Effect of preventive heart failure treatment in mice with arrhythmogenic right ventricular cardiomyopathy type 5 due to mutation in TMEM43

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Background: Arrhythmogenic right ventricular cardiomyopathy type 5 (ARVC5) is an inherited cardiac disease with complete penetrance and a very aggressive clinical course caused by the S358L missense mutation in the TMEM43 gene. Current treatment is merely palliative, based on implantable cardioverter defibrillator (ICD) to prevent sudden cardiac death and antiarrhythmic and anti-heart failure drugs once the phenotype is present. A transgenic mouse model of ARVC5 expressing TMEM43-S358L (TMEMmut) in a cardiac-restricted manner has proven to reproduce the human disease.

Purpose: To determine if drugs that are currently used to treat systolic heart failure (beta blockers (BB), angiontensin-converting enzyme inhibitors (ACEI), mineralcorticoid-receptor antagonists (MRA) or their combination) are useful in order to prevent the development of the ARVC5 phenotype in BL6 transgenic mice expressing TMEM43-S358L.

Methods: TMEMmut mice express TMEM43-S358 under the control of the aMHC promoter. Mice were divided into 6 treatment groups (n=8-12): Metoprolol (BB), Enalapril (ACEI), Spironolactone (MRA), combined therapy (BB+ACEI+MRA), Enalapril+Spironolactone and control. Drugs were dissolved in their drinking water and were maintained from 3 weeks to 4 months of age. Serial electrocardiograms (ECG) and echocardiograms were performed at different stages of disease in treated and control TMEMmut mice.

Results: TMEMmut mice treated with Enalapril and Enalapril+Spironolactone presented a better left ventricular ejection fraction (LVEF) at 4 months compared to controls and metoprolol (38.0% and 39.9% compared to 24.9% and 21.1%,respectively; p <0.05), although it was still depressed as compared to 3 and 5 weeks of age. Left ventricular end diastolic diameter (LVEDD) significantly increased from 5 weeks to 4 months in all groups except Enalapril+Spironolactone and combined therapy. Tricuspid annular plane systolic excursion (TAPSE) was lower in the Metoprolol group as compared to the Enalapril-based treatments at 4 months. Regarding ECG, QRS duration was shorter in all Enalapril-treated groups compared to controls at 4 months (13.76 mm in controls vs. 10.44 mm in Enalapril, 10.91 mm in Enalapril+Spironolactone and 10.96 mm in the combined group; p<0.05).No differences were observed in the Metoprolol treated group vs. controls (Figure 1). QRS voltages were similarly decreased at 4 months in all groups, although it prematurely decreased in the Metoprolol group compared to the other groups at 10 weeks (Figure 1).

Conclusions: Enalapril-based regimens improve ECG and echocardiogram characteristics of ARVC5 mice when therapy is started before the phenotype is present. On the other hand, Metoprolol could be deleterious in these mice causing premature ECG anomalies and worse cardiac function at 4 months. Future studies will hopefully determine whether Enalapril can delay the onset of ARVC5 in humans.
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Additional images showing ECG and echocardiogram data for control, Metoprolol, and Enalapril groups at different time points.