Arterial stiffness and hypertension
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Abstract
Measures of the functional and structural properties of blood vessels can be used to assess preclinical stage of vascular disorders. Recent experimental and population studies show that arterial stiffening precedes development of high blood pressure, and can be used to predict future cardiovascular events. Arterial stiffness was also shown to be reversible in several experimental models of various conditions. Since reversing arterial stiffness could prevent development of hypertension and other clinical conditions, understanding the biological mechanisms of arterial stiffening and investigating potential therapeutic interventions to modulate arterial stiffness are important research topics. For research and application in general clinical settings, it is an important step to develop reliable devices and a standardized arterial stiffness measurement protocol.

Keywords: Hypertension, Arterial, Aortic stiffness, Cardiovascular disease, Vascular biology

Introduction
The walls of large arteries, especially the aorta, lose elasticity over time, and this process results in increased arterial stiffness. Arterial stiffening, at least in part, reflects gradual fragmentation and loss of elastin fibers and accumulation of stiffer collagen fibers in the arterial wall [1]. Increased arterial stiffness is closely linked to increased risk of hypertension and other diseases, such as chronic kidney disease and stroke [2]. In this brief review, I will discuss recent progress in relating arterial stiffness research to hypertension.

Arterial stiffness precedes hypertension
Although the causality between increased arterial stiffness and hypertension is complex because of many confounding factors (e.g., aging, diet, concurrent disease, lifestyle, etc.), recent studies in humans and animals suggest that increased arterial stiffness can precede hypertension. For example, several research projects funded by the NHLBI (National Heart, Lung, and Blood Institute) – the NIH (National Institutes of Health) Institute focused on supporting cardiovascular research – had examined the temporal and causal relationship between arterial stiffness and hypertension [3]. Studies in five different animal models concluded that arterial stiffness precedes high blood pressure. These animal models included: (i) diet-induced obesity model, (ii) elastin gene knock-out model, (iii) stroke-prone Dahl salt-sensitive rat model, (iv) klotho gene knock-out model, and (v) type 2 diabetes model. In clinical studies, a consistent temporal sequence of arterial stiffness preceding hypertension was also observed in the Framingham Heart Cohort Study [4]. However, the biological mechanisms and cellular processes whereby increased arterial stiffness alone can lead to hypertension are still not understood, encouraging further investigation.

Is arterial stiffness reversible?
Both human and animal studies have suggested that arterial stiffness is reversible. In a murine model of diet-induced obesity, the increased pulse wave velocity (PWV: the gold standard in vivo measure for arterial stiffness) in obese mice fed a high fat/high sucrose diet (HFHS) for 5 months was reduced to normal after returning obese mice to standard chow for 2 months [5]. During the 2-month period, indices of metabolic impairment of obese mice such as body weight, fat mass and hyperinsulinemia, returned to normal; PWV and high blood pressure also returned to normal. Further, Fry et al. [6] studied the potential effect of dietary resveratrol on arterial stiffness. The authors found that resveratrol, a polyphenol known to activate the deacetylase sirtuin-1, prevented the HFHS-induced inflammation and excess oxidant production in the arterial wall as well as the
accompanying increase in PWV. Interestingly, administra-
tion of a sirtuin-1 specific activator (SRT1720), after
8 months of HFHS, decreased PWV to normal values
within 2 weeks. The positive effect of dietary resveratrol
on arterial stiffness was further replicated in non-human
primates that were fed high caloric diets [7], underscoring
its translational potential in humans.

Using an aging rat model (i.e., 20 month-old), Steppan
et al. [8] studied the relationship between exercise, tissue
transglutaminase (TG2) activity, and arterial stiffness;
TG2, an enzyme catalyzing protein cross-links, is known
to play a role in vascular stiffness with age [9]. The au-
thors found that there was significant suppression of an
age-associated increase in TG2 activity when animals
were subjected to moderate-intensity exercise, which
was correlated with increased nitric oxide bioavailability
and reduced collagen depositions in the extracellular
matrix. Interestingly, these biochemical changes did not
translate into a significant alteration in vascular stiffness,
supporting the hypothesis that once formed, the TG2
crosslinks may have a long half-life in the vascular
matrix. Thus, it seems that the reversibility of vascular
stiffness may be limited to a certain stage or type of vas-
cular condition leading to stiffness.

In humans, short-term aerobic exercise (3 months) re-
duced arterial stiffness in older adults (> 65 years) with
type 2 diabetes and might thereby lower the risk of car-
diovascular morbidity and mortality [10]. A recent ran-
domized clinical trial study (SAVE: Slow Adverse
Vascular Effects of excess weight) also showed the re-
versibility of vascular stiffness by moderate-to-vigorous
physical activity in overweight or obese young adults
[11]. In addition, some anti-hypertensive medications
(i.e., angiotensin converting enzyme inhibitor or angio-
tensin II receptor I antagonist) are shown to reduce
arterial stiffness significantly [12]. Thus, arterial stiffness
associated with some medical conditions can be reversed
by life style change or treatment.

