Additive Prognostic Value of Coronary Flow Reserve in Patients With Chest Pain Syndrome and Normal or Near-Normal Coronary Arteries

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In patients with angiographically normal coronary arteries and chest pain, pharmacologic stress echocardiography can identify a subgroup of patients with a less benign prognosis. Coronary flow reserve (CFR) in the left anterior descending artery (LAD) can currently be combined with wall motion analysis during vasodilator stress echocardiography. The aim of this study was to assess the prognostic value of CFR response in patients with normal coronary arteries and normal wall motion during stress. We selected 394 patients (171 men, 61 ± 11 years of age) who underwent dipyridamole stress echocardiography (0.84 mg/kg over 6 minutes) with 2-dimensional echocardiography and CFR evaluation of the LAD by Doppler. All had angiographically nonsignificant (<50% quantitatively assessed) stenosis in any major vessel, normal left ventricular function (wall motion score index 1), and test negativity for conventional wall motion criteria. Images were independently read by a core laboratory for wall motion and a core laboratory for CFR. Mean CFR was 2.5 ± 0.6 and 87 patients (22%) had an abnormal CFR <2. During a median follow-up of 51 months, 31 events occurred, namely 4 deaths and 27 nonfatal myocardial infarctions (3 ST-elevated myocardial infarctions and 24 non–ST-elevated myocardial infarctions). Kaplan-Meier survival estimates for hard events showed a better outcome for those patients with a normal CFR compared with those with an abnormal CFR (96% vs 55%, p = 0.001, at 48 months of follow-up). In conclusion, in patients with angiographically normal or near-normal coronary arteries and preserved at-rest regional and global left ventricular function at baseline and during stress, CFR adds incremental value to the prognostic stratification achieved with clinical and angiographic data. © 2009 Elsevier Inc. (Am J Cardiol 2009; 103:626–631)

It has been demonstrated that, in patients with angiographically normal coronary arteries and chest pain, pharmacologic stress echocardiography can identify a subgroup of patients with a less benign prognosis. Coronary flow reserve (CFR) evaluated by pulse Doppler echocardiography associated with vasodilatory stress has recently entered the stress echocardiographic laboratory. The combination of conventional, wall motion analysis with 2-dimensional echocardiography and CFR with pulse Doppler flowmetry of the mid-distal left anterior descending artery (LAD) has been proved to provide an additive and complementary power of prognostication in patients with known or suspected coronary artery disease (CAD). A decreased CFR is an additional parameter of severity of ischemia in the risk stratification of the stress echocardiographic response, whereas patients with a negative test result for wall motion criteria and normal CFR have a favorable outcome during dipyridamole stress echocardiography. CFR provides independent prognostic information also in diabetic and non diabetic patients with known or suspected CAD and negative dipyridamole stress echocardiographic result for wall motion criteria. The aim of the present study was to assess the prognostic value of CFR response in patients with normal coronary arteries and normal wall motion during stress.

Methods

From the Echo Persantine International Cooperative Study (EPIC) databank from 2002 to 2007, 610 patients were selected according to the following criteria: history of chest pain, dipyridamole echocardiographic test (0.84 mg/kg over 6 minutes) performed before (within 15 days) coronary angiography, and coronary angiogram showing absent or nonsignificant (<50% quantitatively assessed) stenosis in any major vessel or secondary branch. Of this initial population, 216 patients were excluded because 82 underwent a previous revascularization, 99 had a wall motion score index >1, 29 had a positive test result for wall motion criteria, and 6 were lost to follow-up. Thus, the study group consisted of 394 patients (171 men, mean age 61 ± 11 years). According to individual needs and physicians’ choices, 221
patients were evaluated after antianginal drugs had been discontinued and 173 patients were evaluated during antianginal treatment (nitrates and/or calcium antagonists and/or β blockers). The subset of patients on β-blocking agents used the highest tolerated dose of metoprolol or atenolol. Coronary angiography and dipyridamole stress echocardiography were separately and independently performed and analyzed by cardiologists unaware of the results of the other tests. Stress echocardiographic data were collected and analyzed by stress echocardiographers not involved in patient care.

Data are entered into the databank at the time of testing on the same day of test performance. Follow-up information on outcome is updated by a dedicated team of technicians supervised by physicians not involved in patient care. Physicians responsible for updating the follow-up information were unaware of stress echocardiographic and coronary angiographic data. The study was approved by the institutional review board. All patients gave their written informed consent when they underwent stress echocardiography and coronary angiography. The decision to perform coronary angiography in the face of a negative stress echocardiographic test result was taken by the referral physicians on the basis of the clinical picture. All patients were followed-up for a median of 51 months (first quartile 27, third quartile 74) with a minimum predefined follow-up time of 3 months.

