

Noon

1001-22 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: UMMP9 = 0.14 ng/ug protein, UMMP2 = 0.24 ng/ug protein, PMMP9 = 712 ng/ml, PMMP2 = 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 MMP 2 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 suggests 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.

Percent of Patients with Elevated MMP Levels

	UMMP9	UMMP2	PMMP9	PMMP2
ACS (n=33)	27.3%	45.4%	25.0%	7.2%
CAD (n=60)	36.7%	48.3%	28.0%	28.0%
HV (n=15)	6.7%	6.7%	0%	0%

Noon

1001-23 Calmodulin Kinase Inhibition Improves Survival in Calcineurin Transgenic Mice

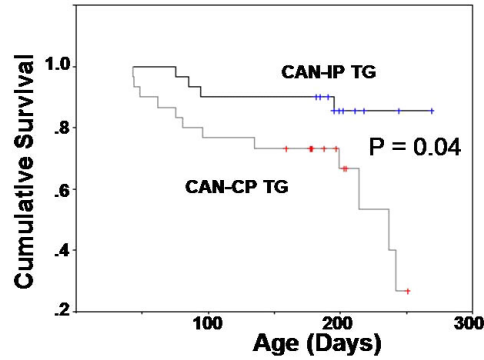
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Background: Transgenic (TG) mice expressing constitutively active calcineurin (CAN) develop severe cardiomyopathy and die prematurely. We previously reported that calmodulin kinase (CaMK) activity is increased in CAN TG mice and pharmacological CaMK 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 nmol/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 = $47.8 \pm 1.9\%$, n = 11) compared to CAN-CP TG mice (FS = $32.0 \pm 1.2\%$, 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.



Noon

1001-24 Long-Term Follow-Up of Safety and Feasibility of Autologous Skeletal Myoblast Transplantation in Patients Undergoing Coronary Artery Bypass Graft Surgery

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Background: Autologous myoblast transplantation (AMT) to repair myocardial infarction has been shown to be safe and effective in preclinical studies. The objective of this study was to demonstrate the safety and feasibility of myoblast transplantation in humans.

Methods: Patients scheduled to undergo elective coronary artery bypass grafting (CABG) were enrolled in the US multicenter clinical trial over a 2-year period. Subjects with previous myocardial infarction and a left ventricular ejection fraction < 40 were eligible to participate. A skeletal muscle biopsy of approximately 2 grams was excised from each patient to isolate and expand myoblasts over 2-5 weeks. Between 3 and 30 direct injections of myoblasts were delivered into the area of infarction using one of 4 escalating doses ranging from 10 to 300 million cells. Pre and post-injection ECG, echocardiogram, Holter monitoring, positron emission tomography (PET) and magnetic resonance imaging (MRI) were performed.

Results: Eighteen patients underwent AMT combined with CABG. The mean age of patients was 54 years. The average baseline ejection fraction (EF) was 26%. Purity of the cells ranged from 47% to 98% CD56+myoblasts. The cells were delivered in all subjects without any perioperative complications. Three serious adverse events occurred; one death due to graft occlusion and two episodes of ventricular tachycardia, 1 non-sustained and 1 sustained, in the first 2 weeks post-operatively. Echocardiography, PET and MRI scans showed evidence of viability in the area of grafted scar. The mean EF of 10 patients improved from 24.8% to 33.9% in (p=0.04).

Conclusion: Results of the first US study indicate that AMT in patients undergoing CABG is feasible and safe. Improvement in viability and wall thickness is encouraging and warrants future clinical trials evaluating the effect of AMT on left ventricular function. Complete follow-up results will be presented.

Noon

1001-25 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 this 10 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-

ity of only 2%. 36 patients were discharged from the ED with a BNP level > 400 pg/ml. The 90 days mortality was 9% in this group, while patients discharged from the ED with a BNP level < 400 pg/ml had 0% mortality at 90 days. Patients who were discharged home from the ED actually had higher BNP levels than those admitted (976 versus 767, p=0.6). Using regression analysis, ED doctor's intention to admit or discharge a patient had no influence on their 90 day mortality, while the BNP level was a strong predictor of 90 day mortality. Conclusion: In patients presenting to the ED with heart failure, there is a strong disconnect between the perceived severity of CHF by ED physicians and severity as determined by BNP levels. The results of this study strongly suggests that BNP levels will aid physicians in making appropriate triage decisions about whether to admit or discharge patients. This should avoid prolonged stays in the ED, unnecessary hospitalizations, inappropriate discharges home and lead to better patient care.

