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Review

Arterial stiffness, atherosclerosis and cardiovascular risk: Pathophysiologic mechanisms and emerging clinical indications

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ABSTRACT

Arterial stiffness results from a degenerative process affecting mainly the extracellular matrix of elastic arteries under the effect of aging and risk factors. Changes in extracellular matrix proteins and in the mechanical properties of the vessel wall related to arterial stiffening may activate number of mechanisms involved also in the process of atherosclerosis. Several noninvasive methods are now available to estimate large artery stiffness in the clinical setting, including carotid-femoral pulse wave velocity, the reference for aortic stiffness estimate, and local distensibility measures of superficial arteries, namely carotid and femoral. An independent predictive value of arterial stiffness for cardiovascular events has been demonstrated in general as well as in selected populations, and reference values adjusted for age and blood pressure have been established. Thus, arterial stiffness is emerging as an interesting tissue biomarker for cardiovascular risk stratification and estimation of the individual "biological age". This paper overviews the mechanisms accounting for development and progression of arterial stiffness and for associations between arterial stiffness, atherosclerotic burden and incident cardiovascular events, summarizes the evidence and caveat for clinical use of stiffness as surrogate marker of cardiovascular risk, and briefly outlines some emerging methods for large artery stiffness characterization.

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A recent issue of Vascular Pharmacology published an interesting experimental paper of Gil-Ortega et al. that provides a novel evidence on some molecular mechanisms underlying arterial stiffening in non-hypertensive mice fed by a high-fat diet [1]. In a mouse model of long-term diet-induced obesity, which provokes endothelial dysfunction without hypertension, authors observed hypertrophic outward remodeling of mesenteric arteries with increased number of smooth muscle cells (SMC), increased segmental aortic stiffness and local arterial stiffness, together with alterations in extracellular matrix (ECM), characterized by changes in elastin organization and by increase of type I collagen. Measures of local and segmental stiffness were positively correlated with oxygen free radicals (O^{-}_{2}) levels in mesenteric artery, insulin and leptin levels, and inversely with arterial nitric oxide (NO) bioavailability and plasma adiponectin levels. Altogether data of this

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study support the postulate that arterial stiffening and atherosclerosis share some common pathophysiological mechanisms, like endothelial dysfunction and insulin resistance, and could be viewed as two synergic processes that may potentiate each other in the development of vascular changes underlying cardiovascular disease.

Arterial stiffening reflects the degenerative changes of ECM in the media layer, and is characterized by elastin fatigue fracture and collagen deposition and cross-linking. From the pathologic point of view arterial stiffening is distinct from atherosclerosis, a process that typically involves the intima layer and is characterized by lipid accumulation, inflammatory cells and vascular SMC migration and foam cell development. On the other hand, both processes often coexist in the same vascular territories, share some mutual risk factors, and are part of the vascular aging process. Furthermore, experimental studies have shown that changes in ECM proteins and in mechanical properties of the vessel wall may activate some pathophysiologic mechanisms involved in the atherosclerotic process, and clinical studies have demonstrated an independent association between arterial stiffness and atherosclerotic load as well as between arterial stiffness and risk of incident cardiovascular events. In the present review we try to summarize the hemodynamic impact of arterial stiffening, the experimental and clinical evidence suggesting the pathophysiologic link between arterial stiffening and atherosclerosis, as well as the perspectives for using arterial stiffness measurements as aid to cardiovascular risk stratification.

