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The Renin-Angiotensin-Aldosterone System in Postmenopausal Women: The Promise of Hormone Therapy

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Abstract

Estradiol (E2) plays an underrecognized role in modulating body-wide systems, including important interactions with the renin-angiotensin-aldosterone system (RAAS). The RAAS is an immunomodulating system that is critical for maintaining homeostasis across multiple organ systems. The diverse interactions between E2 and the RAAS help maintain cardiometabolic homeostasis, including successful physiologic responses to trauma and infectious pathogens. Estradiol deficiency (ie, menopause) results in impaired responses and increased susceptibility to infectious pathogens. Both immune and cardiometabolic function decline with reduced E2 production, in part because the RAAS becomes dysregulated by E2 deficiency, leaving RAAS predominantly in its proinflammatory state and predisposing to systemic low-grade inflammation. Estradiol deficiency and RAAS dysregulation contribute to impaired immune responses and increased incidence of cardiac hypertrophy, hypertension, atherosclerotic cardiovascular disease, arrhythmias, and heart failure. The RAAS consists of dual, counterbalancing pathways—proinflammatory and anti-inflammatory. Estradiol is a signaling agent that plays a major role in determining which RAAS pathway predominates. The proinflammatory pathway is activated early in response to infection or trauma, followed by up-regulation of the anti-inflammatory pathway, to resolve inflammation and to restore homeostasis. Estradiol influences activation of the "switch" to restore the anti-inflammatory state. The dysregulated RAAS is a primary target of current cardiovascular therapeutics focused on blocking portions of its proinflammatory pathway. However, RAAS-modifying pharmaceuticals often provide imperfect solutions to these physiologic disruptions and underscore the need for improved approaches to menopausal medicine. Estradiol therapy and optimal lifestyle practices combined with RAAS-modifying pharmaceuticals may be an ideal strategy to optimize postmenopausal health.

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The loss of female sex hormones during the menopausal years has a marked impact on cardiovascular (CV) health. Notably, hypertension (HTN) affects 45 million American women, and CV events remain the dominant cause of female mortality.[1] Ovarian senescence and the development of estradiol (E2) deficiency result in the loss of the cardiometabolic advantage of the female reproductive years.[2] Metabolic homeostasis is essential for successful reproduction, and E2 is the hormonal support linking successful female fertility with optimal cardiometabolic and immune functions. The ability to successfully reproduce is the prime directive of life, and for that to be realized, a great many body functions need to be successfully managed, including control of blood pressure (BP), regulation of intracellular and extracellular fluid volume, and effective innate responses to trauma and infectious pathogens. As E2 modulates these functions throughout the female body, E2 receptors exist throughout the various organ systems, including vascular tissues, myocardium, gastrointestinal tract, brain, musculoskeletal tract, lungs, kidneys, skin, and immune cells (Table).[3-5]

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A complex and largely unacknowledged relationship exists between E2 and the critically important renin-angiotensin-aldosterone system (RAAS), which is composed of a unique set of enzymes and peptides present throughout the circulatory system and expressed locally within many tissues.[6] Tissue RAAS exists in the heart, blood vessels, kidney, brain, adipose tissue, adrenal gland, pancreas, liver, reproductive system, lymphatic tissue, placenta, and eye and plays a role in cellular growth, proliferation, differentiation, migration, apoptosis, and extracellular matrix remodeling and inflammation. The pathways of the RAAS are modulated by E2, and menopausal loss of ovarian-produced E2 results in profound multiorgan effects, with a marked impact on the RAAS.[7]

Dysregulation of the RAAS contributes to the development of HTN, and pharmacologic treatments that block aspects of the RAAS are pivotal in the treatment of elevated BP and associated CV disease (CVD); but therapeutic results remain imperfect, and a substantial number of adverse CV events continue to occur among postmenopausal (PM) women.[8] Physiologic hormone replacement therapy (HRT) offers the promise of being an effective approach to maintaining a well-functioning RAAS and cardiometabolic well-being during the PM years.[6]

