Mechanical Properties of Diseased Veins

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ABSTRACT: Extensive research exists on arterial mechanical properties and how they change in disease conditions, but substantially less is known about venous mechanics in healthy and disease states. Although the mechanics of both vessel types are determined by the unique layered composition of the vessel wall, the precise distribution of the layers differs greatly between arteries and veins. Thus, vein mechanics must be analyzed and understood independently from those of arteries. This review discusses the compositional attributes that are unique to veins, how these attributes contribute to venous mechanics, and the alterations that occur to both composition and material properties during venous thrombosis and insufficiency. In general, changes to the venous wall during thrombosis increase wall stiffness and decrease extensibility. During venous insufficiency, however, both the stiffness and the extensibility of the venous wall decrease. Characterizing these changes is essential to better understand disease progression and build vein-specific devices for treating venous disease.

INTRODUCTION

There is a striking disparity in cardiovascular research: It is heavily focused on arterial studies but severely lacking with regard to veins. Nonetheless, the venous system houses nearly 70% of a person's total blood volume and, by regulating venous return to the heart, has a large influence on cardiac output.[1] As veins work to return blood to the heart, their function depends largely on their material properties, which are determined by veins' unique microstructural composition. Although the basic structure of arteries and veins is the same, the different pressures experienced by these vessels give rise to differences in the relative distribution of the layers, creating vast differences in vessel mechanics. Thus, a thorough understanding of venous-specific composition and material properties is required to properly treat venous disease. This review briefly discusses the composition and material properties of healthy veins and describes how these properties change in venous disease.

BLOOD VESSEL COMPOSITION AND MATERIAL PROPERTIES

The material properties of blood vessels are dictated by the precise composition of their three unique layers: the intima, media, and adventitia. These layers variably contain vascular endothelial cells (ECs), smooth muscle cells (SMCs), collagen, and elastin (Figure 1).[2] The innermost layer, the intima, is a thin monolayer of ECs that align in the direction of blood flow. The cells are anchored to a basement membrane composed of type IV collagen, laminins, and perlecan.[3] This thin layer of cells has little, if any, effect on the mechanical properties of the vessel wall.

On the other side of the basement membrane is the media, which is composed of a network of elastin and collagen embedded with SMCs. The SMCs are arranged in circumferential sheets with elastin fibers running between them. The elastin forms a network of lamellae that readily allows stress to be distributed to other components of the vessel wall.[4] Although it contributes little to the tensile strength of the wall, elastin is responsible for the vessel's elastic recoil. Collagen types I, III, and V are distributed throughout in dense bundles.[5] The collagen orientation appears random at low pressures, but once strained at high pressures, it quickly aligns circumferentially.[6-8] The collagen in the media exhibits extensive waviness, or crimp, which helps the vessels constrict and dilate as necessary.[9] At high pressures, the collagen fibers prevent over-distention by supporting the tensile load.[4]

Finally, the outer layer, the adventitia, is composed primarily of longitudinally oriented collagen type I.[9] The collagen in this layer forms thick bundles intermixed with elastin, fibroblasts, nerves, and the vasa vasorum and exhibits waviness similar to the media.[9] It is thought that this layer prevents excessive distension of the vessels and rupture at very high pressures.[10] The ability of the venous wall to distend depends on the collagen content, and its elasticity is governed by the elastic fibers.[11] Changes to these extracellular components can alter the mechanical abilities of the tissue. The relative ratios of collagen to elastin differ based on the location of the vessel relative to the heart, and these differences in composition affect the viscoelastic properties of the vessels.[12]

