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CLINICAL RESEARCH

Testosterone improves cardiac function and alters angiotensin II receptors in isoproterenol-induced heart failure

La testostérone améliore la fonction cardiaque et altère les récepteurs à l'angiotensine II dans l'insuffisance cardiaque induite par l'isoprotérénol

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KEYWORDS
Testosterone;
Heart failure;
Angiotensin II receptor;
Apoptosis;
Fibrosis

Summary
Background. — The renin-angiotensin-aldosterone system is known to play an important role in the pathophysiology and development of heart failure. Several studies have reported the benefits of testosterone in heart failure. However, the mechanisms of testosterone-induced effects on heart failure require further study.
Aims. — To determine the effects of castration and testosterone administration on cardiac function and angiotensin II receptor function in rats with isoproterenol-induced heart failure.
Methods. — Wistar rats were divided randomly into control and heart failure groups. The heart failure groups were further divided into the following groups: castration; castration + testosterone replacement; and sham castration. Echocardiography and haemodynamic measurements were used to evaluate cardiac function. Cardiocyte apoptosis and fibrosis were determined using terminal deoxyribonucleotide transferase-mediated dUTP nick-end labelling (TUNEL) staining and Masson's Trichrome staining, respectively. Angiotensin II receptor (AT1 and AT2) messenger ribonucleic acid (mRNA) expression levels were assayed using real-time reverse

Abbreviations: GAPDH, glyceraldehyde 3-phosphate dehydrogenase; HF, heart failure; LV, left ventricle/ventricular; MRNA, messenger ribonucleic acid; POD, peroxidase; PVDF, polyvinylidene difluoride; RAAS, renin-angiotensin-aldosterone system; SDS-PAGE, sodium dodecyl sulphate polyacrylamide gel electrophoresis; TUNEL, terminal deoxyribonucleotide transferase-mediated dUTP nick-end labelling; VW/BW, ventricular weight/body weight.

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transcriptase-polymerase chain reactions, while Western immunoblotting was used to estimate Bcl-2 protein expression levels.
Results. — Castration significantly increased cardiomyocyte apoptosis and fibrosis that was normally induced by isoproterenol ($P < 0.05$). AT2 receptor mRNA expression in the castration group was increased and Bcl-2 protein expression was decreased compared with the castration + testosterone replacement group ($P < 0.05$).
Conclusion. — These data suggest that androgen therapy could play an important role in pathophysiological changes in heart failure and have beneficial effects for its treatment.

MOTS CLÉS
Testostérone ;
Insuffisance cardiaque ;
Récepteur à l'angiotensine II ;
Apoptose ;
Fibrose

Résumé
Justification. — Le système rénine-angiotensine-aldostérone joue un rôle important dans la physiopathologie et l'apparition de l'insuffisance cardiaque. De nombreuses études ont rapporté les bénéfices de l'administration de testostérone dans l'insuffisance cardiaque. Cependant, les mécanismes des essais induits par la testostérone dans l'insuffisance cardiaque sont mal connus.
Objectif. — Déterminer les effets de la castration et de l'administration de testostérone sur la fonction cardiaque et les récepteurs à l'angiotensine II dans un modèle expérimental de rats avec induction d'une insuffisance cardiaque par l'isoprotérénol.
Méthode. — Les rats Wistar ont été divisés de façon randomisée en groupe témoin et en groupe insuffisance cardiaque. Le groupe insuffisance cardiaque a été divisé secondairement en sous-groupes : castration ; castration + substitution testostérone ; et castration *sham*. L'évaluation échocardiographique et hémodynamique de la fonction cardiaque a été effectuée. L'apoptose et la fibrose ont été déterminées en utilisant la transferase déoxyribonucléotide terminale : (TUNEL) et la coloration trichrome Masson respectivement. L'expression des ARM messagers des récepteurs de l'angiotensine II (AT1 et AT2) a été évaluée en utilisant les techniques de PCR sur la *transcriptase-polymerase reverse*, alors que l'immuomarquage Western a été utilisé pour évaluer les niveaux d'expression de la protéine Bcl-2.
Résultats. — La castration augmente de façon significative l'apoptose des cardiomyocytes ainsi que la fibrose induit par l'isoprotérénol ($p < 0,05$). L'expression des ARN messager du récepteur à l'angiotensine 2 AT2 dans le groupe castration est augmentée alors que l'expression de la protéine Bcl-2 est diminuée, comparativement au groupe castration + administration de testostérone ($p < 0,05$).
Conclusion. — Ces résultats suggèrent que la thérapie androgénique pourrait jouer un rôle important dans les modifications physiopathologiques observées dans l'insuffisance cardiaque et avoir des effets bénéfiques pour son traitement.

Background

Chronic HF is a major health problem throughout the world and a leading cause of morbidity and mortality [1]. Sex differences exist when determining the cause of cardiovascular diseases. Most studies have examined these sex differences by focusing on the effects of oestrogen on cardiovascular function. However, numerous additional studies have indicated that androgens can also have an effect on cardiovascular function. Testosterone levels are decreased in men with HF, while testosterone replacement therapy has been associated with significant increases in cardiac output and improved functional capacity as well as reduced symptoms in men with HF [2,3]. The therapeutic benefits of testosterone in those with chronic HF can be attributed to a number of factors. For example, testosterone has vasodilatory properties and acute administration has been shown to lower peripheral vascular resistance, reduce cardiac afterload and increase the cardiac index. In addition, testosterone can modulate immune responses and improve insulin resistance while also exerting its effects on coagulation, obesity, endothelial function and alterations in skeletal muscle [3—5]. However, the exact mechanisms underlying these effects mediated by testosterone on HF remain unclear.

The RAAS is known to play an important role in the pathophysiology and development of HF. RASS activity is increased in patients with HF, which could lead to cardiac remodelling and sympathetic activation. Both angiotensin II receptor type 1 (AT1 receptor) and angiotensin II receptor type 2 (AT2 receptor) are expressed in the heart, with localization on cardiomyocytes [6]. A number of studies have indicated that angiotensin II receptor expression is altered in the hearts of animal models with HF. Moreover, Nio et al. [7] reported that expression of both AT1 and AT2 receptor mRNA was upregulated in the infarcted and non-infarcted portions of the LV following coronary ligation.

A number of interactions between androgens and RAAS have been shown to occur at several organ sites. Androgens and androgen receptor systems are known to exert protective effects on angiotensin II-induced vascular remodelling [8]. Androgens have also been shown to affect AT1a receptor mRNA abundance in the abdominal but not thoracic aortas