Prognostic Value of Coronary Blood Flow Velocity and Myocardial Perfusion in Intermediate Coronary Narrowings and Multivessel Disease

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OBJECTIVES
This study aimed to investigate the roles of intracoronary derived coronary flow velocity reserve (CFVR) and myocardial perfusion scintigraphy (single photon emission computed tomography, or SPECT) for management of an intermediate lesion in patients with multivessel coronary artery disease.

BACKGROUND
Evaluation of the functional significance of intermediate coronary narrowings (40% to 70% diameter stenosis) is important for clinical decision making and risk stratification.

METHODS
In a prospective, multicenter study, SPECT was performed in 191 patients with stable angina and multivessel disease and scheduled for angioplasty (percutaneous transluminal coronary angioplasty, or PTCA) of a severe coronary narrowing. Coronary flow velocity reserve was determined selectively distal to an intermediate lesion in another artery using a Doppler guidewire. Percutaneous transluminal coronary angioplasty of the intermediate lesion was deferred when SPECT was negative or CFVR ≥2.0. Patients were followed for one year to document major cardiac events (death, infarction, revascularization), related to the intermediate lesion.

RESULTS
Reversible perfusion defects were documented in the area of the intermediate lesion in 30 (16%) patients; CFVR was positive in 46 (24%) patients. Percutaneous transluminal coronary angioplasty of the intermediate lesion was deferred in 182 patients. During follow-up, 19 events occurred (3 myocardial infarctions, 16 revascularizations). Coronary flow velocity reserve was a more accurate predictor of cardiac events than was SPECT; relative risk: CFVR 3.9 (1.7 to 9.1), p < 0.05; SPECT 0.5 (0.1 to 3.2), p = NS. Multivariate analysis revealed CFVR as the only significant predictor for cardiac events.

CONCLUSIONS
Deferral of PTCA of intermediate lesions in multivessel disease is safe when CFVR ≥2.0 (event rate 6%). This selective evaluation of coronary lesion severity during cardiac catheterization allows a more accurate risk stratification than does SPECT, which is important for clinical decision making in this patient cohort. (J Am Coll Cardiol 2002;39: 852–8) © 2002 by the American College of Cardiology Foundation

During the last decade, there has been an enormous growth in the number of percutaneous transluminal coronary angioplasty (PTCA) procedures performed. According to large registries, PTCA is increasingly performed for multivessel coronary artery disease (50% to 70%), including intermediate lesions in approximately 30% of the procedures (1,2). Adequate patient selection for PTCA is of utmost importance in view of the potential procedural complications and the incidence of restenosis (1,2). Angiographic estimates using quantitative coronary angiography have been shown to be poor predictors of its functional significance (3–5). The recommended diagnostic approach in multivessel coronary artery disease involves noninvasive cardiac stress imaging modalities (i.e., echocardiography and myocardial perfusion scintigraphy) to identify the functional significance of coronary lesions (6–11), although these techniques are limited in their ability to allocate wall motion or perfusion defects to the “culprit” lesion.

Recently, intracoronary-derived hemodynamic parameters using sensor-tipped angioplasty guidewires have been introduced as an alternative strategy, allowing selective assessment of functional severity of coronary narrowings (12). Previous validation studies showed good agreement (80% to 90%) between these parameters and the results of noninvasive stress tests (13,14). Intracoronary hemodynamic techniques facilitate decision making during diagnos—
tic cardiac catheterization, allowing performance of ad hoc angioplasty within the same session.

To date, a direct comparison between the noninvasive and invasive tests for clinical decision making regarding intermediate coronary lesions in patients with multivessel coronary artery disease has not been performed. Therefore, the purpose of the study was to compare the value of intracoronary derived coronary flow velocity reserve (CFVR) with myocardial perfusion scintigraphy in the context of clinical decision making in these patients: the Intermediate Lesions: Intracoronary Flow Assessment Versus 99mTc-MIBI SPECT (ILIAS) study.

