1141-34 **Assessment of Left Ventricular Diastolic and Systolic Function in Patients With Heart Failure Using Steady State Cine Magnetic Resonance Imaging: Validation Study Using Conductance Catheter**

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Background: Left ventricular systolic and diastolic functions have been recognized as important factors in cardiovascular diseases. Conductance catheter has high temporal resolution and can provide accurate measurements of cardiac functions. However, it has been difficult to obtain an accurate assessment of left ventricular function by using noninvasive techniques. Steady state cine MR imaging is a new MR imaging technique that can demonstrate improved temporal resolution in the cardiac cycle. In addition, high blood-to-myocardial contrast can be obtained in patients with heart failure. The purpose of this study was to evaluate the accuracy of steady state cine MR imaging for assessing left ventricular volumes and functions by using a conductance catheter method as a gold standard. Methods: Fourteen patients (9 men, mean age 60.4±11.3 years) with heart failure (7 with dilated cardiomyopathy, 5 with old myocardial infarction, 2 with constrictive pericarditis) were studied. Left ventricular time-volume curves were obtained with steady state free precession cine MR imaging and with a single-field conductance catheter using a micromanometer. End-diastolic volume (EDV), end-systolic volume (ESV) and ejection fraction (EF) were calculated. In addition, peak ejection rate (PER), time to PER, peak filling rate (PFR) and time to PFR were assessed by the first derivative curve of the left ventricular time volume curve. Temporal resolutions was 26 msec by MR imaging and 3 msec by conductance catheter. Results: Excellent cine MR images were acquired in all patients by using steady state cine MR imaging. Significant linear correlation between the measurements by MR imaging and conductance catheter was found for EDV (r=0.98, p<0.001), ESV (r=0.99, p<0.001), EF (r=0.97, p<0.001), PER (r=0.76, p<0.01), time to PER (r=0.78, p<0.01), PFR (r=0.66, p<0.05) and time to PFR (r=0.77, p<0.01). Conclusion: MR measurements of LV volume, EF, PER and PFR obtained by using a steady state cine MR imaging demonstrated good correlations with those assessed by conductance catheter. Cardiac MR imaging is a noninvasive method that can provide detailed analysis of the cardiac performance in patients with LV dysfunction.

POSTER SESSION

1142 Nuclear

Monday, March 31, 2003, 3:00 p.m.-5:00 p.m.
McCormick Place, Hall A
Presentation Hour: 4:00 p.m.-5:00 p.m.

1142-35 **Higher First-Pass Extraction of ^{99m}Tc-N-NOET Enhances Magnitude of Reversible Defects: Validation of Animal Model in Humans**

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Background: ^{99m}Tc-N-NOET (NOET) is a lipophilic neutral molecular tracer being developed for myocardial perfusion imaging. It differs from the ^{99m}Tc-labeled charged molecules in that it redistributes similarly to ^{201}Tl. We have found in a dog model that the first-pass myocardial extraction was higher for NOET compared to other ^{99m}Tc-labeled tracers. Hypothesis: If this is true in humans, it would imply greater contrast between normal myocardium and stress-induced defects for NOET compared to ^{99m}Tc-sestamibi (MIBI). Methods: Quantitative SPECT studies were obtained on 26 patients (19 males; 60±13 years old; 12 with prior myocardial infarction). Same-day MIBI studies were performed followed within 3 days by exercise-delayed NOET studies. Bruce protocol was used and the same level of exercise was achieved in both tests. Results: In 364 segments quantitatively measured at rest there was good correlation (Pearson r=0.89) and mean segmental uptake was not different (81.08% versus 81.09%, p=0.98). There was a small difference in mean uptake of all 364 segments with stress (80.8% for NOET and 81.6% for MIBI, p=0.01). The difference was greater for 89 reversible defects with averages of 68.4% for NOET versus 71.0% for MIBI (p<0.001). The Gosselin-Stibetz capillary diffusion model was used previously (Glover et al.) to fit the animal data of tracer extraction versus myocardial blood flow. We used the same model with parameters obtained from the animal studies to derive a theoretical relationship for the defect ratio of NOET versus MIBI as a function of defect magnitude. The model prediction, obtained from animal data, fits our human data with p=0.88. Conclusion: This study provides experimental verification that the non-linearity of extraction versus flow is similar in humans and the dog model. The higher ^{99m}Tc-N-NOET extraction results in greater defect contrast and greater magnitude of reversibility in reversible defects. This is in accordance with animal studies measuring tracer extraction as a function of myocardial blood flow.

