Intracoronary derived physiological parameters for clinical decision-making in patients with multi-vessel coronary artery disease

Chamuleau, S.A.J.

Citation for published version (APA):
Fractional flow reserve, absolute and relative coronary blood flow velocity reserve in relation to the results of technetium-99m sestamibi single photon emission computed tomography in patients with two-vessel coronary artery disease
ABSTRACT

OBJECTIVES To perform a direct comparison between the results of perfusion scintigraphy and intracoronary derived hemodynamic parameters (fractional flow reserve, FFR; absolute and relative coronary flow velocity reserve, CFVR and rCFVR respectively) in patients with two-vessel disease.

BACKGROUND There is limited information on the diagnostic accuracy of intracoronary derived parameters (CFVR, FFR and rCFVR) in patients with multivessel disease.

METHODS Dipyridamole $^{99}$Tc-MIBI SPECT was performed in 127 patients. Presence of reversible perfusion defects in the region of interest was determined. Within 1 week, angiography was performed; CFVR, rCFVR and FFR were determined in 161 coronary lesions following intracoronary administration of adenosine. The predictive value for the presence of reversible perfusion defects on MIBI SPECT of CFVR, rCFVR and FFR was evaluated by the area under the curve of the receiver-operating-characteristic curves (AUC's).

RESULTS Mean percentage diameter stenosis was 57% (range 35-85%), as measured by quantitative coronary angiography. Using a per-patient analysis, the AUC's for CFVR (0.70±0.052), rCFVR (0.72±0.051) and FFR (0.76±0.050) were not statistically significant different. Agreement with the results of MIBI SPECT was 76%, 78% and 77%, respectively. A per-lesion analysis, using all 161 measured lesions, yielded similar results.

CONCLUSIONS The diagnostic accuracy of three intracoronary derived hemodynamic parameters compared to the results of perfusion scintigraphy is similar in patients with two-vessel coronary artery disease. Cut-off values of 2.0 for CFVR, 0.65 for rCFVR and 0.75 for FFR respectively, can be used for clinical decision making in this patient cohort. Discordant results were obtained in 23% of the cases that requires prospective evaluation for appropriate patient management.
INTRODUCTION

Decisions regarding intracoronary interventions should be based on objective evidence of functional significance of coronary narrowings. Therefore, documentation of myocardial ischemia related to the culprit lesion is important for clinical decision making. Non-invasive diagnostic tests, such as perfusion scintigraphy, are widely applied for evaluation of coronary artery disease. However, perfusion scintigraphy has a limited capability in particular in multivessel disease to assign the perfusion defect to a specific epicardial coronary narrowing, especially in the so called watershed regions. The introduction of guide wires, equipped with pressure or Doppler sensors, allows selective hemodynamic evaluation of coronary narrowings. Validation studies of fractional flow reserve (FFR, based on intracoronary pressure measurements) and coronary flow velocity reserve (CFVR, based on intracoronary Doppler flow measurements) demonstrated good agreement with the results of perfusion scintigraphy, both in severe and in intermediate narrowed coronary arteries. These studies were performed predominantly in patients with single-vessel disease. It has been postulated that FFR is a more lesion specific parameter, while CFVR is determined by the resistances of both the epicardial coronary narrowing and the distal microvascular bed. Consequently, it can be anticipated that these intracoronary parameters may yield conflicting results. However, a direct comparison of pressure and flow-derived indices has only been performed in a small cohort of patients with single-vessel disease.

The purpose of this study was to compare the predictive value of CFVR, rCFVR and FFR for detection of reversible defects as assessed by perfusion scintigraphy in a large cohort of patients with two-vessel disease.

METHODS

Study population
Patients with two-vessel coronary artery disease and stable angina (class 1-3 according to the Canadian Cardiovascular Society; CCS) or unstable angina (Braunwalds classification I or II) were eligible for inclusion in this study. Furthermore, an angiographically normal reference vessel had to be available. A total of the 127 patients were prospectively studied and gave informed consent. Exclusion criteria were: factors precluding dipyridamole infusion and/or assessment of intracoronary measurements (e.g. occlusions, coronary anatomy); factors influencing coronary hemodynamic parameters (left ventricular hypertrophy, severe valvular heart disease, cardiomyopathy, insulin dependent diabetes, Q-wave myocardial infarction in the region of interest, previous coronary bypass grafting of the segment of interest).


