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Endothelial function predicts 1-year adverse clinical outcome in patients hospitalized in the emergency department chest pain unit☆

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ABSTRACT

Background: Endothelial function is a marker for cardiovascular risk. Thus, abnormal endothelial function may be associated with adverse 1-year outcome in patients presenting to the emergency department chest pain unit (CPU).

Methods: Following endothelial function testing, using EndoPAT 2000 in 300 consecutive subjects with chest pain and no history of coronary artery disease (CAD) presenting to CPU, patients underwent coronary computerized tomographic angiography (CCTA) or single-photon emission computed tomography according to availability.

Results: Mean 10-year Framingham risk score (FRS) was 6.6 ± 5.9%, median reactive hyperemia index (RHI) as a measure of endothelial function 2.08 and mean was 2.0 ± 0.4. During a 1-year follow-up, the 20 (6.6%) patients who developed major adverse cardiovascular end-points (MACE), including all-cause mortality, non-fatal myocardial infarction, hospitalization for heart failure or angina pectoris, stroke, coronary artery bypass grafting and percutaneous coronary interventions, had higher 10-year FRS (10.5 ± 8.2% vs 6.3 ± 5.7%; $p < 0.001$), lower baseline RHI (1.43 ± 0.41 vs 2.10 ± 0.44; $p < 0.001$) and a greater extent of coronary atherosclerosis lesions (70% vs 3.9%, $p < 0.001$) in the CPU CCTA, compared to those without MACE. RHI ≤ the median was associated with higher 1-year MACE (13% vs 0.7%, $p < 0.001$) compared to RHI > the median. Multivariate analysis demonstrated that RHI ≤ the median is an independent predictor of coronary atherosclerosis lesions in the CPU CCTA (OR 5.98, 95% CI 03.29-10.88; $p < 0.001$) and 1-year MACE (OR 15.207, 95% CI 2.00-115.33; $p < 0.01$).

Conclusions: Our findings suggest that non-invasive endothelial function testing may have clinical utility in triaging patients in the CPU and in predicting 1-year MACE.

1. Introduction

Chest pain is a common cause of emergency department (ED) presentation. In the United States, it accounts for 5% to 6% of new ED visits annually [1]. The principal challenge in these patients is to identify those with coronary artery disease (CAD). Early diagnosis allows effective treatment, while premature discharge may have disastrous consequences for both patient and doctor: in the United States, between 2% and 5% of patients with acute myocardial infarctions are discharged from the ED, and 20% of malpractice claims against emergency physicians relate to the management of acute coronary syndrome [2]. Thus, a convenient non-invasive tool should useful to stratify the patients' risk.

Endothelial dysfunction reflects a vascular phenotype prone to atherogenesis and may therefore serve as a marker of inherent atherosclerotic risk [3–8]. Endothelial dysfunction is an independent predictor of cardiovascular events, providing valuable prognostic information additional to that derived from conventional risk factor assessment [8,9]. Interventions, such as risk factor modification and treatment with various drugs, including statins [8] and angiotensin-converting enzyme inhibitors [10], may improve the prognosis of endothelial function [6]. Therefore, given its reversibility and suitability as a diagnostic tool in identifying patients at risk, together with its control over efficacy of therapy in clinical practice, endothelial dysfunction may be an attractive primary target to optimize individualized therapeutic strategies [11] in order to reduce cardiovascular morbidity and mortality.

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Over the past decade a non-invasive technique has been developed to evaluate endothelium-dependent, brachial artery flow-mediated dilation (FMD) [6,12,13]. This stimulus provokes the endothelium to release nitric oxide (NO) with subsequent vasodilation that can be imaged and quantitated as an index of vasomotor function. The advantages of this high-frequency ultrasound imaging of the brachial artery are two-fold: it is non-invasive and also facilitates repeated measurements [6,12].

Measurement of peripheral vasodilator response with fingertip peripheral arterial tonometry (PAT) technology (EndoPAT; Itamar Medical Inc., Caesarea, Israel) is emerging as a useful method for assessing vascular function [6,14]. Although the PAT signal is modulated by various local, systemic, and environmental factors, this parameter is also affected by the bioavailability of NO and, therefore, also depends on endothelial function [6]. Furthermore, endothelial dysfunction was found to be an independent risk factor for future major adverse cardiovascular events [6,15].