1142-36 **Comparison Between the Myocardial Uptake of ^{99m}TcN-DBODC5 and ^{201}Tl During Vasodilator Stress in a Canine Model of a Critical Coronary Stenosis**

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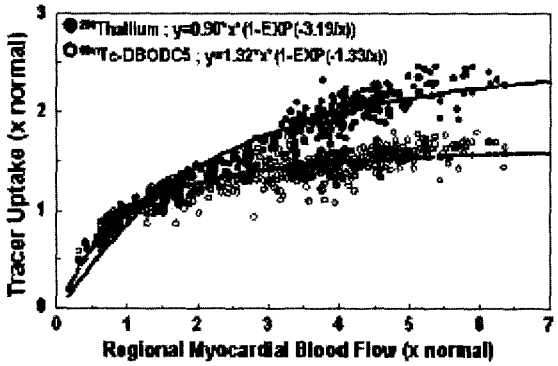
Background: ^{99m}TcN-DBODC5 (DBODC5) is a new lipophilic, cationic myocardial perfusion imaging agent. Previous rat studies from our lab demonstrated high initial heart to background ratio (2.6) and slow washout combined with very rapid liver clearance. **Methods:** The goal of this study was to compare the myocardial extraction of DBODC5 with ^{201}Tl over a wide range of regional myocardial blood flows. Accordingly, 8 anesthetized dogs with critical LAD stenoses were given an i.v. infusion of an adenosine A_{2A} receptor agonist (ATL-146e; 0.3 μg/kg/min) that induced a 4-fold increase in normal LCX zone regional flow (p<0.01) with no change in flow in the stenotic LAD zone. DBODC5 (8 mCi), ^{201}Tl (0.75 mCi), and radioactive microspheres were co-injected at peak flow and the dogs were euthanized 5 min later. Flow and tracer activities in myocardial segments were assessed by gamma well counting. **Results:** As shown below, the myocardial extraction of both DBODC5 and ^{201}Tl plateaued as flow increased, with higher extraction of ^{201}Tl at hyperemic flows. Both tracers underestimated the extent of the flow disparity as the DBODC5 (0.59±0.07) and ^{201}Tl (0.44±0.05) LAD/LCX activity ratios were higher than the microsphere flow ratio (0.25±0.03) at the time of injection. **Conclusions:** The flow-extraction relationship for DBODC5 was comparable to other cationic ^{99m}Tc tracers. The more rapid liver clearance, however, could give it an advantage over other ^{99m}Tc-labeled tracers for clinical imaging.



1142-37 **Myocardial Perfusion Cold Pressor Test ^{99m}Tc MIBI-SPECT Detects Both Microvascular and Epicardial Abnormal Reactivity in Patients With Endothelial Dysfunction and Angiographically Normal Coronary Arteries With Intracoronary Acetylcholine Vasoconstriction**

Néstor A. Perez Baliño, Osvaldo Masoli, Marcela Redruello, Sonia Traverso, Daniel Cragnolino, Alejandro Meretta, Carlos Rapallo, Jorge L. Szarfer, Ricardo Sarmiento, Miguel A. Riccitelli, Hospital General de Agudos Dr. Cosme Argerich GCBA, Buenos Aires, Argentina, Instituto Cardiovascular de Buenos Aires, Buenos Aires, Argentina

