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Review

Some Aspects of the Renin-Angiotensin-System in Hemodialysis Patients

Umar Malik Veena Raizada

University of New Mexico School of Medicine, Albuquerque, New Mexico, USA

Key Words
RAS • Renin-angiotensin system • Angiotensin II • ACE • ACE2 • Hemodialysis • Hypertension • ESRD • Cardiovascular disease

Abstract
Understanding of the renin-angiotensin system (RAS) has changed remarkably over the past decade. Renin, angiotensin converting enzyme (ACE), angiotensin II (Ang II), and Ang II receptors are the main components of the RAS. Recent studies identified the ACE2/Ang 1-7/Mas receptor axis, which counter-regulates the classical RAS. Many studies have examined the effects of the RAS on the progression of cardiovascular disease and chronic kidney disease (CKD). In addition, many studies have documented increased levels of ACE in hemodialysis (HD) patients, raising concerns about the negative effects of RAS activation on the progression of renal disease. Elevated ACE increases the level of Ang II, leading to vasoconstriction and cell proliferation. Ang II stimulation of the sympathetic system leads to renal and cardiovascular complications that are secondary to uncontrolled hypertension. This review provides an overview of the RAS, evaluates new research on the role of ACE2 in dialysis, and reviews the evidence for potentially better treatments for patients undergoing HD. Further understanding of the role of ACE and ACE2 in HD patients may aid the development of targeted therapies that slow the progression of CKD and cardiovascular disease.

Introduction

In 1898, Robert Tigerstedt and his student Per Bergman at the Karolinska Institute in Sweden stumbled across a monumental discovery that forever changed our understanding of renal hemodynamic control. They identified a molecule from the renal tissue of a rabbit that increased blood pressure in nephrectomized animals [1] and named this substance "renin", after the organ from which it was derived. This discovery led to a widespread search

Veena Raizada, MD,
Professor of Medicine

MSC 10-5550, University of New Mexico, Albuquerque
NM 87131-0001 New Mexico (USA)
E-Mail vraizada@salud.unm.edu

for additional compounds with similar characteristics, and eventually to a full elucidation of the now classic renin-angiotensin system (RAS). Our understanding of this system has grown remarkably since these early discoveries. We now know that local RAS pathways exist in diverse tissues, as well as the kidneys, and this further complicates treatment regimens for patients with chronic kidney disease (CKD) [2]. Moreover, renin can activate local RAS systems by binding to its receptor in selected tissues [3]. In addition, research of the various angiotensin II (Ang II) receptors indicated that Ang II can have positive and negative downstream effects on circulation [4]. Most recently, the discovery of angiotensin converting enzyme 2 (ACE2) led to investigations of its counter-regulatory role compared to ACE [5, 6].

These advances in basic research have been matched by the development of therapies that inhibit RAS medications that can improve patient outcomes due to their inhibition of several disease processes. For example, a multicenter, prospective, observational study by Yamamoto et al. showed that patients on hemodialysis who used ACE inhibitors (ACEIs) and aldosterone receptor blockers (ARBs) had a lower rate of fracture-related hospitalization [7]. Medications that inhibit RAS have a large impact on cardiovascular disease (CVD). Thus, Ikeda et al. showed that patients with Stage 5 CKD who used ARBs had a lower prevalence of congestive heart failure (CHF) [8] and Tang et al. showed that long-term hemodialysis (HD) patients with heart failure had reduced all-cause and cardiovascular mortality when they were given RAS blockade with ACEI and/or ARB therapy [9]. Interestingly, a retrospective cohort study of patients with left ventricular ejection fraction (LVEF) of 45% or less (n = 45) showed that only 31% received an ACEI and only 9% received an ARB [10]. A double-blind, placebo-controlled, multicenter trial by Cice et al. showed that the addition of telmisartan (an ARB) with an ACEI reduced all-cause mortality, cardiovascular death, and hospitalization for heart failure in patients with LVEF of 40% or less who were on HD [11]. In addition, a retrospective cohort study by Shireman et al. showed that use of antihypertensive medications -- including ACEIs or ARBs -- reduced the adjusted hazard ratios for mortality in HD patients [12].

