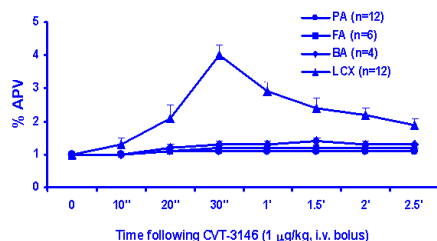


and decrease in mean arterial pressure (12 mmHg). In conclusion, CVT-3146 is a potent, short lasting vasodilator that is highly selective for the coronary vasculature.



1170-143

### Diltiazem Attenuates the Coronary Vasodilatory Response to Adenosine and Reduces the Regional Myocardial Blood Flow Disparity and Sestamibi Defect Magnitude in Dogs With Critical Coronary Stenoses

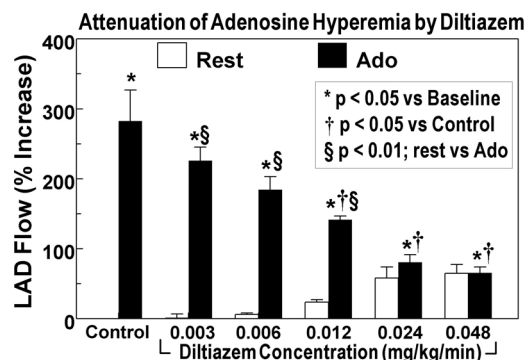
Kenjo Hatada, Mirta Ruiz, Denny D. Watson, George A. Beller, David K. Glover, University of Virginia Health System, Charlottesville, VA

**Background:** We previously showed that verapamil (Ver) markedly attenuates the vasodilatory response to adenosine (Ado) by inhibiting  $K_{ATP}$  channels. It is unknown whether this effect is specific to Ver or if it would also be observed with other calcium channel blockers like diltiazem (Dtz).

**Methods:** In 4 anesthetized dogs, hemodynamic responses to Ado boluses (60 µg/kg) were recorded in the absence or presence of increasing doses of Dtz (0.003-0.048 mg/kg/min i.v.). Next, an occluder was adjusted to produce a critical LAD stenosis and an infusion of Dtz was begun (0.048 mg/kg/min). Ten min later, Ado was infused (250 µg/kg/min) and sestamibi (296 MBq) and microspheres were injected at peak LCx flow. *Ex vivo* imaging of heart slices and gamma well counting was performed.

**Results:** Dtz produced dose-dependent decreases in resting HR and aortic pressure and, as shown, increased resting flow (open bars). As with Ver, Dtz significantly attenuated the LAD flow increase with Ado from 283±45% to 66±8% rest (solid bars) ( $p < 0.05$ ). Likewise, Ado produced only a 2:1 myocardial flow disparity between the normal and stenotic zones and the sestamibi defect magnitude was relatively mild (LAD/LCx count ratio=0.74±0.02) compared with our historical data without Dtz (0.62).

**Conclusion:** Dtz markedly attenuated the vasodilatory response to Ado giving further evidence that calcium channel blockers should be withheld temporarily in patients undergoing Ado stress perfusion imaging to avoid the potential for a submaximal stress test.



1170-144

### Abnormal Hemodynamic Response to Adenosine and Poststress Left Ventricular Ejection Fraction Provide Incremental Prognostic Information in Patients Undergoing Gated Myocardial Perfusion SPECT

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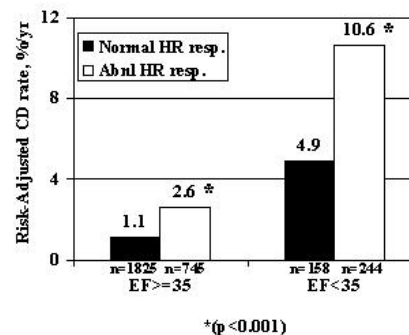
**Background:** Both post-stress LVEF and abnormal heart rate (HR) response to adenosine (Adeno) stress, defined as a low peak/rest HR ratio (Abnl-HRR) have been shown to be a strong independent predictor of cardiac death (CD) in pts undergoing gated myocardial perfusion SPECT (MPS). However, these variables have heretofore been assessed in isolation so that their potential synergistic role in predicting CD is not known.

**Methods:** We identified 2,972 unique pts (49% women, mean age 71±11 yrs) who under-

went Adeno-MPS and were followed up for 2.7±1.3 yrs. Multivariable Cox proportional hazards analysis was used to assess the prognostic value of clinical/MPS variables in predicting CD. Abnl-HRR to Adeno-stress was defined as a presence of the low tertile of peak/rest HR ratio.

