Contribuição Internacional

Prevention and treatment of ischemia and fibrosis associated in hypertensive heart disease

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Abstract

Elevated arterial pressure is a well-established predisposing factor for the development of stroke, hypertensive heart and peripheral artery disease, as well as for cardiac and renal failure. Hypertension-induced alterations in cardiac structure and function manifested as left ventricular hypertrophy (LVH) associated with impaired coronary hemodynamics and ventricular fibrosis accounting for this major risk factor of cardiovascular morbidity and mortality[1-4]. Indeed, cardiac enlargement (or LVH) carries a greater risk than either height of systolic or diastolic pressure[1,4]. Furthermore, a large body of evidence attests to the fact that LVH is a strong independent risk factor for heart failure, sudden death, ventricular dysrhythmias, and coronary artery disease[5-10]. LVH usually begins as compensated hypertrophy, but it eventually progresses to cardiac failure if arterial pressure remains uncontrolled [8]. However, the mechanisms underlying the increased risk associated with LVH have not completely elucidated, although it is likely that a number of factors may contribute. Since all components of the heart seem to affected with LVH (e.g., muscle, vasculature and interstitium), impaired coronary hemodynamics, ventricular fibrosis and dysfunction, increased vulnerability to lethal dysrhythmias, and enhanced coronary atherogenesis might account for the risk[1,3,11-14].

Several metaanalysis have shown that antihypertensive therapy has greater propensity to reduce stroke death than death from coronary heart disease[15,16], suggesting that arterial pressure may exert a greater effect on the cerebral circulation than the coronary. Moreover, this concept points to role of nonhemodynamic factors that participate in the development of hypertension related cardiovascular injury and, therefore, in this risk[17]. Thus, current goals of antihypertensive therapy are to prevent or reverse these additional alterations along with optimal control of arterial pressure. This review focuses primarily on the strategy for pharmacological prevention and reversal of myocardial ischemia and ventricular fibrosis which are also associated with hypertensive heart disease.

Keywords: Hypertensive heart disease; Left ventricular hypertrophy; Ventricular fibrosis; Myocardial ischemia; Angiotensin converting enzyme inhibition; Angiotensin II receptor antagonism; Calcium antagonism; Prevention; Treatment.

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Hypertensive heart disease

Hypertensive heart disease (HHD) is a clinical and pathological entity associated with sustained increase in arterial pressure and is characterized by an increased left ventricular mass, fibrosis and impaired coronary hemodynamics[1-3,18]. The primary factors responsible for the development of LVH are pressure and/or volume overload, but number of nonhemodynamic factors including the pathophysiological effects of catecholamines, components of renin-angiotensin-aldosterone system, growth factors, endothelins, and other peptides all participate[1-3,19-24]. It is now well-established that hypertensive LVH is characterized by cardiac myocytic hypertrophy which is associated with specific biochemical and functional changes, functional and structural alteration of the coronary circulation and ventricular fibrosis[3]. As a result of hypertensive LVH, myocardial tension and oxygen demand are increased, whereas structural and functional alterations of coronary circulation result in diminished blood supply. Additionally, the interstitial and perivascular fibrosis that accompany LVH further compromise the coronary hemodynamics[4,13,18].

Numerous studies have demonstrated that resting coronary blood flow may be normal in clinical and experimental hypertensive models[25-27]. However, with the introduction of the concept of coronary flow reserve[28], it is clear that the ability of coronary vasculature to dilate in response to certain physiological (e.g., exercise, ventricular pacing) or pharmacological (e.g., papaverine, adenosine, dipyridamole) interventions diminishes with hypertension[1,29,30]. The diminished coronary flow reserve (defined as the difference between coronary flow during maximal coronary vasodilatation and basal or resting condition) and increased minimal coronary vascular resistance (the vascular resistance established at maximal vasodilatation) have been confirmed as the most notable changes associated with hypertension in number of experimental and clinical studies, even in asymtomatic patients with borderline hypertension without echocardiographic signs of LVH[27,29-39]. Furthermore, these parameters have become extremely useful hemodynamic indexes to explain the phenomena of silent ischemia or microvascular angina that occur in patient with hypertensive heart disease, especially when epicardial coronary arteries have normal anatomic appearance[11,36-38].

