Left Ventricular Hypertrophy and Renin-Angiotensin System Blockade

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The renin-angiotensin system (RAS), an important control system for blood pressure and intravascular volume, also causes left ventricular hypertrophy (LVH) and fibrosis. The main causal mechanism is the increase in blood pressure, which leads to increased left ventricular wall stress; however, aldosterone release from the adrenals and (more controversially) the direct action of angiotensin II on the cardiomyocytes also play a role. Large clinical trials evaluating the blockade of the RAS with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers have demonstrated an ability to prevent progression and induce regression of left ventricular mass, thereby reducing the significant and independent cardiovascular risk conferred by LVH. Regression of left ventricular mass is also achieved by other medication classes, but the RAS blockers have an additional beneficial effect for the same blood pressure reduction, for which the mechanism is not entirely clear. Studies comparing the efficacy of angiotensin-converting enzyme inhibitors versus angiotensin receptor blockers to achieve LVH regression have not demonstrated any clear benefit of one class over the other.

Introduction

This article reviews the renin-angiotensin system (RAS) and its central role in the development of left ventricular hypertrophy (LVH). It also presents an overview of the pharmaceutical blockades available and the clinical trial evidence for their ability to prevent the progression of LVH or induce its regression, thereby improving clinical outcome.

Left Ventricular Hypertrophy

LVH may be defined as an increase in left ventricular myocardial mass (LVM). The most common cause worldwide is essential hypertension, but other pressure overload states such as aortic stenosis and coarctation of the aorta also cause LVH. Some 65 million adults in the United States alone have hypertension [1], and this remains the leading attributable risk factor for death in the world [2••]. In addition to pressure overload, LVH is also caused by volume overload states such as myocardial infarction or regurgitant valvular disease, or it may result from genetic defects such as hypertrophic cardiomyopathy. The increase of LVM seen with exercise training in elite athletes is considered a special case of "physiologic hypertrophy," which is mediated by different signaling pathways and leads to enhanced cardiac performance without any additional risk of adverse outcomes [3].

The known low sensitivity of electrocardiography in the diagnosis of LVH has led to the widespread use of one-dimensional (M-mode), 2D, and 3D echocardiography to provide a more specific, repeatable, and far more sensitive measure [4]. In the past 10 years, cardiac MRI has become established as the new gold standard, particularly in research trials, because of its high precision, reliability, and ability to measure LVM without the geometric assumptions and correlation formulae required by echocardiography [5]. Detailed 3D mathematical reconstructions of the left ventricle have been described, to further improve the accuracy of this technique [6]. The more restricted access to cardiac MRI and its higher cost have limited the displacement of echocardiography as the routine clinical tool for measuring LVM.

The American Society of Echocardiography subdivides LVH into *eccentric hypertrophy*, in which the relative wall thickness (posterior wall thickness divided by the left ventricular endocardial radius at end-diastole) remains normal, and *concentric hypertrophy*, in which the relative wall thickness is increased. Since LVM scales with body size, it is routinely normalized by a variety of height and weight indices, most commonly body surface area (BSA) and height$^{2.7}$, and separate normal ranges are defined for males and females [7]. It is unfortunate that the cutoffs used to define LVH are not uniformly standardized and vary significantly among research studies.

Left Ventricular Hypertrophy as a Risk Factor

The Framingham study [8] was the first to conclusively show that LVH independently predicts a higher rate of

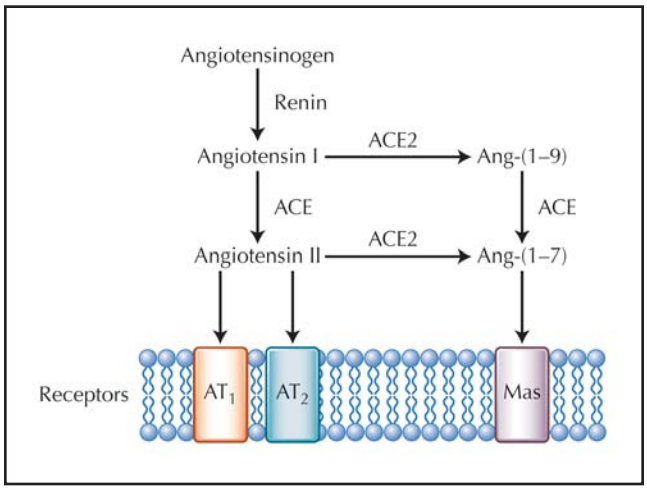

Figure 1. The renin-angiotensin system (RAS) pathway. ACE—angiotensin-converting enzyme; Ang-(1–7)—seven–amino acid peptide; Ang-(1–9)—nine–amino acid peptide; AT_1—angiotensin II type 1 receptor, AT_2—angiotensin II type 2 receptor, Mas—*Mas* receptor.

