Plasma Metalloproteinase Levels Are Correlated With Natriuretic Peptide and Endothelin-1 Levels in Patients With Heart Failure

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Background: Several neurohormones can activate matrix metalloproteinases (MMPs) which regulate extracellular matrix turnover and left ventricular (LV) geometry in the failing myocardium. However, the relationships between the various neurohumoral and MMP systems in heart failure (HF) have not been elucidated.

Methods: Patients with symptomatic HF and LV ejection fraction <0.40 were randomized in the RESOLVD trial to various combination regimens of candesartan, enalapril, and metoprolol. In this substudy, plasma MMP-2, MMP-9, tissue inhibitor of metalloproteinase-1 (TIMP-1), atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), angiotensin-II, aldosterone, and endothelin-1 were measured by ELISA in 184 patients at baseline. Epinephrine and norepinephrine were measured by HPLC.

Results: The relationships between plasma MMP and neurohormone levels are tabulated below.

<table>
<thead>
<tr>
<th>Kendall’s tau correlation</th>
<th>MMP-2</th>
<th>MMP-9</th>
<th>TIMP-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANP</td>
<td>0.26 *</td>
<td>0.060</td>
<td>0.21 *</td>
</tr>
<tr>
<td>BNP</td>
<td>0.21 *</td>
<td>0.030</td>
<td>0.14 **</td>
</tr>
<tr>
<td>Angiotensin-II</td>
<td>-0.084</td>
<td>0.067</td>
<td>0.079</td>
</tr>
<tr>
<td>Aldosterone</td>
<td>0.005</td>
<td>0.096</td>
<td>0.061</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>0.067</td>
<td>0.025</td>
<td>0.005</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>0.041</td>
<td>-0.006</td>
<td>0.047</td>
</tr>
<tr>
<td>Endothelin-1</td>
<td>0.11 †</td>
<td>0.010</td>
<td>0.15 **</td>
</tr>
</tbody>
</table>

**P<0.001
**P<0.01
†P<0.05

Conclusion: Increased plasma MMP-2 and TIMP-1 levels were related to elevated levels of ANP, BNP and endothelin-1. In contrast, the renin-angiotensin-aldosterone and the sympathetic nervous systems, both of which have been historically associated with promoting fibrosis, did not correlate with MMP levels. Therefore, MMP and TIMP levels appear to be differentially regulated by certain bioactive signals, rather than a non-specific global induction in HF. These new findings suggest that these proteolytic pathways can be modulated through specific pharmacological targets.

Pioglitazone Modulates Collagen Synthesis in Fibroblasts in Response to Angiotensin II

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Background and Objectives: Angiotensin II (Ang II) and free radicals are potent mediators of ischemic cardiac dysfunction. Fibroblast growth and activity (collagen formation) characterize this process in response to Ang II and free radicals. Recent studies suggest that PPAR-γ ligands have the potential to modulate the process of acute ischemic injury and its long-term consequences. This study examined the modulation of fibroblast activation in response to Ang II by the PPAR-γ ligand pioglitazone.

Methods and Results: Cultured rat cardiac fibroblasts were treated with Ang II (10−8 to 10−5 M) before exposure to Ang II (10−7 M). Treatment with Ang II resulted in increased collagen-I and reduced MMP-1 protein expression in cardiac fibroblasts (both P<0.01). Ang II treatment also reduced protein kinase B (PKB/Akt) expression. Pretreatment of cells with pioglitazone completely blocked the decreased PKB/Akt expression in Ang II–treated cells, and simultaneously inhibited the effects of Ang II on collagen and MMP expression (all P<0.01 vs. Ang II alone).

Conclusion: This study shows that Ang II enhances collagen and reduces MMP-1 protein expression in fibroblasts. Importantly, pioglitazone blocks these effects of Ang II, most likely by PKB/Akt activity in fibroblasts.

