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# NEW TAKE ON THE ROLE OF ANGIOTENSIN II IN CARDIAC HYPERTROPHY AND FIBROSIS

**Mazen Kurdi**[1,2] and **George W. Booz**[2]

[1]Department of Chemistry and Biochemistry, Faculty of Sciences, Lebanese University, Rafic Hariri Educational Campus, Hadath, Lebanon

[2]Department of Pharmacology and Toxicology, School of Medicine, and the Center for Excellence in Cardiovascular-Renal Research, The University of Mississippi Medical Center, Jackson, Mississippi, USA

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## Introduction

Nearly 4 years ago in *Hypertension*, a brief review was published that called into question the widely held belief at the time that angiotensin II (Ang II) has direct growth promoting effects on cardiac myocytes and fibroblasts relevant to the development of cardiac remodeling in hypertension.[1] The review convincingly argued that the idea Ang II was “cardiotrophic” rested largely on work with cultured cells and was not substantiated by results from genetically modified animals. For many the take home message was that Ang II was not a player in cardiac remodeling seen in hypertension. However, in their conclusion, the authors noted that “these results do not rule out a direct role for Ang II in cardiac remodeling when combined with other humoral, mechanical, or pathological stimuli ...”[1] Indeed, recent evidence supports the conclusion that Ang II acting in concert with other factors plays an important role in the remodeling of the left ventricle produced by hypertension. Here we highlight some of these recent studies, as well as new insights into endogenous counter-regulatory mechanisms that might be exploited therapeutically.

### Context is Everything

In hypertension, the left ventricle of the heart undergoes remodeling that includes both hypertrophy of cardiac myocytes, which initially is a compensatory mechanism to maintain pump function in the face of increased afterload, as well as increased perivascular and interstitial fibrosis. Over time, both hypertrophy and fibrosis compromise heart function. Rather than a straightforward cause-effect relationship, today's evidence supports a more

Address for Correspondence: George W. Booz, Ph.D., FAHA University of Mississippi Medical Center Department of Pharmacology and Toxicology 2500 North State Street Jackson, MS 39216-4505 Tel: (+1) 601-984-4401 Fax: (+1) 601-984-1637 gbooz@umc.edu.

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nuanced role for Ang II in both hypertrophy and fibrosis of the left ventricle associated with hypertension. Ang II, locally-derived in particular, seems to worsen cardiac remodeling within the permissive context of increased blood pressure, which sets into play a low-grade inflammatory state in the heart.[2,3] A local increase in cardiac Ang II is postulated to result from renin deposition from the circulation, increased levels of chymase from endothelial and mast cells, and sequestration of Ang II in part due to increased expression of the Ang II type 1 ($AT_1$) receptor.[3-5] Evidence suggests that cardiac Ang II exacerbates the cardiac remodeling actions of increased blood pressure by further fueling inflammation and oxidative stress, which in turn further induce cardiac Ang II and AT1.

## Blood Pressure

Parsing the actions of Ang II on cardiac remodeling that occur locally from those resulting from its actions in raising blood pressure has proven problematic, but evidence that local Ang II does worsen cardiac remodeling in hypertension separate from an impact on blood pressure was recently provided.[2] By inducing deoxycorticosterone acetate (DOCA)-salt hypertension in mice expressing a fusion protein that releases Ang II specifically from cardiac myocytes, Xu et al. created a model of low circulating renin-Ang II with high cardiac Ang II. Increased cardiac Ang II had no impact on heart phenotype under basal conditions, but exacerbated ventricular hypertrophy and fibrosis with increased blood pressure. Elevated cardiac Ang II enhanced cardiac myocyte apoptosis, macrophage infiltration, and expression of NADPH oxidase 2 (NOX2) and transforming growth factor-$\beta_1$ (TGF-$\beta_1$), while protective signaling was downregulated. Ang II and TGF$\beta_1$ induce NADPH oxidase activity, which is implicated in cardiac fibrosis[6] and hypertrophy.[7]

