Hypertension-induced target organ damage: clinical and experimental evidence

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Abstract

The dysregulation of renin-angiotensin-system (RAS) plays a pivotal role in hypertension and in the development of the related target organ damage (TOD). The main goal of treating hypertension is represented by the long-term reduction of cardiovascular (CV) risk. RAS inhibition either by angiotensin converting enzyme (ACE)-inhibitors or by type 1 Angiotensin II receptors blockers (ARBs), reduce the incidence of CV events in hypertensive patients. Actually, ACE-inhibitors and ARBs have been demonstrated to be effective to prevent, or delay TOD like left ventricular hypertrophy, chronic kidney disease, and atherosclerosis. The beneficial effects of RAS blockers on clinical outcome of hypertensive patients are due to the key role of angiotensin II in the pathogenesis of TOD. In particular, Angiotensin II through an inflammatory-mediated mechanism plays a role in the initiation, progression and vulnerability of atherosclerotic plaque. In addition, Angiotensin II can be considered the hormonal transductor of the pressure overload in cardiac myocytes, and through an autocrine-paracrine mechanism plays a role in the development of left ventricular hypertrophy. Angiotensin II by modulating the redox status and the immune system participates to the development of chronic kidney disease. The RAS blocker should be considered the first therapeutic option in patients with hypertension, even if ACE-inhibitors and ARBs have different impact on CV prevention. ARBs seem to have greater neuro-protective effects, while ACE-inhibitors have greater cardio-protective action.

Introduction

Essential hypertension is one of the major cardiovascular (CV) risk factor. The main objective of treating hypertension is long-term reduction of cardiovascular (CV) risk. This goal can be achieved through: i) the optimal control of blood pressure (BP) [1]; ii) the prevention of hypertension-related target organ damage (TOD) with related metabolic complications; and iii) the reduction of CV events. The dysregulation of renin-angiotensin-system (RAS) plays a pivotal role not only in the genesis of hypertension, but also in the development of TOD, diabetes, obesity, atherosclerosis and occurrence of major CV events. In fact, it has been documented that angiotensin II (Ang II), the effector of RAS, is involved in the regulation of endothelial function, tissue remodeling, inflammation, oxidative stress, differentiation of adipocytes, glucose metabolism and electrolytes homeostasis (Figure 1). Blocking the RAS either with angiotensin converting enzyme (ACE)-inhibitors, or with the type 1 Ang II (AT₁) receptors blockers (ARBs), reduce the incidence of CV events in hypertensives and in patients with high CV risk [2-5]. ACE-inhibitors block the conversion of angiotensin-I into Ang II reducing the circulating and local levels of Ang II. ACE-inhibitors also reduce the release of aldosterone and vasopressin, decrease the activity of sympathetic nervous system, as well as the trophic effects of Ang II on cardiac muscle and vessels. The inhibition of ACE results into an increase in plasma bradykinin levels, which in turn, stimulates type 2 bradykinin receptors leading to the release of nitric oxide.
(NO) and vasoactive prostaglandins (prostacyclin and prostaglandin E2). These pharmacological effects are translated into several biological actions such as a BP reduction associated with a decrease in plasma levels of epinephrine, norepinephrine and vasopressin. There is also an interference with development of vascular and cardiac hypertrophy and extracellular matrix proliferation, and a decrease in renal vascular resistances. Finally, pharmacological intervention might result in an increase of renal blood flow, which in turn, promotes Na⁺ and water excretion, and in the modulation of fibrinolytic balance favoring antithrombotic pathways.

AT1 receptors belong to the superfamily of G-protein–coupled receptors, characterized by 7 trans-membrane regions, and are localized in the kidney, heart, endothelium, vascular smooth muscle cells, brain, adrenal gland, platelets, adipocytes, and placenta. The AT1 receptors mediate most of the detrimental effects of Ang II on CV system. ARBs act by blocking the AT1 receptors and thus prevent the pathophysiological effects mediated by Ang II binding to the AT1 receptor. Moreover, as a consequence of AT1 blockade, ARBs increase systemic and local levels of Ang II. Increased levels of Ang II result in the unopposed stimulation of the AT2 receptors. It has been proposed that stimulation of AT2 receptors exerts an important role in counterbalancing some of the detrimental effects of Ang II on CV system: e.g. the inhibition cell growth, the promotion of cell differentiation, and the synthesis of NO. Finally, for some ARBs has been documented an agonist action on PPAR-γ receptors. Of note, these pharmacologic effects contribute to the improvement of insulin sensitivity. Altogether the latter pharmacological properties contribute to prevent the development of hypertension-induced TOD, and of associated diseases such as diabetes, atherosclerosis, and renal disease. These effects appear to be independent from ARBs-induced BP reduction.

