Water and Electrolyte Homeostasis Section Young Investigator Award Lecture.

The Pathophysiology of Hypertension in Systemic Lupus Erythematosus

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Running Title: SLE Hypertension

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Abstract

Systemic lupus erythematosus (SLE) is a chronic autoimmune inflammatory disorder that predominantly affects women during their reproductive years. Although SLE can affect any organ system, the kidneys are prominently involved in the form of immune complex glomerulonephritis. In addition, women with SLE have a dramatically increased risk for the development of cardiovascular disease. Hypertension is a major risk factor for cardiovascular disease and is highly prevalent in women with SLE. Despite this, little has been explored regarding the pathophysiological mechanisms that promote SLE hypertension. This review discusses the role of several mechanisms, with an emphasis on the kidney, may contribute to SLE hypertension. These include the renin-angiotensin system, endothelin, oxidative stress, sex steroids, metabolic changes, peroxisome proliferator activated receptor gamma, and perhaps most importantly, chronic inflammation and cytokines. Growing evidence suggests a link between chronic inflammation and hypertension. Therefore elucidating mechanisms that promote SLE hypertension may be of significant value not only to patients with SLE, but also for better understanding the basis for essential hypertension.

Key Words: hypertension, lupus, renal, inflammation
Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune inflammatory disorder that prominently affects the kidneys, although any organ system including the skin, joints, or central nervous system can be involved. Kidney involvement occurs in approximately 50% of patients with SLE in the form of immune complex glomerulonephritis that can ultimately lead to renal failure. A positive diagnosis of SLE is established when a patient has had at least four of the symptoms shown in the Table (1). Auto-antibodies to the nucleus are noted in up to 99% of patients with SLE, and up to 70% of patients have specific auto-antibodies to double stranded DNA (dsDNA). Although the presence of auto-antibodies to dsDNA is 95% predictive of SLE (110) and the antibodies are diagnostic, the cause of SLE remains unclear. What is clear is that SLE is a multifactorial disorder with hormonal, genetic, and environmental contributions.

SLE is often considered a disorder of young women and predominantly occurs during the reproductive years at an estimated ratio of 9:1 (women:men). Evidence suggests that short term mortality has decreased in patients with SLE (137). Nevertheless, women with SLE have a significantly lower life expectancy and 10% of patients will die within five years following diagnosis (122). The primary cause of mortality in SLE, particularly in women who survive beyond the first five years, is cardiovascular disease. Indeed, individuals with SLE have a greater than 50-fold risk for cardiac events compared to those without SLE enrolled in the Framingham Heart Study (83). In addition to
prominent renal and cardiac disease, women with SLE also have an increased susceptibility to the development of atherosclerosis (20; 131) and cerebrovascular dysfunction (106).

Hypertension is a major risk factor for the progression of renal, vascular, and cardiac disease. Numerous studies report a high prevalence of hypertension in women with SLE reaching as high as 74% in some cohorts (4; 21; 81; 100; 118). In stark contrast, the prevalence of hypertension in young women who do not have SLE is 2.7% between the ages of 20 and 34 and 14% between the ages of 35 and 44 (2). Despite compelling evidence for the high prevalence of hypertension in individuals with SLE, mechanistic studies on SLE hypertension are scarce.

A growing body of literature supports a role for the immune system and chronic inflammation in the development of hypertension (16; 17). Therefore, understanding how hypertension develops in this chronic autoimmune disorder may have far reaching clinical relevance for patients with SLE and contribute to understanding the role of the immune system and chronic inflammation to the progression of hypertension. Currently, there is no consensus pathway proposed for the etiology of SLE hypertension, although it is likely that inflammatory cytokines play a central role in the pathogenesis since SLE is an autoimmune disorder. In addition, like all forms of hypertension studied thus far, it is predicted that altered renal function plays a central role and is negatively affected by the chronic inflammation. The purpose of this review is to discuss several factors commonly implicated in the development of essential hypertension, whether they are important in
the progression of SLE hypertension, and how they might ultimately contribute to increased inflammatory cytokines and impaired renal function during SLE.