Exaggerated blood pressure variability (EBPV), common in elderly and those with carotid atherosclerosis, is a risk factor for cardiovascular events in persons with hypertension. EPPV, diagnosed from a high standard deviation of sequential blood pressure measurements,[8] is associated with greater end organ damage in hypertension, including greater cardiac hypertrophy and fibrosis.[9] Kudo et al. created a model of EBPV in hypertension by bilateral sinoaortic denervation (SAD) in spontaneously hypertensive rats (SHR) and observed enhanced cardiac fibrosis and left ventricular (LV) myocyte hypertrophy compared to controls.[9] EBPV in SHR was associated with impaired LV function and chronic cardiac inflammation as evidenced by induction of monocyte chemoattractant protein-1 (MCP-1) and macrophage infiltration. Heart activated AT1 receptor levels were increased, along with expression of TGF-β and angiotensinogen. Circulating levels of renin, norepinephrine, and inflammatory cytokines were not affected. Effects of SAD on cardiac remodeling, inflammation, and function were abolished by a subpressor dose of AT1 receptor blocker (ARB). Thus, the adverse cardiac remodeling of EBPV in hypertension likely result from upregulation of cardiac Ang II.

## Co-conspirators

**Sympathetic Nervous System (SNS)—**The renin angiotensin system (RAS) and SNS show extensive interactions that contribute to cardiac remodeling.[10] A relatively unexplored area of interplay between RAS and SNS in mediating cardiac remodeling is cardiac mast cells, which secrete chymase that converts Ang I to Ang II. These cells play a role in LV fibrosis in the hypertensive rat heart.[11] Unexpectedly, sympathectomy increased cardiac mast cell density in SHR, although cardiac fibrosis and hypertension were attenuated and LVM normalized.[12] The authors suggested location within the heart is important in determining the contribution of mast cells to cardiac fibrosis, with the SNS playing a permissive role in cardiac mast cell activation. Consistent with this scenario are the findings that substance P, which is released by afferent nerve fibers, stimulated cardiac mast cell

degranulation and Ang II production by cardiac inflammatory cells, while norepinephrine was ineffective.

**Sodium and Aldosterone—**Another area of crosstalk in remodeling involving Ang II not well understood is with salt and aldosterone, which also contribute to LV hypertrophy independent of effects on blood pressure.[13] du Cailar et al. reported a study involving patients with hypertension treated with an angiotensin-converting enzyme (ACE) inhibitor or ARB.[14] Treatment was associated with decreased LV mass (LVM) index and correlated not only to blood pressure change, but also change in 24 hour urinary sodium excretion (reflecting sodium intake) and aldosterone plasma levels. High sodium intake with high aldosterone was associated with an increase in LVM index, while no impact of circulating aldosterone was observed in patients within the lowest tertile of sodium excretion.

Although Ang II and aldosterone both induce cardiac fibrosis by means partly involving the other, dissecting out their crosstalk in the heart is difficult. A study on mice with cardiomyocyte-restricted overexpression of human aldosterone/mineralocorticoid receptor helped somewhat, since confounding effects of systemic mineralocorticoid receptor signaling were avoided.[15] Mineralocorticoid activation enhanced Ang II's fibrotic effect on the heart, not because of increased inflammation, but due to enhanced oxidative stress from increased NOX2 expression. While wild type and transgenic mice had similar increases in blood pressure with Ang II infusion, cardiac hypertrophy and induction of fibrosis-related genes was greater in transgenics and was associated with diastolic dysfunction, indicating cardiac fibrosis.

Apoptosis signal-regulating kinase 1 (ASK1), which is activated by oxidative stress and leads to activation of p38 and JNK MAP kinases, is important in Ang II-induced cardiac hypertrophy and fibrosis. ASK1 is implicated as well in aldosterone + high salt-induced cardiac fibrosis and inflammation.[16] Indices of aldosterone + high salt-induced cardiac injury improved by ASK1deficiency include interstitial and perivascular fibrosis, macrophage infiltration, and MCP-1 expression. ASK1 deficiency attenuated aldosterone + high salt-induced superoxide generation, likely due to less NOX2 expression. Finally, ASK1 deficiency eliminated increases in cardiac ACE and AT1 seen with aldosterone + high salt infusion.

