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Original Article

Coronary artery disease screening in type II diabetic patients: Prognostic value of rest and stress echocardiography

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ABSTRACT

Aim: Presence of inducible ischemia in type II diabetic patients is associated with an adverse outcome, but less is known about prognostic value of resting wall motion abnormalities (WMA).
Materials and methods: : From October 2006 to May 2008, 278 patients underwent to CAD screening, according to ADA criteria, by dobutamine stress echocardiography (DSE). Between July and September 2009, all patients were contacted to verify the occurrence of new cardiac events.
Results: Resting-WMA were present in 63 patients; 88 subjects showed inducible ischemia. During the follow-up, we observed 24 new cardiac events; patients with a good outcome showed less frequently resting WMA (19 vs 50%). Inducible ischemia (71% vs 28%; $p < 0.001$) and a more extensive area of inducible ischemia, expressed by a higher value of peak WMSI (1.63 ± 0.45 vs 1.17 ± 0.31; $p < 0.0001$), were more frequent in patients with adverse outcome. A Cox regression analysis showed that only a higher peak WMSI (HR 6.645, 95% CI 2.782–15.874, $p < 0.0001$) was associated with a bad outcome. Event-free survival was lower in presence of rest WMA (79% vs 94%, $p < 0.0001$) and a higher peak WMSI (66% vs 95%, $p < 0.0001$).
Conclusions: In diabetic patients presence of an extensive inducible ischemia was independently associated with a worst outcome; resting WMA were associated with reduced event-free survival.

1. Introduction

The vast majority of people with diabetes die from cardiovascular complications [1] and mortality after an acute cardiac ischemic event is higher in diabetic patients [2]. In fact, patients with diabetes have a high incidence of occult CAD and silent myocardial ischemia, that both contribute to a more advanced disease at the time of the first diagnosis and a worse outcome after revascularization procedures [2,3].

American Diabetes Association (ADA) in 1998 [4] recommended CAD screening in type II diabetic patients with the following characteristics: two or more additional risk factors, symptoms or EKG modifications suggesting CAD and presence of carotid or peripheral arterial disease. It was also stated that the EKG stress test showed a poor sensitivity [5,6], so that an imaging modality, both ultrasound and scintigraphy, was recommended. Dobutamine stress echocardiography (DSE) demonstrated repeatedly a good diagnostic and prognostic accuracy in diabetic subjects [7–9].

Although a large amount of paper regarding CAD screening in asymptomatic diabetic patients has been published [10–15], little is known about clinical characteristics and prognostic stratification of patients evaluated according to all ADA criteria.

Aim of this study were: (1) to compare clinical and echocardiographic characteristics of diabetic patients screened according to different ADA criteria; (2) to evaluate prognostic value of resting wall motion abnormalities (WMA) and inducible ischemia during dobutamine stress echo (DSE).

2. Methods

2.1. Study population

We retrospectively analyzed data from 407 patients affected by type 2 diabetes, all without known CAD, referred to our diabetes out-patients clinic for metabolic control evaluation from October

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2006 to May 2008, who met American Diabetes Association criteria to undergo coronary artery disease (CAD) screening.

Diabetes was defined, according to American Diabetes Association criteria, as fasting plasma glucose ≥126 mg/dl or a random value ≥200 mg/dl.

Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg or the use of anti-hypertensive medications; patients were considered to have dyslipidemia if their total cholesterol was ≥200 mg/dl or if they were receiving lipid-lowering-medications. Smoking history was considered positive both for current and previous smokers. Carotid arterial disease was diagnosed in presence of an arterial bruit and/or significant stenoses (>70%) documented with Doppler examination; peripheral arterial disease was diagnosed in presence of intermittent claudication (maximal distance before pain 500 m), arterial bruit, peripheral pulse asymmetry and, whenever present, Doppler evidence of a critical (>70%) arterial stenoses.

Cardiac symptoms included typical or atypical chest pain and effort dyspnea; EKG modification was considered as resting EKG suggestive of ischemia and/or infarction [4].

Glomerular filtration rate (GFR) was calculated according to the modification of diet formula; chronic kidney disease (CKD) was diagnosed in presence of a GFR < 60 ml/min/1.73 m^2.

All patients gave their informed consent and the study is consistent with the principles of the Declaration of Helsinki of clinical research involving human subjects.

