Long-term prognostic value of CFVR and FFR versus perfusion scintigraphy in patients with multivessel disease

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Objective. In this multicentre study, we investigated the long-term prognostic value of intracoronary derived haemodynamic parameters compared with the results of myocardial perfusion scintigraphy (MPS).

Methods. Patients (n=191) who were referred for angioplasty of a severe lesion in the presence of an intermediate lesion in another coronary artery were included. MPS was performed to determine the presence of reversible perfusion defects in the area of the intermediate lesion. Coronary flow velocity reserve (CFVR), and additionally fractional flow reserve (FFR; n=129), were determined distal to the intermediate lesion; CFVR ≥ 2.0 and FFR ≥ 0.75 were considered negative.

Results. In total 67 events occurred in 49 patients (3 deaths, 9 MI, 9 CABG, 46 PTCA) during a mean of 793 days follow-up. Event-free survival was 63% for MPS, 79% for CFVR, and 79% for FFR if a negative test result was obtained. The relative risk was 1.2 (not significant) for MPS, 2.2 (p=0.001) for CFVR, and 2.4 (p=0.004) for FFR.

Conclusion. Selective evaluation of an intermediate lesion using CFVR or FFR allows more adequate risk stratification in patients with multivessel disease than MPS. A CFVR < 2.0 or a FFR < 0.75 was associated with a significant increase of the occurrence of cardiac events during long-term follow-up, predominantly associated with revascularisation. (*Neth Heart J* 2007;15:369-75.)

Keywords: coronary artery disease, myocardial perfusion scintigraphy, coronary flow velocity reserve, fractional flow reserve, angioplasty, risk stratification

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Adequate patient selection for percutaneous transluminal coronary angioplasty (PTCA) is important in view of the potential procedural complications and the incidence of restenosis. Assessment of the functional significance of coronary lesions is mandatory, especially in intermediate coronary narrowings (40 to 70% diameter stenosis). Assessment can be performed noninvasively (using myocardial perfusion scintigraphy; MPS)¹ or invasively during cardiac catheterisation using intracoronary derived haemodynamic indices.² Previous validation studies have shown good agreement (80 to 90%) between these parameters and the results of noninvasive stress tests.³⁻⁵

Previously, we reported the final results of the ILIAS (Intermediate Lesions: Intracoronary flow Assessment versus ^{99m}Tc-MIBI SPECT) study with one-year clinical follow-up.⁶ In this multicentre study, we directly compared the value of intracoronary derived coronary flow velocity reserve (CFVR) with myocardial perfusion scintigraphy in the context of clinical decision-making in patients with an intermediate lesion and multivessel coronary artery disease. We concluded that deferral of PTCA of intermediate lesions in multivessel disease is safe when the CFVR is ≥ 2.0 (event rate 6%); a threefold increase of cardiac events was observed when PTCA was deferred despite a CFVR < 2.0 . This selective evaluation of coronary lesion severity during cardiac catheterisation allows more accurate risk stratification than MPS, which is

of importance for clinical decision-making in this patient cohort. Furthermore, Bech et al. showed an event-free survival rate of 89% at two-year follow-up when PTCA was deferred based on a fractional flow reserve (FFR) of >0.75 .⁷

For clinical practice, intracoronary haemodynamic techniques facilitate decision-making during diagnostic cardiac catheterisation, allowing ad hoc angioplasty within the same session. This strategy is at least as effective as using MPS. However, long-term follow-up (i.e. >1 year) comparing the invasive and noninvasive strategy in patients with multivessel disease has not been performed. It is postulated that cardiac events related to intermediate lesions will take place after a longer period of follow-up. However, long-term data comparing the invasive and noninvasive strategy in patients with multivessel disease are lacking. Therefore, the purpose of the present study was to compare the long-term follow-up (>1 year) prognostic value of intracoronary derived CFVR and FFR with myocardial perfusion scintigraphy in the context of clinical decision-making in these patients.