Although therapies that inhibit RAS provide important benefits to patients on HD, they also have negative side effects. For example, hyperkalemia is associated with ACEI and ARB therapy due to downstream effects on aldosterone, which normally increases uptake of sodium at the expense of potassium. Interestingly, Han et al. showed that use of an ACEI and/or ARB did not increase the risk of hyperkalemia in patients on maintenance HD [13]. The RAS also plays an important role in the secretion of erythropoietin. Vlahakos et al. demonstrated that the RAS stimulated erythropoietin secretion in HD patients [14]. In addition, a systematic review of 29,061 patients by Cheungpasitporn et al. showed an association between development of anemia and use of medications that inhibit RAS, including ACEIs and ARBs [15].

Perhaps of most interest, the alterations in RAS activity can affect the progression of CKD and CVD. Luciano et al. highlight the importance of vitamin D in the progression of CKD, citing evidence for vitamin D analogs reducing proteinuria by suppressing RAS activity [16]. In addition, numerous renin and ACE gene polymorphisms increase the risk for coronary artery disease (CAD) [17, 18]. Lei at al. showed that gene polymorphisms of ACE increased the risk of CAD in individuals with Type II diabetes mellitus (DM) [19] and Kato et al. demonstrated that gene polymorphisms of ACE increased the risk of CVD in individuals with hypertension [20].

In the early 1980's many studies evaluated the discovery of varying ACE levels in HD patients. These studies (see below and Table 1) had conflicting results, and the explanations for these findings were incomplete at that time. Data on ACE activity in HD patients remains limited, but our increasing understanding of the complicated nature of the RAS and its effects in CKD and CVD, as described above, justify exploration of possible mechanisms for these interesting findings.

The RAS has significant effects on CVD and residual renal function. Elevated ACE is important because it increases the level of Ang II, which promotes the progression of CKD and CVD through

vasoconstriction and cell proliferation. In addition, sympathetic activation *via* Ang II leads to uncontrolled hypertension that has negative effects on the renal and cardiovascular systems. Moreover, elevated ACE and increased Ang II lead to secretion of aldosterone from the adrenal cortex. However, the function and importance of aldosterone are beyond the scope of this review, and we will focus on the renin-angiotensin system (RAS) and its importance to patients on HD.

Table 1. Initial studies that measured plasma or serum levels of angiotensin converting enzyme in different patient populations

Authors	Plasma or Serum ACE	Patient population
Patel et al. 1979	Serum	CKD on HD
Muira et al. 1984	Serum	CKD on HD
Silverstein et al. 1984	Serum	CKD on HD
Nielsen et al. 1985	Serum	CKD on HD
Letizia et al. 1995	Serum	CKD on HD
Docci et al. 1988	Serum	CKD on HD
Schweisfurth et al. 1979	Serum	Hepatitis/liver cirrhosis
Lieberman et al. 1980	Serum	Diabetes Mellitus
Koo et al. 1987	Plasma	CKD on HD
Anguiano et al. 2015	Plasma	CKD Stage 3-5

Abbreviations: ACE: angiotensin converting enzyme; CKD: chronic kidney disease; HD: hemodialysis.

Elevated ACE in Hemodialysis Patients

In 1979, Patel et al. performed one of the first and best known evaluations of the levels of ACE in HD patients [21]. They studied 19 patients with CKD on long-term HD and 19 controls, and found that ACE activity was increased in 58% of the patients [21]. They proposed that these increased serum ACE levels might be secondary to increased pulmonary vascular area in patients with renal failure, because ACE was thought to be produced only in the lungs. In 1982, Muira et al. confirmed these results but proposed a different mechanism. They noted that the ACE activity of patients with CKD on regular HD was higher than that of age-matched controls [22], and they also found higher ACE levels in patients on HD for longer than 3 years and in patients with diabetic nephropathy. It is important to note that elevated ACE also occurs in DM [23]. Muira et al. found no relationships of enzyme activity with age and sex [22]. Based on studies reporting accelerated atherosclerosis in patients on maintenance HD, they speculated that advanced endothelial damage could lead to elevated serum ACE in HD patients, because vascular endothelial cells of the lungs and kidneys produce most of the ACE.

