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Prognostic utility of carotid ultrasound and cardiac SPECT imaging in coronary artery bypass patients

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Abstract

BACKGROUND: The aim of our study was to evaluate the role of myocardial perfusion imaging (MPI) and common carotid artery intima-media thickness (CCA IMT) in the prognosis of patients with coronary artery disease referred for coronary artery bypass surgery (CABG) in a newly made prognostic model.
MATERIAL AND METHODS: 63 patients (age 60.36 ± 8.28 years) with angiographically established coronary artery disease referred for CABG were evaluated for: age, smoking, family disposition, dyslipidaemia, arterial hypertension, obesity, diabetes mellitus, previous myocardial infarction and revascularization. Patients underwent nitrate enhanced Gated SPECT myocardial perfusion imaging, with 17-segment analysis for calculation of perfusion scores and viability index. Common carotid artery IMT was measured by B-mode ultrasound. Patients were followed for cardiovascular events 12 months after CABG.
RESULTS: The obtained data reported mean values of left ventricular ejection fraction (LVEF) 46.2 ± 14.4%, viability index 0.76 ± 0.55, SRS 17.76 ± 13.81 and summed nitrate score 12.89 ± 10.36. Ultrasound detected CCA IMT 0.90 ± 0.24 mm, with increased value in 67.2% and presence of carotid plaques in 27.1% of pts. We registered 14 events and 8.8% mortality rate. Multiple regression modelling showed bilateral carotid plaque presence as a predictor of total events. Viability index and CCA IMT have been found as independent death predictors.
CONCLUSIONS: Myocardial perfusion viability index and CCA IMT are predictors, independently associated with prognosis of patients referred for CABG.

Key words: myocardial viability, intima-media thickness, carotid plaque, coronary artery bypass surgery, prognosis

Introduction

The changing profile of patients undergoing coronary surgery operations necessitates continuous updating and revision of risk models. Investigation of the prognostic importance of the extent of viable myocardium may help determine which patients derive the greatest survival benefit from revascularization [1, 2]. Preoperative myocardial perfusion imaging and subsequent coronary revascularization for high-risk patients improve perioperative and long-term outcome. The detection of viable myocardium has become of great clinical importance, due to the major prognostic role and therapeutic implications of myocardial viability [5].

Measurements of carotid IMT may be used to identify high--risk patients with coronary artery disease. Carotid IMT has been shown as a powerful predictor of cardiovascular events in patients with proven coronary artery disease and cardiovascular disease [6, 7]. Intima-media tickness correlates with coronary artery disease, proven angiographically, but not with myocardial scintigraphy [8, 9]. Studies made by Lacroix and Reed refer to the predictive role of increased IMT in clinical outcomes in patients with coronary artery disease after revascularization [10, 11]. Some studies could not find IMT as a predictor of coronary artery disease, or found it only as a predictor of stroke, and less clearly associated with coronary events. It is indicated that carotid plaques are closely associated with coronary artery disease prognosis [12–14]. The occurrence of carotid plaques are a good surrogate for predicting coronary artery disease, expressed as myocardial hypoperfusion by myocardial scintigraphy [9].

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A predictive model for coronary artery bypass patients that includes both methods: myocardial perfusion findings and carotid ultrasound, has not been studied yet.

The aim of this study was to identify preoperative determinants that influence postoperative cardiovascular events in patients with coronary artery disease, who underwent primary isolated CABG. We especially wanted to investigate whether the presence and extent of viable myocardium, values of ejection fraction and extent of non viable tissue influence long-term prognosis in revascularized patients. We also sought to study whether there is an additional role of carotid ultrasound in the prognosis of coronary artery bypass patients, when added to myocardial Gated SPECT imaging findings and traditional risk factors.