The primary objective of this study was to test the hypothesis that abnormal endothelial function as assessed by EndoPAT testing will increase the prediction of the short (in-hospital) and long-term (1-year) outcome of patients presenting to the ED chest pain unit (CPU). The secondary objectives were to compare association of EndoPAT, nuclear single-photon emission cardiac tomography (SPECT) imaging, echocardiographic stress testing and cardiac computed tomographic angiography (CCTA) on short- (in-hospital) and long-term (6 months and 1 year) clinical outcome of patients with chest pain who were admitted to ED CPU.

2. Methods

2.1. Study design and population

This is a prospective, bicenter study (Mayo Clinic ED and Sheba Medical Center ED CPU).

All patients admitted to the ED CPU with low to moderate probability for CAD and negative troponin. They underwent extensive testing on arrival, following clinical evaluation and their consenting to the study, which included: (1) resting electrocardiography (ECG), (2) EndoPAT testing (following an overnight fast for ≥6 h) and finally (3) SPECT imaging, stress echocardiography or CCTA. Except for EndoPAT testing, all other tests were conducted according to the routine CPU protocol. All participant physicians (CPU, nuclear SPECT imaging, stress echocardiography, or CCTA), as well as patients and investigators were blinded to the EndoPAT results until the end of the study. All patients were managed according to the CPU protocol, including 24-h ECG Holter monitoring, repeated resting ECG and exercise tests (nuclear SPECT imaging, stress echocardiography, or CCTA, whichever was available) in addition to repeat clinical and troponin tests evaluations. All clinical data of the recruited subjects were recorded and evaluated after completion of the study by a blinded investigator.

2.2. Reactive hyperemia by PAT (RH-PAT)

RH-PAT signals were obtained using the EndoPAT 2000 device (Itamar Medical Inc., Caesarea, Israel), which had been validated and used previously to assess peripheral arterial tone in other populations [16,16–20]. Specially designed finger probes were placed on the middle finger of each patient's hand. These probes comprised a system of inflatable latex air cuffs connected by pneumatic tubes to an inflating device controlled through a computer algorithm. A constant counter pressure (pre-determined by baseline diastolic blood pressure) was applied through the air cushions. This prevented venous pooling thus avoiding venoarteriolar reflex vasoconstriction. There was no occlusion of arterial blood flow.

Pulsatile volume changes of the distal digit induced pressure alterations in the finger cuff, which were sensed by pressure transducers and transmitted to and recorded by the EndoPAT 2000 device. A decrease in the arterial blood volume in the distal fingertip caused a decrease in pulsatile arterial column changes, resulting from a decrease in the measured PAT signal, and vice versa. Blood pressure and heart rate were measured using an automated blood pressure monitor (Welch Allyn Inc., Beaverton, OR, USA, Vital Signs Monitor 300 Series; model 530 TP).

Endothelial function was measured via an RH-PAT index. The RH-PAT was performed as previously described [15,16,18,21]. An RH protocol consists of a 5 min baseline measurement, after which a blood pressure cuff on the test arm was inflated to 60 mm Hg above baseline systolic blood pressure or at least 200 mm Hg for 5 min. Occlusion of pulsatile arterial flow was confirmed by the reduction of the PAT tracing to zero. After 5 min, the cuff was deflated, and the PAT tracing was recorded for a further 6 min. The ratio of the PAT signal after cuff release compared with baseline was calculated through a computer algorithm automatically normalized for baseline signal and indexed to contra lateral arm. The calculated ratio reflects the RHI. The natural logarithmic scaled RHI was calculated from the same ratio between the digital pulse volume during RH and baseline.

