pediatric stroke

*Commentary*

# Arterial Tortuosity: Mechanisms and Clinical Significance as a Biomarker of Arteriopathy

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***Commentary***

Anokwute MC, et al. report a case of a 9-year-old male with a corkscrew basilar artery, initially discovered on brain MR imaging studies performed to evaluate headaches.[1] The child was concurrently found to have a prolactinoma which was successfully treated with cabergoline. The index basilar artery lesion was characterized by magnetic resonance angiography (MRA), computerized tomographic angiography (CTA) and catheter directed cerebral angiography confirming isolated corkscrew tortuosity without aneurysmal or flow restrictive steno-occlusive features. Clinical and angiographic stability was documented over a 2-year period.

Anokwute MC and colleagues, as other before them, describe the corkscrew basilar artery as an anatomical variant that is the specific product of embryological development.[1,2] Reference is made to fusion of the paired primitive longitudinal neural arteries into the definitive basilar artery as a potential mechanism.[1] Theoretically, the sinusoidal template for a corkscrew architecture may be generated by alternating segmental regression of opposing neural arteries, each persisting segment joined to the nearest persisting opposing counterpart by a short anastomotic bridge (Figure 1). Though possible, the complex rearrangements needed to produce this architecture seem to have no basis in existing paradigms of developmental biology or embryology. As it concerns the cerebral circulation, commonly recognized anatomical variants

can be broadly categorized into fenestration variants, atypical origin variants and dysplastic variants (including vessel aplasia and hypoplasia). Notably dysplastic variants are frequently associated with atypical origin variants. Fenestration variants result from incomplete fusion of a precursor plexiform vascular network into a single discrete vascular trunk during embryological development. Consequently, arteries which form from a coalescence of precursor arteries, may express fenestration variants. Since the basilar artery is formed by condensation of paired primitive longitudinal neural arteries, vertebrobasilar fenestration variants are well-known and have a solid foundation in embryology. Atypical origin variants are the product of a "tug of war" between potential parent arteries struggling for annexation of a vascular territory. Although dominance in the annexation struggle is most often dictated by spatial proximity to the prized territory, shaped by growth of intervening tissues and organs, agenesis or hypoplasia of one of the competing arteries may supervene and determine dominance irrespective of proximity. In most cases, the loser of the annexation struggle involutes, leaving no trace of itself in the mature circulation. All of the primitive carotid-vertebrobasilar anastomoses fall into this category. Dysplastic variants such as internal carotid artery agenesis result from segmental or diffuse interruption of the normal growth and development of a specific blood vessel during embryological development. In many cases, hypoplasia or aplasia is merely the consequence of a lost annexation competition and the involution induced by flow deprivation.

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In the clinical neurosciences, “anatomical variants”, sometimes referred to as “embryological variants” are considered to be anatomical configurations that are deviations from the typical form which generally have no pathological ramifications under ordinary circumstances.[3] Nonetheless, exceptions involving symptomatic anatomical variants abound.[4] Moreover, the degree to which some anatomical variants increase vulnerability to specific vascular pathologies such as aneurysms has been debated.[5,6,7] In most cases, a rigorous evaluation of clinical data suggests that common anatomical variants including fenestrations and atypical origin variants do not significantly increase the risk of major cerebrovascular pathologies.[5] While the corkscrew basilar artery may satisfy some aspects of the anatomical variant definition, we believe that embryological processes have little to do with its development and that classification as an anatomical variant is confusing and misleading. Vascular tortuosity violates the efficiency principle of fluid transport and circulatory system design and would therefore be contraindicated as a variation of “normal” development. In a purely descriptive sense, the corkscrew basilar artery is an extreme tortuosity phenotype. Similar extreme tortuosity phenotypes are expressed by other cerebral arteries, and also by extracranial arteries.[8,9,10] Brinjiki W et al studied a series of 12 patients with intracranial cerebral arterial tortuosities or “coiled arteries”. He proposed the term “pure arterial malformation” for classification.[9] Malformation, in this case, is defined as a

defect in form or structure. Though “malformation” is often erroneously conflated with a defect in the genetically programmed developmental process that gives origin to organs and tissues, malformations are frequently the result of an acquired damage process and the ensuing response to injury that develops in fully mature tissues and organs. A well-known example of a malformation that is acquired after tissue development and maturation are complete is the dural arteriovenous malformation (DAVM).[11] Although the pathogenesis of DAVM relies on abnormal angiogenesis, recent advances in vascular biology indicate that the development of a malformed blood vessel such as a coiled artery, does not necessarily involve angiogenesis, which is the formation and maturation of new blood vessels from existing mature blood vessels through sprouting or intussceptive mechanisms.[12] While, “pure arterial malformation” may adequately describe coiled cerebral arteries, the terminology does not adequately separate other disparate arterial lesions such as aneurysms and stenoses. We propose the alternative, purely descriptive categorical term “extreme tortuosity phenotype”.

