Cardiovascular sclerosis increasingly afflicts our aging, dysmetabolic population, and this hardening of our hearts and arteries has significant physiological consequences. Myocardial stiffening reduces diastolic ventricular filling and function necessary for robust cardiac output during systole. Arterial stiffening impairs Windkessel physiology—the rubbery elasticity of conduit vessels that ensures smooth distal tissue perfusion throughout the cardiac cycle. Thus, in addition to the diastolic heart failure associated with cardiac sclerosis, a type of diastolic perfusion failure occurs with arteriosclerotic conduit vessel stiffening. The inability to store kinetic energy as potential energy in elastic conduit vessels during systole reduces the sustained pressure differential necessary to drive smooth distal perfusion throughout diastole and is manifested by increased arterial pulse wave velocity during systole.

One clinical consequence of diastolic vascular perfusion failure can be well appreciated in the central nervous system. In the Dallas Heart Study, increased aortic stiffness as quantified by pulse wave velocity strongly portends increased brain magnetic resonance imaging white matter hyperintensity volume, a signature of ischemic (not hemorrhagic) histology, independent of other cardiovascular risk factors, including systolic blood pressure. Cognitive decline is a clinical feature of cardiovascular sclerosis increasingly afflicts our aging, dysmetabolic population, and this hardening of our hearts and arteries has significant physiological consequences. Myocardial stiffening reduces diastolic ventricular filling and function necessary for robust cardiac output during systole. Arterial stiffening impairs Windkessel physiology—the rubbery elasticity of conduit vessels that ensures smooth distal tissue perfusion throughout the cardiac cycle. Thus, in addition to the diastolic heart failure associated with cardiac sclerosis, a type of diastolic perfusion failure occurs with arteriosclerotic conduit vessel stiffening. The inability to store kinetic energy as potential energy in elastic conduit vessels during systole reduces the sustained pressure differential necessary to drive smooth distal perfusion throughout diastole and is manifested by increased arterial pulse wave velocity during systole.

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calcification in the global MGP-null background and administration of serine protease inhibitors, including serpinA1 reduced arterial calcification and delayed precocious cardiovascular death, in MGP-null mice. Thus, the authors (1) newly discover that a cadre of serine proteases participate in the EndMT and the Sox2-dependent phenotypic plasticity that drives arterial calcification in the absence of MGP; and (2) demonstrate that serum protease inhibition limits arteriosclerotic disease and demise in this enlightening vasculopathy model.17

The precise proteases driving arterial calcification as responsive to serum protease inhibition in vivo have yet to be unambiguously identified, and future studies will undoubtedly focus on this important aspect. However, it is intriguing to reflect on the responses to recombinant serpinA1 in MGP−/− mice and the significant implications. First, serpin-based biologics, for example, serpinA1 (aka α-1 antitrypsin, AAT), C1 esterase inhibitor, have found important Food and Drug Administration–approved therapeutic niches in molecular medicine.18 Given the results of Yao et al,17 one can envision potential serpin-based strategies to reduce arteriosclerosis in high-risk states, such as chronic kidney disease and diabetes mellitus. Second, although AAT deficiency engenders neutrophil elastase–mediated emphysema in mice that is responsive to AAT replacement (augmentation), the pharmacology of serpinA1/AAT is more complex.19 SerpinA1/AAT targets multiple proteases beyond neutrophil elastase, including certain kallikreins and cathepsins,19,20 that are involved with inflammation and vascular elastin matrix turnover. Considering the emerging role of kallikreins in the EndMT13 and those upregulated in MGP-null mice,17 it is probable that some aspect of the beneficial response to protease inhibition may accrue via modulation of protease-activated receptor signaling in addition to support of internal elastic lamina integrity and reduction in osteogenic elastin degradation products.13 Third, serpinA1 expression is increased in human atherosclerotic plaques, where human genetics points to relevant contributions to cardiometabolic disease risk.22 Thus, although it remains to be determined whether serpinA1/AAT administration is effective in preclinical models of cardiometabolic disease, given the results in MGP-deficient mice17 and the broad substrate specificity and clinical safety profile of serpinA1/AAT,19 potential repurposing for arteriosclerosis deserves additional preclinical and clinical investigation. However, because calcium deposition is not the only determinant of vascular stiffness,7 it will be important to directly assess cardiovascular compliance and function. Finally, regardless of underlying mechanisms, the feed–forward reciprocal relationship between endothelial Sox2 and vascular protease expression discovered in MGP-null mice17 highlights the potential efficacy achieved by targeting this regulatory linchpin as strategy to preserve aortic endothelial phenotype and thus conduit vessel integrity, compliance, and function. As such, a new pharmacological pathway is blazed,17 wherein serpin therapy might help preserve vascular health and end organ function in our patients afflicted with arteriosclerotic disease.3

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References


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Arteriosclerotic Calcification: A Serpi(n)ginous Path to Cardiovascular Health?
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