TCV-116 improves Congestion and Survival in SHR with High-Output Heart Failure.

Jiro Kubota, Masakuni Ueyama, Tatsuhiko Mori, and Keishiro Kawamura.

Third Department of Internal Medicine, Osaka Medical College, Osaka 569.

We have reported a rat model of high-output heart failure in SHR that frequently developed ascites and dyspnea (Oka T et al, Clin Sci 84: 531, 1993). The effects of angiotensin II receptor blockers on hemodynamics and mortality in high-output heart failure have not been established. We evaluate the effects of TCV-116, a novel angiotensin II receptor blocker, on cardiorenal hemodynamics, neurohumoral factors and survival in SHR with high-output heart failure induced by aortocaval fistula.

Eight-week-old male SHR were divided into an aortocaval fistula group and a sham-operation group. Aortocaval fistula was created by side-by-side anastomosis between infra-renal abdominal aorta and inferior vena cava under the ether anesthesia. One mg/kg/day of TCV-116 was administered as suspension in a 2% gum arabic solution by gavage at 8 a.m. for 2 weeks. The 2% solution of gum arabic was used as the vehicle. Conscious blood pressure (BP) was determined weekly by the tail-cuff technique. Two weeks after surgery, rats were anesthetized with pentobarbital (50 mg/kg BW, ip), and left heart catheterization was done using 2F micromanometer-tipped catheter. Cardiac index (CI) was determined by thermodilution method, and renal blood flow (RBF) was assessed by laser-Doppler flowmetry.

In the sham-operated SHR, 2 weeks treatment with TCV-116 decreased BP, left ventricular (LV) weight, and total peripheral resistance ($p < 0.01$), and increased RBF and plasma renin activity (PRA) ($p < 0.01$); CI and LV end-diastolic pressure (LVEDP) were unchanged. Fistula creation induced biventricular hypertrophy, the increase in LVEDP, CI, pulse pressure and plasma norepinephrine (PNE) ($p < 0.01$), and decreased RBF ($p < 0.01$) with ascites and tachypnea. TCV-116 decreased LVEDP ($p < 0.01$), increased RBF ($p < 0.01$), improved survival rate (87.5% vs. 68.2%), and prevented ascites (0% vs. 33%). TCV-116 also increased PRA ($p < 0.01$) and attenuated the increase in PNE ($p < 0.01$). Heart weight, BP and CI were not affected by the treatment.

TCV-116 ameliorated congestion and improved survival rate in SHR with aortocaval fistula without compromising cardiorenal hemodynamics. The venous and renal vascular dilatation, and the attenuation of vasoconstrictive systems may have contributed to the beneficial effects.