IMR Press

Reviews in Cardiovascular Medicine

Editorial

Arterial stiffening in hypertension: is it just high blood pressure?

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DOI:10.31083/j.rcm2204117

Submitted: 17 September 2021 Revised: 10 October 2021 Accepted: 20 October 2021 Published: 22 December 2021

Because of the high prevalence in the general population, arterial hypertension can be considered the most important modifiable cardiovascular risk factor. Arterial vessels, together with heart, brain, and kidneys are the main targets of hypertension-related organ damage. Early, subclinical changes occur in the vasculature of hypertensive patients and there is substantial evidence of a close association between these changes and morbidity and mortality in hypertension. In this context, there has been a tremendous surge of interest on the mechanisms that drive vascular stiffening beyond high blood pressure itself. This is due on one hand to the evidence that arterial stiffening anticipates major cardiovascular events and, on the other hand, to the widespread availability of noninvasive methods that can reliably detect early vascular changes.

Speculation never stops as to whether arterial stiffening is a cause or a consequence of blood pressure increase. In 2015, the American Heart Association published a scientific statement addressing the importance of arterial stiffness in hypertension [1], but as yet the mechanisms that contribute to arterial stiffening in addition to blood pressure elevation remain elusive. While the association of arterial stiffening with aging is not unexpected and is widely recognized, many additional conditions and potential mechanisms have been hypothesized to play a role in the development of hypertension-related early arterial changes. These mechanisms include activation of the tissue renin-angiotensin-aldosterone system (RAAS) as well as changes in other paracrine, and autocrine systems, increased generation of proinflammatory cytokines and adipokines, a prothrombotic state with activation of the hemostatic cascade and decreased fibrinolysis and, last but not least, metabolic conditions that are frequently associated with hypertension [2–4] (Fig. 1).

Previous studies have clearly indicated the possible contribution of abnormalities of glucose metabolism to arterial stiffening. Arterial changes are known to occur as an early phenomenon in patients with diabetes mellitus and have been consistently reported in patients with the metabolic syndrome and other conditions associated with insulin resistance. In middle-aged, nondiabetic patients with uncomplicated essential hypertension, we reported a significant and independent association of carotid artery stiffness with hyperinsulinemia and insulin resistance [5], but no association was observed with blood glucose levels. This suggests that reduced sensitivity to insulin might be the major player in this context and additional observations on conditions that are associated with the metabolic syndrome could support this view. For instance, the Baltimore Longitudinal Study of Aging included subjects who were followed with serial measurements of the pulse wave velocity for 6 years, reporting a significant association between serum levels of uric acid and arterial stiffening [6]. Also, a significant association with arterial stiffening was demonstrated in patients with biopsy-proven nonalcoholic fatty liver disease (NAFLD), a condition commonly found in subjects with the metabolic syndrome and insulin resistance [7]. Excess generation of free fatty acids, a hallmark of insulin resistant states, leads to an increased generation of reactive oxygen species from cultured hepatocytes [8] that could have a role in the pathophysiology of arterial stiffening. Moreover, in nondiabetic-hypertensive patients with ultrasound evidence of NAFLD and associated arterial changes, we observed lower plasma adiponectin levels than in patients without NAFLD [9], supporting the hypothesis that adipokines might also play a role. Thus, substantial evidence suggests that insulin resistance and many of its related conditions could contribute to arterial stiffening in hypertension. This is why interventions that improve insulin sensitivity would be expected to provide benefit to the vascular health of hypertensive patients.

Changes in circulating lipoproteins have also been associated with arterial stiffening in the general population, and the results of the China Stroke Primary Prevention Trial indicate a close interaction between hypertension and some lipid fractions [10]. Also, indirect evidence of potential roles of lipids in hypertension-related arterial stiffening comes from studies conducted with use of statins [11] or dietary interventions [12]. Observational studies have identified a number of diet-related factors that could modify arterial properties in the general population, including sodium restriction and supplementation with potassium, antioxidants, fish oils, polyphenols, fermented milk products, and some vitamins. For instance, short-term oral supplementation with folic acid

