

Sex Differences in Hypertension Recent Advances

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Hypertension is a complex disorder involving multiple organ systems and the primary modifiable risk factor for heart disease, which is the leading cause of death among both men and women in the United States. Although both men and women develop hypertension, distinct gender differences in the incidence and severity of hypertension are well established where men have a higher incidence of hypertension compared with women of the same age until the sixth decade of life.^{1,2} Despite gender differences in human hypertension, the treatment guidelines do not differ by gender.³ The first goal of this review is to examine the clinical data to determine whether this is appropriate, with the remainder of the review focused on basic science research implicating a role for the immune system in mediating sex differences in hypertension.

Should Blood Pressure Guidelines Be Gender Specific?

The Institute of Medicine defined the term sex to classify subjects as men or women according to biology/genetics and the chromosomal complement of the individual. In contrast, the term gender includes socially constructed characteristics and the individual's self-representation as male or female.⁴ In clinical studies, participants are asked to self-identify as men or women. For this reason, the term gender will be used throughout this review when referring to clinical studies, and sex will be used to refer to basic science studies examining males versus females based on phenotype.

A recent study examined age-adjusted awareness, treatment, and blood pressure (BP) control rates among hypertensive men and women from 2003 to 2004 through 2011 to 2012.¹ Awareness of hypertension increased in both men and women during this time period, with the greatest increase in awareness reported in women. Although women were less aware of their hypertension at the beginning of the study, they surpassed men's awareness by the end of the study. One potential stimulus for this increase in awareness among women could be the successful Go Red for Women campaign established by the American Heart Association in 2004 to raise awareness of heart disease and stroke as the number one cause of death among women. In addition, the percent of individuals treated for their hypertension increased from 2003 to 2012, and again this increase was greater in women. Most importantly, however, the increase in treatment was associated with an increase in the percent of hypertensive patients

who achieved BP controlled to the recommended levels from $\approx 43\%$ to 49% in men and from $\approx 37\%$ to 56% among women. Although this reflects a large improvement in the numbers of individuals with controlled BP, this still leaves almost half of the hypertensive population at increased risk for adverse cardiovascular events.

The authors further broke the data down to examine the numbers of men and women with optimal BP, prehypertension, stage I hypertension, and stage II hypertension over the same time frame (2003–2012). Interestingly, the percent of women with prehypertension increased from $\approx 25\%$ to 37% , whereas the percent of men defined as prehypertensive remained constant at $\approx 29\%$. In contrast, more men have stage 1 hypertension than women. The incidence of stage 2 hypertension was relatively comparable between the sexes in 2012 ($\approx 11\%$ versus 13% in men and women, respectively) although this reflects a decrease in the number of women with stage 2 hypertension since 2003 ($\approx 13\%$ versus 23% in men versus women). These findings are indicative of 2 noteworthy trends in hypertension. First, women are more likely to be prehypertensive than men. Second, we are making progress in the treatment and control of hypertension, but we still have a long ways to go. For this study, controlled hypertension was defined as systolic BP of <140 mmHg and diastolic BP of <90 mmHg, which raises 2 important questions: (1) Is this an adequate decrease in BP to allow for optimal decreases in cardiovascular disease risk? (2) Should controlled BP be defined the same in both genders?

The most recent recommendations for the management of hypertension were published in 2014. Although there are age-dependent recommendations for BP goals, the guidelines remain the same irrespective of gender, despite the abundance of evidence supporting sex and gender differences in hypertension.³ The recent findings of SPRINT (Systolic Blood Pressure Intervention Trial) found that more aggressive BP control results in improved health outcomes.⁵ SPRINT was a multicenter, randomized clinical trial of patients aged ≥ 75 years randomized to an intensive treatment group (systolic BP target of <120 mmHg) or standard treatment group (systolic BP target of <140 mmHg). Individuals in the intensive treatment group had a $\approx 25\%$ greater reduction in cardiovascular events compared with those in the standard treatment, supporting a beneficial effect for aggressive BP control. However, whether there are gender-specific implications for SPRINT remains unknown. Although SPRINT planned to clarify

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(*Hypertension*. 2016;68:1322-1327. DOI: 10.1161/HYPERTENSIONAHA.116.06602.)