2.2. Dobutamine stress protocol

β-blockers therapy was withheld the day before the examination. After a baseline echocardiogram (Sequoia, Siemens, Mountain View, CA, USA), all patients underwent DSE according to the standard protocol. Test end-points were achievement of target heart rate, positive response for ischemia as development of new asynergia in two or more myocardial segments, excessive increase (systolic blood pressure, SBP, >240 mmHg) or significant reduction of blood pressure (more than 40 mmHg compared to the preceding phase o SBP <90 mmHg) and repetitive ventricular or supraventricular ectopy. If the test was positive for ischemia, propranolol was infused in incremental doses of 0.5 mg, until symptoms, ECG and echocardiographic modifications resolved.

2.3. Echocardiographic analysis

At baseline, at the end of low-dose (LD) and HD and after recovery, digital images obtained in parasternal long and short axis and apical four and two chambers view were stored on disk, to allow a quad-screen visualization. Left ventricular (LV) regional wall motion was assessed according to the recommendations of the American Society of Echocardiography, with a 16 segments model; each segment was given a kinetic score: 0 = not visualized, 1 = normokinetic, 2 = hypokinetic, 3 = akinetic, 4 = dyskinetic and 5 = aneurism. Wall motion score index (WMSI) was calculated at baseline, after LD and HD infusion as ratio between the cumulative sum score and the number of visualized segments.

Myocardial viability was defined as an increase in kinetic score by at least one grade in four or more segments; inducible ischemia was defined by the development, in at least two segments, of new asynergia or biphasic response (basal asynergia improving at LD and becoming worse at HD. DSE was considered normal when LV global and segmental wall motion were normal both at baseline and at peak stress. To perform the Kaplan–Meyer analysis, baseline WMSI was categorized as normal (= 1) or pathologic (>1); HD WMSI was instead categorized according to the mean value found in our study population, that was 1.6.

2.4. Follow-up data

Between July and September 2009, all patients were contacted by telephone to verify the occurrence of new cardiac events (death, both cardiac and non-cardiac, non-fatal STEMI, percutaneous or surgical revascularization procedures, development of heart failure symptoms and signs). A combined end-point, including cardiovascular death and major cardiovascular event (STEMI, coronary revascularization and heart failure) was calculated to evaluate DSE prognostic value in this population.

2.5. Statistical analysis

Data were analyzed with SPSS program (Version 17, SPSS Inc., Chicago, IL, USA). The values of parametric data were reported as media ± standard deviation. The comparison between groups was made with Anova test. Non-parametric data were analyzed with Fisher exact test.

Variables considered as potential predictors for multivariate modeling were selected by univariate analysis and were subsequently selected by forward method (likelihood ratio method, with variable in by $p < 0.05$, and out $p > 0.10$ to avoid biases due to colinearity) in a Cox regression analysis. Cardiac event rate during follow-up was evaluated by Kaplan–Meier curve analysis.

3. Results

3.1. Clinical and echocardiographic characteristics according to screening criteria

Eighty subjects refused the test and 49 could not perform it for inadequate acoustic window, so that the final study population included 278 subjects. More common screening criteria were presence of typical or atypical symptoms and presence of additional risk factors (Table 1).

Clinical characteristics of the whole study group are shown in Table 1: prevalence of arterial hypertension was very high and more common medications were ACE-inhibitors (46% of the patients), calcium-antagonists (23%) and angiotensin-receptor blockers (23%), assumed in a similar proportion of patients in all screening groups; dyslipidemia was also very common, but only 125 (45%) patients were taking statins. Mean diabetes length was 12 ± 12 years, with a poor metabolic control (mean glycosylated hemoglobin, HbA1c, 7.8 ± 1.4%); 77 (28%) subjects were treated by insulin and 211 (76%) by antidiabetic oral agents.

During the resting echocardiographic exam, patients who underwent DSE for baseline EKG abnormalities showed significantly increased LV diastolic dimension and reduced global LV systolic function (Table 2); resting-WMA were more frequent. During all DSE stages, wall motion score index (WMSI) was significantly higher compared to patients included for other screening criteria, indicating a larger asynergic area; inducible ischemia was significantly more common.

According to screening criteria, we evaluated separately subjects who underwent DSE only for presence of additional risk factors (ARF+), in absence of any symptom or sign of CHD or arterial disease: in ARF+ subjects, a normal DSE was significantly more common (78% in ARF+ vs 57% in ARF−, $p = 0.001$) and inducible ischemia developed less frequently (17% in ARF+ vs 39% in ARF−, $p < 0.0001$).

3.2. Clinical and echocardiographic predictors of inducible ischemia

Resting-WMA were present in 63 (23%) patients, but viability was evidenced in only 15; 88 (32%) subjects showed inducible ischemia during DSE.