Journal of the American College of Cardiology
© 2011 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 58, No. 6, 2011
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2011.03.043

EDITORIAL COMMENT

When Gonads Talk to the Heart

Sex Hormones and Cardiac Endocrine Function*

Aldo Clerico, MD,† Claudio Passino, MD,† Michele Emdin, MD, PHD‡

Pisa, Italy

Cardiovascular risk is significantly lower in normally cycling women compared with men. This difference is abolished after menopause, suggesting a link with sex steroid hormones. Early studies on cardiac endocrine function disclosed higher natriuretic peptide concentrations in women than in men, suggesting the hypothesis that female sex steroid hormones could directly stimulate cardiomyocyte hormone production and secretion (1). Kuroski de Bold (2) hypothesized that an improved cardiovascular risk profile in cycling women could be associated with some estrogen stimulatory effect on cardiac endocrine function. Indeed, cardiac natriuretic peptides exert several protective actions on the heart and vessels, including: 1) vasodilatation; 2) promotion of diuresis/natriuresis; and 3) inhibition of hypertrophy, fibrosis, and apoptosis either directly or via inhibition of the sympathetic and renin-angiotensin-aldosterone systems, as well as the release or action of endothelin and vasopressin (1).

See page 618

More recently, 3 large population-based studies have indicated that male sex steroid hormones might modulate cardiac endocrine function too (3–5). These studies demonstrated a significant inverse association between the circulating levels of B-type natriuretic peptide (BNP) or N-terminal fragment of pro-B-type natriuretic peptide (NT-proBNP) and male sex steroid hormones (i.e., total and free testosterone) in both sexes (3–5), whereas the association with estradiol was found to be weak or not significant at all (3,4). Furthermore, these studies reported that levels of sex hormone–binding globulin (SHBG) are positively associated with NT-proBNP levels in both male and female adolescents (4), as well as in adult women (3,5) and men (5). Testosterone and estradiol circulate in the bloodstream mostly bound to SHBG, with levels that directly influence bioavailability of sex hormones; only a small fraction of total steroid concentration is unbound or "free" (1% to 5%) and biologically active (i.e., able to enter a cell and activate its receptors).

Lam et al. (5), in this issue of the *Journal*, evaluate plasma NT-proBNP, total testosterone, and SHBG concentrations in 4,056 adult men and women from the Framingham Heart Study Third-Generation Cohort; estradiol was not measured. They found lower NT-proBNP plasma levels in men than in age-matched women and higher NT-proBNP levels in women receiving hormonal contraceptives than in women who were not (5). Moreover, serum free (non–protein-bound) testosterone was positively and serum SHBG was negatively related to circulating NT-proBNP levels (5). The investigators suggested the hypothesis that androgens suppress NT-proBNP and that differences in free testosterone levels may largely explain the sex- and hormone-related differences in circulating levels of natriuretic peptides. They concluded that lower levels of circulating androgens and the potentiating effect of exogenous female hormone therapy contribute to the higher circulating NT-proBNP levels in women.

These findings (3–5) need detailed consideration. Data concerning variations in BNP and NT-proBNP values from birth to puberty are poor; indeed, only 2 recent studies reported reference BNP/NT-proBNP values for infants and pre-puberal boys and girls (6,7). In cycling women, estradiol concentrations are greatly variable during the cycle (up to 50-fold). For accurate physiological and clinical studies, blood samples should be collected at the same (estrogenic or luteal) phase of the cycle in all women, and multiple sampling throughout the same cycle (or even repeated on more than 1 cycle) should be considered necessary. Furthermore, environmental, social, economical, and ethnic differences all play an important role in determining the age of onset of both puberty and menopause, greatly increasing the between-subject variability in female sex steroid levels. Because of great biological variability in estradiol concentrations, it is not surprising to find weak or even absent association between estradiol and BNP/NT-proBNP levels in large population-based studies (3,4).

