An Update on Angiotensin-II Mediated Left Ventricular Abnormalities in Chronic Kidney Disease

Authors

Umar Malik, MD
Veena Raizada, MD

University of New Mexico
School of Medicine
Department of Internal Medicine
Division of Cardiovascular Medicine

Umar Malik, MD:
umar@salud.unm.edu
Veena Raizada, MD:
vraizada@salud.unm.edu

correspondence
Veena Raizada, MD
Professor of Medicine,
MSC 10-5550,
University of New Mexico,
Albuquerque,
NM 87131-0001.
vraizada@salud.unm.edu

1. Abstract

We previously reviewed angiotensin-II (ATII) mediated left ventricular (LV) structural changes in chronic kidney disease (CKD) patients [1]. These changes include myocyte hypertrophy, collagen deposition leading to interstitial fibrosis, and excessive myocardial calcium deposition. This manuscript presents updates on the renin-angiotensin system (RAS) and ATII-mediated LV changes in CKD including the use of speckle tracking echocardiography (STE) in understanding subclinical LV changes in early CKD patients, the role of sympathetic activation via ATII, and ATII-induced gene expression leading to cardiac fibrosis. In addition, we discuss the discovery of ACE2 and its counter-regulatory axis which ultimately lead to LV changes in CKD patients. This manuscript also highlights the importance of RAS-mediated medical therapy in the prevalence of CHF and reduction of cardiovascular mortality.

2. Introduction

ATII-mediated left ventricular (LV) structural changes in chronic kidney disease (CKD) patients include myocyte hypertrophy, collagen deposition leading to interstitial fibrosis, and excessive myocardial calcium deposition [1]. This manuscript adds to our previous review with updates on the renin-angiotensin system (RAS) and ATII-mediated LV changes in CKD.

3. LVH and LV Dysfunction

Recent studies have shown that cardiac dysfunction occurs earlier than previously thought in CKD. Furthermore, earlier identification of subclinical cardiac dysfunction may ultimately improve outcomes in patients with CKD. Asp et al. showed that systolic and diastolic dysfunction can be seen in even mild-moderate CKD compared with controls [2]. Seifert et al. also showed that patients with stage 3 CKD had increased LV mass and persistent LV diastolic dysfunction in the setting of normal kidney function, blood pressure and LV systolic function [3]. These findings highlight the clinical significance of cardiovascular disease (CVD) in CKD, the importance of early identification and initiation of appropriate medical therapy. More recently, Speckle Tracking Echocardiography (STE) has emerged as a valuable imaging technique for identifying changes in LV function at an earlier time point. Subclinical abnormalities of both systolic and diastolic LV function are frequently detected using STE.

4. Sympathetic Over-activity and LV abnormalities

Further evidence has found that angiotensin II is capable of inducing sympathetic activation in heart failure via Angiotensin I receptors (AT1R) in the brain [6]. This subsequently leads to LV diastolic dysfunction and contributes to worsening mortality [7]. Identification of these mechanisms serves as a potential target for therapies in the future as well.

5. Angiotensin II-mediated Cardiac Fibrosis

We previously highlighted many of the deleterious effects of angiotensin II on LV dysfunction via myocardial fibrosis. Recently, Suzuki et al. demonstrated the intracellular and extracellular effects of ATII-induced cardiac fibrosis via basigin (Bsg) gene expression [8]. Bsg expression significantly promotes cardiac fibroblast proliferation. This may, in part, lead to worsening LV dysfunction and poor prognosis mediated by ATII.

6. The Counter-regulatory Role of ACE2

More recent research has focused on the discovery and downstream products of angiotensin converting enzyme 2 (ACE2). ACE2 metabolizes ATII to AT (1-7) which causes vasodilation by binding to the Mas receptor, in direct contrast to the vasoconstrictive effects of Ang II [9] (Figure 1). ACE2 expression also preserves endothelial function [10] and decreases cardiac hypertrophy [11]. Rat models have demonstrated that the ACE2/AT (1-7)/Mas axis counter-regulates the classical ACE/ATII/AT1R axis [10, 12]. AT (1-7) has been found to counteract the effects of ATII

in cardiac myocytes, ultimately highlighting the important balance between these two pathways in the development of LV dysfunction [13].

