Effect of Angiotensin II Receptor Antagonist, TCV-116, on Cardiac Hypertrophy and Coronary Circulation in Spontaneously Hypertensive Rats. Hiroshi Fujita, Kazuo Takeda, Kazue Nakamura, Atsushi Uchida, Hiroshi Itoh, Tetsuo Nakata, Susumu Sasaki, and Masao Nakagawa. Second Department of Medicine, Kyoto Prefectural University of Medicine, Kyoto-fu 602.

(Objective) It is well known that hypertension causes cardiac hypertrophy and also impairs coronary circulation. The correction of these impairments is very important for the antihypertensive therapy. Recently, angiotensin II receptor antagonist has been used as antihypertensive drugs in clinical treatment. The objective of this study was to clarify the effects of an angiotensin II receptor antagonist (TCV-116) on cardiac hypertrophy and coronary circulation in the hypertensive heart in SHR.

(Methods) Ten-week-old spontaneously hypertensive rats (SHR) and age-matched Wistar-Kyoto rats (WKY) were used in this study. TCV-116 (10mg/kg/day) was administrated to SHR by gavage once a day for 2 weeks. Control SHR received vehicle alone. Systolic blood pressure was measured by the tail-cuff method once a week. After 2 weeks, the heart was removed and connected to a Langendorff apparatus. The heart was then perfused at constant pressure (75mm Hg) with modified Henselite-Krebs solution and infused with adenosine solution (10^-5M) to maximally dilate coronary artery. Coronary flow was measured using a drop counter. To assess the role of endothelium-derived relaxing factor (EDRF) in coronary circulation, L-NG-monomethylarginine (L-NMMA) solution (10^-4M) and L-arginine (10^-3M) was infused. Finally, the left ventricle (LV) was weighed.

(Results) At 10 weeks of age, the systolic blood pressure was significantly higher in SHR than in WKY. TCV-116 treatment reduced systolic blood pressure in SHR. The LV weight was significantly heavier in control SHR than in WKY (0.369±0.008 vs. 0.285±0.011g/100g BW, P<0.01). TCV-116 treatment regressed LV hypertrophy in SHR (0.314±0.015 vs. 0.369±0.008g/100g BW, P<0.05). Minimum coronary vascular resistance (MCVR) was significantly higher in control SHR than in WKY (0.090±0.011 vs. 0.041±0.004mm Hg/ml per min per 100g, P<0.001). TCV-116 treatment restored MCVR in SHR(0.056±0.011 vs. 0.090±0.011mm Hg/ml per min per 100g, P<0.01). L-NMMA infusion increased coronary flow resistance in all rats. However, the increase was significantly smaller in control SHR than in WKY (9.5±2.6% vs. 66.3±12.4%, P<0.05). TCV-116 treatment improved this diminished response to L-NMMA infusion in SHR (72.8±25.6% vs. 9.5±2.6%, P<0.05). L-arginine (10^-3M) infusion decreased coronary flow resistance to the state of pre L-NMMA infusion in all rats.

(Conclusion) These findings suggest that the oral administration of the angiotensin II receptor antagonist, TCV-116, not only reduces blood pressure, but also improves impaired coronary circulation with regression of cardiac hypertrophy. Reduced production of EDRF in the coronary arteries of SHR was also restored by TCV-116 treatment. These results suggest that TCV-116 has a cardioprotective effect in hypertensive heart with antihypertensive effect.