Transthoracic stress echocardiographic studies were performed with commercially available ultrasound machines (Sonos 7500, and ie33, Philips Ultrasound, Andover, Massachusetts; Sequoia C256, Acuson Siemens, Mountain View, California; Vivid System 7, GE/Vingmed, Milwaukee, Wisconsin) equipped with multifrequency phased-array sector scan probes (S1 to S8 or V3 to V7) and with second harmonic technology. All standard echocardiographic views were obtained when possible, i.e., parasternal long- and short-axis, apical 2-, 3-, and 4-chamber, and substandard views. In addition to classic projections for stress echocardiographic testing, specific projection for LAD imaging is integrated into the cardiac imaging sequence. Two-dimensional echocardiography and 12-lead electrocardiographic monitoring were performed in combination with high-dose dipyridamole (up to 0.84 mg over 6 minutes) in 125 patients (32% of total population). Coronary angiography in multiple views was performed according to standard Judkins and Sones techniques. At least 5 views (including 2 orthogonal views) were acquired for the left coronary arteries and ≥2 orthogonal views for the right coronary arteries, respectively. Additional appropriate projections were obtained in case of superimposition of side branches or foreshortening of the segment of interest. All angiograms were visually evaluated by 2 independent observers who identified stenotic segments and scored control arteries as smooth or irregular. All stenotic segments were evaluated by an automated edge-detection system (GE Healthcare) providing percent stenosis diameter.

Follow-up data were obtained from ≥1 of 4 sources: review of a patient’s hospital record, personal communication with a patient’s physician and review of a patient’s chart, a telephone interview with a patient conducted by trained personnel, and/or a staff physician visiting a patient at regular intervals in the outpatient clinic. According to study protocol follow-up information was obtained every 3 months. Events were defined as death or nonfatal acute coronary syndromes. In patients who died in the hospital or at home, cause of death was elucidated from the medical record, the family, and the local physician who signed the death certificate. The definition of cardiac death required documentation of significant arrhythmias and/or cardiac arrest or death attributable to congestive heart failure or myocardial infarction in the absence of any other precipitating factors. In case of deaths out of hospital for which no autopsy was performed, sudden unexpected death was attributed to a cardiac cause. To avoid misclassification of
cause of death,10 overall mortality was considered. The definition of nonfatal acute coronary syndromes included ST-elevation myocardial infarction (STEMI) or non-STEMI (NSTEMI). STEMI was defined by typical symptoms, ST elevation on electrocardiogram, and cardiac enzyme changes. NSTEMI was an acute coronary syndrome causing typical chest pain, cardiac enzyme increase, and/or electrocardiographic modifications consistent with acute ischemia11 requiring hospitalization. Follow-up data were analyzed for prediction of death, STEMI, or NSTEMI.

Therefore the outcome events were all-cause death (defined as cardiac and noncardiac death) for survival and hard events (death and nonfatal MI [STEMI or NSTEMI]) for infarction-free survival. When $>1$ of these events occurred, the patient was censored at the time of the most severe event.

Statistical analyses included descriptive statistics (frequency and percentage for categorical variables and mean ± SD for continuous variables) and Kaplan-Meier survival curves. The individual effect of certain variables on event-free survival was evaluated with the use of a Cox regression model. The individual effect of a certain variable on event-free survival was evaluated with the use of a Cox regression model. The individual effect of certain variables on event-free survival was evaluated with the use of a Cox regression model. The individual effect of certain variables on event-free survival was evaluated with the use of a Cox regression model. The individual effect of certain variables on event-free survival was evaluated with the use of a Cox regression model. The individual effect of certain variables on event-free survival was evaluated with the use of a Cox regression model.

