesions.

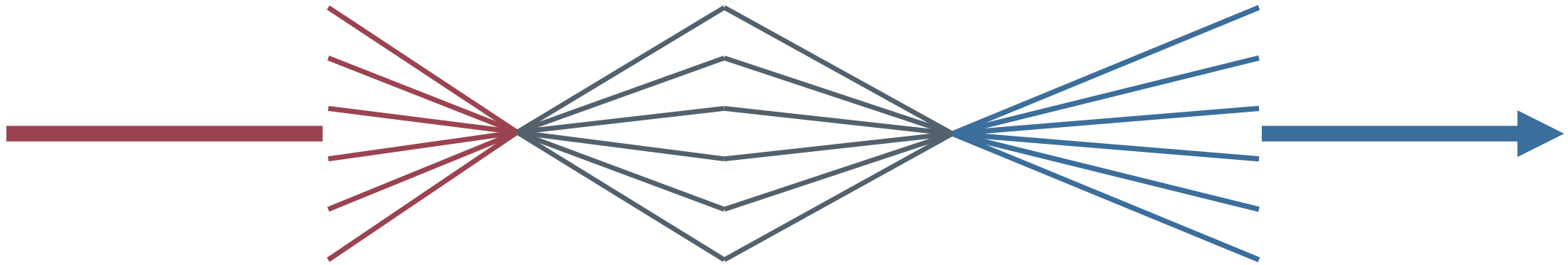
Cerebral vascular malformations are not conventional neoplasms

- These lesions lack the morphologic hallmarks that characterize neoplasms.
- Their vascular anatomy is nonetheless abnormal and clinically consequential.
- Somatic endothelial mutations can contribute to their formation.
- A pathogenic mutation does not, by itself, establish malignancy.

Normal arterial–capillary–venous circulation

Feeding artery

Draining vein



Intervening capillary bed

Schematic illustration — not a specimen

Four principal groups of brain vascular malformations

Category	Pathology focus
Arteriovenous malformation	High-flow shunting; hemorrhage and neurologic symptoms
Cavernous malformation	Low-flow vascular channels; hemorrhagic sequelae
Capillary telangiectasia	One of the four named groups
Venous angioma	One of the four named groups

Clinically consequential hemorrhage risk is not uniform

AVMs and cavernous malformations

- Highlighted as the two categories linked to hemorrhage
- Neurologic symptoms may develop

Capillary telangiectasias and venous angiomas

- Included in the four-group classification
- Their features are not further detailed in this passage

Arteriovenous malformations: Dominant clinical burden

Seizures

Cerebral AVM

Intracerebral bleeding

Subarachnoid bleeding

A lesion can cause bleeding in more than one compartment

Malformed vessels



Vessel rupture



**Intracerebral or subarachnoid
hemorrhage**

The compartment of hemorrhage is a clinical consequence, not a distinct molecular class.

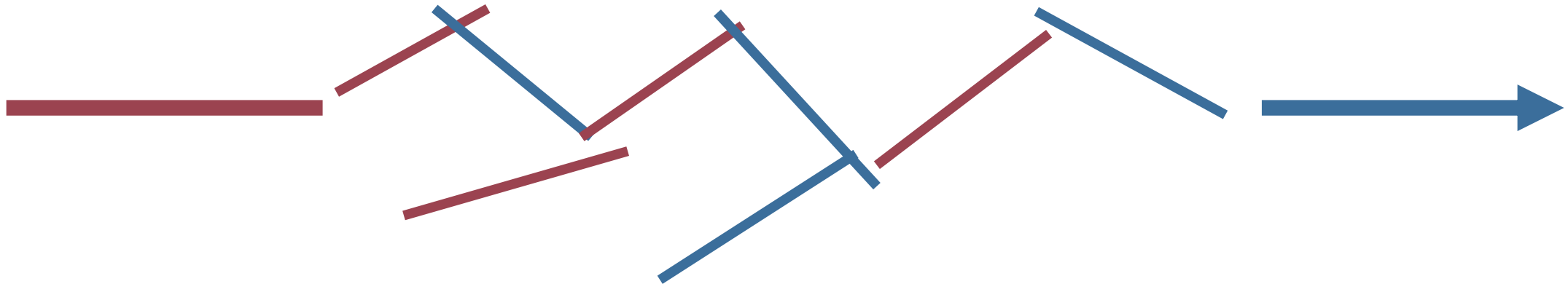
AVM architecture: A disorganized vascular network

- Tangled networks of enlarged, wormlike vascular channels.
- Prominent pulsatile arteriovenous shunting.
- Vessels can involve the brain, subarachnoid space, or both.
- Different vessel-wall phenotypes coexist in one lesion.

