Wenxin Keli regulates mitochondrial oxidative stress and homeostasis improves atrial remodeling in diabetic rats

Tong Liu
Mengqi Gong
Ming Yuan
Meng Lei
Zhiwei Zhang
Gary Tse
Yungang Zhao
Yue Zhang
Meng Yuan
Xue Liang
Guangping Li

Introduction: The pathophysiologic mechanism of atrial fibrillation (AF) in diabetes is unclear. Our previous studies suggest that mitochondrial dysfunction and oxidative stress play a role in this process. Wenxin Keli (WXKL), a compound Chinese medicine for clinical treatment of arrhythmia, has been found to inhibit L-type calcium channel, sodium channel and transient outward potassium channel and thus reduce the incidence of arrhythmia. The mitochondrial dysfunction is related to intracellular calcium overload. This study hypothesized that WXKL improved atrial remodeling in diabetic rats by regulating mitochondrial oxidative stress and homeostasis.

Methods: (1) Atrial fibroblasts were isolated from 1-3 days old neonatal SD rats and divided into 4 groups: control group, hydrogen peroxide (H2O2) group, WXKL 1g/L group and WXKL 3g/L group. The intracellular mitochondrial membrane potential, reactive oxygen species and mitochondrial oxygen consumption were measured by JC-1, DCFH-DA and Seahorse XF24 cell energy analyzer. (2) 8 weeks old SD male rats were selected for adaptive feeding for 1 week and randomly divided into 3 groups: control group, diabetes (DM) group, DM+WXKL group. The control group was always fed a normal diet. The DM group and the DM+WXKL group were fed a 60% high-fat diet. After 4 weeks, a diabetic model was established by tail intravenous injection of 30 mg/kg streptozotocin. After the model was established, the rats of DM+WXKL group were gavaged WXKL at 3g/kg/day. After 8 weeks, all rats were measured echocardiography, hemodynamics and the incidence of atrial fibrillation. The expression of mitochondria-related proteins was detected by Western blot.

Result: (1) After treatment with H2O2, the mitochondrial membrane potential and mitochondrial oxygen consumption of atrial fibroblasts was decreased. The level of reactive oxygen species was increased. WXKL group improved the above indicators, and WXKL 3g/L group improved compared with WXKL 1g/L group. (2) Compared with the control group, the blood glucose of SD rats was significantly higher, and the left atrial diameter was enlarged in DM group. However, there was no difference between the DM+WXKL group and DM group. Compared with the control group, the DM group had increased myocardial fibrosis, atrial conduction velocity decreased, conduction heterogeneity increased, atrial fibrillation induction rate increased, malondialdehyde MDA increased, serum SOD activity decreased, and DM+WXKL group was more than DM group. Indicator improvement. Western
blot results showed that the mitochondrial protein TFAM, the fusion protein Mfn2 and the cleavage protein Drp1 were decreased in the left atrium of the DM group, and the expression of the above protein was increased in the DM+WXKL group. The expression levels of inflammatory proteins TGF-β and NF-κB were increased in the diabetic group compared with the control group, while the DM+WXKL group had no effect on the above proteins.

**Conclusion:** WXKL can enhance the anti-oxidation ability, reduce the mitochondrial ROS production, and have no effect on the inflammatory level by regulating mitochondrial function and homeostasis improving atrial remodeling induced by diabetes and reducing incidence of atrial fibrillation.