

INTRODUCTION

The pathophysiology of systemic hypertension is complex and multifactorial. The main factors modulating the systemic arterial pressure are intravascular volume, sympathetic nervous system, renin-angiotensin-aldosterone system and the functional and structural changes in vasculature. The diameter and the compliance of resistance vessels, that includes small arteries (100-400 μm) and arterioles, predominantly determine the peripheral resistance and thus the arterial pressure. Two kinds of structural changes occur in microcirculation of hypertensive patients. One is rarefaction, defined as abnormally decreased spatial density of small arteries and arterioles. The other, termed vascular remodeling includes the structural modifications of resistance vessels causing reduction of their lumen size. In this article, we briefly review the basic concepts of remodeling, its pathophysiology and the effect of antihypertensive modalities on remodeling.

NOMENCLATURE

According to the terminology proposed by Mulvany et al, vascular remodeling includes any change in diameter in a fully relaxed vessel, as measured under standard intravascular pressure. The process of change in lumen without change in amount (wall cross sectional area) or characteristics of materials is called eutrophic remodeling. The process may involve increase (hypertrophic remodeling) or decrease (hypotrophic remodeling) in wall cross sectional area. Increase or decrease in lumen diameter is classified as external and internal remodeling respectively. For example, the increase in wall thickness, decrease in lumen diameter without any change in wall cross sectional area in resistance vessels of essential hypertension is termed as inner eutropic remodeling.

MECHANISMS OF REMODELING

Based on Laplace law, wall stress (force acting on unit cross sectional area) is calculated as $P \times r/h$, where P is transmural arterial pressure, r is radius of lumen and h is wall thickness. In hypertension, the vascular smooth muscle cells of large elastic arteries are exposed to stretch from the elevated arterial pressure. To normalize the increased wall stress, large arteries like aorta undergo hypertrophy (outward hypertrophic remodeling) while maintaining the lumen size. On exposure to acute raise in arterial pressure, smaller arteries and arterioles undergo constriction through myogenic reflex, thus decreasing the lumen size and increasing the wall thickness so as to decrease R/h ratio and normalize the increased wall

stress. Myogenic reflex is an intrinsic reflex that occur independent of neural innervation or endothelial function. Large arteries cannot autoregulate with constriction in case of raised arterial pressure and hence undergo hypertrophy. This reflex constriction in resistance vessels, when persistent, becomes permanent with structural changes in the form of inward eutropic remodeling. In inner eutropic remodeling, there is reduction in vascular lumen due to closer rearrangement of vascular smooth muscle cells in the extracellular matrix without any change in amount of wall material. This increases the media to lumen ratio (r/h ratio decreases) thus trying to normalize the wall stress. Intermediate sized arteries show features of both hypertrophy and reduction in lumen size in response to elevated pressures.

The myogenic reflex, in resistance vessels, protects capillary bed from exposure to high pressures. Later inward eutropic remodeling does the same. When the reflex is impaired as in diabetes mellitus or in case the reflex is unable to compensate for accelerated hypertension, small arteries undergo inward hypertrophic remodeling. The same is observed in hypertension due to renovascular causes or primary aldosteronism.

The cellular pathways involved in vascular remodeling are not completely understood. Vascular smooth muscle cells are attached to their extracellular protein components through the transmembrane proteins called integrins. Along with these integrins, the cellular response also depends on the components of the extracellular matrix. When extracellular matrix is exposed to increased wall stress, the stretch is transmitted through the integrins to the intracellular protein kinases like Src-family kinases, Focal adhesion kinases (FAK) as well as cytoskeletal proteins like talin, paxillin and actin. This initiates the intracellular pathways and leads to gene expression for vascular remodeling. Initial intracellular event is likely the phosphorylation of Src followed by activation of FAK proteins. This pathway downstream leads to activation of MAPK/ERK (mitogen-activated protein kinases / extracellular signal-regulated kinases) pathway, which leads to expression of proto-oncogenes like c-fos involved in remodeling. Platelet-derived growth factor and epidermal growth factor receptors augment this signaling pathway.

MEDIATORS OF REMODELING

Renin-Angiotensin-Aldosterone System (RAAS): The RAAS contributes to hypertension mainly via the vasoconstriction by angiotensin II (A II) and sodium