Material and methods

Study population

Between January and December 2004, 63 consecutive patients with mean age 60.36 ± 8.28 years, referred for CABG, were studied at our institute. Preoperative ejection fraction of 46 ± 14% was verified with Gated SPECT imaging. Patients undergoing combined procedures as CABG with valvular surgery, angioplasty, aortic or carotid surgery were excluded from the study, as well as patients undergoing urgent surgery and patients with renal failure. Preoperative and postoperative angina and dyspnoea were assessed according to the Canadian Cardiovascular Society (CCS) and the New York Heart Association (NYHA) functional classification. Major clinical indications for surgery were dominating angina pectoris in 45 patients (71%) and dyspnoea in 15 patients (24%). Thirty-four patients (54%) had severe CCS angina and 25 patients (40%) had II/III NYHA functional class preoperatively. The decision to perform CABG was based on clinical and angiographic criteria according to the recommendations of ACC/AHA coronary artery bypass surgery guidelines. All patients gave informed consent as part of the protocol approved by the Ethical Committee on Human Studies at our University.

Study protocol

All patients were evaluated for the following preoperative parameters: age, sex, smoking, family disposition, presence of dyslipidaemia, arterial hypertension, obesity, diabetes mellitus, previous myocardial infarction and coronary revascularization. All patients underwent coronary angiography before MPI. Coronary stenosis equal to or greater than 70% of luminal diameter was considered significant. Left main coronary artery disease was reported in the presence of stenosis equal to or greater than 50% of luminal diameter. Gensini angiographic score was calculated for all patients. Left ventricular ejection fraction with Tc-99m-Sestamibi myocardial Gated-SPECT was evaluated before CABG. Preoperative myocardial viability and carotid ultrasound imaging with CCA intima-media thickness (IMT) were assessed in all patients.

CCA IMT was measured by B-mode ultrasound using a tomographic ultrasound system (HP Agilent S 4500) with a linear transducer (7.5–10 MHz) and presented as mean value of three measurements from both sides. Carotid stenosis (CS) ≥ 60% was considered significant. Carotid IMT was defined as the distance from the leading edge of the first echogenic line to the leading edge of the second echogenic line on the scans, with the first line representing the lumen-intimal interface and the second line representing the collagen-containing upper layer of the adventitia. IMT with value equal to or great than 0.8 mm were defined as increased IMT. Plaque was defined as a localized thickening lesion (≥ 1.1 mm). In each longitudinal projection, the site with the greatest thickness (including plaque) was detected along the vessel from the common carotid artery to the internal carotid artery.

Primary indication for the MPI was evaluation of myocardial viability before CABG. Patients underwent one day rest-nitrate enhanced gated SPECT Tc-99m-Sestamibi protocol with 370/925 MBq, after sublingual application of 0.5 mg nitro-glycerine (NTG). Haemodynamic response to the nitrate was monitored in all patients. Image acquisition was performed 60–90minutes after injection of Tc-99m-Sestamibi using a single headed Sopha Medical Vision DS7 SPECT gamma camera. Attenuation correction was not used. For quantitative analysis of myocardial perfusion, a commercial program for Bull's eye analysis was used. The MultiDim program was included in the software of the gamma camera for assessment of left ventricular function. Image interpretation was done using a 17-segment model and 5-point scoring system to assess perfusion (0 — normal perfusion; 1 — mild hypoperfusion; 2 — moderate; 3 — severe hypoperfusion: and 4 — absent uptake). A segment was predetermined to be viable if the perfusion segment score was ≤ 2 and wall thickening was present. A 5-point scoring system was used to assess wall motion: 0 — normal, 1 — moderate, 2 — severe hypokinesia, 3 — akinesia and 4 — dyskinesia. A segment was predetermined to be viable by function if the segment score was ≤ 2 (2 — normal perfusion, 1 — moderate-severe hypoperfusion; 0 — absent uptake). A viability index (VI) was calculated as value of the Tc-99m-Sestamibi uptake in each segment, divided by the total number of segments evaluated. A viability index > 0.5 was considered as an indication of a significant degree of viable myocardium. The following criteria for myocardial viability were used: 1. Tc-99m-Sestamibi resting uptake >50%; 2. nitrate-induced uptake increase > 10% and nitrate activity ≥ 65%, with resting wall motion abnormality (scores 2–4). The segment target for revascularization were judged either completely viable, partially or totally scared. Summed nitrate score (SNS), summed rest score (SRS) and summed different score (SDS) were calculated.