Arteriovenous shunting bypasses a capillary bed

Feeding artery

Draining vein



Direct high-flow shunt through tortuous channels

Schematic illustration — not a specimen

High flow is intrinsic to AVM architecture

**Abnormal artery–vein
connection**



Prominent shunting



High-flow vascular network

Pulsatile shunting is the defining hemodynamic feature.

AVMs can occupy two anatomic compartments

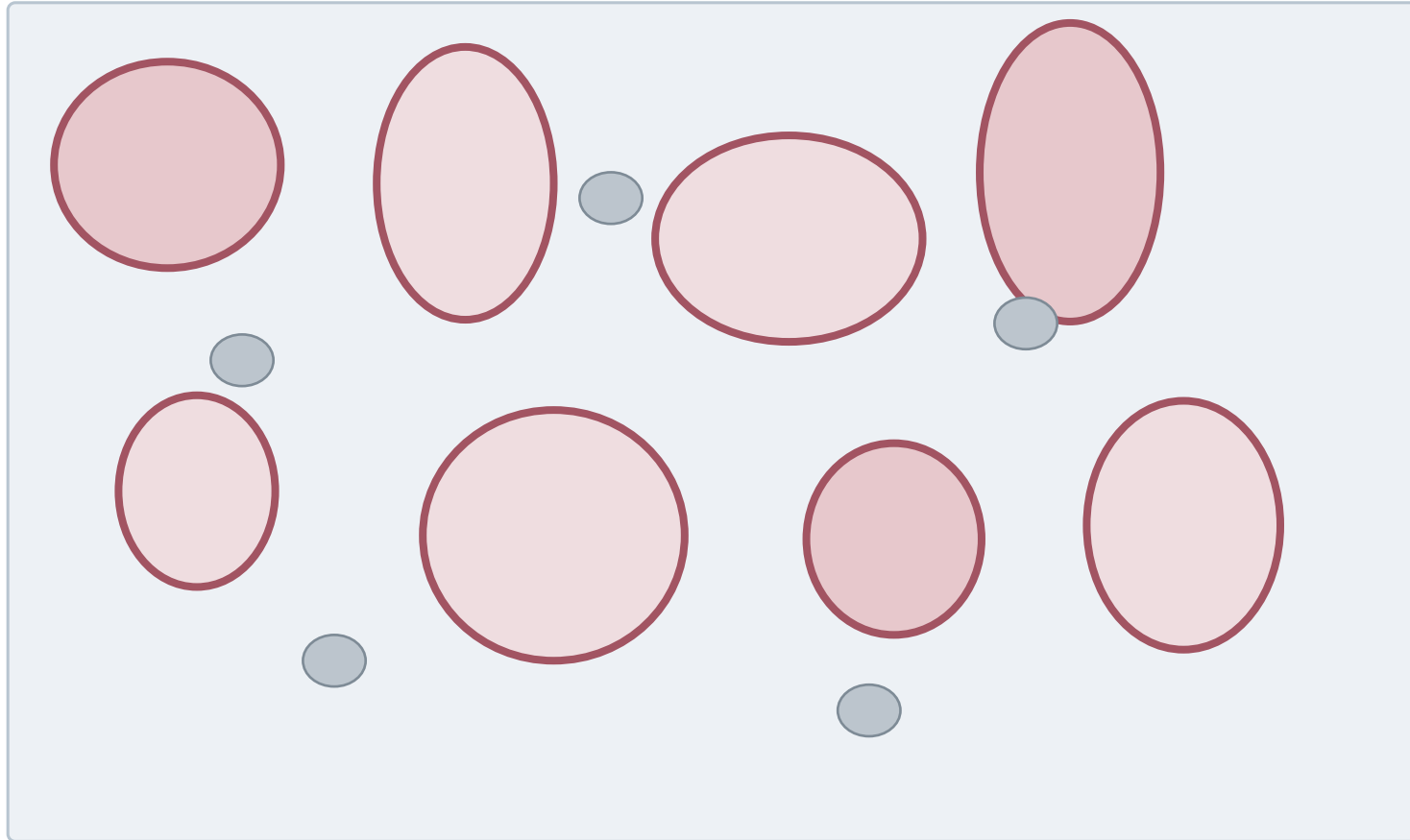
Brain parenchyma

- Large abnormal channels within cerebral tissue
- Parenchymal hemorrhage can occur

Subarachnoid space

- Malformed channels can extend over brain surfaces
- Subarachnoid hemorrhage can occur

AVM gross pathology: Enlarged tortuous channels



Dilated vascular profiles

Intervening reactive brain
tissue

Schematic illustration — not a histologic specimen

AVM vessels are separated by gliotic brain tissue

- Gliosis is a tissue response adjacent to abnormal vessels.
- Microscopy may show enlarged channels interspersed with gliotic parenchyma.
- The presence of gliosis explains why an AVM is not just a bag of isolated vascular spaces.

Evidence of older hemorrhage may accompany AVMs

Abnormal vascular channels



Prior hemorrhage



Residual tissue injury / gliosis

Evidence of previous bleeding in the AVM-associated brain.

An arterial component can retain a distorted elastic lamina

- Some channels can be recognized as arteries.
- Their internal elastic lamina may show duplication.
- Fragmentation of the internal elastic lamina may coexist.
- These abnormalities support arterial wall remodeling.

The media can undergo marked structural change

- Vessel-wall thickening may be prominent.
- The media may be partially replaced by hyalinized connective tissue.
- Marked differences in arterial wall architecture may occur within one AVM.

AVM histology: A mixed population of vascular walls

Arterial-type channels

- Elastic lamina duplication or fragmentation
- Varying medial preservation

Remodeled vascular channels