**Mouse models of SLE**

Our understanding of SLE has been significantly enhanced through experimentation with animal models. More specifically, several different mouse models of SLE have been utilized to examine the underlying genetic and immunologic mechanisms that promote this autoimmune disorder. Perhaps the three most commonly studied models are the BXSB, MRL/lpr, and NZBWF1. All of these models produce auto-antibodies characteristic of SLE (22; 56; 109); however, each has its own unique set of advantages and disadvantages. For example, MRL/lpr mice have a genetic mutation in the lymphoproliferative (lpr) gene that encodes for fas ligand. These mice develop an aggressive form of lupus nephritis typically around 15-20 weeks of age. In addition, the MRL/lpr mice develop arthritis and vasculitis similar to what is observed in human SLE (109). Despite this, the MRL/lpr strain does not become hypertensive (111), thus limiting its usefulness to examine mechanisms that lead to SLE hypertension and the effect of hypertension on cardiovascular risk in SLE.

Another commonly used model, the BXSB mouse, has a mutation in the Y chromosome autoimmune allele (yaa) resulting in the development of SLE only in male mice (56). Like the MRL mice, the BXSB model does not develop hypertension (111). However, when BXSB mice are genetically crossed with New Zealand White (NZW) mice the
resulting offspring develop an autoimmune disorder with a high incidence of coronary artery disease (53). Therefore, while the BXSB mice may be useful for investigating coronary artery disease associated with SLE, they have limited utility for examining mechanisms of SLE hypertension and the possible role of female sex steroids in the progression of SLE.

The NZBWF1 model is generated from a genetic cross between female NZW and male New Zealand Black (NZB) mice and has been utilized as a model of lupus nephritis for more than 40 years. Unlike the MRL/lpr mouse, NZBWF1 mice do not develop obvious signs of arthritis and skin involvement. However, at approximately 25-30 weeks of age, the F1 females begin to develop characteristics of SLE. Female NZBWF1 mice typically die by 45-50 weeks (less than half the normal lifespan of a mouse) and have several characteristics consistent with human SLE. These include immune complex deposition in the glomerulus, dsDNA auto-antibodies, albuminuria, and importantly, hypertension \textit{(Figure 1A)} (22; 111; 113). Also consistent with findings in humans, female NZBWF1 mice are more prominently affected than males and the etiology of SLE in this model is not dependent upon a single genetic mutation. Therefore, SLE in the NZBWF1 mouse is a complex genetic disorder that is also likely influenced by sex steroids. For these reasons, the NZBWF1 model most closely resembles human SLE and is useful for examining the pathophysiological mechanisms that promote SLE hypertension. Recent and ongoing studies in our laboratory utilize the female NZBWF1 model of SLE. Throughout this review, many of the references to animal studies will be related to the female NZBWF1 mice.
The Role of the Kidneys in SLE Hypertension

The importance of the kidneys in the long-term control of blood pressure and the pathogenesis of hypertension is well documented (30; 50; 51). Therefore it is not surprising that impaired renal function is a primary culprit in the progression of SLE hypertension. Given that immune complex glomerulonephritis is estimated to affect approximately 50% of patients with SLE, it is tempting to conclude that SLE hypertension is simply due to the nephritis. However, SLE is a risk factor for hypertension in humans and can occur independently of the nephritis (101; 141). The disconnect between arterial pressure and nephritis can also be observed in mouse models of SLE where both the MRL/lpr and the NZBWF1 mice develop immune complex glomerulonephritis, yet only the NZBWF1 mice develop hypertension. These data suggest that factors such as impaired renal hemodynamics or tubular function, in addition to nephritis and nephron loss, contribute to impaired renal function and the development of SLE hypertension.

*Renal Hemodynamics in SLE hypertension.* In all forms of hypertension, the pressure natriuresis relationship is altered so that a higher pressure is required to excrete the same amount of sodium. Consistent with renal vasoconstriction and a rightward shift in the pressure natriuresis relationship, patients with SLE have reduced glomerular filtration rate (GFR) and renal plasma flow (93). This supports a central role for renal hemodynamics in the development of SLE hypertension, and that the NZBWF1 mouse
model is particularly well suited to examine the role of the kidneys in SLE hypertension. Studies show that, like humans, the female NZBWF1 mice have attenuated estimated renal plasma flow (117), and a reduction in GFR that corresponds with the progression of the disease (66). Consistent with a reduced GFR, these mice also have increased blood urea nitrogen and plasma creatinine (31; 123; 132; 133). While these data suggest a renovascular mechanism for SLE hypertension, the underlying factors that promote renal hemodynamic changes during SLE are not clear. Moreover, the factors that dictate the pressure natriuresis relationship are complex and a potential role for altered renal tubule function may be important to consider.

