

Relation of Exercise Capacity to Sub-Clinical Coronary Artery Disease in Asymptomatic Patients With Type II Diabetes

Idit Dobrecky-Mery¹, Tamar Gaspar², Mali Azencot¹, Basil S Lewis¹, Nathan Peled², Nisan Yaniv¹, Mahmood Drawsha³, Nakhla Dakwar³, Oscar Minuchin³, David A Halon¹

¹ Cardiovascular Medicine, Lady Davis Carmel Medical Center, ² Radiology, Lady Davis Carmel Medical Center, ³ Diabetes Clinic, Lin Clinic, Haifa, Israel

Background: Patients with type 2 diabetes mellitus (DM) may have limited exercise capacity (ExC) despite no clinical history of coronary artery disease (CAD). The importance of sub-clinical CAD in determining ExC is unclear. We examined relation of ExC to sub-clinical CAD, defined by 64 slice coronary computed tomographic angiography (CTA), in diabetic subjects with no history of CAD.

Methods: 423 pts (63±5.3 yrs, 56% women) enrolled in an ongoing prospective study of cardiovascular outcomes in asymptomatic subjects with DM, underwent 1) maximal, symptom limited graded treadmill exercise testing to define ExC (in metabolic equivalents [Mets]) and ECG defined, exercise induced, myocardial ischemia and 2) CTA to define presence of significant (>50%) coronary luminal stenosis, non-obstructive coronary atheroma and coronary calcium score.

Results: Determinants of peak exercise capacity differed in men and women. In men coronary plaque was related to duration of exercise but not in women (Table). Duration of DM correlated with duration of exercise in women ($r=0.27$, $p=0.001$) but not in men ($r=0.09$, ns).

Exercise Capacity

	METS(MEN)	P-VALUE	METS (WOMEN)	p-value
Calcium score <median	11.2±2.3		7.8±2.1	
Calcium score >median	9.6±2.6	<0.001	7.3±2.2	ns
Plaque any +	10.1±2.6		7.6±2.1	
Plaque any -	12.2±1.9	<0.001	7.5±2.4	ns
Multi-vessel plaque+	9.8±2.5		7.2±2.1	
Multi-vessel plaque-	11.6±2.3	<0.001	7.8±2.3	0.07
Stenosis+	9.8±2.5		7.1±2.4	
Stenosis-	10.8±2.6	0.06	7.6±2.1	ns
Multi-vessel Stenosis +	9.4 ±2.0		6.7±2.4	
Multi-vessel Stenosis -	10.5±2.6	ns	7.6±2.2	ns

Conclusions: In men peak exercise capacity decreased in presence of non-obstructive or obstructive coronary artery disease on CTA but was unrelated to longer history of diabetes mellitus. In women peak exercise capacity was not significantly related to presence of sub-clinical coronary artery disease but correlated inversely with duration of DM.

Combined Assessment of C-Reactive Protein and Uric Acid Levels for Risk Stratification in Coronary Heart Disease Patients

Yafim Brodov², Pierre Chouraqui^{2,3}, Ilan Goldenberg¹, Valentina Boyko¹, Shlomo Behar^{1,3}

¹ Neufeld Cardia Research Institute, Israel Society for The Prevention of Heart Attacks, Sheba Medical Center, Tel Hashomer, Ramat Gan, ² Heart Institute, Sheba Medical Center, Tel Hashomer, Ramat Gan, ³ Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