Abnormalities in coronary hemodynamics associated with sustained hypertension are primarily due to structural alteration in coronary resistance vessels (vascular remodeling) manifested as medial wall thickening and increased wall:lumen ratio, periarteriolar fibrosis, and decreased number of small arterioles and capillaries[40,41]. The latter response represents either disproportionate growth of cardiac myocytes and coronary vasculature or loss of vessels without alteration in cardiac myocyte compartment[42]. The increased wall:lumen ratio of coronary resistance vessels can be attributed to high vascular wall stress reflecting the hypertensive coronary perfusion as well as to circulating and local growth hormones (angiotensin II, catecholamines, platelet-derived growth factor, transforming growth factor)[43-46].

It must be emphasized that LVH, *per se*, does not impair coronary flow reserve since coronary reserve remains normal in physiological LVH in trained athletes[30,47] or may be impaired even before clinical LVH is demonstrated in hypertensive patients[39]. Furthermore, a study from our laboratory demonstrated that low doses of angiotensin converting enzyme (ACE) inhibitor[31] and angiotensin II receptor antagonist[32] reduced left ventricular mass without affecting coronary flow and flow reserve in spontaneously hypertensive rats (SHR). In addition to structural factors, functional alterations of the coronary vasculature may contribute to the impaired coronary flow reserve associated with hypertension. Thus, endothelial dysfunction manifested by reduced synthesis and/or increased degradation of nitric oxide and perhaps reduced sensitivity of vascular smooth muscle cells to nitric oxide in the coronary circulation, is associated with hypertension[48-52]. On the other hand, augmented synthesis of endothelium derived contracting factors may also participate[53].

Excessive accumulation of fibrilar collagen in the interstitium of the hypertrophied left ventricle is a now well- accepted aspect of HHD, clearly distinguishing it from physiological LVH (without adverse consequences)[4,18,54-57]. This increased ventricular collagen concentration promotes increased wall stiffness and initiates diastolic dysfunction[4,58], which lead to the eventual appearance of overt heart failure[58-62]. Furthermore, impaired ventricular relaxation associated with the diffuse interstitial fibrosis further decreases myocardial perfusion since coronary flow occurs primarily during diastole. Additionally, the perivascular fibrosis may also impair vasodilatation and consequentially coronary flow.

The circulating as well as locally generated effector hormones of the renin-angiotensin-aldosterone system (i.e., angiotensin II and aldosterone)[13,18,56,57,63] as well as excess salt intake[64,65], independent of arterial pressure, may affect the structural remodeling of the myocardial collagen matrix. However, the underlying mechanisms are still under intensive study. *In vitro* studies have shown that the angiotensin

II induced collagen accumulation results from stimulated collagen synthesis in rat cardiac fibroblast with concomitantly suppressed collagenase activity[66]. Furthermore, it has been proposed that MAP/ER kinase and cAMP-adenosine pathways may contribute to the abnormal proliferation of cardiac fibroblast observed in hypertension[67,68]. Clinical evidence suggesting a role of aldosterone and salt in promoting the increased myocardial collagen concentration in patients have been also recently published[69,70].

Thus, the goal of antihypertensive therapy should be not only to prevent or reduce myocytic hypertrophy, but also to diminish ventricular fibrosis and the structural and functional alterations of the coronary circulation and, of course the optimal control of arterial pressure. For many years we have been studying the ability of various antihypertensive compounds to prevent or reduce these adverse cardiovascular effects of hypertension and the results of these studies will be considered in the discussion that follows.