Although vascular tortuosity was once considered to be a manifestation of elastic buckling instability, which reversibly develops when a constrained column is subjected to axial loading, studies have shown that vascular tortuosity clinically encountered in humans is not a dynamic deformation process.[12] In contrast, it is a fixed structural feature that persists independent of the

surrounding perivascular medium, intraluminal flow or intraluminal vascular pressure.[12] As illuminated by clinical experience and recent advances in mechanobiology, mechanisms of vascular tortuosity include 1) Acute mural disruption with associated luminal distortion and secondary cell mediated remodeling and 2) Subacute or chronic alteration of axial loading and secondary cell mediated maladaptive remodeling influenced by local aberrations in arterial wall microstructure under kinematic constraints.

The former mode of tortuosity relates directly to arterial dissections. It is often observed clinically that the path of a dissection penetrating into the arterial wall through an intimal tear follows a spiral trajectory (Figure 2). Subsequent thrombosis, fibrosis and cicatrization of the false lumen will produce a true lumen that is coiled in a corkscrew manner. Alternatively, if there is distal re-entry of the false lumen and thrombosis of the true lumen, the resulting vessel will also display corkscrew tortuosity. In a few cases, the true and false lumen will both remain patent and a double barrel corkscrew vessel will form. Sequential catheter directed angiograms of evolving cervico-cerebral arterial dissections (extracranial or intracranial) in patients have shown each of these luminal configurations to progressively take shape in real time. It is highly likely therefore that many corkscrew tortuosities represent the endpoint of a healed arterial dissection. Although Brinjiki et al. concluded that arterial dissection is not a likely explanation for coiled cerebral

arteries in their review of 12 cases, we disagree with their reasoning.[9] Their erroneous conclusion is founded on two flawed arguments: 1) since the corkscrew tortuosities found in their patients were not associated with evidence of hemorrhage or cerebral ischemia, arterial dissection could not have been present, and 2) since no intramural hematoma could be detected upon retrospective review of standard T1 weighted MR images, arterial dissection is ruled out. We assert that intracranial arterial dissections frequently heal without hemorrhagic or ischemic sequelae. The literature is rich with cases of acute intracranial arterial dissection in patients whose symptoms are isolated to acute headache.[13,14,15] We have seen many such patients in our own clinical experience. Moreover, intramural hematomas are infrequently demonstrated in cases of known chronic, healed intracranial arterial dissections evaluated by conventional MR imaging sequences.[16] Studies of intracranial arterial dissection show that intramural hematomas usually become isointense and undetectable within 6 months on conventional MR imaging sequences.[17] Consequently, we believe that healed arterial dissections account for a substantial number of corkscrew tortuosities.

The latter mode of vascular tortuosity formation involves a progressive maladaptive mechanobiological remodeling response observed in blood vessels subjected to an alteration in axial loading forces when the vessel is fixed at both ends (Figure 3).[12] The remodeling response

is directed towards restoring mechanical homeostasis by normalization of axial loading stresses. Mechanobiological studies of genetically engineered blood vessels show that maladaptive responses leading to tortuosity depend on microstructural aberrations that create mechanical instabilities within the affected blood vessel wall.[12] Experimentally, such instabilities include non-uniform reductions in vessel wall elasticity, non-uniform alterations in initial vessel geometry, non-uniform alterations of tethering support by the perivascular medium and redistribution of mural collagen fibers from an axial to a circumferential orientation.[12] Clinically, some of these requisite conditions may be created by intramural hematoma, dissection, atherosclerotic plaque, remodeling induced by hypertension and senescence. In the laboratory, experimental arteriopathy induced by homozygous Fibulin 5 knockout results in aortic tortuosity due to decreased mural distensibility and reduced elastic energy storage.[12] Numerous clinically observed monogenic arteriopathies associated with extreme tortuosity phenotypes may produce alterations in mural elasticity, including Marfan's syndrome, Loeys Dietz Syndrome and the Arterial Tortuosity Syndrome.[10, 18] Although the influence of elasticity on vessel wall remodeling is complex, a loss of elasticity creates conditions that favor cumulative plastic deformation of the vessel wall resulting in irreversible and asymmetric vessel elongation. Notably, the clinical course of arteriopathy is frequently complicated by arterial dissection in all of the above noted monogenic arteriopathies. While it is possible that tortuosity predisposes to arterial dissection,

