Sex Differences in Blood Pressure Control
Are T Lymphocytes the Missing Link?

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See related article, pp 384–390

There is an ever expanding literature base implicating T lymphocytes in the development and progression of numerous cardiovascular diseases, including hypertension. T lymphocytes contribute to the development of hypertension in genetic, angiotensin II (Ang-II), and salt-sensitive male experimental animals. Among the most definitive studies implicating T lymphocytes in hypertension are studies conducted in Rag-1−/− mice, which lack B and T lymphocytes. Guzik et al were the first to demonstrate that these mice have a blunted hypertensive response to Ang-II infusion. Adoptive transfer of T lymphocytes into male Rag−/− mice restored the hypertensive response to Ang-II; adoptive transfer of B lymphocytes did not alter the blood pressure (BP) response. Although low-grade inflammation, and T lymphocytes in particular, are now recognized hallmarks of hypertension, the majority of basic science literature in this field has been conducted exclusively in males, despite the fact that females account for 50% of all hypertensive cases in the United States.

Therefore, it was with great interest that we read the study by Pollow et al in the current issue of Hypertension, which was designed to determine (1) whether there are sex differences in the ability of T lymphocytes to induce Ang-II−dependent hypertension and (2) whether sex affects central or renal T lymphocytes infiltration after Ang-II hypertension. Of particular interest, they found that male mice exhibited a significant increase in BP and renal damage to Ang-II after the adoptive transfer of CD3+ T lymphocytes from wild-type male mice. In contrast, BP responses and renal injury to Ang-II were not significantly altered in female Rag−/− mice after adoptive transfer of T lymphocytes from males. Male Rag−/− mice also had greater renal CD3+, CD4+, CD8+, and T-regulatory cells (Tregs) after adoptive transfer than female Rag−/− mice, despite both sexes having comparable BPs, although Ang-II did not significantly affect renal T-lymphocyte infiltration in either sex. Although this may call into question the role of T lymphocytes in Ang-II hypertension in the Rag−/− mice, male mice did express increased mRNA for the inflammatory cytokines interleukin-2, monocyte chemoattractant protein-1, and tumor necrosis factor-α after Ang-II infusion that were not found in the female, suggesting an increase in the overall inflammatory profile only in the male. Regardless, the authors clearly demonstrate that female Rag−/− mice limit the prohypertensive effects of T lymphocytes from males in Ang-II hypertension. Understanding the mechanisms by which females achieve this relative cardioprotection could provide important insight into novel mechanisms to regulate BP in both sexes.

Although it has been established that T lymphocytes play a significant role in the development of hypertension, the effect of different T-lymphocyte subtypes on BP control remains debatable in males and unexplored in females. It should be noted that although the study by Pollow et al did not find an increase in renal T lymphocytes in either sex after Ang-II infusion, T-lymphocyte activation was not assessed and neither were proinflammatory, prohypertensive T helper 17 (Th17) cells. Th17 cells are effector T lymphocytes that exert their effector function by the secretion of interleukin-17, interleukin-21, and interleukin-23. Interestingly, male interleukin-17 knockout mice have an attenuated increase in BP after Ang-II infusion, implicating Th17 cells in Ang-II-induced increases in BP. In line with this observation, we have previously shown that male spontaneously hypertensive rats (SHR) have greater renal Th17 cell infiltration and higher BP than female SHR, and hypertension in SHR is sensitive to Ang-II inhibition. Based on these data, it would have been interesting to know how sex and Ang-II affected Th17 cells in Rag−/− mice. In contrast, Tregs are anti-inflammatory T lymphocytes that suppress immune effector function through the secretion of interleukin-10 and female SHR have more Tregs in their kidneys than males. Direct support for Tregs to modulate BP comes from studies where adoptive transfer of Tregs attenuates Ang-II-induced increases in BP in male mice. Because these T-lymphocyte subtypes potentially have opposing effects on BP regulation, defining T-lymphocyte subtypes and examining the ratio of Th17 cells to Tregs may be critical to understanding the role of T lymphocytes in BP control in both sexes. Moreover, because studies suggest differential roles for these T-lymphocyte subtypes on BP, it is not unreasonable to postulate that the sex difference in the balance of Th17 cells and Tregs may contribute to observed sex differences in BP control.

It is attractive to hypothesize that the current study by Pollow et al and the immune system may hold the key for tying together the extensive literature documenting sex differences in cardiovascular disease. There are numerous reports of sex differences in BP and cardiovascular disease both in genetic models of hypertension and in Ang-II−induced hypertension.
Several different molecular mechanisms have been suggested to account for observed sex differences, including oxidative stress, nitric oxide (NO), endothelin, and the renin–angiotensin system (RAS), yet how all of these mechanisms may relate to one another has remained unknown.