- Hyalinized connective tissue
- Markedly thickened wall segments

A compact morphologic recognition checklist

- Tortuous, greatly enlarged channels rather than a uniform capillary proliferation.
- Mixed vessel-wall appearance, including distorted arteries.
- Gliotic brain tissue separating vascular profiles.
- Possible evidence of prior bleeding.

Molecular pathogenesis is endothelial in origin

**Activating somatic KRAS
mutation**



**Endothelial RAS signaling
dysregulation**



AVM pathogenesis implicated

The findings suggest a pathogenic role for RAS signaling; Not a complete deterministic mechanism.

Somatic KRAS alterations are not germline diagnoses

Somatic in AVM endothelium

- Described within endothelial cells lining malformed channels
- Supports a lesion-local molecular process

What is not established here

- The passage does not describe universal KRAS mutation in every AVM
- It does not define a germline AVM syndrome

Molecular evidence does not turn an AVM into a tumor

Genomic alteration

Activating KRAS may occur in endothelial cells.

Histologic identity

An AVM still lacks typical neoplastic morphology.

The RAS hypothesis has a defined evidentiary boundary

- Frequent activating somatic KRAS mutations in AVM endothelium.
- This association suggests that dysregulated RAS signaling participates in pathogenesis.
- It does not establish a universal mutation or an individual patient's genotype.
- Do not equate an implicated pathway with a validated therapeutic target.

Clinical presentation is often in young patients

- AVMs often present between 10 and 30 years of age.
- The three clinical presentations highlighted are seizures, intraparenchymal hemorrhage and subarachnoid hemorrhage.
- Age is a contextual clue, not a diagnostic criterion.

Seizures can be the presenting manifestation

Malformed cerebral vascular network



Cerebral tissue involvement



Seizure disorder

Seizure disorder among typical AVM presentations; The precise seizure mechanism is not specified.