OVERVIEW

The RAAS is a pivotal immunomodulating system with vital regulatory roles throughout the body. It consists of 2 interrelated, counterbalancing pathways, 1 proinflammatory and 1 anti-inflammatory. Both pathways are essential to the optimal regulation of CV and renal systems, regulating BP and fluid and electrolyte balance.[1] The RAAS is also responsible for a robust, targeted, and complete immune response in the event of exposure to an infectious agent or trauma. A dysregulated, hyperinflammatory RAAS, "stuck" in its proinflammatory pathway, substantially contributes to the development of HTN, diastolic dysfunction, heart failure, arrhythmias, left ventricular hyperplasia, myocardial fibrosis, hypertrophic cardiomyopathy, and peripheral artery disease, resulting in cerebrovascular accidents, myocardial infarctions, and cardiorenal syndrome.[9,10] To reduce such harmful conditions, research has provided clinicians with pharmaceuticals that interfere with the RAAS proinflammatory pathway, and there is currently ongoing research into medications to promote the anti-inflammatory functions. As will be seen, the complex intersection of the proinflammatory and anti-inflammatory RAAS pathways complicates the use of a drug that primarily blocks mainly the proinflammatory side as there will always be an impact on both pathways.[11] As diverse bidirectional interactions exist between the pathways, pharmaceuticals intended to have an impact solely on the proinflammatory pathways can inadvertently also impair the anti-inflammatory effects of the RAAS. In addition, blocking certain aspects of the proinflammatory RAAS can potentially impair the immune response to invading pathogens.[12] Although imperfect, medications that block portions of the RAAS nevertheless provide important clinical benefits[13]; potentially superior to the current approach of modifying the chronically hyperinflammatory RAAS would be the restoration of the body's innate homeostatic mechanisms to regulate and balance the RAAS. Restoring physiologic levels of E2 could potentially achieve that goal.

The RAAS is among the many pathways and systems supported by E2, a powerful messenger molecule that modulates the "switch" between the proinflammatory and anti-inflammatory pathways of the RAAS.[9] In the presence of adequate E2, the default state of the RAAS is anti-inflammatory; but with trauma or invading pathogens, E2 promotes a rapid "switching on" of the RAAS proinflammatory pathway. After resolution of the threat, E2 reinstates the anti-inflammatory pathway, promoting inflammation resolution and restoring homeostasis.[14]

With E2 deficiency present throughout menopause, a chronic state of low-grade inflammation develops and persists, in parallel with the shift of RAAS toward its proinflammatory pathway, driving oxidative stress and CV aging.[10,15,16] By the age of 60 to 65 years, E2 deficiency and RAAS

TABLE. Anti-inflammatory Effects of Estradiol Through Activation of the Renin-Angiotensin-Aldosterone System Pathway

Protective Effects in Heart, Vasculature, Kidneys, and Central Nervous System		
Reduces pro-oxidative LOX-1 (oxidized receptor for low-density lipoprotein)	Reduces proinflammatory intercellular adhesion molecule	Decreases expression of nuclear factor κB target genes
Increases expression of endothelial nitric oxide synthase	Increases vasodilation	Decreases ventricular remodeling
Reduces blood pressure	Increases parasympathetic tone of autonomic nervous system	Decreases sympathetic output (sympathoinhibition)
Blocks release of proinflammatory cytokines by macrophages and mast cells		
Blocks proliferation and migration of vascular smooth muscle cells		

Estrogen, in the dominant form produced by reproductive-aged ovaries, estradiol (E2), is protective to cardiovascular structures through its immunomodulatory effects on the renin-angiotensin-aldosterone system. This provides reproductive-aged women with the "health advantage" they enjoy until menopause. Menopausal loss of ovarian-produced E2 heightens cardiovascular risk—a risk that E2 therapy during the postmenopausal years might reduce.[4,5]

dysregulation contribute to the development of CVD in PM women at rates that mirror those of age-matched men.[17] Loss of systemic E2 results in declining immune competency, loss of metabolic homeostasis, and rising rates of CVD in PM women.[18]

The therapeutic approach, during the PM years, to the dysregulated, proinflammatory RAAS involves the use of angiotensin-converting enzyme (ACE) inhibitors (ACEIs) and angiotensin receptor blockers (ARBs). Pharmaceutical recommendations for male and female patients regarding the selection of an ACEI or ARB are identical despite some data suggesting varied gendered responses to these therapies.[8,19,20] Some research suggests that women respond more favorably to ARB than to ACEI treatment, with ACEIs more impactful in men.[21] In the STATUS II study, an ARB plus a calcium channel blocker achieved better control of HTN in women than in men. Combining E2 with an ARB resulted in better BP lowering in PM women compared with an ARB alone.[22] The approach combining E2 with an ARB may synergize to improve outcomes among PM women.

