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EDITORIAL

Sex Hormone-Binding Globulin and Heart Failure: a Passive Carrier of Steroid Hormones or an Active Hormone Itself?

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Although the links between the endocrine and cardiovascular systems have been neglected for many years, there is increasing evidence that the myocardium, as with all body tissues and organs, remains under constant hormone influences. Experimental and clinical models have indicated that virtually all the hormone receptors are present within cardiomyocytes and other cellular elements of the myocardium. Abnormal levels of thyroid hormones, catecholamines, growth hormone, and steroid hormones, to name but a few, may lead to heart dysfunction, and hormone derangements appear to have even greater clinical relevance in the case of pre-existing heart failure (HF).

Aldosterone and cortisol were first isolated and synthesized over 50 years ago. Since then, cardiologists and cardiovascular scientists have focused on these 2 classes of steroid hormones (mineralocorticoids and glucocorticoids). Nowadays, the multidimensional input of aldosterone and cortisol signaling into the pathogenesis of cardiovascular disease, in particular HF, is undisputed,[1] and aldosterone antagonists have been shown to reduce mortality and morbidity, becoming an obligatory part of standard therapy in HF patients. Four major enzymatic pathways are involved in steroidogenesis, 2 of which are related to the synthesis of mineralocorticoids and glucocorticoids, whilst the others are associated with the synthesis of androgens and estrogens. In functional terms, they create the interrelated system of enzymatic pathways which is indispensable to the synthesis of various steroids.[2] Bearing in mind the established derangements within the mineralocorticoid and glucocorticoid pathways in HF, it is surprising that the rest of this enzymatic system and its hormone products have been neglected for so long.

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We have demonstrated the high prevalence of deficiencies in circulating testosterone and dehydroepiandrosterone sulphate (DHEAS) in men with systolic chronic HF in comparison with healthy peers.[3] We have also showed that reduced and increased levels of serum estradiol are prevalent in men with systolic chronic HF.[4] Moreover, derangements in both androgen and estrogen metabolism have significant clinical and prognostic consequences in these patients.[3-6] We have observed that testosterone deficiency is related to impaired exercise capacity, augmented depressive symptoms, reduced haemoglobin level, and reduced bone mass, whereas DHEAS deficiency is accompanied by high plasma levels of N-terminal pro-B type natriuretic peptide and augmented depressive symptoms in men with systolic chronic HF. In men with systolic chronic HF, deficiencies in circulating testosterone, DHEAS and insulin-like growth factor 1 are independent predictors of high 3-year mortality, even after adjusting for conventional confounders.[3] In addition, we have demonstrated a U-shaped curce relating 3-year mortality in these patients and serum estradiol. In other words, high and low levels of circulating estradiol were related to increased mortality when compared with the middle quintile of estradiol, irrespective of circulating androgen levels and other clinical risk factors.[4]

The study by Pascual Figal et al describing circulating levels of sex hormone binding globulin (SHBG) in men with systolic chronic HF,[7] provides interesting data which expand our knowledge on the functioning of the steroid hormone system in these patients. In this context, SHBG plays two major roles. Firstly, it can modify the balance between circulating steroids and those entering

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peripheral tissues, and it can also interfere with the functioning of target cells.

Originally, SHBG was discovered as a glycoprotein secreted by hepatocytes into the peripheral blood providing storage for circulating steroid hormones (androgens, estrogens, etc), in this way regulating both the availability of these steroid hormones to target tissues and their interaction with nuclear (intracellular) receptors.[8-10] In recent years, our knowledge of the role of SHBG in the hormonal system has substantially increased. It has been shown that it is also produced in peripheral tissues, and that it is present in a variety of steroid hormone-responsive cells. It is considered an element of a novel signal transduction system with specific receptors located on the cell membrane, providing storage for in which cAMP serves as a major second intracellular messenger. The signaling system involving SHBG is different from and independent of a classical system based on intracellular steroid receptors.[8,11,12] However, there is a bi-directional functional link between these 2 systems. Through intracellular molecular changes SHBG can modify the affinity of steroid hormone receptors to their ligands. On the other hand, when binding to SHBG all steroid molecules modify the affinity of SHBG to its membrane receptors, and hence steroid hormones can directly modify the biological function of SHBG, acting as either agonists or antagonists of SHBG receptor-mediated signaling with the final effect being dependent on the type of target cells.[8,13-15]