Prevention and treatment of HHD

Left ventricular hypertrophy. Vigorous use of antihypertensive therapy as soon as persistently elevated arterial pressure is established will prevent LVH[1]. Furthermore, every class of antihypertensive agents will prevent LVH as long as arterial pressure is well-controlled. Even hydralazine, initiated in four week old SHR for 32 weeks, will prevent the onset of hypertension and the LVH[71]. Also, beta-adrenergic antagonists or an ACE inhibitor given from conception through the development stage of SHR hypertension had similar effects[72,73]. On the other hand, large body of experimental and clinical evidence has shown that various antihypertensive agents may differ in their ability to reduce LV mass once it has developed[27,31-35,74-88]. We have repedeatly reported evidence for a dissociation between hemodynamic and structural effects of various antihypertensive drugs (even within the same class of agents), suggesting that reduction in left ventricular mass does not solely depend on the reduction of cardiac afterload[78,81]. For example, cardiac mass remained unchanged or might be increased with hydralazine or minoxidil despite reduced mean arterial pressure[75]. On the other hand, reduced left ventricular mass could also be achieved independent of an effective reduction in arterial pressure[31,32,80].

One of the most important questions that arises is whether ventricular function is preserved when LV mass is decreased[89]. Both experimental and clinical studies have shown that left ventricular performance after reduction in LV mass may be impaired[76,78,81], may remain stable[83,84] or may even be improved[78,81-83,85-88]. The critical question is whether a decrease in LV mass actually reduces the associated risk of cardiovascular morbidity and mortality. At present, there are no major prospective studies that have clearly demonstrated this goal. If such a large multicenter study appears, it must not only demonstrate the benefit from reduction in left ventricular mass itself does occur, it must also show that it is unrelated to other potential effects of antihypertensive therapy: arterial pressure reduction, associated anti-arrhythmic effects, and so further[90].

Coronary insufficiency. In recent years, a number of studies have shown experimentally and clinically, that the coronary hemodynamic impairment in hypertensive LVH may be improved using various antihypertensive agents. In SHR, we have demonstrated decreased minimal coronary vascular resistance and increased coronary flow reserve with calcium antagonists[34], ACE inhibitors[31,32,35], and angiotensin II type 1 receptor blockers[35] as well as with the prolonged administration of the nitric oxide precursor L-arginine[33]. Other experimental studies have shown that reduced medial thickness of intramyocardial arterioles as well as increased capillary density is also a major component of the structural basis for improved coronary hemodynamics associated with ACE inhibitor or calcium antagonist therapy[91-93]. Furthermore, our more recent study in aged SHR demonstrated that drugs that interfere with renin-angiotensin II- aldosterone system may be more effective in reversing coronary impairment associated with hypertension and aging[34]. Moreover, we have also shown that the combination of an ACE inhibitor and angiotensin II type 1 receptor antagonist was superior to either of these two agents was used alone in equidepressor doses[35]. This intervention provided a multiple-locus for interference with the renin-angiotensin II-aldosterone system: reduced generation of angiotensin II preventing vasoconstrictor, hormone-stimulating and mitogenic effects of angiotensin II; increased bradykinin-induced coronary vasodilatation, the beneficial effect of improving the endothelial dysfunction of the coronary circulation by the ACE inhibition; and additional angiotensin II type 1 receptor inhibition especially when angiotensin II is formed by a non-ACE enzymes (e.g., chymase).

More recently clinical data have confirmed the foregoing experimental findings demonstrating that coronary reserve can be improved in hypertensive patients using calcium antagonists[94,95], ACE inhibitors[96-98], and L-arginine[99,100]. Furthermore, significant reduction in minimal coronary vascular resistance after an ACE

inhibitor, but not a beta-adrenergic receptor blocker, may reflect different mechanisms of antihypertensive therapy at a variety of structural and physiological levels[96]. These findings are in agreement with results of those studies that examined the effects of antihypertensive therapy on resistance vessels in humans[101,102]. For example, improved wall:lumen ratio and better functional response of these arteries were achieved after long-term therapy with ACE inhibitor but not with beta-blockers. Furthermore, reduction in myocardial fibrosis was associated with marked improvement in coronary flow reserve and diastolic function after ACE inhibitor treatment in a recent clinical studies[97,103].

