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Effects of AT_1 blockade on myocardial fibrosis in hypertensive heart disease. Beyond the control of blood pressure

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An exaggerated accumulation of fibrillar collagens type I and type III occurs throughout the free wall and interventricular septum of animals and humans with arterial hypertension[1]. A rise in collagen content has been shown to raise myocardial stiffness and promote abnormalities of cardiac function that predispose to heart failure[2]. A number of previous experimental findings suggest that direct fibroblast stimulation by angiotensin II may be involved in myocardial fibrosis associated with arterial hypertension[3]. Furthermore, we have shown recently that AT_1 blockade with losartan at doses that do not normalize blood pressure regress myocardial fibrosis in rats with spontaneous hypertension[4,5]. Thus, in a recent study[6] we have investigated whether chronic blockade of AT_1 receptors reverses myocardial fibrosis in patients with essential hypertension beyond the hemodynamic effect. The study was performed in 37 patients with essential hypertension in which ischemic cardiomyopathy was excluded after a complete medical work-up. After randomization, 21 patients were treated with losartan 50 mg/day and 16 patients received the calcium channel blocker amlodipine (2.5-10 mg/d) as treatment. At baseline and after 12 months, right septal endomyocardial biopsies were performed to quantify myocardial collagen content. Collagen volume fraction (CVF) was determined on picrosirius red-stained sections using an automated image analysis system. The serum concentration of carboxy-terminal propeptide of procollagen type I (PIP), a marker of collagen type I synthesis and deposition at the myocardial level[7], was measured by specific RIA. Time-course changes in blood pressure and final values of blood pressure were similar in the two groups of patients In patients treated with losartan, CVF decreased from 5.65 ± 0.47 to 3.96 ± 0.34% (M ± SEM, $P < 0.01$) and PIP from 127 ± 7 to 99 ± 6 µg/L ($P < 0.01$). Neither CVF nor PIP changed significantly in patients treated with amlodipine. A direct correlation was found between CVF and serum PIP ($r = 0.44$, $P < 0.001$) in all hypertensives before and after treatment. Losartan-treated patients, but nor amlodipine-treated patients exhibited an amelioration of Doppler parameters assessing end-diastolic left ventricular distensibility. These findings suggest that the ability of antihypertensive drugs to regress myocardial fibrosis in hypertensives is beyond its antihypertensive efficacy. In addition, our results suggest that angiotensin II antagonism is associated with inhibition of collagen type I synthesis, regression of myocardial fibrosis and improvement of diastolic function in hypertensive patients. Thus, the cardioreparative ability of losartan may be beneficial in hypertensive heart disease and other cardiac diseases evolving to heart failure via myocardial fibrosis.

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