Expanding research has increased our understanding of the critical role of E2 in RAAS regulation. The "classic" renin-angiotensin system (RAS) was described nearly 50 years ago. The RAS was initially understood as a modulator functioning within the circulatory system, regulating BP and maintaining fluid and electrolyte homeostasis.[23] When aldosterone was identified and its relationship to the RAAS clarified, the name was updated from RAS to RAAS. Adding to our understanding of its complexity, a noncirculating RAAS was discovered, consisting of a tissue (or local) system and an intracellular system.[24]

Initially, only the proinflammatory pathway of the RAAS was recognized, consisting of 2 enzymes, renin and ACE. The enzyme named renin transformed angiotensinogen to the peptide angiotensin (Ang) I. ACE converted Ang I to Ang II , initially described as a powerfully proinflammatory peptide, then thought to have just 1 receptor, angiotensin 1 receptor (AT1R).[25]

Subsequently, a second RAAS pathway with anti-inflammatory effects to counterbalance the proinflammatory pathway was recognized, including the more recently identified enzyme ACE2, the peptide Ang (1-7), and the receptors MAS and angiotensin 2 receptor (AT2R). (The name MAS is derived from the name Massey, whose tissue was used to research the *MAS* gene.[26]) The novel and shared enzymes and peptides composing the anti-inflammatory pathway are now known to be larger, and our understanding of the full complexity of the RAAS continues to evolve.[27] The 2 pathways of the RAAS are essentially mirror images, interconnected and sharing several components, such that after the proinflammatory pathway has been activated, the direction of activity can switch and proceed instead down the anti-inflammatory

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pathway at multiple sites. Angiotensin II, long known to produce extraordinarily proinflammatory effects by binding to AT1R,[24] can also bind to a more recently discovered receptor for AT2R. The binding of Ang II to AT2R produces an entirely different effect than is created by its binding to AT1R, with strongly anti-inflammatory effects. Angiotensin II can no longer be viewed as a proinflammatory peptide as it has the potential to produce anti-inflammatory effect, depending on which receptor it binds to. In the setting of a proinflammatory dysregulated RAAS, its proinflammatory effects will clearly predominate.

In its menopausal, proinflammatory state, Ang II stimulation of AT1R promotes vasoconstriction, yet when activated, AT2R counters the vasoconstriction, creating a vasodilatory effect. These balancing and opposing actions of Ang II on its receptors AT1R and AT2R provide considerable physiologic flexibility, facilitating enhanced survival by up-regulating the proinflammatory pathways when threatened by a pathogen or trauma, followed by inflammation restoration of cardiometabolic homeostasis when the threat is neutralized, as well as maintaining homeostasis when no threat exists.[28] Without physiologic levels of E2, the proinflammatory RAAS pathway dominates, even when circumstances should dictate otherwise. Estradiol has emerged as a powerful immunomodulator that interacts with the RAAS to facilitate its functionality.[29] This knowledge provides a strong foundation supporting the use of E2 with menopausal women.

PROINFLAMMATORY RAAS PATHWAY AND ESTROGEN

Women have robust immune systems; during the reproductive years, they have higher survival rates compared with men after trauma or sepsis. When infection or trauma occurs, survival necessitates the initiation of a robust inflammatory response, triggered, in part, by activation of the proinflammatory RAAS pathway.[30] Innate immune cells produce inflammatory cytokines and toxins directed at pathogens. Chemokines alert leukocytes to amass at infection sites. Vascular permeability increases, enabling leukocytes to travel to, disable, and phagocytose pathogens in areas of infection.[31] Extracellular matrix tissue remodeling facilitates movement of cells to wall off infection and to repair the damage. Blood pressure must be maintained, facilitated by vasoconstriction and fluid retention. Increased coagulability aids in tissue remodeling to wall off infection and to reduce blood loss in the event of trauma.[32]

Inflammation is often understood as a negative, but the inflammatory response is essential and lifesaving. A powerful initial inflammatory response to any invading pathogen, which includes severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is essential for a positive outcome.[33] This initial inflammatory response is substantially governed by the proinflammatory arm of the RAAS, the renin—ACE—Ang II pathway. The conversion of Ang I to Ang II through ACE can occur in lung capillaries and vascular structures of the kidneys, brain, heart, and skeletal muscle. In its proinflammatory role, Ang II exerts strong vasopressor activity and initiates numerous inflammatory effects.[34] It increases expression of nuclear factor κB (NF-κB), a transcription factor that regulates gene expression of inflammatory cytokines and chemokines, including many interleukins, such as interleukin 6. Angiotensin II also regulates inducible nitric oxide, which increases reactive oxygen species.[35] Angiotensin II can be degraded to Ang III and Ang IV, which produce additional proinflammatory effects.[36] The innate immune system is tasked to immediately respond to infections and tissue injury. Macrophages play a critical role in the immune inflammatory response and have estrogen receptors and ACE, which together facilitate the initiation of the immune cells' inflammatory responses.[37,38]

