Editorial Highlight

Are men at risk? The role of testosterone in cardiovascular morbidity

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Right ventricular (RV) function is affected by and contributes to a number of disease processes, including pulmonary hypertension (PH), congenital heart disease, left ventricular (LV) dysfunction, and valvular heart disease. The importance of RV function, however, in diseases of epidemic proportion has generally been underestimated in the past, as it possesses only one-fifth of the muscular mass of the LV, and its function is restricted to pumping blood through a single organ. In recent years, significant attention toward the understanding of the prognostic value of RV function has predicted its important contribution to cardiovascular disease. Although the interdependence between the two ventricles has been well established with the notion that LV failure is a major contributor of RV dysfunction, the knowledge garnered from LV failure is not necessarily to be extrapolated to RV dysfunction. The anatomical features of the RV and the pathophysiology that leads to its dysfunction are categorically different from that of the LV. Specifically, LV mass and function are critically impacted by the dynamics of the systemic circulation whereas RV mass and function are associated with the pulmonary circulation.

Progressive changes in RV conformation, RV dilatation, and dysfunction are universal in idiopathic pulmonary arterial hypertension (IPAH). In parallel, recent advances in research in PH revealed metabolic and biochemical differences between the RV and the LV, thereby suggesting diverging responses to potential therapeutic agents. Sexual dimorphism also has a substantial impact on cardiovascular diseases. Accumulating evidence indicates greater cardioprotection in females than in males. Ventricular structure and function also differ in men from that of women.[1] Men experience significant cardiac myocyte loss with age at a rate at least three times that of women,[2] and are more susceptible to hypoxia.[3] These differences between men and women may be partially explained by hormonal influences.

Anabolic/catabolic imbalance, in favor of catabolism, contributes to the progression of chronic left-sided heart failure, and is a marker of poor prognosis. Although the effects of estrogens are well described, the role of androgens is not well recognized. Previous studies have demonstrated reduced cardiac volume and wall thickness in androgen receptor (AR) gene-knockout male mice.[4] Although ARs are expressed in both ventricles, most research has focused exclusively on LV, where testosterone has been shown to induce cardiomyocyte hypertrophy and increase fibrosis formation. A positive correlation between increased levels of testosterone and RV hypertrophy has recently been reported.[5] In both genders, higher androgen levels are associated with greater RV mass and volume, suggesting pleiotropic effects on RV function. In this context, a large cohort multi-ethnic study of atherosclerosis (MESA) recently revealed higher testosterone levels in men associated with greater RV stroke volume, mass, and greater RV volumes, while higher estradiol levels were associated with higher RV ejection fraction in women.[5] Murine models of myocardial infarction underlying a setting of castration indirectly support these observations as well with a dramatic alleviation of ventricular hypertrophy.[6] Although some studies have reported the beneficial effects of administering testosterone, no trials have reported its role on cardiac morphology or function.[7,8] Furthermore, it is surprising to note that none of these trials listed androgen deficiency as part of the inclusion criteria. The only trial examining the effects of testosterone administration in men with heart failure for a 12-month period was suspended, due to secondary effects.[7] More studies are warranted to