Table 1  
At-rest and stress findings in study population

<table>
<thead>
<tr>
<th>Variable</th>
<th>CFR &gt;2 (n = 307)</th>
<th>CFR &lt;2 (n = 87)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>60 ± 11</td>
<td>65 ± 9</td>
<td>0.000</td>
</tr>
<tr>
<td>Men/women</td>
<td>139/168</td>
<td>32/55</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking habit</td>
<td>98 (32%)</td>
<td>22 (25%)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension</td>
<td>176 (57%)</td>
<td>62 (71%)</td>
<td>0.025</td>
</tr>
<tr>
<td>Diabetes</td>
<td>55 (18%)</td>
<td>14 (16%)</td>
<td>NS</td>
</tr>
<tr>
<td>Left bundle branch block</td>
<td>16 (5%)</td>
<td>4 (5%)</td>
<td>NS</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>59 ± 5</td>
<td>59 ± 5</td>
<td>NS</td>
</tr>
<tr>
<td>CFR in LAD</td>
<td>2.7 ± 0.5</td>
<td>1.8 ± 0.1</td>
<td>0.000</td>
</tr>
<tr>
<td>Test performed during antanginal therapy</td>
<td>122 (40%)</td>
<td>51 (59%)</td>
<td>0.002</td>
</tr>
<tr>
<td>β-blocking agents</td>
<td>73 (24%)</td>
<td>34 (39%)</td>
<td>0.006</td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td>69 (22%)</td>
<td>27 (31%)</td>
<td>NS</td>
</tr>
<tr>
<td>Long-acting nitrates</td>
<td>25 (8%)</td>
<td>14 (16%)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Results

The main clinical and echocardiographic data are presented in Table 1.

By selection all patients had a normal regional and global left ventricular function (wall motion score index 1). Mean CFR value was 2.5 ± 0.6. At individual patient analysis, 307 patients had normal CFR (>2.0) and 87 had abnormal CFR in the LAD. Of the 87 patients with abnormal CFR, 51 were under anti-ischemic medical therapy (59%) as were 122 (40%) of those with normal CFR. Patients with abnormal CFR had a higher incidence of arterial hypertension (71% vs 57%, p = 0.025). CFR was significantly lower in patients with left ventricular hypertrophy compared with those without (2.6 ± 0.6 vs 2.3 ± 0.4, p <0.001). Left ventricular mass index was not a significant parameter when entered in the Cox model (HR 0.9, 95% CI 0.9 to 1.0, p = 0.4).

All patients had “nonsignificant” CAD by selection. However, 282 patients had completely normal, smooth coronary arteries; 28 had “mild” (0% to 20% diameter stenosis, mean 19 ± 2.6) irregularities of $\geq 1$ vessel; 76 had “moderate” (20% to 40% diameter stenosis, mean 34 ± 5) irregularities. CFR was normal in 229 of 282 patients (81%) with totally normal coronary arteries and in 78 of 112 (69%) with near-normal coronary arteries (showing $\geq 1$ of the previously described abnormalities). Mean CFRs in the LAD were 2.6 ± 0.6 in subjects with normal coronary arteries, 2.6 ± 0.6 in subjects with mild abnormalities, and 2.2 ± 0.5 in subjects with moderate abnormalities (p = 0.000, normal coronary arteries vs mild and vs moderate abnormalities). Patients with coronary irregularities were older (65 ± 10 vs 59 ± 12 years, p = 0.005) than patients with completely normal coronary arteries and smoking habit was significantly greater (40% vs 26%, p = 0.011).

During a median follow-up of 51 months (first quartile 27, third quartile 74), a total of 31 (7.8%) events (4 deaths and 27 nonfatal MIs [3 STEMIs and 24 NSTEMIs]) occurred. Considering hard events, there were 6 events in patients with normal CFR versus 25 events in patients with abnormal CFR (1.9% vs 28.7%, p = 0.000). Patients with
coronary irregularities in the LAD did not have a significantly higher event rate than patients with irregularities in another territory (9% vs 7.5%, p = 0.6). Univariable predictors of hard events were hypertension (HR 2.9, 95% CI 1.2 to 7.2) and abnormal CFR (HR 16.7, 95% CI 6.7 to 40.2). Using the Cox proportional hazards model including 6 clinically significant parameters (age, gender, cardiovascular risk factors, left ventricular MI, coronary irregularities at angiography, and aspirin use), only hypertension was an independent predictor of outcome (HR 3.4, 95% CI 1.3 to 8.7); when CFR was included in the model, it remained the sole independent predictor of hard events (HR 16.4, 95% CI 6.7 to 40.2). Kaplan-Meier survival estimates for hard events showed a better outcome for those patients with normal CFR compared with those with abnormal CFR (96% vs 55%, p = 0.001, at 48 months of follow-up; Figure 1). Kaplan-Meier survival estimates for hard events showed no difference of outcome in patients with normal coronary arteries compared with those with irregularities (84% vs 87%, p = 0.4, at 48 months of follow-up; Figure 2).

**Discussion**

In patients with angiographically normal or near-normal coronary arteries and preserved at-rest regional and global left ventricular function at baseline and during stress, CFR adds incremental value to the prognostic stratification achieved with clinical and angiographic data.

