Editorial

A radical idea: men and women are different

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See article by Dantas et al. [8] in this issue.

Gender has a pronounced influence on the type and severity of cardiovascular disease that will likely ensue during one's lifetime. Sex differences have been noted in most major cardiovascular diseases including coronary heart disease, stroke, and hypertension. Aside from the humanitarian benefit, a huge economic incentive exists for developing more effective treatments for hypertension, especially in Western societies. For example, in the United States, one in four adults has high blood pressure, with the estimated economic cost exceeding US$50 billion annually. Until age 55 years, a higher percentage of men than women has hypertension—a sex difference primarily due to a lower incidence in young, white females. Interestingly, in African-American and Mexican-American populations, the sex difference is negligible [1]. The underlying cause of this sexual dimorphism is unknown and has been the focus of much research. Discovering the mechanism for this protective effect should allow the development of novel pharmacological therapies for cardiovascular patients of both sexes.

Endothelial dysfunction is thought by many to be an initiating factor in many vascular diseases, including high blood pressure [2]. Hypertension is associated with impaired nitric oxide (NO)-mediated, endothelium-dependent vasodilation. For almost a decade, evidence has been provided that estrogen increases NO-dependent vasodilation and endothelial nitric oxide synthase (eNOS) protein levels [3]. In normotensives, experimental evidence indicates that the greater eNOS levels in premenopausal females are due to estrogen, and increased bioavailability of NO has been suggested to be a major contributor to cardiovascular disease reduction in premenopausal females. It is thought that enhanced endothelial production of NO not only reduces blood pressure, but may delay the onset and progression of atherosclerosis by numerous mechanisms, including enhancing endothelium-dependent vasodilation [4] and reducing endothelial cell adhesion [5].

In hypertension, the story may not be so straightforward. In models of hypertension, sex differences in eNOS levels and NO production have not been observed despite lower blood pressures in females. This observation has turned the attention of some to the potential for reduced bioavailability of NO in males being central to sex differences in blood pressure regulation. Bioavailability of NO can be reduced by inactivation of NO by reactive oxygen species [e.g. superoxide (O$_2^-$)]. Conversely, O$_2^-$ scavengers (e.g., superoxide dismutase) can increase bioavailability of NO and enhance NO-mediated, endothelium-dependent dilation [6]. In vitro, Ang-II stimulates endothelial cell O$_2^-$ production by NADPH oxidase and can be blocked by the AT1 receptor antagonist, losartan, suggesting that Ang-II-mediated hypertension may be exacerbated by NAPDH oxidase production of O$_2^-$ [7].

In this issue of *Cardiovascular Research*, Dantas et al. [8] report a marked sex difference in the production of O$_2^-$ in the mesenteric microcirculation of spontaneous hypertensive rats (SHR). In vivo generation of O$_2^-$ was found to be about twofold greater in arterioles of males compared to females. This sex difference in O$_2^-$ production was abolished by the NADPH oxidase inhibitor, DPI, and by the AT1 receptor antagonist, losartan. Furthermore, losartan treatment inhibited the overexpression of the NADPH oxidase components p22$_{phox}$, gp91$_{phox}$, p47$_{phox}$ (membrane-bound), and p67$_{phox}$ (cytosolic activator) in arterioles of males without affecting the response in females. The authors conclude that greater O$_2^-$ in male SHR is due to an AT1 receptor-mediated increase in NADPH oxidase expression. It can be speculated that this increased O$_2^-$ reduces NO bioavailability in the resistance microvasculature, contribut-
ing to exacerbated hypertension in males compared to females.

While the study of Dantas et al. represents a significant new direction for determining sex-based differences in vascular disease, important questions remain regarding sex differences in microvascular $O_2^-$ generation and hypertension. Recent clinical trials, such as the HERS trials [9], have underscored our lack of knowledge regarding sex hormone influences on vascular disease. Given the current clinical interest in sex hormone replacement therapy, both of estrogen and androgen, determining the specific contribution of sex hormones to the observed response will be important. In this regard, Dantas et al. did not determine whether the sex differences they observed were indeed sex hormone-driven. The question remains: Does estrogen in females inhibit NADPH oxidase, or does testosterone in males stimulate NADPH oxidase? The former would be consistent with studies showing that estrogen inhibits NADPH oxidase (gp9phox expression) in human umbilical vein endothelial cells [10], while the latter would be consistent with the finding that hypertension in the male SHR was due to testosterone [11]. Also important, Dantas et al. did not investigate whether NADPH oxidase inhibition lowers in vivo blood pressure to a greater extent in males, so the therapeutic potential of this finding remains uncertain.

In summary, the study by Dantas et al. provides the foundation for a new area of investigation regarding sex differences in the pathology of hypertension and perhaps other vascular pathologies, such as coronary heart disease and stroke. Significant information that would allow sex-specific therapies is still needed. However, evidence continues to mount that medicine is not exempt from the basic biological fact that men and women are indeed different, and may need to be treated therapeutically as such.

References