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Vascular Effects of Antihypertensive Drug Therapy

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Abstract Hypertension is associated with structural and functional alterations in the vasculature that lead to hemodynamic disturbances and target organ damage. The benefit of reducing blood pressure on risk reduction is well established. Antihypertensive drugs partially correct hypertensive vascular changes by a number of mechanisms, but their influence may vary in different vascular beds. Recently, combinations of drugs with complementary or synergistic effects have shown favorable effects on the vasculature; these combinations may contribute to risk reduction and improve outcomes in the future. Clinical trial evidence has shown an improvement in morbidity and mortality indicators that could be related to vascular effects of antihypertensive drugs, but this effect needs to be proven in future long-term prospective studies involving simultaneous evaluation of small-artery and large-artery properties.

Keywords Hypertension · Vascular remodeling · Arteries · Cardiovascular disease

Introduction

The benefit of reducing blood pressure (BP) on improved cardiovascular risk and outcomes is well established in essential hypertension in most age groups [1–3]. Hypertension is associated with vascular changes that contribute to its development, progression, and complications [1]. The varying degrees of cardiovascular protection offered by antihypertensive drugs may be related to their ability to regress the vascular remodeling associated with hypertension. Though results from a recent meta-analysis [3] claim that only reduction of BP will improve cardiovascular outcomes, there is growing evidence that antihypertensive drugs have vascular protective effects that should not be ignored. For example, correction of aortic stiffness by some antihypertensive agents [4•, 5•] may have contributed to reductions in central systolic pressure, with improved cardiac afterload favoring coronary perfusion and regression of left ventricular hypertrophy [6, 7], which suggests strongly that these effects are a desirable target [1, 8••]. As well, correction of small-artery remodeling may have protective effects on tissue perfusion [9•]. The use of combination therapy holds potential for improved outcomes and may contribute to greater regression of hypertensive vascular remodeling. The goal of this review is to summarize the more recent evidence of vascular effects of antihypertensive drugs.

Vascular Pathophysiology of Hypertension

The arterial system comprises large and medium-size conduit arteries (elastic and muscular arteries) as well as smaller resistance arteries (small arteries and arterioles). Both types have crucial but distinct functions in maintaining the constant pressure and flow of blood—functions that are critical for tissue perfusion. Total peripheral resistance, a determinant of mean BP and systemic blood flow, is essentially an inverse function of the fourth power of the lumen diameter of small resistance arteries with a lumen less than 350 μm [10, 11]. Accordingly, minor changes in

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lumen diameter significantly increase resistance to flow and BP. On the other hand, large elastic arteries transform the pulsatile flow of blood that results from ventricular contraction and ejection of blood into a more steady flow by their cushioning function during systole, and they maintain a constant peripheral circulation by their elastic recoil during diastole. This cushioning or "windkessel" function of the large arteries is an important determinant of systolic BP (SBP) and depends upon the viscoelastic properties of the vessel wall and vascular biomechanics. In hypertension, elevated pressure is associated with media thickening, with increased collagen deposition and fragmentation of elastic laminae (arteriosclerosis), leading to stiffening of large arteries due to recruitment of fewer elastic fibers and more collagen and fibronectin fibers in the vessel wall. Stiffness of the aorta can be evaluated by carotid-femoral pulse wave velocity (PWV), which is an independent risk factor for all-cause and cardiovascular mortality. The intima of remodeled large conduit arteries is the site of atherosclerotic complications. Carotid intima-media thickness (IMT) is a measure of subclinical atherosclerosis and a predictor of risk for clinical events [12]. As well, vasoconstriction occurs in the microcirculation through the influence of myogenic tone, a stimulated renin-angiotensin-aldosterone system (RAAS), and catecholamines, as well as remodeling in response to RAAS stimulation, catecholamines, and the effects of growth factors [13]. Chronically elevated BP and stretch initiate complex signal transduction cascades leading to vascular remodeling that contributes not only to elevation of blood pressure [13] but also to hypertensive complications [9•]. Remodeled small arteries have a smaller lumen and external diameter, and normal or increased media thickness with increased media-to-lumen ratio but normal media cross-sectional area [10]. Increased media-to-lumen ratio may be one of the first manifestations of hypertensive target organ damage [14] and has been demonstrated to have prognostic significance in relation to cardiovascular events [15, 16•]. In the case of studies of subcutaneous small arteries, a relationship has been demonstrated with coronary flow vasodilator capacity [17], which explains the prognostic significance of remodeling in this vascular bed. Furthermore, these vessels show very similar changes to those of small arteries from brain, myocardium, and kidney cortex in rodents [13, 18•]. In most hypertensive patients, vascular remodeling is associated with endothelial dysfunction [13], which plays a critical role in the development of hypertensive target organ damage and atherosclerosis.