Noon

1001-26 Exchange of Beta-Blocking Therapy in Heart Failure Patients. Experiences From the Post Study Phase of COMET (the Carvedilol or Metoprolol European Trial)

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Background: The COMET study reported a survival benefit for Carvedilol (C), a β_1 , β_2 and α_1 blocking agent, versus Metoprolol (M), a β_1 selective blocker, in 3029 patients (pts) (NYHA class II-IV, LVEF \leq 35%) with chronic heart failure (HF) followed-up for 46-74 months. While withdrawal of β -blockade (BB) is associated to worsening HF and arrhythmias, only limited information exists on exchanging BB in pts with HF.

Methods: At the end of COMET, study BB therapy in pts with stable HF was to be stopped without unblinding and down-titration and immediately replaced by open BB at a dose equivalent to half of the study dose of pts. Thereafter, up-titration to maximum-tolerated or target BB dose was recommended. Pts were followed for 30 days for adverse events.

Results: 1429 pts (47.2%) completed COMET on study BB (C 41 \pm 15 mg, M 82 \pm 30 mg). 1321 (92.4%) were subsequently switched to a post-study BB (1014 pts, 76.8%, to C; 201, 15.2%, to M and 102, 7.7%, to bisoprolol), while 108 pts (7.6%) withdrew BB. Pts staying on the same BB (8.7% on C, 7.4% on M) reported less adverse events than pts switched to a different BB (15.1% from C to M, 14.1% from M to C) or those who withdrew BB (22.2%). Most events occurred in the first week after the transition. The rate of serious events was lower in pts who stayed on C (2.1%) or on M (3.2%), or in pts changing from M to C (3.1%), while higher in those switched from C to M (9.4%) or withdrawing BB (11.1%). Nine pts (0.6%) died, 2 (0.2%) on C, 5 (2.5%) on M and 2 (1.9%) not receiving open BB. HF related events were more frequent in those switching from C to M (4.7%; 4.7% serious) than in pts changing from M to C (2.3%; 1.5% serious). Bradycardia and hypotension were reported in < 1% of pts. Pts on M who were switched to a reduced dose of C (35%) showed a rate of HF events similar to those patients staying on C, but lower than those changing to fully equivalent dose C (65%).

Conclusion: The exchange of BB without down-titration is a practical, safe and well-tolerated strategy in stable HF. The transition from M to a reduced dose of C is associated with the lowest rate of serious and HF related events. Pts on M can be safely switched to C to benefit from the survival advantage demonstrated in the COMET study.

Noon

1001-27 Patients at Risk for Recurrent Embolism After Percutaneous Closure of Patent Foramen Ovale for Presumed Paradoxical Embolism

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Background: Percutaneous closure of a patent foramen ovale (PFO) is an alternative to medical or surgical prevention of recurrent embolism in patients with presumed PFO mediated paradoxical embolism. Risk factors for recurrence after successful PFO closure have not been completely elucidated yet.

Methods: We followed 299 patients with presumed PFO mediated paradoxical embolism after percutaneous PFO closure for a total of 662 patient-years (mean follow-up: 2.2 years, range 0.2 – 8.5 years), assessing postprocedural shunt, recurrent embolic events and device-related morbidity. Freedom of recurrence was calculated according to the Kaplan-Meier method. Predictors of recurrence were calculated using a Cox proportional hazard model.

Results: Twenty recurrent embolic events were observed (14 transient ischemic attacks, 5 events of peripheral embolism, 1 stroke), resulting in an actuarial recurrence rate of 3.8% (95% CI 1.7-6.4%) at 1 year, 7.9 (95% CI 4.9-12.6) at 2 years, and 8.7 (95% CI 5.5-13.7%) at 4 years. Univariate predictors of recurrence were age at implantation > 60 years (hazard ratio 2.7, 95% CI 1.1-6.5), cardiovascular risk factors (hazard ratio 1.5 for every additional factor, 95% CI 1.05-2.1), and most importantly the number of embolic events prior to PFO closure (> 2 events: hazard ratio 4.1, 95% CI 1.7-9.8). Since patients with multiple embolic events prior to PFO closure were older, only the cardiovascular risk profile and > 2 events prior to PFO closure remained significant predictors of recurrence in a multivariate Cox proportional hazard analysis. There was no relation between recurrence rate and atrial septal anatomy (PFO with or without atrial septal aneurysm), gender, residual shunt after 6 months, type or size of device, and embolic index event. **Conclusions:** Patients with > 2 thromboembolic events prior to device implantation

and patients with multiple cardiovascular risk factors are at increased risk for recurrence of embolic events after PFO closure. These findings suggest that alternative mechanisms in addition to paradoxical embolism may be present in this patient group.