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Hypertension is available at <http://hyper.ahajournals.org>

DOI: 10.1161/HYPERTENSIONAHA.116.06602

optimal BP management in both men and women, female enrollment was only $\approx 36\%$ (77 women in the intensive treatment group versus 166 men; 89 women in the standard treatment group versus 230 men), the number of cardiovascular events in enrolled women was below that seen in the general population, and the study was terminated early because of the clear benefits of more aggressive BP control among men.^{5,6} As a result, none of the outcome differences in women reached statistical significance, and no conclusions could be drawn on the effectiveness of intensive BP control in women.

The potential for more aggressive BP control to improve cardiovascular outcomes becomes of even greater interest if there are gender differences in the relationship between elevations in BP with the impact of hypertension on end-organ damage. Boggia et al⁷ assessed the absolute and relative risks associated with conventional and ambulatory BP measurements and cardiovascular complications in men ($n=4960$) and women ($n=4397$). In both genders, 24-hour ambulatory and conventional daytime and nighttime systolic BPs were significant predictors of cardiovascular events. However, women had a significantly higher risk of a cardiovascular event in relation to 24-hour ambulatory systolic BP and nighttime systolic BP compared with men. As a result, women exhibited a steeper increase in risk of a cardiovascular event with increases in BP than men and had a higher proportion of potentially preventable events. These findings suggest that women would have greater cardiovascular benefits from decreases in BP and imply that optimal BP is lower in women than in men. This is further supported by a prospective study of 3344 subjects (1626 women), which found a steeper relationship between higher ambulatory BP and cardiovascular disease risk in women than in men.⁸ This latter study concluded that the optimal outcome-based BP threshold for men was 135/85 mm Hg during the day and 120/70 mm Hg during the night, compared with 125/80 mm Hg during the day 110/65 mm Hg during the night for women. In contrast, a separate meta-analysis of 5018 people (2843 women) examining the relationship between conventional home BP measurements and 10-year cardiovascular risks in men and women and did not find significant differences between the genders.⁹ This discrepancy may be because of the different methods used to measure BP (frequent ambulatory BP measurements compared with isolated conventional BP measurements) or the time of day BP was recorded. Regardless, the data provide sufficient evidence to call into the question current guidelines recommending the same level of BP control in men and women and underscores the importance of continued research.

The remainder of this review is focused on the potential role of the immune system, specifically T cells, in mediating sex differences in hypertension.

Can T Cells Explain Sex Differences in BP Control?

The central role of T cells in the development of hypertension was first reported by Guzik et al¹⁰ using the Rag-1^{-/-} mouse model, which lacks mature B and T cells. Male Rag-1^{-/-} mice have a blunted hypertensive response to chronic angiotensin (Ang) II infusion and deoxycorticosterone acetate-salt compared with wild-type mice. Furthermore, adoptive transfer of

Pan T cells (CD2⁺CD3⁺), but not of B cells, restored the hypertensive effects of Ang II and deoxycorticosterone acetate-salt. This seminal study, reporting the link between T cells and hypertension, was published in 2007. However, it was not until 2012 that the first study was published examining sex differences in T cells in hypertension and not until 2014 that 2 studies were published back-to-back assessing sex differences in Ang II hypertension in male and female Rag-1^{-/-} mice (results summarized in Table 1).

