Dose of furosemide mg/day

<table>
<thead>
<tr>
<th>Dose of furosemide mg/day</th>
<th>Averge NYHA class</th>
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</thead>
<tbody>
<tr>
<td>1.0</td>
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<tr>
<td>1.2</td>
<td>1.4</td>
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<tr>
<td>1.4</td>
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Trandolapril Placebo

1184-87

Elevated plasma xanthine oxidase activity in Chronic Heart Failure: Source of Increased Oxygen Radical Load and Effect of Allopurinol in a Placebo Controlled, Double Blinded Treatment Study

Wolfrem Doehner, Margaret M. Tarpey, Darrell V. Pavitt, Alain P. Boiger, Roland Wensel, Stephan von Haehling, David A. Reaveley, Stefan D. Anker, National Heart & Lung Institute, London, United Kingdom, University of Alabama, Birmingham, AL

Background: Elevated xanthine oxidase (XO) activity contributes to production of reactive oxygen species. Hypoxia in common in chronic heart failure (CHF). However, enzymatic activity of circulating plasma XO has not been studied in CHF. We hypothesised, that plasma XO activity is elevated in CHF compared to healthy controls, paralleled by increased free radical load, and that XO inhibition with allopurinol decreased both. As a marker of the free radical load serum allantoin was measured, which is generated in the humans exclusively via non-enzymatic reactions dependent urate oxidation.

Methods: In 67 CHF patients (Mean age 65±10y, NYHA 2.9±0.7, peak VO2 16.6±6.8 ml/kg/min) and 15 controls (age 39±9y) we measured plasma XO activity (mg/mL), unc-4 acid (UA), and allantoin (gas chromatography-mass spectrometry). In 17 CHF patients with known hyperuricemia (UA 517±95 pmol/L), the effect of allopurinol (300mg od for 1 week) was tested in a placebo controlled double-blinded, cross-over study.

Results: CHF patients were hyperuricemic (UA 461±147 pmol/L; normal range 210-440 pmol/L) and had increased plasma XO activity (14.2±1.51 vs 8.9±1.23 pmol/L, p<0.001). The upper limit of normal was defined as 3.35±4.3 µM/L (normal mean value ±2SD). All but one control and 11 patients (16%) had normal plasma XO activity, but 56 patients (84%) had elevated XO activity (CHF p<0.0001). Allantoin was elevated in CHF compared to reference control values (4.35±2.7± vs 1.3±±1.3± pmol/L). In the double-blinded allopurinol treatment study, plasma XO activity was reduced in all 17 patients by 49% (from 4.35±2.7± to 2.2±±1.3±, p<0.001). Allopurinol also reduced allantoin levels by 18% (from 2.7±±1.3± to 2.2±±1.3±, p<0.02).

Conclusion: The activity of circulating plasma XO is elevated in patients with CHF. Treatment with allopurinol results in reduced plasma XO activity by parallel reduction of xanthine oxidase radical load. Thus, a potentially new therapeutic option emerges to reduce oxygen radical load in CHF.

1184-88

Chronic Monotherapy With Extended Release Metoprolol Succinate Attenuates mRNA Gene Expression for MMP2 and MMP9 In Dogs With Heart Failure

Neha M. Hasija, Hemans C. Gupta, Sudhish Mishra, George Suzuki, Sidney Goldstein, Hani N. Sabbah, Henry Ford Health System, Detroit, MI

Background: Accumulation of collagen in the cardiac interstitium or "reactive interstitial fibrosis" (RIF) occurs in heart failure (HF) and contributes to LV dysfunction and remodeling. Matrix metalloproteinases (MMPs) are upregulated in HF and contribute to RIF. We previously showed that therapy with extended release metoprolol succinate (ER-MET) significantly reduced RIF in dogs with HF. In this study, we examined the effects of chronic therapy with ER-MET on gene expression of MMP2 and MMP9 (gelatinases) and on tissue inhibitors of MMPs (TIMPs) in LV of dogs with microembolization-induced HF.