Patients and Methods

The study protocol has been described earlier.⁶ Briefly, patients with stable or unstable angina were screened in six hospitals in the Netherlands (appendix). 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 catheterisation were selected. Patients were

eligible for entering the study if the severe lesion was accepted for PTCA, and if, from a clinical point of view, no definite strategy had been formulated for the intermediate lesion. The protocol was approved by the Institutional Review Boards of the participating institutions; all patients gave written informed consent.

Study design

All patients underwent MPS for noninvasive assessment of functional severity of the intermediate lesion. Coronary angiography was scheduled within one week after MPS, and was performed using the percutaneous femoral approach. During this procedure, CFVR and FFR measurements were performed distal to the intermediate lesion. Coronary lesion severity was measured using the CMS-QCA software version 3.32 (MEDIS, Leiden, Netherlands) as previously described.⁸ The intermediate lesion was only treated with PTCA if both MPS and CFVR were positive. Otherwise, the intermediate lesion was left untreated. The cardiac catheterisation procedure was completed by performing PTCA of the severe lesion.

Single photon emission computed tomography

MPS was performed using ^{99m}technetium sestamibi, according to a two-day stress/rest standard protocol, as previously described.⁹ Dipyridamole (0.56 mg/kg intravenously for four minutes) was used as a hyperaemic agent. Data acquisition and reconstruction were performed according to the procedure guideline for myocardial perfusion imaging of the Society of Nuclear Medicine.¹⁰ An expert panel of nuclear

Table 1. Baseline characteristics of all patients (n=191).

Patients	Male	71%
	Age in years (mean, range)	61 (32-80)
History	Peripheral vascular disease	9 (5%)
	Previous myocardial infarction	74 (39%)
	Previous PTCA	22 (12%)
	Previous bypass surgery	0
Risk factors	Smoking	144 (75%)
	Hypertension	74 (39%)
	Hypercholesterolaemia	113 (59%)
	Non-insulin dependent diabetes mellitus	16 (8%)
	Positive cardiac family history	106 (56%)
Anginal symptoms	CCS class 1	18 (9%)
	CCS class 2	65 (34%)
	CCS class 3	95 (50%)
	Braunwald I or II	13 (7%)
Location IM lesion	RCA	20%
	LAD	47%
	LCx	33%

CCS=Canadian Cardiovascular Society, RCA=right coronary artery, LAD=left anterior descending coronary artery, LCx=left circumflex coronary artery, IM=intermediate lesion.

medicine physicians, blinded to the angiographic data, evaluated the scintigraphic images. The result was considered 'positive' when a reversible defect was allocated to the perfusion territory of the coronary artery of interest, as previously described.⁶

CFVR and FFR measurements

Operators were blinded for the results of MPS at the time of the intracoronary measurements. CFVR was measured distal to the lesion with a 0.014" Doppler guidewire (FloWire®, Endosonics, Rancho Cordova, CA). Additionally, pressure was measured at the operator's discretion with a 0.014" pressure guidewire (RADI Medical Systems, Upssala, Sweden). Hyperaemia was induced by an intracoronary bolus of adenosine (15 µg in the right, and 20 µg in left coronary artery). CFVR was computed as the ratio of hyperaemic/basal average peak blood flow velocity; CFVR of ≥ 2.0 was considered 'negative'.¹¹ FFR was computed as the ratio of distal/aortic pressure during hyperaemia; FFR ≥ 0.75 was considered 'negative'.²

Outcome events

One-year follow-up was obtained by three scheduled visits (at 3, 6, and 12 months) to the outpatient clinic, according to the ILIAS protocol. The long-term follow-up data were obtained from at least one of four sources: visit to the outpatient clinic; review of the patient's hospital records; personal communication with the patient's physician; a telephone interview with the patient conducted by trained personnel. The primary outcome was defined as the occurrence of any of the following events during 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 or bypass surgery.⁶

Data analysis

Primary outcome event rates for the dichotomised results of MPS, CFVR, and FFR were calculated separately, including relative risks and 95% confidence

intervals (CI). Subanalysis was performed for 'hard events' (e.g. death and myocardial infarction), and events that were attributed to the intermediate lesions by an independent critical event committee. Kaplan-Meier analysis was performed for the time to first event; the log-rank statistic was used. The SPSS 12 software programme was used for statistical analysis.

