Twisted Blood Vessels: Symptoms, Etiology and Biomechanical Mechanisms

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Key Words

Vessel tortuosity · Artery tortuosity · Mechanical buckling · Wall remodeling · Mechanical instability

Abstract

Tortuous arteries and veins are commonly observed in humans and animals. While mild tortuosity is asymptomatic, severe tortuosity can lead to ischemic attack in distal organs. Clinical observations have linked tortuous arteries and veins with aging, atherosclerosis, hypertension, genetic defects and diabetes mellitus. However, the mechanisms of their formation and development are poorly understood. This review summarizes the current clinical and biomechanical studies on the initiation, development and treatment of tortuous blood vessels. We submit a new hypothesis that mechanical instability and remodeling could be mechanisms for the initiation and development of these tortuous vessels.

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Introduction

Tortuous or twisted arteries and veins are commonly seen in humans and animals [1–3]. While mild tortuosity is a common anomaly without clinical symptoms, severe tortuosity can lead to various serious symptoms. Clinical

observations have linked tortuous arteries and veins to aging, atherosclerosis, hypertension, genetic defects and diabetes mellitus [4–8]. However, the mechanisms of tortuous vessel formation and development are poorly understood. Therefore, the mechanisms of vessel tortuosity need careful investigation.

The objectives of this paper are first to review the angiographic findings, clinical symptoms and treatment of tortuous blood vessels, and then to summarize the current clinical and biomechanical studies on their initiation and development.

Symptoms

Clinical Phenotypes of Vessel Tortuosity

Arteries are normally straight conduits that efficiently transport blood to distal organs. However, arteries may take a tortuous path due to abnormal development or vascular disease. Tortuous blood vessels have become a common angiographic finding in many studies and clinical screenings [2, 9, 10]. With the advance of imaging technology, more and more tortuous vessels are being detected [2, 11]. Various forms have been reported in clinical investigations, most commonly curving/curling, angulation, twisting, looping and kinking vessels (fig. 1) [1, 6, 12].

Table 1. Tortuous vessel branches and associated diseases, with references

Vessel branch	Aging	Atherosclerosis	Diabetes	Hypertension	Genetic	Other
Aorta	[118, 121] [48, 166]	[166, 167]		[67]	[7, 94, 97] [67, 101]	[166]
Carotid	[4, 58, 59] [64]	[4, 13, 57, 58]	[113]	[1, 4, 6, 12] [63]	[60, 95]	[73, 98] [122, 168]
Vertebral, lingual, or subclavian	[13, 15]	[13]	[96]	[14, 15]	[14, 15] [99, 101]	[73] [168]
Iliac or femoral	[48]	[57, 129, 167]		[16]	[16]	[2, 10, 62]
Cerebral	[24, 69]		[82, 169]	[5, 69]	[93, 101]	[23, 24, 73] [34–36]
Coronary	[32, 33]	[75]	[74–76]	[25, 32, 74]	[25]	[31, 77]
Retinal	[22, 81]	[88]	[8, 22, 82]	[20, 78, 79, 91]	[79–81]	[18, 88]
Conjunctival			[8, 83, 84]	[8, 83]	[8, 83]	
Capillary	[22]	[47]	[8, 76]	[27, 89, 91]		[25, 26]
Varicose vein	[106, 107]		[107]	[43, 107]		
Collateral	[34]	[47]		[3, 44, 46]	[3, 44, 46]	[33]

Fig. 1. Schematics of various phenotypes of tortuous vessels. Left to right: curving, angulation/kinking, looping and spiral twisting.

Artery Tortuosity Is a Common Anomaly That Frequently Occurs in Many Vessels

Blood vessel tortuosity is a widely observed vascular anomaly affecting a range of vessels, from large arteries and veins to small arterioles and venules, in almost all locations in the body. Tortuosity has often been reported in the aorta and capillaries, as well as in the vertebral, iliac, femoral, coronary, cerebral and internal carotid arteries (see table 1).

