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CANDESARTAN MODIFIES NECROTIC AND APOPTOTIC MYOCYTE CELL DEATH IN THE HEARTS OF SPONTANEOUSLY HYPERTENSIVE RATS.

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BACKGROUND/AIMS：Although the benefit of angiotensin II AT1 receptor blocker (ARB) treatment during and after myocardial injury has been shown in hypertension and activation of the renin-angiotensin system has been implicated, the molecular basis of these actions remains unclear. In this study, we tested the hypothesis that ARB in hypertension would prevent and reverse stress-associated changes in necrotic and apoptotic myocyte cell death in the heart.

METHODS：Spontaneously hypertensive rats (SHR) and Wistar Kyoto (WKY) controls were treated with an ARB (candesartan, 0.3mg/kg per day) via subcutaneous osmotic minipumps for 4 weeks. Heat shock was induced by exposing the rat to high blanket temperature. To determine the effects of heat shock on myocyte cell death, rat were injected with myosin monoclonal antibody for the localization and quantification of necrotic myocyte cell death in the left ventricle (LV). Conversely, the presence of DNA strand breaks in myocyte nuclei, indicative of programmed cell death, was evaluated by the terminal deoxy-nucleotidyl transferase assay and confirmed by DNA laddering.

RESCULTS/CONCLUSIONS：Myocyte necrosis, which involved the LV free wall, progressively increased after heat shock. Programmed myocyte cell death was restricted to the LV free wall and increased at subsequent time intervals after heat shock. The combination of necrosis and apoptosis in the LV free wall were significantly increased in the SHR. Candesartan decreased LV necrotic and apoptotic cell death in SHR and WKY. ARB treatment of SHR-heat shock reduced the number of apoptotic cells to heat shockthe same level as WKY-heat shock ($p<0.05$). There were no significant differences in Bcl-2 protein expressed by hearts among the four groups. WAF-1 mRNA level was increased in both heat shock without ARB groups; in the SHR-heat shock with ARB, the density of WAF-1 mRNA was lower than in SHR-heat shock without ARB. Thus, decreased numbers of necrotic and apoptotic cells were present in heat shock SHR hearts, suggesting the candesartan is associated with a reduction in exaggerated myocyte cell death in hypertension that accompanies heat shock.

Key word: AT1 receptor blocker. Hypertension. Rennin-angiotensin system.