On the other hand, a significant and positive association between SHBG and cardiac natriuretic peptide levels (3–5) may require an alternative interpretation to the one suggested by Lam et al. (5), indicating a relevant influence (instead of no effect) of estrogenic status on BNP/NT-proBNP levels. Indeed, sex steroid hormones regulate the liver production of SHBG in an opposite way: estrogens show a powerful stimulatory action, whereas androgens have an inhibitory one (8). Accordingly, increased SHBG levels should indicate a relative estrogenic activation with respect to the androgenic system (8). Plasma SHBG levels are low at birth, increase gradually, and peak just before puberty, when the levels decrease in parallel with the increase in

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

From the †Scuola Superiore Sant'Anna Pisa, Italy; and the ‡Fondazione CNR-Regione Toscana G. Monasterio, Pisa, Italy. The authors have reported that they have no relationships to disclose.

androgen levels, particularly in boys (9). In adults, SHBG levels in women are on average twice as high as those in men (9). In men, serum SHBG levels gradually increase with age (in the ninth decade, the levels are double those in the third decade) (10), whereas in women, the SHBG levels dip transiently after menopause, increasing thereafter (11).

Actually, causal-effect relationships can be better demonstrated by means of experimental studies, using animal and clinical models, rather than population studies. Unfortunately, there have been only a few studies in animal models specifically designed to investigate the influence of sex steroid hormones on cardiac endocrine function, all regarding atrial natriuretic peptide (ANP) but not BNP (12). In rats, both ovariectomy and orchiectomy decreased atrial ANP mRNA transcripts in vivo, whereas pretreatment of Wistar female rats with estradiol and progesterone for 7 days increased atrial ANP gene expression (13). It was observed in another study that plasma ANP concentrations and atrial stores were increased by orchiectomy in male rats, with testosterone replacement decreasing plasma ANP concentrations but not atrial stores (14). Other studies have shown that testosterone stimulates synthesis and secretion of both ventricular and atrial ANP in newborn rat atrial cultured myocytes (15,16).

Some clinical studies have demonstrated that estrogens, administered for contraception in pre-menopausal women (5) or as hormone replacement therapy in post-menopausal women (17,18), increase the circulating levels of BNP and NT-proBNP. Moreover, androgen receptor blockade, and to a lesser extent, androgen suppression cause an increase in NT-proBNP levels in men with prostate cancer (19).

On the whole, data in the literature have suggested antagonist effects of androgens (inhibitory) and estrogens (excitatory) on cardiac endocrine function, but we still lack information on how this balance exerts its influence in either gender throughout the human life span. The hypothesis that gonadal function may regulate cardiac endocrine function, thus contributing to the gender difference in cardiovascular risk, needs further experimental effort to show 1) the conclusive demonstration that sex steroids are able to affect (increase or decrease) the production/secretion of BNP from mammalian/human cardiomyocytes both in cell cultures and in vivo (12); 2) the knowledge of the exact mechanisms and of the evolution of male/female steroid balanced action on cardiac endocrine function, from childhood to puberty, maturity, and old age; and 3) the evaluation of the relative impact/interplay of male and female sex hormones, SHBG, and cardiac natriuretic peptides, with respect to their predictive value for cardiovascular events in large cohorts, such as the Framingham one.

Reprint requests and correspondence: Dr. Aldo Clerico, Department of Laboratory Medicine, Fondazione G. Monasterio CNR-Regione Toscana, Via Giuseppe Moruzzi 1, 56124 Pisa, Italy. E-mail: clerico@ifc.cnr.it.