Renal Tubules and SLE hypertension. Very little is understood about renal tubular sodium handling in patients with SLE; however, if the primary renal defect occurred in the proximal tubule or Loop of Henle one would expect an increase in GFR due to a macula densa-mediated feedback dilation of afferent arterioles. Nevertheless, it is clear is that tubular lesions are prevalent in humans with SLE and have prognostic value for renal outcomes (36). Preliminary data from our laboratory show that neutrophil gelatinase associated lipocalin (NGAL), a marker of proximal tubular injury (89), is increased in the urine from female NZBWF1 mice (Figure 2) compared to the parental controls (NZW). Therefore, the NZBWF1 model may be useful for exploring the renal tubular changes that occur during SLE that could lead to hypertension.

Glomerulonephritis and SLE. It is important that a role for glomerular injury not be discounted as a contributor to SLE hypertension. Although a substantial loss of nephrons
are required to cause hypertension, progressive glomerular damage and nephron loss can certainly exacerbate renal hemodynamic changes associated with SLE. The most common clinically used indicator of glomerular injury in SLE is the presence of urinary albumin. We and others reported that the NZBWF1 mice excrete high amounts of albumin in the urine as evidence of glomerular injury (113). This model also displays the characteristic “wire loop” glomerular pathology observed in humans (24; 76) caused by immune complex deposition in the glomerular basement membrane. We recently showed that female NZBWF1 mice have increased numbers of monocytes and macrophage in the renal cortex (114) (Figure 3). Thus, the NZBWF1 model of SLE will be useful to gain mechanistic insight for the contribution of glomerular injury to SLE hypertension.

Taken together, it is clear that the kidneys play a central role in the development of SLE hypertension, and while the renal tubules and glomerular injury may contribute, the current evidence is most supportive of a role for impaired renal hemodynamics. Among likely candidates for renal hemodynamic changes during SLE is the possibility of impaired renal vascular endothelial function.

**The Role of Vascular Endothelial Function in SLE Hypertension**

To my knowledge, there are no published reports on renal vascular endothelial function in humans or animal models of SLE. This is somewhat surprising given that this information could provide a basic physiological mechanism for the well known impairment of renal hemodynamics that accompanies SLE. In addition, hypertension is
often associated with impaired endothelial function but whether this is causative in the progression of hypertension is difficult to prove. Numerous studies suggest that the endothelium is prominently affected during SLE as demonstrated by the high risk for the development of atherosclerosis (6; 15). In addition, circulating auto-antibodies and other inflammatory mediators can activate the endothelial cells to express cell adhesion molecules during SLE (15; 130). Increased levels of circulating endothelial cells as a marker for vascular injury are also increased during SLE (27).

Vascular endothelial function measured by brachial artery flow is reported to be impaired in patients with SLE (60; 78; 102). However, the relevance of these studies to an increased risk of hypertension in patients with SLE is difficult to determine because of the diversity in patient populations, severity of SLE, and the therapeutic strategies used to treat SLE. For example, one of the most common treatments for SLE is the use of corticosteroids and chronically elevated levels of corticosteroids can promote endothelial dysfunction and hypertension (86). In another study examining vessel function during SLE, patients with hypertension were excluded entirely (78). Therefore, whether impaired endothelial function contributes to or merely associates with SLE hypertension remains unclear.

We recently examined endothelial function in the NZBWF1 model of SLE and showed that the carotid artery response to acetylcholine is impaired (113) (Figure 1B). These data suggest that endothelial impairment does correspond with hypertension in SLE. The obvious limitation of this study, and those described above from humans, is that vascular
endothelial function in large conduit vessels may not necessarily reflect vascular function in the kidneys. Therefore, despite clear evidence for endothelial dysfunction in SLE, the question of whether this occurs in the kidneys and what are the causative factors have not been answered. Potential candidates for causing impaired vascular function during SLE are the renin-angiotensin and endothelin endocrine systems, both of which are strongly implicated in the development of numerous forms of hypertension.

