Title	Frequency of angiotensin-converting enzyme DD genotype is decreased in patients with hypertension and left ventricular hypertrophy
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Suppression of Myocardial Fibrosis by Valsartan and Monopril in Animals after Acute Myocardial Infarction

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Background: Myocardial remodelling after acute myocardial infarction (AMI) is a progressive process of left ventricular dilatation which contributes to the development of cardiac failure and late mortality. We postulate that myocardial interstitial fibrosis in the non-infarcted regions is a major histopathological change which may be modified by drugs acting on the renin-angiotensin system.

Methods: An animal model of AMI was established by ligating the left anterior descending coronary arteries of the 10-week old male Sprague-Dawley rats. Twenty-seven post-AMI and forty sham-operated rats were randomised to receive monopril (an angiotensin converting enzyme inhibitor, 30mg/kg/day), valsartan (an angiotensin II type Ia receptor antagonist, 30mg/kg/day) or a combination of these 2 agents for 2 or 4 weeks. The amount of interstitial collagen type I and III were assessed by immunohistochemistry and quantified by histomorphometry using a computer programme (LeicaQwin).

Results: There was no difference in body weight between AMI and sham-operated rats. The mean blood pressure (measured by tail-cuff technique) in AMI rats was not different from sham-operated rats but was significantly lower at 2 weeks post-AMI in all the treatment groups, in particular the valsartan and combined therapy groups. At 4 weels post-AMI the blood pressure was significantly lower only in combined therapy rats. In AMI rats, there was a significant increase in type I collagen in the septum (non-infarct region of left ventricle) at 2 and 4 weeks after AMI, but not in the right ventricle. Treatment of both monopril and valsartan is able to decrease the type I collagen content at 2 weeks (Monopril: 1.3±0.7 Vs 0.4±0.2%, $p<0.001$; Valsartan: 1.3±0.7 Vs 0.7±0.6%, $p=0.001$). In 4 weeks, only combined therapy decreased the collagen volume fraction (1.0±0.5 Vs 0.6±0.4%, $p=0.02$), but not individual drugs. There was no significant increase in type I collagen in the right ventricle. The type III collagen content in both the septum and right ventricle was not significantly increased after AMI. , though valsartan is able to decrease the collagen content at both the septum (2.1±0.8 Vs 1.1±0.3%, $p<0.001$) and RV (2.4±0.3 Vs 1.8±0.5%, $p=0.01$).

Conclusion: Myocardial interstitial fibrosis occurs with increased type I, but not type III collagen in the non-infarcted septum after AMI. Treatment with both monopril and valsartan is able to inhibit these pathological changes, while combination therapy may exhibit an additional benefit, but on the expense of more hypotension.

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FREQUENCY OF ANGIOTENSIN-CONVERTING ENZYME DD GENOTYPE IS DECREASED IN PATIENTS WITH HYPERTENSION AND LEFT VENTRICULAR HYPERTROPHY

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Hypertension, left ventricular hypertrophy (LVH) and angiotensin-converting enzyme homozygous deletional (DD) genotype are important cardiovascular risk factors which, if present together, may confer especially high risk. We and others have previously observed that there is a decrease with age in the prevalence of the DD genotype in hypertensive patients, which may be due to decreased survival of such patients. We hypothesise that there might be fewer patients with the DD genotype among patients with hypertensive LVH.

102 normal healthy controls and 85 hypertensive patients were studied. LVH was determined by echocardiography. DNA was extracted from peripheral leucocytes and amplified by PCR using specific primers. Insertion (I) or deletion (D) alleles were identified after electrophoresis of PCR products.

	n	DD	ID	II	D	I
Normal controls	102	22%	32%	46%	0.38	0.62
Hypertensives	85	17%	37%	47%	0.35	0.65
without LVH	52	25%	37%	38%	0.43	0.57
with LVH	33	3%*	36%	61%	0.21**	0.79

*$\chi^2 = 8.0$, $p = 0.02$ **$\chi^2 = 8.6$, $p = 0.004$

The decrease in the frequency of the DD genotype in hypertensive patients with LVH is consistent with the increased cardiovascular risk in these patients.