Large arteries (especially the aorta) lose elasticity and thicken with aging and as a consequence of other conditions, thus leading to central arterial stiffening and associated adverse effects on blood flow and pressure. Arterial stiffness can be defined and measured in different ways, at a local level or systemically. Increases in either the intrinsic (material) stiffness or net structural (combined geometric and material) arterial stiffness, or both, can increase the velocity at which the pressure pulse travels along the arterial tree and central pulse pressure, which can negatively impact downstream resistance vessels and organs (i.e., heart, brain, and kidney). Clarifying temporal and causal relationships between arterial stiffening and hypertension was identified by NHLBI as an important gap of knowledge, with a potential for clinical translation. NIH (National Institutes of Health)-funded studies, more than half of them supported by the NHLBI (Online Figure), have investigated various aspects of arterial stiffening in humans and in experimental models. To enable a more focused research effort on this topic, NHLBI launched a Request for Applications (RFA) HL-10-027, entitled Cellular and Molecular Mechanisms of Arterial Stiffening and Its Relationship to Development of Hypertension (R01). This initiative supported 11 R01 awards during 2010 to 2015 (Online Table II; cumulative ≈$20 million dollars in total costs), which represented a significant component of the overall NHLBI investment in this field. Here, we report a summary of important scientific findings that resulted from this NHLBI-initiated research effort, constituting the basis of >200 original research and review articles (Online Table II), some highlighted here, many conference presentations, and several patents.

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See the Online Supplement for the author affiliations.

Correspondence to Young S. Oh, PhD, Vascular Biology and Hypertension Branch, Division of Cardiovascular Sciences, National Heart, Lung, and Blood Institute, 6701 Rockledge Dr, No. 8106, Bethesda, MD 20892. E-mail yoh@mail.nih.gov

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A Special Report on the NHLBI Initiative to Study Cellular and Molecular Mechanisms of Arterial Stiffness and Its Association With Hypertension

is significantly increased to about twice that of wild-type, and their aortic stiffness is further increased. In elastin heterozygous mice (Eln+/−), which have 50% to 60% of normal elastin levels and a normal life span, arterial stiffness is significantly increased by postnatal day 7, whereas systolic blood pressure is not significantly increased until postnatal day 14.6

Herrera et al7 used stroke-prone Dahl salt-sensitive hypertensive rats, which had increased arterial stiffness compared with nonstroke-prone Dahl salt-sensitive rats starting at 6 weeks of age. At this age, both stroke-prone and nonstroke-prone rats had similar blood pressure. However, at 16 weeks of age, stroke-prone Dahl salt-sensitive rats started to show significantly higher blood pressure than nonstroke-prone Dahl salt-sensitive rats, again consistent with the conclusion that arterial stiffness precedes hypertension.

Raaz et al8 studied a murine model of type 2 diabetes mellitus (db/db mice) and found that progressive structural aortic stiffening preceded the onset of arterial hypertension. The authors performed serial pressure-myography measurements on isolated thoracic aorta starting at 4 weeks of age (ie, when db/db mice are mildly hyperglycemic) and found progressive aortic stiffening at 10 and 20 weeks of age. Statistically significant elevations of blood pressures were observed only at the later stage, 20 weeks of age, not at 10 weeks of age.

Chen et al9 studied the temporal relationship in an animal model with altered klotho gene expression. Klotho is a recently discovered antiaging gene. They found that in klotho heterozygous mice (klotho+/−) PWV started to increase at 14 weeks of age, whereas systolic blood pressure did not increase until 16 weeks of age, again suggesting that arterial stiffness precedes measurable increases in blood pressure.

In summary, studies from 5 different animal models of hypertension or vascular disorders showed that increased arterial stiffness preceded blood pressure elevation. This temporal sequence is consistent with clinical findings of the NHLBI-supported Framingham Heart Study.3

### Cellular and Molecular Mechanisms of Arterial Stiffness

Structural and functional changes in all components of the vascular wall can contribute both directly or indirectly to altering mechanical properties of blood vessels. RFA investigators used a targeted candidate approach to uncover novel and potential targetable pathways that contribute to vascular stiffness. These include alterations in extracellular matrix proteins, such as enhanced collagen and its crosslinking, loss of elastin, as well as immunologic mechanisms that enhance adventitial inflammation and ultimately fibrotic change. A few examples are described below, and more research accomplishments can be found in Online Table II.

