Cardiovascular effects of sex hormones

The impact of sex steroids on the cardiovascular system is of considerable importance and a potential area for therapeutic intervention. In general, animal and human studies of the vascular effects of sex hormones have suggested that oestrogen is beneficial, certain progestins may negate these effects and androgens may be potentially deleterious. In this issue of Clinical Science, Tejera et al. [1] present data on differential constrictor responses to $\alpha_2$-adrenoceptor stimulation in thoracic aortic segments from oestrous phase and ovariectomized female rats and control and castrated male rats [1]. Endogenous oestrogen or androgen increased the contractile responses to clonidine. In all four groups an intact endothelium, predominately via endothelial-dependent NO release, significantly attenuated the constrictor responses; this attenuation seemed to be greater in males. These results are of interest and add to the mosaic of data available on the cardiovascular effects of sex hormones. The effects of sex steroids are complex and are influenced by a variety of factors, including natural versus synthetic hormones, species, age, hormonal status, vessel preparation, endothelial function, disease state, lipid and coagulation factors.

Mechanisms of sex steroid action

(i) Oestrogens

Diverse biological effects of oestrogen have been demonstrated, including effects on intravascular parameters, vasomotor tone, vascular cell growth and atherogenesis. Intravascular effects include improved lipid profiles and lipid-oxidation status, alteration in carbohydrate metabolism and insulin resistance, effects on the renin-angiotensin system and activation of coagulation and fibrinolytic systems [2]. Oestrogen-enhanced vasodilatation has been frequently observed in \textit{in vitro} and \textit{in vivo} studies. Proposed mechanisms include calcium-entry blockade, endothelium-dependent (NO mediated) and endothelium-independent vasodilation, reduced sympathetic activity and reduced responses to endogenous vasoconstrictors. Oestrogen has been shown to inhibit vascular smooth muscle cell proliferation [3] and to ameliorate myointimal hyperplasia in rabbit allografts [4] and in the carotid artery of rats following balloon injury [5]. Oestrogen also appears to attenuate atherosclerotic plaque development, perhaps best appreciated from the cynomolgous monkey model [6]. In a series of studies, oophorectomized monkeys were randomized to placebo, oral or transdermal oestrogen alone or combined hormone-replacement therapy (HRT), with continuous or cyclic progestin during 2 years of an atherogenic diet. Oestrogen alone reduced atherosclerotic plaque by 50% (transdermal) or 70% (oral) compared with placebo, with no influence from addition of natural progesterone or cyclic medroxy progesterone acetate (MPA), but with attenuation from continuous MPA [6]. Human studies have shown that carotid arterial intima-medial thickness is lower in women on HRT [7], and angiographic studies have demonstrated reduced coronary atherosclerotic plaque in oestrogen-treated women [8].

(ii) Progestins

Progestins are rarely prescribed in isolation, but are combined with oestrogen to reduce endometrial disease. They are given as synthetic C-19 and C-21 derivatives and have variable metabolic effects. Progestin addition to oestrogen impacts on intravascular parameters, including lipid profiles and the haemostatic system; however, little is known of other metabolic effects. Progestin subtype and pattern of administration may be highly relevant. The postmenopausal oestrogen/progestin interventions (PEPI) trial [9] showed this variability in effects of different progestins in modulating the effects of oestrogen on plasma high-density lipoprotein. Progestins may oppose beneficial oestrogenic effects on vascular function with reduced arterial dilatation, compliance and blood flow [10]. They may also potentially attenuate anti-atherosclerotic effects of oestrogens [8].