Circulating levels of SHBG are influenced by many factors and are associated with nutritional state as well as lipid and glucose metabolism.[9,16-18] For example, reduced levels of SHBG are seen in central obesity, metabolic syndrome, hyperinsulinaemia, insulin resistance, excess of glucocorticoids, androgens and growth hormone, as well as thyroid hormone and estrogen deficits. Increased circulating SHBG levels have been shown to be associated with malnutrition, cachexia, anorexia nervosa, some cancers, anabolic deficiency, and a predominance of catabolism. Ingreased SHBG levels are observed in the aging process and may also be a side effect taking of certain medications, including some anti-epileptics. The paper by Pascual Figal et al is the first to provide evidence on the range of serum SHBG in men with systolic chronic HF and suggests that high circulating SHBG may be related to poor outcomes.[7] The interpretation of their results is unclear, but increased serum SHBG in men with systolic chronic HF may resemble that observed in aging males, in those with testosterone and/or growth hormone deficiency, or in malnourished or cachectic subjects without heart disease. The precise mechanisms leading to increased production (or/and impaired metabolism) of SHBG in HF remain unknown. In several studies, low levels of SHBG have been associated with a higher cardiovascular risk in asymptomatic men and male patients with coronary heart disease.[19,20] In contrast, the Pascual Figal et al study suggests that high (but not low) levels of SHBG predict unfavorable outcome in men with HF. One may hypothesize that the observed association constitutes another element of the "paradoxical" epidemiology seen in HF patients, where reduced fat mass, low cholesterol, and low blood pressure are linked with increased mortality.

In our opinion, myocardium is not only a target tissue for steroid hormones, but can in fact be considered a specific endocrine organ. Specific receptors for aldosterone, cortisole, androgens, and estrogens have been isolated from cardiomyocytes, and their agonists/antagonists affect the functioning of myocardium; furthermore, several enzymes involved in steroidogenesis are expressed in cardiomyocytes and cardiofibroblasts.[21-23] Nakamura et al have demonstrated that normal hearts primarily produce DHEAS, together with a small amount of aldosterone, whereas in failing hearts aldosterone synthesis increases and DHEAS production is reduced.[22] SHBG (both protein and mRNA, thereby suggesting in situ synthesis) is present in non-hepatic cells that respond to sex steroids, but it remains to be established whether the locally expressed SHBG affects intracellular steroid signaling or acts in an autocrine/paracrine manner.[8,24] Only recently, Schock et al demonstrated that the expression of SHBG is markedly increased in the cardiomyocytes of men with dilated cardiomyopathy.[25] This is the first evidence that the SHBG system exists in the myocardium and is deranged in failing hearts, and that it is not only present in circulation as demonstrated by Pascual Figal et al.[7] The clinical significance of this finding remains unclear.

The issue studied by Pascual Figal et al is novel and very current[7] and represents a further step in the exploration of the influence of sex hormones on myocardium. The interpretation of high circulating SHBG in men with systolic chronic HF and its link with increased mortality is unclear; further comprehensive analyses are needed. It may simply be an epiphenomenon reflecting derangements in lipid metabolism and changes in fat metabolism and body composition,[9,16-18] though it could also reflect the presence of an adaptive mechanism. It is worth noting that, theoretically at least, the SHBG system could be considered a therapeutic target. It has already been demonstrated that certain drugs which target receptors in the SHBG signaling

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system affect tissue growth. Their role in patients with HF with a deranged balance between anabolic and catabolic stimuli may suggest an interesting therapeutic approach, though further studies are warranted.

