

ASNC2008 Late Breaking Clinical Trials
Saturday, September 13, 2008, 10:30 a.m. - Noon

10:30 a.m. Robustness of Iodofiltic Acid I 123 Accuracy for Quantifying Metabolism Across Three Software Packages

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Background: Gender-matched normals databases are frequently used in Nuclear Cardiology to help distinguish normal vs. abnormal perfusion distribution. Currently, there are no commercially available normal databases to evaluate the distribution of Iodofiltic Acid I 123 (¹²³I-IA) cardiac SPECT.

Objectives: To develop a gender-matched normals database for three widely used semi-automatic quantification software packages, and then to identify criteria for abnormality in each software package for emergency department (ED) subjects enrolled in a Phase II clinical trials using ¹²³I-IA cardiac SPECT.

Methods: A set of subjects (40M / 40F) were randomly selected by Cedars-Sinai from a pool of 171 subjects in a Phase II Normals study which enrolled low likelihood subjects for CAD, with an additional constraint of no imaging artifacts. Male and female normal databases were created in QPS™ (Cedars-Sinai), ECTb™ (Emory) and 4DM™ (Michigan) by determining the regional mean normal distribution and standard deviation. Tomographic SPECT data from 102 subjects enrolled in an open-label Phase II ED study, using an injected dose of 2.4-5.4 mCi of ¹²³I-IA, were reconstructed using filtered back projection into short axis slices and imported into each software package. ¹²³I-IA SPECT data for the ED subjects were scored with each software package using the respective normal database. Diagnostic performance of ¹²³I-IA was evaluated by comparison with a true standard of myocardial ischemia prospectively defined by diagnosis algorithms using available clinical data collected in the ED study.

Results: Three ROC curves were generated to assess diagnostic performance of ¹²³I-IA quantitative scores in three software packages. The area under ROC curve statistic showed an overall diagnostic accuracy in detecting ischemia for each software package (p<0.001 for two of them, p<0.05 for the other). Among the three packages, the optimal characteristics were 63-79% for sensitivity and 61-69% for specificity. There were no significant statistical differences in quantitative scoring between software packages (overall test for equality of areas, p=0.05).

Conclusions: Quantifying metabolism using ¹²³I-IA cardiac SPECT demonstrated robust performance characteristics across three widely used software packages. Utilizing the same concepts that have been successful for myocardial perfusion imaging, these preliminary findings confirm the benefit of utilizing software packages to provide quantitative evaluation on ¹²³I-IA diagnostic performance.

10:40 a.m. A multi-center trial for comparison of high-speed myocardial perfusion SPECT versus conventional SPECT: Quantitative results of myocardial perfusion and left ventricular function

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Background: A novel high-speed SPECT camera employing cadmium zinc telluride crystal arrays has been shown in single center studies to detect a similar amount of myocardial perfusion abnormality compared to conventional Anger SPECT camera (conventional SPECT) in up to one seventh the acquisition time. This study compares quantitative results of myocardial perfusion and function by high-speed SPECT to conventional SPECT in a large prospective multi-center trial.

Methods: Two-hundred twenty four patients (127 males) underwent one-day Tc-99m sestamibi rest/ stress SPECT with D-SPECT and A-SPECT at four centers: Cedars-Sinai Medical Center (CSMC) (n=57), Vanderbilt University Medical Center (VUMC) (n=54), Brigham and Women's Hospital (BWH) (n=58) and Miami Baptist Hospital (MBH)(n=55). D-SPECT MPI was performed within 30 min of A-SPECT. Rest/ stress acquisition times were 20 and 15 minutes, respectively for A-SPECT, and 4 and 2 minutes, respectively for D-SPECT. Perfusion was analyzed using QPS software, deriving the total perfusion defect (TPD) of stress and rest, expressing overall extent and severity of perfusion defects. Due to the higher image resolution QPET (rather than QGS) was used for EDV, ESV and EF measurements. Perfusion and function measurements were automatically generated for the stress and rest images of D-SPECT and A-SPECT.

Results: D-SPECT stress and rest TPD in the entire cohort correlated linearly to A-SPECT TPD over a wide range of perfusion abnormality (r=0.96, p<0.0001). High linear correlation between D-SPECT and A-SPECT stress TPD was seen at each of the participating centers (r=0.97, 0.96, 0.97, 0.97 for CSMC, VUMC, BWH, and MBH, respectively, p<0.0001). Normalcy rates (normal defined as TPD<5%) in 61 patients with low prescan likelihood of coronary artery disease were 95.1% and 90.2% for D-SPECT and A-SPECT, respectively, p=ns. Post-stress EF, EDV and ESV by D-SPECT correlated linearly to A-SPECT over a wide range of EF and

volumes ($r=0.88, 0.96, 0.98$, respectively, $p<0.0001$).

