ASSESSING THE EXPRESSION PROFILE OF ADRENERGIC RECEPTORS IN HUMAN HEARTS FROM PATIENTS WITH CKD

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BACKGROUND

Chronotropic Incompetence (CI), defined as an impaired heart rate (HR) response to exercise[1], is a common cardiovascular complication that affects patients with CKD and is independently associated with cardiovascular and all-cause mortality. HR response during exercise is dependent on the degree of sympathetic activity, which is characterized by catecholamine levels, and the sensitivity of adrenergic receptors (ARs) in the heart, specifically β1-AR, to catecholamines.[2] In individuals without CKD, elevated catecholamines from chronic autonomic activity lead to downregulation of β1-adrenergic receptors (β1-ARs).[3,4] Moreover, decreased β1-ARs function is associated with upregulation of α1-ARs, which is purported to be a cardioprotective and compensatory response to chronic stress in patients with heart failure, a common comorbidity in patients with CKD.[5] In CKD, catecholamines are also elevated, but how cardiac ARs are affected in CKD is unknown. Herein, we aim to comprehensively phenotype the ARs expression in the donor hearts of patients with CKD.

METHODS

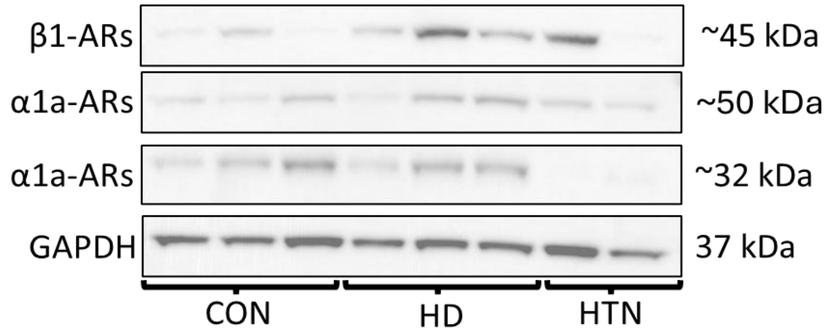
A cross-sectional study was conducted involving 45 donated human left ventricular (LV) tissue samples of patients with advanced CKD (Hemodialysis, HD; n=18), hypertensive controls with preserved kidney function (HTN; n=10), and healthy controls (CON; n=17), from the Cardiovascular Aging in CKD (CAIN) cohort. Tissues were subjected to immunoblotting and bulk RNA sequencing. Antibodies used: ADRB1 (PA1-049, Thermo-Fisher; 1:1000), ADRA1A (H00000148-M01, Abnova; 1:1000), and GAPDH (2118, Cell Signaling Technology; 1:2000). One-way ANOVA and Student's t-test was used for multi-group and pairwise comparisons.

CONCLUSIONS

Our data suggests β1-AR expression is unchanged in hearts from HD patients in our cohort. Additionally, upregulation of the 32kDa α1a-AR isoform in CKD hearts suggests CKD hearts also undergo compensatory mechanisms. Further studies are needed to validate these findings and whether CI in CKD may originate from impaired downstream β1-AR signaling.