Increased pulsatility of conduit arteries is transmitted to small arteries and may contribute to vascular injury in the resistance vasculature [18•]. Moreover, structural alterations of the microcirculation are also a mechanism for development of target organ damage such as ischemic heart disease and cerebral and renal damage [9•]. Vascular alterations in large and small arteries develop in parallel and interact, contributing to progression of hypertension and its complications [18•] (Fig. 1). Correction of small-artery and large-artery structure and function could therefore favorably affect outcomes in hypertension [6, 7, 19].

The correction of vascular structure during antihypertensive treatment may depend on the vasodilatation achieved rather than on BP reduction [20•]. In addition, antihypertensive agents may exert these actions through their antioxidant, anti-inflammatory, antiatherosclerotic, or antifibrinolytic effects [21, 22], improving endothelial function [23, 24], reversing vascular remodeling, and reducing cardiovascular complications. These effects may improve arterial function, reduce peripheral vascular resistance, correct intensity and timing of reflected waves, and reverse structural changes in small and large arteries.

Compared with other antihypertensive agents, antagonists of the RAAS may contribute to a greater reduction of cardiovascular risk beyond BP reduction by inhibiting angiotensin II effects on inflammation, oxidative stress, and vascular remodeling in hypertension [13, 22]. Angiotensin-converting enzyme (ACE) inhibitors reduce adhesion molecules and growth factors, prevent apoptosis [13, 22], and improve endothelial function partly through bradykinin-induced vasodilatation [25•]; bradykinin may also favor angiogenesis, reversing microvascular rarefaction, an effect that could improve target organ damage and slow the progression of hypertension. Angiotensin receptor blockers (ARBs) exert beneficial effects on vascular and renal function and cardiac remodeling [13, 26] by decreasing vascular inflammation, hypertrophy, and thrombosis, thereby inhibiting atherosclerosis and vascular complications. Vascular protection by calcium channel blockers (CCBs) depends partly on their vasodilating action and on calcium channel blockade, which in turn interferes with the activity of kinase cascades involved in growth promotion and cell migration [13, 21]. Dihydropyridine CCBs also exert anti-inflammatory and antioxidant effects [27]. They improve BP and endothelial function, reduce oxidative stress, and increase insulin sensitivity by increasing adiponectin levels, thus improving metabolic parameters [28•].

Newer β-adrenoceptor antagonists that induce vascular production of nitric oxide improve endothelial function [29]. These agents also confer a broader favorable metabolic profile [30] that may be clinically beneficial. Vasodilating β-blockers (eg, carvedilol and nebivolol) improve coronary microvascular function and hyperemic coronary blood flow, which improves left ventricular function [31]. Other agents, such as the mineralocorticoid receptor blocker eplerenone, reduce stiffness of large arteries [32] and small arteries [33••]. Endothelin-receptor antagonists, which inhibit cardiovascular growth, inflammation, and fibrosis, offer promise in preventing complica-

