Urine and Plasma Matrix Metalloproteinase 9 and 2
Levels in Patients With Coronary Artery Disease

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Background: Matrix metalloproteinases (MMPs) are implicated in developing atherosclerosis. Urine (U) MMPs have not been previously evaluated.

Methods: U and plasma (P) MMP9 and MMP2 were measured in 3 groups: ACS = patients (pts) with elevated troponin-I or angiographic findings of a ruptured plaque. Coronary artery disease (CAD) = pts with CAD, but no clinical instability. Healthy volunteers (HV) were <35 years of age with no risk factors for CAD; angiography was not performed in HV. We set the upper limit of normal as the mean + 2 standard deviations.

Results: The upper limits of normal were: U-MMP9 = 0.14 ng/µg protein, U-MMP2 = 0.24 ng/µg protein, P-MMP9 = 712 ng/ml, P-MMP2 = 355 ng/ml. The percent with elevated values is shown in the table. The percent of pts with elevated U or P MMP2 was higher (p<0.01) in the ACS and CAD groups. There was a similar trend (p=0.07) in MMP9 levels, but no difference in the percent of pts with elevated MMP9 or MMP2 levels between those with CAD and ACS.

Conclusion: The percent of pts with elevated U and P MMP2 levels was higher in those with CAD compared to healthy volunteers, and a similar trend existed for MMP9. However, the percent of pts with elevated MMP9 and MMP2 in P or U was not different in those with ACS compared with stable CAD. These data suggest that MMP levels may be a ubiquitous marker of atherosclerosis with U levels appearing to identify more pts than a blood sample. However, because elevated MMPs may be due to atherosclerosis at any location, their usefulness for identifying ACS may be limited.

<table>
<thead>
<tr>
<th>Percent of Patients with Elevated MMP Levels</th>
<th>U-MMP9</th>
<th>U-MMP2</th>
<th>P-MMP9</th>
<th>P-MMP2</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACS (n=33)</td>
<td>27.3%</td>
<td>45.4%</td>
<td>25.0%</td>
<td>7.2%</td>
</tr>
<tr>
<td>CAD (n=60)</td>
<td>36.7%</td>
<td>48.3%</td>
<td>28.0%</td>
<td>28.0%</td>
</tr>
<tr>
<td>HV (n=15)</td>
<td>6.7%</td>
<td>6.7%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Calmodulin Kinase Inhibition Improves Survival in Calcineurin Transgenic Mice

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Background: Transgenic (TG) mice expressing constitutively active calcineurin (CAN) develop severe cardiomyopathy and die prematurely. We previously reported that calmodulin kinase (CaMK) activity is increased in CAN TG mice and pharmacological CaMK inhibition effectively suppressed ventricular arrhythmias.

Methods: We developed TG mice with cardiac expression of a specific CaMK inhibitory peptide, IP, and control mice that express an inactive scrambled peptide, CP. CAN TG mice were crossed with IP TG and CP TG mice to test for functional interaction between CAN and CaMK signaling.

Results: Ventricular homogenates from age- and gender-matched CAN-IP TG mice showed a trend toward reduced CaMK activity compared to CAN-CP mice (3.18 ± 0.20 vs. 4.39 ± 0.50 mmol/min/mg; n = 10 each group; P = 0.07). Echocardiography in conscious mice at 50 days showed significant preservation of left ventricular (LV) fractional shortening (FS) in CAN-IP TG mice (FS = 47.8 ± 1.9%, n = 11) compared to CAN-CP TG mice (FS = 32.0 ± 1.2%, n = 10; P < 0.001). CAN-IP TG mice had improved survival compared with CAN-CP TG mice (Figure). We followed 2 cohorts of 30 CAN-IP and 30 CAN-CP TG mice. At eight months, 12 CAN-CP mice had died suddenly but only 4 CAN-IP TG mice died (P = 0.04).

Conclusion: These results indicate that CaMK activity is critical to the pathology of CAN cardiomyopathy and show CaMK inhibition can be a successful therapeutic intervention in CAN cardiomyopathy by reducing arrhythmias, preserving LV function and improving mortality.

Primary Results of the Rapid Emergency Department Heart Failure Outpatient Trial (REDHOT): A Multicenter Trial Examining B-Type Natriuretic Peptide Levels, Emergency Physician Decision Making and Outcomes in Patients Presenting With Shortness of Breath

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Background: The vast majority of patients seen in the Emergency Department (ED) with CHF are admitted to the hospital, leading to exorbitant costs & resource utilization. There are few tools that aid physicians in decision making with regard to ED treatment followed by discharge vs immediate or delayed hospitalization. BNP correlates with the presence of CHF, disease severity and prognosis. This is the first large cohort that examines BNP in relation to physician decision making, patient disposition, and critical outcomes in emergency medicine. Methods: In this10 center trial, patients seen in the ED with shortness of breath were consented to have BNP levels drawn on arrival, every 3 hrs in the ED & at the time of admission or discharge. Physicians were only told whether the initial BNP level was greater or less than 100 pg/ml & blinded to subsequent BNP levels. Patients were followed up for 90 days after discharge. Results: Of the 504 patients consented, 90% were hospitalized, even though only 68% were designated for hospitalization upon initial evaluation. 66% of patients who were admitted with a NYHA classification of III or IV had BNP levels < 200 pg/ml (11% of total population). This group had a 90-day mortal-