Cardiovascular disease is the leading cause of mortality in patients with systemic lupus erythematosus (SLE), a chronic autoimmune inflammatory disorder that predominantly affects women of reproductive age.1–3 The prevalence of hypertension, a major cardiovascular risk factor, is much higher in women with SLE than age-matched healthy women.4–8 However, the factors that underlie the increased prevalence of hypertension during SLE remain unclear.

Because of the partiality toward women, estrogen is commonly implicated as an important contributor to SLE disease progression. Using an established mouse model of SLE (female NZBWF1), we tested whether estrogen has a causal role in the development of hypertension in adulthood. Thirty-week-old SLE and control mice (NZW/LacJ) underwent either a sham or ovariectomy (OVX) procedure. 17β-Estradiol (E2; 5 μg/mouse, twice/week, subcutaneously) was administered to a subset of OVX mice. Mean arterial pressure (in mmHg) was increased in SLE mice (134±4 versus 119±3 in controls). Contrary to our hypothesis, OVX exacerbated the hypertension in female SLE mice (153±3; P<0.05 versus SLE sham), and repletion of E2 prevented the OVX-induced increase in blood pressure (132±2). The prevalence of albuminuria was increased in SLE mice compared with controls (37% versus 0%). OVX increased the prevalence in SLE mice (70% versus 37% in SLE shams). Repletion of E2 completely prevented albuminuria in OVX SLE mice. Renal cortical tumor necrosis factor α was increased in SLE mice compared with controls and was further increased in OVX SLE. The OVX-induced increase in renal tumor necrosis factor α expression was prevented by repletion of E2. Treatment of OVX SLE mice with the tumor necrosis factor α inhibitor, etanercept, blunted the OVX-induced increase in blood pressure (140±2) and prevalence of albuminuria (22%). These data suggest that 17β-estradiol protects against the progression of hypertension during adulthood in SLE, in part, by reducing tumor necrosis factor α. (Hypertension. 2014;63:616-623.)

Methods and Materials

Abstract—Systemic lupus erythematosus (SLE) is a chronic inflammatory autoimmune disorder with a high prevalence of hypertension and cardiovascular disease. Because SLE predominantly affects women, estrogen is commonly implicated as a contributor to SLE disease progression. Using an established mouse model of SLE (female NZBWF1), we tested whether estrogen has a causal role in the development of hypertension in adulthood. Thirty-week-old SLE and control mice (NZW/LacJ) underwent either a sham or ovariectomy (OVX) procedure. 17β-Estradiol (E2; 5 μg/mouse, twice/week, subcutaneously) was administered to a subset of OVX mice. Mean arterial pressure (in mmHg) was increased in SLE mice (134±4 versus 119±3 in controls). Contrary to our hypothesis, OVX exacerbated the hypertension in female SLE mice (153±3; P<0.05 versus SLE sham), and repletion of E2 prevented the OVX-induced increase in blood pressure (132±2). The prevalence of albuminuria was increased in SLE mice compared with controls (37% versus 0%). OVX increased the prevalence in SLE mice (70% versus 37% in SLE shams). Repletion of E2 completely prevented albuminuria in OVX SLE mice. Renal cortical tumor necrosis factor α was increased in SLE mice compared with controls and was further increased in OVX SLE. The OVX-induced increase in renal tumor necrosis factor α expression was prevented by repletion of E2. Treatment of OVX SLE mice with the tumor necrosis factor α inhibitor, etanercept, blunted the OVX-induced increase in blood pressure (140±2) and prevalence of albuminuria (22%). These data suggest that 17β-estradiol protects against the progression of hypertension during adulthood in SLE, in part, by reducing tumor necrosis factor α.

Key Words: estrogens ■ lupus erythematosus, systemic ■ pressure
Mice were maintained on a 12-hour light/dark cycle in temperature controlled rooms with access to chow and water ad libitum. All studies were performed with the approval of the University of Mississippi Medical Center Institutional Animal Care and Use Committee and in accordance with National Institutes of Health Guide for the Care and Use of Laboratory Animals.

