Coronary Flow Velocity Reserve After Percutaneous Interventions Is Predictive of Periprocedural Outcome

M. Albertal, M. Voskuil, J.J. Piek, B. de Bruyne, G. Van Langenhove, P.I. Kay, M.A. Costa, E. Boersma, T. Beijsterveldt, J.E. Sousa, J.A. Belardi, P.W. Serruys and on Behalf of the Doppler Endpoints Balloon Angioplasty Trial Europe (DEBATE) II Study Group

Circulation 2002;105;1573-1578; originally published online Mar 11, 2002;
DOI: 10.1161/01.CIR.0000012514.15806.DD
Circulation is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 0009-7322. Online ISSN: 1524-4539

Coronary Flow Velocity Reserve After Percutaneous Interventions Is Predictive of Periprocedural Outcome

M. Albertal, MD; M. Voskuil, MD; J.J. Piek, MD, PhD; B. de Bruyne, MD, PhD; G. Van Langenhove, MD, PhD; P.I. Kay, MD; M.A. Costa, MD, PhD; E. Boersma, PhD; T. Beijsterveldt, MD; J.E. Sousa, MD; J.A. Belardi, MD; P.W. Serruys, MD; on Behalf of the Doppler Endpoints Balloon Angioplasty Trial Europe (DEBATE) II Study Group

Background—Because heterogeneous results have been reported, we assessed coronary flow velocity changes in individuals who underwent percutaneous transluminal coronary angioplasty (PTCA) and examined their impact on clinical outcome.

Methods and Results—As part of the Doppler Endpoints Balloon Angioplasty Trial Europe (DEBATE) II study, 379 patients underwent Doppler flow–guided angioplasty. All patients were evaluated according to their coronary flow velocity reserve (CFVR) results (≥2.5 or <2.5) at the end of the procedure. A CFVR <2.5 after angioplasty was associated with an elevated baseline blood flow velocity in both the target artery and reference artery. CFVR before PTCA and CFVR in the reference artery were independent predictors of an optimal CFVR after balloon angioplasty (CFVR before PTCA: odds ratio [OR], 2.26; 95% confidence interval [CI], 1.57 to 3.24; CFVR in reference artery: OR, 1.90; 95% CI, 1.21 to 2.98; both $P<0.001$) and stent implantation (before PTCA: OR, 2.54; 95% CI, 1.47 to 4.36; reference artery: OR, 1.97; 95% CI, 1.07 to 3.87; both $P<0.05$). A low CFVR at the end of the procedure was an independent predictor of major adverse cardiac events (MACE) at 30 days (OR, 4.71; 95% CI, 1.14 to 25.92; $P=0.034$) and at 1 year (OR, 2.06; 95% CI, 1.16 to 3.66; $P=0.014$). After excluding MACE at 30 days, no difference in MACE at 1 year was observed between the patients with and without a CFVR <2.5 at the end of the procedure.

Conclusions—A low postprocedural CFVR was associated with a worse periprocedural outcome (which was related to microcirculatory disturbances), but there was no significant difference at late follow-up. **(*Circulation*. 2002;105:1573-1578.)**

Key Words: angiography ■ imaging ■ microcirculation

Coronary flow velocity reserve (CFVR) has been used in the catheterization laboratory to assess the significance of physiological stenosis and the changes in coronary blood flow after balloon angioplasty.[1] The Doppler Endpoints Balloon Angioplasty Trial Europe (DEBATE) I recently demonstrated that the recurrence of clinical events after percutaneous transluminal coronary angioplasty (PTCA) was markedly larger in patients with a CFVR <2.5 (24% versus 12%).[2]

The DEBATE II clinical trial was designed to test the value of a strategy of provisional stenting, which was defined as stenting only when suboptimal angiographic and CFVR results were observed after angioplasty, compared with a strategy of elective stenting. In patients in the DEBATE II study, in whom the CFVR was monitored throughout the procedure, we analyzed the clinical predictive value of CFVR for major adverse cardiac events (MACE) at short and long-term follow-up. In addition, we evaluated the mechanisms and predictors of an optimal CFVR result after percutaneous interventions.