Estradiol influences the cascade of inflammatory processes triggered by Ang II. Cells with E2 receptors, in addition to macrophages and other immune cells that are targeted by Ang II, include endothelial cells and platelets. Estradiol modulates the entirety of inflammatory responses triggered

by the RAAS, including clotting factors, enzymes involved in tissue remodeling, growth factors, and adhesion molecules. In the initial stages of infection, E2 triggers a rapid activation of NF-κB, alters levels of chemokines, and up-regulates interferon-γ. Interferon-γ increases inducible nitric oxide and cyclooxygenase 2, activates T lymphocytes, and is the most potent activator of macrophages.[39] These powerful immune responses to invading pathogens led many researchers to recognize that women have higher survival rates with SARS-CoV-2 infections in large measure because of their high E2 levels.[40]

Estradiol has strong modulating effects on the RAAS, including increasing levels of angiotensinogen, the precursor to Ang I, which can be converted to Ang II by ACE and subsequently through AT1R can incite proinflammatory effects when appropriate. In most tissues, while ACE is actively converting Ang I to Ang II, E2 simultaneously down-regulates the production of ACE to moderate the state of inflammation.[10] ACE reduces bradykinin, a component of the kallikrein-kinin system, by inducing its conversion to an inactive form.[41] Bradykinin has CV health benefits by promoting vasodilation and induction of protective nitric oxide production. By naturally reducing ACE, E2 supports the CV health benefits afforded by increased levels of bradykinin.[34] In this manner, E2 can dampen the proinflammatory response, preventing it from becoming too extreme. However, unique to the endothelium, E2 can increase ACE levels, facilitating the vascular endothelium to be particularly capable of rapidly developing a proinflammatory state.[42] This special endothelial response facilitates the important role played by the vascular endothelium during an acute systemic infection to transform the endothelium to support rapid leukocyte transmigration across the endothelium to the site of infection. Once immune cells arrive on site, E2 promotes the proinflammatory functions of phagocytosis to engulf and eliminate the pathogen and subsequently supports the resolution of the infection and healing of the damaged tissue. Interestingly, E2 can also stimulate an increase in ACE expression in the endothelium that can influence subsequent anti-inflammatory effects,[42] clearly demonstrating the complexities of and the important role of E2 in this process.

As described, ACE can initiate proinflammatory immune functions beyond facilitating the production of Ang II, functions involving innate and adaptive immune responses that modulate macrophage and neutrophil actions. ACE up-regulates immune cell functions, enhancing their ability to neutralize a pathogen. This newly discovered function of ACE, which is modulated by E2, adds to the robust immune response of young, reproductive-aged women,[43] no doubt contributing to their superior outcomes from trauma and infections compared with men. Understanding this key role of ACE adds a note of caution to the use of ACEIs. Hypothetically, in the event of an infection, ACEIs may create a dual problem—compromising the innate immune system's robust proinflammatory response and potentially also impairing the anti-inflammatory response.[43]

The proinflammatory arm of the RAAS is clearly essential to the successful fight against invading pathogens and trauma.[31] Whereas an inflammatory response is essential to survival, sustained or exaggerated inflammation is extraordinarily harmful. The critically important process of switching from a proinflammatory to an anti-inflammatory state requires adequate E2 (Figure 1). The process of rapidly initiating and balancing the 2 pathways must be based on specific needs of the body. Estradiol can be viewed as a switch, facilitating the rapid transition from one state to the other (Figure 2).

ESTRADIOL SWITCH AND RAAS ANTI-INFLAMMATORY PATHWAY

The 2 interconnected RAAS pathways, proinflammatory and anti-inflammatory, share several constituents and are both modulated by E2.[2] The same peptides and enzymes critical for the inflammatory response function within the anti-inflammatory pathway. The RAAS inflammatory peptides can also support the anti-inflammatory pathway; therefore,