### The Role of Endocrine Systems in SLE Hypertension

*Renin-Angiotensin System in SLE.* Despite the widely known importance of the renin-angiotensin system (RAS) in blood pressure and volume homeostasis, there is little understood about the role for RAS in the progression of SLE and SLE hypertension. The extent of knowledge in this area is largely limited to inconclusive genetic studies, and the suggestion that RAS is activated in some patients with SLE.

In humans, the angiotensin converting enzyme (ACE) gene has two common variants, an insertion and a deletion mutation representing either the presence or absence of a 287 base pair DNA fragment in exon 16. Individuals who are homozygous for the ACE deletion mutation have increased ACE activity, and may have an increased risk for cardiovascular disease and hypertension (63; 124). Numerous genetic association studies and one genetic linkage analysis have been conducted in different populations with SLE (64; 74; 96; 104; 136). The data from these studies fail to provide a definitive link between the RAS and the progression of SLE.
Some studies suggest that SLE is associated with an activated RAS based on evidence of increased renin or effective blood pressure control with ACE inhibitors (54; 88; 120). However, this may not be universal to all patients with SLE and a comprehensive study to evaluate RAS components in SLE has not been conducted. Limited evidence suggests that ACE inhibitors and angiotensin receptor blockers are most effective for controlling blood pressure in SLE patients with evidence of activated RAS (54). While these therapies are largely effective in controlling SLE hypertension and reducing albuminuria, combination therapy (i.e. with diuretics or calcium channel blockers) may be required to attain adequate blood pressure control (54). Thus, whether an individual with SLE hypertension has increased or decreased levels of RAS components may be an important consideration in the treatment plan.

The utility of experimental animal models to examine the role of RAS in SLE hypertension has not been fully characterized. Treatment with ACE inhibitors effectively reduce proteinuria (38; 55; 80) in both the NZBWF1 and MRL/lpr models of SLE; however, an early study showed that both of these models have low plasma renin levels (111). A recent study showed that the skeletal muscle arteriole response to angiotensin II (AngII) is enhanced and that the response to acetylcholine is impaired in the non-hypertensive MRL/lpr model of SLE (11). These data suggest that RAS or sensitivity to RAS may be important in the progression of vascular changes during SLE. Whether similar changes occur in the renal vasculature to impair renal hemodynamics and cause hypertension in SLE has not been previously studied.
**Endothelin and SLE.** In addition to the role of RAS as one of the most important endocrine systems for the control of blood pressure and volume/salt homeostasis, it is also well known that Ang II stimulates the production of endothelin (ET-1) (5; 12). ET-1 is an important factor in the pathophysiology of hypertension through its potent renal vasoconstrictor actions and ability to promote sodium and water retention via endothelin type A receptor (ETA) activation (28; 90; 103). Activation of endothelin type B receptors (ETB) causes a natriuresis and is generally thought to counter the hypertensive actions of endothelin (28; 90; 103). Genetic deletion of ETB receptors causes a salt-sensitive hypertension, further supporting the natriuretic role for ET-1 in the medulla (45; 105).

Importantly, evidence suggests that there is a role for ET-1 in the progression of SLE and SLE hypertension. For example, plasma ET-1 levels are increased in patients with SLE (61). Another study showed that serum from patients with SLE stimulates the release of ET-1 from endothelial cells in culture (148). Recent evidence suggests a role for renal ET-1 in SLE progression and SLE hypertension in the NZBWF1 mouse model. Renal ET-1 mRNA expression progressively increases with age in female NZBWF1 mice (91) and chronic treatment of female NZBWF1 mice with an ETA receptor antagonist prevents renal injury, delays mortality, and lowers blood pressure as measured by tail plethysmography (92). Based on this evidence in humans and in mouse models, increased ET-1 may be an important contributor to SLE hypertension. The NZBWF1
model will be important to discern the role of ET-1 in the impaired renal hemodynamics and hypertension that accompanies SLE.