Shyy and coworkers investigated relationships among fluid-induced wall shear stress, SirT1 (Sirtuin 1) expression, and arterial stiffness. They found that the AMP-activated protein kinase/SirT1 signaling pathway is involved in endothelial nitric oxide synthase–derived nitric oxide (NO) bioavailability, an important determinant of vascular stiffness. Seta and colleagues manipulated the expression level of SirT1 globally or specifically in vascular smooth muscle cells in mice to demonstrate a crucial role of SirT1 in aortic stiffness and structural integrity. Tsao and coworkers identified a novel mechanism of arterial stiffening involving the osteogenic transcription factor, Runx2 (Runt-related transcription factor 2), as an inducer of arterial fibrosis and stiffness.

Harrison and collaborators demonstrated an important role of immune cells in vascular stiffening and hypertension. They found that mice lacking lymphocytes (Rag1−/−) were protected against adventitial collagen deposition and stiffening in angiotensin II–induced hypertension model. Adoptive transfer of T cells, but not B cells, completely restored the collagen deposition and stiffening with hypertension. Larson and colleagues studied roles of immune inhibitory cells (Tregs) and found a protective role of Tregs in vascular stiffening.

Berkowitz, Santhanam, and colleagues demonstrated an important role of tissue transglutaminase 2, an enzyme catalyzing protein cross-links, in increasing vascular stiffness in aging rats and mice. They found that inhibiting transglutaminase 2 activity delayed vascular stiffening in middle-aged rats and discovered that the activity and secretion of transglutaminase 2 were regulated by NO.

### Arterial Wall Mechanics and Hemodynamics

Ferruzzi et al10 presented findings in a fibulin-5–deficient mouse model, suggesting that aortic stiffening can occur primarily via an increase in wall thickness, whereas intrinsic material stiffness remains largely unchanged. They showed that one of the greatest changes associated with thickening (ie, structural stiffening) is a lost capability by the wall to store elastic energy. They further developed a set of novel computational tools (ie, 3-dimensional fluid–solid interaction models) that can be used to better interpret in vivo vascular alterations in mouse models and to study spatiotemporal changes in arterial stiffening and their effects on global hemodynamics. This open-source software is available at http://www.crimson.software/.

### Conclusion, Challenges, and Future Directions

Studies using 5 different animal models of hypertension or vascular disorders, supported by the RFA HL-10-027, showed that large artery stiffening preceded high blood pressure, consistent with the temporal sequence observed in several clinical studies. This concordance supports the notion that measurement of arterial stiffness may present opportunities for early detection of hypertension and better CV risk stratification. However, none of the studies published to date have clearly determined a process whether or how increased arterial stiffness alone can lead to hypertension, which requires further investigation. Studies supported through this RFA and other studies also suggested that arterial stiffness could be prevented or reversed in certain vascular conditions and therefore is amenable to drug therapy. As discussed in this report, some of the specific pathways and molecules (eg, collagen deposition, elastin loss, SirT1, Runx2, klotho, transglutaminase 2) may suggest specific future intervention targets. In the future, it will be important to identify the origin of signals that target these pathways and molecules.

A major challenge to study arterial stiffness is that stiffening can have effects at multiple length scales and levels...
(ie, molecular, cellular, tissue, and systemic levels), and these scales and levels can interact and feedback to each other. Thus, identifying one mechanism may be difficult to establish. In this regard, a more systems-based interpretation of data (including genetics, risk factors, hemodynamics, and computational models) may be required. In addition, causality between stiffness and hypertension is difficult to demonstrate because it would require large- vessel-specific tools (eg, knockout, overexpression, pharmacological tools which target aorta and large vessels) without affecting small resistance vessels (which regulate blood pressure). Currently, no such tools are available.

We should keep in mind that the relationship between arterial stiffness and blood pressure is very complex. The fact that several pathways connected stiffness and hypertension in different experimental models suggests that multiple and possibly redundant mechanisms contribute to arterial stiffness. Whether increased arterial stiffness leads to microvascular damage and hypertension remains to be determined. In addition, positive feedback loops exist between the local mechanobiology and global pathophysiology such that increased vascular stiffness elevates blood pressure, while elevated blood pressure further stimulates aortic wall remodeling and stiffening (Figure). Therefore, we must not underestimate the clinical challenges of controlling blood pressure.

Emerging information on clinical associations between genetic polymorphisms and arterial stiffening suggests possible new pathways connecting arterial stiffening and CV outcomes. Moreover, recent genetic intercross linkage studies in Dahl rats revealed sex-specific quantitative trait loci affecting arterial stiffness, implying the existence of differential genetic mechanisms underlying vascular stiffening in males and females. This research area requires further investigation.

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Disclosures

None.

References


Key Words: aorta ■ blood pressure ■ cardiovascular disease ■ elasticity ■ hypertension

![Figure](image_url)
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