Tortuosity and redundancy of the internal carotid artery is a common angiographic and MR angiographic finding [1, 2, 9]. In one of the largest angiographic studies conducted by Weibel and Fields [1], internal carotid artery tortuosity and angulation, respectively, were observed in 35 and 5% of 1,438 consecutive patients. Tortuous vertebral, subclavian and lingual arteries have also been reported [13–15]. Tortuous iliac and femoral arteries

have been reported in some patients and cyclists [2, 16]. Though rare, tortuosity has also been observed in other vascular branches in the arterial tree. These branches include, but are not limited to: the ulnar artery and radial and digital arteries [17–19]. It seems that tortuosity can affect almost all medial-sized arterial branches.

Tortuosity has also been frequently reported for small arteries and veins, most commonly in retinal and conjunctival vessels, due to their easy accessibility. Tortuous retinal arteries and veins have often been observed in patients with retinopathy and other diseases [20–22]. Tortuosity also happens in arterioles [5, 23, 24] and capillaries [22, 25–28] in the skeletal muscle, myocardium and brain tissues, as well as in tumors [28, 29]. Tortuous coronary arteries have been observed in patients with hypertension and myocardial infarction [13, 30–33]. Tortuous cerebral arteries have been frequently reported, including the basilar, communicating, anterior and posterior cerebrals and the arterioles in white matter [5, 23, 24, 34–36].

In addition, tortuosity also occurs in veins and vascular grafts [37–39]. Arteries and veins may become tortuous after bypass grafting and reconstructive vascular surgery [40, 41]. Twisting of vein grafts affects the patency of vein grafts [37–39]. Tortuous veins also occur in many patients with varicose veins due to vein valve disease [42, 43].

Furthermore, tortuosity often develops in collateral arteries after stenotic or occlusive disease in a major artery (fig. 2) [44–46]. The so-called ‘corkscrew collaterals’ are a widely observed phenomenon that hinders collateral development, a necessary component of arteriogenesis and tissue regeneration [3, 46, 47].

Fig. 2. Tortuous collaterals form after occlusion of a femoral artery (from [45]).

Measurement of Vessel Tortuosity

The level of vessel tortuosity is often described by the tortuosity indices. A commonly used tortuosity index is defined as the ratio of vessel curve length over the line distance between the two ends [32, 35, 48] (see fig. 3).

Alternatively, the tortuosity index can be defined as the total curvature or mean curvature, which calculates the cumulative sum of the angle between segment vectors normalized by vessel length [48–52]. A simplification of the index is the use of the ratio of deflection amplitude versus the wavelength [53, 54].

These indices can be determined from the images obtained from angiography and MR angiography and automatic approaches have been developed for the calculations [49, 52, 55, 56]. In general, these indices depend on wavelength, wave number and wave amplitude. Vessel caliber may also play a role in evaluating the severity of vessel tortuosity [11].

Etiology: Association with Vessel Diseases and Clinical Consequences

With the advance of imaging technology and its wider application, many asymptomatic tortuous arteries are being diagnosed. While mild tortuosity in some patients is

Fig. 3. Definitions of tortuosity indices. The integrated curvature of the middle panel is equal to the cumulative sum of angles α_1 – α_4 .

asymptotic and often largely ignored, many others show symptoms linked to various vascular diseases (see table 1).

Extensive clinical studies have shown that artery tortuosity is associated with hypertension, aging, atherosclerosis and other pathological changes in the arteries [4–8, 13, 24, 33, 57]. It is often reported in elderly populations with severe tortuosity and angulation being associated with aging; it rarely occurs in children [4, 58, 59]. The prevalence of artery kinking is tripled in the aged population and is quadrupled in the aged hypertensive population [6]. Severely tortuous arteries can hinder the blood flow and lead to a transit ischemic attack of distal organs [60]. Recent clinical studies have demonstrated that hypertensive pressure is a risk factor for artery tortuosity [4–6, 20]. Below is a summary of some commonly seen vessel tortuosities and their associated diseases.

