Effect of Angiotensin Receptor Neprilysin Inhibition in Atrial and Ventricular Arrhythmogenesis following Left Atrial Appendage Closure in Animal Model

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Introduction: LAA closure decreases ANP level which indirectly causes increased risk of atrial and ventricular arrhythmogenesis especially in heart failure. The study aims to determine the effect of ARNi in atrial and ventricular arrhythmogenesis following LAA closure in animal models.

Methods: Twenty-four rabbits were randomized to four groups: (1) control, (2) with LAA closure, (3) heart failure with LAA closure, and (4) HF-LAA closure with Sacubitril/Valsartan. Heart failure models were developed in groups 3 and 4 by RV pacing. Epicardial LAA closure was performed in groups 2, 3 and 4. ANP levels were measured at baseline and after LAA closure. Electrophysiologic study were performed individually in each group. Atrial and ventricular myocardia were harvested for Western blot and Trichrome stain.

Result: Right and left atrial effective refractory periods (ERPs) were prolonged in group 3 following LAA closure, while ERPs were restored to baseline in group 4 after neprilysin inhibition (Fig. A). Left ventricular ERPs were longest in group 3, while no difference was noted between groups 1 and 4 (Fig. B). AF window of vulnerability was significantly elevated in groups 2 and 4, but group 4 is lower when compared to that of group 3 (Fig. C). The VF inducibility was highest in Gr 3 (51±5%, p<0.001) followed by Gr 2(30±4%, p=0.006) while groups 1 and 4 had no significant difference in VF inducibility (25±5%, p=0.11 vs 18±4%, respectively). Atrial ANP was decreased in group 2 (785±103 pg/ml, p=0.03), and failed to increase in group 3 (917±172 pg/ml, p=0.3), increased in group 4 (1524±126 pg/ml, p<0.01) when compared to group 1 (1014±56 pg/ml). Ventricular ANP level was not elevated in group 3 (781±191, p=0.54), but elevated in group 4 (1524±126, p<0.01) when compared to group 1 (932±102 pg/ml). Western blot showed extensively decreased expressions of atrial calcium handle proteins (CaV1.2, RyR, SERCA and NCX) in groups 2 & 3, moderately decreased in group 4, compared group 1 (Fig. D). Changes of ventricular Ca handling proteins (CaV1.2, SERCA and NCX) were observed in groups 2 & 3, when compared to group 1, while it restored to baseline in group 4 (Fig. E). Advanced fibrosis was noted in groups 2,3 & 4 in both ventricles, when compared to group 1 (Fig F, H).

Conclusion: LAA closure causes neurohormonal remodeling with decreasing ANP, which in turn increases AF and VF inducibility. Atrial and ventricular arrhythmogenesis were both suppressed by ARNi.