Methods

Patient Selection and Study Objectives

In summary, patients scheduled to undergo single native coronary angioplasty who were amenable for stent implantation were eligible for the DEBATE II trial. Patients with total coronary occlusion or ostial, bifurcated, or tortuous lesions were excluded from the study, as were patients with previous Q-wave infarction in the myocardial territory supplied by the target vessel or evolving myocardial infarction (MI) in the previous week. Every patient provided written, informed consent

A total of 618 patients recruited in DEBATE II were randomized to elective stenting (n=97) and CFVR and quantitative coronary angiography (QCA)–guided coronary angioplasty (n=521). Patients without Doppler flow data available (n=13) or who underwent

Received October 23, 2001; revision received January 23, 2002; accepted January 24, 2002.

From Thoraxcenter, Rotterdam, the Netherlands (M.A., G.V.L., P.I.K., M.A.C., E.B., T.B., P.W.S.); the Academic Medical Center, Amsterdam, the Netherlands (M.V., J.J.P.); Onze Lieve Vrouwe Kliniek, Aalst, Belgium (B.d.B.); institutop Dante Pazzanesse de Cardiologia, San Pablo, Brasil (J.E.S.); and the Instituto Cardiovascular de Buenos Aires, Buenos Aires, Argentina (J.A.B.).

Correspondence to P.W. Serruys, MD, PhD, FACC, FESC, Professor of Interventional Cardiology, Head of Interventional Department, Thoraxcenter, Bd 418, University Hospital Dijkzigt, Dr Molewaterplein 40, 3015 GD Rotterdam, The Netherlands. E-mail serruys@card.azr.nl

Circulation **is available at http://www.circulationaha.org** **DOI: 10.1161/01.CIR.0000012514.15806.DD**

bailout stenting (n=129) were excluded from the guided-angioplasty group.

Regardless of the CFVR results after balloon angioplasty, the remaining 379 patients underwent a second randomization to additional stenting (n=187) or no further treatment (n=192). In the present study, the guided-angioplasty group (n=379) was divided according to the absolute CFVR results at the end of the percutaneous intervention: optimal was defined as a CFVR ≥2.5 (n=240) and suboptimal as a CFVR <2.5 (n=139). In contrast to the DEBATE II study protocol, in the present study, QCA data after PTCA were not used to define optimal and suboptimal groups.

Guided Balloon Angioplasty

In all patients, QCA and CFVR measurements were performed throughout the procedure to achieve an optimal result according to the above-mentioned preset criteria.

Optimal CFVR and QCA were defined as ≥2.5 and a percentage diameter stenosis <35%, respectively. An "optimal result" (QCA and CFVR) was expected to be achieved by increasing the size of the balloon and/or increasing the inflation pressure. Bailout stenting was allowed in the following situations: a residual stenosis >50%; dissection type D, E, or F; persistent myocardial ischemia along with a dissection type C; drop in TIMI flow grade of at least 1 grade; or TIMI grade 0 or 1. After an optimal result was achieved or when further attempts to improve the result were deemed unsafe by the operator, the final diameter stenosis and CFVR were assessed. Thereafter, and irrespective of these measurements, the second randomization was performed.

Quantitative Coronary Angiography

At least 2 cine angiograms were performed before the procedure and then repeated in the same projections at the end of the procedure. QCA was performed using edge detection contour (CAAS II system), as described previously.

CFVR Measurement

A 0.014-inch Doppler guidewire (Cardiometrics FloWire; EndoSonics) was used.[3] The Doppler wire was advanced distal to the lesion, and velocity recordings were obtained under basal and hyperemic conditions. Maximal hyperemia was induced by an intracoronary bolus injection (12 μg for the right coronary artery and 18 μg for the left coronary artery) or intravenous infusion (140 $\mu g \cdot kg^{-1} \cdot min^{-1}$) of adenosine. Target vessel Doppler measurements were performed before and after angioplasty and again after stent implantation. In addition, Doppler measurements of an adjacent angiographically normal vessel (<30% diameter stenosis) were performed. Absolute CFVR was calculated as the ratio of hyperemic to baseline time-averaged peak velocity. Relative CFVR was calculated as the ratio of the absolute CFVR in the target vessel to the absolute CFVR in the reference artery.[4] The CFVR was considered normalized when the relative CFVR was ≥0.8.[5,6]