RAS inhibition and hypertension-related TOD

Heart, kidney, arteries, brain are target organs of hypertension. Hypertension-induced TODs are important determinants of CV risk and represent a key target of antihypertensive therapy. Notably the combination of different TODs like LVH plus chronic kidney disease (CKD) has an additive effect on the incidence of CV events [6]. Ang II plays a critical role in the pathogenesis and progression of TODs and, in general, in the continuum of CV diseases (Figure 2). Thus, the RAS blockade must be considered as the first choice therapy of hypertensive patients with evidence of TODs.

Left ventricular hypertrophy

Left ventricular hypertrophy (LVH) is an independent risk factor for morbidity and mortality for CV diseases. BP is an important determinant of LVH, and a substantial percentage of patients with hypertension develop this complication. However, the development of LVH is complex and multifactorial involving genetic and metabolic abnormalities, neuro-hormonal stimulation, mechanical

Figure 1. Pleiotropic effects of Angiotensin II. Angiotensin II plays a key role in the control of several pathogenic mechanisms that ultimately are involved in the development of hypertension-induced target organ damage. ACE, angiotensin converting enzyme.
forces, and inflammatory response (Figure 3). For instance, in newly diagnosed hypertensive patients, naïve to therapy, metabolic and anthropomorphic abnormalities together with systolic BP values were shown to be independent predictors of LVH [7].

Clinical evidence: Several studies analyzed the effects of different classes of antihypertensive drugs on LVH. The first meta-analysis assessing the ability of various antihypertensive agents to reduce left ventricular hypertrophy was published in 1996 by Schmieder et al. [8]. After adjustment for different treatment durations, left ventricular mass decreased by 13% with ACE inhibitors, 9% with calcium channel blockers, 6% with beta-blockers, and 7% with diuretics. There was a significant difference between classes of drugs: e.g. ACE inhibitors reduced left ventricular mass more than beta-blockers and diuretics, suggesting ACE inhibitors might be the first-line drugs to reduce LVH. Note, ARBs were not yet commercially available at the time. In 2003 was published another meta-analysis including also clinical trials investigating ARBs [9]: here, ARBs, calcium antagonists, and ACE-inhibitors were shown to be the most effective drugs to reducing left ventricular mass in patients with essential hypertension (Figure 4). In 2009 a meta-regression-analysis [10] showed that ARBs induce the largest regression of LVH. In addition, ARBs are able also to interfere with the development of myocardial fibrosis. In fact, a sub-analysis of the LIFE study showed that ARBs decreased myocardial collagen content, whereas other drugs did not [11]. These studies indicate that RAS inhibition with both ACE-inhibitors or ARBs represents a valid pharmacologic strategy to prevent or reduce LVH.

Experimental data: The results of several experimental and pioneering studies suggest that Ang II plays a key role in the pathogenesis of LVH. For instance, treatment with an ACE inhibitor or ARBs causes regression or prevents the development of LVH [12,13] in animal models of pressure overload. Moreover, ACE inhibitor treatment is able to ameliorate the survival in a murine model of pressure overload [14]. These results are consistent with

