

Latest PAT Publications



Peripheral endothelial function and cardiovascular events in high-risk patients.

Matsuzawa Y, Sugiyama S, Sumida H, Sugamura K, Nozaki T, Ohba K, Matsubara J, Kurokawa H, Fujisue K, Konishi M, Akiyama E, Suzuki H, Nagayoshi Y, Yamamuro M, Sakamoto K, Iwashita S, Jinnouchi H, Taguri M, Morita S, Matsui K, Kimura K, Umemura S, Ogawa H.
J Am Heart Assoc. 2013 Nov 25;2(6):e000426.
doi: 10.1161/JAHA.113.000426.

Determine the added prognostic value of endothelial dysfunction (ED), detected by EndoPAT-RHI, to the Synergy between percutaneous coronary intervention (PCI), with Taxus and Cardiac Surgery Score (SYNTAXsc) and Framingham Risk Score (FRS), in predicting cardiovascular events (CV death, MI, unstable angina, ischemic stroke, coronary revascularization, heart failure-induced hospitalization, aortic disease, and peripheral arterial disease), in 528 stable patients at high-risk for cardiovascular events, in a two-center prospective study from 2006-2011 until August 2012, (1,468 person-years follow-up).

RESULTS: 105 patients developed cardiovascular events. Multivariate Cox proportional hazards analysis identified as independent cardiovascular event predictors B-type natriuretic peptide (BNP) ($P=0.023$), SYNTAXsc ($P<0.0001$), and RHI ($P<0.0001$). When RHI was added to FRS, BNP, and SYNTAXsc, net reclassification index was significantly improved ($P<0.0001$), with a significant increase in the C-statistic from 0.728 to 0.766 ($P=0.031$).

CONCLUSION: RHI detected advanced ED, significantly correlated with near future cardiovascular events in high-risk patients, and significantly improved risk discrimination when added to FRS, BNP, and SYNTAXsc.

<http://www.ncbi.nlm.nih.gov/pubmed/24275629>



Relationship between Birth Weight and Metabolic Status in Obese Adolescents.

Hill DJ, Prapavessis H, Shoemaker JK, Jackman M, Mahmud FH, Clarson C.

ISRN Obes. 2013 Aug 28;2013:490923.
doi: 10.1155/2013/490923. eCollection 2013.

Examined the relationships between birth weight and body mass index, percent body fat, blood lipids, glycemia, insulin resistance, adipokines, blood pressure, and endothelial function in a cohort of 95 obese adolescents aged 10-16 years with Body Mass Index (BMI) >95th centile.

RESULTS: Body mass index z-score correlated positively with birth weight ($P = 0.03$), but not percent body fat. Insulin resistance and fasting plasma insulin, negatively correlated with birth weight ($P<0.001$ for both), both being significantly greater for subjects of small versus large birth weight.

Leptin, blood pressure z-scores, and EndoPAT-RHI values were not positively correlated with birth weight, but Adiponectin was ($P = 0.008$).

CONCLUSION: Excess BMI in obese adolescents was positively related to birth weight. Birth weight was not associated with cardiovascular risk factors but represented a significant determinant of insulin resistance.

<http://www.ncbi.nlm.nih.gov/pubmed/24555145>



Assessment of endothelial dysfunction in childhood obesity and clinical use.

Bruyndonckx L, Hoymans VY, Van Craenenbroeck AH, Vissers DK, Vrints CJ, Ramet J, Conraads VM.
Oxid Med Cell Longev. 2013;2013:174782. doi:
10.1155/2013/174782. Epub 2013 Apr 3.

Review of the assessment of endothelial dysfunction in childhood obesity, and its clinical use, covering an in-depth description of the mechanisms affecting endothelial damage and repair, the effects of lifestyle interventions and pharmacotherapy on endothelial dysfunction, and a critical overview of in-vivo and in-vitro markers for endothelial integrity.

In reviewing EndoPAT, the authors state that; "Feasibility and reproducibility of Endo-PAT in adults are excellent [ref]. The technique also appears highly reproducible in adolescents and causes hardly any discomfort".

Authors further point out that; "Pubertal development and its associated hormonal changes complicate the study of endothelial function in children. RHI increases during puberty in both genders [ref] and correlates to changes in estradiol and dehydroepiandrosterone sulfate in peripheral blood [ref].", (both of which upregulate eNOS).