End Points

For the DEBATE II study, the efficacy end point was a composite of MACE within 12 months of the procedure and included death from any cause, nonfatal MI, and percutaneous or surgical target lesion revascularization. MI was defined as the development of a new Q-wave or a 2-fold rise of serum creatinine kinases, together with an abnormal plasma level of myocardial isoenzymes. Enzymes were systematically sampled twice within the first 24 hours. After hospital discharge, patients were seen at the outpatient clinic at 1, 6, and 12 months. Each visit included the recording of the angina status, the cardiac medications, a 12-lead ECG, and a complete physical examination. No follow-up angiogram was performed unless clinically indicated.

Statistical Analysis

Continuous variables are expressed as mean±SD, and differences between groups of patients were studied using the unpaired Student's *t* test or one-way ANOVA, whichever was appropriate. Categorical variables are presented as percentages, and differences between groups were evaluated using Fisher's exact test, χ^2, or long-rank test whenever appropriate. Odds ratio (OR) and 95% confidence intervals (CI) are presented. A 2-tailed, paired *t* test was used to detect variation within patients. Multivariate logistic regression analysis was used to study the diagnostic value of the clinical and angiographic without or with Doppler-derived data to predict an optimal CFVR result. In addition, multivariate regression analysis was performed to examine the predictive value of the final absolute and relative CFVR for MACE at 30 days and 1 year. All statistical tests were 2-tailed, and significance was stated at the 0.05 level.

TABLE 1. Baseline Characteristics of the Patients With a CFVR ≥2.5 and <2.5 at the End of the Procedure

Characteristics	CFVR ≥2.5 (n=240)	CFVR <2.5 (n=139)	*P*
Age, y	57±10	61±11	<0.01
Female sex, n (%)	50 (21)	44 (32)	0.03
Diabetes mellitus, n (%)	20 (8)	15 (11)	NS
Hypertension, n (%)	83 (35)	56 (40)	NS
Hypercholesterolemia, n (%)	122 (57)	67 (48)	NS
Previous MI, n (%)	66 (28)	49 (35)	NS
Previous angioplasty, n (%)	23 (10)	17 (12)	NS
Smoking, n (%)	166 (70)	105 (76)	NS
CCS class, n (%)			
I/II	87 (36)	45 (32)	NS
III/IV	61 (25)	27 (19)	NS
Unstable angina, n (%)	71 (30)	55 (40)	0.05
Medication, n (%)			
Lipid-lowering	66 (28)	31 (22)	NS
Aspirin	212 (88)	119 (86)	NS
β-Blockade	158 (66)	88 (63)	NS
Ca-antagonist	115 (48)	71 (51)	NS
Nitrate	157 (65)	87 (63)	NS
Hemodynamics			
Heart rate, bpm	68±12	69±12	NS
Double product, mm Hg/bpm	6420±1623	6219±1511	NS

Values are mean±SD or n (%). CCS indicates Canadian Cardiovascular Society.

Results

Baseline Characteristics

Table 1 illustrates the baseline characteristics of the overall study population. In the overall population (n=379), 240 patients seemed to have an optimal CFVR (defined as a CFVR ≥2.5) after the intervention, but 139 patients did not meet this criterion. Patients with an optimal CFVR seemed to be slightly younger and included a lower percentage of female patients. No significant differences in drug treatment before the procedure (aspirin, β-blockers, nitrates, and calcium-channel blockers) were found between patients with and without an optimal CFVR at the end of the procedure. Heart rate and double-product values were not significantly different when comparing patients with and without an impaired CFVR. A total of 308 patients underwent CFVR measurements of a reference artery (150 and 158 patients in the optimal and suboptimal groups, respectively).