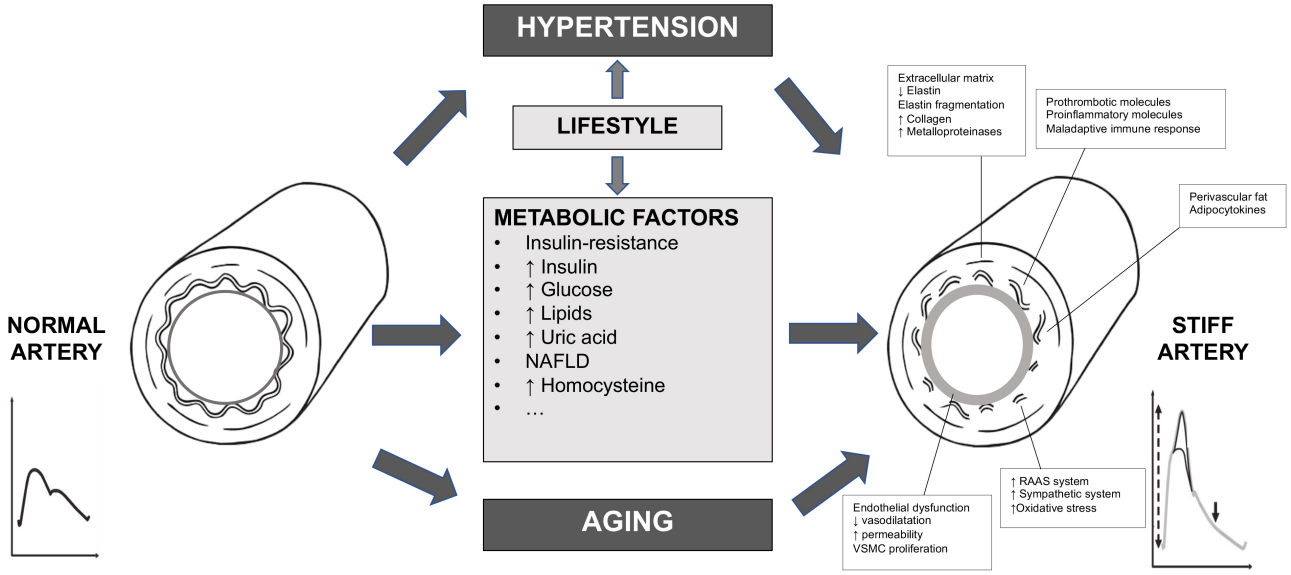

Fig. 1. Metabolic factors and insulin resistance as major players in the development of arterial stiffening in hypertension.

was suggested to reduce arterial stiffness in hypertensive patients [13], an effect that may result from changes in the circulating levels of homocysteine [14]. Also, aerobic exercise has been very attractive for reducing arterial stiffness, but observations in hypertensive patients remain controversial, inasmuch as it is difficult to separate the effects on the arteries from those on blood pressure.

In addition to the classical RAAS that is primarily involved in regulation of systemic blood pressure, tissue-specific RAASs act locally as regulators of tissue trophism and cell turnover. Activation of the vascular RAAS has been reported in humans and animal models of hypertension and is recognized as an important factor that could contribute to arterial stiffening. Local production of angiotensin II and aldosterone is associated with inhibition of insulin intracellular signalling, contributing together to an imbalance of the endothelial function that results in decreased production of vasodilatory nitric oxide and increased activity of vasoconstrictive endothelin-1. Also, in hypertensive patients a strong association was reported between RAAS components and markers of a prothrombotic state [15] that might additionally contribute to changes in the arterial wall, thereby leading to further loss of distensibility. With these premises, it is clear why cumulative analyses indicate RAAS blockers together with calcium-channel antagonist as the preferred antihypertensive agents for reduction of arterial stiffness.

In summary, current evidence strongly suggests that many metabolic conditions that are closely linked to insulin resistance and are frequently detected in patients with high blood pressure might play an important role in the process of stiffening of the arterial tree in these patients (Fig. 1). Although many novel treatments have proved to be successful in improving arterial distensibility in clinical and animal studies (Table 1), at present the only established treatment for pre-

Table 1. Interventions with potential benefit on arterial stiffness in arterial hypertension.

Physical activity
Smoking withdrawal
Dietary measures
● Weight loss
● Salt restriction
● Potassium supplementation
● Additional dietary compounds (red wine, garlic, dark chocolate, polyphenols, isoflavones, fish oil, watermelon)
Antihypertensive drugs
● Angiotensin-converting enzyme inhibitors
● Angiotensin receptor antagonists
● Calcium-channel blockers
● Vasodilatory beta blockers
● Mineralocorticoid receptor antagonists
Antidiabetic drugs
● Thiazolidinediones
● Dipeptidyl peptidase-4 inhibitors
● Sodium-glucose transporter-2 inhibitors
Hypolipemic drugs
● Statins
● Omega-3 fatty acids
Estrogen modulators
● Raloxifene
Experimental drugs
● Alagebrium (advanced glycation end-product crosslink breaker)
● Vitamin K supplementation (inhibition of matrix Gla-protein)
● Sylibin
● Berberine
● Relaxin
● CD-147 inhibitors

vention/reduction of arterial stiffening in hypertensive patients remains to effectively decrease blood pressure. In the future, vigorous treatment of overweight/obesity and coexisting metabolic conditions might improve arterial distensibility in hypertensive patients and thereby contribute to a more effective prevention of cardiovascular events.

Ethics approval and consent to participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This research was funded by Piersilverio Nassimbeni Foundation.

Conflict of interest

The authors declare no conflict of interest.

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