Background: Since invasive methods to evaluate endothelial function have important limitations, studies should attempt to assess it in a noninvasive way. We previously reported a close correlation between myocardial perfusion defects ^{99m}Tc MIBI-SPECT and abnormal intracoronary acetylcholine (ACH) response. Other authors showed correlation between Cold pressor test (CPT) and ACH. Objective: To correlate ACH vasoconstriction response with CPT-SPECT myocardial perfusion abnormalities in patients with endothelial dysfunction and angiographically normal coronary arteries. Methods: 18 patients (aged 45±10, 8 males) with angiographically normal coronary arteries and vasoconstriction response to ACH were studied with CPT ^{99m}Tc MIBI SPECT imaging perfusion. Vasomotor response to intracoronary increasing doses of ACH and a single dose of nitroglycerin (NTG) was assessed with digital quantitative angiography. Regional myocardial perfusion was evaluated at rest and after CPT by a semiquantitative score analysis in a 17 segment model. Correlation curves between: Epicardial Basal Lumen diameter (BL), ACH L, NTG L, and myocardial perfusion score (PS) were obtained. Results: all patients had regional perfusion defects. Myocardial perfusion score was at CPT 7±3.8, rest 1.3±4.2 (p<0.00001). Mean BL was: 3.4±0.9mm, ACH L 2.3±0.7, decreased 30% (p<0.00003). NTG L 3.6± 1mm vs. ACH L p<0.00001. Positive correlation was found between:1) BL and ACH L (r = 0.83 p< 0.002). 2) BL and NTG L (r = 0.87 p< 0.001). No correlation was found between:1) CPT-PS and ACH L (p:ns). 2) CPT- PS and BL (p:ns). Conclusions: These results suggest that CPT SPECT perfusion abnormalities may be related to epicardial and microvascular coronary reactivity in patients with endothelial dysfunction and angiographically normal coronary arteries.

1142-38 **Myocardial Perfusion Imaging With a Novel Selective A2a Adenosine Receptor Agonist (CVT-3146): Important Differences in Radiotracer Behavior**

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Background: Use of a selective A2a adenosine receptor agonist, CVT-3146 (CVT), for perfusion imaging may reduce side effects, however, the effects of CVT on radiotracer myocardial uptake is undefined. Methods: To determine myocardial uptake of thallium-201 (TL) and Tc99m-sestamibi (MIBI) in relation to coronary flow (FL) during CVT stress, a proximal LCX stenosis was created in anesthetized open chest dogs (n = 6), using a hydraulic occluder, which was adjusted to blunt reactive hyperemia without reducing rest FL. FL was measured with FL probes and radiolabeled microspheres (mSPH). CVT (2.5 ug/kg) was administered as a 30 sec i.v. bolus, followed 10 sec later by simultaneous i.v. injection of TL (1.5 mCi), and MIBI (25 mCi), and left atrial injection of a second mSPH for determination of stress FL. At 5 min after tracer injection, hearts were excised and cast for ex vivo SPECT imaging. Images were quantified using circumferential count profile

analysis, and TL and MIBI integrated defect magnitude (% left ventricle (LV)) calculated. Hearts were sliced (5 mm thick), and each slice divided into 8 segments (segs). Myocardial tracer activity and mSPH flow were determined by gamma well counting. Ischemic (IS) segs were defined by a coronary flow reserve (CFR) of 2.5. IS/NI tracer and flow ratios were calculated. Results: In IS segs, FL (ml/min/g) at rest was not reduced (IS: 0.62±0.04; NI: 0.61±0.04; p=ns), although CVT stress FL in IS segs was significantly reduced compared to NI (IS: 0.70±0.06; NI: 1.90±0.21; p<0.001). CVT stress IS/NI FL ratio (0.38±0.02) was significantly reduced compared to rest (p<0.001). TL and MIBI uptake ratios both under estimated the FL deficit (TL: 0.54±0.02, p<0.001 vs Stress FL; MIBI: 0.69±0.05, p<0.001 vs Stress FL). The TL IS/NI ratio provided a better index of the flow deficit than MIBI during CVT stress (p<0.001). The SPECT TL defects (22±3.1 %LV) were also significantly larger than MIBI (16.4±2.1 %LV, p<0.05). Conclusions: CVT administered as a bolus created marked flow heterogeneity, and significant TL and MIBI perfusion defects in the presence of a critical coronary stenosis. However, during CVT stress, TL tracked flow better than MIBI, and produced larger SPECT defects.

1142-39 Targeting Vitronectin Receptors for Noninvasive Radionuclide Imaging of Atherosclerosis

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Background: Vitronectin receptor plays a pivotal role in smooth muscle cell (SMC) migration in vascular injury, neointimal proliferation during plaque development and progression, and post-angioplastic restenosis. We investigated the feasibility of targeting vitronectin receptors for noninvasive imaging of experimentally induced atherosclerotic lesions.