It has been consistently reported across species and strains of rodents that males have greater increases in BP to Ang II than females.¹⁴⁻¹⁶ However, sex differences in Ang II hypertension are absent in Rag-1^{-/-} mice, and this seems to be mediated by an attenuation of Ang II hypertension in males.^{11,12} Consistent with the previous study,¹⁰ adoptive transfer of Pan T cells from a male donor to male Rag-1^{-/-} mice restored Ang II responses.^{11,12} In contrast, female Rag-1^{-/-} mice are resistant to Ang II–induced increases in BP after adoptive transfer of Pan T cells from a male donor,¹² and adoptive transfer of Pan T cells from a female donor did not increase Ang II hypertension in male Rag-1^{-/-} mice.¹¹ Additional studies extended these findings from total Pan T cells to CD4⁺ and CD8⁺ T cells.¹³ Similar as to what is observed with adoptive transfer of Pan T cells, male Rag-1^{-/-} mice exhibit increases in Ang II hypertension after adoptive transfer of either CD4⁺ or CD8⁺ T cells if the cells are from a male donor, with no change in BP if the T cells are from a female donor. These data provide critical insight about sex differences in BP control and support the hypothesis that T cells underlie sex differences in BP responses to Ang II. Specifically, male T cells in male experimental

Table 1. BP Response to Ang II in Rag1^{-/-} Mice Compared With Control

Recipient Sex	T-Cell Type	T-Cell Sex	Effect on BP	Source
M	Blunted hypertensive response	Guzik et al, ¹⁰ Ji et al, ¹¹ Pollow et al ¹²
F	Blunted hypertensive response	Ji et al, ¹¹ Pollow et al ¹²
M	Pan	M	Hypertensive response restored	Guzik et al, ¹⁰ Ji et al, ¹¹ Pollow et al ¹²
F	Pan	M	Blunted hypertensive response	Pollow et al ¹²
M	CD4 ⁺	M	Hypertensive response restored	Sandberg et al ¹³
M	CD4 ⁺	F	Blunted hypertensive response	Sandberg et al ¹³
M	CD8 ⁺	M	Hypertensive response restored	Sandberg et al ¹³
M	CD8 ⁺	F	Blunted hypertensive response	Sandberg et al ¹³

Ang II indicates angiotensin II; BP, blood pressure; F, female; and M, male.

animals are necessary for the development of a full hypertensive response to Ang II. Moreover, the attenuated hypertensive response to Ang II in females relative to males is mediated by both the whole animal and the female T cell because (1) male T cells do not alter BP in female animals and (2) female T cells do not exacerbate Ang II hypertension in the male. These findings suggest basic differences between the sexes in their immune systems and raise fundamental questions about how sex and hypertension impact the T-cell profile.

The adoptive transfer studies described above focused on the prohypertensive effects of CD3⁺, CD4⁺, and CD8⁺ T cells; however, there is growing evidence to support an antihypertensive role for T-regulatory cells (Tregs),¹⁷ and our group has consistently shown that hypertensive females have more Tregs than males (results summarized in Table 2).^{18,19} We first published a sex difference in the renal T-cell profile in 2012²¹; male spontaneously hypertensive rats (SHR) have a greater population of proinflammatory Th17 cells, whereas female SHR have more anti-inflammatory Tregs. Follow-up studies explored the mechanism responsible for sex differences in the renal T-cell profile by examining the roles of sex hormones and BP.²² Sex hormones are anti-inflammatory in both sexes, indicating that sex hormones cannot explain sex differences in the T-cell profile. To determine whether increases in BP affect the renal T-cell profile, male and female SHR were treated with hydrochlorothiazide and reserpine from 6 to 12 weeks of age to prevent the age-related progression of hypertension or from 11 to 13 weeks of age to reverse established hypertension; both lowering BP and abolishing the sex difference in BP eliminated the sex difference in Tregs. Based on the established role for Tregs to lower BP and protect against cardiovascular injury in male experimental animal models of hypertension,¹⁷ we hypothesize that increases in Tregs with

increases in BP is a compensatory protective mechanism in females to limit increases in BP.