Patients were followed up, prospectively for cardiovascular events 12 months after the CABG: cardiovascular death, myocardial infarction, new onset of angina, stroke, new revascularization and hospital referral due to episodes of heart failure. Events were subsequently analysed as primary end points, detected using available inpatient and outpatient medical records, patient interviews and regular cardiac visits. Early (< 30 days) perioperative events were censored.

SPSS 10 packet for statistical analysis was used. Data are expressed as mean ± SD. Group comparisons were performed using *t*-tests for continuous, normally distributed data. P value ≤ 0.05 was considered statistically significant. The following variables were entered into Cox regression models (univariate and multivariate) to elaborate the factors that determine the postoperative course.

Results

The male sex was dominant in study population (82.5% *vs.* 17.5%). 42.9% of estimated patients were diabetics, 57.1% had hypertension and 15.9% of patients were obese. Previous myocardial infarction was detected in 74.6% and history of pervious revascularization in 15.9% of the study population. Baseline clinical data is presented in Table 1.

Carotid ultrasound variables

A common carotid artery intima-media thickness mean value of 0.9 ± 0.15 mm was detected. Increased value of CCA IMT (≥ 0.8) was found in 43 patients (68.3%). In 59 patients (93.7%) unilateral bulbs plaques were detected and in 42 patients (66.7%) bilateral carotid plaques were detected. Population with increased IMT and carotid plaques was AGED 62.09 ± 8.27, with no difference in mean age of the whole population studied.

Myocardial perfusion findings

Myocardial perfusion Gated SPECT studies showed important alterations in both global and regional wall motion and perfusion analysis (Table 2). Mean ejection fraction calculated by this method was 46.2 ± 14.4%. We analyzed a total of 1,071 myocardial segments, of which 720 showed abnormal wall motion (67.2%). Of these 720 segments, approximately two-thirds (540 segments) were hypokinetic and one-third (150 segments) were akinetic. Thirty segments were dyskinetic. Mean viability index was 0.75 ± 0.16, mean SNS 14.89 ± 12.19, and mean SRS 19.62 ± 14.81. The average percentage of fixed perfusion defects was 19.13 ± 14.09% of the left ventricular myocardium. Fixed defects were more extensive in patients with previous myocardial infarction. Patients with cardiac events during the follow up period showed an average percentage of fixed defects of 23 ± 9%, compared to the event-free patients, in which the mean percentage of fixed defects was 11 ± 7% ($p < 0.05$). The amount of fixed defects was higher in patients with cardiac death (28 ± 4%). Hibernated myocardium was found in 38 patients (60.3%), with average values 15.72 ± 10.48% of left ventricular myocardium. All cardiovascular caused events were more prevalent in patients with mean viability index < 0.65.

Tc-99m-Sestamibi demonstrated preserved perfusion, with perfusion score < 2 in 403 segments (56%) from the 720 dysfunctional segments. The majority of them were severely hypokinetic. In the other 317 segments perfusion was severely impaired, with perfusion scores > 3.

Angiography and coronary surgery characteristic of population

Coronary disease extension was as follows: single vessel disease was found in 6 patients (9.5%), double vessel disease in 22 patients (35%) and triple vessel disease in 34 patients (54.5%). Calculated mean value of Gensini score was 15.75 ± 5.48. Complete revascularization was performed in 52 patients (82%). Left mammary artery (LIMA) was put in all revascularized patients. There were 82 arterial grafts and 55 vein grafts implanted. Due to incomplete revascularization in 11 patients, parts of the viable segments were probably still left jeopardized.

Cardiovascular events

A total of 14 events were registered in fourteen patients over one year, with an incidence of 4.5% per patient per year. 6 of them were fatal cardiovascular events. Among the 8 detected nonfatal events, 3 were cerebrovascular events, two were episodes of heart failure, two were new onset of angina and one event was defined as new revascularization.