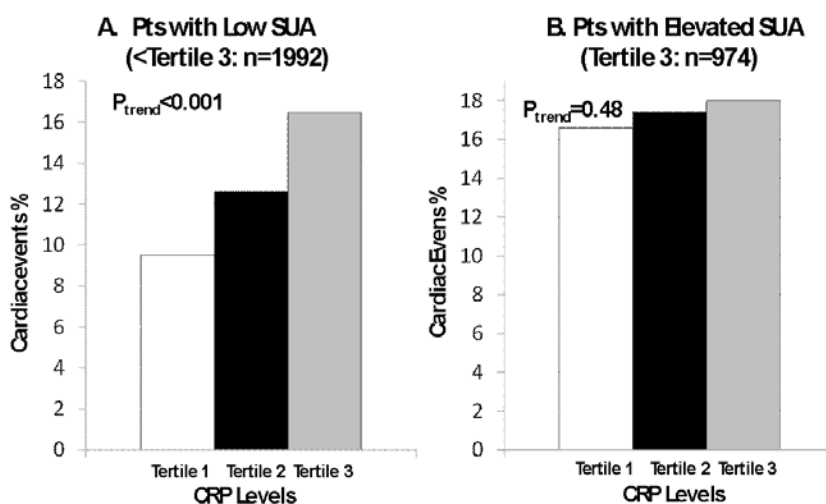
Background: C-reactive protein (CRP) is an established risk factor for cardiac events in coronary heart disease (CHD) patients. Recently, elevated serum uric acid (SUA) was also suggested to be associated with adverse outcome in this population. We hypothesized that combined assessment of CRP and SUA would provide incremental prognostic information to single marker measurement.

Methods: The risk of major cardiac events (comprising fatal or nonfatal myocardial infarction or sudden cardiac death) during mean follow-up period of 6.2 years was related to increasing tertiles of CRP and SUA levels, in a population of 2966 CHD patients enrolled in the Bezafibrate Infarction Prevention (BIP) trial.

Results: The rate of major cardiac events was directly related to increasing tertiles (1 to 3) of both CRP (11.4%, 14.2%, and 17.3%, respectively; p for trend < 0.001) and SUA (12.6%, 12.9%, and 17.6%, respectively; p for trend = 0.002). However, when combined assessment of the 2 markers was employed, CRP levels were shown to be associated with adverse outcome only in patients with low SUA (Figure 1A), whereas among patients with elevated SUA cardiac event rate was increased at all levels of CRP (Figure 1B). Consistently, in multivariate analysis elevated CRP was independently associated with outcome in patients with low SUA (HR=1.55; $p=0.007$), but was not a risk factor among patients with elevated SUA (HR=1.04; $p=0.83$).

Conclusions: Combined assessment of CRP and SUA improves risk stratification in CHD patients. Patients with elevated SUA exhibit a high risk of cardiac events regardless of CRP levels.

Figure 1: Rate of Cardiac Events by CRP Tertiles



Aspirin Resistance among Stable Coronary Artery Disease Patients

Danny Dvir, Alejandro Solodky, Aviv Mager, David Brosh, Ido Tamari, Abid Assali,
Alexander Battler, Ran Kornowski, Eli I Lev

*Cardiology, Rabin Medical Center, Sackler Faculty of Medicine, Tel-Aviv University, Petach
Tikva, Israel*

Background: Low response to aspirin has been associated with adverse clinical outcome. There is limited data that characterizes patients with stable coronary artery disease (CAD) who are resistant to the anti-platelet effects of aspirin. Our objectives were to identify the prevalence and the characteristics of patients with stable CAD who have reduced anti-platelet response to aspirin treatment.

Methods: We evaluated 227 stable patients with CAD who have been treated with aspirin for at least one week. Aspirin resistance was defined by at least 2 of 3 criteria: VerifyNow Aspirin (Accumetrics) score ≥ 550 , $5\mu\text{M}$ adenosine diphosphate-induced platelet aggregation $\geq 70\%$ and 0.5mg/ml arachidonic acid-induced platelet aggregation $\geq 20\%$.

Results: Of the patients studied 13 (6%) were aspirin resistant. Aspirin resistant patients were more likely to be women and less likely to have hypertension. Other characteristics are shown in the table.

Conclusions: A relatively low percentage of patients with stable CAD are resistant to the effect of aspirin. The main clinical feature found in our study is a higher proportion of women among aspirin resistant patients. This finding may contribute to the low benefit of aspirin treatment in women, recently reported in primary prevention trials.