2.3. Long-term clinical follow-up

All patients were followed by telephone contact after 6 and 12 months for combined major adverse cardiovascular end-points (MACE) by a trained intensive care cardiac unit nurse who was blinded to the patients' baseline clinical status and endothelial function (assessed by EndoPAT) results. These endpoints included all-cause mortality, non-fatal myocardial infarction, hospitalization for heart failure or angina pectoris, stroke, coronary artery bypass grafting and percutaneous coronary interventions. All clinical MACE were validated by a review of medical records by a senior cardiologist who was blinded to the endothelial function results. All subjects were registered in the Ministry of Health computerized central registry. All hospitalizations, diagnoses and procedures [including operations, catheterizations, physician/clinic consultations, non-invasive tests, laboratory examinations, pathological tests, computerized tomography, X-rays, ECGs, etc.] were listed in the registry which, together with phone calls, was used for follow-up. On-line access to this information facilitated verification of good documentation of all events. In the event of any MACE, written medical records were reviewed by a cardiologist.

The hospital review board at both centers approved the study, and all participants gave written informed consent.

2.4. Statistical analysis

Data were analyzed with SPSS software version 23.0. (SPSS Inc. Headquarters, 233 S. Wacker Drive, 11th floor Chicago, Illinois 60606, USA). A p value of 0.05 was set as a threshold for significance. Baseline characteristic and risk factors are presented as means and standard deviations for continuous variables and as frequencies and percentages for categorical variables. Chi-square tests and independent *t*-tests were performed to compare demographic data and risk factors by median RHI and by 1-year cardiac hospitalizations, for categorical and continuous variables, respectively.

Multivariate analysis for prediction of long-term composite cardiovascular endpoints was performed by logistic regression model, and odds ratios with 95% confidence intervals were calculated. The analyses included independent variables/covariates that were statistically significant in the univariate analyses. Model suitability to the events rates observed was evaluated by the Hosmer-Lemeshow statistic.

The Kaplan-Meier survival curve demonstrates survival until first composite adverse cardiovascular endpoint (all-cause mortality, non-fatal myocardial infarction, heart failure or angina pectoris hospitalization, stroke, coronary artery bypass grafting and percutaneous coronary interventions) in subjects with RHI above the median (green line) and RHI less or equal to the median (blue line).

2.5. Power calculation

Power was calculated according to estimates from the Rubinshtein et al. study [16]. The estimated cohort size was based on the following parameters: On the assumption that the mean natural logarithmic scaled reactive hyperemia index (L_RHI) was 0.5 and the standard deviation 0.4 [16], then by dividing the continuous variable by 2 (> and <0.4), the predicted percent for adverse events was 0.3 and the percent difference of adverse events between those with low compared to high-endothelial function was at least 20%. Accordingly, for at least 80% power, we estimated the total number of enrolled subjects to be 200 (with an estimated minimum of 60 events). However, for multivariate analysis of extended data, the study cohort was estimated at 300 patients.

3. Results

The study population comprised 300 patients, 248 (83%) men, 52 (17%) women, mean age 50 ± 10 (range 17–81) years and body mass index 28 ± 5 kg/m^2 (Table 1). The study population included 73 (24%) subjects with hypertension, 105 (35%) with hypercholesterolemia (>200 mg/dL), 36 (12%) with type 2 diabetes, 91 (30%) current cigarette smokers and 109 (36%) with a family history of premature CAD. No patient had previous known CAD.

Mean total cholesterol was 181 ± 36 mg/dL, low-density lipoprotein cholesterol (LDL-C) 118 ± 29 mg/dL, triglycerides 150 ± 97 mg/dL and high-density lipoprotein cholesterol (HDL-C) 41 ± 9 mg/dL. Fasting serum glucose was 106 ± 30 mg/dL, systolic blood pressure 123 ± 14 mmHg, diastolic blood pressure 77 ± 10 mmHg and mean LVEF 60 ± 3% (Table 1). Mean 10-year Framingham Risk Score (FRS) was relatively low (6.6 ± 5.9) and 282 (94%) were working subjects. Twenty-three percent of patients were on statin therapy, while 16% on low-dose (≤100 mg/day) aspirin and 8% on angiotenstin converting-enzyme inhibitors (ACE-I) or beta blocking agents (Table 1).

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