Ovariectomy
Ovariectomy (OVX) was performed through a dorsal midline incision. The abdominal muscle and peritoneum were incised, and a silk ligature was tied below the ovaries to remove them. To confirm the efficacy of OVX, the uterus was collected and weighed at the conclusion of the study.

17β-Estradiol Repletion
17β-Estradiol 17-valerate (E2: 5 µg/mouse; Sigma, St. Louis, MO, Catalog no. E1631) dissolved in 0.1 mL corn oil14–18 was injected subcutaneously twice per week for 4 weeks. Mice not receiving E2 were injected with 0.1 mL corn oil.

Etanercept Administration
A subset of mice was administered the tumor necrosis factor α (TNF-α) inhibitor etanercept (Wyeth, Thousand Oaks, CA: 0.8 mg/kg) or sterile water by subcutaneous injection once weekly for 4 weeks as we previously published.19

Blood Pressure Measurements
Mean arterial pressure (MAP; in mm Hg) was recorded via indwelling carotid artery catheters in conscious mice as previously described by our laboratory.20

Autoantibody Production
Plasma anti-double-stranded DNA (dsDNA) antibodies, a hallmark of SLE disease, were measured by commercial ELISA (Alpha Diagnostic International, San Antonio, TX) as previously described.21

Albuminuria
Urinary albumin was monitored weekly by dipstick analysis (Albusstix, Tarrytown, NY) of overnight urine samples. Animals were considered to be positive for albuminuria at ≥100 mg/dL as previously described.21 Urinary albumin was confirmed by ELISA (Alpha Diagnostic International, San Antonio, TX) in urine samples collected at the end of the study as previously published by our laboratory.21

Renal TNF-α
Renal cortical protein expression of TNF-α was determined using standard Western blot technique as previously published by our laboratory.19 A mouse monoclonal anti–TNF-α antibody (1:250; Santa Cruz Biotechnology, Dallas, TX) and rabbit anti–β-actin (1:4000; Abcam Inc, Cambridge, MA) were used. Proteins were visualized using an IR700-conjugated donkey anti-mouse IgG (1:2000) and IR800-conjugated donkey anti-rabbit IgG (1:2000; Rockland Immunologicals, Gilbertsville, PA). Blots were analyzed using the Odyssey Infrared Scanner (LI-COR Biosciences, Lincoln, NE). Data are presented as units of protein, based on band optical density, normalized to β-actin.

Protocol 1
Thirty-week-old SLE and control mice underwent either OVX or sham operation. Both SLE and control mice were assigned to one of the following treatment groups: sham, OVX, or OVX+E2. Sham and OVX mice in the E2 repletion study that were injected with oil were grouped with all other sham or OVX, respectively, because vehicle had no effect on any parameters measured. Body weight was measured weekly. Urine was collected weekly and assessed for the presence of albumin. MAP was measured at 34 weeks of age, and tissues were collected.

Protocol 2
A subset of 30-week-old female OVX SLE and OVX Ctrl mice was administered etanercept via subcutaneous injection once a week for 4 weeks. Mice were followed to 34 weeks of age for measurement of MAP and tissue collection.

Statistical Analysis
Data are presented as mean±SEM. Statistical analyses were performed using GraphPad Prism 6 software. A 1-way ANOVA was used to test for treatment interactions with a Tukey multiple comparison post hoc test. *P<0.05 was considered statistically significant.

Results
To test the hypothesis that estrogen, which is commonly considered an important factor in the development of SLE, has a causal role in the development of hypertension in adulthood, 30-week-old control and NZBWF1 mice were subjected to either OVX or sham operation. Consistent with our previously published work, MAP was increased in SLE shams compared with control shams (134±4 versus 119±3 mm Hg; P<0.05; SLE versus Ctrl; 2-way ANOVA). Contrary to our hypothesis, MAP was significantly increased in OVX SLE mice compared with SLE shams (Figure 1B; 153±3 mm Hg; P<0.05). MAP was not altered by OVX in control mice (Figure 1A; 114±3 mm Hg). In a subset of animals, E2 was administered to OVX SLE and control mice to determine whether the loss of E2, rather than other ovarian hormones such as progesterone, was responsible for the further increase in blood pressure. Repletion of E2 in OVX SLE mice prevented the increase in MAP caused by OVX