Carotid Artery Tortuosity

Clinical studies have shown that internal carotid artery tortuosity may lead to symptoms including dizziness, vertigo, syncope, blackout or persistent tinnitus (ringing in the ears) [61]. Severe tortuosity may lead to arterial kinking (acute angulation) which causes artery occlusion and is associated with severe symptoms including transient ischemic attack, stroke [60], hemiplegia and

other cerebrovascular deficiencies [6, 9, 62]. Tortuous carotid arteries are often reported in hypertensive patients [4, 6, 63]. They are often associated with atherosclerosis [4, 13, 57] and there is speculation that they could be a factor leading to atherosclerosis [57]. Carotid artery tortuosity is often reported in elderly populations with severe tortuosity and angulation being associated with aging [4, 58, 59, 64]. Reduced wall thickness or lumen diameter is associated with a higher prevalence of tortuosity, although there is discrepancy among the clinical reports on the correlation between atherosclerosis and artery tortuosity [63, 65]. Arterial degenerative disease is often concomitant with internal carotid artery tortuosity, but is not always associated with it [1, 66–68].

Cerebral Artery Tortuosity

Tortuous cerebrals often occur in basilar, communicating, anterior and posterior cerebrals as well as in arterioles in the white matter [5, 23, 24, 34–36]. Tortuosity of cerebral arteries has been reported for aged, hypertensive patients [5, 23, 24, 69] and in patients with ‘Moyamoya’ disease [70–72]. Cerebral arteries may also become tortuous due to malformation [73] or increased flow [34, 35] associated with elastin degradation. Tortuosity of cerebral arteries was found to be associated with the severity of hypertension [5].

Coronary Artery Tortuosity

Tortuosity of coronary arteries occurs in patients with hypertension and myocardial infarction [13, 30–33, 74]. Tortuosity is associated with increased acute occlusion of coronary arteries [75], diabetes [74–76] and coronary artery fistula [77]. Tortuous coronary arteries hamper ventricular function [31] and have been proposed as an indicator of ventricular dysfunction [30, 31].

Retinal Artery and Vein Tortuosity

Tortuous retinal arteries and veins are associated with hypertension, diabetes and genetic disorders [8, 20, 22, 78–81]. Tortuous conjunctival arteries and veins are also reported in patients with diabetic retinopathy [8, 82–84] and hypertension [84, 85]. Tortuosity of retinal vessels has been suggested as an indicator of arterial hypertension, retinopathy, cerebral vessel disease, stroke and ischemic heart disease [49, 51, 86–88].

Tortuosity of Capillaries

Tortuous capillaries have been observed in both skeletal muscles and in the myocardium [25–27, 76, 89] as well as in other organs [8, 22, 90]. Capillary tortuosity

level increases and decreases with muscle contraction and relaxation allowing the vessel surface area and permeability to remain the same [26]; a higher level of tortuosity has been associated with hypertension and diabetes [8, 76, 89, 91].

Artery Tortuosity Syndrome

Artery tortuosity syndrome (ATS) is a rare condition caused by an autosomal recessive disorder (such as mutation of the SLC2A10 gene [7]) and characterized by tortuosity, elongation and aneurysm formation in major arteries due to the disruption of elastic fiber in the medial layer of the arterial wall. ATS is seen in members of the same family and affects all major arteries [7, 92, 93]. In addition, tortuous aortas have been observed in mice with an elastin gene knockout [79, 94–97].

Loeys-Dietz Syndrome

Artery tortuosity can also be associated with aneurysms [48, 98]. Loeys-Dietz syndrome is a recently defined syndrome. Patients demonstrate tortuous aneurysmal vessels [99–101]. It is considered to be due to mutations in the TGFβ receptor [100, 102]. As aneurysmal arteries are prone to tortuosity, it is possible that tortuosity affects wall stress in aneurysms [48, 103], but the interaction needs further study.

