Vascularization as a Potential Enemy in Valvular Heart Disease

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Valvular heart disease remains a major problem worldwide and is responsible for >20 000 deaths each year in the United States, with an estimated 99 000 inpatient valve procedures performed annually.1 The mitral and tricuspid valve complexes comprise the valve leaflets, valvular annulus, papillary muscles, and chordae tendineae, which anchor the leaflets to the papillary muscles. As papillary muscles contract, chordae tendineae transmit tension to the valves, directing the valve leaflets to their correct position during the cardiac cycle. Rupture of the chordae tendineae occurs as a consequence of infective endocarditis, myxomatous degeneration, rheumatic fever, or rarely, osteogenesis imperfecta or relapsing polychondritis.2 In addition, ischemia-induced dysfunction of papillary muscles can cause stretching and ultimately rupture of the chordae tendineae, as well as release of chordal attachment sites of papillary muscle necrosis.

Chordae tendineae are similar to tendons connecting our skeletal muscles to bones in that both structures are avascular connective tissues. Chordae tendineae are ∼80% collagen; the remaining 20% is elastic fibers and layers of endothelial cells on a basal lamina.3 A wavy arrangement of collagen surrounded by elastic fibers is well adapted for the cyclic stresses to which the chordae are continuously subjected.3 Chordal disruption can be sudden and precipitate acute heart failure, and why these avascular structures suddenly rupture is often unclear. In this issue, Kimura et al4 provide evidence that rupture of the chordae tendineae is associated with local angiogenesis accompanied by the absence of tenomodulin, a potent angiogenesis inhibitor. Their findings suggest a novel paradigm for rupture of the chordae tendineae in response to mechanical or hypoxic stress and indicate that vascularization, usually considered a friend in the myocardium, could be an enemy in the cardiac valves.

Neovascularization is a common feature of degenerative tendon diseases as a marker of but potentially also as a facilitator of inflammation.5 Kimura et al suggest a role of neovessel ingrowth in the pathogenesis of degenerative chordae. Under mechanical overload, the chordae tendineae undergo remodeling; however, if the mechanical overload continues, this remodeling could lead to a degenerative process. In this degeneration, loss of tenomodulin may play a role in promoting local angiogenesis and activation of matrix metalloproteinases. This scenario is consistent with their previous study showing that dysregulation of an endogenous inhibitor of angiogenesis, chondromodulin-I, leads to local angiogenesis, thickening of the cardiac valves, and valvular stenosis.6 Thus, neovascularization may be pathogenic in tendons, valves, and chordae, and tonic inhibition of angiogenesis may be necessary to maintain normal functional properties of these avascular tissues.

An important question is how the invasion of neovessels in an avascularized region results in weakening of the normal chordae structure. A variety of growth factors can regulate angiogenesis in connective tissues. Vascular endothelial growth factor (VEGF)-A has a key role in the migration and proliferation of endothelial cells.7 VEGF-A is a potent inducer of matrix-degrading metalloproteinases,8 which play an essential role in VEGF-A–induced endothelial migration. To form new vessels, the endothelial cell layer must break down diverse extracellular matrix components, including collagen, laminin, and fibronectin. Local production of proteolytic enzymes such as matrix metalloproteinases that degrade fibrillar collagen or proteoglycan core proteins permits endothelial cells to form a sprouting vessel by migration.9,10 Because degradation of the extracellular matrix is required for the sprouting and invasion of new blood vessels into avascularized chordae, angiogenesis can weaken the chordal extracellular matrix.11 Thus, angiogenesis not only contributes to the repair and remodeling of tissues but also may compromise mechanical stability by proteolysis of the extracellular matrix.

Under normal conditions in adults, angiogenesis is constitutively relatively quiet, with a balance between angiogenic and antiangiogenic factors.12 Kimura et al identify tenomodulin as a novel antiangiogenic factor abundantly expressed in the outer layer of normal chordae tendineae. Tenomodulin is a type II transmembrane glycoprotein (317 amino acid residues) that contains a C-terminal domain with homology to the secreted form of chondromodulin-I, a cartilage-derived angiogenesis inhibitor.13 The secreted, truncated form of tenomodulin (the C-terminal domain) is abundant in chordae tendineae, indicating that the extracellular domain is cleaved and released from cells in a soluble form by ectodomain shedding. This finding is in agreement with a previous report showing the potential processing site (position 233 to 236) between the N-terminal glycosylation domain and the C-terminal action domain in tenomodulin protein.14 The C-terminal domain of tenomodulin has robust antiangiogenic activity when expressed in a secreted form.13 In vitro angi-o-
growth factor, fibroblast growth factor, platelet-derived growth factors, cytokines, hormones, and growth factors such as epidermal growth factor, transforming growth factor-β, and insulin-like growth factor-1 all can regulate induction of VEGF-A. A frenemy is an enemy disguised as a friend. This term is a recent addition to popular lexicon, but the concept is as old as history. Angiogenesis is certainly a friend in ischemic tissues, but it can be an enemy in tumors, the retina, and connective tissues like tendon. Kimura et al present the interesting possibility that neovascularization may be an important component of chordal disruption. Their finding that a proteolytically cleaved glycoprotein, tenomodulin, may play a role in local angiogenesis of the chordae tendineae offers a new molecular insight into the sudden and sometimes dramatic event of chordal disruption.

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None.

**References**


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