Introduction: Long-term cardiac hypertrophy causes heart failure. One of the mechanisms of this transition from hypertrophy to heart failure is collapse of hypoxic response and angiogenesis. Heat shock protein 27 (HSP27) was found to act as an anti-apoptotic protein and its phosphorylation is responsible for the protection of cells against heat stress. HSP27 has been reported to regulate p53 expression, which contributes to down-regulate angiogenic factors through hypoxia inducible factor-1α (HIF-1α). We have reported that thermal therapy, namely Waon therapy, improves cardiac and vascular function in patients with chronic heart failure. However, the effect of this therapy on cardiac hypertrophy due to pressure overload is unknown. The purpose of this study is to investigate the effects and mechanisms of thermal therapy (Waon therapy) on the transition from cardiac hypertrophy to heart failure after pressure overload.

Methods: Cardiac hypertrophy was induced by transverse aortic constriction (TAC) in C57BL/6 mice. At 2 weeks after TAC, all mice were examined by echocardiography and showed left ventricular hypertrophy. Then, mice were randomly divided into thermal therapy or untreated group. Thermal therapy group received thermal therapy using an experimental far infrared ray dry sauna, which elevates the core temperature by 1 degree Celsius for 30 minutes, daily for 4 weeks. Sham operated mice were used as control. At 6 weeks after TAC, we measured body weight, heart rate and blood pressure before sacrifice, and eviscerated heart and leg muscle. Western blot analysis of p53, phosphorylated HSP27, HIF-1α and vascular endothelial growth factor (VEGF) was performed using extracted protein form heart.

Results: At 6 weeks after TAC, body weight, heart rate and blood pressure did not differ in three groups. Echocardiography showed that left ventricular fractional shortening of thermal therapy group was significantly larger than that of untreated group (Sham vs. Untreated vs. Thermal; 50.0 ± 1.7 vs. 36.7 ± 1.3 vs. 46.2 ± 0.5, P<0.01, n=6 each). Heart weight/tibia length ratio of thermal therapy group was significantly smaller than that of untreated group (6.7 ± 0.1 vs. 9.7 ± 0.5 vs. 7.9 ± 0.2, P<0.01, n=9 each). Western blot showed that thermal therapy increased phosphorylation of HSP27 and reduced p53. Thermal therapy also increased HIF-1α and VEGF at 6 weeks after TAC. Capillary/myofiber ratio was larger in thermal therapy group than that in untreated group (1.71 ± 0.05 vs. 2.04 ± 0.04 vs. 2.41 ± 0.10, P<0.01, n=4 each).

Conclusion: Thermal therapy, namely Waon therapy, prevented the transition from cardiac hypertrophy to heart failure induced by pressure overload in mice. As the mechanism, thermal therapy amplified the phosphorylation of HSP27 and inhibited p53, increased HIF-1α and VEGF, and then increased angiogenesis.

Keywords: Waon therapy, Thermal therapy, Heart failure