METHODS

Patient selection. Patients with stable or unstable angina (class 1 to 3 according to the Canadian Cardiovascular Society; CCS or Braunwald’s classification I or II) were screened between April 1997 and October 1999 for study participation in six cardiac intervention centers in the Netherlands. Coronary narrowing severity was determined by visual assessment by a “heart team.” The team consisted of an interventional cardiologist and a cardiac surgeon. Patients with multivessel coronary artery disease, showing one intermediate (defined as 40% to 70% diameter narrowing) and at least one severe coronary narrowing (>70% diameter narrowing) in another artery at diagnostic cardiac catheterization, were selected. Patients were eligible to participate in the study if the severe lesion was accepted for PTCA and if, from a clinical point of view, no definite strategy was formulated for the intermediate lesion. Exclusion criteria were as follows: patients with unstable angina (according to Braunwald’s classification III), factors precluding dipyridamole infusion and/or assessment of intracoronary flow velocity, factors influencing coronary hemodynamic parameters (e.g., left ventricular hypertrophy, insulin dependent diabetes, previous myocardial infarction in the area of interest, previous PTCA or coronary bypass grafting of the segment of interest, significant left main coronary artery stenosis). The protocol was approved by the Institutional Review Boards of the participating institutions; all patients gave written informed consent.

Study design. Patients were screened when the results of the diagnostic cardiac catheterization were reviewed by the heart team; inclusion and exclusion were verified. All patients underwent single photon emission computed tomography (SPECT) imaging for noninvasive assessment of functional severity of the intermediate lesion. A SPECT was defined negative if no reversible perfusion defect was determined in the area of the intermediate lesion. For the purpose of this study, a negative SPECT includes normal perfusion, reversible perfusion defects not allocated to the area of interest and persistent defects.

Percutaneous transluminal coronary angioplasty of the severe lesion was scheduled within one week after SPECT. Coronary angiography was performed using the percutaneous femoral approach. During this procedure, CFVR measurements were performed distal to the intermediate lesion to determine its functional severity. A CFVR of ≥2.0 was considered negative (12,15,16). Coronary lesion severity was measured off line by quantitative coronary angiography (QCA), using the CMS-QCA software version 3.32 (MEDIS, Leiden, Netherlands), as previously described (17). The intermediate lesion was treated with PTCA if both SPECT and CFVR were positive. Otherwise, the intermediate lesion was left untreated. The cardiac catheterization procedure was completed by performing PTCA of the severe lesion.

Clinical follow-up was performed at 3, 6 and 12 months. In the event of persistent or recurrent anginal complaints, SPECT imaging was repeated. CFVR was measured again when repeat coronary angiography was performed. The protocol warranted a (repeat) PTCA of the intermediate lesion or coronary artery bypass grafting during follow-up if angina was related to the intermediate lesion as determined by a positive SPECT or a positive CFVR (i.e., CFVR < 2.0).

Single photon emission computed tomography (SPECT). Single photon emission computed tomography was performed using 99mTc-technetium-sestamibi, according to a two-day stress/rest standard protocol, as previously described (18). Dipyridamole (0.56 mg/kg intravenously during 4 min) was used as a hyperemic agent. Data acquisition and reconstruction were performed according to the procedure guideline for myocardial perfusion imaging of the Society of Nuclear Medicine (19). Briefly, SPECT acquisition was performed with a three-headed gamma camera equipped with low-energy, high-resolution collimators. Images were reconstructed using filtered back projection; no attenuation correction was used.