REFERENCES

1. Funder JW, Mihailidou AS. Aldosterone and mineralocorticoid receptors: Clinical studies and basic biology. Mol Cell Endocrinol. 2009;301:2-6.
2. Auchus RJ, Miller WL. The principles, pathways, and enzymes of human steroidogenesis. In: DeGroot LJ, Jameson JL, editores. Endocrinology. Philadelphia: Elsevier Saunders; 2006. p. 2263-85.
3. Jankowska EA, Biel B, Majda J, Szklarska A, Lopuszanska M, Medras M, et al. Anabolic deficiency in men with chronic heart failure: prevalence and detrimental impact on survival. Circulation. 2006;114:1829-37.
4. Jankowska EA, Rozentryt P, Ponikowska B, Hartmann O, Kustrzycka-Kratochwil D, Reczuch K, et al. Circulating estradiol and mortality in men with systolic chronic heart failure. JAMA. 2009;301:1892-901.
5. Jankowska EA, Filippatos G, Ponikowska B, Borodulin-Nadzieja L, Anker SD, Banasiak W, et al. Reduction in circulating testosterone relates to exercise capacity in men with chronic heart failure. J Card Fail. 2009;15:442-50.
6. Jankowska EA, Jakubaszko J, Cwynar A, Majda J, Ponikowska B, Kustrzycka-Kratochwil D, et al. Bone mineral status and bone loss over time in men with chronic systolic heart failure and their clinical and hormonal determinants. Eur J Heart Fail. 2009;11:28-38.
7. Pascual Figal DA, Tornel PL, Nicolás F, Sánchez-Más J, Martínez MD, Gracia MR, et al. Globulina transportadora de hormonas sexuales: nuevo marcador de severidad y pronóstico en varones con insuficiencia cardiaca crónica. Rev Esp Cardiol. 2009;62:1381-7.
8. Kahn SM, Hryb DJ, Nakhla AM, Romas NA, Rosner W. Sex hormone-binding globulin is synthesized in target cells. J Endocrinol. 2002;175:113-20.
9. Caldwell JD, Jirikowski GF. Sex hormone binding globulin and aging. Horm Metab Res. 2009;41:173-82.
10. Fortunati N. Sex hormone-binding globulin: not only a transport protein. What news is around the corner? J Endocrinol Invest. 1999;22:223-34.
11. Rosner W, Hryb DJ, Khan MS, Nakhla AM, Romas NA. Sex hormone-binding globulin mediates steroid hormone signal transduction at the plasma membrane. J Steroid Biochem Mol Biol. 1999;69:481-5.
12. Nakhla AM, Leonard J, Hryb DJ, Rosner W. Sex hormonebinding globulin receptor signal transduction proceeds via a G protein. Steroids. 1999;64:213-6.
13. Fortunati N, Becchis M, Catalano MG, Comba A, Ferrera P, Raineri M, et al. Sex hormone-binding globulin, its membrane receptor, and breast cancer: a new approach to the modulation of estradiol action in neoplastic cells. J Steroid Biochem Mol Biol. 1999;69:473-9.
14. Fortunati N, Catalano MG. Sex hormone-binding globulin (SHBG) and estradiol cross-talk in breast cancer cells. Horm Metab Res. 2006;38:236-40.
15. Catalano MG, Frairia R, Boccuzzi G, Fortunati N. Sex hormonebinding globulin antagonizes the anti-apoptotic effect of estradiol in breast cancer cells. Mol Cell Endocrinol. 2005;230:31-7.
16. Morisset AS, Blouin K, Tchernof A. Impact of diet and adiposity on circulating levels of sex hormone-binding globulin and androgens. Nutr Rev. 2008;66:506-16.
17. Onat A, Hergenç G, Karabulut A, Albayrak S, Can G, Kaya Z. Serum sex hormone-binding globulin, a determinant of cardiometabolic disorders independent of abdominal obesity and insulin resistance in elderly men and women. Metabolism. 2007;56:1356-62.
18. Pascal N, Amouzou EK, Sanni A, Namour F, Abdelmouttaleb I, Vidailhet M, et al. Serum concentrations of sex hormone binding globulin are elevated in kwashiorkor and anorexia nervosa but not in marasmus. Am J Clin Nutr. 2002;76:239-44.
19. Kalme T, Seppälä M, Qiao Q, Koistinen R, Nissinen A, Harrela M, et al. Sex hormone-binding globulin and insulinlike growth factor-binding protein-1 as indicators of metabolic syndrome, cardiovascular risk, and mortality in elderly men. J Clin Endocrinol Metab. 2005;90:1550-6.
20. Goodman-Gruen D, Barrett-Connor E. A prospective study of sex hormone-binding globulin and fatal cardiovascular disease in Rancho Bernardo men and women. J Clin Endocrinol Metab. 1996;81:2999-3003.
21. Thum T, Borlak J. Testosterone, cytochrome P450, and cardiac hypertrophy. FASEB J. 2002;16:1537-49.
22. Nakamura S, Yoshimura M, Nakayama M, Ito T, Mizuno Y, Harada E, et al. Possible association of heart failure status with synthetic balance between aldosterone and dehydroepiandrosterone in human heart. Circulation. 2004; 110:1787-93.
23. Mahmoodzadeh S, Eder S, Nordmeyer J, Ehler E, Huber O, Martus P, et al. Estrogen receptor alpha up-regulation and redistribution in human heart failure. FASEB J. 2006;20:926-34.
24. Noé G. Sex hormone binding globulin expression and colocalization with estrogen receptor in the human Fallopian tube. J Steroid Biochem Mol Biol. 1999;68:111-7.
25. Schock HW, Herbert Z, Sigusch H, Figulla HR, Jirikowski GF, Lotze U. Expression of androgen-binding protein (ABP) in human cardiac myocytes. Horm Metab Res. 2006;38:225-9.