CONCLUSION: Authors allude to the imperative of avoiding "the catastrophic rise in CV morbidity and mortality, which will accompany obese children into adulthood", and to the importance of "the so-called surrogate endpoints, such as the correction of endothelial function.", in facilitating clinical research to this end.

<http://www.ncbi.nlm.nih.gov/pubmed/23691262>



Effects of Endothelial Dysfunction on Residual Platelet Aggregability After Dual Antiplatelet Therapy With Aspirin and Clopidogrel in Patients With Stable Coronary Artery Disease.

Fujisue K, Sugiyama S, Ono T, Matsuzawa Y, Akiyama E, Sugamura K, Matsubara J, Kurokawa H, Kaikita K, Iwashita S, Sumida H, Hokimoto S, Oniki K, Nakagawa K, Matsui K, Ogawa H.
Circ Cardiovasc Interv. 2013 Aug;6(4):452-9.

Evaluated the association of endothelial function (EndoPAT-RHI), with high residual platelet reactivity (high rpr) after dual antiplatelet therapy in 103 patients with stable coronary artery disease who lacked cyp2c19*2 or *3 loss-of-function allele, to minimize the effect of this gene on high rpr.

All patients received aspirin and clopidogrel before testing platelet aggregability, assessed as p2y12 reaction.

RESULTS: The 53 patients exhibiting high rpr were significantly older, had higher levels of b-type natriuretic peptide, were predominantly hypertensive, and had significantly lower RHI values compared with nonhigh rpr patients (0.46 ± 0.15 vs. 0.61 ± 0.18 ; $P<0.001$). RHI was also linearly correlated to p2y12 ($r=0.32$; $p=0.001$). Multivariable logistic regression analysis identified RHI as an independent and significant determinant of high rpr (odds ratio, 0.55; 95% confidence interval, 0.39–0.78; $P=0.001$).

CONCLUSION: In patients with stable coronary artery disease, RHI was significantly impaired in high rpr patients, and was independently correlated with high rpr after dual antiplatelet therapy.

<http://www.ncbi.nlm.nih.gov/pubmed/23922147>



Cardiovascular Risk Factors in Children and Adolescents with Psoriasis: A Case-control Study.

Jensen P, Zachariae C, Iversen L, Hansen PR, Skov L.
Acta Derm Venereol. 2014 Jan;94(1):76-8.

Measured anthropometric data and cardiovascular risk factors in 30 10 to 18 year old patients with psoriasis, vs. 30 healthy matched controls. Psoriasis severity was assessed with the Psoriasis Area and Severity Index (PASI). Subject's weight, height, waist and hip circumferences, systolic and diastolic blood pressures, resting heart rate, blood glucose, urate, high-sensitivity C-reactive protein (hs-CRP), glycated haemoglobin (HbA1c), total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, very-low-density lipoprotein cholesterol, triglycerides, and EndoPAT-RHI, were determined.

RESULTS: Psoriasis patients had significantly higher BMI, abdominal circumference, systolic blood pressure, plasma glucose, and hs-CRP, but comparable height, weight, hip circumference, diastolic blood pressure, resting heart rate, urate, HbA1c, and lipid levels. RHI was not significantly different compared with controls (1.69 (1.25–2.00) vs. 2.03 (1.53–2.19) median (IQR), respectively, $p=0.083$).

CONCLUSION: More studies are warranted to assess the impact of PAT investigations in subjects with more severe psoriasis.

<http://www.ncbi.nlm.nih.gov/pubmed/23722258>



The effect of ischemia-reperfusion injury on measures of vascular function.

Alhejily W, Aleksy A, Martin BJ, Anderson TJ.
Clin Hemorheol Microcirc. 2013 May 29. [Epub ahead of print]

Simultaneously assessed the effects of ischemia-reperfusion injury on microvascular function including EndoPAT-RHI, and on conduit vessel function, (brachial artery), using ultrasound determined flow-mediated dilation (FMD) and hyperemic velocity (VTI - a measure of microvascular function), in 45 healthy volunteers free of cardiovascular disease (mean age 35 ± 14 yrs, 29 men) following a 5-minute forearm cuff occlusion, both before and within 15 mins after ischemia was induced by a 15-minute upper arm occlusion.