**Study protocol**

All patients underwent dipyridamole myocardial perfusion scintigraphy within one week prior angiography, during which intracoronary measurements were performed. Patients had two coronary narrowings, resulting in a total of 254 lesions; in 59 lesions (23%) intracoronary measurements were not performed based on the operator's interpretation (e.g. technically impossible; total coronary occlusions, lesion location etc.); in 34 severe lesions (13%) it was not possible to measure both flow velocity and pressure. Thus, both flow velocity and pressure derived hemodynamic parameters were measured in 161 lesions. Angioplasty of the lesions was performed if a reversible defect was present in the area of interest on MIBI SPECT and, if available, the CFVR was less than 2.0.

This study protocol was approved by the Medical Ethics Committee of our institution; all patients gave written informed consent.

**Myocardial perfusion scintigraphy**

Single photon emission computed tomography (SPECT) was performed using 

\(^{99m}\text{Te}\) technetium labeled methoxyisobutylisonitrile (MIBI), according to a two day stress/rest protocol. Dipyridamole (0.56 mg/kg intravenously during 4 minutes) was used as hyperaemic agent. Anti-anginal medication was discontinued 48 hours before the stress MIBI SPECT. All patients fasted the day of the MIBI SPECT. \(^{99m}\text{Te}\)-MIBI (± 400 MBq) was injected 4 minutes after the onset of the administration of dipyridamole and the next day for the rest images. SPECT acquisition was performed using a three headed gamma-camera equipped with low energy high resolution collimators (*Siemens, Hoffman Estate, Illinois*), starting 1 hour following administration of MIBI. Acquisition was performed using a 360° non-circular orbit, a 64x64 matrix size, and an acquisition time of 60 frames of 45 seconds. Standard filtered back projection was performed without applying attenuation correction. Stress and rest tomographic images were displayed side by side in the short axis, horizontal long axis and vertical long axis reconstruction panel.

A panel of experienced nuclear medicine physicians, blinded to the angiographic data, evaluated the scintigraphic images. Stress and rest images were semi-quantitatively scored as normal or abnormal. Perfusion defect severity was classified as dubious, mild, moderate or severe defect. 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 LAD; defects in the lateral wall to the LCx; and inferior defects to the 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 the allocation to the vascular bed of a coronary artery.
Validation of CFVR, rCFVR and FFR vs. SPECT

Angiography
All patients were treated with aspirin (100 mg) prior to the procedure; heparin was given (5,000 IU) as an intravenous bolus at the beginning of the procedure. Coronary angiography, including the intracoronary hemodynamic measurements, was performed according to standard procedure by percutaneous femoral approach, using a 6 French guiding catheter without sideholes. Coronary angiography was performed after the administration of an intracoronary bolus nitroglycerin (0.1 mg), in at least two different, preferably orthogonal, views displaying each index lesion with minimal foreshortening and no vessel overlap. Coronary lesion severity was measured by quantitative coronary angiography, using the CMS-QCA software version 3.32 (MEDIS, Leiden, Netherlands) as previously described. Percentage diameter stenosis was assessed in two views; the most severe one was used in the analysis.

Intracoronary measurements
At the time of performing the intracoronary measurements, the observer was not aware of the results of the MIBI SPECT. If possible, intracoronary flow velocity was measured distally to both lesions and also in an angiographically normal coronary artery. It was at the operators discretion to exchange wires to obtain subsequent intracoronary pressure measurements distal to the lesion(s). An intracoronary bolus of 0.1 mg nitroglycerin was administered every 30 minutes. All measurements were performed at baseline and during hyperaemia. Hyperaemia was induced by administering an intracoronary bolus of adenosine (15 μg in the right coronary artery and 20 μg in the left coronary artery).