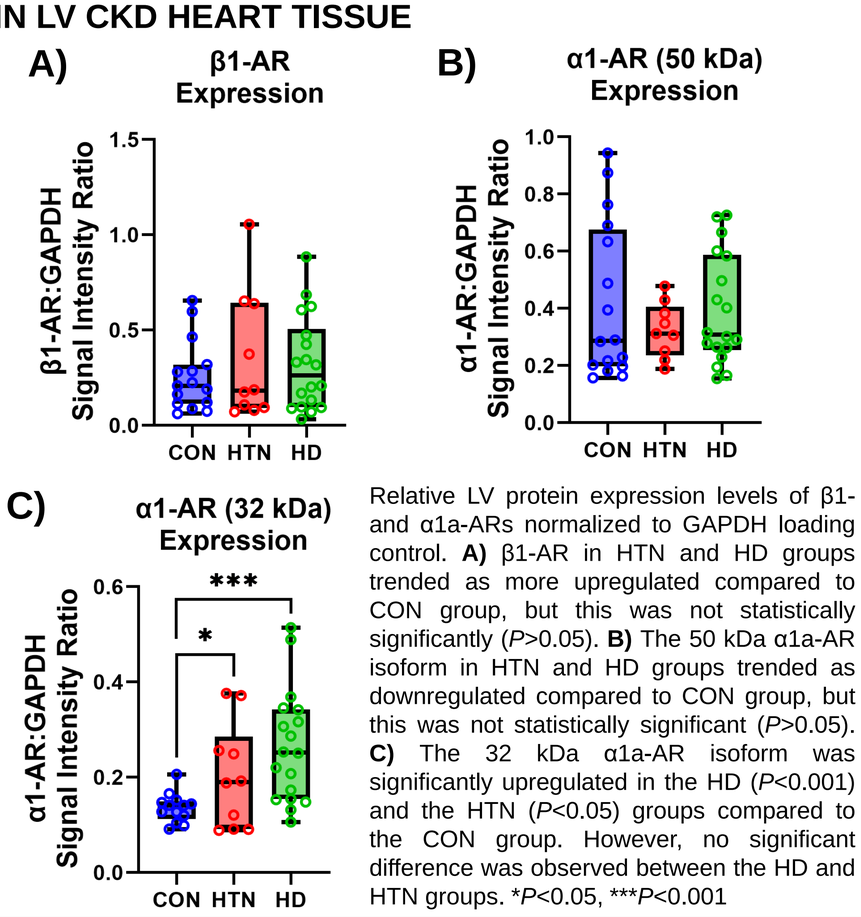
RESULTS

FIGURE 1: POTENTIAL MULTIPLE α1A-AR ISOFORMS DETECTED IN HUMAN HEARTS



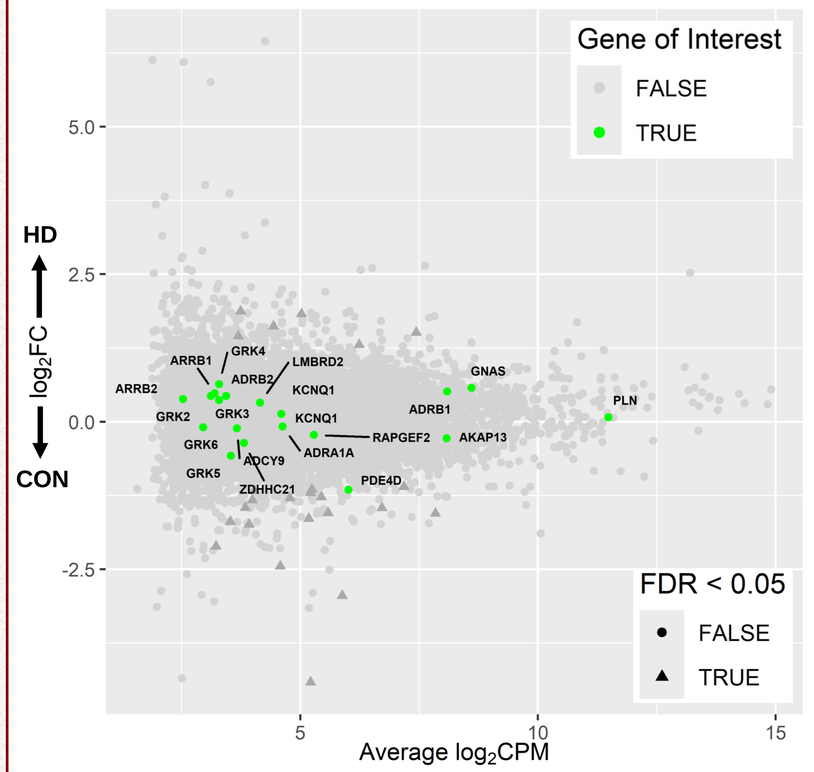
Representative immunoblots of β1-AR, α1a-ARs, and GAPDH. The two prominent α1a-AR band patterns represent two isoforms, 50 and 32 kDa, recognized in protein databases.

FIGURE 2: α1-AR 32kDa ISOFORM IS UPREGULATED IN LV CKD HEART TISSUE



Relative LV protein expression levels of β1- and α1a-ARs normalized to GAPDH loading control. **A)** β1-AR in HTN and HD groups trended as more upregulated compared to CON group, but this was not statistically significantly (P>0.05). **B)** The 50 kDa α1a-AR isoform in HTN and HD groups trended as downregulated compared to CON group, but this was not statistically significant (P>0.05). **C)** The 32 kDa α1a-AR isoform was significantly upregulated in the HD (P<0.001) and the HTN (P<0.05) groups compared to the CON group. However, no significant difference was observed between the HD and HTN groups. *P<0.05, ***P<0.001

FIGURE 3: DIFFERENTIAL TRANSCRIPTIONAL EXPRESSION OF ADRENERGIC RECEPTOR SIGNALING PATHWAY GENES



Bulk RNA sequencing of LV tissue from HD (n=13) and CON (n=5) groups. Genes related to adrenergic receptor signaling are highlighted in green (Gene of Interest). Adrenergic receptor signaling-related genes, including β1-AR and α1a-ARs, were not differentially expressed transcriptionally between HD and CON hearts (FDR>0.05). However, phosphodiesterase 4D (PDE4D), which regulates β2-AR contribution to heart rate, trended as downregulated in HD versus CON hearts (FDR<0.1).

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