Ventricular fibrosis. Related to the concept of hormone-induced myocardial fibrosis, the ACE inhibitors but not hydralazine, were able to prevent the appearance of myocardial fibrosis in SHR[104,105]. Moreover, in rats with increased circulating levels of effector hormones of the renin-angiotensin II-aldosterone system due to unilateral renal ischemia or hyperaldosteronism, the aldosterone receptor antagonist spironolactone or the ACE inhibitor captopril attenuated the development of myocardial fibrosis[106,107]. Thus, in a number of studies, reduced LV mass produced by various antihypertensive agents, was associated with a reduced fibrilar collagen deposition within the cardiac interstitium[34,35,43,85,93,97,103,107]. In this respect, agents that interfere with renin-angiotensin-aldosterone system have demonstrated these cardioprotective properties[85,34,93,97,103]. More recently, studies from our laboratory have demonstrated that the angiotensin II type 1 receptor antagonist candesartan was extremely effective in reversing the adverse cardiovascular effects of hypertension in SHR including normalization of arterial pressure, improving markedly systemic and coronary hemodynamics, and reducing left ventricular mass and hydroxyproline concentration in both ventricles (unpublished data). It is of particular note that concomitant administration of the angiotensin II type 2 receptor antagonist PD 123319 slightly reduced the hypotensive action of the AT1 receptor inhibitor, and prevented the antifibrotic effect of the angiotensin II type 1 receptor antagonist on myocardial hydroxyproline concentration. Since these findings suggest an important role of AT2 receptor activation in reducing ventricular fibrosis with AT1 receptor antagonism, selective stimulation of AT2 could provide an additional valuable cardioprotective feature of AT1 blockade in hypertensive patients predisposed to cardiac failure. Reduced left ventricular collagen concentration and improved coronary hemodynamics have also been achieved with an ACE inhibitor or a calcium antagonist in aged SHR[34]. It was of interest in this and more other studies that the calcium antagonist increased right ventricular mass and collagen in the SHR[34,83]. This profibrotic effect on the right ventricle was prevented by cotreatment with an ACE inhibitor even though left ventricular collagen was not decreased further with the calcium antagonist[83,108]. In addition, we confirmed the early increase in right ventricular wall thickness with a calcium antagonist in patients[109]. It seems clear that these agents did not affect collagen content in the right ventricle wall through similar mechanisms as in the left ventricle; and these findings continue to warrant further investigation. Other experimental studies have shed further light on the underlying antifibrotic mechanisms of action by agents that interfere with renin-angiotensin II-aldosterone system. They suggest the possibilities of inhibition of collagen type 1 synthesis[110] and enhanced collagen degradation by activation of collagenase activity[85]. We and others have also demonstrated an antifibrotic effect of prolonged L-arginine[35], the beta-adrenergic antagonist carvedilol[111], aspirin, and methylprednisolone administration[112].

Furthermore, very recent clinical studies have demonstrated that long-term treatment with ACE inhibitors promoted reduction of interstitial collagen and periarteriolar fibrosis of resistance vessels accompanied with marked improvement in coronary flow reserve and diastolic function[97,103]. These clinical findings are very promising and strongly suggest that hemodynamic and structural alterations associated with HHD are not necessarily irreversible and can be corrected with certain specific therapeutic interventions.

Conclusion

In order to recommend the best therapeutic strategies for HHD, all the mechanisms leading to structural and functional cardiovascular alterations associated with sustained increase in arterial pressure must be considered. Thus, it is important to analyze carefully and to clearly delineate the effects of each antihypertensive agent with respect to its ability to optimally control arterial pressure and to prevent or reverse the coronary hemodynamics, myocardial alterations, and adverse extracellular effects. Future clinical trials must address the potential efficacy and drug actions in the same manner. Although it may seem an extra ambitious goal, most recent clinical studies suggest they can be and must be pursued.

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