Connexin Gene Transfer Preserves Conduction Velocity and Prevents Atrial Fibrillation

Tomonori Igarashi¹ ², J. Emanuel Finet¹, Maria Strom¹, Ian D. Greener¹, David S. Rosenbaum¹, J. Kevin Donahue¹

¹Heart and Vascular Research Center, MetroHealth Campus, Case Western Reserve University, Cleveland, Ohio, USA, ²The Second Department of Internal Medicine, University of Occupational and Environmental Health, Kitakyushu, Japan

Introduction: Fibrosis, cellular dysfunction and gap junction protein alterations occur in AF and cause conduction delay. We performed this study to test the hypothesis that gap junction protein overexpression would improve conduction and prevent AF. Methods and Results: Thirty Yorkshire swine were randomized into sinus rhythm (SR) and AF groups (n=15 per group). Each group included 3 subgroups: sham-operated control, gene therapy with adeno virus expressing connexin (Cx) 40 and Cx43, with 5 animals in each subgroup. All animals had epicardial gene painting; the AF group had burst atrial pacing. All animals underwent terminal study 7 days after gene transfer. SR animals had strong transgene expression but no atrial conduction changes. In AF animals, controls had reduced and lateralized Cx43 expression, and Cx43 gene transfer restored the expression of total and phosphorylated Cx43 to SR control levels. Immunohistochemical analysis revealed connexin localization to the intercalated disk after gene transfer. In the AF group, both Cx40 and Cx43 gene transfer improved conduction and reduced AF relative to controls. Conclusions: Atrial-specific gene therapy with gap junction protein preserved atrial conduction velocity and prevented AF. Keywords: atrial fibrillation, connexin, gene therapy