In the absence of CAD, CFR can be decreased in microvascular disease (e.g., in syndrome X, arterial hypertension, diabetes, and/or left ventricular hypertrophy), which may perse decrease CFR independently of microvascular damage. In this condition, angina with ST-segment depression can occur with regional perfusion changes, typically in the absence of any regional wall motion abnormalities during stress. Milder forms of decrease in regional CFR and/or abnormal coronary microcirculatory function may occur in patients with angiographically normal coronary arteries and may give rise to a positive perfusion scan result or to a strictly subendocardial decreased perfusion of limited extent to decrease regional CFR but not severe enough and/or transmurally extended to give rise to transient wall motion abnormalities. In more advanced degrees of decrease in CFR, subendocardial underperfusion above the threshold necessary to reach a critical ischemic mass may evoke transient dysynergy, the prerequisite of stress echocardiographic positivity by wall motion criteria. The latter is not the case for the present study in which, by selection, only patients with negative stress echocardiogram by wall motion criteria were investigated.

It is considered that chest pain with the angiographic label of “normal coronary arteries” readily identifies a prognostically benign subset. However, there can be substantial morphologic heterogeneity within this cohort, encompassing truly normal, smooth coronary arteries and nonsignificant stenoses, which may be mild or moderate, isolated or multiple, in ≥1 vessel. Another important angiographic sign can be coronary calcification, which is known to be associated with more extensive coronary atherosclerosis and worse prognosis. In fact, the subset of patients with minor abnormalities had a lower value of CFR. In a study by Zimmerman et al. no significant difference was found in survival rates in patients with normal arteries and minimal or moderate disease, but the reinfarction rate was higher in those with minimal and moderate disease (11% and 16%, respectively, p = 0.0002) than in patients with angiographically normal arteries. Two recent meta-analyses have shown that patients with chest pain and normal or nonobstructive angiograms are predominantly women, and many have a prognosis that is not as benign as commonly thought; this applies also to patients with non-ST-segment elevation acute coronary syndromes with nonobstructive CAD detected by angiography who have a substantial risk of subsequent coronary events within 1 year. We demonstrated in a previous study that pharmacologic stress echocardiographic positivity in patients with chest pain and angiographically normal or near-normal coronary arteries is associated with a worse long-term survival. The “anatomic lies” of stress echocardiography, i.e., false positive responses occurring in patients with nonsignificant epicardial CAD, can be overturned into “prognostic truth” when long-term outcome is considered. CFR assessed by intracoronary Doppler in normal to mildly diseased arteries has been demonstrated to be an independent predictor of long-term prognosis of atherosclerosis: the subset of pa-
tients in the lowest tertile of CFR had a cardiovascular event. CFR in the LAD provides additional prognostic value over stress echocardiographic results in patients with known or suspected CAD and allows effective risk stratification in different clinical settings, including diabetic patients with negative stress echocardiogram by wall motion criteria. In fact, regional wall motion and CFR provided additive, not redundant, prognostic information. Indeed, coronary endothelial dysfunction, left ventricular hypertrophy, and coronary microcirculatory dysfunction do not normally induce wall motion abnormalities but have been linked to adverse outcome.

CFR was sampled only in the LAD. There is no doubt that the 3-coronary approach would be more fruitful, but currently it remains too technically challenging for a large-scale assessment. It has been demonstrated with several techniques that microcirculatory dysfunction affects the left ventricle globally and regionally, and therefore CFR assessment in the LAD, which would be inadequate for CAD detection, is an excellent option for evaluating global coronary microcirculation conditions in these patients. Doppler assessment of CFR has some limitations. Assessment of absolute blood velocity can be limited in some patients by the large incident angle between the Doppler beam and blood flow. However, calculation of flow reserve allows assessment of flow patterns without the need for absolute values. More importantly, velocity ratio is used as a surrogate of flow reserve: flow within the coronary artery is not calculated because cross-sectional visualization of the vessel does not allow accurate measurement of the diameter of the vessel. Estimated flow reserve can be accurate if the coronary functions only as a conduit, without changing in diameter during drug infusion. This assumption is reasonable with dipyridamole and less valid with dobutamine; this is an additional reason to stress CFR with vasodilators. Our study design was observational, not randomized, and the analysis was retrospective, although the data were acquired in a prospective fashion and entered into the database at the time of initial assessment. Selection criteria included all patients referred for stress echocardiography with subsequent documentation of normal coronary arteries in the same hospital admission. This led to inclusion of patients with different clinical conditions and heterogeneous angiographic patterns.

Abnormal CFR in the LAD and test negativity for wall motion criteria during vasodilator stress testing and normal coronary arteries can identify a subgroup of patients with a less benign prognosis. It is conceivable that these higher-risk patients should be treated more aggressively in terms of lifestyle changes and risk-factor modifications.