Figure 2. The key role of angiotensin II in the continuum of cardiovascular disease. Angiotensin II plays a key role in the pathogenesis of conventional cardiovascular risk factors, in the development and progression of target damage, in pathogenesis of major cardiovascular events and in their remodeling in final organ damage, and in the occurrence of death. CV, cardiovascular; LVH, left ventricular hypertrophy; CKD, chronic kidney disease; ESKD, end-stage kidney disease.
the involvement of RAS in the pathogenesis of LVH, and its activation by the hemodynamic loading in vivo. The role of Ang II as a critical mediator of stretch-induced hypertrophy has been shown in the neonatal rat cardiac myocyte system in vitro. Ang II receptor antagonists like [Sar1 Ile8]-Ang II (antagonist for the Ang II type I and II receptors) and losartan and TCV11974 (antagonists for the Ang II type I receptor) inhibit the stretch-induced hypertrophy of cardiac myocytes [15], suggesting that Ang II plays a critical role in stretch-induced hypertrophy. In addition, several data are consistent with the concept that cardiac RAS is chronically upregulated in loading-induced hypertrophy. In fact, mRNA expression of angiotensinogen, of renin, of ACE, and of Ang II receptors results in an upregulated cardiac hypertrophy induced by pressure overload and ischemia [16]. The upregulation of the cardiac RAS was also observed in vitro, in neonatal rat cardiac myocytes in response to mechanical stretch [17]. Treatment of cultured cardiac myocytes with exogenous Ang II also upregulates mRNA expression of angiotensinogen, renin, and ACE, but not of Ang II receptor [18]. This suggests that mechanical stretch initially causes acute secretion of preformed Ang II, and that secreted Ang II through an autocrine-paracrine mechanism may initiate a positive feedback, thereby upregulating the local RAS over the time (Figure 5). Further studies demonstrated an additive molecular mechanism that account for Ang II-mediated development of LVH. In particular, Bendall et al. demonstrated, in transgenic mice lacking the gp91phox subunit of NADPH oxidase, that 2 week-stimulation of subpressor doses of Ang II stimulation failed to induce LVH, this was associated with inhibition to superoxide production [19]. The result of this study indicated that oxidative stress is centrally involved in the direct cardiac hypertrophic response to Ang II.

**Chronic kidney disease**

Development of CKD is one of the TODs secondary to essential hypertension. Ang II plays a key role in the pathogenesis of CKD. In particular, Ang II stimulation induces endothelial dysfunction, which in the kidneys can evolve to glomerulosclerosis, tubulointerstitial fibrosis and vascular sclerosis. These abnormalities are responsible of the development of overt nephropathy that can evolve to end-stage renal disease (ESRD). Clinical manifestations of hypertension-induced nephropathy are: i) macroalbuminuria or proteinuria; ii) decrease of glomerular filtration rate (GFR); iii) increase in serum creatinine levels. In the last decades, the role of microalbuminuria has also emerged as an important determinant of CV events [20,21]. Although the achievement of a tight BP control is an important goal to prevent CKD, this strategy alone often is not enough to prevent the development and progression of CKD. The benefit of ACE inhibitor therapy in reducing proteinuria and
the progression of CKD in non-diabetic patients are known since 1990s; similarly, beneficial effects were demonstrated also for ARBs in nondiabetic nephropathies [22]. Thus, antihypertensive drugs that interfere with RAS confer renal protection with other classes of antihypertensive agents.

Clinical evidence: The first convincing demonstration of the ability of ACE-inhibitors to interfere with the progression of CKD comes from the REIN study. This study showed that patients who had proteinuria of ≥3 g/day and were treated with the ACE inhibitor showed a significant lower rate of decline in GFR and a reduced risk of doubling serum creatinine or end-stage renal failure as compared with patients who received the conventional therapy [23]. The favorable effects of ACE-inhibitors in the delay of CKD were confirmed by several meta-analyses [24-26]. CKD represents also an independent risk factor for the development of LVH and heart failure; at this regard, it is noteworthy that in patients with ESRD, ARBs reduce LVH [27]. The beneficial effects of ARBs were also documented in diabetic nephropathy, as well as in patients with non-diabetic nephropathy. The Japanese Losartan Therapy Intended for the Global Renal Protection in HyperTensive Patients (JLIGHT) study examined the effect of Losartan in comparison with Amlodipine. This study showed that although Losartan and Amlodipine had a comparable antihypertensive effect, Losartan based treatment significantly reduced the severity of proteinuria [28]. In addition, the Angiotensin II Receptor Antagonist Micardis in Isolated Systolic hypertension (ARAMIS) study compared the antihypertensive efficacy of Telmisartan versus Hydrochlorothiazide or placebo in patients with isolated systolic hypertension. This study showed that, despite comparable reductions in systolic BP with both drugs, Telmisartan treatment significantly reduced urinary albumin excretion than hydrochlorothiazide [29].