When the obtained patients were divided in two subgroups, patients with events, and patients with no events, a significant difference was found between the two subgroups in terms of sex and NYHA classification (Table 3). The presence of plaques, as well as the value of IMT ≥ 0.8 significantly differs between the

Table 1. Preoperative clinical data

Preoperative clinical data	Number of patients (%)
Men	52 (82.5%)
Women	11 (17.5%)
Diabetes mellitus	27 (42.9%)
Hypertension	36 (57.1%)
Previous MI	47 (74.6%)
Obesity	10 (15.9%)
Previous revisualization	10 (15.9%)
Smoking	24 (38.1%)
Family disposition	18 (28.6%)

MI — myocardial infarction; % — percent of total population evaluated

Table 2. Mean values of myocardial perfusion scintigraphy variables

Variables	Average values
LVEF	45.30 ± 14.26
Viability index	0.75 ± 0.16
Fixed defects (%)	19.13 ± 14.09
Viable myocardium (%)	15.75 ± 10.48
SRS	19.62 ± 14.81
SNS	14.89 ± 12.19

LVEF — left ventricular ejection fraction; SRS — summed rest score; SNS — summed nitrate score

Table 3. Differences between patients with events *vs.* without events

Variables	Events group	No events group	p
Categorical			
Male	14/14	38/49	0.05
EF < 40%	6/14	7/49	0.03
IMT ≥ 0.8	14/14	29/49	0.002
Carotid plaque	14/14	28/49	0.01
Viability index ≤ 0.55	5/14	1/49	0.001
Continuous			
SNS	20.71	12.02	0.04
Fixed defects	25.6%	17.2%	0.04

Table presented only variables with significant p between two subgroups. EF — ejection fraction; IMT — intima-media thickness; SNS — summed nitrate score

Table 4. Two models of Cox regression analysis of predictors of events/mortality

	Model 1			Model 2		
Variable	Score	Sig	R	Score	Sig	R
Prior MI	2.4621	0.1166	0.0631	2.0426	0.1530	0.0293
IMT	3.0089	0.0828	0.0933	**4.5886**	**0.0322**	**0.2282**
HLP	0.0318	0.8584	0.0000	0.4909	0.4835	0.0000
HTA	0.2917	0.5892	0.0000	0.2222	0.6374	0.0000
Diabetes mellitus	1.1667	0.2801	0.0000	1.6806	0.1949	0.0000
Obesity	0.7991	0.3714	0.0000	0.3195	0.5719	0.0000
Fam.disp	0.0000	1.0000	0.0000	1.1321	0.2873	0.0000
EF<40	**4.2215**	**0.0399**	**0.1384**	3.1592	0.0755	0.1527
SRS	2.1884	0.1391	0.0403	1.3157	0.2514	0.0000
Smoking	1.6490	0.1991	0.0000	1.1683	0.2798	0.0000
Carotid plaque (U)	0.0148	0.9031	0.0000	0.4068	0.5236	0.0000
Previous revascularization	0.7991	0.3714	0.0000	0.0028	0.9576	0.0000
IMT ≥ 0.8	**6.5116**	**0.0107**	**0.1972**	2.7907	0.0948	0.1261
VI	4.8380	0.0278	0.1564	4.3079	0.0379	0.2155
SNS	3.2476	0.0715	0.1037	1.0714	0.3006	0.0000
Gensini	0.7019	0.4021	0.0000	0.2778	0.5982	0.0000
Carotid plaque B	**7.0000**	**0.0082**	**0.2076**	3.0000	0.0833	0.1418
Fixed defects	2.1596	0.1417	0.0371	0.7103	0.3993	0.0000
Hiber. myoc	0.0424	0.8368	0.0000	0.0234	0.8785	0.0000
Age	0.1757	0.6751	0.0000	2.8210	0.0930	0.1285

Method: Forward Stepwise (Conditional LR). Model 1 for variables related to total events, Model 2 for variables related to mortality. MI — myocardial infarction; IMT — intima-media thickness; HLP — hyperlipidaemia; HTA — hypertension; EF — left ventricular ejection fraction; SRS — summed rest score; VI — viability index; SNS — summed nitrate score

Table 5. Multivariate analysis of predictors of events/mortality

Variable	B	S.E.	Wald	Sig	R	Exp (B)
Model 1						
Carotid plaque (b)	–3.6483	2.3729	2.3638	0.1242	–0.0560	0.0260
Model 2						
IMT	7.8666	3.5458	4.9220	0.0265	0.2424	2608.6945
VI	–6.4902	3.1663	4.2015	0.0404	–0.2104	0.0015

Model 1 for variables related to total events, Model 2 for variables related to mortality. Variables IMT and VI are presented by mean value; IMT — intima media thickness; VI — viability index

two subgroups. Obtained values of SNS and fixed defects differ in the two subgroups as well. The most significant difference was found between the viability index values between the two groups.