TABLE 2. Doppler-Derived Data of the Patients With and Without an Optimal CFVR After PTCA

	CFVR ≥2.5 (n=240)			CFVR <2.5 (n=139)		
	Reference	Before PTCA	After PTCA	Reference	Before PTCA	After PTCA
Diameter stenosis, %	...	68±11	15±11*	...	70±11	16±11*
Relative CFVR	...	0.60±0.27	1.01±0.34*†	...	0.58±0.18	0.81±0.25*
CFVR	3.10±0.77†	1.71±0.64†	3.12±0.62*†	2.45±0.60	1.47±0.36	1.90±0.37*
Baseline APV	14±7†	14±7	18±9*†	21±9	15±8	22±9*
Hyperemic APV	48±18	23±14	48±18*†	47±20	21±11	43±18*

*$P<0.05$ vs before PTCA in the same group; †$P<0.05$ vs simultaneous measurements in suboptimal group (CFVR <2.5).

Coronary Flow Data in the Optimal and Suboptimal CFVR Groups

As shown in Table 2, patients with a CFVR ≥2.5 after PTCA had a lower baseline average peak flow velocity (APV; 18±9 versus 22±9 cm/s; $P<0.05$) and a higher hyperemic peak flow velocity (48±18 versus 43±18 cm/s; $P<0.05$) in the target artery. In addition, patients with a CFVR ≥2.5 had higher CFVR values in the reference artery than patients with a CFVR <2.5 (3.10±0.77 versus 2.45±0.60; $P<0.001$) due to a lower baseline APV in the reference artery (14±7 versus 21±9 cm/s; $P<0.05$). Relative CFVR was lower in patients with a CFVR <2.5 after completion of the procedure (0.81±0.25 versus 1.01±0.34; $P<0.001$). No difference was seen in the angiographic result of the intervention between the 2 groups. Patients with unstable angina had lower CFVR values in the reference and target arteries after PTCA than patients with stable angina (2.73±0.78 versus 2.93±0.77 and 2.53±0.79 versus 2.74±0.80, respectively; both $P<0.05$). A total of 144 patients (75%) of the patients with a CFVR ≥2.5 and 52 (45%) of the patients with a CFVR <2.5 had a relative CFVR ≥0.8 after the intervention ($P<0.001$). Figure 1 illustrates the significant linear relationship observed between the CFVR after PTCA and the reference artery CFVR ($P<0.001$).

Cardiac Enzyme Analysis After the Intervention

The level of total creatine kinase (CK) was increased in the patients with a CFVR <2.5 after PTCA compared with patients with a CFVR ≥2.5 (103±233 versus 61±48 IU/L; $P=0.03$). Likewise, levels of CK-MB were increased in patients with a suboptimal result (11±15 versus 6±6 IU/L; $P=0.011$).

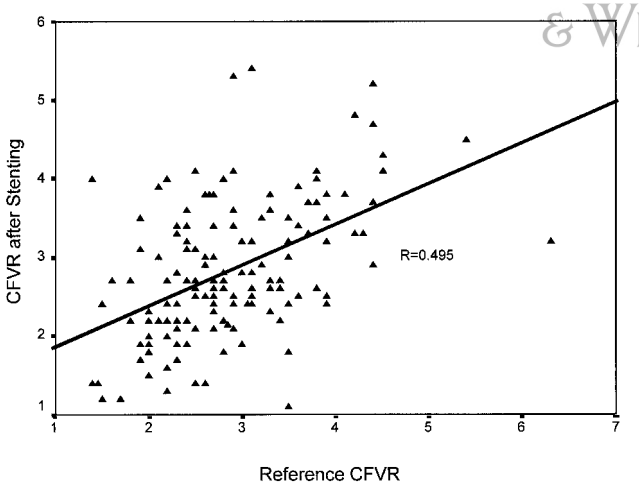

Figure 1. Linear relationship between reference CFVR and CFVR in the target artery after stenting ($R=0.495$; $P<0.001$).