AVMs are a cause of intracerebral hemorrhage

**AVM with vulnerable
abnormal vessels**



Rupture



**Primary intraparenchymal
hemorrhage**

Cerebrovascular context: AVM is one contributor to nontraumatic brain hemorrhage.

Subarachnoid hemorrhage can also arise from AVM

AVM-associated SAH

- AVM may involve subarachnoid vessels
- Hemorrhage may enter the subarachnoid space

Another key cause

- Ruptured saccular aneurysm
- Discussed separately in the neighboring cerebrovascular section

Typical AVM topography: Middle cerebral artery territory

- The middle cerebral artery territory is the most common site noted.
- Posterior branches of the MCA are particularly emphasized.
- The territorial predilection is not exclusive or a formal diagnostic rule.

Neonatal presentation differs from older-patient AVM

Older child / young adult

- Seizure disorder
- Intracerebral hemorrhage
- Subarachnoid hemorrhage

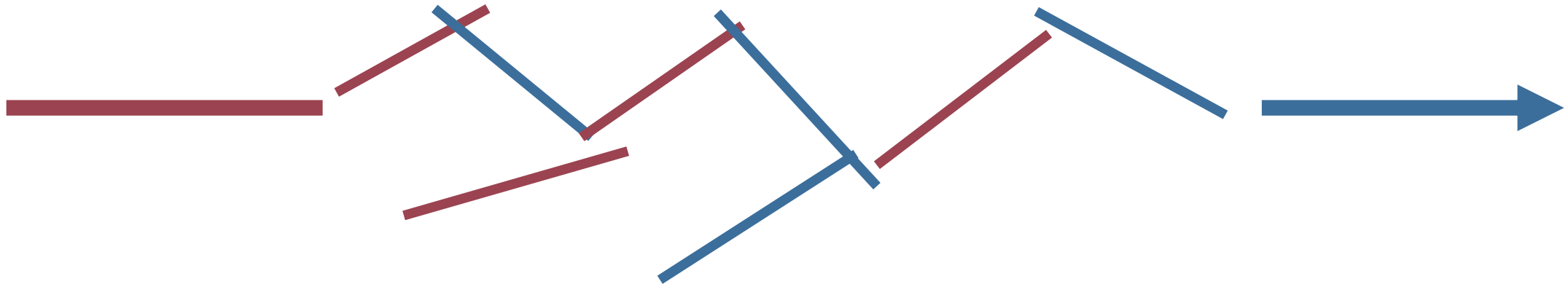
Newborn with large AVM

- Marked arteriovenous shunting
- Congestive cardiac failure may dominate

Vein of Galen malformation: Abnormal flow path

Feeding artery

Draining vein



Direct high-flow shunt through tortuous channels

Schematic illustration — not a specimen

Conceptual depiction of arterial blood entering venous channels without a normal capillary interface.

Why a large neonatal shunt can cause heart failure

**High-pressure arterial
inflow**



**Direct venous
shunting**



**Cardiac volume
burden**



**Congestive heart
failure**

Large neonatal AVMs can produce this systemic consequence, especially with vein of Galen involvement.

The vein of Galen example is anatomically specific

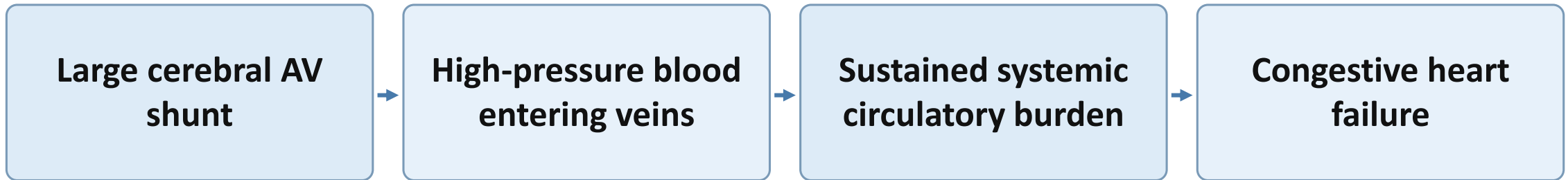
- Malformed arteries connect directly to veins instead of traversing capillaries.
- High-pressure arterial inflow reaches the venous circulation.
- A sufficiently large shunt can compromise cardiac function in a newborn.