Results

Patient and lesion characteristics

A total of 191 patients (71% male, mean age 61) were evaluated; baseline characteristics have been reported previously and are summarised in table 1.⁶ The mean percentage diameter stenosis using quantitative coronary angiography was 54% (range 34 to 74%) for the intermediate lesions and 79% (range 50 to 99%) for the severe lesions.

MPS, CFVR, and FFR data

MPS 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; 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. Additional FFR was measured in 129 patients; 22 (17%) had an FFR < 0.75 . In all patients PTCA was performed of the severe lesion, additional PTCA of the intermediate lesion was performed in only nine patients, according to the study protocol.

Outcome events

The mean follow-up time was 793 days (range 360 to 1525). Long-term follow-up was obtained in 171 patients; for the remaining 20 patients one-year follow-up was available, during which five patients had an event. In total, 67 cardiac events occurred in 49 patients: three deaths, nine myocardial infarctions, nine

Table 2. Overview of all events for positive and negative test results per diagnostic modality (67 events for MPS and CFVR, and 47 events for FFR).

		Death	MI	CABG	PTCA	Total
MPS	Neg (n=161)	3 (2%)	8 (5%)	7 (4%)	39 (24%)	57 (35%)
	Pos (n=30)	0 (0%)	1 (3%)	2 (7%)	7 (23%)	10 (33%)
CFVR	Neg (n=145)	3 (2%)	5 (3%)	3 (2%)	24 (17%)	35 (24%)
	Pos (n=46)	0 (0%)	4 (9%)	6 (13%)	22 (48%)	32 (70%)
FFR	Neg (n=107)	1 (1%)	5 (5%)	4 (4%)	23 (22%)	33 (31%)
	Pos (n=22)	1 (5%)	2 (9%)	1 (5%)	10 (46%)	14 (64%)

MPS=myocardial perfusion scintigraphy, CFVR=coronary flow velocity reserve, FFR=fractional flow reserve, Pos=positive test results, Neg=negative test results (see text for explanation).

Table 3. Long-term follow-up: outcome of first events for the results of MPS, CFVR, and FFR.

		n	Events	(%)	95% CI
MPS					
Negative	(no reversible perfusion defect in AOI)	161	40	25	
Positive	(reversible perfusion defect in AOI)	30	9	30	
			RR	1.2	0.7-2.2
CFVR					
Negative	(CFVR ≥ 2.0)	145	29	20	
Positive	(CFVR < 2.0)	46	20	44	
			RR	2.2*	1.4-3.5
FFR					
Negative	(FFR ≥ 0.75)	107	22	21	
Positive	(FFR < 0.75)	22	11	50	
			RR	2.4*	1.4-4.3

* $p < 0.05$ as compared with MPS. MPS=myocardial perfusion scintigraphy, CFVR=coronary flow velocity reserve, FFR=fractional flow reserve, AOI=area of interest, CI=confidence interval, RR=relative risk.

bypass operations, and 46 PTCA's (table 2). In 12 patients two events, and in 3 patients three events occurred, respectively. More than one event occurred in 10, 2 and 1 patients with a positive result for CFVR, FFR, and MPS, respectively.

Primary outcome event rates for patients with positive and negative test results for MPS, CFVR and FFR are depicted in table 3. A significant difference was found for CFVR vs. MPS and FFR vs. MPS; no difference was found for FFR vs. CFVR. A subanalysis, focused on events related to the intermediate lesions, also showed a significant difference between CFVR and MPS (relative risk 2.6 and 0.4, respectively). During one-year follow-up these relative risks were 3.9 and 0.5, respectively.⁶ A subanalysis, focused only on hard events (infarct plus death; 12 patients) showed no difference

for CFVR (RR 1.8; 95% CI 0.6 to 5.9; ns), FFR (RR 1.6; 95% CI 0.4 to 7.5; ns) and MPS (RR 0.5; 95% CI 0.1 to 4.0; ns).