Translesional blood flow velocity was measured with a 0.014" Doppler guide wire (FloWire®, Endosonics, Rancho Cordova, CA). The FloWire was advanced distal to the stenosis, avoiding placement adjacent to side branches. A distance from the stenosis greater than 5 times the vessel diameter was maintained in order to avoid post-stenotic turbulent flow and to allow full development of a parabolic flow profile. Distal flow baseline and hyperaemic velocity data were obtained and the Doppler signals were processed by a real time spectral analyzer, using the Flowmap (Endosonics, Rancho Cordova, CA). CFVR was computed as the ratio of hyperemic/basal average peak blood flow velocity. CFVR was also obtained in an angiographically normal reference coronary artery. Relative CFVR (rCFVR) was defined as the ratio of CFVR of the narrowed vessel and CFVR of the reference coronary artery.

Intracoronary pressure was measured with a 0.014" pressure guide wire, connected to the pressure console (RADI Medical Systems, Uppsala, Sweden). After calibration with the pressure console, the accuracy of the system was verified using the aortic pressure as measured through the guiding catheter. The wire was advanced with the pressure sensor at least 3 cm distal to the lesion. During maximal hyperemia, FFR was calculated as the ratio of the mean distal and the mean aortic pressure.
**Data analysis**

Data analysis was performed using the SPSS 10.0.5 software package for Windows (SPSS Inc. 1999, Arlington, VA, USA). As 34 of the 127 patients contributed 2 lesions which were measured with the hemodynamic parameters, within-patient effects could not be excluded beforehand. Therefore, we performed a per-patient analysis instead of a per-lesion analysis. Of the 34 patients with 2 lesions, one randomly chosen lesion was used for analysis. Of note, this procedure was repeated 8 times to verify consistency. Furthermore, for completeness the results of the per-lesion analysis were also calculated.

For the three intracoronary hemodynamic parameters (CFVR, rCFVR and FFR), the area under curve (AUC) was calculated using the receiver operating characteristic (ROC) curve in comparison with the dichotomized results of MIBI SPECT. A direct comparison between of the AUC’s of the 3 parameters was performed using the software package ‘ROC Curve Analyzer’ (written by R.M. Centor & J. Keightley). Accuracy was calculated for predefined and widely used cut-off values as determined in earlier studies in single vessel disease (CFVR 2.0, FFR 0.75 and rCFVR 0.65; see also table 3) and for the best cut-off value (BCV) of the current data set, defined as the highest sum of sensitivity and specificity. Furthermore, the kappa statistic was used to evaluate the cut-off values of the hemodynamic parameters versus the results of MIBI SPECT. Values are presented as mean ± standard deviation (SD), unless indicated otherwise. Linear regression analysis was used to compare CFVR, rCFVR and FFR. Continuous data were compared using the students-t-test; binomial data were compared using the χ²-test. A p-value of less than 0.05 was considered statistically significant.

**RESULTS**

Baseline characteristics of the 127 studied patients were: 73% was male, the mean age was 61 (range: 37-80). Patient had the following risk factors: 70% smoking; 33% hypertension; 58% hypercholesterolemia; 9% non-insulin dependent diabetes; and 54% positive cardiac family history. Most patients had moderate to severe anginal complaints (2% CCS 1; 18% CCS 2; 59% CCS 3; 21% Braunwald I or II). Patient used cardiac medication as follows: 79% beta blockers; 58% calcium antagonists; 65% nitrates; 56% statins; 19% ACE inhibitors. Initial hemodynamic data are presented in table 1 of the in total 161 lesions measured and the 127 lesions studied for the per-patient analysis. All patients underwent myocardial perfusion scintigraphy within 1 week before cardiac catheterization. In total, a reversible perfusion defect on MIBI SPECT was found in 52 (32%) of the 161 areas of interest.
Validation of CFVR, rCFVR and FFR vs. SPECT

**Table 1:** Angiographic and hemodynamic data of in total 161 coronary lesions (127 patients), and for the randomly chosen 127 lesion for the per-patient analysis.