With this in mind, could sex differences in the T-cell profile explain sex differences in Ang II hypertension in Rag-1^{-/-} mice? If Tregs represent a greater proportion of the Pan T-cell profile in females, this could explain the lack of a BP response to Ang II when the T-cell donor is female. Similarly, if the cytokine environment of the female promotes greater Treg formation after adoptive transfer, this could explain the attenuated increase in BP if the recipient mouse is female. Tregs were measured in spleen, kidney, and brain after adoptive transfer of male Pan T cells into male and female Rag-1^{-/-} mice¹² and in blood, perivascular adipose tissue, and kidneys of male Rag-1^{-/-} mice after adoptive transfer of Pan T cells from either a male or female donor.¹¹ Although splenic and whole-brain Tregs were comparable in control male and female Rag-1^{-/-} mice after Pan T-cell adoptive transfer, males had greater renal Tregs than females after adoptive transfer of Pan T cells from a male donor. Because the donor was male in both cases, it is assumed that comparable numbers of Tregs were transferred into the hosts. Therefore, the finding that the male host/male donor combination yielded more Tregs in the kidney is intriguing and could call into question the stability of male Tregs in a female environment. This becomes an even more interesting question to ponder when changing the sex of the donor as opposed to that of the host. Tregs were again comparable in perivascular adipose tissue and kidney of male Rag-1^{-/-} regardless of the sex of the T-cell donor; however, wild-type female mice had more splenic Tregs than male mice so it could be assumed that more Tregs were transferred into the male if the T-cell donor was female. If this is true, the lack of a sex difference after adoptive transfer could reflect a loss of female Tregs in the male environment. Consistent with this, male Rag-1^{-/-} mice had more splenic Tregs after adoptive transfer of Pan T cell from a male donor than from a female donor. However, more studies are needed to directly assess the viability of male and female Tregs in the opposite sex. It would be interesting to know whether adoptive transfer of female Tregs into male and female Rag-1^{-/-} mice results in greater Treg infiltration in females.

Alternatively, proinflammatory, prohypertensive T cells could represent a greater proportion of the Pan T-cell profile in males, and the male environment and Ang II could promote the formation and differentiation of more proinflammatory T cells after adoptive transfer. Consistent with what was observed with Tregs, the total numbers of splenic and whole-brain CD3⁺, CD4⁺, and CD8⁺ T cells were comparable in control male and female Rag-1^{-/-} mice after Pan T-cell adoptive transfer from male donors, confirming comparable T-cell engraftment in both sexes.¹² However, males had greater T-cell counts in the kidney (CD3⁺, CD4⁺, and CD8⁺ T cells) and SFO-region of the brain (CD3⁺ T cells) than females. Ang II had no effect on T-cell counts in either sex. In addition, male Rag-1^{-/-} mice that received Pan T cells from a female donor had more splenic total T cells (CD3⁺) and more CD3⁺, CD4⁺, and CD8⁺ T cells in peripheral blood and perivascular adipose tissue after Ang II infusion than if the donor T cells were from a male¹¹; there were no differences in renal T cells based on sex of the T-cell donor. Together, these data could

Table 2. Sex Differences in T Cells

Strain	Tissue	Sex Effect on T Cells	Source
Sprague–Dawley Rats: vehicle and Ang II	Kidney	Males have more CD3 ⁺ T cells, CD4 ⁺ T cells, and Th17 cells; females have more Tregs	Zimmerman et al ²⁰
SHR	Blood	Males have more Tregs; females have more CD3 ⁺ T cells, CD4 ⁺ T cells, and Th17 cells	Tipton et al ²¹
SHR	Kidney	Males have more CD3 ⁺ T cells, CD4 ⁺ T cells, and Th17 cells; females have more CD8 ⁺ T cells and Tregs	Tipton et al ^{21,22}
SHR+6 wk HCTZ/reserpine	Kidney	Males have more Th17 cells; females have more CD8 ⁺ T cells	Tipton et al ²²
SHR+2 wk HCTZ/reserpine	Kidney	No sex differences	Tipton et al ²²
WKY	Kidney	No sex differences	Tipton et al ²²

Ang II indicates angiotensin II; HCTZ, hydrochlorothiazide; SHR, spontaneously hypertensive rats; and WKY, Wistar Kyoto rat.

be interpreted as male sex, not male T cells, as the deciding factor dictating a proinflammatory immune response, which is consistent with the lack of an increase in Tregs in male mice receiving T cells from a female donor.