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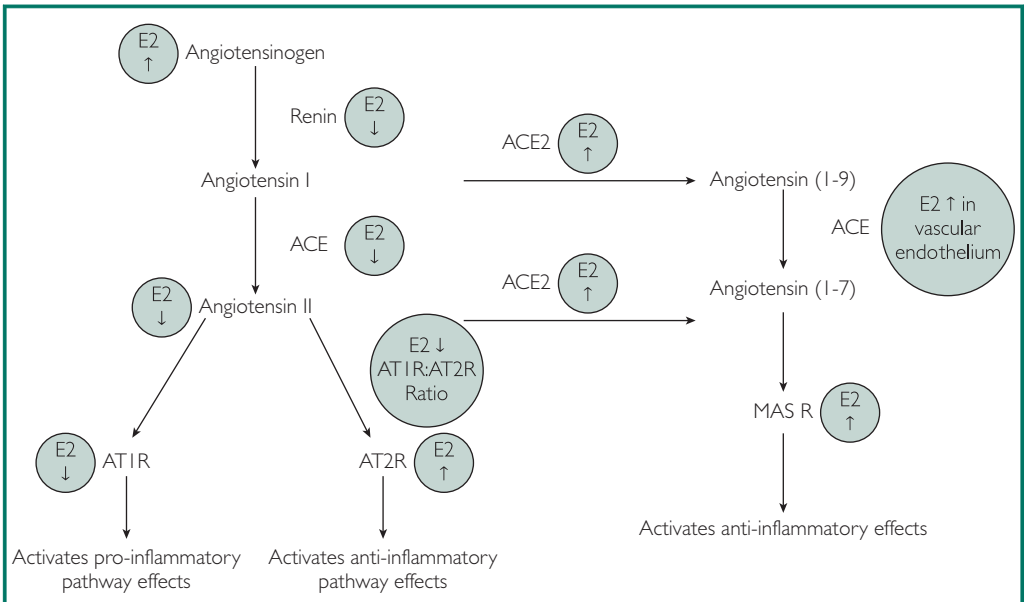

FIGURE 1. Mechanisms involved in cardioprotection: estradiol (E2) and the renin-angiotensin-aldosterone system (RAAS). Estradiol functions as an immunomodulator of the RAAS. It helps facilitate the initiation of the robust inflammatory response needed if infection or trauma occurs by supporting the activation of the proinflammatory RAAS pathway and subsequently supports the "switch" to facilitate the activation of the anti-inflammatory RAAS pathway to promote healing, inflammation resolution, and restoration of homeostasis. AT1R, angiotensin 1 receptor; AT2R, angiotensin 2 receptor.

pharmaceuticals that reduce the function of a "classically" proinflammatory RAAS enzyme, peptide, or receptor could potentially have the unintended effect of impairing the anti-inflammatory pathway.

The principal pathway of the anti-inflammatory RAAS consists of ACE2—Ang (1-7)—Mas receptor (MasR). As previously stated, new research reveals a greater complexity. The primary enzyme of the anti-inflammatory RAAS pathway is ACE2, a homologue of ACE. ACE2 drives the production of multiple anti-inflammatory products that are essential to inflammation resolution and CV health.[1] Mice bred to have no ACE2 function develop cardiomyopathy with hypertrophy, increased oxidative stress, elevated collagenase, inflammation with neutrophil infiltration, and high levels of inflammatory cytokines[44,45]; however, with the addition of E2, the blood clotting propensity was reduced in vascular endothelium, and the myocardium was better protected.[46]

Not only has Ang II been found to be proinflammatory, but it is a critical substrate for the RAAS anti-inflammatory pathway.[47] Angiotensin II can be converted by ACE2 into Ang (1-7), the primary peptide of the anti-inflammatory pathway.[48] Angiotensin II additionally has anti-inflammatory effects by binding to AT2R, which antagonizes AT1R activation and creates anti-inflammatory effects, providing a more nuanced view of Ang II. Understanding this bimodal path of Ang II is essential to understanding potential pitfalls of current ACE inhibition and for the development of optimal therapeutic approaches.[30]

ACE2 has additional anti-inflammatory functions, transforming Ang II to the anti-inflammatory peptide Ang (1-9). Angiotensin (1-9) can bind to the anti-inflammatory—inducing AT2R, protecting the heart and blood vessels from adverse CV remodeling associated with heart failure and HTN. Angiotensin (1-9) can subsequently be converted to the even more anti-inflammatory peptide Ang (1-7) by ACE.[49] Angiotensin (1-7) inhibits cell growth, improves insulin sensitivity, is antiarrhythmogenic, and has antithrombotic effects. It suppresses the