1. Hemodynamic impact of arterial stiffness

In physiologic conditions, there is a stiffness gradient from proximal, distensible elastic arteries to distal, muscular arteries, which contributes to the wave reflection phenomenon. In a stiff arterial tree, the speed of propagation of the arterial pulse through the aorta is increased, and the increased speed of the forward traveling wave implies an earlier reflection of backward traveling wave from the periphery. Backward wave arrives to ascending aorta in systole instead of in diastole, and this shift in timing leads to an augmentation of aortic systolic pressure and pulse pressure, to a decrease in diastolic coronary perfusion pressure [2–4] and, therefore, to diminished myocardial oxygen delivery. Elevated aortic systolic pressure also increases left ventricular afterload and therefore myocardial workload, myocardial mass and oxygen demand. Resulting mismatch between increased oxygen demand and reduced oxygen delivery may lead to increased susceptibility of subendocardial myocardial fibers to ischemia (Fig. 1). Moreover, as arterial stiffening usually involves mainly the proximal arteries, the stiffness gradient between proximal elastic arteries and more distal muscular arteries decreases [5]. This phenomenon may result in a diminution of the amplitude of wave reflection from the resistance vessels, and consequently, in an increased transmission of pressure to the microcirculation, potentially dangerous mainly for brain and kidney. Thus, the net effect of arterial stiffness on target organs is determined by the increase in regional pulse wave velocity on one side, and by the decrease in stiffness gradient between elastic and muscular arteries, on the other side (Fig. 1).

Regional arterial stiffness estimates the propagation speed of the arterial pulse wave (pulse wave velocity; PWV) and is measured directly, as a ratio of distance between two measurement points divided by the time required for the pressure wave to travel this distance. Carotid-femoral PWV (cf-PWV) reflects above all the aortic stiffness and represents a gold standard for arterial stiffness measurement [6,7]. Local measures of large artery stiffness (carotid and femoral arteries) are based upon the assessment of diameter/volume change during the cardiac cycle for the corresponding change in pressure (i.e. pulse pressure) [8].

2. Possible mechanisms linking arterial stiffness and atherosclerosis

The nature of the possible link between arterial stiffness and atherosclerosis is not clearly established due to the fact that their interrelationship is complex and may involve number of different hemodynamic, mechanical, metabolic and enzymatic mechanisms that can interact among themselves with a variable relative weight (Fig. 2). Furthermore, different mechanisms may have different impact in diverse segments of the arterial tree.

2.1. Risk factors

The association between arterial stiffness and atherosclerosis might be incidental, as the two processes occur at similar sites of the arterial tree and both progress with age, or might be explained by the impact

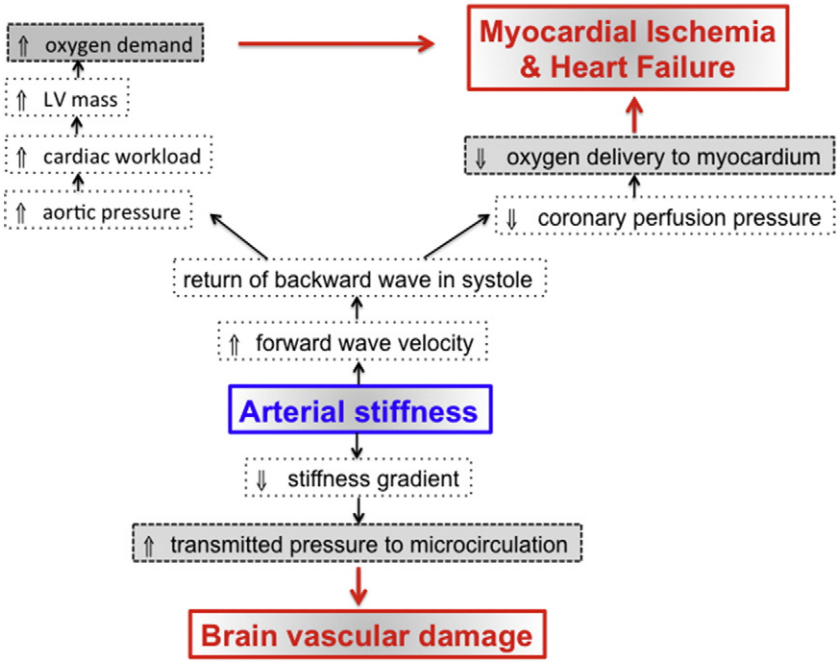

Fig. 1. Scheme representing hemodynamic links between arterial stiffness and target organ damage.