Vessels are constantly under multiple types of stress, including shear stress induced by blood flow along the intima, longitudinal stress caused by tethering of the adventitia to other organs and tissues, and circumferential stress exerted on the vessel wall by blood pressure.[4] Blood vessels are in constant tension, which is
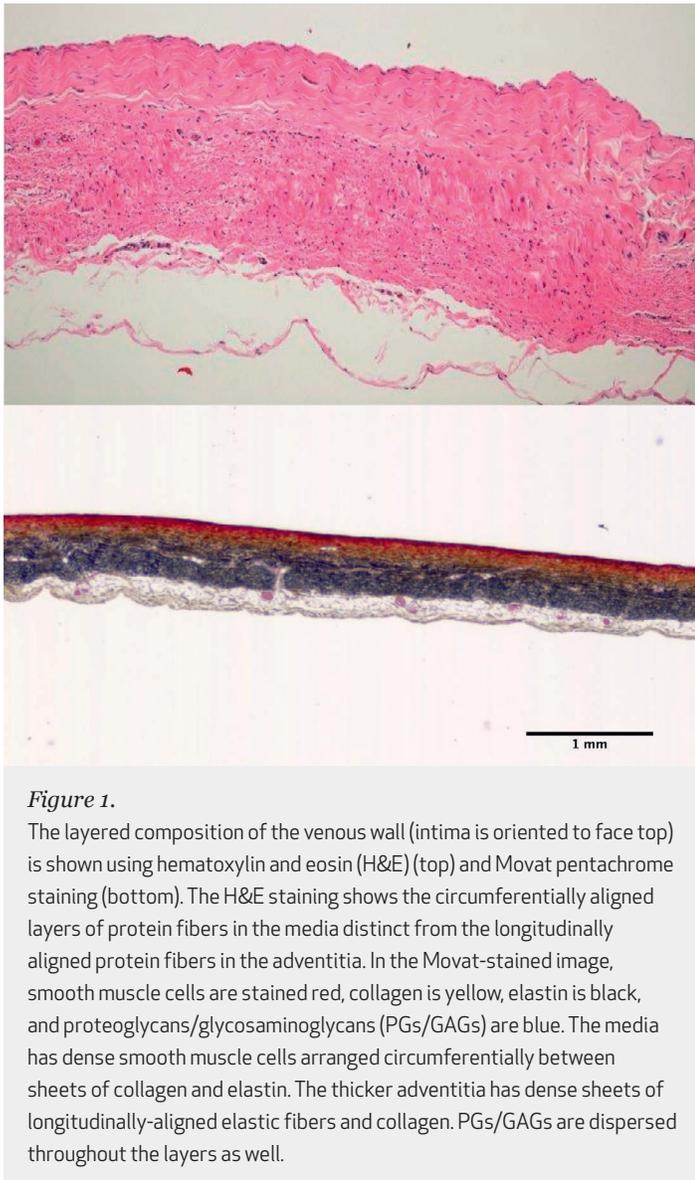
Figure 1.
The layered composition of the venous wall (intima is oriented to face top) is shown using hematoxylin and eosin (H&E) (top) and Movat pentachrome staining (bottom). The H&E staining shows the circumferentially aligned layers of protein fibers in the media distinct from the longitudinally aligned protein fibers in the adventitia. In the Movat-stained image, smooth muscle cells are stained red, collagen is yellow, elastin is black, and proteoglycans/glycosaminoglycans (PGs/GAGs) are blue. The media has dense smooth muscle cells arranged circumferentially between sheets of collagen and elastin. The thicker adventitia has dense sheets of longitudinally-aligned elastic fibers and collagen. PGs/GAGs are dispersed throughout the layers as well.

evidenced by the 20% to 50% decrease in length and diameter when a vessel is excised from the body.[13] Although ECs have little effect on the mechanical properties of the vessel wall, they are essential in sensing and transducing shear stress from blood flow.[14] Shear stress can affect the structure and gene expression of ECs through altered integrin-ECM connections.[15] The SMCs are responsible for contracting the diameter of the vessel, and excited SMCs can cause a 20% to 50% decrease in vessel diameter.[16]

Blood vessel mechanics are dominated by the behavior of collagen and elastin with contributions from the SMCs. As such, vessels exhibit a nonlinear stress-strain curve with two phases: Elastin fibers are responsible for the extensible behavior at low strains,

and collagen and SMCs are responsible for the inextensible, stiff behavior at high strains.[17] The physiological strain range falls somewhere between the low- and high-strain regions and thus allows an optimal combination of vessel extension and contraction throughout the cardiac cycle.[4] The varying composition of different segments of venous tissue leads to differences in the elastic modulus, and values range greatly between kilopascals and megapascals based on the location of the segment and the transmural pressure of the vein.[12] SMC contraction shifts the stress-strain curve to the left, thereby increasing the apparent stiffness of the vessel, whereas SMC relaxation shifts the curve to the right, decreasing apparent stiffness.[16]

The exact dimensions and properties of each segment of vessel are optimized for the specific set of forces it experiences, thus giving rise to the differences between veins and arteries. Veins have larger diameters and larger lumens than arteries to house approximately two-thirds of the body's blood volume.[18] Veins tend to have thinner, less-organized walls since they do not experience the high pressures coming directly from the heart. Pressures in veins and the inferior vena cava are typically steady between 3 mm Hg and 20 mm Hg, whereas pressures in the aorta and arteries fluctuate vastly in response to pressures of the cardiac cycle (typically between 80-130 mm Hg). Veins have a thicker adventitia and thinner media, higher collagen content, and fewer SMCs compared to arteries.[2,19] The thinner walls and lower magnitudes of experienced pressure cause veins to exhibit higher compliance, higher extensibility, and lower elastic modulus compared to arteries.[20] Blood flow in veins is relatively unaffected by the changing pressures of the cardiac cycle, so the flow is steadier and dependent on valves and muscles that work against gravity to return blood to the heart.