<table>
<thead>
<tr>
<th>Coronal lesions:</th>
<th>161 lesions:</th>
<th>127 lesions:</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCA</td>
<td>51 (32%)</td>
<td>37 (29%)</td>
</tr>
<tr>
<td>LAD</td>
<td>76 (47%)</td>
<td>63 (50%)</td>
</tr>
<tr>
<td>LCx</td>
<td>34 (21%)</td>
<td>27 (21%)</td>
</tr>
<tr>
<td>DS in % (range)</td>
<td>57 (35-85)</td>
<td>57 (35-85)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hemodynamic parameters (mean±SD):</th>
<th>161 lesions:</th>
<th>127 lesions:</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFVR</td>
<td>2.21 ± 0.76</td>
<td>2.25 ± 0.72</td>
</tr>
<tr>
<td>b-APV</td>
<td>17.1 ± 9.6</td>
<td>16.5 ± 8.7</td>
</tr>
<tr>
<td>h-APV</td>
<td>36.2 ± 17.6</td>
<td>36.7 ± 16.1</td>
</tr>
<tr>
<td>CFVR reference vessel</td>
<td>2.88 ± 0.70</td>
<td>2.90 ± 0.65</td>
</tr>
<tr>
<td>b-APV</td>
<td>18.3 ± 6.9</td>
<td>18.2 ± 7.1</td>
</tr>
<tr>
<td>h-APV</td>
<td>51.0 ± 17.6</td>
<td>50.6 ± 17.4</td>
</tr>
<tr>
<td>rCFVR</td>
<td>0.79 ± 0.27</td>
<td>0.82 ± 0.27</td>
</tr>
<tr>
<td>FFR</td>
<td>0.75 ± 0.18</td>
<td>0.76 ± 0.17</td>
</tr>
<tr>
<td>$P_{\text{distal}}$</td>
<td>73.3 ± 18.0</td>
<td>73.2 ± 18.3</td>
</tr>
<tr>
<td>$P_{\text{aorta}}$</td>
<td>97.1 ± 13.6</td>
<td>94.5 ± 14.1</td>
</tr>
</tbody>
</table>

No significant differences were present.

b-APV indicates baseline average peak flow velocity; CFVR, coronary flow velocity reserve; DS, diameter stenosis; FFR, fractional flow reserve; h-APV, hyperemic APV; LAD, left anterior descending artery; LCx, left circumflex artery; $P_{\text{distal}}$, pressure distal to lesion during hyperemia; $P_{\text{aorta}}$, aortic pressure during hyperemia; RCA, right coronary artery; rCFVR, relative CFVR; SD, standard deviation.
TABLE 2: Per-patient analysis (n=127): Accuracy for CFVR, rCFVR and FFR versus the results of MIBI SPECT, calculated for best and predefined cut-off values; the area under the curves for CFVR, rCFVR and FFR (0.70, 0.72 and 0.76 respectively) did not significantly differ.

<table>
<thead>
<tr>
<th></th>
<th>Best CV</th>
<th>Accuracy</th>
<th>95% CI</th>
<th>kappa</th>
<th>Predefined CV</th>
<th>Accuracy</th>
<th>95% CI</th>
<th>kappa</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFVR</td>
<td>1.7</td>
<td>76%*</td>
<td>68-83</td>
<td>0.40</td>
<td>2.0</td>
<td>69%†</td>
<td>60-76</td>
<td>0.28</td>
</tr>
<tr>
<td>rCFVR</td>
<td>0.60</td>
<td>78%*</td>
<td>70-85</td>
<td>0.44</td>
<td>0.65</td>
<td>75%†</td>
<td>66-82</td>
<td>0.37</td>
</tr>
<tr>
<td>FFR</td>
<td>0.74</td>
<td>77%*</td>
<td>69-84</td>
<td>0.47</td>
<td>0.75</td>
<td>75%†</td>
<td>66-82</td>
<td>0.43</td>
</tr>
</tbody>
</table>

*and †: Differences were not statistically significant

CV indicates cut-off value; CFVR, coronary flow velocity reserve; CI, confidence interval; FFR, fractional flow reserve; rCFVR, relative CFVR.