	Aspirin resistant (n=13)	Aspirin sensitive (n=214)
Age (years)	68.8 \pm 9.6	68 \pm 9.7
Gender (women)	38.5%*	13.6%*
Weight (kg)	70.7 \pm 12.8 \dagger	77.5 \pm 12.9 \dagger
Height (cm)	163.5 \pm 9.1*	169.1 \pm 8.5*
BMI (kg/m ²)	26.5 \pm 4.6	27 \pm 3.6
Diabetes Mellitus	30.8%	41.5%
Hypertension	38.5% \dagger	63.8% \dagger
Hypercholesterolemia	84.6%	78.7%
Smoker	22.2%	17%
Family History	58.3%	57.9%
Previous MI	61.5%	58.1%
Previous PCI	84.6%	90.5%
Previous CABG	53.8%	36.9%
Clopidogrel	7.7%	21.1%
Statins	100%	89.5%
Beta Blockers	69.2%	69.3%
ACE Inhibitors	61.5%	58.5%
* $p < 0.05$, $\dagger p = 0.06$		

Prevalence of Migraine in Patients with Patent Foramen Ovale

Rachel Hering-Hanit^{1,4}, Margalit Rosenfeld⁴, Sergio Kobal^{2,5}, Yoram Neuman³

¹Neurology, Meir Medical Center, Kfar Saba, ²Cardiology, Soroka University Medical Center, Beer Sheva, ³Cardiology, Meir Medical Center, Kfar Saba, ⁴Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, ⁵Goldman Faculty of Medicine, Ben-Gurion University, Beer Sheva, Israel

Introduction: Migraine is a common neurological disorder with a prevalence of 11-12% in the general population and a great impact on the quality of life and on social activities. Patent foramen ovale (PFO) is an inter-atrial left-to-right shunt with a prevalence of 25% in the general population. Recent epidemiological data suggest a bidirectional link between PFO and migraine with aura. PFO closure might improve migraine symptoms and serves as an effective treatment modality for migraines. **Objectives:** To investigate the prevalence of migraine with and without aura in a consecutive unselected cohort of young patients with PFO. **Methods:** Patients with PFO between 18-65 years of age were retrieved from database of the echocardiography laboratories at the Meir and Soroka medical centers. Patients were interviewed by phone for headache and migraine using a standard migraine questionnaire and MIDAS questionnaire for quality of life. **Results:** One hundred and eighty-four patients with PFO were included. The prevalence of headache was 51%. Thirty-six percents fulfilled criteria for migraine compared to 12% in the general population ($p < 0.001$). Fifty percents of the migraine sufferers had migraine with aura compared to 5-15% in the general population ($p < 0.001$). **Conclusions:** Our findings confirm previous observations of higher incidence of migraine with aura in patients with PFO compared to the general population. Echocardiography study should be included in the workup of patients with migraine especially in migraine with aura.

High Frequency ECG – a Novel Tool for Improving the Diagnostic Accuracy of Exercise Testing in the Community Setting

Ronit Shohat-Zabarski¹, Arie Shefer², Monica Feldman¹, Ilan Auerbach¹, Edgar Sucher¹,
Simcha Rosenblatt¹, Haim Silber¹

¹ *Cardiology Department, Maccabi Healthcare Services, Tel Aviv*, ² *Cardiology Department, Maccabi Healthcare Services, Haifa, Israel*

ECG based detection of exercise-induced myocardial ischemia relies on identifying ST changes, representing the repolarization phase. Recently, a new technology utilizing high-resolution ECG was reported to better identify stress-induced ischemia. This approach quantifies subtle ischemic-induced changes in the depolarization phase using analysis of high frequency QRS components (HFQRS). Our aim was to test the clinical applicability of this novel technique in a large patient population in three community cardiology centers.