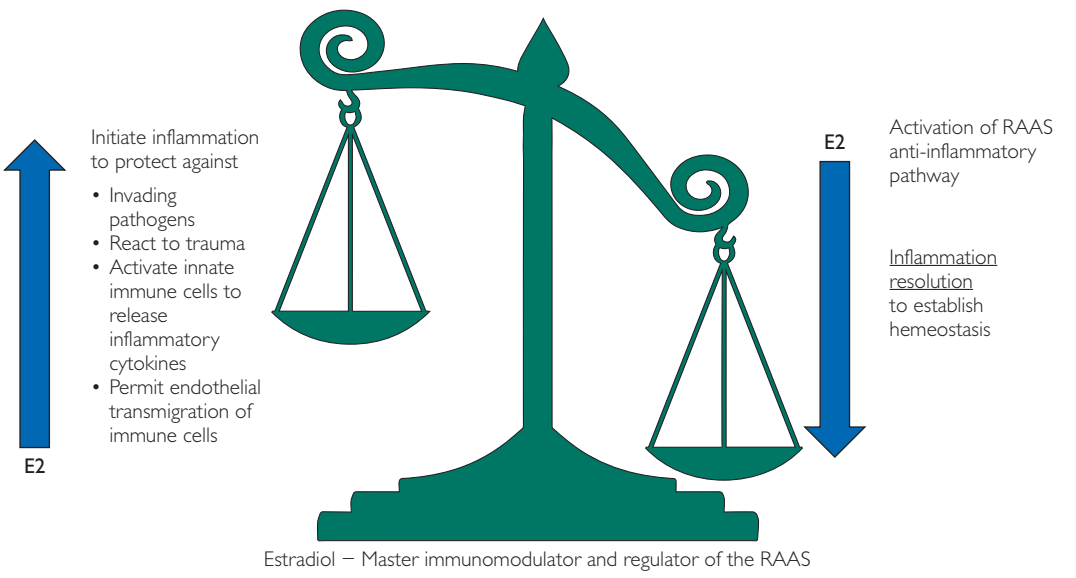

FIGURE 2. Activation of the renin-angiotensin-aldosterone system (RAAS) proinflammatory pathway. Maintaining the proper balance between the proinflammatory and anti-inflammatory pathways of the RAAS is facilitated in women during the reproductive years by physiologic levels of ovarian-produced estradiol. After menopause, when the female body suffers from a state of estrogen deficiency, the RAAS becomes imbalanced and becomes a proinflammatory system, which threatens the health status of the cardiovascular system.

NF-κB pathway, shutting down its production of inflammatory cytokines. Angiotensin (1-7) also works through the MasR to down-regulate inflammation through metabolic products that create antifibrotic, vasodilatory, BP-lowering, and antiproliferative effects.[50] ACE2, Ang (1-7), and the MasR have been isolated from multiple tissues, including endothelial tissue and myocardium.[51] The RAAS is a complex modulating system that, although previously seen as highly proinflammatory, retains both proinflammatory and anti-inflammatory roles.[30] The 2 pathways of the RAAS perfectly balance and complement each other to facilitate health and survival.

Recognizing the critical necessity to balance the proinflammatory and anti-inflammatory arms of the RAAS facilitates an appreciation for the myriad ways in which E2 functions to modulate the RAAS in addition to the profound potential for harm when it is deficient within the female body during the PM years. The role of E2 in the initiation of the immune system's proinflammatory response involving immune cells was discussed, facilitating a robust immune response. Regarding its support of the anti-inflammatory response, E2 up-regulates the expression of ACE2, enhancing its functionality and increasing expression of the AT2R and the MasR, further enhancing production of anti-inflammatory products and peptides. In studies of female mice, E2 was found to modulate the magnitude of the Ang (1-7) vasodilatory response.[52] Further supporting the critical role of E2, the vasodilatory effect of Ang (1-7) was absent in the aorta of old female rats, but a full response to Ang (1-7) was found in the vessels of young females that had physiologic levels of estrogen.[53] Supporting the supposition that HRT would be beneficial in PM women, replacing E2 in the old female rats restored the vasodilatory effect, normalized receptor functions and levels of nitric oxide, and lowered the production of reactive oxygen species.[54,55]

Estradiol further enhances the RAAS anti-inflammatory pathway, dramatically

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decreasing expression of AT1R and redirecting Ang II to bind with AT2R, which reduces the proinflammatory impact of Ang II and enhances the promotion of an anti-inflammatory state.[56] Estradiol also lowers the levels of the enzyme renin, reducing its actions on angiotensinogen to produce Ang I, the precursor to Ang II.[34] Adding to the complexity, E2 increases angiotensinogen production.[57] It is a possibility that the ratios of renin and angiotensinogen may influence the E2 switch, steering the system to the appropriate pathway. In overview, greater amounts of E2 result in higher levels of ACE2, angiotensinogen,[57] AT2R, Mas, Ang (1-7), and Ang (1-9) and simultaneously lower levels of renin and AT1R. In most tissues, ACE levels also decrease, thereby lowering Ang II production.[6] In the endothelium, where ACE may increase, under the influence of E2, higher amounts of Ang II could act as an anti-inflammatory agent, converted by ACE2 to Ang (1-7).[42] In this manner, E2 can modify and lower the Ang II—Ang (1-7) ratio, promoting inflammation resolution and tissue healing.