Using a per-patient analysis, the AUC (as measured by ROC analysis) was 0.70 for CFVR, 0.72 for rCFVR and 0.76 for FFR, respectively. The direct comparison of the ROC analysis by AUC's of the hemodynamic parameters did not significantly differ (CFVR vs. FFR, p=0.15; CFVR vs. rCFVR, p=0.27; FFR vs. rCFVR, p=0.32). In table 2 the accuracy is presented for BCV and predefined cut-off values for the current data set. There were no significant differences in accuracy's, as illustrated by the 95% confidence intervals. Kappa values indicated moderate agreement at determined BCV (table 2). Also the per-lesion analysis, using all 161 lesions, yielded similar best cut-off values (1.7 for CFVR, 0.60 for rCFVR, and 0.74 for FFR, respectively) and did not reveal significant differences between the AUC's (0.72 for CFVR, 0.73 for rCFVR, and 0.77 for FFR, respectively). The accuracy data were similar to the per-patient analysis, ranging from 68-77%. Plots for CFVR, rCFVR and FFR of sensitivity and specificity, as calculated with ROC analysis (with the patient as unit of analysis) are presented in figures la-c. Linear regression analysis of CFVR versus FFR (y=0.13x+0.48; r=0.53; p<0.001), CFVR versus rCFVR (y=0.24x+0.29; r=0.62; p<0.001) en rCFVR versus FFR (y=0.87x+0.16; r=0.55; p<0.001) yielded similar results.
**Validation of CFVR, rCFVR and FFR vs. SPECT**

**TABLE 3: Results of previous validation studies for intracoronary derived CFVR, FFR and rCFVR versus the results of non-invasive stress testing**

<table>
<thead>
<tr>
<th>First author</th>
<th>Year (reference)</th>
<th>No. of patients</th>
<th>Non invasive stress-test</th>
<th>Reported cut-off value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFVR:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miller</td>
<td>1994^3</td>
<td>33</td>
<td>SPECT</td>
<td>2.0</td>
</tr>
<tr>
<td>Joye</td>
<td>1994^4</td>
<td>30</td>
<td>SPECT</td>
<td>2.0</td>
</tr>
<tr>
<td>Deychack</td>
<td>1995^19</td>
<td>17</td>
<td>SPECT</td>
<td>1.8</td>
</tr>
<tr>
<td>Heller</td>
<td>1997^7</td>
<td>55</td>
<td>SPECT</td>
<td>1.7</td>
</tr>
<tr>
<td>Danzi</td>
<td>1998^18</td>
<td>30</td>
<td>Stress-echo</td>
<td>2.0</td>
</tr>
<tr>
<td>Verberne</td>
<td>1999^8</td>
<td>37</td>
<td>SPECT</td>
<td>1.9</td>
</tr>
<tr>
<td>FFR:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pijls</td>
<td>1995^2</td>
<td>60</td>
<td>X-ECG</td>
<td>0.74</td>
</tr>
<tr>
<td>De Bruyne</td>
<td>1995^5</td>
<td>60</td>
<td>X-ECG</td>
<td>0.72</td>
</tr>
<tr>
<td>Pijls</td>
<td>1996^6</td>
<td>45</td>
<td>X-ECG,SPECT&amp;Stress-echo</td>
<td>0.75</td>
</tr>
<tr>
<td>Bartunek</td>
<td>1997^20</td>
<td>37</td>
<td>Stress-echo</td>
<td>0.68</td>
</tr>
<tr>
<td>rCFVR:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verberne</td>
<td>1999^8</td>
<td>37</td>
<td>SPECT</td>
<td>0.65</td>
</tr>
</tbody>
</table>

CFVR indicates coronary flow velocity reserve; FFR, fractional flow reserve; rCFVR, relative CFVR; SPECT, Single Photon Emission Computed Tomography; X-ECG, exercise electrocardiography;

**FIGURE 1A-C (see next page): Plots for CFVR (A), rCFVR (B) and FFR (C) of sensitivity and specificity, as calculated with ROC analysis on a per-patient basis (n=127). The BCV (best cut-off value), defined as the highest sum of sensitivity and specificity, is indicated.
A

BCV = 1.7

- Sensitivity
- Specificity

CFVR value

B

BCV = 0.60

- Sensitivity
- Specificity

relative CFVR value

C

BCV = 0.74

- Sensitivity
- Specificity

FFR value
DISCUSSION

This is the first report of a direct comparison of between the results of MIBI SPECT and intracoronary hemodynamic parameters in a large cohort of patients (127) with two-vessel coronary artery disease. There were no significant differences in the predictive value of CFVR, rCFVR and FFR using receiver operator characteristic curves for reversible perfusion defects.