Patients With Prior MI

A total of 37 patients with a Q-wave MI in the non-target vascular territory and 78 patients with previous non-Q-wave MI in the target or nontarget vascular territory were included. These patients with a history of MI had a slightly lower CFVR at the end of the procedure compared with patients without prior MI (2.54±0.7 versus 2.72±0.8; $P<0.05$). Nevertheless, the percentage of MACE in the patients with prior MI was similar to that in the patients without a history of MI during 12 months of follow-up (18 of 115 patients [16%] versus 36 of 264 patients [14%]; P=NS]. Furthermore, patients who had a history of MI in combination with a decreased CFVR (<2.5) at the end of the intervention did not have an increased percentage of MACE compared with patients with a decreased CFVR without prior MI (10 of 49 patients [20%] versus 18 of 90 patients [20%]; P=NS].

Multivariate Predictors of an Optimal CFVR After Balloon Angioplasty

The patients with optimal CFVR results after balloon angioplasty were younger (58±10 versus 61±11 years; $P<0.05$), had a lower proportion of women (20% versus 33%; $P=0.005$), a lower baseline heart rate (66±11 versus 70±12 bpm; $P=0.001$), and a higher diastolic blood pressure (75±16 versus 72±13 mm Hg; $P=0.022$) than those in the suboptimal CFVR group. The optimal group presented with a higher baseline CFVR in the target artery (1.73±0.62 versus 1.47±0.39; $P<0.0001$) and in the reference artery (3.09±0.72 versus 2.50±0.64; $P<0.0001$) compared with the suboptimal group.

By multivariate analysis, an elevated diastolic blood pressure and the absence of unstable angina were found to be the independent clinical predictors of an optimal CFVR result after balloon angioplasty (Table 3). However, after including Doppler-derived data, an elevated diastolic blood pressure and the CFVR values before angioplasty and in the reference artery were found to be the only independent predictors of an optimal balloon CFVR.

Multivariate Predictors of an Optimal CFVR After Stent Implantation

Patients with optimal CFVR results after stent implantation were younger (56±10 versus 60±11 years; $P=0.024$), had a

TABLE 3. Multivariate Predictors of an Optimal CFVR After Balloon Angioplasty

	Clinical Data Alone		Clinical and Doppler	
Variables*	OR (95% CI)	*P*	OR (95% CI)	*P*
Unstable angina	0.45 (0.23 to 0.90)	0.023	...	...
Diastolic blood pressure	1.02 (1.01 to 1.04)	0.002	1.04 (1.01 to 1.08)	0.012
Baseline CFVR	...	...	2.26 (1.57 to 3.24)	<0.001
Baseline reference CFVR	...	...	1.90 (1.21 to 2.98)	<0.001

*Variables include sex, diabetes, hypertension, previous MI or revascularization, baseline heart rate, systolic blood pressure, and diameter stenosis. Lesion characteristics (angulation, calcification, bifurcation, and contour) were not independent predictors.

lower proportion of smokers (53% versus 70%; $P=0.017$), and presented with a higher diastolic blood pressure (76±13 versus 71±12 mm Hg; $P=0.024$) than the suboptimal group. Moreover, higher CFVRs at baseline (1.70±0.68 versus 1.46±0.33; $P<0.0001$), after angioplasty (3.13±0.71 versus 1.89±0.50; $P<0.0001$), and at the reference artery (3.11±0.83 versus 2.41±0.56; $P<0.0001$) were consistently found in the optimal versus the suboptimal stent CFVR group.

In addition, the optimal stent group had a greater proportion of eccentric lesions than in the suboptimal group (45% versus 26%; $P=0.011$). After adjusting for clinical variables, an elevated diastolic blood pressure and the absence of eccentric lesions were found to be associated with an optimal CFVR result after stent implantation (Table 4). After including Doppler-derived variables, the absence of eccentric lesions and elevated values of diastolic blood pressure and CFVR values before angioplasty and at the reference artery were found to be independent predictors of an optimal stent CFVR result.

Independent Predictors of Early and Late Clinical Outcome

During the first 30 days, the event-free survival was 98% for all patients, 99% (1 event) for those with a CFVR ≥2.5, and 96% (7 events) for those with a CFVR <2.5 ($P=0.024$). All these early events occurred during the first 24 hours (1 patient died, 4 patients underwent a repeat angioplasty, and 3 patients had a periprocedural MI).