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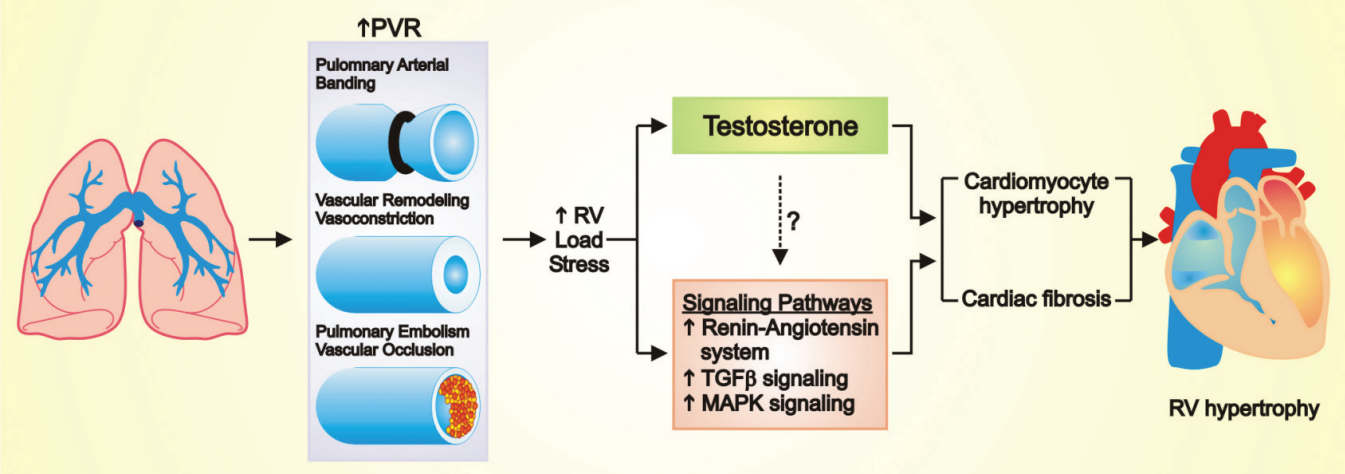

Figure 1: Potential role of testosterone in RV hypertrophy. Increase PVR due to pulmonary arterial banding, vascular remodeling, vasoconstriction, and/or pulmonary embolism leads to increased RV load stress. The study by Hemnes et al. demonstrates that under conditions of increased RV load stress, testosterone contributes to RV hypertrophy by increasing cardiomyocyte size and causing increased cardiac fibrosis, possibly through signaling pathways known to be involved in load stress-induced RV hypertrophy.

understand the elemental mechanisms of RV dysfunction with reference to its structure and function. Additionally, categorizing the role of testosterone in maintaining the RV structure and function will certainly help design novel targeted therapies.

The current study by Hemnes et al.,[9] published in this issue of *Pulmonary Circulation,* is the first experimental evidence to present the potential link between testosterone and RV function. Using an elegant combination of techniques including castration and pulmonary artery banding (PAB) in mice, Hemnes et al. demonstrate that depriving testosterone ameliorates PAB-mediated RV hypertrophy. Furthermore, castration results in improved survival after PAB in male mice. This study provides the first evidence that testosterone plays a role in load stress-induced RV hypertrophy possibly by contributing to increased cardiomyocyte size and increased fibrosis (Fig. 1). The exact molecular mechanisms by which testosterone promotes RV dysfunction, however, have yet to be identified. Given that RV pressure overload causes upregulation of the renin-angiotensin system, increased TGFβ signaling, and increased MAPK signaling resulting in cardiac hypertrophy and fibrosis,[10] it is possible that testosterone may interact with these established signaling pathways leading to RV remodeling. Conventional monocrotaline (MCT) or hypoxia models of PH and RV dysfunction may provide further insight into the role of testosterone in RV function. These rodent models of PH with associated RV phenotypes are well established and described in terms of cellular mechanisms over the PAB model and would provide an added dimension of exploration to investigations on testosterone. Experimentally, rodent models also provide enhanced apical imaging windows to accurately estimate RV systolic pressure and pulmonary arterial pressure.

At the cellular level, understanding the molecular signaling mechanisms of testosterone in RV remodeling may assist in developing new therapeutic modalities to diagnose, prevent, and treat RV dysfunction. Subsequently, establishing novel transgenic models associated with testosterone signaling may be a worthwhile approach to further dissect the chamber-specific molecular responses. Additionally, investigating a broad array of co-regulatory proteins essential for hormone receptor functioning may be consequential. This information may indeed help institute appropriate and novel combinations of hormonal antagonists as therapy for RV dysfunction. Therefore, this first experimental evidence of the relationship between testosterone and RV function by Hemnes et al. enhances our understanding of RV function and provides a new window of investigation into PH and RV dysfunction.

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