Left Ventricular Hypertrophy and Angiotensin II Receptor Blocking Agents


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Abstract: Angiotensin II plays a significant role in cell growth and proliferation in model systems and in humans. Numerous studies have shown that left ventricular hypertrophy (LVH) increases the risk of coronary heart disease, congestive heart failure, stroke or transient ischemic attack; all-cause deaths, and sudden death. The use of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) has provided beneficial effects on LVH regression and on cardiac remodeling in the presence of hypertension and heart failure. The new class of ARBs appears to provide cardioprotective effects that are similar to those of the ACE inhibitors. Most of the beneficial effects provided by these agents appear to be related to a more complete blockade of the angiotensin II type 1 (AT1) receptor. However, costimulation of the angiotensin II type 2 (AT2) receptor appears to increase nitric oxide and thus causes some bradykinin-like effects. Evidence for the role of angiotensin II in promoting LVH as well as abnormal regulation of the angiotensin II signal transduction pathways in model systems and in humans has been reviewed. Secondly, the mechanisms for the beneficial effects of angiotensin II receptor blockers studied in model systems and in humans, including possible involvement in the formation of reactive oxygen species by mononuclear cells, are presented. Finally, results from large-scale interventions such as the Losartan Intervention For Endpoint reduction (LIFE) study, as well as an overview of the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial involving the use of ARB in high-risk patients, are presented.

Key Words: Angiotensin II, hypertrophy, AT1 receptor, AT2 receptor, monocyte, oxidative stress, inflammation, C-reactive protein.

INTRODUCTION

The transition from left ventricular hypertrophy (LVH) toward congestive heart failure (CHF) is mediated by many mechanisms. Among these mechanisms, increased systemic and cardiac neurohumoral activation and apoptosis appear to play an important role. Angiotensin II appears to play a role in both mechanisms. In addition to its systemic and tissue effects, it also increases cardiac sympathetic activity in vivo [1] and promotes myocyte apoptosis in vitro [2].

Angiotensin-converting enzyme (ACE) inhibitors have been shown to improve functional capacity and quality of life, and decreases LVH in patients with essential hypertension (3). The discovery of angiotensin II receptor blockers (ARBs), which block the effects of angiotensin II by blockade of the angiotensin II type 1 (AT1) receptor [4,5] has stimulated interest in the roles of angiotensin II and bradykinin in cardioprotection, and whether angiotensin II antagonists can be equivalent to ACE inhibitors in the treatment of hypertension, LVH and CHF. Interest in directly blocking the AT1 receptor was generated by the finding that, although ACE generates up to 80% of angiotensin II produced locally in the human heart, other specific enzyme pathways, such as chymase, also generate angiotensin II [6].

Thus, the ARB directly blocks the actions of angiotensin II regardless of the contribution of known ACE pathways. Furthermore, there is mounting evidence that selective AT1 receptor blockade increases the level of angiotensin II, which can stimulate the unopposed angiotensin II type 2 (AT2) receptor, causing an increase in nitric oxide [7]. In the present study, the effect of ARBs on LVH will be presented from the cellular level to the hypertensive patients.

PHARMACOLOGY OF ARBs

Structure

The ARBs are non-peptide compounds with varied structures, derived from imidazole-5-acetic acid. Most ARBs (e.g. candesartan cilexitil, losartan, irbesartan, and valsartan) have a common tetrazolo-biphenyl structure. All active ARBs, expect for irbesartan have a carboxylic acid group. The variation in the molecular structure of the ARBs results in differences in the binding affinity to the receptor and the pharmacokinetic profiles of the various agents (Table 1).

Pharmacokinetics

There are differences in lipid solubility, absorption, distribution, oral availability, metabolism, plasma half-life, and systemic elimination of the ARBs that influence their time of onset, duration of action, and efficacy.

After oral administration, the ARBs are rapidly absorbed (time for peak plasma levels = 0.5-4h) but have a wide range
Table 1. Human pharmacokinetics of AT1 receptor antagonists.

<table>
<thead>
<tr>
<th>Drug</th>
<th>F (%)</th>
<th>Food effect</th>
<th>Active metabolite</th>
<th>t½ (h)</th>
<th>VD (l)</th>
<th>Renal clearance (%)</th>
<th>P4503A4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irbessartan</td>
<td>70</td>
<td>No</td>
<td>No</td>
<td>12-20</td>
<td>70</td>
<td>20</td>
<td>No</td>
</tr>
<tr>
<td>Losartan</td>
<td>33</td>
<td>No</td>
<td>Yes</td>
<td>6-9*</td>
<td>12*</td>
<td>50*</td>
<td>Yes</td>
</tr>
<tr>
<td>Valsartan</td>
<td>23</td>
<td>Yes</td>
<td>No</td>
<td>6</td>
<td>17</td>
<td>10-15</td>
<td>No</td>
</tr>
<tr>
<td>Candesartan</td>
<td>42</td>
<td>No</td>
<td>Given as prodrug</td>
<td>9</td>
<td>10</td>
<td>13</td>
<td>No</td>
</tr>
<tr>
<td>Termisartan</td>
<td>42</td>
<td>Yes</td>
<td>No</td>
<td>16</td>
<td>485</td>
<td>2</td>
<td>No</td>
</tr>
<tr>
<td>Olmesartan</td>
<td>26</td>
<td>No</td>
<td>Yes</td>
<td>10</td>
<td>25</td>
<td>30</td>
<td>No</td>
</tr>
</tbody>
</table>

