Sex differences in the prevalence and progression of numerous cardiovascular diseases are well documented, with males typically exhibiting greater severity and progression of disease compared with age-matched females. In contrast, females are more likely to develop autoimmune disease compared with age-matched males, both clinically and experimentally. Nevertheless, there is growing evidence that certain autoimmune diseases, including systemic lupus erythematosus (SLE), are associated with an increased risk of developing cardiovascular disease. Based on the expanding literature linking the immune system with cardiovascular disease, the question arises if females lose their cardiovascular protection with immune dysfunction and the molecular mechanisms driving cardiovascular disease in SLE.

Historically, female sex hormones have been thought to contribute to the lower incidence of cardiovascular disease in premenopausal women. However, despite numerous studies designed to investigate the role of female sex hormones in cardiovascular disease, data from both animal and clinical research remain controversial. Therefore, it was with great interest that we read the study by Gilbert et al in the current issue of Hypertension, which was designed to determine whether estrogen has a causal role in the development of hypertension in adulthood in SLE, an autoimmune disease with high prevalence of hypertension and cardiovascular disease. Using an established mouse model of SLE (female NZBWF1), Gilbert et al have directly confirmed a protective role for 17β-estradiol against SLE-mediated hypertension and proteinuria in adult female mice, in part, by reducing tumor necrosis factor-α. In this study, animals were ovariectomized at 30 weeks and studied at 34 weeks, and the results are in contrast to those obtained where estrogens potentiate the onset of SLE when mice are ovariectomized at 6 to 8 weeks. Together, these studies suggest that female sex hormones may act as a double-edged sword in the development and progression of hypertension in SLE, with timing being the critical determinant of the inflammatory and cardiovascular impact of estrogen. The authors suggest that there are temporal effects of estrogens in SLE, with estrogens promoting humoral immunity during subclinical disease but protecting against inflammation and disease progression in adulthood.

It is well established that 17β-estradiol binds to its cognate receptors (ie, estrogen receptorα and estrogen receptorβ) to initiate extranuclear cytotoxic signaling pathways and nuclear expression of specific genes by associating with transcriptional cofactors. Nongenomic mechanisms trigger downstream signaling events through rapid post-translational modifications of numerous membrane and cytosolic signaling molecules, including mitogen-activated protein kinase, phosphatidylinositol 3 kinase, Akt, and endothelial nitric oxide (NO) synthase, which are critical in initiating an immediate response. One result of this concerted signaling cascade is an elevation of NO bioavailability, and NO has been suggested to be a primary mechanism for the protection of females against cardiovascular diseases and may contribute to the better resistance against infection among females.

However, during conditions of oxidative stress even an increase in NO could do a disservice through the formation of deleterious peroxynitrite and protein nitration, which contributes to additional cellular damage. There is evidence supporting an NO deficiency in SLE; therefore, any additional decrease in NO may potentiate disease progression in SLE, as well as many other cardiovascular diseases. Importantly, these detrimental effects will be primarily evident in acute pathological events, when the antioxidant properties of estrogens have a limited time to affect antioxidant potential compared with the robust increase in free radical production. SLE is known to be associated with increases in oxidative stress, apoptosis, and cellular injury. Indeed, the formation of autoantibodies against epitopes from apoptotic cells is known to be among the earliest symptoms and a hallmark of SLE. Moreover, elevated levels of anti-nitrotyrosine antibodies in serum of patients with SLE have been suggested to be responsible for the breakdown or bypass of self-tolerance. Therefore, under certain conditions, estrogen could actually promote increases in oxidative damage and disease progression. Alternatively, because decreases in NO bioavailability promote inflammation, and early loss of estrogen in SLE may promote disease progression, it could be speculated that the early loss of NO promotes SLE-induced cardiovascular disease.

In contrast, chronic low-level inflammation in established SLE may provide an adequate amount of time to reveal the protective properties of estrogen, as evidenced in the study by Gilbert et al, where mice were allowed to mature fully and were well into adulthood before sex hormones were removed. NO not only acts as a potent vasodilator, but also possesses...
antithrombotic, anti-inflammatory, and antiproliferative properties. Estrogen also elicits genomic mechanisms mediating relatively slow changes in gene expression, including antioxidant proteins. Therefore, long-term exposure to estrogens has the potential to induce multiple lines of defense against the development of cardiovascular disease. Our group recently reported that treatment with the nonselective NO synthase inhibitor NG-nitro-L-arginine methyl ester resulted in greater increases in blood pressure in female spontaneously hypertensive rats than males. Moreover, this increase was associated with greater increases in renal adhesion molecule expression and Th17 cell infiltration, which have been linked to the development of autoimmune disease. Our data suggest that NO is a critical regulator of blood pressure and the immune cell profile, particularly in females. Hence, an increase in NO bioavailability induced by estrogen, while damaging during acute oxidative stress, could postpone the development of cardiovascular complications, as demonstrated by Gilbert et al.

In conclusion, the present study provides a new paradigm for a dual role of estrogen in the initiation and progression of SLE, as well as offering protection against the progression of disease. Future investigations that directly confirm the particular molecular mechanisms behind female sex hormone dualism will allow for more defined control of estrogenic activity to achieve beneficial effects regardless of the stage of immune disease.

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