The ORs for MACE at 30 days and at 1 year for a CFVR <2.5 compared with a CFVR ≥2.5 were 9.2 (95% CI, 1.1 to 75) and 1.9 (95% CI, 1.1 to 3.4), respectively. After 30 days, no significant difference in event-free survival was observed between patients with and without an optimal CFVR at the end of the procedure (90% versus 85%; $P=0.139$).

The 1-year event-free survival was 86% for all patients, 90% for those with a CFVR ≥2.5, and 82% for those with a CFVR <2.5 at the end of the procedure ($P=0.014$ by log-rank test). Figure 2 shows the estimated event-free survival distribution according to the CFVR results at the end of the intervention.

By multivariate logistic analysis, a final CFVR <2.5 was an independent predictor of MACE at 30 days [OR, 4.71; 95% CI, 1.14 to 25.92; $P=0.034$] and 1-year follow-up (OR, 2.06; 95% CI, 1.16 to 3.66; $P=0.014$). In addition, final diameter stenosis was an independent predictor of MACE at 1-year follow-up (OR, 1.04; 95% CI, 1.01 to 1.06; $P=0.03$).

Discussion

The results of this study show that a suboptimal result after angioplasty (CFVR <2.5) is associated with a high risk of early cardiac events. A low CFVR after PTCA was determined by the CFVR before PTCA and the CFVR in the reference artery, which suggest that preexisting microvascular disturbances were a cause of the low CFVR. Furthermore, the association with elevated CK and CK-MB values suggest that microembolization may also explain a low CFVR at the end of the intervention.

Determinants of Impaired CFVR After Angioplasty

In agreement with several studies,[5–7] we found an elevation of baseline APV as a contributing factor for a low postproce-

TABLE 4. Multivariate Predictors of an Optimal CFVR After Stent Implantation

	Clinical Data Alone		Clinical and Doppler	
Variables*	OR (95% CI)	*P*	OR (95% CI)	*P*
Diastolic blood pressure	1.04 (1.01 to 1.06)	0.009	1.06 (1.02 to 1.10)	0.004
Eccentric lesion	0.39 (0.20 to 0.76)	0.006	0.31 (0.13 to 0.77)	0.012
Baseline CFVR	...	...	2.54 (1.47 to 4.36)	0.001
Baseline reference CFVR	...	...	1.97 (1.07 to 3.87)	0.024

*Variables include age, sex; and a history of diabetes, hypertension, smoking, previous MI, or revascularization. Functional angina class; baseline heart rate, systolic blood pressure, and diameter stenosis; and lesion characteristics (angulation, calcification, bifurcation, and contour) were not independent predictors.

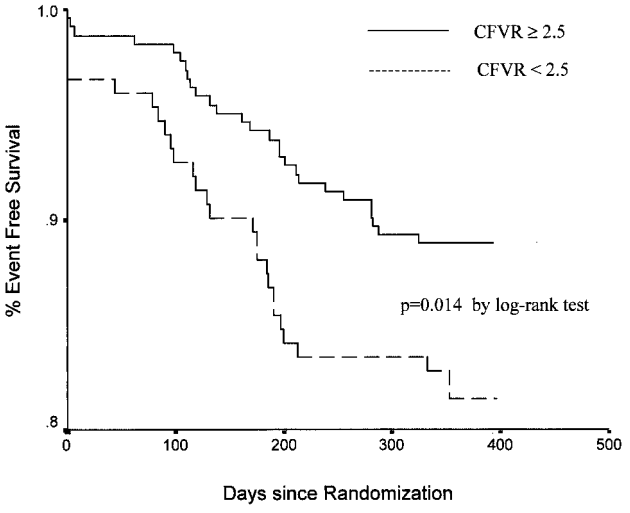

Figure 2. Kaplan-Meier curve of the percentage of event-free survival in the patients with a CFVR ≥2.5 and <2.5 after PTCA.

dural CFVR. Several mechanisms have been postulated for this finding, including (1) epicardial vasoconstriction,[8] (2) delay in the recovery of autoregulation,[1] (3) distal embolization of microparticles,[9] and (4) postocclusive hyperemia. Our data show that a low CFVR after PTCA is determined by the CFVR before PTCA and the CFVR of the reference artery. This phenomenon may be related to several clinical conditions associated with microvascular abnormalities (eg, diabetes mellitus, left ventricular hypertrophy, and diffuse atherosclerotic disease). Furthermore, our results show elevated CK and CK-MB levels in patients with an impaired CFVR after PTCA. This suggests that microembolization may serve as an alternative explanation for the observed microcirculatory disturbances.