There is compelling evidence that RAS blockade obtained with either ACE-inhibitors or ARBs reduce proteinuria, halting or slowing the decline of GFR in patients with hypertension, even in those with ESRD. However, not all patients treated with ACE inhibitors or ARBs achieve an adequate nephroprotective effect. This phenomenon might be explained by an incomplete blockade of RAS, due to the escape of Ang II. In particular, different pathways (mainly chymases), especially in diabetic nephropathy, can account for an alternative pathway of Ang II synthesis. The combination of ACE inhibitor plus ARBs may potentially help to overcome the escape of Ang II. The nephro-protective effects of dual RAS blockade with both ACE inhibitor and ARBs were evaluated by two meta-analyses [30,31] showing favorable synergistic actions in reducing proteinuria and slowing CKD progression. However, these actions were not confirmed by the ONTARGET study [4] in which patients were randomized to receive ACE-inhibitor (ramipril 10 mg daily) or ARB (telmisartan 80 mg daily) or both drugs. In particular, this study reported an increased incidence of dialysis, doubling of serum creatinine and of death during the combined therapy of ACE inhibitor and ARBs compared with the monotherapy. Nowadays there are no
clinical evidence that the combination of ACE inhibitors plus ARBs has an additive effect in terms of nephroprotection, and this association is not recommended.

**Experimental data:** The main pathogenic mechanism responsible for the development of CKD involves chronic inflammation, oxidative stress, endothelial dysfunction, and vascular calcification. Ang II exerts in the kidney a control on cell growth, inflammation, and fibrosis [32]. These experimental data indicate that Ang II plays a pivotal role in the genesis of CKD by modulating the redox status and the immune system. In fact, Ang II increases tumor necrosis factor-alpha production and upregulates other pro-inflammatory mediators, including interleukin-6, monocyte chemotactic protein-1, and nuclear factor-kB [33]. In addition, Ang II is involved into the pathogenesis of CKD by also modulating the activation and infiltration of immunocompetent cells. Altogether these actions result in a complex network of glomerular stresses. There is some evidence demonstrating that the beneficial effects of the RAS blockade may be related to anti-inflammatory properties of ACE-inhibitors and ARBs [34]. In particular, the exposure of monocytes to captopril affects the cytokine-induced translocation of nuclear factor-kB translocation from the cytoplasm to the nucleus [35]. Furthermore, in patients with ESRD, ACE-inhibitor-based treatment reduces plasma levels of tumor necrosis factor-alpha and C-reactive protein.

These studies indicate that the main pathogenic mechanism that account of development of CKD in hypertension is an Ang II-evoked inflammatory response, and the blockade of RAS reduces the mediators of this response.

### Atherosclerosis

Essential hypertension is an established risk factor for the development of atherosclerosis. Both clinical and experimental data indicate that hypertension promotes and accelerates the atherosclerotic process through Ang II-mediated mechanisms. In particular, Ang II promotes the inflammatory processes and oxidative stress that lead to the formation of atherosclerotic plaques and increases its vulnerability. Interference with RAS has been demonstrated to reduce the progression of the atherogenic process.

**Clinical evidence:** The first large, randomized trial that demonstrated the beneficial effects of ACE-inhibitor on CV morbidity and mortality was the HOPE study. Although many patients included in this study were not affected by essential hypertension, this study demonstrated in high-risk patients that the addition of ramipril to the standard therapy significantly reduced the rate of the primary composite endpoint [36]. Interestingly, in this study the use of ramipril reduced not only the cardio- and cerebro-vascular events, but also interfered with the progression of atherosclerotic disease. In fact, the SECURE study, a substudy of the HOPE trial, demonstrated that the rate of progression of the maximum carotid artery intima-media thickness (IMT) was significantly lower in the group randomized to Ramipril compared with placebo (p=0.028) [37]. In hypertensive patients, candesartan and losartan [38,39] respectively slow the progression of carotid artery remodeling. The effects of RAS blockade were repeatedly shown to impact on the mechanisms involved in the development and progression of atherosclerosis. In particular, Candesartan significantly decreases plasma levels of plasminogen activator inhibitor type-1 (PAI-1), as well as monocyte chemoattractant protein-1 [40] and circulating levels of adhesion molecules ICAM-1 and VCAM-1 [41]. Similar actions have been reported for ibesartan, valsartan and losartan. In addition, Olmesartan medoxomil-based therapies interfere with the vascular inflammation and progression of atherosclerosis not only in carotids, but also in coronary arteries. In particular, the OLIVUS study showed that olmesartan medoxomil decreased the rate of coronary atheroma progression in patients with stable angina pectoris [42].