**Results:** 201 CD (6.8%) occurred during follow-up. In a multivariable model the significant predictors of CD were age, diabetes, shortness of breath, peak/rest HR ratio, post-stress EF, extent and severity of stress perfusion defect, and inability to perform an adjunctive walk, with interaction peak/rest HR\*adjunctive walk. Pts with post-stress EF<35% more often had Abnl-HRR, compared to those with higher EF (61% vs. 29%,  $p < 0.001$ ); however, after risk adjustment Abnl-HRR further risk-stratified pts within each EF category (Figure).

**Conclusion:** An Abnl-HRR to Adeno-stress is a common finding in pts with LVEF<35%. Abnl-HRR has an independent and incremental prognostic value among pts with either normal or abnormal LVEF.



1170-145

### Caffeine Acutely Decreases Coronary Flow Reserve in Patients With Coronary Artery Disease

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**Aim:** Caffeine antagonizes adenosine-induced hyperemic myocardial blood flow (MBF). Its impact on exercise-induced coronary flow reserve (CFR) remains unknown. As exercise may induce hyperemia via adenosine mediated mechanisms, our aim was to determine the acute effect of caffeine on CFR during bicycle exercise.

**Methods:** 15O-labelled H<sub>2</sub>O and Positron Emission Tomography (PET) was used to measure CFR in 7 patients with coronary artery disease (mean age 55y ± 9) before and 50 minutes after oral ingestion of caffeine (200mg). Supine bicycle exercise (mean workload 98% of predicted) was used as stress.

**Results:** Caffeine levels were zero at baseline in all subjects and increased to 18 ± 9mmol/l fifty minutes after caffeine intake. Rate pressure product (rest and exercise) was not affected by caffeine. Caffeine did not affect resting MBF, whereas hyperemic MBF decreased significantly by 20±/20% (2.8±/0.64 ml/min/mg vs. 2.19±/0.58 ml/min/mg,  $p = 0.05$ ), resulting in a decrease in CFR of 23% (2.16±/0.45 vs. 1.59±/0.33,  $p < 0.05$ ).

**Conclusions:** Intake of a caffeine dose equivalent to two cups of coffee significantly reduces CFR in patients with CAD during physical exercise. This might raise some concerns about safety of caffeine-containing food or beverages particularly when consumed shortly before physical exercise.

1170-146

### Effect of Caffeine on Fractional Flow Reserve

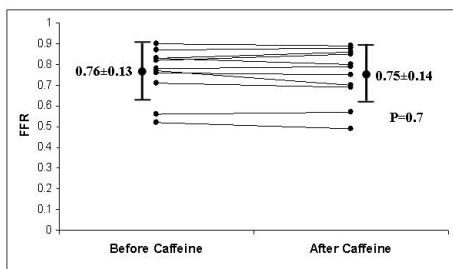
Gilbert J. Zoghbi, Raed Aqel, James Trimm, Shawn Baldwin, Ami Iskandrian, University of Alabama at Birmingham, Birmingham, AL

**Background:** Caffeine is believed to attenuate the coronary hyperemic response to adenosine by blocking the A<sub>2a</sub> receptors. We studied the effect of caffeine on adenosine-induced myocardial hyperemia measured by fractional flow reserve (FFR) after intracoronary adenosine administration.

**Methods:** Patients undergoing coronary angiography and FFR determination were enrolled (10 men, age 53±8 years, 8 whites). The FFR was measured before and 5 minutes after intravenous bolus caffeine administration (4mg/kg). Mean, diastolic, and systolic aortic and distal coronary pressures and heart rate were measured at 1-minute intervals for 5 minutes after the caffeine bolus.

**Results:** The area stenosis by quantitative coronary angiography was 74 ± 9.0 %. The baseline, 5 and 10-minute caffeine levels (mg/L) were 0.0±0.0, 3.7±1.8 and 3.8±1.3 respectively. Before caffeine, adenosine produced an increase in heart rate (64.7±13.8 at rest Vs 67.6±12.9 beats/minute after adenosine,  $P = 0.001$ ) and a decrease in mean aortic pressure (96.5±16.1 at rest Vs 89.4±14.1 mm Hg after adenosine,  $P = 0.04$ ). At 5 minutes after caffeine administration, both mean aortic pressure (105.6±12.5 Vs 93.1±15.9 mm Hg at baseline,  $P = 0.005$ ) and distal coronary pressure (94.2±14.3 Vs 82.8±15.1 mm Hg at baseline,  $P = 0.001$ ) increased. The FFR before and after caffeine did not change (Figure).