it is also possible that the microstructural instabilities and maladaptive responses that lead to tortuosity also lead to dissection, aneurysms and arterial ischemic stroke irrespective of tortuosity. Quantitative studies of arterial tortuosity in children with intracranial arterial aneurysms and children with arterial ischemic stroke show that even small degrees of tortuosity may indicate an underlying occult arteriopathy capable of producing severe clinical complications.[19, 20] Thus, numerous clinical and laboratory studies show that tortuosity is a powerful quantitative biomarker of mural instability and maladaptive vascular remodeling.

The previously reported association of unilateral internal carotid artery agenesis with corkscrew basilar artery in a 41-year-old woman has been cited as evidence of the embryological origin of the corkscrew basilar artery by Lim YC and Chung J.[1] Recent advances in mechanobiology suggest however that kinematic constraints imposed by internal carotid artery agenesis and tethering of the basilar artery by the posterior communicating artery, may have engendered the progressive development of tortuosity over time, and that corkscrew tortuosity did not develop contemporaneously with internal carotid agenesis. Thus, embryological variations may contribute structural instabilities that lead to the development of tortuosity, but the development of tortuosity is not a direct product of embryology in those cases. Moser FG, et al. suggested that the corkscrew tortuosity of the basilar artery is due to excessive axial growth

caused by overexpression of angiogenic growth factor.[21] While current models of vascular tortuosity based on maladaptive remodeling implicate axial growth of vessels, potentially mediated by angiogenic growth factors, as an integral component of the tortuosity mechanism, overexpression of angiogenic growth factors is not the primary driver of the maladaptive response.

In the case reported by Anokwute MC, et al., it is possible that the pituitary tumor has a merely coincidental relationship with the corkscrew basilar artery, though it is tempting to speculate that the tumor may have played a critical role in the development of the corkscrew basilar artery.[1] One possibility is that elevation of the circle of Willis caused by the tumor produced a traction force on the basilar artery, inducing axial loading of the basilar trunk. This is suggested by vertical straightening of the posterior cerebral artery P1 segments in Figure 1B from the index article by Anokwute MC, et al.[1] As shown by Weiss D and colleagues, axial loading is an important trigger for the type of maladaptive remodeling that leads to vascular tortuosity.[12] Although one may wonder if successful treatment of the adenoma would restore normal basilar artery morphology, multiple studies have shown that once formed, vascular tortuosity cannot be reversed, even when the underlying drivers are eliminated.[12] Another possibility that links corkscrew tortuosity to the tumor invokes a reported association of cerebral arteriopathy with pituitary adenomas.[22]

In this case, cerebral aneurysms are considered to be a surrogate for cerebral arteriopathy. Notably, although the association with intracranial aneurysms (i.e., cerebral arteriopathy) is strongest for growth hormone secreting macroadenomas, there is a general association of cerebral aneurysms with pituitary adenomas.[22] Hence, according to the mechanobiological model of maladaptive remodeling described by Weiss D, et al., the pituitary tumor may represent an axial loading stimulus and/or a marker of arteriopathy that forms a requisite microstructural aberration of the arterial wall.[12]