Varicose Veins

Tortuous varicose veins cause morbidity and are a common manifestation of chronic venous disease [43]. Varicose veins are often associated with venous hypertension and valvular insufficiency [42, 43] and have a high prevalence in over one third of the population aged 50 years or older [104–107].

In addition to tortuous retinal veins, tortuous venules have been observed in cerebral, coronary, digital and other vascular beds [24, 33, 108, 109]. Vein grafts may become tortuous under arterial pressure if not stretched sufficiently in the axial direction [40, 110]. Venous tortuosity may affect blood flow and venous wall remodeling and therefore be associated with venous diseases; it has been reported that it leads to sluggish blood flow and thrombosis [111, 112].

While evidence strongly demonstrates the association of artery tortuosity and vein tortuosity with vascular diseases, the underlying mechanisms remain unclear and warrant further study to be understood.

Surgical Treatment of Tortuous Vessels

While many mild tortuous arteries are left untreated, severely tortuous arteries with clinical symptoms can be treated with reconstructive surgery [61]. Severely tortuous or kinking carotid arteries have often been treated by surgical shortening reconstruction [9, 113, 114]. The surgical 'stripping' technique has been used [115]. The arteries are often treated while performing surgery for other vascular diseases such as stenosis, aneurysm or atherosclerosis [9, 116]. Generally, surgical treatment achieves a better prognosis for symptomatic patients [15, 117].

Mechanical Changes in Tortuous Arteries

Clinical and experimental studies have demonstrated a strong association between vessel tortuosity and mechanical factors, such as blood pressure, blood flow, axial tension and wall structural changes.

First, artery tortuosity has been shown to be associated with hypertension [4, 5, 33]. Tortuosity of cerebral arteries was found to be associated with the severity of hypertension [5]. Vein pressure has also been associated with tortuosity in retinal veins [87, 91].

Second, artery tortuosity has been associated with reduced axial tension or elongation of the arteries. Normal arteries are subjected to a significant axial tension *in vivo* [118, 119]. Certain levels of axial tension are essential in maintaining the stability of the arteries and preventing tortuosity. Axial tension may decrease with excessive growth of arteries and reduces with aging [118, 120, 121]; Jackson et al. [122] showed in a rabbit model that reduced axial tension by interpositional grafting in carotid arteries can lead to artery tortuosity.

Third, weakening of the arterial wall has been associated with tortuous vessels. Degradation of elastin, an important extracellular matrix component, weakens the arterial wall [123] and leads to tortuosity [98]. Elastin deficiency has been associated with tortuous arteries in patients with arterial tortuosity syndrome and Loeys-Dietz syndrome as well as in mice with an elastin gene knockout [79, 94–97, 124]. Increased blood flow also leads to tortuous cerebral arteries associated with elastin degradation [34, 35]. The fragmentation of elastin has been reported in the artery wall of subjects with artery tortuosity and has been considered a cause of vessel lengthening [66, 68, 121].

In addition, tortuous vessels occur when surrounding connective tissue degradation happens. It was reported

that tortuous arterioles were associated with the development of small lacuna cavities (*status lacunaris*) in human basal ganglia [23]. In contrast, enhanced support of the surrounding tissue prevented vessel tortuosity [40, 125, 126].

Combined, this evidence strongly suggests that hypertensive pressure, reduced axial tension and weakened wall stiffness may play an important role in the development of artery tortuosity.

On the other hand, tortuosity increases the resistance to blood flow and severe tortuosity can obstruct or even occlude blood flow [33, 62]. Lumen shear stress and wall stress are also altered in tortuous arteries [127] (fig. 4). Computational simulations have confirmed this [128–131]. Tortuous veins may also lead to thrombosis due to changes in the blood flow and shear stress [111, 132, 133].

While the clinical evidence strongly suggests that mechanical factors may play an important role in tortuous blood vessels, few studies have been conducted to determine the possible biomechanical mechanisms involved.

