Editorial Commentary

Gender Dependency in the Pathogenesis of Cardiac Hypertrophy

Effect of Norepinephrine on Transforming Growth Factor-β Release in Female Heart

Ian M.C. Dixon, Vanja Drobic

Representing the most numerous nonmyocytes in the myocardium, adult cardiac fibroblasts (and myofibroblasts) function to synthesize fibrillar collagens and thus maintain the integrity of the cardiac extracellular matrix (matrix). Matrix remodeling is manifest as interstitial fibrosis of the remnant heart or the progressive evolution of the structure of the infarct scar in the etiology of post-myocardial infarction heart failure. In normal heart tissue, matrix protein secretion and deposition is carried out exclusively by cardiac fibroblasts with relatively low turnover of proteins, whereas contractile and hypertrophic myofibroblasts are the relevant phenotypic variant in wound healing or in hypertrophied and fibroblasts with relatively low turnover of proteins, whereas secretion and deposition is carried out exclusively by cardiac infarction heart failure. In normal heart tissue, matrix protein structure of the infarct scar in the etiology of post-myocardial infarction heart failure. In normal heart tissue, matrix protein structure of the infarct scar in the etiology of post-myocardial infarction heart failure.1 In normal heart tissue, matrix protein structure of the infarct scar in the etiology of post-myocardial infarction heart failure.1 In normal heart tissue, matrix protein structure of the infarct scar in the etiology of post-myocardial infarction heart failure.1

Much of the current literature that addresses cardiac fibroblast or myofibroblast function deals with the effects of a limited number of profibrotic factors and frequently addresses the interplay of these stimuli. Whereas interstitial fibrosis is a component of cardiac hypertrophy and contributes to the development of heart failure and norepinephrine stimulation of nonmyocytes is linked to the activation of collagen genes, the precise mechanisms of cardiac myofibroblast activation by this ligand are not well understood.

Recently, a direct relation between increased sympathetic activity and hypertensive left ventricular hypertrophy was demonstrated in a small human cohort (notably, ≈35% of these patients were female). Indeed, β-blockers are again among the agents of choice in the clinician’s armament for treatment of cardiac hypertrophy and heart failure. In contrast, α-blockers have attracted relatively little attention in the clinical setting. Despite the association between plasma norepinephrine and incidence of maladaptive cardiac hypertrophy, the role of norepinephrine as a synergistic partner with common trophic cytokines, such as members of the transforming growth factor (TGF)-β superfamily, in the pathogenesis of cardiac hypertrophy heart is undefined.

Precisely how myofibroblasts integrate norepinephrine and TGF-β (TGF-β1, TGF-β2, and TGF-β3) signals in cardiac hypertrophy and failure is unclear at the level of ligand release. In contrast, it is well known that suppression of angiotensin results in improved outcomes in animal models and patients with maladaptive cardiac hypertrophy and failure secondary to myocardial infarction, and this is in part related to a reduction of cytokine expression. TGF-β1 is a known stimulus for cardiac myocyte growth as well as for fibrillar collagen secretion by cardiac fibroblasts and myofibroblasts.

Despite the number of clinical and basic science reports in recent years that have dealt with aspects of heart failure, female patient participation in heart failure trials is usually a fraction of that of their male counterparts. Support for the argument of gender differences in profile (including age of onset and comorbidities) and management of congestive heart failure exists, justifying further investigation of gender-dependency in the pathogenesis of cardiac hypertrophy and failure. There is little data that deals specifically with development of cardiac hypertrophy in female animal models. Whether the male myocardium differs from the female in release or effects of TGF-β in the diseased heart remains an open question. Data presented by Briest et al in this issue of Hypertension supports the induction of TGF-β1 in female rat heart subjected to norepinephrine infusion. The current study also includes novel data about TGF-β1, TGF-β2, and TGF-β3 release in female hearts and how this event is linked to functional changes in cardiac fibroblasts.

Cardiac Hypertrophy

In response to one of a number of pathological stimuli (e.g., myocardial infarction), the overloaded heart adapts with increased muscle mass (cardiac hypertrophy), usually preceding the occurrence of congestive heart failure, a major cause of death in the North American population. Severe hypertrophy is associated with increased myocyte size and decreased intrinsic cardiac performance.

The development of fibrosis in congestive heart failure is a complex process and may involve input from multiple factors. It is becoming clear that myofibroblast behavior may also potentiate wound healing and eventual cardiac fibrosis. TGF-β1 is widely studied as a stimulus for fibroblast and myofibroblast function, that is, extracellular matrix deposition, in the setting of cardiac dysfunction. TGF-β1 is known to stimulate focal adhesion supermaturation in myofibroblasts, which is associated with reduced turnover and protein synthesis in these cells.

The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

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Hypertension is available at http://www.hypertensionaha.org
DOI: 10.1161/01.HYP.0000141484.53649.6f
decreased cell motility. Thus, a clear understanding of control of TGF-β release in heart is of considerable importance to understanding the pathogenesis of hypertrophy.

**Biology of TGF-β in the Heart and the Putative Role of Norepinephrine in Control of Expression**

With respect to myofibroblast function, TGF-β1 mediates cell growth and differentiation, tissue wound repair, and extracellular matrix production, including regulation of fibrillar collagens, and is expressed in the normal and hypertrophied myocardium. In primary fibroblasts, TGF-β1 is likely to exert effects that impair motility and reduce overall proliferation. TGF-β1 ligand signaling from cell-surface receptors to the nucleus is transduced by Smads and their DNA-binding partners. TGF-β1 receptor type I and II are Ser/Thr kinase class proteins and signal through receptor-regulated Smads (R-Smad 2 or 3) by specific recognition and phosphorylation steps. Smad access to Ser/Thr kinase receptors is regulated by Smad anchor for receptor activation (SARA) proteins that bind unphosphorylated R-Smads. Activated R-Smads dissociate from SARA and complex with common Smad 4 as heterologimers (dimers and trimers) that translocate to the nucleus where binding to a DNA-binding protein occurs. R-Smad activation has been linked to activation of collagen genes.

Although crosstalk between angiotensin and TGF-β1 ligands has been addressed, very little work has been done to examine the role of putative interplay between norepinephrine and TGF-β in heart failure. The work by Briest et al provides support for this concept in adult myocardium.

In this issue, it is demonstrated that ratios of TGF-β1/β2/β3 mRNAs are differentially expressed in male versus female rat heart either in basal conditions or with norepinephrine treatment in both nonmyocyte and myocyte fractions of the left ventricle. Defining the distinguishing mechanisms between female versus male cardiac hypertrophy and heart failure and outlining their similarities are of paramount importance. We suggest that the benefits gained by the addition of an increased number of basic science articles using experimental models of cardiac hypertrophy and failure that focus attention on female/male comparisons may be profound. Thus, the current article begins to add to basic research data that will add to information gained from clinical trials that include significant numbers of women in their test groups.

**Acknowledgments**

V.D. is supported by a studentship from the St. Boniface General Hospital Research Foundation. I.M.C.D. holds the Myles Robinson Heart Fund Scholarship at the University of Manitoba.

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Hypertension. 2004;44:392-393; originally published online August 23, 2004;
doi: 10.1161/01.HYP.0000141484.53649.6f
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2004 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/44/4/392

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