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Utility of both carotid intima–media thickness and endothelial function for cardiovascular risk stratification in patients with angina-like symptoms☆

Yasushi Matsuzawa [a], Sara Svedlund [b], Tatsuo Aoki [a], Raviteja R. Guddeti [a], Taek-Geun Kwon [a], Rebecca Cilluffo [a], R.Jay. Widmer [a], Rebecca E. Nelson [a], Ryan J. Lennon [c], Lilach O. Lerman [d], Sinsia Gao [b], Peter Ganz [e,f], Li-Ming Gan [b,g,*], Amir Lerman [a,**]

[a] Division of Cardiovascular Diseases, Mayo Clinic, Rochester, MN, USA
[b] Department of Clinical Physiology, Department of Molecular and Clinical Medicine, Institute of Medicine at Sahlgrenska Academy, University of Gothenburg and Sahlgrenska University Hospital, Gothenburg, Sweden
[c] Division of biomedical Statistics and Informatics, Mayo Clinic, Rochester, MN, USA
[d] Division of Nephrology and Hypertension, Mayo Clinic, Rochester, MN, USA
[e] Division of Cardiology, San Francisco General Hospital, San Francisco, CA, USA
[f] Department of Medicine, University of California, San Francisco, CA, USA
[g] AstraZeneca R&D, Mölndal, Sweden

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ABSTRACT

Background: Myocardial perfusion scintigraphy (MPS) is used widely to assess cardiovascular risk in patients with chest pain. The utility of carotid intima–media thickness (CIMT) and endothelial function as assessed by reactive hyperemia-peripheral arterial tonometry index (RHI) in risk stratifying patients with angina-like symptoms needs to be defined. We investigated whether the addition of CIMT and RHI to Framingham Cardiovascular Risk Score (FCVRS) and MPS improves comprehensive cardiovascular risk prediction in patients presenting with angina-like symptoms.

Methods: We enrolled 343 consecutive patients with angina-like symptoms suspected of having stable angina. MPS, CIMT, and RHI were performed and patients were followed for cardiovascular events for a median of 5.3 years (range 4.4–6.2). Patients were stratified by FCVRS and MPS.

Results: During the follow-up, 57 patients (16.6%) had cardiovascular events. Among patients without perfusion defect, low RHI was significantly associated with cardiovascular events in the intermediate and high FCVRS groups (hazard ratio (HR) [95% confidence interval (CI)] of RHI $\leq$ 2.11 was 6.99 [1.34–128] in the intermediate FCVRS group and 6.08 [1.08–114] in the high FCVRS group). Furthermore, although MPS did not predict, only RHI predicted hard cardiovascular events (cardiovascular death, myocardial infarction, and stroke) independent from FCVRS, and adding RHI to FCVRS improved net reclassification index (20.9%, 95% CI 0.8–41.1, $p = 0.04$). Especially, RHI was significantly associated with hard cardiovascular events in the high FCVRS group (HR [95% CI] of RHI $\leq$ 1.93 was 5.66 [1.54–36.4], $p = 0.007$).

Conclusions: Peripheral endothelial function may improve discrimination in identifying at-risk patients for future cardiovascular events when added to FCVRS–MPS-based risk stratification.

1. Introduction

Atherosclerotic cardiovascular disease is the leading cause of mortality in the world [1]. The management of atherosclerotic cardiovascular disease is based on the absolute risk of adverse cardiovascular outcomes [2]. Current practice guidelines recommend classifying individuals as high, intermediate, or low risk, for example, using by Framingham Cardiovascular Risk Score (FCVRS), SCORE risk score by European Society of Cardiology, PROCAM risk score, or other similar risk prediction models which are based on identifying the established risk factors for atherosclerotic diseases [3–5]. The cardiovascular risk score recently published

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; CIMT, carotid intima–media thickness; FCVRS, Framingham Cardiovascular Risk Score; MPS, stress myocardial perfusion scintigraphy; RHI, reactive hyperemia-peripheral arterial tonometry index; RH-PAT, reactive hyperemia-peripheral arterial tonometry.

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

* Correspondence to: L.-M. Gan, Department of Molecular and Clinical Medicine, Institute of Medicine at Sahlgrenska Academy, 413 45 Gothenburg, Sweden.
** Correspondence to: A. Lerman, Division of Cardiovascular Diseases, Mayo Clinic, Rochester, MN, USA.
E-mail addresses: li-ming.gan@gu.se (L.-M. Gan), lerman.amir@mayo.edu (A. Lerman).

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by the Framingham study group includes the risk for future overall cardiovascular events, including stroke and heart failure [6]. Stress myocardial perfusion scintigraphy (MPS) is an established, widely used method in detecting coronary artery disease and predicting future cardiovascular events in patients complaining of angina-like symptoms, and is also recommended by current guidelines [7,8].

Carotid intima–media thickness (CIMT) and reactive hyperemia-peripheral arterial tonometry (RH-PAT) index (RHI) have shown promise in improving risk stratification for cardiovascular events [9–11]. MPS reflects myocardial perfusion reserve including microvascular and macrovascular diseases, whereas these 2 techniques assess different aspects of atherosclerotic vascular disease: CIMT reflects structural changes in the arterial wall, and RHI reflects peripheral endothelial function [12–14]. It has been reported that peripheral endothelial function as assessed by RHI well correlates with coronary artery endothelial function as invasively assessed by catheterization [15]. A comprehensive cardiovascular evaluation using assessment of myocardial perfusion, arterial wall structural change, and endothelial function might improve cardiovascular risk stratification. However, it is not clear whether CIMT and RHI when added to the established Framingham risk model and myocardial perfusion assessment are effective in improving risk prediction of future cardiovascular events.