Kaplan-Meier analysis showed a significant difference in time to first event for abnormal CFVR and FFR, in contrast to MPS (figures 1A-C), with an event-free survival at 1525 days of 79% for CFVR, 79% for FFR and 63% for MPS in case of a normal test result.

Discussion

To the best of our knowledge this is the first study to report long-term clinical results for the management of patients with multivessel coronary artery disease, in a direct comparison of the value of three frequently used (non)invasive diagnostic modalities: MPS, CFVR and FFR. It shows that intracoronary derived

Figure 1. Kaplan-Meier curves for MPS (A), CFVR (B), and FFR (C), and for the time to the first event.

haemodynamic parameters have a better prognostic value than MPS, with a two-fold increase in cardiac events at a mean follow-up time of 26 months. Table 2 shows that these events are predominantly associated with revascularisations; moreover, a subanalysis on death and MI did not show significant results for all three modalities. The results of the present study are in accordance with the results of previous studies with one-year follow-up, implicating that deferral of PTCA in lesions with normal haemodynamic values is safe for a sustained period of time.

Haemodynamic indices and follow-up

In the initial ILIAS study, multivariate analysis revealed CFVR as the only significant predictor for cardiac events. Numerous studies have shown that deferral of PTCA is safe based on normal values of CFVR and/or FFR.² However, only a few other studies have addressed the value of CFVR and FFR with respect to long-term follow-up (i.e. more than one year), none of them in direct comparison with noninvasive assessment of myocardial ischaemia.^{7,12-14} Bech et al. reported an 11% event rate at 24 months' follow-up if PTCA was deferred based on an FFR >0.75, in coronary stenosis without noninvasive evidence of ischaemia; in our study 16% had a positive MPS.⁷ In a study with 61 patients and a mean follow-up time of 5.5 years, the event rate was 19.7% in patients in which PTCA was deferred based on either a CFVR ≥ 2.0 or an FFR ≥ 0.75 .¹² This is in line with the event rate of 20% found in our study. Mates and colleagues reported an event rate of 13% after 22.6 months follow-up in 85 patients with an FFR ≥ 0.75 . They concluded that deferring coronary interventions of intermediate stenosis based on FFR measurement is safe with respect to long-term follow-up, irrespective of the extent of coronary artery disease.¹³ Finally, Berger and colleagues studied 102 patients with multivessel disease. They treated 113 lesions (FFR <0.75) with PTCA, and deferred PTCA in 127 lesions, based on an FFR >0.75. In total, 22 (13%) major cardiac events were noted after 36 months, eight (6.3%) of which were attributed to the initial deferred lesion.¹⁴ In the present study, we choose to perform an analysis based on all events, as assignment to a specific lesion is not always easy, especially in case of death and bypass surgery (unless MPS and/or haemodynamic measurements are systematically repeated). However, in the ILIAS study we showed that nine (6.3%) events, related to the intermediate lesion, occurred during the first year of follow-up in the group with a normal CFVR (≥ 2.0 ; n=143).⁶ The majority of events occurred during the first year, which is just partially explained by events related to restenosis of initially treated lesions. This study also shows that haemodynamically significant but untreated lesions give rise to events in the short term. In the present study, nearly half of the events (32/67, 48%) were related to significant lesions (CFVR <2.0).