Mechanical Stability of Blood Vessels

Arteries are subjected to significant mechanical stresses generated by lumen blood flow, pressure and surrounding tissue tethering. These stresses are influenced by movement of the body, e.g. from walking, exercise and gravity. It has been well documented that mechanical stresses play important roles in regulating the function of vascular cells [134–137]. A high mechanical stress can lead to injury to the cells and damage to the vascular wall. It can also lead to mechanical instability and buckling of the blood vessels as tubular structures [138, 139]. While the mechanical stress and strength of the arterial wall as a biological tissue have been extensively studied, there are few studies on the stability of arteries as a functional structure. The stability of blood vessels under lumen pressure is essential to maintain their physiological function. The complete understanding of arterial function and disease cannot be achieved without understanding the mechanical stability of arteries under pressure and flow.

It has been well documented that blood vessel lumen may collapse when internal pressure is too low or the external pressure exceeds the lumen pressure by a critical value [140]. Collapsible tube models have been developed to determine the critical pressures [125, 140–142]. Re-

Fig. 4. Comparison of stresses in normal and tortuous arteries. **a** Illustration of uniformly distributed lumen shear stress (τ) and tensile stresses in the axial, circumferential, axial and radial directions (σ_z , σ_θ and σ_r , respectively). **b** Velocity profile at 3 axial locations and wall shear stress variation along the bottom side in a sinusoidal vessel obtained from computational simulations. **c** Axial wall stress distribution along the circumference at 2 peak deflection locations.

cently, Han [138, 139] demonstrated that long vessel segments under lumen pressure can become unstable when the lumen pressure exceeds a critical value. The phenomenon was termed 'vessel buckling' because it is similar to column-beam buckling. Buckling equations were estab-

lished to estimate the critical pressure [138, 139, 143]. In fact, there were a few reports that modeled blood vessels as close-ended vessel segments under axial compression and used the linear elastic Euler buckling equation to estimate the critical pressure [87, 144, 145].

Artery Buckling under Lumen Pressure

Using both adjacent equilibrium and potential energy approaches, Han established an artery buckling model that predicted the critical load for bent buckling of long vessel segments [138, 139, 143]. The buckling equation is:

$$p_{cr} = \frac{N}{\pi r_i^2} + \frac{EI}{\pi r_i^2} \left(\frac{n\pi}{l} \right)^2 + \frac{k_s}{\pi r_i^2} \left(\frac{l}{n\pi} \right)^2 \quad (1)$$

where k_s is the modulus of the surrounding matrix, N is the axial force, EI is the cross-sectional bending modulus, l is the vessel length, r_i is the lumen radius and n is the wave number of the buckling mode shape [138, 139]. Both N and EI are functions of the transmural pressure p and the strains.

This model equation demonstrates that arteries buckle (and thus become tortuous) when lumen pressure exceeds a critical pressure at a given length. The critical pressures of blood vessels are determined by vessel dimensions, wall stiffness and axial tension [53, 146]. The critical pressure decreases when there is a decrease in the axial stretch (tension), the mechanical stiffness of the arterial wall and/or the stiffness of the surrounding tissue. According to this equation, without surrounding matrix support ($k_s = 0$), p_{cr} is minimal at $n = 1$ and with matrix support ($k_s > 0$); the 2nd term in the equation increases with increasing wave number n while the 3rd term decreases. So a minimum buckling pressure is reached at a wave number $n > 1$. Therefore, arteries buckle into multiple wave shapes within the surrounding tissue matrix at a higher critical pressure [138].

Experimental testing using porcine carotid arteries validated these model predictions. The critical pressures of porcine carotid arteries and veins decrease with reduced axial tension/stretch [53, 54, 127, 147, 148]. Although the classic linear elastic Euler column buckling model predicts a sudden, large, catastrophic increase of deflection with buckling, arteries do not show a sudden large deflection and catastrophic failure at buckling, but only a small deflection due to geometric nonlinearity [139, 149]. The deflection of a buckled artery increases after buckling with increasing lumen pressure [148]. While arteries submerged in saline solution (without matrix support) buckle into single-wave shapes, arteries embedded in gelatin gel buckle into multi-wave shapes (fig. 5) [148]. It has also been observed that elastin degradation by elastase reduces the critical pressure of arteries associated with a reduced mechanical stiffness of the arterial wall [148].