## Inflammation and Oxidative Stress

Increased oxidative stress is implicated in Ang II-induced cardiac hypertrophy and fibrosis. Thus, Ang II's actions on cardiac remodeling are predicted to be enhanced when cellular anti-oxidant defense mechanisms are compromised, as with diabetes, heart failure, and advanced age. Such was the case with mice lacking glutathione peroxidase 1 (Gpx1), an enzyme that eliminates cellular peroxides.[17] Accelerated Ang II-induced cardiac hypertrophy and systolic dysfunction was observed in Gpx1-deficiant mice compared to wild type mice, while both had similar increases in blood pressure. Conversely, the anti-oxidative and anti-inflammatory properties of high density lipoprotein (HDL) may explain the attenuation with HDL in Ang II-induced cardiac hypertrophy in mice.[18]

Although human relevance is unsettled,[19] Zhang et al. reported C-reactive protein (CRP), a cardiovascular disease biomarker, may be a mediator of Ang II cardiac remodeling.[20] Overexpressing human CRP in mice enhanced Ang II-induced cardiac remodeling, without any additional blood pressure increase. Fibrosis and inflammation were exacerbated and cardiac function further impaired. Enhanced remodeling was associated with enhanced expression of AT1 receptor and TGF-β1, as well as Smad and nuclear factor-κB (NF-κB) signaling in response to Ang II. TGF-β1/Smad signaling is important for Ang II-induced cardiac fibrosis and inflammation,[21,22] and NF-κB for inflammatory gene expression.

Findings on Ang II-induced atrial fibrosis and cardiac myocyte hypertrophy place TGF-β/Smad3 downstream of NADPH oxidase activation and reactive oxygen species (ROS) generation.[23] Although Ang II enhances NADPH oxidase expression and activity directly, other intermediaries are likely, e.g., tissue thrombin. Deficiency of heparin cofactor II (HCII), which inactivates thrombin, enhanced Ang II-induced cardiac fibrosis and hypertrophy, as well as oxidative stress.[24] Augmented cardiac remodeling and TGF-β expression with Ang II in HCII deficient mice was blocked by giving human HCII.

The importance of oxidative stress to hypertensive cardiac hypertrophy has been questioned. Evidence from animal models indicates that increased oxidative stress does play a key role in cardiac hypertrophy resulting from rapid pressure increases.[25,26] With Ang II infusion, the source of that oxidative stress has been identified as NOX2 and has been linked to the activation of a number of hypertrophic intracellular signaling pathways.[25,26] NOX2 has also been linked to cardiac hypertrophy after chronic MI.[26] For pressure overload due to aortic banding, recent evidence implicates NOX4, which is found in mitochondria, and suggests that cardiac hypertrophy is secondary to NOX4-induced cell death and cardiac dysfunction.[26] Of note, Ang II and other hypertrophic agonists induce NOX4 expression in cardiac myocytes. However, oxidative stress and NOX isoforms were found not to have a role in the development of cardiac hypertrophy in a mouse model in which hypertension and cardiac hypertrophy developed gradually with maturity due to chronic activation of the RAS.[27] Arguably, this model better mimics human hypertension. However, in this model of chronic hypertension, ROS generation did contribute to increased interstitial fibrosis.

## Innate Regulation

AT1 receptor-associated protein (ATRAP) promotes AT1 receptor internalization.[28] Wakui et al. reported that Ang II-induced cardiac hypertrophy in a murine model was associated with decreased cardiac ATRAP levels, while AT1 receptor levels were unchanged.[28] Targeted ATRAP overexpression in cardiac myocytes prevented cardiac hypertrophy and related changes in gene expression due to Ang II infusion in mice, although blood pressure rise was unaffected. RALT (receptor-associated late transducer) is the comparable feedback inhibitor for the epidermal growth factor receptor, which mediates many growth-promoting actions of Ang II via receptor transactivation. Cai et al. showed that cardiac RALT overexpression in mice attenuated Ang II-induced hypertrophy, fibrosis, and inflammation.[29]

Cellular FLICE-inhibitory protein long form (c-FLIP$_L$) is a modulator of tumor necrosis factor signaling by inhibiting caspase 8 activation.[30] In mice with decreased c-FLIP$_L$, Ang II-induced cardiac hypertrophy and fibrosis were enhanced.[31] ERK1/2 signaling was enhanced, as was phosphorylation of the downstream hypertrophic transcription factor GATA4. Smad 2/3 activation, known to be involved in fibrosis, was seen. In contrast, Ang II remodeling was attenuated in mice overexpressing human c-FLIP$_L$ in cardiac myocytes. The beneficial effects of c-FLIP$_L$ occurred at least in part through direct association with and inhibition of ERK kinase, MEK1.

