Role of atrial lymphatics in atrial myocardial fibrosis and atrial fibrillation: a human and mouse study

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Background/Introduction: Cardiac lymphatics maintain myocardial fluid and immune cell homeostasis, but its effects on atrial fibrosis and atrial fibrillation (AF) have not been clarified.

Purpose: To address this issue, we first evaluated the left atrial appendage (LAA) in humans histologically and biologically. We then studied mice to elucidate the mechanisms.

Methods: Human LAA samples were collected from 34 consecutive AF patients during cardiovascular surgery. They were assigned to the paroxysmal AF (PAF) group (n=17, 70.9±11.6 years) and the persistent AF (PeAF) group (n=17, 72.1±7.2 years). In the mouse experiments, 8-week-old male C57BL/6 mice were administrated subcutaneously with vehicle or Angiotensin II (AngII) (2.0 mg/kg/day) for 4 weeks. In some mice, VEGFC, a pro-lymphangiogenesis inducer, was administrated subcutaneously at a dose of 50 μg/kg/day simultaneously with AngII. AF was induced by transesophageal burst pacing in vivo, and by burst pacing in isolated perfused hearts using a Langendorff apparatus.

Results: In human LAA samples, mRNA expression of lymphangiogenesis-related genes (LYVE1, PROX1, and VEGFR3) was significantly lower in the PeAF group compared to the PAF group (p=0.037, 0.029, and 0.041). The number of LYVE1-positive atrial lymphatic endothelial cells (LECs) was also significantly lower in the PeAF group compared to the PAF group (p=0.026). There was a negative correlation between the number of LYVE1-positive atrial LECs and the area percentage of atrial myocardial fibrosis (r=-0.609, p<0.001). In mouse experiments, continuous infusion of AngII suppressed the mRNA expression of lymphangiogenesis-related genes, including Lyve1, Prox1, and Vegfr3 (n=6 in each group, p<0.001, p=0.003, and p<0.001, respectively). AngII infusion reduced the number of LYVE1-positive atrial LECs (p<0.001) and increased the mRNA expression of fibrosis-related genes (Tgfb, Col1a1, and Col3a1). The area percentage of fibrosis in atrial myocardium was also increased by AngII. Treatment with VEGFC for 4 weeks effectively reversed the effects of AngII, i.e., suppression of lymphangiogenesis-related genes expression, reduction of LYVE1-positive atrial LECs, increase in fibrosis-related genes expression, and increase in atrial fibrosis. Additionally, VEGFC treatment attenuated AngII-induced enhancement of vulnerability to AF in vivo experiments (n=8 in each group, p=0.007) and in isolated perfused hearts (n=8 in each group, p=0.007).

Conclusions: Our study with human LAA demonstrated a strong association between atrial lymphatics and atrial myocardial fibrosis/progression of AF. Our mouse study showed that VEGFC reversed AngII-induced increase in atrial myocardial fibrosis and vulnerability to AF, possibly via promotion of lymphangiogenesis. Defects of lymphangiogenesis may be involved in atrial myocardial fibrosis and AF, and may be a therapeutic target for atrial cardiomyopathy.