Myocardial perfusion scintigraphy and follow-up

Hachamovitch and colleagues followed 1270 consecutive patients with no previous revascularisation or myocardial infarction (MI), with a pre-exercise tolerance test (ETT) likelihood of CAD ≥ 0.85 , who underwent exercise or adenosine stress. In patients treated medically after MPS, normal MPS had a low risk of cardiac death and hard events (0.6 and 1.3% per year, respectively, during a mean follow-up of 2.2 years). With increasing extent and severity of MPS defects, the risk of both cardiac death and hard events increased significantly.¹⁵ Moreover, they showed that in patients with a high likelihood of coronary artery disease, MPS appeared to be a cost-saving approach compared with a strategy of direct referral to catheterisation. They conclude that a strategy of initial stress imaging in this patient cohort is a reasonable alternative to direct referral to catheterisation. In a review, Berman and colleagues state that a normal MPS study defines patients at low risk for subsequent cardiac events. Because of this evidence, physicians today can comfortably manage most patients with normal MPS without resorting to myocardial revascularisation, confident that angiographic assessment is unlikely to yield further benefit.¹⁶ The lower prognostic value of MPS in the our study possibly relays the extensive multivessel disease: all patients had known coronary artery disease with at least one severe, and one intermediate lesion. Therefore, it is thought that assignment of perfusion defects to a specific coronary artery, which was necessary in this study protocol, is sometimes difficult especially in the watershed regions between perfusion territories of adjacent arteries. However, the present study was performed in a specific subset of patients with multivessel disease, and does not challenge the fact that a large number of class I indications exist for MPS in risk assessment of patients with an intermediate or high likelihood of CAD.¹⁶

Study limitations

In contrast to our initial study, long-term follow-up data were not collected with scheduled visits by protocol. Therefore, there are differences in the duration of the follow-up, as can be appreciated from the data from the Kaplan-Meier analysis. These results cannot be extrapolated without any reserve to other patient cohorts selected for elective coronary angioplasty.

FFR was measured in only 129 patients (68%), as it was optional in the study protocol. The main reason for omitting an FFR measurement was lack of time. The additional prognostic value over MPS was similar to CFVR, which is important since intracoronary pressure measurements are used for risk stratification in numerous catheterisation laboratories. This study did not specify the use of either FFR or CFVR; in our opinion that is at the operators' discretion, since both indices show similar prognostic value.

The endpoint consisted predominantly of revascularisation procedures (55/67; 82%). In the initial

ILIAS study, an independent critical event committee considered objective evidence that is indicative for myocardial ischaemia present in 81% of the events, based on the clinical and angiographic findings, the results of perfusion scintigraphy and/or CFVR measurements. These results indicate that the need for revascularisation was not driven by hidden biases of patients and/or physicians.

Clinical implications

Implementation of CFVR and/or FFR measurements during cardiac catheterisation facilitates subsequent PTCA if necessary, which avoids additional scintigraphic testing and repeat cardiac catheterisation, reducing patient discomfort and procedural costs. This selective evaluation of coronary lesion severity during cardiac catheterisation allows risk stratification: it identifies patients in whom it is safe to defer intervention for a sustained period of time based on normal indices. Moreover, it shows that haemodynamically significant but untreated lesions give rise to events in the short term, predominantly associated with revascularisations. We and others have shown in extensive cost-effectiveness analyses that the use of CFVR and FFR is justified from a societal point of view.^{17,18} The additional value of this study is that it provides proof of a sustained beneficial prognostic effect during long-term follow-up, which supports a conservative treatment strategy when cut-off values for CFVR and/or FFR are implemented in daily clinical practice. ■

Acknowledgements

The outstanding secretarial help of Angelina de Jong is gratefully acknowledged. This study was supported by the Dutch Health Insurance Board (grant 96-036) and by a grant from the Netherlands Heart Foundation (grant 2000.090). J.J. Piek is clinical investigator for the Netherlands Heart Foundation (grant D96.020).

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Appendix 1. Participating centres and numbers of patients.

Academic Medical Centre Amsterdam (n=130)

Chamuleau, Dijkgraaf, Van Eck-Smit, De Jong, Koch, Kooij, Van Liebergen, Meuwissen, Piek, Spijkerboer, Tijssen, Verberne

University Medical Centre Groningen (n=23)

Monnick, Piers, Tio, Wijkstra

VU University Medical Centre Amsterdam (n=21)

DeCock, Pijpers, Vis

Maastricht University Hospital (n=15)

Van Asseldonk, Braat, De Muinck, Spanjers

Catharina Hospital, Eindhoven (n=9)

Bech, Huysmans, Pijls

Onze Lieve Vrouwe Gasthuis, Amsterdam (n=3)

Van der Heijden, Laarman, Van Unnik, Zonneveld