Accordingly, the purpose of the present study was to examine whether a combination of CIMT and RHI with FCVRS–MPS-based risk stratification improves predictive value for cardiovascular events in patients presenting with stable angina-like symptoms.

2. Methods

This is a prospective observational study, conducted at the Department of Clinical Physiology, Sahlgrenska University Hospital, Sweden from February 2006 to November 2008. Three hundred and forty three patients with angina-like symptoms who were suspected of having stable angina pectoris, but without past history of angiographically proven coronary artery disease, were consecutively enrolled and MPS, carotid ultrasound, and RH-PAT were performed within a week after enrolment (Fig. 1). Physicians referring to MPS examinations were blinded to results of CIMT and RHI which therefore did not alter the clinical decision process in this study. The study was approved by the Local Ethics Committee in Gothenburg, and complies with the Declaration of Helsinki.

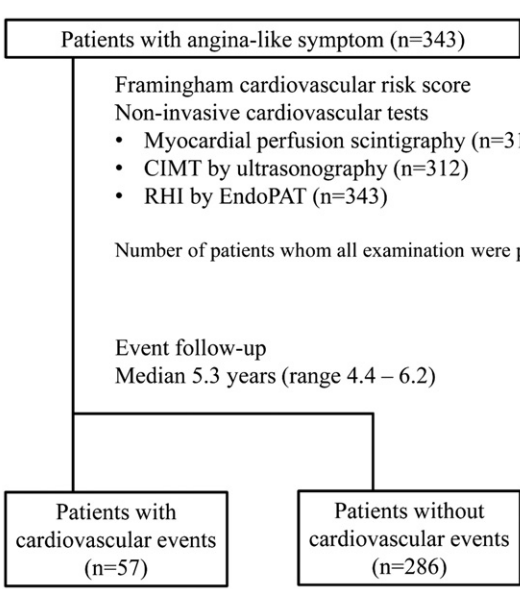

Fig. 1. Study design. CIMT: carotid intima–media thickness, and RHI: reactive hyperemia-peripheral arterial tonometry index.

2.1. Myocardial perfusion scintigraphy (MPS)

Gated single-photon emission computed tomography images were acquired using two different dual-head cameras (Infinia or Millennium VG, GE Healthcare, Milwaukee, Wisconsin, USA) with standard clinical 2-day stress/rest protocol using ^{99m}Tc-sestamibi. Stress test was performed according to the physician's discretion; either by symptom-limited exercise test on an ergometric bike or by standard pharmacological challenge using adenosine infusion (6-minute infusion at 140 μg/kg/min). Reversible myocardial ischemia was detected by the software ECT-tool box.

2.2. Carotid intima–media thickness (CIMT)

Carotid ultrasound was performed by experienced sonographers using the Acuson Sequoia 512 ultrasound system (Siemens Medical Solutions Inc.) with an 8 MHz transducer (Sequoia 8L5C). CIMT was measured with a standardized protocol recommended by "Mannheim Carotid IMT consensus update (2004–2006)" [16]. CINE-looped images of the common carotid arteries and carotid bifurcations were obtained using B-mode real-time ultrasound and were stored for offline analysis. CIMT was defined as the distance from the lumen–intimal interface to the medial–adventitial border. Mean CIMT was averaged for both the right and left common carotid arteries. The reproducibility of the CIMT measurement has been reported to be adequate [17].

2.3. Reactive hyperemia-peripheral arterial tonometry index (RHI)

EndoPAT 2000 device (Itamar Medical Ltd., Caesarea, Israel) was used to evaluate peripheral arterial endothelial function, as described previously [10,14,18–21]. Pneumatic probes were applied to the tip of one finger on each hand to measure digital volume changes accompanying arteriolar tone changes. After a 5-minute equilibration period, the blood pressure cuff was inflated on one arm to 60 mm Hg above systolic pressure or 200 mm Hg for 5 min, and then deflated to induce reactive hyperemia. RH-PAT data was analyzed by a computer in an operator-independent manner and RHI was calculated as the ratio of average amplitude of the PAT signal over a 1-minute time interval, starting 1.5 min after cuff deflation, divided by its average amplitude over a 2.5-minute time period before cuff inflation (baseline), through a computer algorithm. Previous studies have demonstrated good reproducibility (intra-class correlation coefficient 0.61 to 0.78) of the RH-PAT data recorded by this procedure [22–24].

2.4. Coronary risk factors and atherosclerotic disease risk scores

Coronary risk factors were defined as current smoking (within one year), diabetes mellitus (patient history and/or need for insulin or oral hypoglycemic agents), and presence of a family history of cardiovascular disease in first-degree relatives <55 years (male) or <65 years (female). Low density lipoprotein cholesterol was calculated by using the equation of Friedewald et al. [25]. Ten-year general cardiovascular disease risk was calculated using FCVRS, which includes age, diabetes, smoking, treated or untreated systolic blood pressure, total cholesterol, and high-density lipoprotein cholesterol [6]. The Framingham Heart Study defines cardiovascular diseases as a composite of coronary death, myocardial infarction, coronary insufficiency, angina, stroke, peripheral arterial disease, and heart failure, the end-points of our study. Patients were classified accordingly as low (<6%), intermediate (6–20%), or high (>20%) risk [6]. In order to assess the additional value of non-invasive tests in predicting hard cardiovascular events, a 10-year atherosclerotic cardiovascular disease (ASCVD) risk score by the Pooled Cohort Equation was calculated, and patients were classified