Direct comparison of CFVR, rCFVR and FFR

CFVR is determined by the integrity of both the epicardial conduit artery and the distal microvascular bed. rCFVR is defined as the ratio between CFVR of the target vessel and CFVR of the angiographically normal reference coronary artery, thus theoretically focusing on the contribution of the epicardial narrowing by correcting for microcirculatory disturbances. This concept of rCFVR was introduced by Gould and colleagues and validated in experimental and clinical studies.13 The concept of FFR was introduced by Pijls and De Bruyne and considered to be independent of hemodynamic and microcirculatory confounding factors.2,6,9

It has been suggested that FFR and rCFVR are more lesion specific parameters than CFVR.8,14,15 However, in the present study (127 patients) we could not demonstrate a better correlation between rCFVR and FFR (r=0.55) compared to CFVR and FFR (r=0.53), suggesting that the aforementioned confounding factors influencing CFVR are less pronounced than previously presumed to be operative in patients with coronary artery disease. This interpretation also explains why the rCFVR did not improve the diagnostic accuracy of the CFVR, which is in contrast to the findings of Baumgart et al. in a small cohort of patients with single vessel disease.11 A uniform CFVR distribution is described in patients without coronary artery disease.16 However, an apparently angiographically normal reference artery does not exclude presence of atherosclerotic disease. This was shown in numerous studies using intravascular ultrasound, where multivessel disease (among other parameters) was an independent predictor of diffuse vessel wall abnormalities in angiographically normal reference segments.17 Heterogeneity of the CFVR in target and reference vessels within patients with multivessel coronary artery disease could also explain the failure of the rCFVR in improving the relation of Doppler flow data with FFR in our cohort of patients.

CFVR, rCFVR and FFR versus the results of perfusion scintigraphy

Previous validation studies using Doppler or pressure guidewires were predominantly performed in patients with single vessel disease (see table 3), showing cut-off values of 1.7-2.0 for CFVR3,4,7,8,18,19 0.65 for rCFVR8; and 0.68-0.75 for FFR2,5,6,20. The results of this study show that cut-off values validated for single vessel are in accordance with the values obtained in two-vessel disease. The practical usefulness of the intracoronary derived indices is reflected in the applicability in a general set of patients. Therefore, currently used cut-off values in clinical
practice (CFVR: 2.0; FFR: 0.75, rCFVR: 0.65) were compared to the ones found in the present study. This study supports the use of a cut-off value for FFR of 0.75 for clinical decision making in both single and two-vessel disease. Accordingly, a cut-off value of 0.65 can be used for the rCFVR in clinical practice. For CFVR, a cut-off value of 2.0 is widely used for single vessel disease. However, the present study reports a best cut-off value of 1.7 for two vessel disease. As shown in figure 1a, the sensitivity is equal for the range in the so-called 'gray zone' 1.7-2.0 (approximately 50-55%). Furthermore, several studies have demonstrated a safe deferral of PTCA at CFVR values ≥ 2.0. These arguments are in favour of using a CFVR cut-off value of 2.0 for clinical decision making. Therefore, we suggest a cut-off value of 2.0 for CFVR in patients with single or two-vessel coronary artery disease. As shown in table 2, no significant differences were observed in accuracy between CFVR, FFR and rCFVR using these predefined cut-off values.