Methods: A radiolabeled $\alpha v\beta 3$ integrin antagonist (^{111}In-RP 748, Bristol-Myers Squibb) was utilized for imaging in 6 NZW rabbits with experimentally induced atherosclerotic lesions and in 7 unmanipulated control rabbits. Atherosclerosis was induced by abdominal aorta deendothelialization followed by a cholesterol rich diet (1%+6% peanut oil) for 12 weeks. Control rabbits were fed normal chow for 12 weeks. Gamma images were obtained until 3H after ^{111}In-RP 748 administration.

Results: Atherosclerotic lesions were clearly visible in all six rabbits. Quantitative ^{111}In-RP 748 uptake in atherosclerotic lesions was 5 times higher than the background activity in the corresponding regions of the control rabbits (mean percent injected dose per gram, 0.07+/-0.01 versus 0.01+/-0.004; P<0.05). Correlation between histopathologic indices of SMC proliferation, macrophage proliferation, and radioligand uptake was performed.

Conclusion: Noninvasive imaging of experimentally induced atherosclerotic lesions using ^{111}In-RP 748 is feasible and may be useful for early detection of SMC proliferation such as post-angioplastic restenosis.

1142-40 Increased Tc-99m-Annexin Uptake in Doxorubicin Induced Myocardial Apoptosis

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Background: Doxorubicin (Dox) treatment is limited by irreversible cardiomyopathy; apoptosis may contribute to myocardial damage. Simultaneously, induction of apoptosis in the malignant tissue is necessary for oncolysis. Since phosphatidylserine is exposed on the cell surface during apoptotic process and Annexin V has a high affinity for membrane bound phosphatidylserine, we used Tc-99m-labeled Annexin V (TAN) imaging to study acute and chronic Dox induced myocardial apoptosis in rats.

Methods: Eight male Sprague Dawley rats weighing 250-300 g were injected with Dox, group1: single dose 6 mg /kg i.v. (acute group, n=4) and group 2: biweekly for 4 weeks 2.5 mg/kg i.p. (chronic group, n=4). Four control animals were included in each group and treated with saline. Both groups were imaged using TAN at the end of 2 and 5 weeks respectively. Gamma imaging was performed at 3 hours after i.v. injection of 1.0-1.2 mCi TAN. Hearts were excised and sliced into four segments and percent injected dose per gram (% ID/g) of Annexin V uptake was measured. Myocardial specimens were submitted for histopathologic examination and TUNEL and caspase-3 staining.

Results: On ex-vivo imaging, Dox treated animals showed increased activity in their hearts as compared to their respective controls. The highest uptake was visualized in group2. % ID/g TAN uptake was 0.98 ± 0.14 % in group 2 and 0.88 ± 0.26 % in group 1,which were significantly higher than corresponding controls (0.43 ± 0.15 % and 0.52 ± 0.005 % respectively; p< 0.0001). Basal myocardial segments in both groups showed highest increase in TAN.

Conclusion: Doxorubicin induces myocardial apoptosis in rats and it should be possible to image myocardial damage and remission of tumor mass simultaneously by TAN.

1142-41 Mechanism of Sestamibi Retention and Clearance From Myocardium and Other Organs

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Background: Tc-99m-sestamibi (MIBI), is widely used for myocardial perfusion imaging. Following iv administration, MIBI has stable myocardial retention whereas it clears from all other organs. The exact mechanism of its selective retention in the myocardium is not clear.

Methods: Hepatic clearance of MIBI after intrasplenic injection by serial imaging was studied in following groups of animals: inbred wild-type FVB/N normal mice (n=5), knockout FVB/N mice with specific P-glycoprotein deficiencies (n=18), normal Long-Evans Agouti (LEA) rats (n=4) and mutant Long-Evans Cinnamon (LEC) rat (n=4) with liver disease following copper toxicosis but intact P-glycoprotein expression.

Results: After intrasplenic injection, MIBI rapidly incorporated in the liver of normal mice and rats, with maximal accumulation at 102±31 and 109±16 sec respectively (p=ns). In normal mice and rats, 55±11% and 55±6%, respectively, of maximal MIBI activity was retained in the liver at 1 hour. In mice lacking both homologs of the single human multidrug resistance gene 1, mdr1a and mdr1b genes (double knockout mice, n=6), 88±11% of maximal activity remained in the liver at 1 hour, (p<0.001). In single knockout mice deficient in either mdr1a (n=5) or mdr2 gene (homolog of MDR3 gene in humans) (n=7), hepatic MIBI excretion was also impaired (p<0.05). Hepatic MIBI excretion was unchanged in LEC rats despite significant liver disease compared to the normal rats.

