Extracellular ATP Evokes Infiltration of Macrophage in Stretched Atrium

Tetsuo Sasano1, Sakiko Oishi2, Noriko Tamura1, Mitsuaki Isobe1, Tetsushi Furukawa2

1Department of Cardiovascular Medicine, Tokyo Medical and Dental University, Tokyo, Japan, 2Department of Bio-informational Pharmacology, Medical Research Institute, Tokyo Medical and Dental University

Introduction:
Atrial inflammation and dilatation are risk factors for atrial fibrillation. We aimed to clarify the mechanism of macrophage infiltration in stretched atrium.

Methods:
In vitro studies were performed using murine atrial myocytes (HL-1). Murine macrophages were co-cultured with mechanically stretched HL-1 cells using modified Boyden chamber, with or without drugs including carbenoxolone (CBX, a gap junction channel blocker), apyrase, and pyridoxalphosphate-6-azophenyl-2',4'-disulphonic acid (PPADS). Extracellular ATP concentration was measured under mechanically stretched HL-1.

In vivo study, mice underwent transverse aortic constriction (TAC) to induce atrial stretch, with or without CBX administration. Mice were sacrificed 10 days after the surgery for histological evaluation. Electrophysiological study including induction of atrial tachyarrhythmias (AT) was done in Langendorff-perfused heart.

Results:
Migration of macrophage was significantly increased from control to stretched condition, which was inhibited by CBX, apyrase, and PPADS. Extracellular ATP was increased from control to stretched condition, which was also inhibited by CBX. TAC induced infiltration of macrophage and deposition of collagen fiber in atrium. Inducibility of AT was significantly higher in TAC operated mice. These changes were inhibited by CBX administration.

Conclusions:
ATP released from stretched myocytes via gap junction channel is involved in macrophage recruitment and atrial arrhythmogeneity.

Keywords: atrial fibrillation, inflammation, ATP