The aforementioned studies showed a 80-90% agreement with the results of several non-invasive tests. Our results of patients with two-vessel disease showed a lower agreement (approximately 77%, table 2) using the BCV's. This may be related to the patient population, i.e. multivessel versus single vessel coronary artery disease. It is known that perfusion scintigraphy has a limited capability, in particular in multivessel disease, to assign the perfusion defect to a specific epicardial coronary narrowing. It is possible that the assignment of the reversible perfusion defect, as detected by MIBI SPECT, to the perfusion territory of one of the three main coronary arteries (RCA, LAD and LCx) was inappropriate, especially in the so-called watershed regions. Knowledge of the anatomical distribution pattern of the coronary arteries is a prerequisite for appropriate allocation of the culprit coronary artery. However, in this study, the panel of nuclear medicine physicians and the interventional cardiologist were blinded to angiographic data and the results of MIBI SPECT respectively, to ensure an objective comparison. Finally, hyperemia was differently induced during scintigraphy (intravenously dipyridamole) and cardiac catheterization (intracoronary adenosine). Recently, similar diagnostic accuracy was reported for exercise stress testing, adenosine and dipyridamole in inducing maximal hyperemia for myocardial perfusion scintigraphy. Furthermore, a recent study showed no difference in hyperemic response, as measured by intracoronary Doppler flow velocity, between adenosine and ATP (both intravenously and intracoronary administered) in comparison with papavarine. These findings indicate that different agents for vasodilation and routes of administration were not a major drawback of the current study.

**Limitations**

In this study, 161 of the 254 lesions present were evaluated with CFVR, FFR and rCFVR; so 93 lesions were not measured with both intracoronary flow velocity and pressure. This was related to factors precluding assessment of intracoronary measurements (e.g. occlusions, coronary anatomy, lesion location etc.). As, at present, intracoronary flow velocity and pressure have to be
measured with two different guidewires, it was at the operators discretion to use both wires in a particular lesion. In general, the more severe lesions were not suitable for evaluation with both flow velocity and pressure measurements. Most lesions studied were of intermediate severity (mean QCA 57%; range 35-85%). However, clinical decision making remains challenging in this cohort of intermediate lesions and QCA is a poor predictor for the occurrence of events.  

The detection of a reversible perfusion defect as detected by perfusion scintigraphy as well as the allocation of this defect to a coronary artery was performed by an experienced panel of nuclear medicine physicians. In this study, 100 (79%) of the 127 patients (with in total 254 lesions) showed one or more reversible defects on scintigraphic images. As mentioned above, flow velocity and pressure measurements were performed in 161 of the in total 254 lesions. QCA of these 161 lesions ranged from 35-85% diameter stenosis. Only 52 (32%) of the 161 areas of interest were identified by the panel by allocation of the perfusion defect to the territory of the culprit coronary vessel. This could explain the lower agreement found in the current study between the results of perfusion scintigraphy and the hemodynamic parameters.

**Clinical implications**

The value of intracoronary hemodynamic measurements is important for clinical decision making, both during elective angiography in patients with coronary artery disease and in the setting of ad hoc PTCA. This study shows that CFVR, rCFVR and FFR are all three useful hemodynamic parameters for clinical decision making during cardiac catheterization in patients with two-vessel coronary artery disease. The currently used cut-off values for clinical decision making in single vessel disease (CFVR 2.0; FFR 0.75; and rCFVR 0.65) can be applied in patients two-vessel disease. In our opinion, FFR is preferable from a practical point of view for clinical decision making in patients with coronary artery disease, as (1) the cut-off value of 0.74 found in the present study is close to the value (0.75) widely used in single vessel disease, and (2) FFR is easy to measure, in particular for inexperienced operators. However, the present study shows that ROC analysis did not reveal significant differences between FFR, CFVR and rCFVR. Long term follow-up is mandatory in these patients with discordant results between the invasive indices and the results of perfusion scintigraphy to establish which of these diagnostic methods has the highest clinical relevance from a prognostic point of view.
ACKNOWLEDGMENT

The enthusiastic and skillful help of the paramedical personnel of the cardiac catheterization laboratory (head: Martin Meesterman, R.N.), cardiology ward (head: Sjouk Boomstra, R.N.) and the technicians of the department of Nuclear Medicine (head technician: Ankie Lagerwaard) are gratefully acknowledged. Marcel G.W. Dijkgraaf, Ph.D. is acknowledged for his useful statistical comments.

J.J. Piek is clinical investigator for the Netherlands Heart Foundation (grant D96.020)
This study was supported by the Dutch Health Insurance Board (grant 96-036); RADI Medical Systems, Uppsala, Sweden; and Endosonics, Rancho Cordova, CA, USA.

REFERENCES