Animal and human data have shown an enhanced coronary flow after miocroembolization.[10,11] This phenomenon seems to be due to adenosine-induced hyperemia of the myocardium surrounding the embolized microregions.[12] This interpretation is further supported by a study reporting that patients who experienced a prolonged hyperemic response after a percutaneous intervention had higher creatine phosphokinase values than patients without hyperemia.[13] Similar to those findings, we found a significant difference in cardiac enzyme levels between the patients with an optimal and suboptimal postprocedural CFVR value.

In our study, a low hyperemic response was also responsible for a suboptimal CFVR after balloon angioplasty. The latter has been previously reported, thus underscoring the important role of luminal enlargement for the achievement of an adequate CFVR after balloon angioplasty.[6,14]

We found a significant relationship between the target and the reference artery CFVR after stent implantation, further supporting the concept of a strong influence exerted by the microcirculation on the postprocedural CFVR results. Therefore, a combination of microvascular dysfunction and the severity of the residual stenosis seem to explain a suboptimal CFVR result after angioplasty. After stent implantation, normalization of the CFVR seems to depend primarily on the integrity of the microcirculatory function.

Determination of left ventricular ejection fraction was not performed before the inclusion of the DEBATE II trial. Patients were excluded if they had an ejection fraction <30%. Furthermore, patients were excluded if they had a Q-wave MI in the target vascular territory. However, it is conceivable that the cohort of patients with a Q-wave MI in the nontarget vascular territory or with a previous non–Q-wave MI in the target or nontarget vascular territory included patients with mildly impaired left ventricular function. Analysis showed that the patients with a history of MI (and probably mildly impaired left ventricular function) had a slightly lower CFVR at the end of the procedure compared with patients without prior MI. Nevertheless, the percentage of MACE in the patients with prior MI was similar to that in the patients without a history of MI.

Impaired CFVR After Angioplasty in Relation to Clinical Outcome

In the present study, we observed that the early risk of MACE among the patients with a CFVR <2.5 at the end of the intervention was 9 times as high as that among the patients with an optimal CFVR. After excluding 30-day MACE, no differences in MACE at 1-year follow-up was observed between the patients with and without a CFVR <2.5 at the end of the procedure. Thus, low postprocedural CFVR was associated with a worse periprocedural outcome, although there was no significant difference at late follow-up.

Although the methods used for the evaluation of the clinical outcome were different between our study and DEBATE I, an agreement in short-term results was observed between both studies. In DEBATE I, a postprocedural CFVR <2.5 was associated with a higher recurrence of angina (25% versus 12%; $P=0.19$) and a greater proportion of patients with objective evidence of ischemia (21% versus 8%; $P=0.018$) at the 1-month follow-up compared with their counterparts.

It is conceivable that the elevated risk of early events observed in patients with an impaired postprocedural CFVR was not only related to the residual stenosis geometry but also to microvascular alterations. A low CFVR after PTCA, as an independent predictor of clinical outcome, was determined by the CFVR before PTCA and the CFVR of the reference artery. This suggests that the preexisting microcirculatory disturbances of both the target and reference artery may influence clinical outcome after PTCA. Furthermore, the observed elevated cardiac enzyme levels in patients with an impaired CFVR after PTCA suggest that microembolization may serve as an alternative explanation for the observed microcirculatory disturbances and consequent worse clinical outcome.