**Oxidative Stress and SLE Hypertension**

One potential mechanism that could mediate impaired renal hemodynamics and hypertension in SLE patients, particularly those with activated RAS and/or ET-1 systems, is the generation of oxidative stress. Both the RAS and ET-1 systems are important for generating reactive oxygen species through the NADPH oxidase, a major superoxide generating enzyme. Importantly, the role of reactive oxygen species is well recognized in immune system function with the “respiratory burst” from macrophage and neutrophils. The overproduction (or impaired scavenging) of reactive oxygen species promotes oxidative stress and is recognized as important in the pathogenesis of hypertension. The role of oxidative stress in hypertension is supported largely by evidence from experimental rodent models that are treated with antioxidants or from mice with genetic deletions of the enzymes important for the production or scavenging of reactive oxygen species (35; 48; 62; 70). The mechanisms by which oxidative stress promote hypertension are reviewed elsewhere and are related to vascular dysfunction, renal injury, and increased sodium reabsorption (71; 82; 144).

Several studies suggest that oxidative stress is important in the pathogenesis of SLE (6; 7; 10; 25; 126; 135). There is a direct correlation between SLE disease activity score and the production of superoxide from peripherally circulating mononuclear cells (142).
Similarly, SLE disease activity correlates directly with serum malondialdehyde levels (marker of oxidative stress) and correlates inversely with serum levels of superoxide dismutase and glutathione peroxidase (antioxidant enzymes) (128). The importance of oxidative stress in the pathogenesis of SLE is also supported in experimental animal models. Treatment of NZBWF1 mice with antioxidant therapies such as selenium or N-acetylcysteine increased survival and reduced albuminuria (127). In the MRL/lpr model of SLE, treatment with vitamin E improved survival and decreased albuminuria (143). While animal models appear to benefit from antioxidant therapies, the effect of this on the impaired renal hemodynamics and the hypertension during SLE have not been determined. Therefore, although evidence supports a role for oxidative stress in nephritis and renal injury, further studies need to be conducted to determine the importance of oxidative stress in SLE hypertension.

**Metabolic Factors and SLE Hypertension**

*Obesity, Leptin, Insulin and SLE.* Obesity and diabetes are major risk factors for the development of renal disease and hypertension. In addition, it is increasingly recognized that inflammatory cytokines such as IL-6 and TNF-α are increased in metabolic syndrome and may have a pathogenic role (42; 72; 145). The mechanistic role of inflammatory cytokines in metabolic syndrome associated hypertension is not fully understood. Although there are few studies pertaining to possible metabolic changes and SLE, those available suggest that women with SLE are more prone to alterations in body composition, including a decrease in fat free mass and increased adiposity (67; 68).
Consistent with an increased adiposity, the adipokine leptin is reportedly increased in women with SLE, and can even be increased independently of body mass index (44; 116). Leptin, widely recognized as a satiety factor, is critically important for immune system function (79) and is also important for the development of obesity hypertension through stimulation of sympathetic nerves to increase renal sodium reabsorption (52; 107). The likelihood of developing insulin resistance is increased in women with SLE (134) and there are case reports where individuals with SLE produce antibodies to the insulin receptor. These auto-antibodies lead to what has been termed Type B insulin resistance (46). Cytokines such as interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-a) that are commonly increased in SLE have also been implicated in the development of insulin resistance (18; 140).

These observations support a potentially important role for SLE in the development of characteristics of the metabolic syndrome. Alternatively, the data could be interpreted to mean that metabolic changes may play an important role in SLE progression. The link between metabolic changes, SLE, and hypertension has not been extensively studied. We recently reported that the NZBWF1 mouse model of SLE has several characteristics of the metabolic syndrome including insulin resistance (Figure 4), central obesity, increased inflammatory cells in the adipose, and hyperleptinemia (114). Therefore, the NZBWF1 model may prove to be an important experimental tool to examine these links.