Fig. 5. Photographs of an artery within a supporting matrix under elevated internal pressure buckling into tortuous shapes. **a** Under an internal pressure (140 mm Hg) beyond its critical pressure (80 mm Hg) in PBS solution. **b** Under an internal pressure (230 mm Hg) beyond its critical pressure (150 mm Hg) in gelatin. (Photographed by Mr. Shawn Lamm in the author's laboratory).

Vessel buckling has been observed in vivo as well. Buckling of vein grafts under arterial pressure has been observed in vivo (e.g. [150]). It has been observed that canine vein grafts sometimes become tortuous immediately after being exposed to arterial pressure, and this buckling can be corrected by shortening the length of the graft (to increase the axial tension) [40, 126].

Further model analysis demonstrated that geometric variations such as initial curvature, tapering, eccentric or oval cross sections, stenosis and aneurysm often reduce the stability, as shown by the reduced critical pressures [103, 131, 135, 143, 151].

Comparison of Artery Buckling and Tortuosity

Buckling is an instant deflection under internal pressure due to mechanical instability; arterial tortuosity is a chronic presentation as a result of arterial remodeling. Artery buckling initiates a small deflection that gradually increases if the pressure continues to increase [53, 148]. Tortuous vessels often demonstrate a finite amplitude of waviness.

While vessel buckling and vessel tortuosity are two different phenomena, buckled arteries and tortuous arteries demonstrate great similarities. First, their curved shapes look alike. Arteries surrounded by elastic matrix (gel) buckle into wavy shapes in vitro and tortuous arteries in vivo demonstrate waviness within the surrounding tissues. Second, the mechanical factors that cause buck-

Fig. 6. A proposed new mechanism for the initiation and development of vessel tortuosity.

ling are a risk factor for patients. High blood pressure (hypertension), weakened wall due to internal elastic lamina/elastic fiber degradation and reduced axial stretch/tension not only lead to artery buckling in vitro and in vivo, but are also associated with a high prevalence of tortuosity in patients (as described in previous sections). A straight artery may develop into wavy tortuous shapes when the surrounding tissues are weakened by degenerative diseases. These similarities suggest a possible link between vessel buckling and vessel tortuosity. Furthermore, a recent in vivo experiment of rabbit carotid arteries and our ex vivo experimental evidence showed that axially offloaded arteries adapt over time and may become permanently tortuous in shape, suggesting that buckling may lead to tortuosity [122]. More research needs to be done to further elucidate the relationship between artery buckling and tortuosity.

A New Hypothesis

Based on the lines of evidence presented above, we submit a new hypothesis that mechanical instability and remodeling could be mechanisms for the initiation and development of tortuous blood vessels. We propose that mechanical buckling and the loss of mechanical stability could initiate the development of tortuous arteries. Buckling stimulates wall remodeling and the interaction between artery dynamics, buckling and wall remodeling leads to further development of vessel tortuosity.

Tortuosity may be caused by multiple factors: genetic factors, degenerative vascular diseases and an alteration

in blood flow and pressure. Previous studies indicated that degenerative diseases, aging and genetic defects could also lead to artery buckling by altering wall properties and thus reducing the critical pressure (fig. 6). While buckling may not be the only possible mechanism of tortuosity, it seems to be a mechanism that links many of the factors that cause tortuosity.

Future Challenges

While we have gained some understanding of the development of tortuous vessels, there is a long way to go. There are many unanswered questions yet to be investigated.

Buckling and Mechanical Stability under Pulsatile Flow Need Investigation

Arteries in vivo are under pulsatile pressure and flow. Artery buckling can lead to cyclic bending under pulsatile pressure. Dynamic analysis of artery stability demonstrated that arteries may become unstable under certain pulsatile pressures [152, 153]. Recent studies from the author's laboratory suggested that arteries under pulsatile pressure buckle when the peak pressure reaches the critical pressure as determined under static pressure [154]. However, further work needs to be done to better understand the artery buckling behavior under pulsatile pressure.