Animal studies further illuminate the benefits of E2 and the implications to health when E2 is deficient. Estradiol depletion in rats resulted in severe HTN, left ventricular cardiac remodeling, diastolic dysfunction, and oxidative stress. Estradiol treatment limited these many adverse events, in part through modulation of the RAAS. Estradiol treatment reduced cardiac fibrosis, improved myocardial relaxation, and blocked the rise in cardiac Ang II that occurred without E2 treatment.[58] Other rodent studies documented the benefits of E2 on high BP and its reduction of oxidative stress and impact on increased levels of nitric oxide.[59] When long-term Ang II infusions were given, greater increases in BP resulted in ovariectomized female mice and in those receiving an estrogen receptor antagonist compared with estrogenized mice. In mice without estrogen, when an infusion of E2 was given to the central nervous system, there was a reversal of the negative effect of Ang II on BP.[60]

In support of hormonal therapy for PM women, E2 therapy has been found to lower systemic inflammation by lowering systemic ACE, reducing conversion of Ang I to Ang II, and down-regulating the AT1R in the kidney.[61]

Chronic low-grade systemic inflammation and oxidative stress underlie most diseases associated with aging.[62] Estradiol deficiency and a dysregulated RAAS are important contributors to the process of female aging. Although more human data are warranted, animal data document that providing E2 attenuates the low-grade inflammation and oxidative stress due to E2 deficiency.

CURRENT KNOWLEDGE AND FUTURE DIRECTIONS

A growing body of scientific data confirms the essential role of E2 in the function of the CV system and of the role of E2 as an immunomodulator that influences the RAAS switch and its proinflammatory and anti-inflammatory status.[63] Without physiologic levels of E2, the RAAS tends to remain in a dysfunctional proinflammatory state. Chronic low-level systemic inflammation is a driver of endothelial dysfunction, vascular disease, myocardial remodeling, myocardial dysfunction, and a variety of arrhythmias.[64] The dysregulated RAAS is also associated with an impaired response to an infectious pathogen.[12] There is a marked difference in the immune response of older PM women compared with young, reproductive-aged women as loss of ovarian E2 is an important contributor to that altered response.[65] The dysregulated RAAS is a primary target of current therapeutics, which focus on blocking portions of the RAAS, conferring clear therapeutic benefits; but this approach also possesses inherent risks of inadvertently altering the anti-inflammatory pathways that have more recently been delineated.[66] Studies on ACE inhibitors and ARBs have reported a variable impact on ACE2 expression ranging from increase or decrease to no effect on ACE2 levels.[66]

In women who develop vascular cardiac dysfunction or HTN, combining E2 treatment with a pharmaceutical that modulates the RAAS may create a synergy that offers the

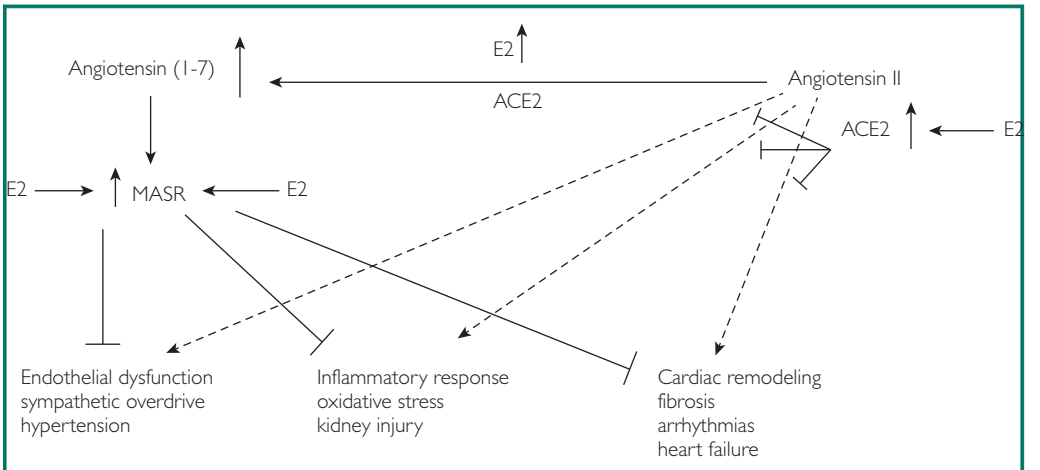

FIGURE 3. Mechanisms involved in cardioprotection: estradiol (E2) and the renin-angiotensin-aldosterone system (RAAS). Estradiol supports the anti-inflammatory pathway of the RAAS to reestablish and to maintain homeostasis by facilitating the action of certain RAAS enzymes and receptors while blocking others.