An expert panel of nuclear medicine physicians, blinded to the angiographic data, evaluated the scintigraphic images. Perfusion defect severity was classified as dubious, mild, moderate or severe. Improvement at rest of more than one grade was considered to be a reversible perfusion defect. Improvement of just one grade or no improvement was considered to be a persistent perfusion defect. The result was considered positive when a reversible defect was allocated to the perfusion territory of the coronary artery of...
interest. Defects located in the anterior wall and septal region were allocated to the left anterior descending artery (LAD), defects in the lateral wall to the left circumflex coronary artery (LCx) and inferior defects to the right coronary artery (RCA). Apical defects were considered to be located in the LAD region unless the defect extended to the lateral (LCx) or inferior (RCA) wall. In the watershed regions, the extension of a defect to either anterior wall (LAD), lateral wall (LCx) or inferior wall (RCA) was decisive for allocation to the vascular bed of a coronary artery.

Coronary flow velocity reserve (CFVR) measurements. Flow velocity was measured with a 0.014-inch Doppler guidewire (FloWire, Endosonics, Rancho Cordova, California). This wire was advanced distal to the coronary narrowing. Distal flow velocity data at baseline and during hyperemia (induced by an intracoronary bolus of adenosine, 15 μg in the right coronary artery and 20 μg in the left coronary artery) were obtained; Doppler signals were processed by real-time spectral analysis (20). The operator was not aware of the results of the SPECT at the time of the intracoronary measurements. Coronary flow velocity reserve was computed as the ratio of hyperemic/basal average peak blood flow velocity (21). Coronary flow velocity reserve values were prospectively categorized according to the previous established cut-off value of 2.0 (12,15,16).

Outcome events. The primary outcome was defined as the occurrence of one of the following events, related to the intermediate lesion, during one year of follow-up: cardiac death, myocardial infarction (defined as a total creatine kinase concentration of more than twice the upper limit and/or documented ST elevation or new Q-waves in at least two electrocardiographic leads), or (repeat) PTCA of the intermediate lesion or coronary artery bypass grafting. An independent Critical Event Committee assigned the events to the intermediate or the severe lesion, using all available clinical and angiographical data but blinded to the initial results of CFVR and SPECT. Moreover, they indicated if these events were ischemia driven (i.e., objective evidence that is predictive for a coronary narrowing causing myocardial ischemia).

Data analysis. Patients were included in the final analysis if results of both SPECT and CFVR were available for the intermediate lesion. Based on these results, four groups were identified: (A) both SPECT and CFVR negative, (B) SPECT negative, CFVR positive, (C) SPECT positive and CFVR negative and (D) both SPECT and CFVR positive. Primary outcome event rates for the dichotomized results of SPECT and CFVR were calculated separately for those patients in whom a PTCA was deferred based on the protocol (groups A, B and C), including relative risks and 95% confidence intervals (CI).

Univariate analysis was performed on relevant clinical, angiographic and scintigraphic data for prediction of primary outcome events. Multivariate backward stepwise logistic regression analysis was performed for the prediction of the primary outcome event (model 1), using those parameters that revealed a p < 0.1 with univariate analysis. Continuous variables were dichotomized on their median. Subsequently, the dichotomized results of CFVR (model 2) were added to model 1, and the predictive value of these two models were compared using the chi-square statistic.

RESULTS

A total of 201 patients gave informed consent; 10 patients were excluded from analysis because results of SPECT or CFVR were not available for various reasons. Thus, 191 patients were evaluated according to the study protocol (Table 1). The intermediate lesion was located in the RCA in 20%, LAD in 47%, and LCx in 33%. The mean percentage diameter stenosis on QCA was 54% (range 34% to 74%) for the intermediate lesions and 79% (range 50% to 99%) for the severe lesions.

Single photon emission computed tomography showed one or more reversible perfusion defects in 157 patients (82%) and persistent defects in 67 patients (35%). More specifically, in 30 patients (16%), a reversible perfusion defect was allocated to the region of the intermediate lesion by the panel of nuclear medicine physicians; no persistent perfusion defects were present in these regions. A reversible defect was allocated to the initial severe lesion in 153 (80%) of the patients.