The possibility that tortuosity itself is a structural instability that confers vulnerability to cerebrovascular complications such as aneurysm formation and arterial ischemic stroke is compelling, though unproven. Experimental studies show that tortuosity increases the work of fluid transport by increasing vascular resistance, increases turbulence, increases non-uniform shear stress, increases axial tension and induces wall thinning along the convex wall of curves.[12] Clinical studies show that the arterial tortuosity index correlates with the risk of arterial dissection in patients with clinically overt arteriopathies.[23] A third of coiled arteries in Brinjiki's series had focal aneurysms, and almost one half were partially calcified indicating a tendency toward mural degeneration.[9] Anokwute, MC et al. propose that tortuosity of the basilar artery may involve asymmetric lengthening and narrowing of perforating branch arteries causing a

restriction of blood flow and ischemia in microvascular territories. It is likely that this mechanism of ischemia contributes to the pathogenesis of vertebrobasilar dolichoectasia. It is also possible that disruption of laminar flow within corkscrew tortuosities promotes formation of platelet thrombi capable of mediating microvascular ischemic injury. Anokwute, MC et al also suggest that increased wall shear stress created by a corkscrew vascular morphology may promote aneurysm formation.[1] Finite element analysis studies reveal a complex yet poorly understood relationship between shear stress, biaxial strain and aneurysmal degeneration of the arterial wall.[24,25] Owing to advances in neuroimaging and interventional flow diversion technologies, these relationships continue to be elucidated at a dizzying pace. In support of the notion that tortuosity is itself a structural instability that confers vulnerability to cerebrovascular complications, laboratory studies show that wall thinning develops on the convex outer wall of tortuous curves. Since wall thinning is the first stage of aneurysm development, it follows logically that the convex wall of tortuous curves will be hot spots for aneurysm formation.[26] Indeed, a prior reported case of corkscrew basilar artery was associated with a ruptured aneurysm on the convex wall of a tortuous basilar artery curve.[2]

Notwithstanding questions that remain about the pathogenesis and clinical significance of arterial tortuosity, we agree with Anokwute, MC and colleagues that the initial definitive

diagnostic evaluation of intracranial corkscrew tortuosities should be performed by catheter directed angiography. Catheter directed angiography enables differentiation of fusiform aneurysms, and other entities that can mimic corkscrew tortuosities on cross-sectional imaging studies such as CTA and MRA. Catheter directed angiography also enables confident identification of intimal flaps, intraluminal thrombus, focal aneurysmal dilatations and steno-occlusive changes that may influence the clinical behavior of intracranial vascular tortuosities and prompt specific therapeutic measures such as aneurysm occlusion or anti-thrombotic drugs. We also agree that serial surveillance vascular imaging by sequential MRA should be performed to intermittently reassess intracranial corkscrew tortuosities for new aneurysmal changes. Follow up MRI and MRA studies are preferred to mitigate cumulative exposure to ionizing radiation. Any change with respect to baseline MR imaging studies should prompt catheter directed angiography for further evaluation.

One of the entities considered by the authors in their differential diagnosis of an intracranial arterial corkscrew tortuosity is fibromuscular dysplasia (FMD). According to international consensus, FMD is defined as an idiopathic segmental, non-atherosclerotic, non-inflammatory disease process affecting the musculature of medium sized arteries.[27] The disease is characterized by cellular proliferation which irreversibly distorts the architecture of the arterial

wall and leads to tubular or beaded forms of fixed luminal narrowing. Intimal, medial and peri-adventitial patterns have been histologically differentiated. The extracranial vertebral arteries, extracranial internal carotid arteries, external carotid artery branches and renal arteries are commonly affected. Given the diversity of anatomical, angiographic and histological traits that characterize FMD, it is likely that FMD is a non-specific maladaptive remodeling process expressed by multiple distinct arteriopathy conditions. Although there are multiple isolated case reports that claim to show examples of intracranial FMD, the vast majority of these cases correspond to misdiagnosed cases of intracranial atherosclerosis, vasculitis, arterial tortuosity syndromes, intracranial arterial dissection, reversible cerebral vasoconstriction syndrome (RCVS), focal cerebral arteriopathies (FCA) of childhood and other miscellaneous cerebral arteriopathies.

As with most idiopathic conditions, the diagnosis of FMD is to a large extent based on exclusion. FMD lesions do not resolve spontaneously or in response to vasodilators, must not be associated with atheromatous mural changes and must not be associated with vascular inflammation either as an isolated condition or as a component of a systemic process. Flawed reports falsely alleging intracranial FMD typically fail to satisfy these fundamental diagnostic requirements. In recent years, dissecting and inflammatory subtypes of focal cerebral

arteriopathy have been recognized as distinct entities commonly associated with childhood stroke. It was not long ago that such cases were routinely misdiagnosed and published as examples of intracranial FMD.[28]