(iii) Androgens

The cardiovascular effects of androgens have been much less studied than those of oestrogens, but reported results include deleterious effects on lipid metabolism, blood-pressure elevation and activation of the haemostatic system [11,12]. Gender differences exist in endothelial function and this may relate to greater release of NO from female than male animals [13]. However, the results presented by Tejera et al. [1] appear to suggest the reverse. In men, clinical scenarios for androgen use are diverse and include physiological replacement in hypogonadal males and supraphysiological replacement in males for either contraception or anabolic steroid abuse for enhancement of athletic performance. The most comprehensive data exist in the field of male contraception, where World Health Organization trials have documented a consistent 10% reduction in high-density lipoprotein levels with a 2–3-fold increase in endogenous androgen levels. With the increasing use of androgen therapy in postmenopausal women there is a need for
carefully controlled studies to evaluate the cardiovascular effects of androgens in humans.

**HRT and cardiovascular disease**

Observational human data, primarily focusing on HRT in postmenopausal women, have consistently suggested cardiovascular benefits [14]. A protective role of oestrogen is suggested by the low risk of cardiovascular heart disease (CHD) premenopause, a narrowing of the gender gap postmenopause, and the potential (now controversial) for reduced risk of CHD with postmenopausal HRT. Extensive observational data support a reduced risk of coronary artery disease in HRT users compared with non-users, with a meta-analysis showing a mean relative risk of 0.5 in current users, and 0.65 in ever users compared with non-users [14,15]. As with all observational data, these studies may be inherently biased, including the healthy user bias and the limited inclusion of participants taking progestin therapy (12%). However, these limited data do not support a significant adverse impact of progestins on the apparent HRT cardio-protective effects. Observational data pertaining to androgens are even more scant, especially pertaining to supra-physiological androgen treatment. Interestingly, hypogonadal males with low endogenous androgen levels have a high risk of cardiovascular disease. Endogenous androgen levels in females have been positively correlated to cardiovascular risk factors and, in women with polycystic ovarian syndrome, hyperandrogenism is associated with adverse metabolic profiles and insulin resistance. Literature on androgen replacement in women is again very scant, with effects likely to be confounded by interactions with other sex steroids.

There has been only one reported controlled interventional study in women: a secondary prevention study focusing on HRT effects on cardiovascular end-points in 2763 postmenopausal women who had pre-existing coronary artery disease. Despite improvements in plasma lipids, the 4 year study failed to show a net cardio-protective effect of combined oral HRT [16]. An initial increased event rate was noted, which then fell progressively to a mean relative risk of 0.67, yet no overall benefit was noted. A randomized, controlled trial of high-dose oestrogen in males also demonstrated increased cardiovascular events [17]. One potential explanation for the inconsistency between the results of these controlled trials and the previous observational studies may be the adverse influence of HRT on coagulation. Combined HRT activates coagulation based on haemostatic markers, confirmed by observational and controlled data, with a 3-fold increase in venous thrombosis. Potentially, this prothrombotic state may affect not only the venous but the arterial system, increasing the risk of cardiovascular events, especially in patients with pre-existing atherosclerosis who are prone to plaque rupture and vessel occlusion.

**Conclusions**

Research on sex steroids conducted in *in vitro* studies under non-physiological circumstances can provide useful information on potential mechanisms of action. But these endogenous hormones have an extraordinary range of effects in *in vivo* and it is hazardous to extrapolate to the clinical setting. We should not assume clinical benefits based on biologically plausible mechanisms of action, nor indeed on the wealth of cross-sectional observational data. Recent interpretations of oestrogen-related effects on arterial compliance and flow-mediated dilation must equally be treated with circumspection. Androgens are being used increasingly in both men and women. Moreover, the heterogeneity of the oestrogen receptor is now appreciated and the use of selective oestrogen receptor modulating substances (SERMs) is a reality, with both pharmaceutical products and plant-based compounds (phytooestrogens). In this setting, and armed with the lessons learned from research on oestrogens, it is clear we need further controlled clinical trials applied to all sex steroids.

HELENA TEEDE and BARRY McGRATH

Cardiovascular Research Unit, Department of Medicine, Monash University, Monash Medical Centre, Clayton, Victoria 3168, Australia

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**REFERENCES**