Univariate analysis of variables that influence future events, presented with predictive value: EF < 40 (score = 4.2215, p = 0.0399), IMT > 0.8 (score = 6.5116, p = 0.0107), VI (score = = 4.8380, p = 0.0278) and the presence of bilateral carotid plaques (score = 7.0000, p = 0.0082) were determined. Results of univariate analysis are summarized in table 4, model 1. The presence of bilateral carotid plaques emerged in the multivariate model, but did not show any significant value, as shown in Table 5.

Model 2 was built to define predictors of mortality. CCA IMT by univariate analysis was presented with score = 4.5886, p = = 0.0322 and viability index with score = 4.3079, p = 0.0379. These variables: CCA IMT (OR: 2608.6945, p = 0.0265, 95% CI: 2.5016 to 27.2038 10^5) and viability index (OR: 0.0015, p = 0.0404, 95%: CI: 0.063 10^{-6} to 0.7525), stepped into the multivariate model and performed independent predictive values (Table 5). Viability index has been found as a predictor of cardiac events (OR: 3.471 10^{-05} 95% CI: 7.177 10^{-8} to 0.0168), and IMT as a predictor of cerebrovascular events (OR: 6673.7442, 95% CI: 3.9686 to 1122.2732 10^4).

Discussion

Preoperative assessment of coronary artery by-pass patients is not a simple task. There have been many studies addressing this question and many attempts to build an ideal preoperative risk model [12–15]. Preoperative determination of myocardial viability and left ventricular ejection fraction with myocardial Gated SPECT has prognostic value for new events, determined by our study's univariate analysis.

The detection of viable myocardium has become of great clinical importance, due to the major prognostic role and therapeutic implications of myocardial viability [4]. Clinically it is very important to perform proper preoperative patient selection, aimed at achieving postoperative benefits, left ventricular functional and clinical improvements [19–23]. The functional assessment of hibernation myocardium and the presence of viability are clinically challenging and have paramount importance for the selection of the most appropriate individual treatment for patients with chronic severe LV dysfunction [20]. Hibernated myocardium needs to be revascularized soon after its evaluation, and it needs time to recover. It is estimated that there is a need of 25–30% of viable jeopardized myocardium before revascularization in order to achieve post revascularization left ventricular functional recovery. Revascularization of viable myocardium also decreases the risk of further LV deterioration and remodelling as well as eliminating anginal symptoms, diminishing the risk of malignant arrhythmias and the risk of sudden cardiac death.

Previous studies have demonstrated the prognostic role of IMT in patients with coronary artery disease who underwent percutaneous revascularization or surgical revascularization [10, 11]. A summary of the relation of IMT and prognosis in pts with CAD presents CCA IMT with independent relative risk for both coronary and cerebrovascular events [30]. No previous study has analysed the role of IMT in clinical outcome of pts after coronary surgical revascularization, or the preoperative predictive value of both variables: myocardial perfusion imaging findings and common carotid artery intima-media thickness (CCA IMT) in patients with coronary artery disease, in relation to mortality rate. According to our data, the value of IMT for predicting total cardiovascular events after coronary surgery is small. Using increased IMT $\geq$ 0.8 mm as a parameter in univariate analysis facilitates its predictive ability. Increased IMT indicated a worse outcome in the postrevascularization period. Some authors reported carotid plaques to be very important for coronary artery disease outcome [12–14]. In our study, the predictive value of bilateral carotid plaques was only presented by univariate analysis. Patients with bilateral carotid plaques were significantly more likely to suffer cardiovascular events compared to patients with unilateral plaque, or without plaque.