RESULTS: Ischemia caused a significant reduction in FMD (7.9 ± 4.0 to 4.7 ± 3.5 , $p = 0.0001$). Neither hyperemic VTI, (92 ± 30 vs. 97 ± 37 cm, $p = 0.236$), nor RHI (2.07 ± 0.8 vs. 2.04 ± 0.7 , $p = 0.742$), were affected following ischemia-reperfusion intervention.

CONCLUSION: Ischemia-reperfusion caused conduit and not resistance vessel endothelial dysfunction. The RHI was unchanged suggesting that this measure is more closely aligned with resistance than conduit vessel function.

<http://www.ncbi.nlm.nih.gov/pubmed/23719421>



Reproducibility of peripheral arterial tonometry for the assessment of endothelial function in adults.

Brant LC, Barreto SM, Passos VM, Ribeiro AL.
J Hypertens. 2013 Oct;31(10):1984-90.

Assessed the feasibility and reproducibility of EndoPAT-RHI determinations in 123 adults, based on two measurements 2-6 hours apart on the same day, in the Brazilian Longitudinal Study of Adult Health – (ELSA-Brasil) cohort. Agreement of RHI values was compared by Bland-Altman method, coefficient of variation (COV) and coefficient of repeatability. Reliability was assessed by intraclass correlation coefficient (ICC).

RESULTS: Mean RHI values did not differ significantly between tests (1.92 ± 0.56 vs. 1.96 ± 0.58 , $P=0.48$). There were no systematic errors between the exams. Measurement error was 0.35, COV was 18.0% and ICC was 0.61. Sex, age or the presence of obesity did not have a considerable influence on the reproducibility of PAT.

CONCLUSION: EndoPAT-RHI is feasible and has acceptable reproducibility in adults when compared with other noninvasive methods for endothelial function assessment, making EndoPAT-RHI a promising method for future clinical and epidemiological studies.

<http://www.ncbi.nlm.nih.gov/pubmed/23751970>



Migliitol improves postprandial endothelial dysfunction in patients with acute coronary syndrome and new-onset postprandial hyperglycemia.

Kitano D, Chiku M, Li Y, Okumura Y, Fukamachi D, Takayama T, Hiro T, Saito S, Hirayama A.
Cardiovasc Diabetol. 2013 Jun 19;12:92. doi: 10.1186/1475-2840-12-92.

Assessed the effect of miglitol (Alpha-glucosidase inhibitor), on EndoPAT-RHI determined endothelial function in 54 patients with acute coronary syndrome (ACS), who underwent primary percutaneous coronary intervention, 18 with normal glucose tolerance (NGT), and 36 with new-onset postprandial hyperglycemia (PPHG), of whom 18 were given 50 mg of miglitol with each meal for 1 week. The other 18 PPHG patients and the 18 NGT patients were not given any anti-diabetic agent for 1 week, and RHI was assessed before and after the 1-week period in all cases.

RESULTS: Postprandial RHI decreased significantly in PPHG. Miglitol significantly improved PPHG and postprandial RHI ($p = 0.007$). Postprandial change in RHI was inversely correlated with postprandial fasting-to-60-minutes surge in glucose ($r = -0.382$, $p = 0.009$), and the improvement in RHI correlated with a reduced postprandial glucose surge with miglitol ($r = -0.462$, $p = 0.001$).

CONCLUSION: Postprandial changes in glucose are related to endothelial dysfunction in ACS. Miglitol-based PPHG improvement appears to improve RHI. The effect of miglitol on glucose-dependent endothelial function might improve outcomes of ACS.

<http://www.ncbi.nlm.nih.gov/pubmed/23777506>



Rationale and design of a randomized trial on the effectiveness of aerobic interval training in patients with coronary artery disease: The SAINTEX-CAD study.

Conraads VM, Van Craenenbroeck EM, Pattyn N, Cornelissen VA, Beckers PJ, Coeckelberghs E, De Maeyer C, Denollet J, Frederix G, Goetschalckx K, Hoymans VY, Possemiers N, Schepers D, Shivalkar B, Vanhees L.
Int J Cardiol. 2013 Oct 9;168(4):3532-6.

Proposed study to test whether aerobic interval training (AIT) yields a larger gain in peak aerobic capacity (peakVO₂) compared to a similar training programme of moderate continuous training (MCT) in CAD patients, in a multicentre study involving 200 stable CAD patients with left ventricular ejection fraction >40% after recent myocardial infarction or revascularization (PCI or CABG), in a 12-week programme of three weekly sessions of either AIT (85-90% of peak oxygen uptake [peakVO₂], 90-95% of peak heart rate) or MCT (60-70% of peakVO₂, 65-75% of peak heart rate).