**PPARγ and SLE.** An important recent advancement in the treatment insulin resistance was the development of the thiazolidinedione drugs. Thiazolidinediones (including
rosiglitazone, pioglitazone, and ciglitazone) are agonists for a nuclear transcription factor peroxisome proliferator activated receptor gamma (PPARγ). PPARγ is highly expressed in adipose tissue, but is also expressed in endothelial and smooth muscle cells, medullary collecting duct, and multiple cells of the immune system including T cells, B cells, and monocytes (49; 95). When a ligand binds PPARγ it forms a heterodimer with retinoid X receptor to promote transactivation of a variety of genes. PPARγ activation can also lead to transrepression of gene transcription most likely through inhibition of NFκB activity. Numerous lines of evidence suggest a pleiotropic role for PPARγ. In addition to their insulin sensitizing effects, PPARγ activators may be used to lower blood pressure (75), protect the kidney (49), decrease oxidative stress (57), and reduce inflammation (95; 97). As a result of these actions, the therapeutic benefit of PPARγ agonists for a variety of pathologies have been tested including Alzheimer’s disease (59), cancer (112), glomerulosclerosis (49), and steatohepatitis (94) to name a few. Given the high prevalence of hypertension, renal injury, oxidative stress, and inflammation in patients with SLE, it may be of great value to investigate the importance of PPARγ and PPARγ activators in the progression and treatment of SLE hypertension.

Little is currently known about the importance of PPARγ in humans or in animal models of SLE. One genetic association study suggests that a common proline to alanine variant at amino acid position twelve of PPARγ2 does not associate with SLE (41). A second study (available only in abstract form) reports that PPARγ expression is increased in the glomerulus of patients with SLE, perhaps as a compensatory mechanism to the chronic inflammation (147). The MRL/lpr model of SLE is reported to have decreased renal
PPARγ expression that could promote overproduction of nitric oxide and exacerbate renal injury (33). Similarly, treatment of MRL/lpr mice with conjugated linoleic acid (an endogenous activator of PPARγ) reduces the production of inflammatory cytokines and auto-antibodies (14). My laboratory is currently examining the potential therapeutic benefit of rosiglitazone in the treatment of SLE hypertension and renal injury using the NZBWF1 mouse model. Because of its pleiotropic actions, PPARγ may be an important therapeutic target in SLE and SLE hypertension.

**Estrogen and SLE Hypertension**

Because of the strong predilection of SLE for women, sex steroids such as estrogen may play an important pathogenic role. Estrogen has strong immunomodulatory effects and can stimulate autoreactive B cells to increase auto-antibody production (29; 98; 99). In addition, recent evidence suggests that estrogen can increase leukocyte adherence to endothelial cells as well as stimulate cytokine production (26). The potential for oral contraceptives, hormone replacement therapy, and pregnancy, to promote SLE disease progression has been previously reviewed (9; 47). In the NZBWF1 model, studies show that pharmacological blockade of estrogen reduced auto-antibodies, proteinuria, and delayed mortality (125; 146). A recent study elegantly showed that the genetic deletion of the estrogen receptor alpha reduces mortality and renal histopathology in the NZBWF1 mice (23). These data support a role for estrogen at least in the renal pathology associated with SLE. Whether estrogen promotes hypertension during SLE has not been investigated. This is a potentially important question because SLE affects women during
their child bearing years, a time when they are typically expected to have a low risk for cardiovascular disease and hypertension.

**Inflammatory cytokines and SLE**

Recent evidence supports a close relationship between inflammatory mediators and hypertension. In humans, for example, blood pressure directly correlates with circulating inflammatory cytokines such as tumor necrosis factor alpha (TNF-α), interleukin 6 (IL-6), and C-reactive protein (CRP) (13; 16; 119; 139). These and other inflammatory cytokines are well known to be increased in the tissues and circulation of patients with SLE. Therefore, inflammatory cytokines are likely to be central mediators in the development of renal vascular changes that promote SLE hypertension. In further support of a possible central role in SLE hypertension, cytokines are potentially involved in all of the mechanisms described above. For example, cytokines promote renal vascular endothelial dysfunction (121), the development of AngII hypertension, the production of ET-1 (84), the generation of oxidative stress (138), and the progression of insulin resistance (18; 140). Moreover, a reduction in PPARγ expression or estrogen mediated immune cell modulation may promote the release of inflammatory cytokines. All of these are possible factors implicated in the development of SLE hypertension.