Noon

1001-28 Chronotropic Incompetence in Children With Late Postoperative Atrial Flutter: A Case-Control Study

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Background: Atrial flutter (AF) causes late postoperative (postop) morbidity in congenital heart patients. Sinoatrial node dysfunction (SAND) is often present but has not been systematically evaluated as an AF risk factor. **Methods:** An institutionally approved retrospective single-center case-control study was performed. A computerized cardiology database search identified patients aged \leq 18 years with documented late AF (\geq 6 months postop; excluded if AF present at 1-6 months), and with \geq 1 graded exercise test (GXT) and/or 24-hour outpatient ambulatory ECG (Holter). AF-free controls were matched for surgical procedures and year of birth \pm 3 (median difference 0.4) years, with postop follow-up at least equivalent to time points of first AF documentation in corresponding cases. Non-AF heart rate (HR) data were extracted from all GXT (median 2/case, 2/control) and Holter (2/case, 1/control) records. Percent of maximum (max) predicted HR achieved (%pred) was based on $HR_{max}/(220 - \text{age in years})$, where $HR_{max} = \text{max HR on GXT or Holter}$. Data were analyzed using mixed linear regression for repeated measures. **Results:** There was 85% concordance for 125 open heart operations in 42 case-control pairs. AF onset in cases was at age 9.4 ± 5.0 (mean \pm SD) years. Cases had lower average HR, max HR, and %pred than controls (**Table**). **Conclusion:** Chronotropic reserve is reduced but minimum HR is similar in AF patients versus controls. Chronotropic incompetence is thus an important feature of SAND in patients with late postop AF.

Table

	Minimum HR (Holter, beats/min)	Average HR (Holter, beats/min)	Max HR (GXT and Holter, beats/min)	%pred
Case (N=42)	55 \pm 18	76 \pm 10	146 \pm 31	70 \pm 15
Control (N=42)	56 \pm 14	83 \pm 17	169 \pm 22	81 \pm 10
P	NS	<0.001	<0.0001	<0.0001

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1001-29 Impact of Gender on Long-Term Mortality in 4,234 Women and 6,898 Men Evaluated With Exercise and Dobutamine Stress Echocardiography

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Background: Prior research is limited regarding the diagnostic and prognostic accuracy of cardiac imaging modalities in women. The purpose of the current report was to examine 5-year mortality in 4,234 women and 6,898 men undergoing exercise or dobutamine stress echocardiography at 3 hospitals.

Methods: Univariable and multivariable Cox proportional hazards models were used to estimate time to cardiac death in this multicenter, observational registry.

Results: In this cohort of 11,132 patients, women had a greater frequency of cardiac risk factors (p<0.0001). However, men more often had a history of coronary disease including a greater frequency of stress-induced ischemia (p<0.0001). During the 5 years of follow-up, 103 women and 226 men died from coronary artery disease (p<0.0001). From the echocardiographic examination, estimates of left ventricular function (p<0.0001) and the extent of ischemia (p<0.0001) noted during peak stress were highly predictive of cardiac death. At 5 years, risk-adjusted survival was 99.4%, 97.6%, and 95% for exercising women with no, single, and multiple vascular territories with ischemia (p<0.0001). For women undergoing dobutamine stress, 5-year survival was 95%, 89%, and 86.6% for those with no, 1, and 2 or 3 vessel ischemia (p<0.0001). For exercising men, cardiac death at 5 years was higher at 1.1% to 4.5% for 0 to 3 vessel ischemia (p<0.0001). Significantly worsening cardiac survival was noted for the 1,568 men undergoing dobutamine stress echocardiography (p<0.0001). No inducible ischemia was associated with a 92% survival as compared with cardiac death rates of \geq 16% for men with ischemia on dobutamine stress echocardiography (p<0.0001).

Conclusion: Echocardiographic measures of inducible wall motion abnormalities and global and regional left ventricular function are highly predictive of long term outcome for women and men, alike.