ENDPOINTS: Primary endpoint is the change of peakVO₂ after 12 weeks training. Secondary endpoints include safety, changes in peripheral endothelial vascular function (simultaneous EndoPAT-RHI & Brachial artery FMD), evolution of traditional cardiovascular risk factors, quality of life and the number and function of circulating endothelial progenitor cells as well as endothelial microparticles. Differences of long-term adherence to exercise regimens will be assessed and peak VO₂ measured after 12 months.

<http://www.ncbi.nlm.nih.gov/pubmed/23711446>



Thoracic periaortic and visceral adipose tissue and their cross-sectional associations with measures of vascular function.

Britton KA, Wang N, Palmisano J, Corsini E, Schlett CL, Hoffmann U, Larson MG, Vasan RS, Vita JA, Mitchell GF, Benjamin EJ, Hamburg NM, Fox CS.
Obesity (Silver Spring). 2013 Jul;21(7):1496-503.

Evaluated whether thoracic periaortic adipose tissue (TAT), and visceral adipose tissue (VAT) were associated with vascular function. TAT and VAT were quantified in 2,735 Framingham Heart Study participants; (48% women); mean age, 50 years, using multidetector-computed tomography; vascular function was assessed using brachial artery vasodilator function (FMD), EndoPAT ratio, and arterial tonometry. Relationships between TAT, VAT, and vascular measures were examined while adjusting for cardiovascular risk factors, using multiple linear regression.

RESULTS: TAT and VAT were associated with multiple vascular function measures after multivariable adjustment. After BMI adjustment, TAT and VAT remained negatively associated with EndoPAT ratio and inverse carotid femoral pulse wave velocity ($P < 0.02$); TAT was negatively associated with hyperemic mean flow velocity ($P = 0.03$). Associations of TAT with vascular function were attenuated after VAT adjustment (all $P > 0.06$).

CONCLUSION: Thoracic periaortic and visceral fat are associated with EndoPAT ratio and large artery stiffness after BMI adjustment. These findings support the growing recognition of associations between ectopic fat and vascular function.

<http://www.ncbi.nlm.nih.gov/pubmed/23754461>



Glycosaminoglycan metabolism defects and atherosclerosis: frequent association of endothelial dysfunction in patients with Mucopolysaccharidosis.

Yano S, Moseley K, Wong L, Castelnovi C, Azen C, Pavlova Z.
J Inherit Metab Dis. 2013 Jul 27. [Epub ahead of print]

Cardiovascular lesions, including coronary artery stenosis, occur frequently in patients with genetic defects of glycosaminoglycan (GAG) metabolism, and can cause sudden death, thus early diagnosis of coronary artery lesions is potentially lifesaving.

Impairment in EndoPAT-RHI has been validated to correlate to coronary microvascular function in patients with atherosclerosis, and RHI is thought to reflect endothelial NO production. Immunohistological staining of endothelial NOS was performed in the stenotic lesions in the coronary artery of a 3-year-old patient with Mucopolysaccharidosis-I, showing decreased activity, prompting a study to measure EndoPAT-RHI in patients with GAG metabolism defects for early diagnosis of endothelial dysfunction in the coronary arteries as an early sign of coronary artery changes.

RESULTS: RHI determination in 30 patients with variable genetic defects in GAG metabolism revealed significantly decreased values compared to 12 controls.

CONCLUSION: Evaluation of EndoPAT-RHI in patients with GAG metabolism defects may detect coronary artery lesions that can be otherwise under-diagnosed by other measures such as coronary angiography. Use of this method may prove vital in the management of patients with GAG metabolism defects.

<http://www.ncbi.nlm.nih.gov/pubmed/23893050>



Peripheral microvascular dysfunction predicts residual risk in coronary artery disease patients on statin therapy.

Matsue Y, Yoshida K, Nagahori W, Ohno M, Suzuki M, Matsumura A, Hashimoto Y, Yoshida M.
Atherosclerosis. 2014 Jan;232(1):186-90.

Measured log-transformed EndoPAT-RHI (L_RHI), in 213 CAD patients who had achieved LDL-C <100 by statin therapy. Patients were divided into two groups: L_RHI ≥ 0.54 ($n=99$) and L_RHI < 0.54 ($n=114$), and followed-up for secondary coronary artery events (CAE), for a median 2.7 years.