**Conclusions:** FFR was not affected by intravenous caffeine at a comparable dose to oral consumption. Results may have implications to adenosine stress testing.



**1170-147 Effect of Tadalafil, a Phosphodiesterase 5 Inhibitor, on Myocardial Blood Flow in Patients With Coronary Artery Disease**

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**Background:** Erectile dysfunction (ED) and coronary artery disease (CAD) share similar risk factors. Tadalafil is a phosphodiesterase 5 (PDE5) inhibitor used to treat ED. Although PDE5 inhibitors do not adversely affect hemodynamic parameters or exercise tolerance in patients with CAD, their direct effects on myocardial blood flow (MBF) are unknown.

**Methods:** In a randomized, double blind, crossover study we examined the effects of tadalafil 20 mg and placebo on MBF in subjects with stable CAD (N=7; 52-73 years old). MBF was measured (PET imaging with <sup>13</sup>N-ammonia) at rest, during adenosine (maximal vasodilation; 0.14 mg/kg/min, IV over 6 minutes), and during dobutamine (increased myocardial workload). Dobutamine was titrated to achieve 75% of predicted maximal heart rate or 10 ug/kg/min, IV. PET images were interpreted based on a 9-segment model with segments defined as normal or abnormal (< 75% maximum perfusion during adenosine).

**Results:** Tadalafil had no significant effect on resting MBF or on adenosine-induced increases in MBF (Table). However, tadalafil increased MBF during adrenergic stimulation with dobutamine in normal segments (p<.001), and there was a trend for a tadalafil-induced increase in MBF during dobutamine infusion in abnormal segments.

**Conclusion:** This study demonstrates that tadalafil has no adverse effects on MBF in subjects with stable CAD and that tadalafil may actually improve MBF during periods of increased workload (dobutamine) in normal and poorly perfused myocardium.

	Placebo		Tadalafil 20 mg	
	Normal (n=46)	Abnormal (n=17)	Normal (n=46)	Abnormal (n=17)
	MBF (ml/g/min)		MBF (ml/g/min)	
Resting	0.80 ± .15	0.77 ± .17	0.82 ± .22	0.80 ± .23
Adenosine	2.14 ± .57	1.45 ± .49	2.07 ± .45	1.47 ± .52
Dobutamine	1.56 ± .37	1.36 ± .36	1.79 ± .56*	1.46 ± .44

V values = mean ± SD, n=number of segments, \* p<.001 vs placebo by paired t-test

**1170-148 Comparison of the Diagnostic Performance of Totally Automatic Software for the Quantification of Myocardial Perfusion SPECT**

**Cesar A. Santana**, Gabriel B. Grossman, Rusell D. Folks, Angela Hunsche, C. David Cooke, Tracy L. Faber, Raghuvver Halkar, Ernest V. Garcia, Emory University, Atlanta, GA

This study was done to compare the diagnostic performance of ECTb (Emory), QPS (Cedars), and 4DMSPECT (Michigan) quantitative programs in the assessment of CAD.

**Methods:** We selected 126 patients who had rest thallium and maximal exercise ECG-gated Tc99m-sestamibi myocardial perfusion SPECT, 32 with <5% likelihood of CAD (LLK) and 94 with coronary angiography (CA). Sixty-five of the 94 patients had coronary stenosis >50% (LAD: 51, LCX: 36, RCA: 31). All images were totally automatically processed by each program using the e-soft workstation. Automatic parameter selection failed in 4 patients using ECTb, 2 using QPS and 8 using 4DMSPECT, and was manually corrected. Normalcy, sensitivity (SEN), specificity (SPC), and accuracy (ACC) were calculated using LLK or CA as gold standard. No functional parameters were used in this analysis.

**Results:** ECTb and 4DMSPECT demonstrated higher normalcy, higher sensitivity and lower specificity in comparison with QPS. Nevertheless, the accuracies of the programs

were not statistically different. The normalcy of QPS improved to 90% when manually correcting the automatic base selection. Specificity was artificially lowered due to patient referral bias, particularly ECTb specificity.