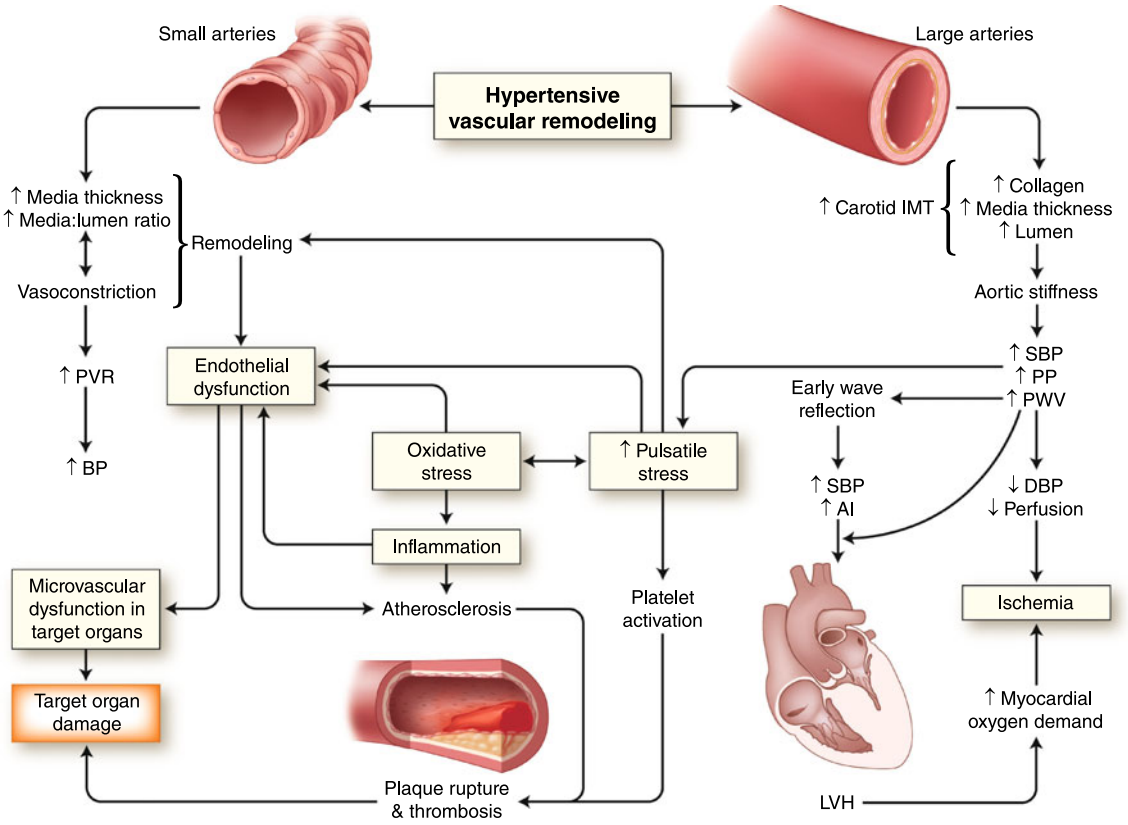

Fig. 1 The role of vascular remodeling in the progression and complications of hypertension. *AI* augmentation index; *BP* blood pressure; *DBP* diastolic blood pressure; *IMT* intima-media thickness; *LVH* left ventricular hypertrophy; *PP* pulse pressure; *PVR* peripheral vascular resistance; *PWV* pulse wave velocity; *SBP* systolic blood pressure

tions of hypertension, atherosclerosis, and diabetes [34]. They may also be particularly useful in resistant hypertension [35]. Drug combinations with complementary modes of action improve BP control and may improve cardiovascular protection by targeting separate signaling pathways pivotal to the regulation of vascular function [36].

Effect of Antihypertensive Drugs on Large Arteries

ACE inhibitors improve endothelial function, reduce stiffness of large and muscular arteries [37], and reduce wave reflections and the aortic systolic pressure and augmentation index [38, 39]. Similarly, ARBs and CCBs reduce arterial stiffness [40]. In contrast to first-generation β-blockers, vascular protective effects of the newer antioxidant β-blockers have been demonstrated in experimental and human studies [41]. Nebivolol reduced vascular stiffness in patients with coronary artery disease [42] and in hypertensive diabetic patients [43].

Chronic ACE inhibition with trandolapril decreased fibronectin-integrin complexes, modulating extracellular matrix components of the arterial wall and leading to improved mechanotransduction, with a greater reduction in central pulse pressure and carotid artery incremental elastic modulus compared with amlodipine [44••]. For a similar reduction in BP, 1-year treatment with both perindopril and atenolol improved brachial flow-mediated dilatation corrected for resting diameter but did not affect small-artery relaxation to acetylcholine [45].

Although longer duration of treatment may be needed for reversal of vascular remodeling [46], improvement after short-term treatment has also been observed. Treatment of patients with stage 1 hypertension with valsartan and metoprolol for 3 months showed similar effects on large-artery functional properties assessed by endothelial function, brachial and carotid artery distensibility coefficients, PWV, carotid IMT, and elastic modulus [47•]. Treatment for 4 weeks with an extended-release CCB, felodipine, not only lowered BP but also reduced production of endothelial vasoactive substances including endothelin, angiotensin II, and thromboxane A [48]. Thus, vasculoprotective effects of CCBs may occur rapidly.

Recently, combination therapy has become increasingly popular. The REASON study (Preterax in Regression of Arterial Stiffness in a Controlled Double-Blind Study) showed greater vascular protection offered by a 1-year treatment with a fixed-dose ACE inhibitor–diuretic combi-

nation (perindopril/indapamide) compared with atenolol [6]. Treatment with the same combination for 2 years improved brachial artery endothelial function in comparison with atenolol in hypertensive patients in a pressure-independent manner through improved nitric oxide (NO) bioavailability and increased sensitivity of vascular smooth-muscle cells to exogenous NO [49•].