Figure 1. Effect of ovariectomy (OVX), estradiol (E2) repletion, and etanercept (Etan) on mean arterial pressure (MAP) in control mice (A) and systemic lupus erythematosus (SLE) mice (B). A. Neither OVX, E2 repletion, nor etanercept altered MAP in comparison with control sham mice (n=25). B. MAP was significantly higher in OVX SLE mice (n=11) compared with sham (n=16). Repletion of E2 prevented the OVX-induced increase in MAP in SLE mice (n=6). Treatment with etanercept blunted the exaggerated increase in MAP in OVX SLE mice (n=6). *P<0.05 vs SLE sham.
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Repletion of E2 in O VX control mice did not alter MAP (Figure 1A).

Because repletion of E2 prevented the OVX-induced increase in MAP, the question of the mechanism by which this protection occurs was examined. Estradiol has known anti-inflammatory effects and reduces proinflammatory cytokines including TNF-α, previously shown by us to mechanistically contribute to hypertension in female NZBWF1. Renal cortical TNF-α expression was significantly increased in SLE sham mice compared with controls (Figure 2; 1.8±0.4 versus 1.0±0.1; P<0.05). In OVX SLE mice, renal cortical TNF-α expression was increased (3.2±0.8), and repletion of E2 after OVX prevented the OVX-induced increase in renal cortical TNF-α expression (2.2±0.3). Renal TNF-α expression was not altered in controls by OVX or repletion of E2 after OVX.

To determine whether the increased TNF-α after OVX contributes to the OVX-induced increase in blood pressure in adult SLE mice, OVX SLE and control mice were treated with etanercept, an inhibitor of TNF-α biological activity. Treatment with etanercept in OVX SLE mice ameliorated the OVX-induced increase in MAP in female SLE mice (Figure 1B; 140±2 mm Hg), suggesting that the exacerbated hypertension caused by OVX was mediated, in part, by TNF-α. This is consistent with our previously published work related to the effect of etanercept on blood pressure during SLE. Treatment with etanercept did not alter MAP in controls.

The efficacy of OVX and E2 repletion was confirmed in these studies by measuring uterine weight at the time of euthanization. As expected after OVX in adult mice, uterine weight was significantly reduced in both control (Figure 3A; Ctrl sham: 0.097±0.012 g versus Ctrl OVX: 0.042±0.006 g; P<0.05) and SLE mice (Figure 3B; SLE sham: 0.094±0.008 g; SLE OVX: 0.045±0.008 g; P<0.05). Uterine weight in mice replete with estradiol was significantly greater than corresponding sham controls (Ctrl OVX+E2: 0.25±0.02 g; SLE OVX+E2: 0.2±0.02 g; P<0.05). Treatment with etanercept after OVX did not alter uterine weight in comparison with OVX mice (Ctrl OVX+E2: 0.035±0.002 g; SLE OVX+E2: 0.039±0.01 g).

SLE is characterized by renal injury including albuminuria, and previous work from our laboratory shows that the prevalence of albuminuria in the adult female SLE mice at 34 weeks of age as assessed by dipstick assay is ≈40%. Consistent with this, the prevalence of albuminuria in 34-week-old SLE shams in this study reached 37% (Figure 4A). No control mice developed urinary albumin during the course of the study (data not shown). Urinary albumin, as measured by ELISA in samples collected at 34 weeks of age, was increased in SLE mice compared with controls as previously shown in our laboratory (Figure 4B and 4C; 3.20±1.5 versus 0.02±0.0 mg/mL; P<0.05; SLE versus Ctrl; 2-way ANOVA). The percentage of SLE mice with albuminuria was increased to 70% after OVX,

**Figure 2.** Effect of estradiol on renal cortical tumor necrosis factor α (TNF-α) protein expression in control and systemic lupus erythematosus (SLE) mice. TNF-α protein expression was significantly increased in the renal cortex of SLE mice compared with controls. Ovariectomy (OVX) increased TNF-α expression in SLE mice, and repletion of estradiol blunted this increase. *P<0.05 vs Ctrl.