Additional studies have found similar results, but only select articles postulated possible mechanisms. Silverstein et al. showed elevated serum ACE in 16 of 48 non-HD patients ($p < 0.001$) who had various types of CKD [24]. They also found increased serum ACE in 17 of 52 patients on maintenance HD ($p < 0.001$) in a comparison with healthy adult controls. Nielsen et al. showed that serum ACE levels increased by 14.3% ($p < 0.001$) in patients after a 240 min session of HD [25]. They suggested that increased serum ACE was due to a complement-mediated sequestration of leukocytes within the pulmonary vasculature, as previously described by Craddock et al. [26]. This accumulation of leukocytes leads to injury of the vascular endothelium with interstitial edema and subsequently to pulmonary abnormalities, as also postulated by Muira et al. [22]. Koo et al. showed that serum ACE was significantly elevated in patients with CKD at 5 h after an HD session ($p < 0.001$) [27]. They suggested that elevated ACE in HD patients is more closely related to the HD procedure than to the renal disease itself. In support, Craddock et al. have shown complement-mediated pulmonary dysfunction in patients after HD sessions [28].

Letizia et al. showed that patients with CKD on HD and patients who received renal transplantation had significantly higher serum ACE activity than healthy controls [29]. Plasma renin activity (PRA) and plasma aldosterone (PA) also increased after an HD session ($p < 0.026$ and $p < 0.044$, respectively). Iitake et al. also documented elevations of PRA in

HD patients [30]. These elevations in PRA raise additional concerns regarding the negative effects of the RAS on HD patients. As such, research into renin inhibitors has produced some promising results regarding the control of these effects in HD patients. Ishimitsu et al. showed that PRA decreased following administration of aliskiren (a direct renin inhibitor) and this was accompanied by a modest decrease in blood pressure [31]. Morishita et al. also demonstrated that use of aliskiren was associated with decreased BP and cardio-protective effects in hypertensive patients on long-term HD [32]. Ito et al. showed that aliskiren and an ARB had similar effects on BP control, but there was a significant decrease in PRA with aliskiren but not with an ARB [33]. In addition, Moriya et al. demonstrated that aliskiren improved vascular endothelial function in patients on hemodialysis [34]. These findings were independent of antihypertensive effect from the medication. Advances by Xiong et al. have demonstrated the importance of the CD38 gene in mice on the intracellular regulation of renin production [35]. This study provides some insight into this poorly understood mechanism and may highlight future studies aimed at developing more targeted therapies for suppressing PRA. Overall, these studies illustrate the importance of appropriate RAS blockade for patients on long-term HD.

In contrast to Koo et al., Letizia's group found no significant difference in serum ACE activity before and after an HD session. Ulrich et al. examined ACE expression in monocytes of HD patients with CVD and controls with normal renal function and found that HD patients had greater ACE expression [36]. Docci et al. compared the effect of different dialyzer membranes on serum ACE, and found that all tested membranes caused similar increases in ACE. They proposed that the elevation of ACE was less a cause of the HD procedure itself, and instead was secondary to hemoconcentration [37]. Table 1 summarizes the above studies that examined serum and plasma levels of ACE in various patient populations.

Clinical Implications

The increased ACE in HD patients and the consequent elevation of Ang II can promote the progression of CVD and renal disease. Patients on maintenance HD often suffer from hypertension at baseline, and ultrafiltration during the HD procedure typically normalizes blood pressure by reducing volume overload. However, some patients on HD have the opposite response, and suffer from hypertension during or after the HD procedure. Previous studies have postulated several possible mechanisms for this intradialytic hypertension, including electrolyte imbalance, removal of antihypertensive medications during HD, and activation of the RAS [38-41]. RAS activation can occur due to the decreased intravascular volume during the ultrafiltration process of HD [42, 43]. Activation of RAS leads to subsequent elevation of Ang II, and this enzyme can cause vasoconstriction, salt and water retention mediated *via* aldosterone, and cell proliferation. In addition, sympathetic activation occurs because Ang II acts on Ang II receptor type 1 (AT1 receptor) in the central nervous system, leading to increased systemic vascular resistance [44]. As such, Ang II promotes hypertension through water retention, vasoconstriction, and sympathetic activation, underlining the important role of ACE inhibitors in the treatment of hypertension in HD patients. Thus, treatment of high blood pressure in HD patients with elevated ACE may be particularly challenging because increased activation of local-RAS systems -- independent of the primary RAS -- may contribute to hypertension that is sustained and difficult to treat.