In total, 46 patients (24%) had a CFVR < 2.0 in the coronary artery with the intermediate lesion. In total, 124 patients entered group A, 37 group B, 21 group C and 9 group D. Thus, discordant results between SPECT and CFVR concerning the intermediate lesion were observed in 58 (groups B and C) of the 191 patients (30% disagreement; kappa 0.058, p = 0.41). A PTCA of the intermediate lesion was performed in 9 (group D) and deferred in 182 (groups A, B and C) patients, according to the study protocol.
Table 2. Overview of Patients With Events Related to the Intermediate Lesion During One Year Follow-Up

<table>
<thead>
<tr>
<th>Artery With IM</th>
<th>SPECT</th>
<th>CFVR</th>
<th>Event</th>
<th>Days to Event</th>
<th>SPECT</th>
<th>CFVR</th>
<th>Ischemia Driven</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAD</td>
<td>–</td>
<td>+</td>
<td>PTCA</td>
<td>10</td>
<td>NA</td>
<td>+</td>
<td>Yes</td>
<td>UAP; Echo: wall motion abnormalities apex and septum; CAG: no significant lesions in RCA and LCx.</td>
</tr>
<tr>
<td>LCx</td>
<td>–</td>
<td>+</td>
<td>PTCA</td>
<td>37</td>
<td>–</td>
<td>+</td>
<td>Yes</td>
<td>PTCA performed following period of UAP with ST depression in leads V1-V4.</td>
</tr>
<tr>
<td>LAD</td>
<td>–</td>
<td>–</td>
<td>PTCA</td>
<td>74</td>
<td>NA</td>
<td>NA</td>
<td>Yes</td>
<td>PTCA performed based on clinical and angiographic data only (in another hospital).</td>
</tr>
<tr>
<td>LCx</td>
<td>–</td>
<td>+</td>
<td>PTCA</td>
<td>98</td>
<td>+</td>
<td>–</td>
<td>Yes</td>
<td>Patient refused SPECT; X-ECG was positive (ST depression in leads V3-V4).</td>
</tr>
<tr>
<td>RCA</td>
<td>–</td>
<td>–</td>
<td>PTCA</td>
<td>119</td>
<td>–</td>
<td>+</td>
<td>Yes</td>
<td>Inferior MI (Q), objectified by ECG changes</td>
</tr>
<tr>
<td>LAD</td>
<td>+</td>
<td>–</td>
<td>PTCA</td>
<td>170</td>
<td>–</td>
<td>+</td>
<td>Yes</td>
<td>Inferior MI (non-Q), objectified by ECG changes</td>
</tr>
<tr>
<td>LAD</td>
<td>–</td>
<td>–</td>
<td>PTCA</td>
<td>179</td>
<td>–</td>
<td>+</td>
<td>Yes</td>
<td>CAG: thrombus in RCA</td>
</tr>
<tr>
<td>LAD</td>
<td>–</td>
<td>+</td>
<td>PTCA</td>
<td>198</td>
<td>NA</td>
<td>NA</td>
<td>Yes</td>
<td>X-ECG was positive, without specification</td>
</tr>
<tr>
<td>RCA</td>
<td>–</td>
<td>37</td>
<td>MI</td>
<td>270</td>
<td>+</td>
<td>+</td>
<td>Yes</td>
<td>Inferior MI (Q), objectified by ECG changes</td>
</tr>
<tr>
<td>LAD</td>
<td>–</td>
<td>156</td>
<td>NA</td>
<td>324</td>
<td>NA</td>
<td>NA</td>
<td>No</td>
<td>CAG: no significant lesions in LAD and RCA; CAG: after failure of PTCA LCx (mainstem dissection)</td>
</tr>
<tr>
<td>RCA</td>
<td>–</td>
<td>156</td>
<td>MI</td>
<td>190</td>
<td>NA</td>
<td>NA</td>
<td>?</td>
<td>Inferior MI (Q), objectified by ECG changes</td>
</tr>
<tr>
<td>LAD</td>
<td>+</td>
<td>190</td>
<td>CABG</td>
<td>207</td>
<td>+</td>
<td>+</td>
<td>Yes</td>
<td>Inferior MI (non-Q), objectified by ECG changes</td>
</tr>
<tr>
<td>LAD</td>
<td>–</td>
<td>207</td>
<td>CABG</td>
<td>156</td>
<td>NA</td>
<td>NA</td>
<td>?</td>
<td>CAG: thrombus in RCA</td>
</tr>
<tr>
<td>LAD</td>
<td>–</td>
<td>156</td>
<td>MI</td>
<td>297</td>
<td>NA</td>
<td>NA</td>
<td>Yes</td>
<td>Inferior MI (Q), objectified by ECG changes</td>
</tr>
</tbody>
</table>