Cocclusion: MIBI is a substrate for MDR1 and MDR3 gene products. These genes are abundantly expressed in liver and other organs but not expressed in the heart. A lack of MDR gene expression in the normal myocardium explains a relative lack of myocardial clearance of MIBI. Inactivation of MDR gene results in marked impairment of hepatic MIBI clearance. Other MDR substrates may also have potential for use as myocardial perfusion imaging agents.

1142-42 Ischemic Stroke Causes Regional Denervation in Rat Myocardium

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Background: Electrocardiographic abnormalities, cardiac enzyme release, and myocardial contraction band necrosis have been reported after central nervous system (CNS) injury. Coronary disease, vasospasm, and increased left ventricular loading are often cited as the likely causes of this cardiac injury. The goal of this study was to demonstrate that ischemic stroke in rats causes myocardial denervation, supporting the alternate hypothesis that myocardial injury is neurally mediated.

Methods: Six male Wistar rats underwent right middle cerebral artery occlusion (MCAO) under isoflurane anesthesia, using an intraluminal suture introduced through the extracranial internal carotid artery. Two rats underwent sham surgery (controls). Brain magnetic resonance imaging (MRI) was used to quantify cerebral infarction. Four of the rats were sacrificed after 72 hours and two of the rats were sacrificed 1 week after MCAO. Prior to sacrifice, the rats were injected with I125-metaiodobenzylguanidine (MIBG), a marker of adrenergic neuron function, and with 99mTc-sestamibi (MIBI), a marker of myocardial perfusion. Hearts were extracted, sectioned, and mounted. Myocardial slices were exposed to storage phosphor imaging plates and the distribution of the MIBI and MIBG were scanned using a phosphorimager. Each pair of autoradiographs was compared on a pixel-by-pixel basis by a previously validated color method. The outcome variable, myocardial percent denervation, was quantified based on a reduction in MIBG relative to MIBI.

Results: Brain MRI confirmed the presence of cerebral infarcts of varying sizes in all of the rats that underwent MCAO. All four of the rats that were sacrificed within 72 hours after surgery showed evidence of myocardial denervation. Percent denervation ranged from 18%-80% (mean 42%). Mean percent denervation in the 2 rats that were sacrificed 1 week after MCAO was 4%. Mean percent denervation in the controls was 7%.

Conclusion: This study provides unique evidence that myocardial denervation occurs after CNS injury, strongly supporting the theory that this form of cardiac dysfunction is neurally mediated.

1142-43 Persistant Myocardial Sympathetic Denervation in Patients With Neurocardiogenic Injury

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Introduction: ECG changes, troponin release and reduced left ventricular ejection fraction (LVEF) are known to occur after subarachnoid hemorrhage (SAH). An association of LV systolic dysfunction with myocardial sympathetic denervation in SAH patients has been reported. We aimed to describe the time course of neurocardiogenic injury and sympathetic denervation after 6 months of follow-up.

Methods: Over 2 years, echocardiography was performed on 173 consecutive patients admitted with SAH. In 21 cases with evidence of global or regional LV systolic dysfunction, myocardial scintigraphy with technetium sestabamibi (MIBI) and meta-[123I]iodobenzylguanidine (MIBG) was performed to assess myocardial perfusion and sympathetic innervation, respectively. Patients surviving to discharge were invited for follow-up echocardiographic and scintigraphic imaging after 6 months. Blinded observers interpreted all echo and nuclear data.

Results (see table): Ten patients returned for follow-up. All initial and follow-up MIBI scans were normal. Each patient was classified based on their MIBG results as follows: normal initial and follow-up, abnormal initial with normal follow-up, abnormal initial and follow-up. Clinical data including Hunt-Hess score (SAH severity grade, 1=headache, 5=coma) for the groups are shown in the table.

Conclusion: Persistent sympathetic denervation occurs in some patients with SAH, though LV systolic dysfunction appears to be reversible in most cases.