A growing body of literature suggests that anti-inflammatory and/or immune suppressive treatments may be an important therapeutic strategy for hypertension and cardiovascular disease. Studies in experimental animal models have shown that immune suppressive
drugs such as mycophenolate mofetil (MMF) decrease blood pressure and protect the kidneys (85). Genetic mouse models with deletions of inflammatory mediators such as chemokine receptor 2 (CCR2) or IL-6 are protected from AngII-mediated hypertension (73; 77).

Despite these types of studies, the exact role of the immune system and chronic inflammation in the progression of hypertension has not been fully elucidated. Therefore, understanding mechanisms that promote hypertension in SLE, a chronic inflammatory disorder, may prove valuable for better understanding the basis of essential hypertension. Inflammatory cytokines including, but not limited to, IL-6, TNF-α, CRP, and interferon gamma (IFNγ) figure prominently into the pathogenesis of human SLE and has been reviewed extensively (39; 65). Whether these cytokines are important in the progression of SLE hypertension has not been determined. The remainder of this review will focus on the possible role of IL-6 and TNF-α because of the evidence for their role in human essential hypertension. In addition to increased levels in humans with SLE, tissue levels of both IL-6 and TNF-α are increased in the NZBWF1 mouse model of SLE (19; 87; 91).

**Interleukin 6 and SLE.** Several lines of evidence suggest that IL-6 plays an important role in the pathogenesis of SLE. IL-6 is can promote B cell hyperactivity leading to increased production of auto-antibodies (34). In humans with SLE, serum levels of IL-6 are increased and generally correlate directly with disease activity (37; 129). In the NZBWF1 mouse model of SLE, data support a role for IL-6 administration to enhance glomerulonephritis through its immunostimulatory effects rather than through direct
effects on renal mesangial cells (115). Moreover, data from another study using the NZBWF1 model demonstrate that treatment with monoclonal antibodies to IL-6 decreases the production of auto-antibodies, proteinuria, and mortality (43). Despite these data, the role of IL-6 in the pathogenesis of SLE hypertension is not clear.

**TNF-α and SLE.** The role of TNF-α in the progression of SLE is controversial. Clinically, TNF-α antagonists are used in the treatment of rheumatoid arthritis (40); however, the efficacy of these drugs as a therapy for human SLE remains unclear. Serum levels and renal TNF-α expression correlate directly with SLE disease activity in humans suggesting that it may be important in the pathogenesis of SLE (3; 37). In support of this, a recent study showed that blockade of TNF-α with infliximab in humans with SLE decreased urinary protein and joint swelling despite causing an increase in dsDNA auto-antibodies (8). Contrary to this, another study reported that blockade of TNF-α promoted symptoms of SLE including the production of dsDNA auto-antibodies in patients with rheumatoid arthritis (32; 108). Therefore, the role of TNF-α in SLE remains unclear.

Similar to the conflicting observations in humans, evidence for the importance of TNF-α in the progression of SLE in NZBWF1 mice is also conflicting. One study reported that infusion of TNF-α in the NZBWF1 model of SLE accelerates the disease (19) while another reported that TNF-α infusion protects against the progression of SLE (58). This disparity may be explained by the infusion of different amounts of TNF-α in these studies. Further complicating the picture, a recent study utilized a genetic cross between one of the parental strains (NZB) for the NZBWF1 mice and TNF-α knockout mice (69).
The resulting F1 offspring developed nephritis, B cell hyperactivity, and dsDNA auto-antibodies (69). These data, therefore, suggest that TNF-α may have a protective role against SLE progression. Since the role of TNF-α in SLE remains uncertain, it is not surprising that the role of TNF-α in SLE hypertension has not been explored. Our preliminary data show that blockade of TNF-α lowers blood pressure and albuminuria in female NZBWF1 mice; however, the production of dsDNA auto-antibodies is increased. Further studies will be needed to determine the mechanism for the reduction in blood pressure by TNF-α antagonists.