adverse clinical events, including death. The risk conferred is additional to the risk due to hypertension when that is the underlying cause, and it is also additional to other traditional cardiovascular risk factors such as smoking, hypercholesterolemia, diabetes, and age. Further work since Framingham has shown that a continuous relationship exists between cardiovascular risk and LVH even when the LVM is within the "normal" range [9]. A review summarizing more than four decades of research including 48,545 patients found that the adjusted overall relative risk of all-cause mortality associated with LVH was 2.5 (range, 1.5–8.0) [10]. Ghali et al. [11] reported that all-cause mortality (per 100 patient years) in patients without coronary artery disease varied depending on the geometry of the hypertrophy, from 1.5% without LVH to 1.7% for eccentric LVH and 2.2% for concentric LVH. Additional mortality was seen in patients with coronary artery disease, but the same pattern persisted. The exact mechanism of this strong association remains elusive, but it is likely that LVM is a measure that reflects the long-term cumulative effect of a number of risk factors for cardiovascular disease.

Efforts to prevent LVH are directed at treating the underlying cause, such as hypertension, but considerable effort has also focused on the reversal of established LVH. There is now good evidence that regression of LVH results in improved prognosis [12,13].

The Renin-Angiotensin System

The RAS is a hormonal system that regulates blood pressure (BP) and blood volume. The basic principles of its cardiovascular regulation were first described in 1898 by Tigerstedt and Bergman [14]. Since then, new pathways and end effects have been elucidated.

In overview, the juxtaglomerular apparatus in the kidney releases renin into the circulation in response to three primary inputs: baroreceptor detection of lowered renal perfusion pressure; decreased sodium chloride in the ultrafiltrate of the nephron, detected by the macula densa; and β_1-adrenergic stimulation from the sympathetic nervous system. Renin is the rate-limiting step for the entire RAS and acts by cleaving five amino acids off the hepatically synthesized circulating peptide angiotensinogen to produce the inactive decapeptide angiotensin I (Ang I). A further two amino acids are cleaved off by the angiotensin-converting enzyme (ACE) found in vascular endothelium, particularly in the lungs, to form the active molecule angiotensin II (Ang II), which is responsible for almost all of the end effects of the system.

Ang II has at least two receptors, AT_1 and AT_2, with AT_1 mediating the classic effects of the RAS. These include sodium conservation by the kidney, mineralocorticoid (aldosterone) secretion by the adrenal cortex, vasoconstriction, inotropic and chronotropic effects on the myocardium, and central nervous system–mediated increase in thirst, vasopressin release, and sympathetic nervous system activation. In contrast, the AT_2 receptor mediates vasodilatation, decrease in cell growth, and apoptosis [15]. It is well established that Ang II is produced not only in the ACE pathway but also at the local level by a variety of organs, including the heart, and this is known as the "tissue" RAS [16•].

A homolog of ACE (known as ACE2) has been described [17] and was shown to convert Ang I to Ang-(1–9), a nine–amino acid peptide that results from the cleavage of the carboxy terminal leucine from Ang I. This pathway (Fig. 1) results in the binding of Ang-(1–7), a heptapeptide derived from Ang-(1–9), to the *Mas* protooncogene [18]. Although showing significant similarities to ACE, ACE2 is not inhibited by the ACE inhibitors lisinopril or captopril. Although Ang-(1–7) was previously thought to be inactive, its coinfusion into rats treated with Ang II has shown it to reduce the resulting hypertrophy and fibrosis without significant effects on BP [19•]. Additional evidence for a cardioprotective effect of Ang-(1–7) has been demonstrated by a study using a fusion protein to overexpress Ang-(1–7) in rats, which demonstrated significant resistance to induction of hypertrophy in response to isoproterenol infusion [20]. A study that took the opposite approach by deleting the Ang-(1–7) receptor *Mas* resulted in impaired cardiac function and marked changes toward a profibrotic state in the extracellular matrix [21]. The beneficial effects of both ACE2 and Ang-(1–7) on hypertrophy and fibrosis in the animal model make this an area of interest for potential future therapeutic intervention.