Ang-(1-7), present in the heart because of ACE2, opposes many adverse effects of Ang II on cardiac function and remodeling. For instance, hearts of transgenic rats with increased circulating Ang-(1-7) levels were protected against Ang II-induced hypertrophy.[32] Enhanced NO/cGMP signaling, which is antihypertrophic,[33] likely contributes to Ang-(1-7)'s protective actions, since transgenic rats exhibited increased nNOS expression. However, increased circulating Ang-(1-7) prevented Ang II-induced increase in blood pressure. More convincing evidence of blood pressure-independent actions for Ang-(1-7) opposing cardiac remodeling comes from the DOCA-salt hypertension model.[34] In this model, Ang-(1-7)

overexpression seems better at preventing cardiac hypertrophy and fibrosis than attenuating blood pressure.

Adiponectin, produced by adipose tissue, was shown to attenuate Ang II-induced cardiac hypertrophy and fibrosis by activating AMP-activated protein kinase (AMPK) and suppressing ERK1/2.[35] Pioglitazone, a peroxisome proliferator-activated receptor-γ (PPAR-γ) ligand, increases circulating adiponectin and prevents hypertension-related cardiac remodeling. Li et al. have now shown that pioglitazone inhibits Ang II-induced cardiac hypertrophy in mice by increasing circulating adiponectin levels.[35]

Ang II was recently found to activate the nuclear factor erythroid-2-related factor 2 (Nrf2) in cardiac myocytes, a protein that enhances expression of a number of antioxidant genes.[36] Activation was secondary to increased ROS and was shown to oppose Ang II-induced cardiac hypertrophy, which in turn was linked to ROS-induced down regulation of $p27^{kip1}$. Hearts of $Nrf2^{-/-}$ mice chronically treated with Ang II showed enhanced oxidative stress, reduced induction of antioxidant genes, and greater hypertrophy, although the increase in blood pressure was comparable to that in wild type mice. Thus, the Nrf-$p27^{kip1}$ axis serves as an endogenous negative feedback mechanism for the aggravating actions of Ang II on cardiac remodeling attributable to increased oxidative stress.

## Conclusion

LVM is an independent predictor of adverse cardiovascular events with essential hypertension, while its regression through blood pressure control reduces the risk of adverse events.[33] Increased blood pressure renders the heart susceptible to the growth-promoting and remodeling actions of Ang II, which occur part and parcel with inflammatory signaling.[2] Although no longer billed as the leading actor in hypertension-induced cardiac remodeling, Ang II is no mere bit player either. Studies over the last several years have elucidated how Ang II synergizes with the SNS, aldosterone, inflammation, and oxidative stress to drive cardiac hypertrophy and fibrosis in the face of high blood pressure.

### Future Perspectives

Therapies that target the cardiac actions of Ang II may enhance the effectiveness of blood pressure reduction in reducing morbidity and mortality associated with hypertension. Of note, poor control of systolic blood pressure is still a problem in more than half the patients treated for hypertension.[37] That fact, as well as untoward actions of ACE inhibitors and ARBs, indicate that new therapeutic strategies that directly target events in cardiac remodeling downstream of increased blood pressure may have clinical benefit. New innate counter-regulatory mechanisms to Ang II signaling have been described and shown capable of manipulation to limit cardiac remodeling. Enhancing anti-oxidant gene expression may also prove to be a strategy for opposing cardiac hypertrophy; however, though contributing to cardiac fibrosis, oxidative stress may not have much of a role in cardiac hypertrophy resulting from gradually developing or chronic hypertension. We now know that AT1 and other $G_{q/11}$-coupled receptors function as mechanosensers to translate increased blood pressure into hypertrophic signaling independent of agonist and signaling of these receptors could be selectively targeted.[38] Still many questions remain, such as the nature of the regulatory mechanisms that modulate the interplay between Ang II and inflammatory cytokines in driving oxidative stress and cardiac remodeling. Undoubtedly other surprises await discovery.

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