The Effect of Bent Buckling on Blood Flow Needs Investigation

Blood flow in the curved arteries, especially in the aorta, superior femoral arteries and coronary arteries, has

been studied via experimental tests and numerical simulations [129, 155, 156]. Back et al. [156, 157] examined the flow in a human femoral artery model with reverse curvature and measured the flow in a sinusoidal coronary artery model. These and many other studies have shown that vessel curvature has significant effects on blood flow. Curvature increases pressure loss, flow resistance and secondary flow, as well as pressure and lumen shear stress on the outer curvature [129, 158]. Results from computational fluid dynamics showed that the shear stress is approximately 60% higher on the outer wall than on the inner wall of a curved human right coronary artery [158]. However, buckled arteries and tortuous corkscrew collaterals are often severely tortuous. More studies are needed for severely and continuously tortuous arteries. It is unclear how the severity of arterial tortuosity is related to the level of flow alteration. However, artery buckling or tortuosity will lead to complex wall stress distributions in the arterial wall that vary circumferentially and longitudinally compared to the axisymmetric wall stress in straight cylindrical arteries [53, 151, 159]. A systemic study of the blood flow and wall stress analysis is needed to fully illustrate the stress alterations in the tortuous arteries due to the buckling effect.

It has been suggested that arterial tortuosity affects blood flow and may make the arteries prone to atherosclerosis [4, 57, 129]. By causing increased local stress concentrations, tortuosity may also render atherosclerotic plaques prone to rupture [160–162].

Wall Remodeling in Buckled Arteries

It is well known that both wall stress and shear stress influence vascular cell biology [134–137]. However, it is unclear how the tortuosity-induced flow and wall stress alterations affect the vascular cells and extracellular matrix and thus arterial wall remodeling. Previous studies have shown that the cyclic flexure of porcine femoral arteries affects extracellular matrix gene expression and cell proliferation [163, 164] and is related to atherosclerosis [159]. Similarly, our laboratory recently observed non-symmetric cell proliferation in buckled arteries [165]. Further studies are needed to understand the long-term adaptation of the buckled artery.

Recent experimental evidence from animal models demonstrated that the development of tortuosity in cerebral arteries, secondary to flow increase, occurs as a gradual increase of the waviness that progresses over days and weeks [34, 35]. The development of tortuosity of an artery is likely to stem from instability, i.e. the growth of small waviness. Such tortuosity development would have to in-

volve interactions between arterial dynamics and active vascular remodeling. Mechanical buckling creates uneven mechanical stress on the inner and outer curve sides of the arterial wall and stimulates gradual, uneven wall remodeling [165] which creates an imperfection in the arterial wall and thus decreases the critical pressure for buckling. So the deflection will gradually magnify and buckling effects will be exacerbated under the same pressure. Future work is needed to investigate the development process of the buckling tortuosity.

Conclusions

Tortuosity is a common anomaly in arteries and veins associated with various vascular diseases and aging. The mechanisms underlying the initiation and development of tortuous arteries remain unclear. Fundamental understanding of the biomechanical mechanisms of artery tortuosity will have wide applications in vascular biology, physiology and pathology, as well as in vascular surgery. It will also be useful in understanding the ‘corkscrew collateral’ phenomenon in the development of collateral arteries, which is important in studying arteriogenesis and tissue regeneration.

Biomechanical studies of vessel buckling (mechanical instability) provide a promising new approach to elucidate the underlying mechanism of the initiation and development of vessel tortuosity. They also provide a basis for developing new techniques for the prevention and treatment of vessel tortuosity.

Acknowledgments

This work was supported by CAREER award No. 0644646 from the National Science Foundation and grant R01HL095852 from the National Institute of Health.

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