Left Ventricular Hypertrophy and the RAS

The finding that cardiac myocytes terminally differentiate early in their development explains the hypertrophic response of these cells by the addition of actin and myosin fibers rather than a hyperplastic response with the proliferation of new cells. In contrast, the fibrosis that frequently accompanies LVH is due to fibroblast hyperplasia.

The RAS is proposed to cause LVH and cardiac fibrosis by three mechanisms: increase of BP, direct action of circulating and local Ang II on the cardiac myocyte via the AT_1 receptor, and aldosterone-mediated effects. Because of the difficulty of separating out these interrelated effects in humans, much of the direct evidence for these mechanisms comes from cell culture and animal studies.

Increased blood pressure

The primary mechanism by which activation of the RAS system leads to LVH is by an increase in BP. This increase in mechanical load must be sensed and then initiates biochemical events that lead to the modification of gene transcription in the nucleus. The most likely candidate for the sensor is the focal adhesion complex, which connects the internal cytoskeleton of the cell to the extracellular matrix. Although the pathways are not well understood, the search for the key biochemical activator of clinical hypertrophy has recently focused on a number of molecules, including calcineurin [22].

Angiotensin II effects on myocytes

It is well established that Ang II has a hypertrophic effect on cardiomyocytes in culture [23]. It is more difficult, however, to determine the relative importance of this local mechanism in an intact animal, where Ang II has a multitude of other effects, most notably that of increasing BP. The magnitude of the direct hypertrophic and fibrotic action of Ang II on the cardiomyocyte, relative to that mediated through an increase in BP (and therefore wall stress) remains controversial [24••].

The experimental evidence for the local effect of Ang II comes primarily from transgenic rodent studies, in which the α-myosin heavy chain (α-MHC) gene is used to increase the local expression of Ang II or the number of AT_1 receptors on the cardiomyocyte.

An early study by Mazzolai et al. [25] increased the local cardiac Ang II concentration in transgenic mice by engineering them to express rat angiotensinogen and showed that this change led to hypertrophy (but not fibrosis) in two strains of mice, one hypertensive and one normotensive. Although the levels of plasma and cardiac Ang II were not measured, treatment with an AT_1 blocker reversed the LVH. Critics of this study's methodology have suggested that angiotensinogen may have leaked out from the heart and produced Ang II elsewhere, or that the mice were more hypertensive than originally thought [24••].

In contrast to this in vivo study and other in vitro studies demonstrating a direct link between Ang II and hypertrophy, evidence is now emerging that challenges this pathway relative to direct BP effects. A study by Xiao et al. [26] increased the expression of the ACE gene in mouse cardiomyocytes 100-fold while removing ACE expression from both the kidney and vascular endothelium; they achieved a fourfold increase in local cardiac Ang II. This led to slightly low BP, marked atrial enlargement, and a high incidence of sudden death, but no hypertrophy or fibrosis. Van Kats et al. [27] engineered transgenic mice to express an Ang II–producing fusion protein exclusively in cardiomyocytes. The resulting 20-fold to 40-fold increase in local cardiac Ang II led to the development of some interstitial fibrosis, but again no hypertrophy. The amount of Ang II leaking from the heart was insufficient to affect either plasma Ang II or systolic BP, and an exogenous challenge of Ang II confirmed that these mice had a normal hypertrophic response to raised circulating levels. When a degradation-resistant form of Ang II was expressed, the Ang II level in the heart reached thousands of times the normal level and began to spill into the circulation, but hypertrophy did not occur until BP began to rise in response to the circulating Ang II.

In addition to these experiments designed to increase the concentration of Ang II in the cardiomyocyte, other animal-model experiments have focused on increasing the local expression of the AT_1 receptor, with conflicting results. Paradis et al. [28] showed that an overexpression of human AT_1 receptor did induce hypertrophy and fibrosis, leading to premature death from heart failure. In contrast, a study using transplanted kidneys deficient in the AT_1 receptor in mice showed that the extent of cardiac hypertrophy correlated solely with BP and found no evidence for a direct action of AT_1 receptors in the heart to promote LVH [29].

The hypertrophic response of cardiomyocytes to Ang II in culture has led to widespread acceptance of a direct Ang II hypertrophic effect that is not universally supported by experiments in intact animals. It is likely that Ang II alone is sufficient to stimulate cardiac fibroblasts to produce extracellular matrix and fibrosis [30] but is not sufficient for hypertrophy, which may require an interaction with the epidermal growth factor receptor [16•]. The AT_1 receptor may be the limiting factor in the local pathway, so conditions that increase the expression of the AT_1 receptor may be more likely to lead to hypertrophy [24••].