	Normalcy (%)	CAD (%)			LAD (%)			LCX (%)			RCA (%)		
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	SEN	SPC	ACC	SEN	SPC	ACC	SEN	SPC	ACC	SEN	SPC	ACC
ECT	81 <sup>1</sup>	91 <sup>3</sup>	17	68	59	49	54	50 <sup>6</sup>	72	64	61	73 <sup>9</sup>
QPS	59	69	52 <sup>4</sup>	64	59	40	50	22	95 <sup>7,8</sup>	67	71	62
4DM	88 <sup>2</sup>	80	34	66	47	63 <sup>5</sup>	54	50 <sup>6</sup>	57	54	77	56

1: p=0.05 vs. QPS, 2: p= 0.01 vs. QPS, 3: p= 0.002 vs. QPS, 4: p= 0.005 vs. ECTb, 5: p= 0.031 vs. QPS, 6: p= 0.014 vs. QPS, 7: p<0.0001 vs. 4DMSPECT, 8: p= 0.001 vs. ECTb, 9: p=0.04 vs. 4DMSPECT

**Conclusions:** The accuracy of ECTb, QPS and 4DMSPECT are similar in the diagnosis of CAD. Nevertheless, diagnosticians should be aware of differences in sensitivity, specificity and normalcy when comparing results from serial studies in the same patient processed with different programs.

**1170-149 A Novel Approach in Risk Stratification: Combined Assessment of Regional Perfusion and Function From Rest/Stress Tc-99m Sestamibi Gated SPECT**

**Cynthia C. Taub**, Alan W. Ahlberg, Deborah Katten, Michael G. Platt, Scott D. Werden, David M. O'Sullivan, Mark I. Travin, William E. Boden, Gary V. Heller, Hartford Hospital, Hartford, CT

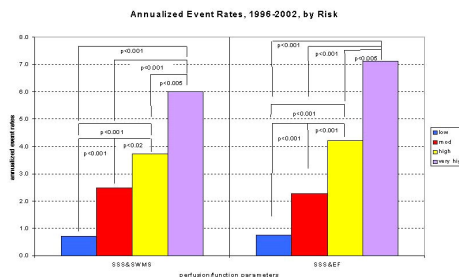
**Background:** Global assessment of ejection fraction (EF) from gated SPECT adds incremental prognostic value to stress myocardial perfusion imaging. The value of assessment of regional wall motion is unknown.

**Methods:** A prospectively gathered database of 9,460 patients (1996-2002) who underwent rest/stress Tc-99m sestamibi gated SPECT was analyzed. Patients revascularized within 60 days after gated SPECT (n=453) were censored. Perfusion and wall motion were assessed using an 8 and 5-region model, respectively. Summed stress score (SSS) and summed wall motion score (SWMS) were calculated. EF was generated using QGS software. Patients were followed (91% complete) for myocardial infarction and cardiac death over 29 +/- 17 months. Level of risk was categorized by using SSS in combination with either SWMS or EF: low risk: SSS<=1 and either SWMS<=1 or EF >= 50%; moderate risk: SSS 2-4 and either SWMS 2-5 or EF 35-49%; high risk: SSS>4 and either SWMS>5 or EF<35% (table).

**Results:** The annualized event rates increased significantly as risk increased using either SWMS or EF in combination with SSS (figure). There were no differences in risk stratification between techniques.

**Conclusion:** This novel approach of combining perfusion and function from rest/stress Tc-99m sestamibi gated SPECT in risk stratification is highly effective in the prediction of future cardiac events.

SSS <=1	SWMS <=1 or EF >= 50%	SSS 2-4	SWMS 2-5 or EF 35-49%	SSS >4	SWMS >5 or EF < 35%
Low Risk	Low Risk	Moderate Risk	Moderate Risk	High Risk	High Risk
Moderate Risk	Moderate Risk	High Risk	High Risk	Very High Risk	Very High Risk



**1170-150 Evaluation of the Roll-off of Radiotracer Uptake Under Adenosine, Dobutamine and Nitroglycerin Stress: Demonstration of Flow Dependence**

**Kailasnath Purushothaman**, Neda Jahanshad, Nicholas Gross, Patti Cavaliere, Xiaoyue Hu, Brian Bourke, Albert J. Sinusas, Yale University School of Medicine, New Haven, CT

**Background:** Pharmacological stressors (ST) are thought to have different effects on radiotracer uptake. To evaluate ST effects we have studied permeability surface area product (PS), a unique index of radiotracer 'roll-off' emerging from uptake theory.

**Methods:** PS was evaluated from uptake (U) vs flow (Q) data for two radiotracers: Thallium-201 (TL) and Tc99m-sestaMIBI (MIBI) and three STs: Adenosine (AD), Dobutamine (DB), and Nitroglycerin (NG). Anesthetized dogs (n = 16) were injected with radiolabeled microspheres at rest. Another set of microspheres and TL & MIBI were injected under ST. Dogs were euthanized 5 min. later and the left ventricle cut into ~ 1000 cubes of size 4 mm. 3-dimensional U and Q maps from well-counting were analyzed with the U = C\*Q\*[1-exp(-PS/Q)] theory using new analyses that eliminate normalization biases. Indi-