Conclusions: The results of this prospective multicenter clinical trial demonstrate that the novel high-speed SPECT technology provides objective quantitative measures of myocardial perfusion and function, comparable to conventional SPECT imaging at up to one seventh the acquisition time.

10:50 a.m. What is the Optimal Method for Ischemia Evaluation in Women: Preliminary Data from the WOMENs Trial

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Background: The WOMEN Study, What is the Optimal Method for Ischemia Evaluation in Women, is a prospective, randomized investigator-initiated multicenter trial to examine the results of different noninvasive testing strategies on outcomes in women at intermediate to high pre-test likelihood of CAD.

Methods: Entry criteria were based on ACC guidelines and ability to exercise determined by the Duke Activity Status (DASI) questionnaire. Women were randomized to either ECG exercise tolerance testing (ETT) alone or ETT with Tc-99m tetrofosmin SPECT myocardial perfusion imaging (SPECT). Ongoing results were monitored by a DSMB with all events adjudicated; MACE will be evaluated at 1 and 2 years. Additionally, serial evaluation of quality of life and activity measures will be obtained using the Seattle Angina Questionnaire and DASI.

Results: During a 2 year recruitment period, 826 patients were enrolled from 46 sites, 413 in ETT and 413 in SPECT. To date, follow-up information is complete in 98% of patients.

Conclusions: Baseline data including demographics, pre-test likelihood of CAD, and test results (including the percentage of abnormal ECG and SPECT imaging results) will be presented. ETT and SPECT results will be compared with subject characteristics and pre-test likelihood of disease.

11:00 a.m. Novel Ultrafast Cardiac Camera in Myocardial Perfusion SPECT: Initial Multicenter Comparison With Standard Dual Detector Cameras

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Objective: To prospectively compare myocardial perfusion SPECT imaging using a novel ultrafast dedicated cardiac camera (UFC), (GE Healthcare), with standard dual detector cameras (S-SPECT) in patients with known or suspected coronary artery disease (CAD).

Methods: Forty-two patients (25 men, mean age 62.6 ± 13.5 years) underwent one-day Tc-99m tetrofosmin rest/stress myocardial perfusion imaging (results from 150 patients are anticipated to be presented). Rest/stress UFC images were acquired on list mode immediately prior to S-SPECT images. The UFC is equipped with cadmium zinc telluride solid state detectors and has no moving parts. Rest and stress acquisition times were 4 and 2 min for UFC and 14 and 12 min for S-SPECT. Emory Cardiac Toolbox (ECTb) software was used for processing and interpretation. Two readers blinded to clinical information independently scored all scans using a standard 5-point scale on a patient level and on a vascular territory level. A third blinded reader scored the discordant cases. Image quality was qualitatively assessed and automated left ventricular ejection fractions (LVEF) were compared.

Results: For UFC, both rest and stress image quality were considered excellent in 70/84 (83%) cases, adequate in 13/84 (16%) and suboptimal in 1/84 (1%). For S-SPECT, stress image quality was considered excellent in 51/84 (61%) and adequate in 33/84 (39%) cases and for rest 55/84 (66%) excellent, 28/84 (33%) adequate and 1/84 (1%) suboptimal. There was a high correlation between UFC and S-SPECT for rest ($r=.93, p<0.001$) and stress ($r=.91, p<0.001$) automated LVEF. The table shows the % agreement rates between UFC and S-SPECT based on the presence or absence of stress perfusion defects using S-SPECT as the gold standard.

% agreement	CAD	LAD	LCX	RCA
Abnormal	100 (7/7)	100 (2/2)	100 (4/4)	100 (5/5)
Normal	89 (31/35)	98 (39/40)	95 (36/38)	92 (34/37)

Conclusions: These preliminary results suggest that UFC provides diagnostic performance comparable to S-SPECT. Acquisitions can be done in a significantly shorter time with high image quality because of its improved count sensitivity over S-SPECT cameras.