Univariate analysis showed that gender, age, percentage diameter stenosis on QCA, positive family history for cardiac disease and CFVR (cut-off value 2.0) were significant predictors (p < 0.1) of primary outcome events. For other geometric parameters measured with QCA (percentage area stenosis, minimal lumen diameter and reference area of interest; CFVR = coronary flow velocity reserve; CI = confidence interval; RR = relative risk; SPECT = single photon emission computed tomography.

Table 3. Primary Outcome Events Related to the Intermediate Lesion Presented for the Dichotomized Results of CFVR and SPECT for Patients in Whom a PTCA Was Deferred and Follow-Up Was Available (Groups A, B and C; n = 180)

<table>
<thead>
<tr>
<th>CFVR</th>
<th>Events (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative (CFVR ≥2.0)</td>
<td>143</td>
<td>9 (6.3%)</td>
</tr>
<tr>
<td>Positive (CFVR &lt;2.0)</td>
<td>37</td>
<td>9 (24.3%)</td>
</tr>
<tr>
<td>RR</td>
<td>3.9*</td>
<td>1.7–9.1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SPECT</th>
<th>Events (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative (no reversible perfusion defect in AOI)</td>
<td>159</td>
<td>17 (10.7%)</td>
</tr>
<tr>
<td>Positive (reversible perfusion defect in AOI)</td>
<td>21</td>
<td>1 (4.8%)</td>
</tr>
<tr>
<td>RR</td>
<td>0.5*</td>
<td>0.1–3.2</td>
</tr>
</tbody>
</table>

*p < 0.05 between both RRs.

AOI = area of interest; CFVR = coronary flow velocity reserve; CI = confidence interval; RR = relative risk; SPECT = single photon emission computed tomography.

Outcome events. No follow-up was available for two patients (both group A). These patients were excluded from further analysis. During the one year of follow-up, 59 cardiac events occurred. Cardiac deaths did not occur. The Critical Event Committee assigned 19 of these 59 events to the intermediate lesion (primary outcome): 3 myocardial infarctions, 3 coronary artery bypass grafting and 13 PTCA procedures. In total, 8 (6%) events occurred in group A, 9 (24%) in group B, 1 (5%) in group C, and 1 (11%) in group D. The Critical Event Committee considered objective evidence that is predictive for a coronary narrowing causing myocardial ischemia present in 13 of the 16 revascularizations (81%) (Table 2). There was uncertainty regarding this evidence in two patients; it was absent in one patient.

Primary outcome event rates for patients with positive and negative test results of SPECT versus positive and negative test results of CFVR were determined separately for the 180 patients of group A, B and C (Table 3). The relative risk for the primary outcome event of a positive CFVR was 3.9 (95% CI: 1.7 to 9.1; p < 0.05). In contrast, the relative risk of a positive SPECT was 0.5 (95% CI: 0.1 to 3.2; p = NS). These relative risks were statistically significantly different (p < 0.05).
Table 4. Results of 2 Multivariate Logistic Regression Models for Prediction of Primary Outcome Events, Using the 180 Patients (Groups A, B and C) in Whom a PTCA of the Intermediate Lesion was Deferred and Follow-Up Was Available