An excess of Ang II may also be deleterious in other patient groups. For example, elevated Ang II increases the morbidity and mortality of patients with CHF despite ACE inhibitor therapy [45]. This indicates the growing need to understand RAS activation in renal diseases and CVDs. ACE is upregulated in the proximal tubules of rats with proteinuria, likely resulting in further renal damage and progression of renal disease [46]. Sustained progression of renal and CVD in HD patients may also be linked to increased proteinuria, so therapies that decrease proteinuria may benefit such patients.

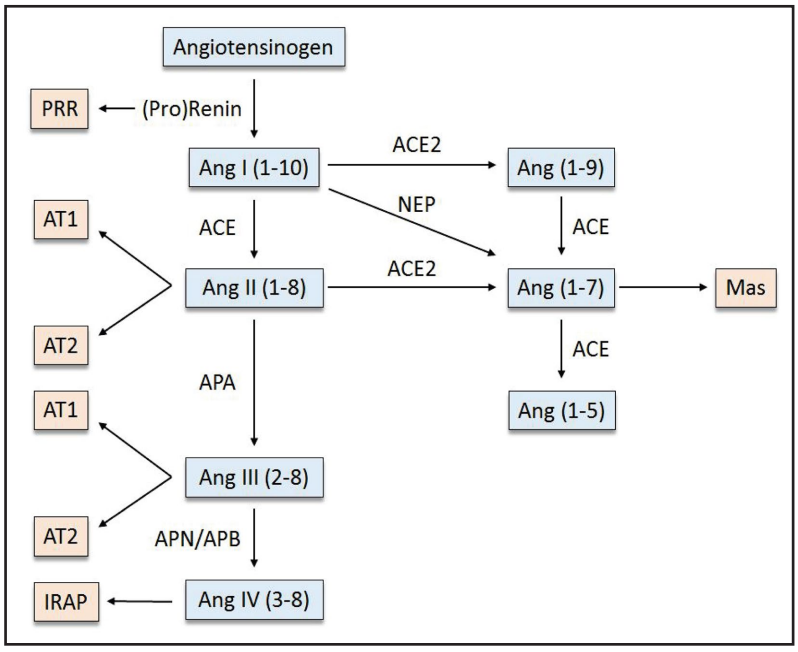

Fig. 1. Renin-Angiotensin System (RAS). Recent advances in our understanding of the RAS system has led to the updated version shown here. Several active metabolites are products of Ang II metabolism. ACE2 catalyzes the formation of Ang (1-7) from Ang II (1-8). Ang (1-7) causes vasodilation through the 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; IRAP: insulin-regulated aminopeptidase; ACE2: angiotensin converting enzyme 2; NEP: neutral endopeptidase; APA: aminopeptidase A; APB: aminopeptidase B; APN: aminopeptidase N.

Counter-regulatory role of ACE2

Studies of ACE2 and its role in the RAS have led to discoveries of many new mediators of the classical ACE pathway (Figure 1). Of note, Ang (1-7), whose formation is catalyzed from Ang II by ACE2, plays a large role in producing vasodilation by binding to the Mas receptor, in contrast to the vasoconstrictive effects of Ang II. In rat models, the ACE2/Ang 1-7/Mas axis counter-regulates the ACE/Ang II/AT I receptor axis [47, 48].

More recent studies have evaluated the levels of ACE2 in patients with renal disease. ACE2 converts Ang II to Ang (1-7) and therefore has favorable effects on the cardiovascular and renal systems through its induction of vasodilation, its anti-inflammatory properties, and its prevention of endothelial dysfunction. Mizuiri et al. performed immunohistochemical analysis of the kidney tissues of patients with diabetic nephropathy and found elevated ACE and decreased ACE2 expression, indicating that an additional factor mediates the progression of renal and CVD [49]. Anguiano et al. found decreased plasma ACE2 and increased circulating ACE among patients with stage 3-5 CKD who had no CVD [50]. Decreased ACE2 in ESRD patients on dialysis may lead to elevated Ang II, because ACE2 is responsible for Ang II degradation. ACE2 overexpression can also preserve endothelial function [47], and the ACE2/Ang 1-7/Mas axis has anti-inflammatory properties [48]. The renal ischemia/reperfusion model of acute kidney injury (AKI) in rats showed elevated renal Ang II and decreased renal Ang 1-7 levels, indicating the occurrence of important physiologic changes associated with the RAS as a consequence of AKI [51].