Annual mortality rates in our population were 8.8%. This value is higher than in randomised studies that evaluated revascularization benefits in ischemic heart disease [24–26]. Such a high mortality is attributed to a higher prevalence of poor prognostic factors in our patients compared to other studies, a history of previous myocardial infarction in 74.6% of patients and significantly impaired ventricular function in more than a half of them. More recently reported postoperative mortality rates in highly selected patients were 6.6%, presumably as a result of advances in the identification of hibernating myocardium and improvements in surgical and myocardial protection techniques [16, 22, 23]. Nevertheless, the enthusiasm of surgeons to perform high-risk surgery may dampen unless non-risk stratified surgical results are used as key performance indicators.

The only variables with independent predictive values for mortality, shown in our multivariate analysis, were IMT and viability index. In view of our results, our study has confirmed that viability and survival in revascularized patients is clear and unquestionable. The presence of viability alone is not that important, but rather it is the reperfusion of viable myocardium which matters. Low ejection fraction is an important marker of risk modelling and is not a contraindication for surgery, providing that the large areas of viability are identified, since ejection fraction is a functional parameter, not simply a number. The average value of viability index in event free patients in our study was 0.78. Mean VI in patients with cardiovascular events was 0.71. Our study showed a statistically significant difference between the percentage of fixed perfusion defects and in patients with and without cardiovascular events. Viability index has high negative predictive value for cardiovascular events (NPV 0.15% fold risk for cardiac death). The higher value of viability index before revascularization predicts better post revascularization outcome. The importance of assessing viability with regard to predicting and improving clinical outcome after revascularization was reported by Pagley [27]. A viability index based on image findings from this study was significantly related to 3-year event free mortality survival, independent of other variables including left ventricular ejection fraction. Thus, preoperative assessment of myocardial viability, expressed by viability index is highly valuable for identifying patients who are more likely to benefit from bypass grafting. Our results showed that patients with the least amount of viable myocardium and large areas of fibroses tissue did very poorly in spite of revascularization with 8.8% dying within one year. A recent meta-analysis found an annual mortality of 7.7% in revascularized patients with limited viability [28, 29].

There are many studies in the literature dealing with myocardial viability assessment and postoperative recovery of LV function as well us follow up of the cardiac events [31]. The Allman's meta-analysis showed that in patients with predominant viability revascularization was associated with 80% reduction in annual mortality rate [28]. The decision to revascularize must balance the risk of myocardial damage and the benefit of revascularizing hibernated segments [19, 20]. Although now we have the opportunity to detect viable myocardium with reasonable accuracy, controlled studies of the effects of revisualization of patients with viable myocardium are still a clinical challenge and are quite rare.

Measurement of CCA IMT value responds to coronary patients own risk factor burden [30]. On our study CCA IMT mean value CCA IMT is closely related to cerebrovascular events and contributes significantly to prediction of cardiovascular death in coronary artery bypass patients in the post revascularization intermediate period. Therefore it could be suggested as marker for global cardiovascular risk stratification in these patients.

Study limitations

This study with one-year follow up does not cover a large population group. Overestimation of myocardial viability by perfusion scintigraphy could not be excluded. It relates to several factors: first, scintigraphy may detect islands of vital myocardial cells of inadequate size to revel left ventricular dysfunction despite successful revascularization, or second, functional recovery sometimes takes a longer time if the degree of structural myocardial changes is very advanced. Observers were not blinded to the angiographic and myocardial perfusion results. But there was not any inter-observer disagreement with regard to perfusion image interpretation and between the cath lab operator and the supervisor of the lab. Using variables as carotid plaque surface or volume, with 3D ultrasound might be a more sensitive marker for prognosis. Follow up myocardial perfusion study was not included in our study. We did not find statistically significant early events, nor was it the goal of our study. We can not exclude graft occlusion as the cause of cardiovascular events in our patients.

Conclusions

Our results indicate that myocardial perfusion viability index and common carotid artery intima-media thickness are predictors, independently associated with prognosis of patients referred for CABG, according to this study's newly made model, not assessed in previous studies. Application of these methods: carotid ultrasound and myocardial perfusion scintigraphy, has an important and additional clinical usefulness in the risk assessment approach of coronary artery bypass patients.

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