Any alterations to the forces experienced by a vein may cause the cells to remodel their extracellular matrix, thereby altering the composition of the vessel and, in turn, changing its mechanical properties. These alterations to mechanical properties can greatly affect the function of the vessels and may ultimately lead to disease or even heart failure.[4]

VENOUS DISEASES

Venous diseases generally fall into one of two categories: (1) venous thrombosis, or blood clot, and (2) venous insufficiency, or inadequate blood return to the heart.[21] A summary of pathological changes to mechanical properties during the two disease types is given in Table 1.

Mechanics of Venous Thrombosis

Within the category of thrombotic disease, patients may present with superficial thrombophlebitis or deep vein

	HEALTHY	THROMBOSIS	INSUFFICIENCY
Pathology	-	Nonphysiological blood clot	Obstruction of blood flow, dilation of veins
Blood pressure	3-20 mm Hg	Increased	Increased
Elastin modulus of venous wall	kPa-MPa based on the location and pressure of vein	Increased	Decreased
Extensibility of venous wall	20-40%	Decreased	Decreased
Thickness of venous wall	300-700 μm	Increased	Increased

Table 1.
Summary of pathological changes during venous disease. kPa: kilopascals; MPa: megapascals

thrombosis (DVT). Thrombosis involves the creation of a nonphysiological blood clot, or thrombus, of abnormal extent or in an intact vessel. Superficial thrombophlebitis is a blood clot in the superficial veins that is accompanied by inflammation.[21] DVT occurs specifically in the deep veins of the legs and may be difficult to detect due to a low (50%) occurrence of symptoms in patients.[21] It has an incidence rate of 0.1% and carries a high risk of pulmonary embolism, which can lead to shortness of breath, heart attack, or even death.[21,22] DVT can block blood flow to the heart through the deep veins, thereby causing formation of collateral veins that return blood with decreased efficiency. Reduced blood flow increases pressure within the vein segments and may cause fluid to leak, leading to swelling of the legs. DVT can also lead to inflammation.[21]

Venous thrombi typically occur at sites of blood flow stasis and are attached by focal adhesions to the endothelial cells lining the veins.[18] Since their attachments may be weak, they can become fragmented or subject to embolism. By the time a thrombus is 2 weeks old, it has usually undergone fibrotic transformation, which makes it difficult to lyse.[23] A thrombus may be incorporated into the vessel wall by ingrowth of endothelial cells, SMCs, and fibroblasts.[18] When this happens, channels form around the thrombus to facilitate blood flow through a decreased diameter lumen. Recanalization will continue over time, and the thrombus may eventually be remodeled to a small fibrous mass on the vessel wall.

Computation fluid dynamics (CFD) has shown that the low blood velocity found in the inlets of the portal vein is ideal for thrombus formation, and the velocity of blood flow increases due to a decrease in diameter. This velocity increases proportionally to the size of the thrombus. At the edges of the thrombus, blood flow is obstructed, leading to a low-velocity region that further promotes thrombosis. In addition, as thrombus size increases, blockage of the vessel can cause the shear stress on the venous wall to increase up to five times higher than that without thrombus. In the CFD model, the increase in shear stress affects a larger area on the vessel wall opposite the thrombus than it does on the wall with the thrombus. Increased shear stress can damage the endothelial cells of the intima and elicit vessel remodeling, thereby altering the material properties of the vessel wall.[24]

The processes of thrombus formation and resolution impact the composition and material properties of the venous wall. Thrombus formation has been found to change the mechanical behavior of the glycosaminoglycans (GAGs) and proteoglycans (PGs) and increase the stiffness of the collagen and elastin fibers; ultimately, this increases the stiffness of the venous wall and reduces the vessel's distention ability in response to pressure changes. It is theorized that these changes result from alterations to the interaction between the GAGs/PGs and the structural fibers or changes to the extent of cross-linking between fibers.[25]