Clinical case: A newborn with cardiac failure

A newborn has severe congestive heart failure. Assessment shows a very large cerebral high-flow vascular lesion with direct arterial connections into deep cerebral venous drainage.

What hemodynamic mechanism links the brain lesion to the heart?

Case interpretation: Cardiac burden from cerebral shunting

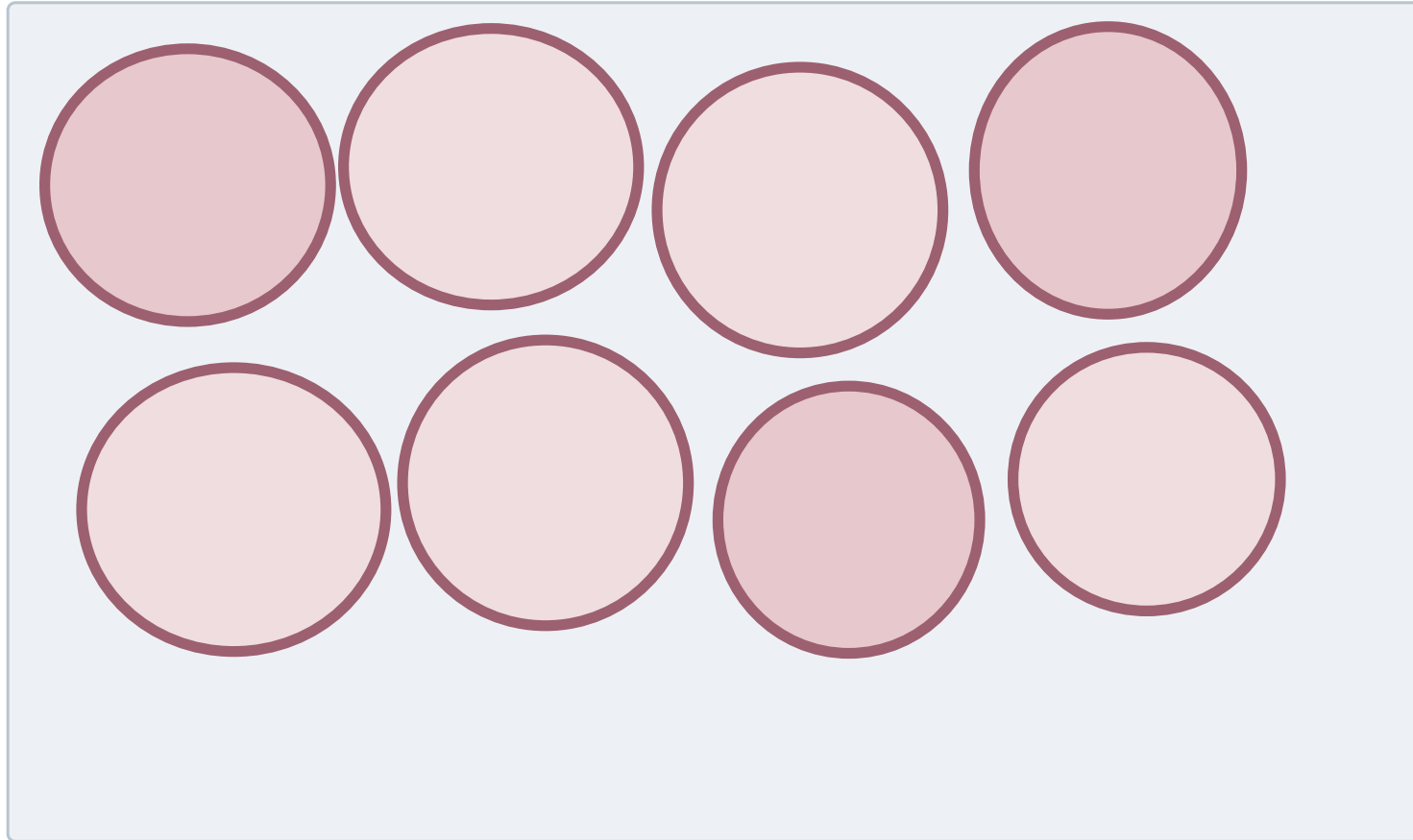


Source-consistent reasoning from the neonatal vein of Galen example.