11:10 a.m. Additive value of MPI to CTA for Assessing Functional Significance of Intermediate Lesions in Patients with Acute Chest Pain. A Sub-group Analysis Design of the CT-STAT Trial

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BACKGROUND: SPECT MPI has been used as a standard of care to assess pts with acute CP (ACP) presented in the ER over the last decade. The recent application of Cardiac CTA to ACP pts has been gaining attention with its advantage of fast scanning and accuracy in the diagnosis of CAD. However, CTA is limited in pts with coronary calcification or intermediate coronary lesions. The diagnostic accuracy and prognostic power of functional perfusion in this patient population has not been well studied in the acute setting.

AIMS: This study is designed to assess the additive values (diagnostic and prognostic) of functional imaging in patients who crossover from CTA to MPI enrolled in the CT-STAT Trial.

METHODS: CT-STAT is the 1st prospective, randomized, multi-center trial, currently on going, to assess safety, diagnostic efficacy and efficiency comparing CTA with SPECT in ACP patients presenting in the ER. An estimated 200 (~25% of total 750) patients, who crossover from the CT arm to SPECT arm due to intermediate lesions or suboptimal imaging quality, are included in the study. Patient history, hemodynamic characteristics (HR, BP) and CTA imaging quality will be analyzed. Coronary stenosis and MPI perfusion defects will be quantified using established coronary scoring and summed stress score respectively. The primary endpoint is major adverse cardiac events (MACE) at 30 days and 6 months, with secondary endpoints being diagnostic efficacy (vs. catheterization) and cost efficiency (total cost). The additive value and the predictive power of MPI vs. CTA will be analyzed using multivariate analysis and Cox proportional hazards regression analysis.

CONCLUSION: This study will help to determine the additive value of functional imaging in patients with ACP with intermediate or suboptimal CTA results for accurate diagnosis of CAD, cost effectiveness and prediction of MACE. In addition, SPECT might be considered as the 1st choice imaging modality in some pts with certain medical and hemodynamic characteristics instead of CTA.

11:20 a.m. Is Pharmacologic Stress SPECT Risk Stratification Generalizable to Daily Practice? Results from an International, Prospective, Multicenter Registry

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Background. Although extensive literature supports the prognostic application of pharmacologic stress (PS) SPECT myocardial perfusion imaging (MPI), these studies are primarily from a handful of academic centers. We sought to investigate the generalizability of these results by examining the prognostic performance of PS MPI in a prospective, multicenter, international registry recruiting patients (pts) from various practice settings.

Methods. Pts referred for clinically indicated PS MPI were recruited from 89 centers in 8 countries. Pts were followed for revascularization (REVASC), and all-cause death (ACD) for 1 year after MPI [mean follow-up: 327 days]. MPI were interpreted by local site investigators using 17-segment, 4-point scoring model. Summed stress, rest, and reversible scores were calculated. Abnormal MPI were categorized as abnormal with reversible but no fixed defects (SDS \geq 2, SRS<3), fixed but no reversible defects (SDS<2, SRS \geq 3), and both reversible and fixed defects (SDS \geq 2, SRS \geq 3). Multivariable Cox proportional hazards models (CPH) were used to examine the association between MPI findings and ACD.

Results. Follow-up and complete data was available in 4989 pts (96.4% of all pts; mean age: 66 years, 48% male, 42% with prior CAD). Pts were diverse geographically [US (66%), Canada (13%), Europe (9%), and Latin America (12%)], and with respect to practice type where tested (26% private, 48% tertiary center, 26% community). PS was performed with adenosine (55%), dipyridamole (40%), or dobutamine (5%); 18% had low-level exercise with vasodilator stress.

At 1-year follow-up, 212 of patients (4.2%) had early REVASC [<90 days after testing]; and 152 had ACD (3.3%). ACD rates were 2.2% and 3.7% in normal and abnormal MPI, respectively (p=.003). ACD risk was greatest in pts with both reversible and fixed defects compared to pts with fixed but no reversible defects or pts with reversible but no fixed defects (5.4%, 3.2%, and 2.5%, respectively, p=.024 and .002). After excluding pts with early REVASC, CPH models revealed that after adjusting for demographic, clinical, and historical data, MPI results were highly predictive of one-year ACD risk (p=.004).

Conclusions. PS MPI results add prognostic value and risk stratify pts with respect to ACD in a cohort drawn from diverse practice types and geographic regions.

11:30 a.m. Similar Prevalence of Silent Myocardial Ischemia in UK Indian Asians and European Whites With Comparable levels of Coronary Calcification

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Background: Coronary heart disease (CHD) mortality is 70% higher amongst Indian Asians (IA) than European whites (EW). This excess is unexplained by conventional risk factors. Coronary artery calcification (CAC) is highly correlated with coronary plaque burden, and high CAC predicts silent myocardial ischaemia on myocardial perfusion imaging (MPI). We hypothesised that IA have increased silent myocardial ischaemia compared to EW, for similar amounts of coronary calcium, and this may explain their excess coronary mortality.