Methods: Total RNA was isolated from LV tissue of 14 dogs with HF randomised to 3 months therapy with ER-MET (50 mg, once daily, n=7) or to no therapy at all (n=7) and from LV of normal (NL) dogs. mRNA expression for MMP2 and 9 and TIMP1 and 2 was measured using reverse transcriptase polymerase chain reaction and bands quantified in densitometric units. Results: Results are shown in the table. There were no differences in expression of TIMP1 and 2 among the 3 study groups. Expression of MMP2 and 9 was increased in untreated-HF dogs compared to NL. ER-MET significantly reduced this increase in expression of MMP2 and 9. Conclusions: In dogs with HF, mRNA gene expression of Timp2 is unchanged while expression of MMP2 and 9 is increased. Therapy with ER-MET does not influence TIMPs but reduces expression of MMP2 and 9, a finding consistent with reduced RIF following chronic therapy with the ER-MET.

NL HF-Unreated HF+ ER-MET

<table>
<thead>
<tr>
<th>Staining</th>
<th>Baseline</th>
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<tbody>
<tr>
<td>TIMP1</td>
<td>2.33±0.35</td>
<td>2.83±0.40</td>
</tr>
<tr>
<td>TIMP2</td>
<td>1.31±0.04</td>
<td>1.39±0.02</td>
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<tr>
<td>MMP2</td>
<td>1.30±0.18</td>
<td>2.04±0.11</td>
</tr>
<tr>
<td>MMP9</td>
<td>1.22±0.14</td>
<td>2.50±0.04</td>
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</table>

*P<0.05 vs. NL; **P<0.05 vs. HF-Unreated

1184-89

Dietary Fish Oil Supplementation Improves Endothelial Function in Patients With Congestive Heart Failure

David P. Morgan, Linda J. Dixon, Colin G. Harrathy, Sinead M. Hughes, William J. Leahey, Naglaa A. El-Sherbeeny, G. Dennis Johnston, Gary E. McVeigh, Queen's University Belfast, Belfast, United Kingdom

Background: Systemic vasodilatation and reduced peripheral perfusion are hallmarks of congestive heart failure (CHF). Endothelial dysfunction is a frequent finding in CHF and is associated with reduced bioavailability of the vasodilator nitric oxide (NO). Omega-3 fatty acids (fish oils) have been shown to have beneficial effects on endothelial function and vascular responses in a number of vascular diseases which may be secondary to increased NO bioavailability. We conducted a study to establish whether addition of omega-3 fatty acids to background therapy in patients with CHF would improve endothelial dysfunction.

Methods: 20 patients with grade II and III CHF (15 male) mean age 73 were recruited. Sodium nitroprusside (SNP) (6, 9, 15mol/min/ml) and acecyloxycholine (ACh) (130, 198, 240nmol/min/ml) were infused into the non-dominant brachial artery. Forearm blood flow (FABF) responses assessed by venous occlusion plethysmography. Patients received fish oil or olive oil drink for 6 weeks in a double blinded randomised cross over trial with assessment of FABF at baseline and after each treatment.

Results: See table

Conclusions: Dietary fish oil significantly improved endothelial function as assessed by FABF responses to ACh. There are several possible mechanisms by which fish oils could potentially improve endothelial function in CHF. Further studies are required to attempt to elucidate the mechanism for this improvement and to establish whether will be associated with improved outcomes.

Baseline 1 14.42 (10.93,17.51) 7.95 (6.11,11.80)
Fish oil 11.66 (8.17,15.15) 11.27 (7.31,15.23)
Baseline 2 13.55 (7.4,16.36) 7.68 (4.95,10.41)
Olive oil 14.38 (11.67,17.09) 7.27 (4.66,9.88)

**P<0.01

POSTER SESSION

1185 Cardiac Transplantation: Cellular Mechanisms and Rejection

Tuesday, April 01, 2003, Noon-2:00 p.m.
McCormick Place, Hall A
Presentation Hour: 1:00 p.m.-2:00 p.m.

1185-59

Acute Rejection in Human Heart Transplantation: Identification and Characterization of Two Important Markers (MIP-1B and VE-Cadherin)

Ana L. E. Duarte-Lopes, Olivier Nassy, Lake Chaldeyressy, George Dureau, Catherine Girard, Pascale Bossonnial, Lauret Sebbaug, Jean-Paul Gare, Jean-Francois Obadia, Jean Ninet, Olivier Bastien, Françoise Thivold-Bejui, Jean L. McGregor, Hôpital Cardioïaque Louis Pradel, Lyon, France. INSERM, Lyon, France

Background: An extensive number of molecules are involved in acute rejection (AR) following heart transplantation. We have previously identified the expression of 2 of these genes, MIP-1B and VE-Cadherin, in the present study as potential new markers of AR in cardiac tissue following human heart transplantation.

Methods: We have previously studied the expression profile of genes involved in AR