Thrombus resolution also affects the material properties of veins. A clinical study showed that regardless of whether or not DVT is resolved, the venous wall increases in thickness 1.5- to 1.8-fold after 6 months compared to healthy controls, and patients who had thrombus resolution had 1.4-fold thicker vein walls that those whose thrombus did not resolve. This thickening suggests that the cells of the vein remodel in response to thrombosis and continue this response even when the thrombus resolves, indicating that the changes in composition and material properties may be enduring.[26]

Increased matrix metalloproteinase-9 (MMP-9) has been implicated in changing the material properties of veins during DVT, and several studies have shown that thrombus resolution further increases its expression.[26-28] MMP-9, a matrix remodeling protein known for its ability to lyse both elastin and collagen, plays a role in thrombus resolution but is also responsible for degrading

the extracellular matrix and basement membrane of the venous wall adjacent to the thrombus, leading to fibrosis. The result is decreased wall compliance due to increased stiffness of collagen and elastin in both longitudinal and circumferential axes.[27]

Mechanics of Venous Insufficiency

Venous disease also presents in the form of chronic venous insufficiency and varicose veins. Chronic venous insufficiency is generally found in the deep veins and can be caused by obstruction of blood flow from the limbs or by leaky venous valves, which leads to backflow of blood.[21] This disease is evidenced by swelling and pain in the legs and dark, coarse skin. Insufficiency of the superficial veins, on the other hand, is more commonly referred to as varicose veins. A structural abnormality in the vein, such as dilation, can lead to damaged valves, backflow of blood, and blood pooling, thereby increasing venous pressure. These changes can ultimately lead to skin ulcers or blood clots. Varicose veins appear more often in women, and their prevalence increases with age.[11]

Varicose veins often become dilated due to venous valve malfunction, which leads to backflow of blood and an increase of vein pressure. While hemodynamics are an important contributor to disease progression, changes to the composition of the vein wall are extensive and affect the material properties of the tissue. Venous insufficiency can alter the structural components of the venous wall, but it is often the case that diseased regions of vein appear in patches, alternating between healthy regions. The vein wall has been measured to be thicker in varicose veins compared to controls.[29]

In addition, the layered extracellular matrix becomes disorganized in varicose veins. The intima often undergoes thickening

or fibrosis resulting from deposits of collagen beneath the endothelium.[30] The media experiences extensive damage to its organized layers of SMCs, which show an irregular morphology, with disordered collagen and elastic fiber interspersed throughout.[31] The adventitia also has an increase in collagen and irregular SMCs that proliferate and migrate at greater rates than cells in controls.[32] Throughout the venous wall, varicose veins have reduced deposits of collagen type III, which are replaced by pathological collagen type I.[11] The venous wall also has markedly decreased elastin, and the elastic fibers that do remain become fragmented and disorganized.[33]

Studies assessing the role of matrix remodeling enzymes such as MMPs and tissue inhibitors of matrix metalloproteinases (TIMPs) have produced conflicting results, with some studies showing increases in the expression of these enzymes and others showing no significant changes. A reason for the inconsistencies may lie in the ratio between MMPs and TIMPs; one study showed that varicose veins had an increased TIMP/MMP ratio compared to healthy veins, which allowed matrix proteins to accumulate within the venous wall.[34] Another study indicated that increased vein pressure and tension in varicose veins lead to increased MMP expression, which then reduces the ability of the veins to contract, leading to vein dilation.[35] Although this interpretation is consistent with changes seen in the disease, further studies need to be done to corroborate the role of matrix remodeling enzymes in this process.

The changes to the composition of the venous wall in varicose veins necessarily affect the vein's material properties. For instance, the shift to collagen I from collagen III leads to decreased extensibility.[11] In addition, the elastic modulus of veins in patients with varicose veins is decreased compared to that of healthy control veins.[36] Reduced levels

of elastin also lead to reduced elastic recoil and dilation, which can hinder the vein from pumping blood back to the heart and thereby lead to venous pooling.[29,33] Histological analysis has also found that reduced communication between endothelial cells may contribute to decreased vasocontractility within varicose veins.[37]

CONCLUSION

Venous disease continues to be understudied despite its widespread prevalence. In order to best understand and treat venous thrombosis and insufficiency, it is important to elucidate how the composition and material properties of the tissue change throughout disease progression. While current studies give us some insight into material alterations during venous disease and how they affect venous function, further studies are needed to fully characterize the cellular and tissue processes involved in these changes.

KEY POINTS

- Venous mechanics are dependent on the unique layered tissue composition, which differs from that of arteries.
- Venous thrombosis increases the stiffness and decreases the extensibility of the venous wall.
- Venous insufficiency decreases the stiffness and the extensibility of the venous wall.

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