Values for EXP3174 (active metabolite of losartan). Abbreviations: F=oral availability, t½=elimination half-life, VD=volume of distribution.

of bioavailability. Losartan has a relatively low bioavailability due predominantly to first pass metabolism by the P450 enzymes 2C9 and 3A4 [8].

Losartan, valsartan, irbesartan, eprosartan and telmisartan do not inhibit CYP2A6-, CYP2D6- or CYP2E1-associated activities to any significant extent. Losartan and irbesartan inhibit the CYP2C9-associated tolbutamid methyl-hydroxylation more potently than valsartan, candesartan or eprosartan. In fact, inheritance of the poor metabolizing form of the 2C9 gene impairs losartan conversion to its active metabolite [9]. This low theoretical potential for P450 drug interactions with the ARBs (apart from those involving CYP2C9 [10]) has been borne out by clinical studies and a large post-marketing experience.

In fact, no clinically significant drug-drug interactions have been reported with valsartan, irbesartan or candesartan [11]. Multiple oral doses of irbesartan (300 mg per day) have no clinically relevant influence on the pharmacokinetic profiles of warfarin or nifedipine, but do increase the area under the curve of fluconazole [12]. In contrast, clinically significant drug interactions have been reported with P450 enzyme inducers and inhibitors and losartan, as it undergoes substantial first pass metabolism by both 3A4 and 2C9. Telmisartan can cause increased digoxin concentrations that may be of clinical relevance.

Special Groups

The hepatic clearance of losartan is dependent on hepatic blood flow. Thus, reduced liver blood flow (e.g. in patients with chronic heart failure or hepatic cirrhosis) reduces the hepatic metabolism of losartan, which may lead to unpredictable plasma concentrations [13]. Losartan is metabolized to the active metabolite EXP3174, which is 50% renally eliminated. Thus, dosage reduction is also necessary for patients with advanced renal impairment.

Valsartan is predominantly excreted in the faeces via biliary excretion, so is not recommended for patients with severe hepatic dysfunction and/or biliary cirrhosis. Initial dose adjustment based on age per se is not warranted, although for an average 70-year-old patient, plasma clearance of valsartan is predicted to fall by 22% compared with an average 55-year-old. Thus, dose reduction should be considered in this group [14] as with those with severe renal impairment (creatinine clearance less than 10 ml min⁻¹) [15,16]. In general though, as the fraction of ARB excreted unchanged by the kidney is small (apart from the active metabolite of losartan), dose reductions in patients with mild-to-moderate renal impairment or the elderly do not routinely have to be considered with ARBs [17].

**BASIC STUDIES**

**Mechanism of Action**

ARBs specifically block the interaction of angiotensin II with the AT1 receptor. The binding of angiotensin to this receptor results in endothelial dysfunction, vasoconstriction, vascular smooth and cardiac muscle cell growth, enhanced coagulation and activated sympathetic activity, all of which can be deleterious within the cardiovascular system. In humans, angiotensin II can also bind to the AT2 receptor causing vasodilatation. Thus, selective blockade of the AT1 receptor subtype by ARBs reduces deleterious haemodynamic effects, whilst increased AI levels due to receptor blockade permit enhanced stimulation of the potentially beneficial effects mediated by the AT2 receptors. Experimental studies have indeed confirmed that ARB abolishes or attenuates the effects of angiotensin on the AT1 receptor. For example, losartan abolishes AT1-receptor-mediated increase in oxidative stress[18].

**Actions of Angiotensin II in the Heart**

Depending on the species, angiotensin II receptors of both subtypes, AT1 and AT2, are almost equally expressed in the heart and in isolated cardiomyocytes [19-23]. Cardiac fibroblasts express only AT1 receptors under normal conditions [24,25] but can reactivate AT2 receptors in heart failure [26-28]. The potential mechanisms of actions of AT1 and AT2 receptor-mediated cardiac hypertrophy are summarized in Table 2.

Of prime importance are the hypertrophic and profibrotic actions of angiotensin II on cardiomyocytes. Accordingly, models of left ventricular hypertrophy such as the spontaneously hypertensive rat. human renin gene transgenic
Left Ventricular Hypertrophy and Angiotensin

Table 2. Mechanism of AT1 and AT2 Receptor-mediated Cardiac Hypertrophy.