REFERENCES

1. Clerico A, Recchia FA, Passino C, Emdin M. Cardiac endocrine function is an essential component of the homeostatic regulation network: physiological and clinical implications. Am J Physiol Heart Circ Physiol 2006;290:H17–29.
2. Kuroski de Bold ML. Estrogen, natriuretic peptides and the renin–angiotensin system. Cardiovasc Res 1999;41:524–31.
3. Chang AY, Abdullah SM, Jain T. Associations among androgens, estrogens, and natriuretic peptides in young women: observations from the Dallas Heart Study. J Am Coll Cardiol 2007;49:109–16.
4. Saenger AK, Dalenberg DA, Bryant SC, Grebe SK, Jaffe AS. Pediatric brain natriuretic peptide concentrations vary with age and sex and appear to be modulated by testosterone. Clin Chem 2009;55:1869–75.
5. Lam CSP, Cheng S, Choong K, et al. Influence of sex and hormone status on circulating natriuretic peptides. J Am Coll Cardiol 2011;58:618–26.
6. Cantinotti M, Storti S, Parri MS, Prontera C, Murzi B, Clerico A. Reference intervals for brain natriuretic peptide in healthy newborns and infants measured with an automated immunoassay platform. Clin Chem Lab Med 2010;48:697–700.
7. Nir A, Lindinger A, Rauh M, et al. NT-pro-B-type natriuretic peptide in infants and children: reference values based on combined data from four studies. Pediatr Cardiol 2009;30:3–8.
8. Pugeat M, Nader N, Hogeveen K, Raverot G, Déchaud H, Grenot C. Sex hormone-binding globulin gene expression in the liver: drugs and the metabolic syndrome. Mol Cell Endocrinol 2010;316:53–9.
9. Cunningham SK, Loughlin T, Culliton M, et al. Plasma sex hormone-binding globulin levels decrease during the second decade of life irrespective of pubertal status. J Clin Endocrinol Metab 1984;58:915–8.
10. Vermeulen A, Rubens R, Verdonck L. Testosterone secretion and metabolism in male senescence. J Clin Endocrinol Metab 1972;34:730–5.
11. Preziosi P, Barrett-Connor E, Papoz L, et al. Interrelation between plasma sex hormone-binding globulin and plasma insulin in healthy adult women: the Telecom study. J Clin Endocrinol Metab 1993;76:283–7.
12. Clerico A, Fontana M, Vittorini S, Emdin M. The search for a pathophysiological link between gender, cardiac endocrine function, body mass regulation and cardiac mortality: proposal for a working hypothesis. Clin Chim Acta 2009;405:1–7.
13. Hong M, Yan Q, Tao B, et al. Estradiol, progesterone and testosterone exposures affect the atrial natriuretic peptide gene expression in vivo in rats. Biol Chem Hoppe Seyler 1992;373:213–8.
14. Hwu CM, Tsai SC, Lau CP, et al. Increased concentrations of atrial and plasma atrial natriuretic peptide in castrated male rats. Life Sci 1993;52:205–12.
15. Matsubara H, Hirata Y, Yoshimi H, et al. Effects of steroid and thyroid hormones on synthesis of atrial natriuretic peptide by cultured atrial myocytes of rat. Biochem Biophys Res Commun 1987;145:336–43.
16. Matsubara H, Hirata Y, Yoshimi H, et al. Ventricular myocytes from neonatal rats are more responsive to dexamethasone than atrial myocytes in synthesis of atrial natriuretic peptide. Biochem Biophys Res Commun 1987;148:1030–8.
17. Maffei S, Del Ry S, Prontera C, Clerico A. Increase in circulating levels of cardiac natriuretic peptides after hormone replacement therapy in postmenopausal women. Clin Sci (Lond) 2001;101:447–53.
18. Karjalainen AH, Ruskoaho H, Vuolteenaho O, et al. Effects of estrogen replacement therapy on natriuretic peptides and blood pressure. Maturitas 2004;47:201–8.
19. Dockery F, Bulpitt CJ, Agarwal S, et al. Anti-androgens increase N-terminal pro-BNP levels in men with prostate cancer. Clin Endocrinol 2008;68:59–65.

Key Words: BNP ■ cardiovascular risk ■ estradiol ■ NT-proBNP ■ sex steroids ■ SHBG ■ testosterone.