Methods: High-resolution ECG was acquired (HyperQ™ System, BSP, Israel) during clinically indicated exercise test (ETT) in 1205 consecutive patients (age 57±9 yo, 64% men). The relative intensity change of HFQRS components (HyperQ™) during exercise was used as an index of ischemia. HFQRS data were evaluated automatically using computerized analysis. Patients with evidence of ischemia in exercise ECG or HFQRS data, or those with inconclusive test results were referred for follow-up imaging tests (FIT; stress echocardiography, SPECT perfusion imaging, CT angiography, or angiography, n=172). The follow-up imaging tests were used as the gold standard for presence of IHD.

Results: Based on FIT results, addition of HFQRS to ETT significantly improved specificity (74% combined vs. 51% for ETT alone, p<0.005) and enhanced accuracy (76% combined vs. 59% for ETT, p<0.05), although sensitivity was similar. Negative predictive value of HFQRS was > 93% irrespective of ETT result. The positive predictive value for patients with positive ETT and positive HFQRS was 86%. HFQRS was particularly useful in patients with inconclusive ETT.

Conclusions: This is the first large scale study to evaluate the utility of the HFQRS technique in a realistic clinical scenario. HFQRS analysis is complementary and additive to conventional ETT. Integrating HFQRS into the clinical decision process could markedly improve the standard of care and decrease unnecessary invasive procedures.

Ectatic Coronary Arteries are Associated with Peripheral Vascular Endothelial Dysfunction in Patients with Chest Pain

Arik Asman^{1,2}, Pierre Chouraqui¹, Avi Livne², Michael Shechter¹

¹ Heart Institute, ² Department of Medicine F, Chaim Sheba Medical Center and the Sackler Faculty of Medicine, Tel Aviv University, Tel Hashomer, Ramat Gan, Israel

Background: Endothelial dysfunction is an important prognostic factor in determining atherosclerosis. Prognosis, treatment, and etiology of coronary artery ectasia, abnormal enlargement of coronary arteries, remain unresolved. Current literature suggests that even without the presence of coronary stenosis, ectatic coronary arteries are subject to thrombus formation, vasospasm, and spontaneous dissection.

Objective: To evaluate the association of flow-mediated dilation (FMD), assessed by brachial artery vasoreactivity in patients with chest pain and ectatic coronary arteries.

Methods and Results: FMD in 40 subjects with chest pain and ectatic coronaries [35 (88%) men, mean age 66±9 years, mean body mass index 28±5 kg/m²] was compared to FMD in 40 age- and sex-matched patients with chest pain and normal coronaries. After overnight fasting and discontinuation of all medications for ≥12 hours, percent improvement in endothelium-dependent brachial artery FMD (%FMD) and endothelium-independent nitroglycerin (%NTG)-mediated vasodilatation were assessed using high resolution(15 MHz) linear array ultrasound (Table).

	Ectatic Coronaries (n=40)	Normal Coronaries (n=40)	p-value
Systolic BP (mmHg)	142±22	144±2	0.77
Diastolic BP (mmHg)	82±10	78±9	0.36
Resting heart rate (bpm)	63±9	65±10	0.76
Brachial artery diameter (mm)	6.25±0.93	5.24±0.98	<0.0001
%FMD	7.2±5.0	12.0±5.0	<0.001
%NTG	12.1±4.8	14.3±5.1	0.38

Values are expressed as mean±SD; BP=blood pressure; %FMD, %NTG=% change from baseline in brachial artery diameter caused by FMD and NTG, respectively.

Conclusions: Ectatic coronary arteries in patients with chest pain are associated with endothelial dysfunction, compared to normal coronary arteries, suggesting a potential mechanism whereby ectatic coronaries contribute to cardiovascular risk. Long-term follow-up is warranted to further elucidate our findings.

