[gw22-e0927]

**MIRNAS AND CARDIAC ARRHYTHMOGENESIS:
ROLE IN ATRIAL FIBRILLATION**

Yanjie Lu, Hongli Shan, Zhenwei Pan, Benzhi Cai, Yong Zhang, Baofeng Yang *Department of Pharmacology, The State-Province Key Laboratories of Biomedicine-Pharmaceutics of China, Key Laboratory of Cardiovascular Research, Ministry of Education, Harbin Medical University, Harbin, Heilongjiang, China*

10.1136/heartjnl-2011-300867.107

Background Atrial fibrillation (AF) is a highly prevalent condition associated with pronounced morbidity, mortality, and socioeconomic burden. A characteristic of both clinical and experimental AF is atrial electric remodelling associated with profound reduction of L-type Ca^{2+} current and shortening of the action potential duration. The possibility that microRNAs (miRNAs) may be involved in this process has not been tested. Accordingly, we assessed the potential role of miRNAs in regulating experimental AF.

Methods The miRNA transcriptome was analysed by microarray and verified by real-time RT-PCR with left atrial samples from dogs with AF established by right atrial tachypacing for eight weeks and from human atrial samples from AF patients with rheumatic heart disease.

Results miR-101, miR-320, and miR-499 were found to be downregulated by at least 50%, whereas miR-223, miR-328, and miR-664 were upregulated by more than twofold. In particular, miR-328 level was elevated by 3.9-fold in AF dogs and 3.5-fold in AF patients relative to non-AF subjects. Computational prediction identified CACNA1C and CACNB1, which encode cardiac L-type Ca^{2+} channel α_{1c} - and β_1 subunits, respectively, as potential targets for miR-328. Forced expression of miR-328 through adenovirus infection in canine atrium and transgenic approach in mice recapitulated the phenotypes of AF, exemplified by enhanced AF vulnerability, diminished L-type Ca^{2+} current, and shortened atrial action potential duration. Normalisation of miR-328 level with antagomiR reversed the conditions, and genetic knockdown of endogenous miR-328 dampened AF vulnerability. CACNA1C and CACNB1 as the cognate target genes for miR-328 were confirmed by Western blot and luciferase activity assay showing the reciprocal relationship between the levels of miR-328 and L-type Ca^{2+} channel protein subunits.

Conclusions Our finding indicates that miRNA can function as a potent regulator of atrial fibrillation and represents a potential therapeutic target for arrhythmias in general.