Despite the lack of a sex difference in the numbers of proinflammatory T cells after Ang II infusion, the combination of male sex and male T cells was associated with the greatest increases in BP.^{11,12} This suggests a sex difference in the activation status of T cells before and after Ang II infusion. Indeed, Ang II increased proinflammatory cytokines in kidneys of male, but not of female Rag-1^{-/-} mice after adoptive transfer of Pan T cells from a male donor; alterations in T-cell function could account for the increase in Ang II hypertension only in the male.¹² Moreover, although male Rag-1^{-/-} mice had greater increases in T cells if the donor was female, they exhibited greater increases in the proinflammatory cytokines tumor necrosis factor- α and interleukin (IL)-17 in the spleen when the Pan T-cell donor was male,¹¹ further supporting the notion that the combination of male sex and male T cells promotes the most proinflammatory and prohypertensive response. Likewise, this suggests that T cells from females are resistant to the proinflammatory effects of Ang II. Based on known sex differences in the renin-angiotensin system (RAS), it is not unreasonable to hypothesize that not only do T cells underlie sex differences in response to Ang II but also the RAS underlies sex differences in T cells, resulting in a complex interplay between these 2 key systems that regulate overall cardiovascular health.

Do Sex Differences in the RAS Drive Sex Differences in the Immune Response?

There are well-established sex differences in the RAS where males have greater expression levels and physiological responses to activation of the classical RAS (Ang II, angiotensin type 1 receptor [AT₁], and angiotensin-converting enzyme), whereas females have greater expression and physiological responses to activation of the nonclassical RAS (Ang [1-7], angiotensin type 2 receptor [AT₂], mas receptor, and angiotensin-converting enzyme 2).¹⁴⁻¹⁶ Many recent studies have focused on the role of the AT₂ receptor in the control of BP and renal function. Greater AT₂ expression in females compared with males is dependent on both estrogen and sex chromosome complement,²³ and there is growing evidence to support a sex-specific role for the AT₂ receptor in offering cardiovascular protection to females.

The AT₂ receptor plays a critical role in regulating pressure-natriuresis by controlling sodium excretion. Blockade of the AT₂ receptor results in a comparable rightward shift in the pressure-natriuresis relationship in male and female Sprague-Dawley rats, but decreases the autoregulation of renal blood flow and glomerular filtration rate and enhances renal vasoconstrictor responses to Ang II only in female rats,²⁴ supporting a sex-specific role for the AT₂ receptor in the control of renal function. Further studies utilizing AT₂ receptor knockout mice explored the impact of the AT₂ receptor on BP and tubuloglomerular feedback in response to Ang II infusion in male and female mice.²⁵ Male wild-type mice have greater increases in BP and tubuloglomerular feedback after Ang II infusion compared with female mice and this sex difference was abolished

in AT₂ receptor knockout mice, indicating a critical role for the AT₂ receptor to offer cardiovascular protection to young females. Further supporting this hypothesis, graded infusion of the AT₂ receptor agonist, Compound 21 (C21), increased renal blood flow and sodium excretion in female SHR with no effect on BP or glomerular filtration rate, implying a direct impact of AT₂ receptor activation on renal tubular function; C21 did not affect any of these parameters in male SHR.²⁶

Despite growing evidence to support functional and physiological differences in AT₁- and AT₂-mediated control of cardiovascular and renal function in males versus females, much less is known on how these differences impact events downstream of receptor activation, including the impact on inflammation. Ji et al¹¹ began to directly examine the possibility that sex of the T cell is an important determinant of the direction and magnitude of the inflammatory response to Ang II using isolated, activated lymph node cells from male and female wild-type mice. Under Th17-polarizing conditions *in vitro*, Ang II increased IL-17A and tumor necrosis factor- α levels in male T cells, but decreased these cytokines in T cells from females, suggesting that Ang II has sex-specific effects on T cells selectively increasing the proinflammatory cytokines in males. Therefore, greater activation of the classical RAS in males may be promoting this proinflammatory profile.