The beneficial effects of RAS inhibition on the development

![Figure 5. The role of renin angiotensin system in stretch-induced cardiac myocytes hypertrophy. Mechanical stretch initially causes acute secretion of preformed Angiotensin II, simultaneously stimulates gene expression of all components of tissue renin angiotensin system like angiotensinogen, renin, ACE, and Ang II receptor. Together these adaptive responses initiate a positive feedback mechanism that is responsible for the hypertrophic growth. Ang II, angiotensin II; ACE, angiotensin converting enzyme; AT1, Type 1 Ang II receptor.](image-url)
and progression of atherosclerosis are corroborated by several studies that evaluated the capability of ACE-inhibitors and ARBs to prevent the major cerebrovascular and cardiovascular events (i.e. stroke and myocardial infarction). The beneficial effects of RAS inhibition on the incidence of stroke in hypertensive patients is well documented. The first meta-analysis was published by Turnbull et al. in 2003 [43]. This showed that ACE-inhibitors reduced the risk of stroke compared with placebo by 28%; while ARBs reduced the risk of stroke compared with control regimens by 21%. In 2008, Reboldi et al. showed that the administration of ARBs was associated with a small but statistically significant reduction in the risk of stroke compared with the administration of ACE-inhibitors [44]. This last meta-analysis seems to indicate that ARBs compared with ACE-inhibitors, have a slightly greater protective effect on stroke. However, in 2009 it was published a further meta-analysis that showed no difference in terms of neuroprotection between ACE-inhibitors and ARBs [45].

The effects of RAS inhibition on prevention of myocardial infarction are still debated and in some cases controversial. This controversy started from the publication of results of the VALUE study [46] in which a significant increase of myocardial infarction was detected in theValsartan group compared with the Amlodipine group. On these bases, Verma and Strauss raised the hypothesis that ARBs, unlike ACE inhibitors, might increase the rates of myocardial infarction despite their beneficial effects on reducing BP [47]. This theory, called “ARB-myocardial infarction paradox” was not confirmed by the meta-analysis of Bangalore et al. [48]. Here, ARBs were not associated with any increase in the risk of myocardial infarction. These authors concluded that ARBs do not increase the risk of myocardial infarction; however, they do not have any beneficial effect on both myocardial infarction and cardiovascular mortality. However, further meta-analyses showed opposite results. In particular, Stauss and Hall [49] showed that only incidence of stroke was lower in patients treated with ARBs compared with placebo. Overall death was not reduced by ARBs whereas myocardial infarction was significantly increased by 8%. The results of this meta-analysis clearly demonstrate that compared with placebo, ACE inhibitors reduce the incidence of myocardial infarction and CV death, whereas there is no evidence than an ARBs are better than placebo. The same authors 10 years later, in a point of view underlined the current clinical relevance of their meta-analysis [50]. These observations are consistent with the concept that the use of ACE-inhibitors is more effective in reducing overall and cardiovascular death as compared with ARBs [51].

Experimental evidence: Vascular inflammation is considered nowadays the principal pathogenic mechanism of atherosclerosis [52]. Ang II plays a pivotal role not only in the development of atherosclerosis but also in the vulnerability of atherosclerotic plaques through the modulation of inflammation state. In fact, Ang II regulates the gene expression and synthesis of adhesion molecule (VCAM-1, ICAM-1, P-selectin), cytokine, chemokine, and growth factor of the arterial wall. In addition, RAS positively regulates the complement system, resulting in vascular inflammation and mobilization/and activation of inflammatory cells. The RAS stimulates also coagulation cascade and platelet aggregation. In particular, Ang II is a potent stimulator of tissue factor in monocytes and vascular endothelial cells [53], which in concert with further mediators contribute to the pathogenesis of coronary heart disease in patients with hypertension [54]. Bench tests indicate that RAS blockade exerts potent antithrombotic effects, through anti-inflammatory, antiproliferative, and antioxidant actions [55]. Treatment with the ACE-inhibitor trandolapril reduces endothelial dysfunction in hyperlipidemic rabbits [56]. In addition, administra-

Highlights and clinical implications

- Hypertension-induced TODs account for enhanced CV risk.
- RAS through the inflammatory response in an important pathogenic mechanism of TODs.
- Inhibition of RAS with ACE-inhibitors or with ARS is able to prevent or delay the development of TOD.
- ACE-inhibitors and ARBs have different impact on CV prevention. ARBs seem to have greater neuroprotective effects, while ACE-inhibitors have greater cardioprotective action.

References


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