Synergistic Effects of the Addition of Candesartan to Enalapril on Myocardial Fibrosis and Left Ventricular Diastolic Function in Dogs With Heart Failure

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Backgrounds: Angiotensin II (AngII) type 1 receptor blocker, candesartan reduced relevant cardiovascular events when added to ACE inhibitors in patients with congestive heart failure (CHF). Candesartan prevents myocardial fibrosis due to the effective inhibition of AngII in animals with non-ACE pathway, while ACE inhibitor acts on myocardial fibrosis partly through the bradykinin-mediated mechanism as well as the inhibition of AngII. Therefore, we hypothesized that the addition of candesartan to enalapril synergistically prevented myocardial fibrosis and improved left ventricular (LV) diastolic function to the greater extent than each drug alone in CHF.

Methods: Twenty-eight dogs were assigned to the following treatment protocols on the 8th day of a 4-week rapid pacing: (A) rapid ventricular pacing (240 bpm, n=7), (B) enalapril (1.9 mg/kg/day) and pacing (n=7), (C) candesartan (1.5 mg/kg/day) and pacing (n=7), (D) combined enalapril (0.95 mg/kg/day) and candesartan (0.75 mg/kg/day) and pacing (n=7).

Results: Although there was no difference in myocardial AngII levels among all groups, concomitant use of enalapril and candesartan significantly decreased LV end-diastolic pressure and LV stiffness estimated by LV pressure-volume plane to the greatest extent than each drug alone. Furthermore, it suppressed the expression of the collagen-type I and 3 mRNA (p<0.001), and decreased the values of LV collagen volume fraction evaluated with picrosirius red stain (A 6±1, B 4±1*, C 3±1*, D 2±1* †, ‡ %, respectively, *p<0.05 vs. A, †p<0.05 vs. B, ‡p<0.05 vs. C). Conclusion: Concomitant use of enalapril and candesartan synergistically prevented LV fibrosis and improved LV diastolic function during the development of CHF. Thus, the addition of candesartan to ACE inhibitor may become an important strategy for the prevention of cardiac remodeling.

Early Serum Levels of Tissue Inhibitor of Metalloproteinase-1 but Not Matrix Metalloproteinase-1 Are Associated With Cardiovascular Death After Complicated Myocardial Infarction

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Background: The complex process of early remodeling in acute myocardial infarction (AMI) involves activation of matrix metalloproteinases (MMPs). We related increased serum levels of MMP-1 and type I collagen antagonist metalloproteinases (TIMP-1) to adjudicated cardiovascular mortality in patients following complicated AMI.

Methods: Serum from 253 patients in the OPTIMAAL trial which included patients following AMI with heart failure and/or left ventricular dysfunction was sampled at randomization (mean 3 days after index MI).

Results: Mean MMP-1 and TIMP-1 for all patients were 6.5 (± 6.6) and 1610 (± 623) ng/ml, respectively. During a mean follow-up of 2.6 years cardiovascular death occurred in 29 patients. Non-survivors had significantly higher serum levels of TIMP-1 but not MMP-1 compared to survivors during follow-up (mean 1960 (± 749) vs. 1660 (±588) ng/ml, p=0.03 for TIMP-1 and mean 8.2 (± 7.9) vs. 6.2 (± 4.6) ng/ml, p=0.07 for MMP-1). Patients above and below mean TIMP-1 values had a mortality rate of 18.1% and 9.5% respectively (log rank p=0.031 (fig.)

Conclusion: Increased levels of TIMP-1 are associated with increased cardiovascular mortality following high risk AMI. As TIMP-1 also is upregulated by free MMPs other than MMP-1, this finding suggests that other MMP subtypes are activated during the acute phase following complicated AMI.

Transforming Growth Factor Beta and Factor Xlla Are Constituents of the Cardiacoid Heart Endocardial Layer: A Study by Confocal Laser Microscopy

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The detailed composition of the cardiacoid right ventricular endocardial layer and the pathogenesis are still unresolved. One common explanation is that fibrosis occurs as a consequence to microlesions induced by high levels of circulating serotonin and bradykinin.

Methods: The right ventricular endocardomyocardial biopsy of 7 patients (5 female, mean age 43.9 ± 11.4 y) with established cardiacoid syndrome and right ventricular disease