Many authors have misunderstood FMD as nothing more than an angiographic pattern that may be observed on imaging studies depicting vascular lumen morphology. As a diagnostic term, FMD specifies maladaptive overgrowth of mural smooth muscle tissue in the absence of immuno-inflammatory drivers or inciting lipid deposits. These features cannot be demonstrated on angiographic studies yet attempts to diagnose FMD based purely on angiographic patterns persists. The problem is amplified by the fact that FMD has varying degrees of angiographic overlap with other well defined arteriopathies including atherosclerosis, vasculitis, RCVS and FCA. Angiographic differentiation of FMD from these arteriopathies, though non-specific, relies on subtle distinctions that are difficult for the non-expert. Thus, examples of intracranial FMD reported in the literature commonly correspond to pseudo-FMD. The accumulation of pseudo-FMD cases mislabeled as FMD have contributed to an increasingly pervasive lack of clarity on the topic of cerebral arteriopathy. Kirton et al, as cited by Anokwute et al, have recognized this problem.[29] They attempted to increase diagnostic specificity by applying strict pathological criteria to the diagnosis of FMD. Using this approach, they found that classic angiographic

patterns attributed to FMD do not correlate with histological patterns of FMD. The authors concluded that pathological confirmation is the only means by which FMD can be confirmed. They further stated that a high proportion of “clinically suspected” FMD represents FCA. In cases that the authors assessed as “pathologically proven” FMD, the tissues that were histologically examined varied widely (most commonly renal artery and pulmonary) with only a minority of cases being clinically evaluated for evidence of vasculitis. Histological criteria for FMD involving the intracranial cerebral arteries have not been delineated, and it is unclear how the findings overlap with other forms of cerebral arteriopathy such as moyamoya disease. Kirton et al. acknowledged that the distinction between moyamoya and FMD is not well defined histologically. We believe that the report by Kirton et al. further calls into question the concept of intracranial FMD as a distinct disease entity. Thus, in the absence of clear diagnostic criteria for intracranial FMD, we propose that the ambiguous and misleading diagnostic label should be avoided. Nonetheless FMD as described in the cervical arteries, fits well into the theoretical framework of arterial tortuosity as a maladaptive biomechanical remodeling response to axial loading forces. Specifically, segmental overgrowth of mural tissue as expressed in FMD can serve as the focal structural aberration that reduces arterial wall elasticity and is required for the initiation of tortuosity. Histological criteria for the diagnosis of intracranial FMD is not realistic, nor in the interest of patients. Recent advances in intracranial vessel wall imaging

enable noninvasive phenotyping of cerebral arteriopathies and may allow for improved diagnostic specificity relative to angiographic and clinical criteria alone.

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**Figure 1a-d** Theoretical model of corkscrew tortuosity as a variation of embryonic development.

Hypothetical paired longitudinal arteries are depicted on each side of the embryonic midline, each contributing segmental arteries at 4 hypothetical embryonic segmental levels (a). At each segmental level, sprouting angiogenesis results in extension of a midline angiogenic bud from the longitudinal arteries (b). The segmental midline angiogenic buds form anastomoses that join the longitudinal arteries across the midline at each segmental level. At the same time alternating segments of the longitudinal arteries involute (c). The resulting configuration of blood vessels is shown to have a sinusoidal tortuosity or corkscrew geometry.