Cavernous malformations: Low-flow vascular lesions

- Composed of distended, loosely organized vascular channels.
- Channels are low-flow rather than high-flow shunts.
- They do not participate in arteriovenous shunting.
- Their pathology and molecular biology differ from AVMs.

Cavernous channels are arranged back-to-back



Contiguous distended spaces

Little intervening tissue is typical

Schematic illustration — not a histologic specimen

Cavernous malformations have collagenized walls

- The walls of the malformed channels contain collagen.
- Wall thickness can vary substantially from channel to channel.
- The channels appear loosely organized but closely apposed.

Intervening brain is usually absent, not invariably absent

Typical pattern

Back-to-back abnormal vascular spaces with no brain tissue between them.

Important exception

Robbins explicitly allows occasional intervening parenchyma; Do not overstate an absolute rule.

The preferred locations of cavernous malformations

Relative order in Robbins	Region
Most frequent	Cerebellum
Next	Pons
Then	Subcortical regions

Cavernous lesions can leave hemorrhagic footprints

- Old hemorrhage is commonly seen around abnormal channels.
- Surrounding infarction may also be present.
- Calcification may accompany the lesion.
- These changes indicate associated tissue injury over time.

Anatomic architecture: AVM versus cavernous lesion

Arteriovenous malformation

- Tortuous vessels with substantial shunting
- Gliotic parenchyma often lies between channels

Cavernous malformation

- Back-to-back distended vascular spaces
- Parenchyma is usually absent between channels

The cerebral cavernous malformation protein complex

CCM protein complex



Limits vascular growth



**Maintains a brake on
malformation development**

The complex as heterotrimeric.

Loss-of-function mutations disable the CCM brake

Loss of function in CCM-complex genes



Reduced CCM-complex restraint



Permissive abnormal vessel growth

Schematic interpretation of the function and loss-of-function relationship stated.

PIK3CA gain of function is a second molecular signal

Activating PIK3CA mutation



Pro-malformation signaling



**Clinically significant lesion
growth**

Gain-of-function PIK3CA alterations in rapidly growing clinically significant lesions.

Clinically significant cavernomas may accumulate mutations

CCM-complex genes

- Loss-of-function changes
- Remove a growth-limiting function

PIK3CA

- Gain-of-function changes
- Promote malformation growth

Molecular profiles explain distinct pathogenesis models

Lesion type	Reported endothelial alterations	Interpretation
AVM	Activating somatic KRAS	Dysregulated RAS signaling implicated
Cavernous	CCM-complex loss of function; often PIK3CA gain of function in rapidly growing lesions	Reduced growth restraint with pro-growth signaling

Familial cavernous malformations are a major subgroup

- Familial cavernous malformations are relatively common.
- Their inheritance is autosomal dominant.
- Causative variants affect genes encoding CCM-complex subunits.
- Affected individuals generally have multiple lesions.

Autosomal dominant inheritance explains familial clustering

Pathogenic familial CCM gene variant



Autosomal dominant transmission



Multiple cavernous lesions often occur

Inheritance and lesion multiplicity are stated for familial forms; No penetrance estimate is given.

Multiplicity is a useful clinical clue

Multiple cavernous lesions

- Characteristic of the familial form
- Should prompt consideration of inherited disease

A solitary lesion

- Does not by itself establish or exclude a genetic contribution
- The source does not specify a formal diagnostic algorithm

Integrated molecular comparison

AVM: KRAS–RAS

Activating somatic KRAS in vascular endothelium; RAS signaling implicated.

Cavernoma: CCM–PIK3CA

Loss of CCM-complex function with PIK3CA activation in significant growing lesions.

Blood-flow behavior is a major discriminator

AVM • high flow

Prominent pulsatile arteriovenous shunting drives a high-flow tangle.