Historically, evaluation of the classical RAS pathway and the ACE/Ang II/AT 1 receptor axis led to the development of numerous ACEIs and ARBs that can slow the progression of renal disease. These therapies have remained mainstays in the treatment of cardiovascular and renal disease. Perhaps further evaluation and exploration of the ACE2/Ang 1-7/Mas axis will lead to the development of better treatments for these common diseases. In addition, special consideration must be given to the subtle balance between the ACE/Ang II/AT 1 axis and the ACE2/Ang 1-7/Mas axis.

Local-RAS pathways

Our review of the role of the RAS in HD patients will conclude with a discussion of the local RAS, one of the most recent discoveries in this field. It is now widely accepted that the kidneys themselves have a local RAS. Although the liver produces most of the angiotensinogen (Agt), epithelial cells of the proximal tubule also synthesize this hormone, and it can even be detected in urine [52]. The collecting tubule is another source of renin, and renin expression is linked with stimulation of Ang II [53, 54]. ACE occurs in the brush border membrane of the proximal tubule [52]. Thus, the presence of these important compounds may lead to intrarenal production of Ang II. This local system may affect serum ACE levels (*i.e.* at the level of the whole body) in patients with renal disease. Interestingly, studies have shown that patients given ACE inhibitors still have elevated intrarenal Ang II production. This indicates a role of other pathways in the conversion of Ang I to Ang II [55]. The intrarenal-RAS is not yet fully understood and the role of this system in patients undergoing HD is unknown. A more complete understanding of the intrarenal-RAS is needed because it can alter ACE levels in patients with CKD who are on maintenance HD.

Conclusion

In this article, we reviewed numerous studies that examined the effect of elevated ACE in patients with CKD who were undergoing HD. There are several possible explanations for the elevated serum ACE in these patients. For example, existing underlying diseases, such as DM and liver disease, may contribute to the elevated ACE in these patients [23, 56]. Another possibility is that the diseased kidney secretes ACE into the serum, although the evidence for this is weak. In fact, Patel et al. found that plasma ACE was elevated in patients with bilateral nephrectomies [21]. It is possible that elevated ACE in HD patients is due to decreased degradation of the enzyme or decreased excretion by the kidney. Several of the studies reviewed here suggest that elevated ACE may be due to the effects of HD on the pulmonary vasculature *via* complement-mediated pathways [26, 28].

Another possibility is that ACE is elevated in patients with CKD due to disruption of its negative feedback loop by Ang II [57]. It is possible that dysregulation of the negative feedback mechanism of Ang II upon renin in the presence of CKD may increase RAS activity and the levels of ACE [58]. As discussed above, prorenin itself can activate local-RAS pathways through the pro-renin receptor (PRR) [3]. This activation may further increase serum ACE levels, secondary to the dysregulation of the negative feedback mechanism of the RAS. The intrarenal-RAS may affect whole body levels of ACE through diffusion abnormalities within the diseased kidney, although this requires further study. Immuno-staining experiments showed increased ACE expression within the glomerular and renal vasculature of rats with DM and albuminuria [59]. Soler et al. also showed increased ACE expression in the renal vessels of diabetic mice [60] and immunohistochemical studies in patients with non-insulin dependent DM indicated increased ACE in those with nephropathy [61].

It is important to know whether the elevation of ACE in HD patients is due to renal disease itself, the HD procedure, or both. However, the mechanisms underlying the elevation of ACE are likely multifaceted and related to multiple interactions. It is important to understand these mechanisms in order to develop better treatments, slow disease progression, and reduce the severity of CKD and CVD in HD patients. Although the RAS is associated with development of hypertension and DM, ACE/ACE2 levels are not directly related to the progression of CKD. Hypertension and DM develop as consequences of many different factors and have many potential etiologies. Future studies are needed to provide answers to these questions and to develop new questions in our quest to better understand, treat, and prevent these diseases. Further evaluation and determination of these mechanisms is imperative in our ever-changing understanding of the once simple RAS, originally discovered by Tigerstedt and Bergman.

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