RESULTS: During follow-up, CAE occurred in 4 (4.0%) patients in the L_RHI ≥ 0.54 group and 18 (15.8%) in the L_RHI < 0.54 group ($P = 0.006$). Cox regression analysis indicated that L_RHI was an independent predictor for CAE even after adjustment by Framingham traditional risk factors (FRF), and estimated glomerular filtration rate (eGFR) for secondary CAE. ROC analysis for CAE prediction showed that the AUC for models including FRF only, FRF + eGFR, and FRF + eGFR + L_RHI were 0.60, 0.71, and 0.77, respectively. Adding eGFR to FRF only (0.63, $P = 0.003$) and adding L_RHI to the FRF + eGFR model were associated with significant net reclassification improvement (0.79, $P = 0.007$).

CONCLUSION: EndoPAT-RHI adds incremental predictive ability to traditional risk factors for prognosis of CAD patients successfully treated with statins.

<http://www.ncbi.nlm.nih.gov/pubmed/24401235>



THE NEWS

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Spotlight on

Farid Mahmud, MD



Dr. Farid Mahmud is a pediatric endocrinologist, and Director and Principal Investigator of the SickKids Diabetes Clinical Research Program at the Hospital for Sick Children (SickKids), and Associate Scientist in Physiology & Experimental Medicine, and Associate Professor in Paediatrics at the University of Toronto, Canada.

He has a special interest in the field of endothelial function and early assessment of cardiovascular risk dating back to his fellowship training in Endocrinology at the Mayo Clinic, and his research interests and

publications include the evaluation of early atherosclerosis in pediatric patients at high risk of cardiovascular disease including type 1 and type 2 diabetes, early biomarkers of diabetes microvascular complications, insulin resistance and obesity as well as inherited genetic conditions (Turners Syndrome) and post-treatment cancer survivors. These studies are evaluating interrelated risk factors and the effectiveness of lifestyle, diet and drug therapy treatment strategies. Dr. Mahmud is an investigator in the AddIT (Adolescent Type 1 Diabetes Cardio-Renal Intervention Trial) evaluating the protective effects of angiotensin converting enzyme inhibitors and Statins on renal and cardiovascular outcomes in high-risk type 1 diabetes adolescents.

Dr. Mahmud, together with his colleagues, are making significant contributions to the scientific base and clinical acceptance of the EndoPAT, as evidenced by the following publications:

Hill DJ, Prapavessis H, Shoemaker JK, Jackman M, Mahmud FH, Clarson C.

Relationship between Birth Weight and Metabolic Status in Obese Adolescents. ISRN Obes. 2013 Aug 28;2013:490923. doi: 10.1155/2013/490923.

O'Gorman CS, Syme C, Bradley T, Hamilton J, & Mahmud FH. **Impaired endothelial function in pediatric patients with Turner Syndrome and healthy controls: A case-control study.** Int J Pediatr Endocrinol 2012; 2012(1):5.

Zelcer S, Chen B, Mangel J, Vujovic O, Thiessen-Philbrook HR, Reider M, & Mahmud FH. **Impaired vascular function in asymptomatic young adult survivors of Hodgkin Lymphoma following mediastinal radiation.** J Cancer Surviv 2010; 4(3):218-24.

Mahmud FH, Hill DJ, Cuerden MS, & Clarson CL. **Impaired Vascular Function in Obese Adolescents with Insulin Resistance.** J Pediatr 2009; 155(5):678-82.

Mahmud FH, Van Uum S, Kanji N, Thiessen-Philbrook H, & Clarson CL. **Impaired endothelial function in adolescents with type 1 diabetes mellitus.** J Pediatr 2008; 152(4):557-62.

Haller MJ, Stein J, Shuster J, Theriaque D, Silverstein J, Schatz DA, Earing MG, Lerman A, & Mahmud FH. **Peripheral Artery Tonometry Demonstrates Altered Endothelial Function in Children With Type 1 Diabetes Pediatric Diabetes.** Pediatric Diabetes 2007; 8(4):193-198.

Mahmud FH, Earing MG, Lee RA, Lteif AN, Driscoll DJ, & Lerman A. **Altered Endothelial Function in Asymptomatic Male Adolescents with Type 1 Diabetes.** Congenital Heart Disease 2006; 1(3):98-103.