Cavernoma • low flow

Low-flow vascular channels without direct arteriovenous shunting.

Microscopic comparison: Do not use one feature alone

Feature	AVM	Cavernous malformation
Arrangement	Enlarged tortuous mixed channels	Distended spaces back-to-back
Intervening brain	Gliotic tissue described	Usually absent; not invariable
Wall structure	Distorted elastic lamina / media	Variable collagenized wall
Prior injury	Evidence of prior hemorrhage	Old bleed, infarct, calcification

Clinical comparison is complementary to histology

Domain	AVM	Cavernous malformation
Hemodynamics	High-flow shunting	Low-flow; no AV shunt
Clinical context	Seizures and two hemorrhage compartments	Hemorrhage and neurologic symptoms
Inheritance	Somatic KRAS often described	Familial autosomal dominant CCM variants
Anatomic clue	MCA territory often involved	Cerebellum, pons, subcortical

The other two named groups require a limited claim

- Capillary telangiectasias and venous angiomas complete the four-class list.
- This Robbins section emphasizes AVMs and cavernous malformations as symptomatic hemorrhage-risk lesions.
- The passage does not provide detailed morphology, genetics or clinical criteria for the other two categories.
- Do not invent those omitted specifics from the excerpt.

Four-category synthesis

Group	Hemodynamic / pathologic cue	Source coverage
AVM	High-flow arteriovenous shunting	Detailed
Cavernous	Low-flow juxtaposed vascular spaces	Detailed
Capillary telangiectasia	Named category	Not elaborated
Venous angioma	Named category	Not elaborated

A morphology-first classification pathway

**Abnormal cerebral vascular
channels**



**Assess shunting and wall
pattern**



**High-flow AVM vs low-flow
cavernous**

Histology and flow behavior provide complementary—not independently definitive—evidence.

Nontraumatic hemorrhage has several vascular causes

Distribution / context	Major source-derived considerations
Deep ganglionic hemorrhage	Hypertensive small-vessel disease
Lobar hemorrhage	Cerebral amyloid angiopathy
Subarachnoid hemorrhage	Saccular aneurysm or AVM
Any relevant site	Vascular malformation among broader causes

Case: A young patient with seizure and vascular tangle

A 19-year-old presents with a first seizure. A cerebral lesion contains tortuous enlarged vessels, gliotic intervening tissue and abnormal arterial elastic laminae.

Which of the four vascular malformations is favored?

Case interpretation: Arteriovenous malformation

- The age and seizure presentation fit Robbins' typical AVM context.
- Tortuous channels plus distorted arterial elastic laminae favor AVM morphology.
- Intervening gliotic parenchyma supports the described architectural pattern.
- Molecularly, endothelial KRAS activation is a possible mechanism, not a patient-level assumption.

Case: Multiple low-flow lesions in a family

Several family members have cerebral low-flow vascular lesions. Histology shows distended back-to-back channels with collagenized walls and old bleeding.

What lesion and inheritance pattern are most likely?

Case interpretation: Familial cavernous malformations

- Low-flow back-to-back spaces favor cavernous malformation.
- Variable collagenized vascular walls support the distinction from AVM.
- Autosomal dominant CCM-complex mutations explain familial clustering.
- Multiple lesions are characteristic in affected family members.

Five principles to retain

- Four main cerebral vascular malformation groups are recognized.
- AVMs are high-flow lesions with arterial–venous shunting and characteristic vessel-wall remodeling.
- Cavernous malformations are low-flow, back-to-back collagenized vascular channels.
- Endothelial KRAS alterations implicate RAS in AVMs; CCM and PIK3CA alterations are linked to cavernomas.
- Morphology, molecular pathogenesis and clinical context must be interpreted together.

Diagnostic self-check: classify the abnormal vessels

- Are there direct high-flow connections between arteries and veins?
- Is the lesion a tangle of remodeled channels with gliotic intervening brain?
- Or are there low-flow, back-to-back spaces with collagenized walls?
- Does the family history or lesion multiplicity suggest inherited CCM-complex disease?