**The Sexual Dimorphism of Cardiovascular Disease:
Lessons from Rodent Models**

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Epidemiological studies have defined a sexually dimorphic pattern in the development of atherosclerotic vascular disease in humans. The incidence of cardiovascular disease is lower in premenopausal women than in age-matched men, but rises steadily after menopause. Postmenopausal women on hormone replacement therapy have less severe coronary artery disease and a lower risk for cardiovascular mortality than women without hormone treatment. Thus, estrogens, alone and in combination with progestins, inhibit the development of atherosclerotic cardiovascular disease in women. The mechanisms of this vasoprotective effect are complex and involve alterations in lipid metabolism, endothelial function, vascular smooth muscle cell (VSMC) proliferation and associated extracellular matrix formation, and vascular reactivity. Rodent models of vascular injury have been used to examine these mechanisms. Neointima formation after balloon injury of the carotid artery is reduced in intact female Sprague-Dawley rats compared to age-matched males. This sexual dimorphism is dependent on estrogen rather than testosterone since physiologic levels of exogenous estrogen can prevent neointima formation in damaged vessels of gonadectomized rats of both sexes, while neither endogenous or exogenous testosterone at physiologic levels affects neointima formation in this model. Estrogen inhibits the myointimal response to balloon injury by ~60%, an effect comparable to results observed with a variety of other antiproliferative agents in the rat carotid injury model. Exogenous progestin (medroxyprogesterone acetate) given alone does not alter the vascular injury response, but addition of progestin blocks the vasoprotective effect of estrogen on the vascular injury response in gonadectomized rats of both sexes. Progestin enhances the neointimal response in intact females, presumably by blocking the production of endogenous estrogen. In contrast, intact male rats are resistant to the

vasoprotective effects of exogenous estrogen despite attainment of physiologic (for females) serum estrogen levels. Functional (assessed by the ACh-induced relaxation response) and anatomic (assessed by the Evans blue dye technique) reendothelialization of the damaged vessel is more rapid in females than males and is further accelerated by administration of exogenous estrogen. These responses correlated with increased nitric oxide formation and may account, at least in part, for the vasoprotective effect of estrogen in this model.