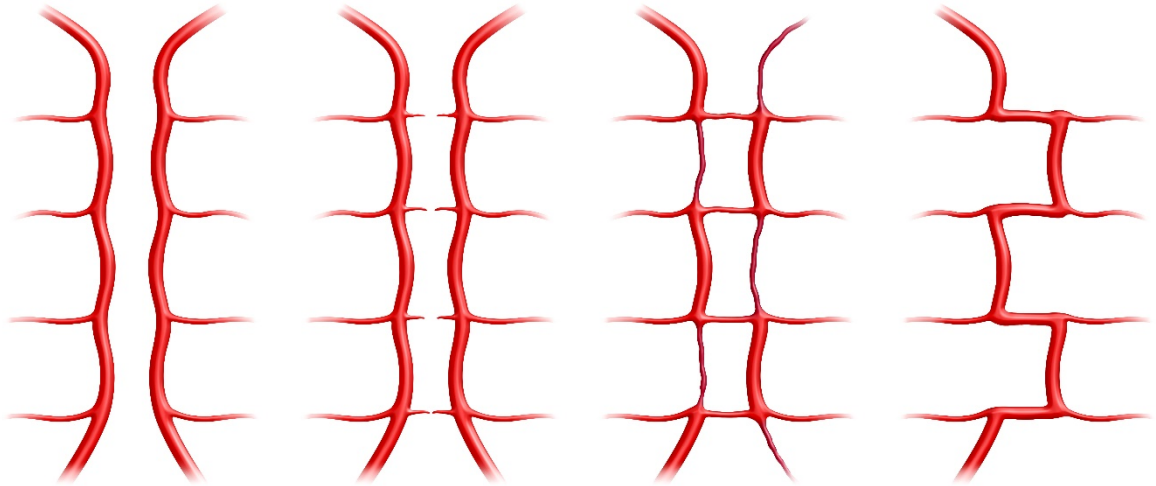


**Figure 2a, b** Tortuosity as a sequelae of arterial dissection. Two fates of a hypothetical spiral arterial dissection are depicted. In each case, the false lumen has a spiral path through the arterial wall, and there is a distal re-entry zone that reconnects the false lumen with the true lumen. In one case, the spiral false lumen is thrombosed and resealed by apposition of the intimal flap. The true lumen is deformed into a spiral, or corkscrew geometry by the constricting false lumen that bulges into the true lumen (a). In the second case, the intimal flap seals the true lumen and results in thrombosis of the true lumen. The recanalized spiral or corkscrew false lumen bridges proximal and distal segments of true lumen across the dissection (b).

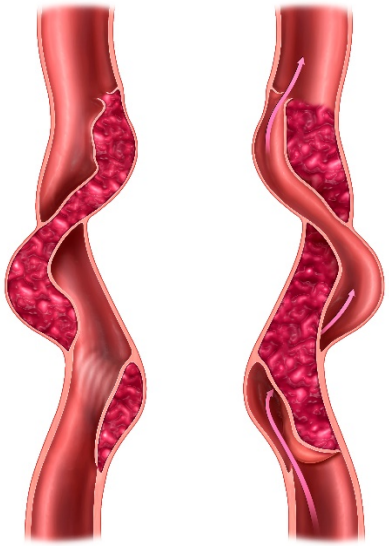
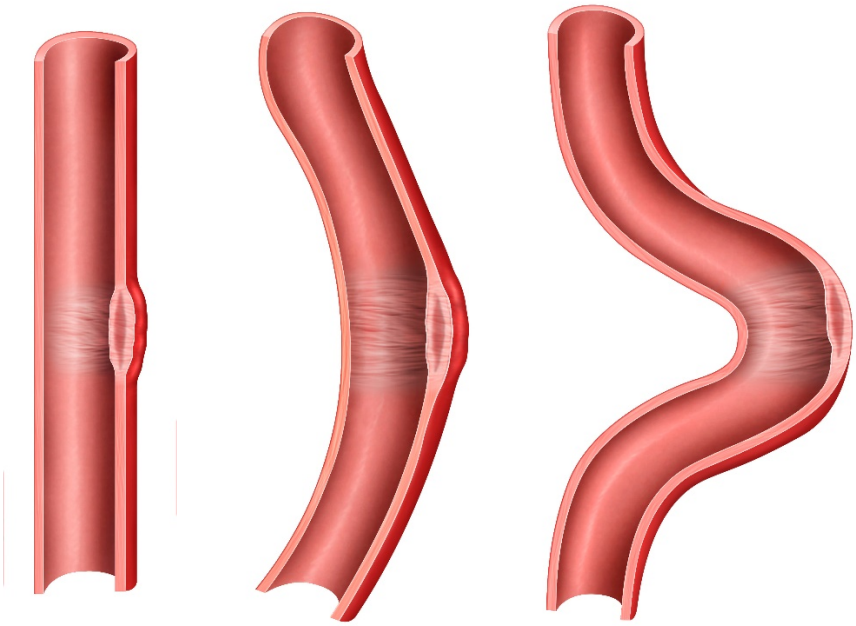


**Figure 3a-c** Tortuosity as a maladaptive mechanobiological remodeling response to axial tension forces in diseased arteries. An intramural hematoma associated with concentric rings of fibrosis forms a focal microstructural aberration with reduced vessel wall elasticity (a). The structural changes resist circumferential expansion and promote increased longitudinal expansion (b). Maladaptive remodeling in response to axial tension forces results in the development of tortuosity (c).



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