**Summary and Conclusions**

SLE is a chronic autoimmune inflammatory disorder with a high prevalence of hypertension, renal disease, and cardiovascular risk. The mechanisms that contribute to SLE hypertension are likely multifactorial as would be expected with a complex genetic disorder. However, central to these multiple factors are inflammatory cytokines that can promote increased renal vascular resistance and reduced GFR leading to SLE hypertension. Inflammatory cytokines can mediate renal vascular changes resulting from an activated RAS or endothelin system, through increased oxidative stress, or through promoting oxidative stress. In addition, reductions in PPARγ expression or the immunomodulatory role of estrogens may promote inflammation. Thus, Figure 5 illustrates a general hypothesis for the central role of inflammatory cytokines to promote SLE hypertension and how multiple systems contribute to this final common pathway. It is my hope that understanding factors that lead to SLE hypertension will prove useful for
patients with SLE and ultimately yield new clues relevant to mechanisms causing human essential hypertension. Animal models of SLE such as the NZBWF1 mice will be a useful experimental tool to explore these mechanisms and work towards understanding the immunological basis for hypertension and SLE hypertension.
Figures

Figure 1. (A) Mean arterial pressure is increased in female NZBW1 mice (SLE) compared to the NZW parental controls. The pressure was measured in conscious tethered mice via indwelling carotid artery catheters. (Adapted from Ryan et al. Hypertension 48:988-993, 2006 with the permission of the publisher). (B) Acetylcholine mediated relaxation, an indication of endothelial function, is impaired in the carotid artery of NZBW1 mice compared with controls. Vessels were precontracted with the thromboxane mimetic U46619. (Adapted from Ryan et al. Am J Physiol Regul Integr Comp Physiol 292:R736, 2007 with the permission of the publisher).

Figure 2. Neutrophil Gelatinase Associated Lipocalin (NGAL), a marker of proximal tubule injury, is present in the urine of female NZBW1 mice with SLE but not parental controls (NZW). Lanes 1-3 and 4-6 represent individual control and SLE mice, respectively.

Figure 3. The renal cortex from female NZBW1 mice with SLE have increased monocyte and macrophage infiltration as assessed using the F4/80 antibody. The black arrows indicate the presence of monocytes and macrophage. (Adapted from Ryan et al. Hypertension 48:988-993, 2006 with the permission of the publisher).

Figure 4. Female NZBW1 mice with SLE are insulin resistant. Compared with parental controls, the NZBW1 mice have an impaired glucose tolerance test (Left) and
increased fasted plasma insulin levels. (Adapted from Ryan et al. Hypertension 48:988-993, 2006 with the permission of the publisher).

**Figure 5.** Flow diagram depicting possible pathways that promote SLE hypertension
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Figure 2

[Image of a gel showing lanes labeled Control 1, 2, 3 and SLE 4, 5, 6. An arrow points to NGAL.]
Figure 3
Figure 4
Figure 5

- SLE
- Inflammatory Cytokines (e.g., TNF-α, IL-6)
- RAS
- ET-1
- ROS
- PPARγ

↑ Pressure Natriuresis

↑ RVR/↓ RBF

Immune Cell Activation

↑ Auto-Antibody

Nephritis

SLE Hypertension

Estrogen

Leptin
<table>
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<tr>
<th>Criterion</th>
<th>Description</th>
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<tr>
<td>Malar Rash</td>
<td><em>“butterfly”</em> shaped rash across the cheeks</td>
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<tr>
<td>Discoid Rash</td>
<td>Skin rash in the shape of a coin or oval</td>
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<td>Photosensitivity</td>
<td>Skin rash caused by reaction to sunlight</td>
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<td>Oral Ulcers</td>
<td>Oral or nasopharyngeal ulcers</td>
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<td>Nonerosive Arthritis</td>
<td>Tenderness, swelling, or effusion of peripheral joints</td>
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<tr>
<td>Pleuritis, Pericarditis</td>
<td>Inflammation or effusion of the covering protecting the heart and lungs</td>
</tr>
<tr>
<td>Renal Disorder</td>
<td>Proteinuria, cellular casts</td>
</tr>
<tr>
<td>Neurological Disorder</td>
<td>Seizures, psychosis</td>
</tr>
<tr>
<td>Hematologic Disorder</td>
<td>Hemolytic anemia, leukopenia, lymphopenia, or thrombocytopenia</td>
</tr>
<tr>
<td>Immunologic Disorder</td>
<td>Anti-DNA, anti-Sm, or Anti-phospholipid antibodies</td>
</tr>
<tr>
<td>Positive Antinuclear Antibody</td>
<td>Anti-nuclear antibodies</td>
</tr>
</tbody>
</table>