<table>
<thead>
<tr>
<th></th>
<th>AT1 receptors</th>
<th>AT2 receptors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiomyocytes</td>
<td>Hypertrophy DNA synthesis → protein synthesis ↑</td>
<td>antigrowth effect DNA synthesis → protein synthesis ↓</td>
</tr>
<tr>
<td></td>
<td>gene reprogramming atrial natriuretic factor ↑</td>
<td>functional role in cardiac hypertrophy in vivo. vascular endothelial growth factor ↑ insulin-like growth factor-1 ↑ atrial natriuretic factor ↓</td>
</tr>
<tr>
<td></td>
<td>necrosis</td>
<td></td>
</tr>
<tr>
<td>Cardiac Fibroblasts</td>
<td>Proliferation DNA synthesis ↑ protein synthesis ↑</td>
<td>Inhibitory effect of angiotensin II-induced mitogen signal in vivo. DNA synthesis ↓ protein synthesis ↓</td>
</tr>
<tr>
<td></td>
<td>gene upregulation TGF-β1 ↑ fibronectin ↑</td>
<td></td>
</tr>
</tbody>
</table>

Transgenic Animal Models

Transgenic animal models have been generated to solve the question whether mechanical stretch or cardiac RAS alone is able to induce cardiac hypertrophy independently. Mice lacking AT1 receptors [45, 46] develop cardiac hypertrophy after volume or pressure overload, respectively. Cardiomyocytes isolated from angiotensinogen knockout mice respond to mechanical stretch by activating MAP kinases as do control cells. However, in contrast to control cells, this effect is not blocked by AT1 antagonists [47]. These results indicate that there are redundant pathways of growth induction by stretch in cardiomyocytes circumventing the RAS. However, the default mechanism involves angiotensin II and the AT1 receptor.

Early findings employing AT2 antagonists showed the antigrowth effects of this receptor [23]. Nevertheless, recent studies using AT2-knockout mice have shown that this receptor is essential for hypertrophy induction by pressure overload or angiotensin II infusion [48,49]. This effect may be mediated by reduced phosphorylation of S6. A transgenic mouse overexpressing the AT2 receptor in cardiomyocytes was less susceptible to AT1-mediated hypertensive and chronotrophic actions, compared to controls [50]. However, these mice developed the same degree of hypertrophy after angiotensin II infusion [51]. Taken together, cardiomyocyte AT2 receptors do not cause hypertrophy on their own, but AT2 receptors in cardiac myocytes or fibroblasts or even in other tissues may be essential for hypertrophy induction via the AT1 receptor.

HUMAN STUDIES

Mechanism of Action in Humans

LVH is a strong predictor of cardiovascular morbidity and mortality independent of other cardiovascular risk factors. The relationship between LVH and cardiovascular events is mainly due to the association of LVH with other cardiovascular risk factors. LVH is also associated with increased likelihood of death from cardiovascular causes. LVH is associated with a higher risk of cardiovascular events, including stroke, myocardial infarction, and heart failure. LVH is also associated with a higher risk of death from cardiovascular causes, including sudden cardiac death, heart failure, and stroke. LVH is associated with a higher risk of death from cardiovascular causes, including sudden cardiac death, heart failure, and stroke.
factors, including blood pressure itself [52,53]. ACE inhibitors, calcium antagonists and ARBs are currently accepted as the most effective classes at causing regression of LVH [54, 55]. However, treatment with valsartan, 80 mg daily for 8 months, has been shown, in a randomized double-blind study of 69 predominantly previously untreated hypertensive people with LVH, to reduce left ventricular mass index by 21 gm$^{-2}$ as compared to 10 gm$^{-2}$ with atenolol ($R=0.91; 90\% \ CI 0.85-0.97$ vs atenolol), despite similar blood pressure reductions [56].

Increased reactive oxygen species (ROS) formation by mononuclear cells (MNCs), measured by flow cytometry [57, 58] can lead to increased expression of cell surface adhesion molecules that are considered to be marker of inflammation. We have reported a study comparing 80mg of valsartan daily with 5mg of amlodipine daily for 8 months in hypertensive patients with LVH [59]. Blood pressure was lowered equally well in both groups (valsartan vs. amlodipine; 12 vs.11 mmHg in systolic blood pressure, $n=50, p=0.48$, 7 vs.8 mmHg in diastolic blood pressure, $n=50, p=0.52$). The results favoured valsartan in decreasing left ventricular mass (LV mass) (valsartan vs. amlodipine; 16\% vs. 1.2\%, $n=50, p<0.01$) (Figure 1), with the concomitant decrease in ROS formation by MNCs (valsartan vs. amlodipine; 28\% vs. 2\%, $n=50, p<0.01$) (Figure 2). Linear regression analysis showed a significant correlation between the decrease in LV mass and the decrease in ROS formation by MNCs in the valsartan group ($r=0.61, p<0.01$) (Figure 3), but not in the amlodipine group ($r=0.54, p=0.89$). ROS formation by MNCs can be not only a marker of inflammation, but also a marker of LV mass in hypertensive patients with LVH.