Elevated ACE and decreased ACE2 expression have been found via immunohistochemical analysis of kidney tissues of patients with diabetic nephropathy [14]. Decreased ACE2 and increased circulating ACE has also been found among patients with stage 3-5 CKD who had no CVD [15]. In addition, the ACE2/AT (1-7)/Mas axis has been shown to have protection from obesity-related kidney injury [16]. Findings of decreased ACE2 in ESRD patients may lead to elevated ATII and ultimately, its deleterious effects on cardiovascular disease.

7. Clinical Implications

Medications that inhibit RAS have been shown to have a large impact on cardiovascular disease. Patients with Stage 5 CKD on aldosterone receptor blockers (ARBs) had a lower prevalence of congestive heart failure (CHF) [17]. Tang et al. showed that patients with long-term hemodialysis and heart failure had reduced all-cause and cardiovascular mortality when given RAS blockade with an ACEI and/or ARB therapy [18]. A double-blind, placebo-controlled, multicenter trial by Cice et al. showed that ARB plus ACEI reduced all-cause mortality, cardiovascular death, and hospitalization for heart failure in patients with LVEF of 40% or less who had CKD [19].

The use of RAS inhibitors is associated with reduction of fracture risk in hemodialysis patients with secondary hyperparathyroidism. Treatment with RAS inhibitors should be considered along with the conventional treatment for patients with dialysis associated mineral and bone disorder [20].

8. Conclusion

This brief review serves as an update to our prior manuscript detailing ATII-mediated LV changes in CKD patients. More recent research has explored the use of STE in understanding subclinical LV changes in early CKD patients, evaluates the role of sympathetic activation by ATII and highlights ATII-induced gene expression leading to cardiac fibrosis. Furthermore, the discovery of ACE2 and its counter-regulatory axis promotes a better understanding of the imbalances which ultimately lead to LV changes in CKD patients. Finally, several studies highlight the importance of RAS-mediated medical therapy in the prevalence of CHF, reduction of cardiovascular mortality, and hospitalization for heart failure.

9. References

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10. Figures

Figure 1. Renin-Angiotensin System (RAS).

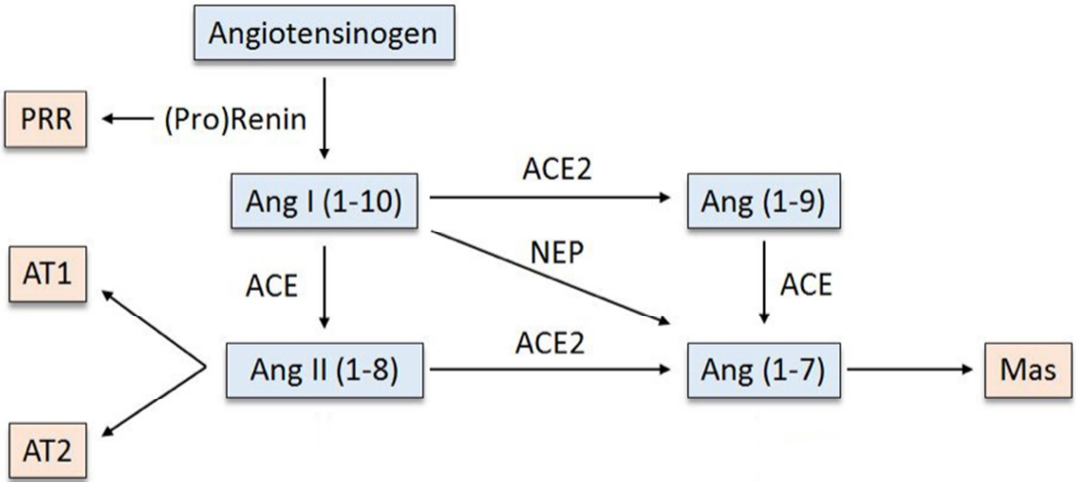

Figure 1. Renin-Angiotensin System (RAS). Several active metabolites are products of Ang II metabolism. ACE2 catalyzes the formation of Ang (1-7) from Ang II (1-8). Ang (1-7) causes vasodilation through the Mas receptor, and exhibits additional effects that counteract the effects of Ang II and the classical RAS pathway. Hormones are in blue boxes, receptors are in pink boxes, and enzymes are not in boxes.

Abbreviations: PRR: prorenin receptor; Ang: angiotensin; AT1: angiotensin receptor 1; AT2: angiotensin receptor 2; ACE2: angiotensin converting enzyme 2; NEP: neutral endopeptidase;