Greater expression and activation of the nonclassical RAS, and the AT₂ receptor in particular may promote a more anti-inflammatory immune profile in females. Although this has not been directly examined, there is evidence supporting an anti-inflammatory role for the AT₂ receptor. Treatment of human kidney proximal tubule epithelial cells with C21 dose-dependently increases the anti-inflammatory cytokine IL-10 and attenuates lipopolysaccharide-induced release of the proinflammatory cytokines tumor necrosis factor- α and IL-6.²⁷ Moreover, treatment of male obese Zucker rats with C21 reduces plasma and renal cortical tumor necrosis factor- α and IL-6 levels, as well as renal monocyte/macrophage infiltration. Although C21 did not increase IL-10 levels in these rats, treatment with an AT₂ receptor antagonist decreased circulating and renal IL-10. Similarly, C21 attenuates renal inflammation in diabetic male mice,²⁸ supporting an anti-inflammatory role for the AT₂ receptor in male experimental animals. Based on the more prominent role of the AT₂ receptor in the control of cardiovascular and renal health in females compared with males, it is feasible that the enhanced anti-inflammatory profile in females is related to greater AT₂ receptor expression in females. Studies are needed to directly test this hypothesis.

In addition, recent studies have also implicated AT₁ receptors on T cells in Ang II-mediated hypertensive injury. Male mice genetically deficient in the AT₁ receptor on T cells have exacerbated kidney injury in response to Ang II infusion, without any further effect on BP.²⁹ Furthermore, *in vitro* studies reported an increase in proinflammatory cytokine release from T-cell AT₁ receptor^{-/-} male mice compared with the wild-type mice, indicating that chronic Ang II treatment suppresses Th1 cytokine production in an AT₁ receptor-dependent manner. These data suggest a beneficial role for T-cell AT₁ stimulation in males that is independent of BP. Although little is known about the role of AT₂ receptors on T cells in Ang II hypertension, intramyocardial injection of T cells expressing

the AT₂ receptor reduced infarct size and improved cardiac performance post myocardial infarction in male rats suggesting a beneficial role for T-cell AT₂ receptors in cardiovascular disease as well.³⁰ RAS receptor expression on T cells in females have yet to be studied although sex differences in AT₁/AT₂ receptor expression on immune cells may also serve as a potential mediator for the observed sex difference in T cells. Further studies are needed to better elucidate the role of T-cell RAS receptors in both sexes.

Summary and Conclusions

Recent advances in basic science research have identified several possible mechanisms responsible for the observed sex differences in hypertension. In this review, we focused on recent publications implicating the divergent role of the immune system in hypertensive males and females. We propose that the greater anti-inflammatory immune profile in females during hypertension may act as a compensatory mechanism to limit increases in BP compared with males who exhibit a more proinflammatory immune profile. However, the mechanisms underlying these changes in immune cells in hypertensive males and females are not yet well understood. One possible mediator is the AT₂ receptor, which has previously been shown to have greater activity in females, and recent studies indicate the AT₂ receptor promotes an anti-inflammatory immune profile. Further research to elucidate the complex role of the immune system in hypertension in both sexes is critical and may aid in discovering new therapeutic pathways to better control BP in both sexes.

Sources of Funding

This study was supported by HL127091 to J.C. Sullivan.

Disclosures

None.

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Ellen E. Gillis and Jennifer C. Sullivan

Hypertension. 2016;68:1322-1327; originally published online October 24, 2016;

doi: 10.1161/HYPERTENSIONAHA.116.06602

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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