Dual Therapy with Statins and Antioxidants is Superior to Statins Alone in Decreasing the Cardiovascular Disease Risk of Individuals with Diabetes Mellitus and the Haptoglobin 2-2 Genotype

Shany Blum¹, Uzi Milman², Chen Shapira², Rachel Miller-Lotan¹, Yefim Anbinder¹, Junia Alshiek¹, Lawrence Bennett², Maria Kostenko², Michele Landau⁵, Shlomo Keidar³, Yishai Levy³, Alexander Khemlin², Arman Radan², Andrew Levy¹

¹ *Laboratory of Vascular Medicine, Faculty of Medicine, Technion-Israel Institute of Technology,* ² *Haifa and Western Galilee District, Clalit Health Services,* ³ *Internal Medicine,* ⁴ *Cardiology Department, Rambam Medical Center, Haifa,* ⁵ *PharmaBrains Israel, Tel Aviv, Israel*

Background. Oxidative stress is an important mediator of DM atherosclerosis. Paradoxically, antioxidants have not been found to provide CVD benefit to DM individuals. The Haptoglobin gene, an antioxidant protein, is polymorphic in man with two classes of alleles denoted 1 and 2. Diabetic individuals with the Haptoglobin 2-2 genotype, have increased CVD risk. These individuals have high oxidative stress and may benefit from antioxidant therapy. We sought to determine if antioxidant therapy could be demonstrated to provide benefit to Haptoglobin 2-2 DM individuals also taking statins which are currently recommended for all DM individuals.

Methods. The ICARE was a double blind prospective study in 1434 DM individuals with the Haptoglobin 2-2 genotype randomized to vitamin E or placebo. We showed a 50% decrease in CVD events (MI, stroke, CVD death) with Vitamin E treatment. We present here a secondary analysis of the CVD event rate in ICARE stratified by vitamin E and statin use.

Results. The event rate among individuals who did not receive antioxidants or statins was 6.1%. As expected we found that statins reduced the event rate in this population compared to individuals who did not take statins. However, unexpectedly we found that the addition of vitamins to statin treatment dramatically reduced the event rate (4.1% vs. 1.3%, $p < 0.01$), significantly more than statin or vitamin E treatment alone.

Conclusions. Dual therapy with antioxidants and statins appears to provide superior cardiovascular protection to Hp 2-2 DM individuals as compared to statins alone.

Exercise ECG Testing: Low Tech, High Impact

Ori Galante¹, Lior Fuchs¹, Reuben Ilia², Sergio L Kobal²

¹ Internal Medicine, ² Cardiology, Soroka University Medical Center, Ben Gurion University, Beer Sheva, Israel

Background: Currently, reliance on noninvasive imaging tests and cardiac catheterization in diagnosing the etiology of chest pain (CP) raises questions about the role of exercise ECG testing (EET) in its evaluation. We assessed the impact of EET on the diagnosis and management of hospitalized pts with CP.

Methods: Pts hospitalized with CP without dynamic ECG changes and troponin elevation were referred to treadmill EET. Internal medicine physicians responsible for the pts completed a questionnaire pre and post EET which included a hypothetical question about the management of those pts if EET could not be performed.

Results: Physicians filled out the questionnaire for 57 pts, age 51 ± 10 years, 32/57 considered to be of low probability for ischemic heart disease and 25/57 pts of intermediate probability. Based on EET results, physicians confirmed their clinical diagnosis in 68%, modified their diagnosis in 28%, and EET was unhelpful in 4% of the pts. Level of physicians' confidence in their diagnosis at pre-test was 6 (from 1 to 10) and rose to 9 post-test. EET had major impact on the continuing management of the referred pts (Table1) by allowing physicians to discharge 61% (35/57) of the pts who otherwise would have remained hospitalized for additional diagnostic procedures. No major cardiac events were noted as a consequence of the EET study.

Conclusions: For many hospitalized pts with CP, EET is a safe procedure that helps physicians to increase their diagnostic rate and diagnostic level of confidence. EET renders significant benefit in the management of these pts by modifying diagnostic strategies, shortening hospitalization, and avoiding inappropriate discharge.

Table1

	PRE-EET		POST-EET. Discharged
Candidate for	Cardiac catheterization	6	5
	Non invasive imaging test	15	12
	In hospital follow-up	9	8
	Discharged	27	26