**Figure 3.** Effect of ovariectomy (OVX) and estradiol (E2) repletion on uterine weight in control mice (A) and systemic lupus erythematosus (SLE) mice (B). OVX significantly reduced uterine weight in both control and SLE mice. Repletion of E2 after OVX significantly increased uterine weight in comparison with respective shams. *P<0.05 vs sham and OVX+E2. #P<0.05 vs sham, OVX, and OVX+Etan.
and urinary albumin increased compared with SLE shams (10.2±3.9 mg/mL). The OVX SLE mice replete with E2 did not develop albuminuria as measured by dipstick, which was confirmed by ELISA (0.01±0.003 mg/mL). The prevalence of albuminuria in OVX SLE mice treated with etanercept was blunted (22%) as was urinary albumin in OVX SLE mice. *P<0.05 vs OVX+E2.

Discussion

The prevalence of hypertension is markedly increased in women with SLE and represents a major independent risk factor for mortality in this patient population; however, the mechanisms contributing to the prevalent hypertension have not been widely studied. Using an established mouse model of SLE, we previously investigated some of the underlying factors that promote hypertension. These include impaired renal hemodynamic function, peripheral vascular function, inflammatory cytokines, and oxidative stress. Based on their presumed role to promote SLE disease progression, the present study sought to test whether estrogens could be contributing to the development of hypertension. The major new findings of this study are that (1) in adulthood, OVX accelerates rather than protects against the development of hypertension and albuminuria during SLE; (2) the exacerbation of hypertension caused by OVX in adulthood during SLE is mediated by a loss of 17β-estradiol and is associated with increased renal TNF-α expression; and (3) the increased renal TNF-α expression mechanistically contributes to the exacerbated hypertension in adult SLE mice because etanercept blunts the effect of OVX. These data provide new insight for...
understanding the complex role that estrogens have in SLE disease progression and the associated cardiovascular risk factors such as hypertension.

Estrogens have been widely implicated in the development of SLE, in part, based on the strong predilection of the disorder for women of reproductive age. A role for estrogens in autoimmunity has been supported by reports that the production of immunoglobulins (IgG and IgM) is increased in human peripheral blood mononuclear cells incubated with 17β-estradiol but not other estrogenic compounds (ie, estrone, estriol).\textsuperscript{29} Studies in experimental animal models have also consistently supported an important role for estrogens in SLE disease progression. For example, NZBWF1 estrogen receptor (ER)-α knockout mice exhibited reduced development of anti-dsDNA autoantibodies over time that correlated with increased survival time.\textsuperscript{30} OVX NZBWF1 mice, treated with a selective ER-α agonist, had increased levels of anti-dsDNA IgG-specific antibodies.\textsuperscript{31} These studies support earlier data in the literature, which show that autoantibody production and mortality are increased by estrogen supplementation in female NZBWF1 mice castrated at 2 weeks of age.\textsuperscript{11} However, it is worth noting that the dose of E2 (6–7 mg in silastic tubing) used in this previous work is considerably higher than the dose used in the present study and could have caused nonspecific effects, including enlarged bladder and associated kidney injury from the chronic muscle relaxation.\textsuperscript{32,33} Finally, treatment of NZBWF1 mice with tamoxifen, a selective ER modulator, starting at 6 to 8 weeks of age increased survival but did not affect antibody production.\textsuperscript{34}

Based on this work, we anticipated that removal of the ovaries would reduce autoantibody production, decrease albuminuria, and protect against the development of hypertension; however, this was not the case. In fact, the data clearly demonstrate a protective role for estrogens against hypertension and albuminuria, independent of changes in antibody production. The finding that estradiol has a protective role against the further progression of hypertension is important because blood pressure is a critical factor for increasing cardiovascular risk, the leading cause of death in women with SLE.\textsuperscript{22,23} Whether this protection translates to delayed mortality could not be addressed with the current experimental design.