**Large-Scale Interventions**

Recently, LIFE (losartan intervention for endpoint reduction), a comparison of losartan versus atenolol in hypertensive patients with ECG evidence of LVH, also showed reductions in cardiovascular mortality endpoints with losartan as compared to atenolol [60] despite statistically similar blood pressure reductions between the groups. In the diabetes subgroup, the primary endpoint (cardiovascular morbidity) occurred less frequently in the losartan group with a relative risk of 0.76 (95\% CI 0.58-0.98), $P=0.031$. The relative risk of dying from cardiovascular disease was 0.63 (0.42-0.95), $P=0.028$ in the losartan group compared to the amlodipine group. Mortality from all causes was also reduced in the losartan group, with a relative risk of 0.61 (0.45-0.84), $P=0.002$, thus suggesting that losartan has benefits beyond blood pressure reduction.

Most recently, the valsartan antihypertensive long-term use evaluation (VALUE) trial, which is evaluating the effect of valsartan versus amlodipine, is currently testing whether ARBs reduce major cardiovascular endpoints (cardiac mortality or morbidity, defined as sudden cardiac death, fatal acute MI, death during or post PTCA or CABG, death due to heart failure or evidence of acute MI at autopsy) in patients with hypertension at similar levels of blood pressure control [61]. The hypothesis of the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial of cardiovascular events in hypertension [61] was that, for the same achieved blood pressure, there would be differences in cardiac

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**Fig. (1).** Effect of valsartan ($n=50$) and amlodipine ($n=50$) on LVMI.
The open circle and bars are mean $\pm$ SD of each value.

$P<0.01$ between value at baseline and 6 months later in the valsartan group.

$P<0.01$ between value at baseline and 6 months later in the amlodipine group [Ref. 59].

![Figure 1](image_url)
outcomes between valsartan and amlodipine patients. But inequalities in blood pressure, favouring amlodipine, throughout the multiyear trial precluded a comparison of the outcomes. In baseline characteristics, about 6% of hypertensive patients with left ventricular hypertrophy (LVH) were enrolled in the VALUE trial, which was different from those in the Losartan Intervention For Endpoint reduction (LIFE) study [60], in which all patients had LVH and the same resulting blood pressure with losartan and atenolol. As stated in the previous section, we have reported a study comparing 80mg of valsartan with 5mg of amlodipine daily for 8 months in essential hypertensive patients with LVH [59]. Blood pressure was lowered equally in both groups. The results favoured valsartan in decreasing left ventricular mass (valsartan vs. amlodipine; 16% vs. 1.2%, n=50, p<0.01) (Figure 2). These results may explain the results of VALUE trial in which after serial matching including systolic blood pressure, admission to hospital for heart failure was significantly lower with valsartan [62]. We would like to point out that ARBs may be more effective than amlodipine in essential hypertensive patients with LVH.

CONCLUSIONS
The new class of ARBs are now widely used in the daily treatment of hypertension all over the world. The use of ARB has provided beneficial effects on LVH regression and on cardiac remodeling in the presence of hypertension. Most

Fig. (2). Effect of valsartan (n=50) and amlodipine (n=50) on ROS formation by monocytes.
The open circle and bars are mean ± SD of each value.
P<0.01 between value at baseline and 6 months later in the valsartan group.
P=0.1 between value at baseline and 6 months later in the amlodipine group [Ref. 59].

Fig. (3). Relationship between the decrease in ROS formation by monocytes and the decrease in LVMI, and between the decrease in CRP and the decrease in LVMI in the valsartan treated group (n=50) [Ref.59].
of the beneficial effects provided by these agents appear to be related to a more complete blockade of the AT1 receptor. Evidence for the role of angiotensin II in promoting LVH in cardiac myocytes and fibroblasts suggests that ARBs are effective in reducing LV mass in vitro. The mechanisms for the beneficial effects of ARBs studied in experimental animals including SHR and transgenic animals of RAS systems and in humans, including possible involvement in the formation of ROS by MNCs suggest that angiotensin II mediated process including vascular inflammation may be related to LV mass in humans. Results from large-scale interventions such as the LIFE study, as well as VALUE trial involving the use of ARB in high-risk patients suggest that ARBs are effective in reducing LVH and may have some beneficial effects beyond blood pressure reduction.

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REFERENCES

[16] Schmieder, R.; Martus, P.; Klingbel, A.