Effect of Antihypertensive Drugs on Small Arteries

Antihypertensive agents have been shown to partially correct the remodeling and impaired endothelial function of small arteries and arterioles in both experimental models and human hypertension [11]. Regression of structural abnormalities in gluteal subcutaneous arteries from hypertensive patients correlates with improved structure and function of other, more critical vascular beds such as the coronary circulation [17, 50]. ACE inhibitors normalized the structure of subcutaneous gluteal small arteries [51, 52] and improved endothelium-dependent relaxation after 1 to 2 years of treatment [53]. ARBs also corrected small-artery structure and endothelial function [24, 54]. Similar results were observed with ACE inhibitors and ARBs in hypertensive diabetic patients [55, 56]. CCBs also normalized small-artery structure and improved endothelial function [57, 58]. Although the β-blocker atenolol has appeared ineffective in improving small-artery structural or functional abnormalities associated with hypertension [22, 51–54, 56–58], carvedilol improved endothelial function in resistance arteries from stroke-prone, spontaneously hypertensive rats (SHR-sp) [59]. Angiotensin II-induced vascular relaxation (occurring in the presence of an ARB in the bath when the experiment was performed) was found in precontracted subcutaneous resistance arteries from hypertensive diabetic patients treated for 1 year with valsartan but not in arteries from patients treated with atenolol. This finding was associated with an upregulation of angiotensin II type 2 (AT_2) receptors [60•], which induce NO release. BP control for 1 year with atenolol resulted in increased wall stiffness of resistance arteries, whereas treatment with eplerenone, a mineralocorticoid receptor antagonist, reduced stiffness, decreased the collagen/elastin ratio, and decreased inflammatory mediators (osteopontin, monocyte chemoattractant protein-1, basic fibroblast growth factor, interleukin-8, and interleukin-10) [33••].

The effects of some combinations of antihypertensive agents on small arteries have been reported. Combining olmesartan with nifedipine, amlodipine, or azelnidipine in C57BL/6J mice showed greater inhibition of neointimal formation, oxidative stress, and inflammatory markers in the injured femoral artery with azelnidipine than with the other CCBs [61•]. In patients with a family history of hypertension and cardiovascular disease who had newly diagnosed hypertension, chronic verapamil treatment improved endothelial function and trandolapril prevented structural changes, whereas a combination of the two drugs both improved endothelial function and prevented structural changes in forearm resistance arteries [62]. Aliskiren (a direct renin inhibitor) or valsartan similarly suppressed cardiac hypertrophy, inflammation, and fibrosis, as well as coronary remodeling; prevented cuff injury-induced arterial intimal thickening; and reduced urinary albumin excretion, glomerular inflammation, and glomerulosclerosis in endothelial NO synthase-deficient mice [63]. These beneficial effects were associated with attenuation of tissue oxidative stress. A low-dose combination of the two drugs yielded more pronounced improvement in the above parameters than did monotherapy.

Beneficial vascular effects have also been observed by combining antihypertensive drugs with drugs targeting other cardiovascular risk factors such as dyslipidemia or hyperglycemia, based on the shared pathophysiologic pathways of vascular injury and atherosclerosis through inflammation and increased oxidative stress. Short-term treatment (4 weeks) of hypertensive, hypercholesterolemic patients with simvastatin and either telmisartan or bisoprolol improved forearm blood flow and reduced vascular resistance with the simvastatin-telmisartan combination but not with the bisoprolol combination [64]. We previously showed beneficial effects of peroxisome proliferator activated-receptor gamma (PPARγ) activators, thiazolidinediones or glitazones, on the vascular structure and function in experimental studies [65]. These results suggested the potential of these agents in treating hypertension associated with metabolic abnormalities [66]. Combining pioglitazone and candesartan suppressed cardiac hypertrophy, inflammation, and interstitial fibrosis and reduced vascular endothelial dysfunction in stroke-prone spontaneously hypertensive rats more than either monotherapy, owing to a greater reduction of oxidative stress [67]. However, recent studies in rodents suggest that in conditions of high cardiometabolic risk, PPARγ activation may have some beneficial effects but could, through upregulation of protein arginine methyltransferase-1 (PRMT-1), lead to increased concentrations of asymmetric dimethyl arginine (ADMA), a condition that induces endothelial dysfunction [68•].

Conclusions

Antihypertensive drugs have shown the ability to reverse or correct structural and functional alterations in large and small arteries. It remains to be determined, however, whether it is the reduction in BP or the reversal of

hypertensive vascular changes that improves cardiovascular outcomes. The importance of lowering BP to reduce cardiovascular and cerebrovascular risk regardless of the drug class has been emphasized, suggesting that BP reduction should be the major aim of antihypertensive pharmacotherapy [3]. However, for similar BP reduction, a relatively greater influence of some agents on central BP and large-artery stiffness on one hand, and on endothelial function and small-artery structure on the other, may at least partly explain BP-independent advantages of some antihypertensive drugs over others. Short-term risk reduction may depend on adequate control of BP, whereas long-term improved outcomes may be related to improvement in vascular function and reversal of hypertensive vascular injury. Whether this hypothesis is true needs to be investigated in studies longer than the 3 to 5 years of clinical trials. There is also need for further evaluation of the beneficial vascular effects of vasodilating β-blockers, endothelin receptor antagonists, and newer agents such as aliskiren and potassium channel openers, which may offer promise in long-term studies and in different vascular territories. Drugs combining several mechanisms of action or combinations of antihypertensive drugs with those targeting other risk factors also may reduce overall cardiovascular risk and need to be further investigated.

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