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Model 1 (Chi-Square = 8.412)</th>
<th>Model 2* (Chi-Square = 14.304)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>0.41</td>
<td>0.15–1.15</td>
</tr>
<tr>
<td>Family history</td>
<td>2.51</td>
<td>0.76–8.35</td>
</tr>
<tr>
<td>% DS &gt;55 on QCA</td>
<td>2.13</td>
<td>0.77–5.88</td>
</tr>
<tr>
<td>CFVR &lt;2.0</td>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>

Model 1 is based on clinical, angiographic and scintigraphic data; in Model 2, the value of CFVR is added to model 1.

*Model 2 (including CFVR) versus Model 1: p = 0.013 (see text). *p < 0.05

Medium = coronary flow velocity reserve; CI = confidence interval; DS = diameter stenosis; OR = odds ratio (for the presence of the parameter); QCA = quantitative coronary angiography.

diameter), no significant predictive value was detected using univariate analysis. The multivariate models are depicted in Table 4. Coronary flow velocity reserve was the only significant predictor in model 2. Model 2 constituted a statistically significant improvement over model 1 ($\Delta \chi^2 = 5.89$; p = 0.013).

**DISCUSSION**

The present study shows that intracoronary measurement of a Doppler flow velocity parameter (CFVR) is useful for management of an intermediate lesion in multivessel coronary artery disease. Deferral of PTCA based on a cut-off value of CFVR $\geq 2.0$ is safe, as demonstrated by a lower event rate (6%), in contrast to a high event rate in case of a CFVR $<2.0$ (24%; relative risk 3.9); the prognostic value was more accurate for CFVR than it was for SPECT (relative risk 0.5). Measurement of CFVR allows selective evaluation of functional severity of intermediate coronary lesions, which facilitates risk stratification and may help avoid unnecessary coronary interventions.

**CFVR versus SPECT for clinical decision making.** The protocol was designed to compare a standard test (SPECT) with an intracoronary diagnostic technique (CFVR). Within one week, all patients underwent both tests, conforming to the recommendations for study designs for a comparison of two diagnostic tests (22). Patients were already scheduled for a PTCA procedure of a severe lesion; CFVR of the intermediate lesion was measured during the same session.

Extent and severity of perfusion abnormalities on SPECT are the markers for cardiovascular risk (23,24). As expected, severe myocardial perfusion defects were mainly located in the region of the severe lesion, all treated with PTCA. However, this study protocol was designed to separately assess the functional status of multiple stenoses. This required an allocation of the perfusion defects to the severe and intermediate lesion and was scored as positive or negative, which was necessary for the clinical decision to perform or defer PTCA of that particular lesion.

The incidence of cardiac events related to the intermediate lesion was relatively low (19/191, 9.9%). Nevertheless, CFVR had a better predictive value than did SPECT for the occurrence of primary outcome events, predominantly associated with coronary revascularizations, after an expectative strategy (groups A, B and C) for the intermediate lesion (relative risk 3.9 for CFVR 3.9, 0.5 for SPECT; p < 0.05, Table 3). These results suggest that SPECT is less adequate than CFVR for clinical decision making in these patients with multivessel disease, with respect to intermediate coronary lesions. The value of CFVR is also reflected by the results of the multivariate logistic model, showing that CFVR $<2.0$ is the only statistically significant predictor of cardiac events during one year of follow-up (Table 4).

These findings may be explained by the ability of CFVR to help evaluate coronary narrowings selectively, in contrast to SPECT with its inherent limitation to allocate perfusion defects to the culprit lesion in multivessel disease. This may account for the lower concordance (70%) between SPECT and CFVR than reported in previous validation studies, predominantly concerning single vessel disease (80% to 90%) (13,15,16). Moreover, the pressure drop across the intermediate lesion may induce a reduction of flow to collateral dependent vascular territories in a minority of patients, resulting in a larger reversible perfusion defect of the vascular territory of the severe lesion rather than in a separate reversible defect in the area of the intermediate lesion (25).