A major difference between our study and the work of others that may account for these, initially, unanticipated findings is the timing of estrogen removal. Our study was focused on the role of estrogens in adult female mice (30 weeks of age), whereas previous studies by others were designed to assess the role of estrogens starting in young female mice either from birth as in the case of Bynoté et al\textsuperscript{19} or in mice <8 weeks of age.\textsuperscript{11,12,30,34} Therefore, the findings of the present study suggest that there may be distinct temporal roles for estrogens in the progression of SLE and its sequelae with estrogens promoting humoral immunity during subclinical disease but possibly protecting against the tissue inflammation that contributes to disease symptoms in adulthood. There is evidence in the literature supporting distinct temporal effects of estrogen in other diseases. For example, treatment of a mouse model of experimental autoimmune encephalomyelitis with E2 before disease onset ameliorated disease severity; however, when treatment was initiated after the development of active disease, the severity of the disease course was not changed.\textsuperscript{35} Disease severity was also dependent on the timing of treatment with E2 in a study of ovariectomized DBA/1 mice with collagen type II arthritis.\textsuperscript{36} These studies suggest a high likelihood that estrogen has different temporal effects during inflammatory diseases. One possible explanation for the changing roles of estradiol may be related to alterations in the expression of the ER over time. Roa et al\textsuperscript{17} showed that NZBWFI mice have fewer ERs per mg cytosol protein than nonautoimmune BALB/c mice. ER receptor abundance per mg cytosol protein in the liver was increased in NZBWFI mice and the parental NZW strain compared with the parental NZB strain, whereas no differences were seen in thymus, spleen, or uterus.\textsuperscript{38} Another study noted changes in binding affinity and capacity of the ER in MRL mice, a model of lupus, with aging.\textsuperscript{39} Whether NZBWFI mice exhibit similar changes with aging is not known.

Although studies in both humans and experimental models of SLE have examined and speculated on the role of estrogens, the effect of estrogens on blood pressure during SLE has not been carefully examined until now. In addition to the fact that hypertension is an independent predictor of mortality and that blood pressure control is an important clinical consideration for reducing cardiovascular and renal risks in women with SLE, understanding the role of estrogens in blood pressure control in adulthood during SLE is especially important to this patient population because the risk of premature ovarian failure and early menopause is high.\textsuperscript{13,40,41} Several studies report that hormone therapy in women with SLE is well tolerated,\textsuperscript{42–45} despite the assumption that estrogens promote SLE disease. In one study assessing the relationship between cardiovascular disease risks and hormone therapy in women with SLE, hormone therapy did not predispose to coronary artery disease.\textsuperscript{46} In addition, hormone therapy in the SLENA (Safety of Estrogens in Lupus Erythematosus-National Assessment) study of 351 women with SLE did not lead to cardiovascular events.\textsuperscript{42} Similarly, in the LUMINA (Lupus in Minorities: Nature vs Nurture) study, hormone therapy was not associated with vascular arterial events,\textsuperscript{47} and Fernández et al\textsuperscript{48} even speculated that hormone therapy may be a protective factor against the development of arterial vascular events in women with SLE. Our data are consistent with these studies, suggesting a potential cardioprotective role for estrogens in adulthood during SLE.

To gain insight into the mechanism by which estrogen could protect against hypertension, we focused on the inflammatory cytokine, TNF-α. Our previously published work showed renal TNF-α to be an important factor in the pathogenesis of hypertension in this model.\textsuperscript{19} In addition, low levels of estrogen or removal of estrogen promotes a proinflammatory response and the production of cytokines.\textsuperscript{22,23} For example, TNF-α is increased in postmenopausal women compared with premenopausal women.\textsuperscript{49,50} In experimental animal studies, estrogen-deficient rats have increased serum levels of TNF-α that are reduced after estrogen repletion, and TNF-α inhibition in estrogen-deficient rats was associated with improved vascular function.\textsuperscript{24} Consistent with
these data, we show that OVX adult female SLE mice have increased renal cortical protein expression of TNF-α and that the enhanced blood pressure response caused by OVX was largely prevented by treatment with etanercept. Although these data suggest that TNF-α is an important mediator of the OVX-induced increase in pressure, it is possible that etanercept prevents the increased pressure caused by OVX, independent of the blood pressure–lowering effects of E2.