Pollow et al. examine the role of T lymphocytes during Ang-II hypertension, and there are well established sex differences in the RAS and in physiological responses to Ang-II. Males typically have greater expression of classical RAS components and greater increases in BP to Ang-II than females. Our laboratory and others have shown that males have greater Ang-II–stimulated increases in oxidative stress that contributes to enhanced increases in BP in males relative to females. Harrison’s group has proposed that Ang-II stimulates oxidative stress in the brain, resulting in increased sympathetic outflow enhancing Ang-II activation of T lymphocytes, leading to target tissue infiltration of T lymphocytes and further increases in oxidative stress and BP. Recent studies demonstrated that deletion of p22phox, a key nicotinamide adenine dinucleotide phosphate oxidase subunit, in the subformical organ blunts Ang-II–induced increases in BP in male mice and abolishes Ang-II–induced aortic T-lymphocyte infiltration. Therefore, greater oxidative stress in males likely correlates with higher levels of T-lymphocyte activation and is consistent with higher BP in males under both basal conditions and after Ang-II hypertension. Moreover, female mice have greater NO synthase expression in the subformical organ than males, and central infusion of a nonspecific NO synthase inhibitor attenuates Ang-II hypertension only in female mice. Thus, NO attenuates Ang-II–induced increases in BP in females through reduced sympathetic outflow relative to the males, which is consistent with female mice having less renal T-lymphocyte activation relative to males. In support of this idea, we recently published that female SHR are more dependent on NO for BP control than males and females have greater increases in renal T-cell infiltration after NO synthase inhibition. These results support the hypothesis that NO protects females from immune cell infiltration relative to males, which further contributes to their lower BP. With the studies of Pollow et al., there is now direct evidence that sex differences in Ang-II hypertension extend to T lymphocytes, and the sex difference in T lymphocytes may underlie and explain sex differences in the RAS, oxidative stress, and NO (Figure).

Females have greater nonclassical RAS activation, including Ang (1–7), which blunts Ang-II–induced increases in BP. Overexpression of Ang (1–7) in monocrotaline-treated male Sprague-Dawley rats increases production of the anti-inflammatory cytokine interleukin-10 and attenuates pro-inflammatory cytokines including tumor necrosis factor-α, interleukin-1β, and interleukin-6. Further support for an anti-inflammatory role for Ang (1–7) comes from studies modulating angiotensin-converting enzyme 2; angiotensin-converting enzyme 2 is a critical enzyme in the formation of Ang (1–7). Angiotensin-converting enzyme 2 deficiency results in greater increases in renal cytokine and T-lymphocyte infiltration after unilateral ureteral obstruction compared with wild-type littermates, and renal ischemia–reperfusion results in greater T-lymphocyte infiltration in angiotensin-converting enzyme 2 knockout mice compared with wild-type mice. Therefore, greater Ang (1–7) may also actively limit Ang-II–induced increases in T-lymphocyte activation and BP in females. This may also be related to sex differences in oxidative stress and NO because Ang (1–7) stimulates NO, further linking the RAS, NO, and inflammation. With this in mind, it would be intriguing to determine the effect of Ang (1–7) infusion on BP and the immune profile after adoptive transfer of CD3+ T lymphocytes in males and females.

Although there are few studies that have directly examined the role of individual T-cell subtypes in hypertensive men and women, there is also clinical evidence linking immune system activation to cardiovascular disease and BP. HIV+ men and women have a lower prevalence of hypertension compared with healthy individuals, and treatment with antiretroviral therapy is positively associated with increases in CD4+ T cells and BP. In addition, nonspecific inhibition of B and T lymphocytes using mycophenolate mofetil significantly decreases BP in hypertensive men and women. Consistent with experimental studies suggesting that increases in Th17 cells promote hypertension, levels of circulating interleukin-17 are increased in patients with diabetes mellitus with hypertension compared with normotensive patients. Although less has been done clinically to assess Tregs and interleukin-10 in essential hypertension, preeclampsia has been shown to be associated with decreases in these anti-inflammatory factors. Based on our expanding understanding of the potential complex role played by the immune system in BP control, more clinical work is needed in this field to determine the potential clinical application of immune system modulation for the treatment of hypertension.

In closing, of the 68 million Americans with hypertension, <46% have their BP adequately controlled and women are more likely than men to have uncontrolled hypertension. This...
underscores the critical need for new treatment options for both men and women. Greater understanding of the mechanisms by which females are able to maintain their cardiovascular protection holds the potential to provide better treatment options for all patients with hypertension. The current work by Pollow et al,3 as well as others, in this field may hold the promise of explaining a fundamental difference between males and females that underlies a wide-ranging scope of biochemical and physiological sex differences allowing for greater understanding and better treatment options that have remained elusive for decades.

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References
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