**Deferral of PTCA.** The aim of risk stratification is to identify patients with a high likelihood of future major cardiac events who may benefit from invasive treatment. The present study showed that deferral of PTCA is safe in patients with CFVR $\geq 2.0$; they had a relatively low event rate of 6% (groups A and C). This contrasts with a 24% event rate, predominantly determined by the need for revascularization, in case of a positive CFVR. Against this, if deferral would have been based solely on negative SPECT (i.e., no reversible perfusion defect in the area of the intermediate lesion), these patients would have experienced a cardiac event rate of 11% (groups A and B), which is higher than would be expected.

For noninvasive stress testing, low event rates (death and nonfatal myocardial infarction) have been described for patients with coronary artery disease, with and without reversible perfusion defects determined by SPECT (4% to
27% and 0% to 5%, respectively) (23,24,26–28). However, the composite endpoint in the present study included clinical and/or ischemia-driven revascularization procedures, next to death and nonfatal myocardial infarction. For invasive diagnostic strategies, safe deferral of PTCA with low event rates (5% to 10%) has also been reported using Doppler flow parameters (29,30). These studies did not include a comparison with standard noninvasive diagnostic techniques for clinical decision making.

Study limitations. The incidence of reversible perfusion defects in the area of the intermediate lesion (16%) and a CFVR <2.0 of this lesion (24%) was relatively low, indicating that patients’ complaints were predominantly determined by the severe coronary narrowing. Consequently, the absolute number of cardiac events related to the intermediate lesion during follow-up was low. Nevertheless, these data showed that a clinically important risk stratification is possible using CFVR with respect to cardiac events in those patients in whom a PTCA was deferred.

Scintigraphic and flow velocity data analysis was performed at the participating centers, instead of at independent core laboratories. Nevertheless, this approach reflects daily practice for clinical decision making in patients with coronary artery disease.

Hyperemia was induced differently in this study for SPECT (dipyridamole) and CFVR (adenosine). However, diagnostic accuracies for adenosine were reported similar to those of dipyridamole for SPECT (31).

It was anticipated that a high number of “hard” events (i.e., myocardial infarction, death) related to the intermediate lesion would not occur during a relatively short follow-up period of 12 months. The “hard” event rate was 1.6%. Therefore, the endpoint consisted predominantly of revascularization procedures (16/19, 84%). The independent Critical Event Committee considered objective evidence that is indicative for myocardial ischemia present in 13 of these 16 revascularizations (81%, Table 2) based on the clinical and angiographic findings, the results of perfusion scintigraphy and/or CFVR measurements. These results indicate that the need for revascularization was not driven by hidden biases of patients and/or physicians.

The results of this study were obtained in a selected cohort of patients with stable angina and multivessel disease as diagnosed during a cardiac catheterization and, therefore, cannot be extrapolated without any reserve to other patient cohorts selected for elective coronary angioplasty.

Clinical implications. It is commonly accepted that diagnostic cardiac catheterization should be preceded by objective evidence that is predictive for a coronary narrowing causing myocardial ischemia. This includes noninvasive stress testing using perfusion scintigraphy in case of nonconclusive electrocardiographic exercise testing. However, the present study showed that the role of SPECT is limited for clinical decision making about intermediate lesions in the presence of multivessel coronary artery disease.

Deferral of PTCA of intermediate lesions in multivessel disease is safe when CFVR is negative. Implementation of CFVR measurements during cardiac catheterization facilitates subsequent PTCA if necessary, which avoids additional scintigraphic testing and repeat cardiac catheterization, reducing patient discomfort and procedural costs. Selective evaluation of coronary lesion severity during cardiac catheterization using CFVR allows risk stratification; it identifies patients who will have a significantly higher event rate, predominantly associated with revascularizations, during follow-up.

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