Methods: 2389 asymptomatic IA and EW men and women, aged 35 to 75 years were recruited from the practice lists of 58 family physicians in West London, as part of the London Life Sciences Prospective Population (LOLIPOP) study. CAC was measured for all participants using electron beam computed tomography. 500 patients had CAC > 100 Agatston units and were invited for a MPI scan. 262 patients responded and MPI was performed. There was no significant difference in characteristics between responders and non responders.

Results: In comparison to Europeans, IA were younger, had ~2-fold higher prevalence of hypertension and type-2 diabetes, higher waist-hip ratio, and lower HDL cholesterol (table). Cigarette smoking was lower in IA compared to EW. There was no difference in prevalence of silent myocardial ischaemia in IA and EW, following adjustment for conventional risk factors. Type 2 diabetes and CAC were independent predictors for silent myocardial ischaemia in both IA and EW.

Conclusion: Presence of Type II diabetes and coronary artery calcification increases risk of silent myocardial ischaemia in both IA and EW. Similar silent myocardial ischaemia for any given level of CAC, in Indian Asians and Europeans, contrasts with almost 2-fold higher risk of myocardial infarction and CHD mortality in Asians.

	EW (103)	IA (159)	P value
Age	64 (± 7)	62(±8)	.004
Agatston score(95% CI)	696 (535-857)	530(421-639)	0.06
Type 2 diabetes (%)	18	39	<0.001
Total cholesterol	5.4(±1.19)	5.2(±1.14)	0.086
Hypertension (%)	38	62	<0.001
Waist-hip ratio	0.95(±0.06)	0.97(±0.06)	<0.001
Current smokers (%)	21	9	0.003
Triglycerides	1.6(±0.85)	1.7(±0.89)	0.438
HDL cholesterol	1.3(±0.32)	1.19(±0.25)	<0.001
Myocardial perfusion defects (95%CI)	25%(16-33)	25(18-31)	1.0

11:40 Screening for Ischemia in Asymptomatic Patients with Type 2 Diabetes: 5-Year Outcomes in the DIAD Study

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Coronary artery disease (CAD) is a major cause of morbidity in patients with Type 2 diabetes (T2DM). Silent myocardial ischemia (SMI) is common and cardiac death or myocardial infarction (cardiac events [CE]) may be the first manifestation of CAD. In the Detection of Ischemia in Asymptomatic Diabetics (DIAD) study, 1123 T2DM patients without symptomatic or previously diagnosed CAD were randomized to either screening with stress adenosine myocardial perfusion imaging (MPI; 561) or standard care without screening (562). The mean age was 60±7 yrs, DM duration 8±7 yrs, 54% male, 22% ethnic minorities, HbA1c 7.1±1.5 %; both groups were clinically comparable. 22 % of screened patients had inducible ischemia. Subsequent diagnostic testing/treatment were performed at the discretion of primary care givers. Over a mean follow-up of 4.8±0.8 yrs, the cumulative CE rate was 3.3% (0.5%/yr.) There was no difference in CE rates between groups: screening 15/558; standard care 16/561. In those randomized to screening, normal MPI and small MPI defects were associated with a low cumulative 5-yr CE rates of 2.1 % and 2.0%, respectively (<0.8 %/yr). Those with moderate/large MPI defects and those with non-perfusion abnormalities (e.g. ischemic ECG changes) had higher CE rates: 12.3 % and 6.8%, respectively (p=.01). Predictors of CE by Cox regression were: male gender (HR 2.6; p=.03), peripheral vascular disease (HR 3.2; p=.01), LDL-C (HR 1.16 per 10 mg/dl increase; p=.008), creatinine (HR 1.6 per 1 mg/dl increase; p<.0001), abnormal heart rate response to standing (HR 3.6; p=.001), moderate/large MPI defect (HR=6.2; p=.001) and non-perfusion abnormality (HR 4.8; p=.04). The use of aspirin, statins and ACE-inhibitors increased significantly (p=.0001) during the course of DIAD study and was similar in both groups. Thus, unexpectedly, asymptomatic T2DM patients without symptomatic or previously diagnosed CAD have an overall highly favorable 5-yr prognosis with contemporary therapy. Clinical factors and significant inducible ischemia both identify higher risk patients with T2DM, but overall CE rates are equivalent whether or not patients underwent initial screening.