potential to ameliorate the harms of RAAS dysregulation that occur during the PM years.[67] There is a need for more sex-specific research with PM women and the use of ACEIs and ARBs. The ACEIs block the ability of ACE to produce Ang II, which could hypothetically impair either the proinflammatory or anti-inflammatory pathway of the RAAS and reduce the ability of immune cells to fight invading pathogens. Studies have suggested that in PM women with HTN, ARBs may be a better option than ACEIs,[68] especially when combined with E2.[69]

Estradiol may be sufficient for many women, but if HTN occurs, the synergistic combination of E2 and ARBs holds the promise of helping many PM women with HTN and CVD to optimize their health. Future studies involving pharmaceuticals that have an impact on the RAAS to address HTN and CVD need to be sex specific, and these pharmaceuticals should be studied both with and without E2 therapy. On the basis of current data showing long-term safety with the use of transdermal E2 and oral progesterone, healthy, newly PM women should be offered human-identical HRT as a preventive step to thwarting the otherwise inevitable development of a dysregulated RAAS.[70] It is important when HRT is prescribed that the use of oral estrogens and progestins be avoided, as it is their use that increases the risk of breast cancer and thromboses.[71] When physiologic doses of human-identical hormones are used, accompanied by an optimal lifestyle, PM women are provided with the greatest potential for managing the RAAS and achieving healthy longevity (Figure 3).

We are currently in a pandemic with SARS-CoV-2. Although deaths are fewer at this time, many in the United States have declined receiving the vaccine, and there remains a dire shortage worldwide. Postmenopausal women will undoubtedly continue to perish from the COVID-19 pandemic. The knowledge we have gained concerning the impact of E2 on the female immune system and its interactions with the RAAS should be immediately used clinically. Physiologic levels of E2 are likely to enhance survival.[72] Postmenopausal women within 10 years of menopause onset should be considered for initiation of transdermal E2 and oral progesterone, even if they have received a vaccine. If possible, further studies on even older women using PM HRT should be initiated.

Considering previous research, an attempt should be made to determine whether an ARB is safer than an ACEI in

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women, should an infection occur with SARS-CoV-2. Many studies have looked at ACEI and ARB in patients with SARS-CoV-2 infections, and the data appear reassuring.[73] Nevertheless, data have not always clearly separated results by the sex and menopausal status of the study participant.

CONCLUSION

The RAAS consists of a complex and dynamic set of counterbalancing pathways with overlapping peptides and enzymes that have proinflammatory or anti-inflammatory effects, often varying on the basis of circumstances and E2 status. A deficiency of E2 results in the RAAS becoming stuck in the proinflammatory pathway, potentiating a state of chronic systemic inflammation and a reduced immune response to an infectious pathogen, increasing adverse outcomes. After the onset of menopause and loss of ovarian E2 production, PM women have high rates of HTN and CVD and increased mortality from invading pathogens causing infections.

For healthy immune function and metabolic homeostasis, maintaining an optimal RAAS would be preferred to the option of attempting to disable portions of it. Replacing E2 at physiologic levels offers a viable solution to the inevitable PM dysregulation of the RAAS. Understanding the connection between the immunomodulating role of E2 and the dual pathways of the RAAS unlocks a great potential for PM women to preserve CV health through physiologic dosing with human-identical hormones and to reduce the loss of life after trauma or infections.

Abbreviations and Acronyms: **ACE,** angiotensin-converting enzyme; **ACEI,** angiotensin-converting enzyme inhibitor; **Ang,** angiotensin; **ARB,** angiotensin receptor blocker; **ACE2,** angiotensin-converting enzyme 2; **AT1R,** angiotensin I receptor; **AT2R,** angiotensin 2 receptor; **BP,** blood pressure; **CV,** cardiovascular; **CVD,** cardiovascular disease; **E2,** estradiol; **HTN,** hypertension; **HRT,** hormone replacement therapy; **MasR,** Mas receptor; **NF-κB,** nuclear factor κB; **PM,** postmenopausal; **RAAS,** renin-angiotensin-aldosterone system; **RAS,** renin-angiotensin system; **SARS-CoV-2,** severe acute respiratory syndrome coronavirus 2

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