Separating changes in albuminuria from changes in blood pressure is always difficult. Female NZBW1F1 mice represent a long-established model of SLE with immune complex–mediated glomerulonephritis; therefore, it is unlikely that the development of albuminuria is strictly related to hypertension. In support of this, we recently published work showing that bilateral renal denervation in this model ameliorates albuminuria independent of changes in blood pressure.51 In addition, studies in the NZBW1F1 model show that lowering blood pressure alone is not sufficient to reduce renal injury.52 Nevertheless, the albuminuria caused by OVX seems to track well with the increase in blood pressure. Interestingly, however, albuminuria was ameliorated in the SLE mice replete with 17β-estradiol, although the blood pressure is similar to the sham SLE group. The reason for the marked effect of 17β-estradiol on albuminuria is not clear. The dose of estradiol selected for this study was based on previously published work of others,14–18 and the regimen (twice per week) was chosen to better mimic estrous cycling. However, based on the fact that uterine weights were increased over sham controls in animals replete with estradiol, the circulating levels of estradiol achieved were most likely high. We did not measure serum estradiol in this study because levels in mice are low (<5 pg/mL), which typically falls below the sensitivity of even liquid chromatography–mass spectrometry methods and leads to significant variability in radioimmunoassays, even when comparing OVX with intact animals.53 Irrespective of the absolute circulating levels of estradiol, these data support the idea that the albuminuria in this model is not solely the result of increased arterial pressure. Taken together, the results of these studies showing a protective role of estradiol in adulthood during SLE highlight the need to carefully examine the temporal effects of estrogen on disease activity and may help to explain why there is considerable variability in human data with regard to the role of estrogens.

**Perspectives**

The role of estrogens in adult women with SLE is much less clear than what is commonly presumed. Therefore, it may be particularly informative to consider more carefully these data in the context of what is known about SLE in women. For example, during the course of a normal menstrual cycle, women with SLE report greater disease activity during menstruation but not during the normal hormonal surge that is associated with the highest levels of estrogen during the estrus cycle.54 Estrogen-based oral contraceptive use is generally associated with the highest levels of estrogen during the estrus cycle.54 Additionally, disease flares were reduced in pregnant women with SLE during the third trimester when estrogen levels are at their highest,37 and in some studies, lower levels of estrogen are associated with increased SLE disease activity.55 In the present study, we show that removal of estrogen during adulthood in female NZBW1F1 SLE mice exacerbates hypertension and increases renal injury and renal TNF-α, all of which are prevented by repletion of estrogen. These data suggest that estrogen may play a protective role against a major cardiovascular risk factor in adulthood during SLE. In addition, these data suggest that hormone therapy or repletion of estrogen can be cardioprotective during SLE while not altering autoantibody levels or encouraging SLE disease activity.

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**Disclosures**

None.

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**Novelty and Significance**

**What Is New?**
- In adulthood, loss of estrogen accelerates rather than protects against the development of high blood pressure and kidney injury during lupus disease.
- The exacerbation of high blood pressure caused by loss of estrogen in adulthood during systemic lupus erythematosus (SLE) is associated with increased inflammation in the kidney.

**What Is Relevant?**
- Cardiovascular disease is the leading cause of death during SLE. Furthermore, hypertension, a major cardiovascular risk factor, is highly prevalent in women with SLE for reasons that remain unclear.

**Summary**
Estrogen plays a protective role during adulthood in SLE at least against the progression of hypertension, a major cardiovascular risk factor. These data provide new insight for understanding the complex role that estrogens have in SLE disease progression and the associated cardiovascular risk factors such as hypertension.
17β-Estradiol Protects Against the Progression of Hypertension During Adulthood in a Mouse Model of Systemic Lupus Erythematosus
Emily L. Gilbert, Keisa W. Mathis and Michael J. Ryan

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