The natriuretic peptide (NP) hormone system has intrigued cardiovascular scientists since the first report of a biological response to intravenous injection of rat atrial extract by de Bold in 1981 (1). A host of protective biological functions of atrial and B-type natriuretic peptides (ANP and BNP) have subsequently been confirmed, including natriuresis, vasodilation, antiproliferative effects in the vasculature and in cardiac muscle, lusitropy, and even lipolysis (2). Measurement of BNP and the N-terminal fragment of its pro-hormone (NT-proBNP) are now routinely performed for heart failure diagnosis, and for risk assessment across multiple cardiac conditions. These uses capitalize on the counter-regulatory response of the NP system to the pathophysiological stimulus of myocyte stretch, rather than assessing potential primary or even primordial protective roles of this hormone system.

Given the favorable biological effects of ANP and BNP, it is plausible that natural variation in hormone levels may contribute to the development of cardiovascular conditions such as hypertension, left ventricular hypertrophy, and heart failure, and potentially even metabolic conditions such as visceral obesity and diabetes. Individuals with lower circulating NP levels, due to heritable or environmental factors, may thus be predisposed to cardiometabolic disease. This concept has been aptly termed a natriuretic peptide “handicap” (3). However, studying these primary protective NP effects in humans is difficult, requiring careful control for factors that may drive a counter-regulatory release of NPs, and thereby obscure or even reverse the direction of putative protective associations.

In carefully conducted observational studies performed in healthy adults, several noncardiac factors have been identified that contribute to NP variation among individuals without clinically evident cardiovascular disease. For example, African-American race/ethnicity, male sex, and higher body mass consistently associate with lower NP levels in healthy adults (3-6). Race/ethnic differences in NP levels appear to be mediated in part by heritable factors, because genetic admixture studies have demonstrated lower NT-proBNP among individuals with a greater proportion of African ancestry (7,8). Moreover, variants in the NP A and B gene among whites (9) and in the corin gene among African-Americans (10,11) associate with hypertension and left ventricular hypertrophy. By contrast, variation in NP by body mass and sex appears to be mediated in part through differences in sex hormones.

Obesity has long been known to associate with lower NP levels (3). This had been thought to be due to increased BNP clearance via enhanced expression of the natriuretic peptide clearance receptor (NPR-C) in adipocytes. However, this hypothesis was largely disproven by studies using dual-energy x-ray absorptiometry scanning, which found that the association of body mass with NP levels was explained by lean mass rather than fat mass (5). Moreover, the inverse association of body mass with NP levels was identical for BNP and NT-proBNP, indicating the effect of body mass must be through NP synthesis and/or release, rather than clearance, because NPR-C does not bind NT-proBNP.

NP differences between men and women, and between pre- versus postmenopausal women, had
originally been attributed to differences in estrogens (12). However, free testosterone levels differ by as much as 40-fold between men and women, far exceeding differences in estrogens. Moreover, androgen levels fall much less than estrogens after menopause, leading to a relative androgen excess in postmenopausal women. The first large observational study associating sex hormones with natriuretic peptide levels was performed among women enrolled in the Dallas Heart Study (13). This study found a strong inverse and independent association between free testosterone, but not estrogens, and NT-proBNP and BNP levels. Intriguingly, the inclusion of androgens into models that included body composition led to marked attenuation of the association of body composition with natriuretic peptide levels, suggesting that sex, menopausal status, and body mass associations with NPs may all be mediated in part through androgen suppression of NP synthesis and/or release.

Subsequently, Lam et al. (14), using the Framingham cohort, extended the observation of an inverse association of androgens and NT-proBNP to men, and further demonstrated that accounting for free testosterone attenuated the association of both sex and menopausal status with NP levels. Importantly, the proportion of variance explained by androgens in these cohorts was at least as large as that explained by cardiovascular risk factors or renal function (13,14).

These observational data have been supported by several natural experiments and small clinical trials. For example, in an observational study in men with prostate cancer, androgen inhibition was associated with rising NT-proBNP levels (15). In a randomized controlled trial of 51 women with hypopituitarism, transdermal testosterone administration decreased NT-proBNP levels proportionately with the increase in free testosterone (16). Similarly, in a randomized controlled trial of 88 men with diabetes and low testosterone levels, intramuscular testosterone injections lowered NT-proBNP compared with placebo (17).

In this issue of the Journal, Bachmann et al. (18) use a simple, but elegant, approach to directly test the hypothesis that androgens suppress natriuretic peptide hormone levels. In a study of 151 healthy men, goserelin acetate was administered to suppress endogenous production of gonadal steroids, along with anastrozole to suppress conversion of testosterone to estradiol. The latter intervention is particularly important because prior studies had not specifically suppressed the conversion from testosterone to estradiol, and thus could potentially have conflated effects of estrogens and testosterone on natriuretic peptide levels. After suppression of gonadal steroids, subjects were randomized to either placebo or testosterone replacement. Those individuals who did not receive testosterone replacement had very low serum testosterone levels and, over time, manifested modest, but statistically significant, increases in NT-proBNP levels. Testosterone replacement markedly attenuated the NT-proBNP increase.

Key strengths of this study were enrolling healthy participants, completely suppressing testosterone and conversion to estradiol, and then replacing testosterone in a randomized stepped dose fashion to physiological levels. This allowed the investigators to isolate the effects of testosterone on NP levels, minimizing the impact of drivers of counter-regulatory release of NPs. Testosterone levels varied 10-fold across the range of replacement doses, whereas estradiol was effectively suppressed. The authors should be applauded for an experiment that very precisely answers the mechanistic question of interest.

What are the implications of the present study? Bachmann et al. (18) provide additional insight into factors that may lead to NP differences, both between men and women and across the lifespan. Decreases in androgen levels occur with male aging, whereas in women, a relative androgen excess is seen after menopause. Differences in androgens, as acknowledged by the authors, are unlikely to fully explain sex-based differences in NPs, but certainly play an important role.

Because this is a mechanistic trial, there are no direct clinical implications. Moreover, despite the variation in testosterone levels achieved in the study, changes in NP levels were modest, with an absolute difference in NT-proBNP of approximately 10 pg/ml between men with 90% suppression and those with full replacement. Thus, the impact of androgen-related NP suppression on relevant downstream cardiac and metabolic outcomes is uncertain. Although it is possible that strategies to raise natriuretic peptide levels, such as via neprolysin inhibition, may offer preventive benefits to individuals at risk for cardiometabolic disease, it is not clear that the magnitude of any potential benefit would vary by androgen levels. It would be of interest to embed sex hormone measurements within future trials testing administration of neprolysin inhibitors in various clinical and prevention scenarios.

In summary, this definitive experiment by Bachmann et al. (18) builds upon prior observational
studies and smaller clinical trials, and provides convincing evidence of suppression of natriuretic peptide synthesis via androgens. Additional study is needed to determine whether the modest differences seen in NP levels across wide variation in testosterone provides actionable clinical information.

**REFERENCES**


**KEY WORDS** androgens, BNP, natriuretic peptides, sex hormones
Natriuretic peptides are a family of three structurally related hormone/paracrine factors. Atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP) are secreted from the cardiac atria and ventricles, respectively. ANP signals in an endocrine and paracrine manner to decrease blood pressure and cardiac hypertrophy. BNP acts locally to reduce ventricular fibrosis. C-type natriuretic peptide (CNP) primarily stimulates long bone growth but likely serves unappreciated functions as well. ANP and BNP activate the transmembrane guanylyl cyclase, natriuretic peptide receptor-A (NPR-A). CNP