**Conclusion and perspectives**

Arterial stiffness is an important arterial phenotype and
an excellent indicator of cardiovascular morbidity and
mortality [13]. It is an independent predictor of hyper-
tension and cardiovascular diseases. Recent studies in
animal models showed that large artery stiffening pre-
ceded development of high blood pressure. This tem-
poral sequence was also observed in clinical studies.
Nevertheless, it should be kept in mind that the relation-
ship between arterial stiffness and blood pressure can be
complex. For example, there are patients who have high
blood pressure with normal PWV values [14].

Both arterial stiffness and hypertension are positively
associated with aging. Studies from animals and humans
suggest that arterial stiffness can be reversible under cer-
tain conditions (Fig. 1). Niiranen et al. [15] have recently
studied healthy vascular aging (HVA) - defined as ab-
sence of hypertension and lack of arterial stiffness – in
more than 3100 participants (aged ≥ 50 years) of the
Framingham Heart Study and have found that maintain-
ing HVA beyond age 70 is extremely challenging. With
rapid population aging, it will be important in the future
to explore the possibility of prevention or reversal of ar-
terial stiffness as a potential therapeutic strategy to con-
trol hypertension and/or hypertension-related diseases.
In this regard, the European Society of Hypertension
and the European Society of Cardiology published a
guideline in 2013 to suggest the measurement of arterial
stiffness as a way of evaluating hypertensive patients at
high cardiovascular risk [2]. In recognizing the clinical
importance of arterial stiffness, the American Heart

![Critical Zone (Fig. 1)](image-url)
Association also published a scientific statement to encourage further improvement and standardization of arterial stiffness measurements for clinical use and vascular research [13]. Once a standardized measurement protocol and reliable devices are available, arterial stiffness can provide us valuable information about the risk of hypertension, cardiovascular disease, and early vascular aging.

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References
1. Wagenseil JE, Mecham RP. Elastin in large artery stiffness and hypertension. J Cardiovasc Transl Res. 2012;5(3):264–73.
2. Mancia G, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens. 2013;31(7):1281–357.
3. Oh YS, et al. A special report on the NHLBI initiative to study cellular and molecular mechanisms of arterial stiffness and its association with hypertension. Circ Res. 2017;121(11):1216–8.
4. Kaess BM, et al. Aortic stiffness, blood pressure progression, and incident hypertension. JAMA. 2012;308(9):875–81.
5. Weissbrod RM, et al. Arterial stiffening precedes systolic hypertension in diet-induced obesity. Hypertension. 2013;62(6):1105–10.
6. Fry JL, et al. Vascular smooth muscle Sirtuin-1 protects against diet-induced aortic stiffness. Hypertension. 2016;68(3):775–84.
7. Mattison JA, et al. Resveratrol prevents high fat/sucrose diet-induced central arterial wall inflammation and stiffening in nonhuman primates. Cell Metab. 2014;20(1):183–90.
8. Stepan J, et al. Exercise, vascular stiffness, and tissue transglutaminase. J Am Heart Assoc. 2014;3(2):e000599.
9. Santhanam L, et al. Decreased S-nitrosylation of tissue transglutaminase contributes to age-related increases in vascular stiffness. Circ Res. 2010;107(1):117–25.
10. Maddern KM, et al. Short-term aerobic exercise reduces arterial stiffness in older adults with type 2 diabetes, hypertension, and hypercholesterolemia. Diabetes Care. 2009;32(8):1531–5.
11. Hawkins M, et al. The impact of change in physical activity on change in arterial stiffness in overweight or obese sedentary young adults. Vasc Med. 2014;19(4):257–63.
12. Ja G, et al. Potential role of antihypertensive medications in preventing excessive arterial stiffening. Curr Hypertens Rep. 2018;20(9):76.
13. Townsend RR, et al. Recommendations for improving and standardizing vascular research on arterial stiffness: a scientific statement from the American Heart Association. Hypertension. 2015;66(3):698–722.
14. Nilsson, P.M., et al., Characteristics of healthy vascular ageing in pooled population-based cohort studies: the global metabolic syndrome and artery REsearch consortium. J Hypertens, 2018. doi: https://doi.org/10.1097/HJH.0000000000001824.
15. Niiranen TJ, et al. Prevalence, correlates, and prognosis of healthy vascular aging in a Western community-dwelling cohort: the Framingham heart study. Hypertension. 2017;70(2):267–74.