retention by aldosterone. Angiotensin II participates in the inflammation and remodeling of the small arteries, atherosclerosis of large arteries and contributes to vascular inflammation, fibrosis and other structural changes in target end organs. At cellular level, angiotensin II binds to angiotensin II type 1 receptors (AT1R) which leads to activation of tyrosine kinase receptors like epidermal growth factor receptor and platelet derived growth factor receptor and intracellular tyrosine kinases like Src family. It also activates NAD (P)H oxidase leading to production of reactive oxygen species (ROS), which in turn stimulate the MAP/ERK kinase pathway, growth promoting transcription factors like cytoplasmic nuclear factor κ B (NF κ B) and matrix metalloproteinases. Angiotensin II may down-regulate peroxisome proliferator-activated receptors (PPARs), which has anti-inflammatory effects. Angiotensin II also promotes expression of proinflammatory molecules like vascular cell adhesion molecule -1, intracellular adhesion molecule -1 etc. Aldosterone or mineralocorticoid receptor activation also plays a role in activation of inflammation and oxidative stress causing impairment of endothelial function and vascular remodeling. This occurs through complex molecular interactions of aldosterone on cellular pathways of angiotensin II and also by stimulation of mineralocorticoid receptor by angiotensin II. RAAS blockade can have positive impact on vascular remodeling. Apart from RAAS, increased endothelin 1 production also plays a role in vascular remodeling through its direct and indirect hypertrophic effects.

Inflammation and Endothelial Dysfunction: Chronic persistent inflammation contributes to the pathogenesis of hypertension. Angiotensin II may be the major mediator of vascular inflammation by activating nuclear factor κ B (NF κ B), which up-regulates the cytokines, chemokines and the leucocyte adhesion molecules. It also causes oxidative stress and increased endothelin 1 synthesis leading to vasoconstriction. These all lead to endothelial dysfunction and vascular remodeling. Life style modifications and drugs blocking RAAS (independent of their vasodilation property) may reduce the vascular inflammation.

Immunity: Both the innate and adaptive immunity contribute to the low grade inflammation seen in hypertension. Effector T cells including Th1 lymphocytes, Th2 lymphocytes and Th 17 lymphocytes as well as T suppressor lymphocytes including regulatory T cells are involved in vascular remodeling, mediated through the action of angiotensin II and aldosterone. Th1 cells predominantly promote remodeling while T regulatory cells may exert protective effects through their anti-inflammatory action of IL-10. The initiating stimulus for immune activation is not clear but neo-antigens produced by elevated arterial pressure or other stimuli are proposed as likely cause.

Obesity, Diabetes Mellitus and Metabolic Syndrome: These conditions can exhibit hypertrophic remodeling in small arteries even in normotensive. This may be attributed to the increased oxidative stress and inflammation

associated with obesity or impaired myogenic reflex in diabetes. Life style modifications to control these can have a favorable impact on remodeling.

REMODELING AND CLINICAL IMPLICATIONS

Remodeling in large arteries increases the arterial stiffness and wave reflection that leads to an elevated pulse pressure and systolic blood pressure. Studies have shown that an increased arterial stiffness as measured by aortic augmentation index or pulse wave velocity is an adverse prognostic factor of cardiovascular disease. In hypertension, vascular remodeling may be the earliest evidence of target organ damage. Increased media to lumen ratio and increased hypertrophy are associated with elevated risk of cardiovascular morbidity. In retina, a decrease in lumen diameter is associated with an increased risk of cerebrovascular accident. The vascular remodeling in small resistance arteries and arterioles may have significant role and prognostic significance in ischemic heart disease, cerebrovascular disease and chronic kidney disease. Lowering of arterial BP alone may not be sufficient in improving outcomes in hypertension unless other factors involved in impaired vascular function and remodeling are corrected. Conditions like diabetes mellitus with impaired myogenic reflex or accelerated hypertension or renovascular hypertension, hypertrophic inward remodeling is seen instead of eutrophic remodeling and these conditions are at higher risk target end organ damage than seen in essential hypertension and needs early and aggressive intervention.

Anti-hypertensive agents ACE inhibitors, Angiotensin receptor blockers (ARBs), aldosterone antagonists and calcium channel blockers (CCBs) tend to decrease the arterial stiffness in both the large and small arteries. These effects are likely to be mediated through the down regulation of Transforming growth factor – beta (TGF- β) expression, thus displaying anti-fibrotic effect. ACE inhibitors, ARBs and CCBs can reverse the remodeling in small arteries and the effect may be primarily due to their vasodilatory action. Atenolol and likely other beta blockers do not reverse the remodeling in spite of their BP lowering effect, probably due to lack of vasodilatory action. Peroxisome proliferator-activated receptor γ (PPAR γ) agonists like rosiglitazone can prevent and reverse the remodeling in hypertension. Exercise training apart from its anti-inflammatory effects, can help to reduce the arterial wall thickness. Positive life style modifications to control the obesity and the metabolic syndrome improve the vascular remodeling associated with these conditions.

CONCLUSIONS

The pathophysiological effects and the prognostic importance of vascular remodeling in hypertension are under active research and the exact role of remodeling either as cause or consequence of hypertension needs to be clearly evaluated with further studies. A better understanding of the molecules and the cellular pathways involved in hypertension and remodeling may help in development of more targeted treatment options and better clinical outcomes.

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