The mechanism by which RAS inhibitors achieve therapeutic effectiveness exceeding their BP-lowering effect is likely to be related to their influence on the RAS, but the exact details of this mechanism have not yet been fully elucidated.

Aldosterone-mediated effects

When patients with primary hyperaldosteronism are compared with a hypertensive group with the same BP, those with hyperaldosteronism have greater left ventricular wall thickness and LVM [31]. After surgical excision of an aldosterone-producing adenoma, LVM decreased dramatically, but in patients who did not have surgery but received medical treatment (including an aldosterone blocker) that succeeded in controlling their BP, LVM remained elevated. In a more recent, longitudinal study of patients with normal or near-normal BP [32], change in LVM over a 2-year follow-up period was correlated with change in urinary aldosterone but not with change in BP, weight, or sodium intake. Interestingly, the aldosterone response of these

subjects to an Ang II infusion at baseline was also correlated with change in LVM. There is increasing evidence that aldosterone causes cardiac remodeling independently of its hemodynamic effects by stimulating oxidative stress, inflammation, and fibrosis via an interaction that includes the mineralocorticoid receptor and AT_1 [33].

Blockade of the RAS

The RAS may be blocked at a number of sites. The first blockers to be developed were the ACE inhibitors, which block the conversion of Ang I to Ang II. More recently, the angiotensin receptor blockers (ARBs), which block the target effect of Ang II on the AT_1 receptor, have entered clinical use and have been the subject of large clinical trials. ARBs have a theoretical advantage over ACE inhibitors: they block the effect of locally produced Ang II but do not block the potentially beneficial effects of Ang II mediated by the AT_2 receptor. In general, clinicians tend to regard ACE inhibitors and ARBs as substantially equivalent [2••], although there is good evidence that ARBs are better tolerated, with a lower incidence of cough and angioedema, because they do not block the ACE breakdown of bradykinin and substance P [34].

Other RAS blockers include renin inhibitors such as aliskiren, which has recently been approved for clinical use [35], and more novel approaches such as vaccination against Ang I or Ang II, which has the advantage of monthly or longer dosing. A vaccine targeting Ang I raised antibody titers but did not reduce BP [36], and a vaccine against Ang II has had immunogenicity and phase 1 safety trials recently reported in humans [37].

Finally, as some of the downstream effects of Ang II are mediated by aldosterone, aldosterone receptor blockers such as spironolactone and eplerenone can be considered as blockers of the effects of the RAS.

Clinical Trial Evidence for LVH Regression

There is now strong clinical trial evidence that most antihypertensive medications produce regression of LVH. In a meta-analysis by Klingbeil et al. [38], 80 double-blind, randomized controlled trials in essential hypertension showed that ARBs decreased LVM by 13%, calcium channel blockers (CCBs) by 11%, ACE inhibitors by 10%, diuretics by 8%, and β-blockers by 6%.

ACE inhibitors and the HOPE study

The Heart Outcomes Prevention Evaluation (HOPE) study recruited 9541 patients with either high-risk vascular disease or diabetes who had at least one other additional cardiovascular risk factor, and excluded patients with heart failure or an ejection fraction of less than 40% [13]. Randomization was to placebo or the ACE inhibitor ramipril, and LVH was assessed by electrocardiogram. At a 4.5-year follow-up, significantly more ramipril patients had regression of LVH than controls, and this ACE inhibitor effect was found to be independent of hypertension and BP reduction, supporting the hypothesis that ACE inhibitors have a direct antihypertrophic effect.

ARBs and the LIFE study

The Losartan Intervention For Endpoint Reduction in Hypertension Study (LIFE) randomized 9222 participants with essential hypertension and LVH diagnosed by electrocardiogram to either the ARB losartan or the β-blocker atenolol and observed them for an average of 4.8 years [39]. In this group, all of whom had LVH, those treated with losartan had a better clinical outcome as measured by the composite end point of cardiovascular death, stroke, and myocardial infarction, with stroke being the most powerful contributor. In an important substudy to the LIFE trial, 960 patients had annual LVM measurements with echocardiography, which showed that losartan induced a greater reduction in LVH after adjustment for LVM and BP at baseline as well as in-treatment BP [40]. This finding led the authors to the conclusion that the ARB losartan had superior efficacy for reversing LVH compared with the β-blocker atenolol, despite the same lowering of BP.

