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Reclassification of cardiovascular risk by myocardial perfusion imaging in diabetic patients with abnormal resting electrocardiogram

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Abstract *Background and aims:* Despite an extensive use of stress myocardial perfusion single-photon emission computed tomography (MPS), no study addressed the role of perfusion imaging in diabetic patients with abnormal resting electrocardiogram (ECG). We compared analytical approaches to assess the added value of stress MPS variables in estimating coronary heart disease outcomes in diabetic patients with abnormal resting ECG.
Methods and results: A total of 416 patients with diabetes and abnormal resting ECG who underwent stress MPS were prospectively followed up after the index study. The end point was the occurrence of a major cardiac event, including cardiac death and nonfatal myocardial infarction. At the end of follow-up (median 58 months), 42 patients experienced events. MPS data increased the predictive value of a model including traditional cardiovascular risk factors and left ventricular (LV) ejection fraction (likelihood ratio χ^2 from 17.54 to 24.15, $p < 0.05$, with a C statistic of 0.72, 95% confidence interval: 0.65–0.79). The addition of MPS data resulted in reclassification of 25% of the sample with a net reclassification improvement of 0.20 (95% confidence interval: 0.05–0.36). Overall, 63 patients were reclassified to a lower risk category, with a 5-year event rate of 3.5%, and 40 patients were reclassified to a higher risk category, with a 5-year event rate of 20%.
Conclusion: The addition of MPS findings to a model based on traditional cardiovascular risk factors and LV ejection fraction improves risk classification for incident cardiac events in diabetic patients with abnormal resting ECG.

Introduction

Coronary artery disease (CAD) is the leading cause of morbidity and mortality in patients with diabetes mellitus [1]. In these patients, the prognostic value of stress myocardial perfusion single-photon emission computed tomography (MPS) has been largely investigated [2–5]. Yet, how to correctly identify diabetic patients in need of testing remains to be defined [6–8]. In a recent position statement on standards of medical care in diabetes [9], the American Diabetes Association (ADA) does not recommend screening for CAD in asymptomatic patients because it does not improve outcomes as long as cardiovascular risk factors are treated. Net reclassification improvement (NRI) has been adopted in diabetic patients with suspected or known CAD to evaluate the extent to which adding

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stress MPS imaging data to a model based on traditional risk factors and stress electrocardiogram (ECG) data correctly reclassifies the risk of subsequent cardiac events during a long-term follow-up [10–12]. In patients with diabetes mellitus, a variety of resting ECG abnormalities has been described, not only resulting from ischemia [13]. These abnormalities are predictive for adverse outcome independently of multiple risk factor adjustment [14,15]. So far no study addressed the prognostic role of stress MPS in a population of diabetic patients without known CAD and an abnormal resting ECG. The aim of this study was to compare analytical approaches to assess the added value of stress MPS variables in estimating CAD outcomes in diabetic patients with abnormal resting ECG.

Methods

Study population

The study population included consecutive patients ($n = 433$) with at least a 5-year history of type 2 diabetes presenting with an abnormal resting ECG, referred for stress MPS for the detection of inducible myocardial ischemia. Of these patients, 212 were part of the Impact of inDucible Ischemia by Stress MPS (IDIS) investigation [16]. Abnormal resting ECG was defined as ST-segment elevation $\geq$2 mm in 2 or more contiguous leads ($n = 59$), T-wave inversion of at least 1 mm ($n = 124$), presence of Q-wave $\geq$1 mm in depth ($n = 149$), ST-depression $\geq$1 mm ($n = 12$), left ($n = 57$) or right ($n = 36$) bundle branch block [17]. Patients have been excluded for: 1) clinical history of prior myocardial infarction; 2) recent acute coronary syndrome, recent stroke or transient ischemic attack (last 3 months); 3) uncompensated congestive heart failure or recent admission for congestive heart failure; 4) atrial fibrillation/flutter; 5) prior myocardial revascularization procedures; or 6) a concomitant noncardiac illness that would limit follow-up for at least 1 year. As part of the baseline examination, beside diabetes and its complications (including neuropathy, nephropathy, peripheral vascular disease, and retinopathy), clinical teams collected information on traditional cardiovascular risk factors (including age, sex, body mass index, dyslipidemia, smoking, hypertension, family history of CAD), and chest pain symptoms. From these variables the Morise clinical risk score was calculated for each patient [18]. The study was approved by the local Ethics Advisory Committee and carried out according to the Helsinki declaration. Participants gave written informed consent prior to the study.

MPS

All patients underwent same-day Tc-99m sestamibi rest and stress gated MPS by exercise or dipyridamole stress test, according to the recommendations of the European Association of Nuclear Medicine and European Society of Cardiology [19], as previously described in details [16]. An automated software program (e-soft, 2.5, QGS/QPS, Cedars-Sinai Medical Center, Los Angeles, California) was used to calculate left ventricular (LV) ejection fraction and the scores incorporating both the extent and severity of perfusion defects [20], using standardized segmentation of 17 myocardial regions. Each segment was scored from normal (score = 0) to absent perfusion (score = 4). The summed stress score is obtained by adding the scores of the 17 segments of the stress images. A similar procedure is applied to the resting images to calculate the summed rest score. The summed difference score represents the difference between the stress and rest scores and is taken to be an index of ischemic burden. Patients were considered to have an abnormal MPS with a summed stress score >3. Significant ischemia was defined by a summed difference score $\geq$2, and classified as mild (2–6) and moderate-severe (>6) [21].

Follow-up

Patient follow-up was prospectively obtained by use of a questionnaire administered by phone call to all patients, general practitioners or cardiologists and by review of hospital or physicians' records by individuals blinded to the patient's test results. The end point was the occurrence of a major adverse cardiac event (MACE) whichever occurred first, including cardiac death and nonfatal myocardial infarction. Cardiac death, defined as due to acute myocardial infarction, ventricular arrhythmias, refractory heart failure or cardiogenic shock, was confirmed by review of death certificate, hospital chart or physician's records. Nonfatal myocardial infarction was defined based on the criteria of typical chest pain, elevated cardiac enzyme levels and typical alterations of the ECG. The interval to an event was defined as the duration from the baseline MPS study to MACE, or the end of follow-up.

Statistical analysis

Continuous variables were expressed as mean $\pm$ standard deviation and categorical data as percentages. Differences between groups were analyzed by t test and χ^2 analysis, as appropriate. A two-tailed p value <0.05 was considered statistically significant. Cumulative event rates as function of time were calculated with the Kaplan–Meier method. Univariable associations with MACE were determined by Cox proportional hazards regression, and hazard ratios (HR) and 95% confidence intervals (CI) were calculated. To assess the added value of LV ejection fraction and MPS data in risk prediction, we considered a series of Cox models. Model 1 was based on clinical risk factors: age, sex, body mass index, dyslipidemia, smoking, hypertension, family history of CAD, and chest pain symptoms. In model 2, we added LV ejection fraction to the aforementioned risk factors. Model 3 added MPS data to model 2. The statistical significance of the contribution of the added variables was assessed with the likelihood ratio test [22]. In addition, we assessed for significant incremental changes in model C statistic [23]. The incremental value of LV ejection fraction and MPS data for predicting MACE was also evaluated using the NRI. The goal was to determine