Although this additional benefit of RAS blockade on LVH over other medication classes is widely accepted, it has been challenged by O'Rourke and Safar [41], who cite evidence that ACE inhibitors and ARBs reduce central aortic and LV systolic pressure considerably more (5.2 mm Hg in the case of ramipril) than atenolol, and that studies that measure only the brachial BP may misinterpret this additional afterload reduction as a BP-independent effect of RAS blockade [42].

Comparisons of ACE inhibitors and ARBs

A review that included 61 studies of the relative effectiveness of ACE inhibitors versus ARBs for treating hypertension showed no difference in BP control in 37 of the 47 randomized controlled trials in the analysis [2••]. There was no consistent difference in death, cardiovascular events, quality of life, progression to diabetes, cardiac function, or renal disease. Only six studies (four randomized controlled trials)—which were rated as only fair or poor in quality—compared LVM reduction between ACE inhibitors and ARBs in the meta-analysis, which concluded that there was no statistically significant difference between the two.

The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) enrolled 25,620 patients with a history of coronary artery disease, peripheral arterial disease, cerebrovascular disease, or diabetes mellitus with end-organ damage to investigate the differences in clinical end points between an ACE inhibitor (ramipril, 10 mg), an ARB (telmisartan, 80 mg), and combination therapy with both medications [43•]. The cardiac MRI substudy to ONTARGET used cardiac MRI and 3D analysis to accurately quantify LVM in 330 patients. The results (unpublished data) showed

LVM regression by 4.8% in the ramipril group, 3.3% in the telmisartan group, and 5.8% in the combination group, but did not demonstrate any significant differences between the treatment groups after 2 years. The reduction in LVM was lower than previously reported, a difference thought to be due to the high level of preexisting and ongoing concomitant therapy. (Two thirds of patients were on β-blockers and one third on CCBs.)

The ONTARGET study supports the finding that there is no clinically significant difference in the regression of LVM between ACE inhibitors, ARBs, and combination therapy. As both HOPE and ONTARGET recruited patients with a variable cardiac phenotype rather than simple hypertensive pressure overload, undetected differential effects may have occurred in some subgroups.

Aldosterone receptor blockers and the RALES trial

The landmark Randomized Aldactone Evaluation Study (RALES) established the clear mortality benefit of treating severe heart failure with spironolactone, an aldosterone receptor blocker [44]. A substudy to RALES found that high levels of serum markers of cardiac fibrosis were associated with poor outcome and that spironolactone was able to decrease these levels [45]. They suggest that limiting excessive extracellular matrix turnover may be one of the various extrarenal mechanisms contributing to the beneficial effect of spironolactone in heart failure.

Comparison of aldosterone blockers and ACE inhibitors

The 4E–Left Ventricular Hypertrophy Study compared the effectiveness of a selective aldosterone blocker, eplerenone, versus an ACE inhibitor, enalapril, and combination therapy to regress LVM (as measured by MRI) in patients with hypertension and LVH [46]. Both eplerenone and enalapril were equally effective, but the combination was significantly better than eplerenone alone. The greater lowering of BP by combination therapy may have contributed to this effect, but there was a relatively poor correlation between BP lowering and reduction in LVM for all patients taking eplerenone, either alone or in combination.

Comparison of ACE inhibitors and CCBs

In keeping with meta-analysis evidence that CCBs are not inferior to ACE inhibitors in producing LVH regression [38], the Prospective Randomized Enalapril Study Evaluating Regression of Ventricular Enlargement (PRESERVE) [47] showed no difference between enalapril and nifedipine after 1 year of treatment in a hypertensive population.

Conclusions

The RAS has a central role in the development of LVH through its effect on BP, the direct action of Ang II on the cardiomyocyte, and the release of aldosterone. It is well established that LVH is an important risk factor for cardiovascular events and that blockade of the RAS with either ACE inhibitors or ARBs can slow progression or induce regression of LVH, with consequent reduction in cardiovascular risk. Both classes of medications seem equally able to achieve a greater effect on LVM than other medication classes despite the same lowering of BP, with ONTARGET demonstrating no additional benefit of using them in combination. The most important clinical consideration in choosing between the two classes is probably the reported greater tolerability of ARBs.

Disclosure

No potential conflicts of interest relevant to this article were reported.

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