Recent data showed that the relative CFVR seems to be a more specific index of persistent conduit obstruction, which may have a role in the postprocedural stratification of the coronary blood flow impairments.[4,5] A good long-term outcome has recently been reported after stent implantation in patients with a relative CFVR >0.88 and minimal luminal diameter >2.77 mm.[15] Moreover, relative CFVR may identify patients with global microcirculatory disease. However, relative CFVR was not a predictor of CFRV after balloon

angioplasty or stent implantation using a univariate analysis. A suboptimal result after PTCA (CFVR <2.5) was associated with a lower relative CFVR compared with patients with an optimal result after PTCA. Nevertheless, relative CFVR was not an independent predictor of clinical outcome after PTCA in a multivariate analysis. These contrasting results might be explained by differences in population size. In the latter study,[15] the authors included only 150 patients; 308 patients with available relative CFVR measurements were included in the present study. Stratification of coronary flow impairments according to relative CFVR results assumes a uniform microcirculatory function.[16] However, this might not be the case even in patients with single-vessel disease.[17]

Limitations

Limitations in Doppler measurements have been extensively described.[18] In the present study, trans-stenotic guidewire pressure-derived fractional flow reserve was not routinely performed. In patients with a low relative CFVR, fractional flow reserve could have helped us verify the presence of a significant residual conduit obstruction and further understand the role of the postprocedural relative CFVR in the guidance of a percutaneous intervention.

The post hoc nature of our analysis prevents us from drawing definitive conclusions, and a prospective evaluation is warranted to confirm our results. Furthermore, this study only included patients with 1-vessel disease and normal left ventricular function.

Clinical Implications

After angioplasty, an impaired absolute CFVR was mainly due to microcirculatory abnormalities that may be either preexisting or caused by periprocedural microembolization. The presence of an impaired postprocedural CFVR warrants monitoring patients more closely because this parameter is associated with a worse short-term clinical outcome, particularly during the first 24 hours after the procedure.

References

1. Uren NG, Crake T, Lefroy DC, et al. Delayed recovery of coronary resistive vessel function after coronary angioplasty. *J Am Coll Cardiol.* 1993;21:612–621.
2. Serruys PW, di Mario C, Piek J, et al. Prognostic value of intracoronary flow velocity and diameter stenosis in assessing the short- and long-term outcomes of coronary balloon angioplasty: the DEBATE Study (Doppler Endpoints Balloon Angioplasty Trial Europe). *Circulation*. 1997;96:3369–3377.
3. Doucette JW, Corl PD, Payne HM, et al. Validation of a Doppler guide wire for intravascular measurement of coronary artery flow velocity. *Circulation*. 1992;85:1899–1911.
4. Baumgart D, Haude M, Goerge G, et al. Improved assessment of coronary stenosis severity using the relative flow velocity reserve. *Circulation*. 1998;98:40–46.
5. Kern MJ, Puri S, Bach RG, et al. Abnormal coronary flow velocity reserve after coronary artery stenting in patients: role of relative coronary reserve to assess potential mechanisms. *Circulation*. 1999;100:2491–2498.
6. van Liebergen RA, Piek JJ, Koch KT, et al. Immediate and long-term effect of balloon angioplasty or stent implantation on the absolute and relative coronary blood flow velocity reserve. *Circulation*. 1998;98:2133–2140.
7. Wilson RF, Johnson MR, Marcus ML, et. The effect of coronary angioplasty on coronary flow reserve. *Circulation*. 1988;77:873–885.
8. el-Tamimi H, Davies GJ, Crea F, et al. Response of human coronary arteries to acetylcholine after injury by coronary angioplasty. *J Am Coll Cardiol*. 1993;21:1152–1157.
9. Hori M, Tamai J, Kitakaze M, et al. Adenosine-induced hyperemia attenuates myocardial ischemia in coronary microembolization in dogs. *Am J Physiol*. 1989;257:H244–H251.
10. Erbel R, Heusch G. Coronary microembolization. *J Am Coll Cardiol*. 2000;36:22–24.
11. Hori M, Inoue M, Kitakaze M, et al. Role of adenosine in hyperemic response of coronary blood flow in microembolization. *Am J Physiol*. 1986;250:H509–H518.
12. Hori M, Gotoh K, Kitakaze M, et al. Role of oxygen-derived free radicals in myocardial edema and ischemia in coronary microvascular embolization. *Circulation*. 1991;84:828–840.
13. Herrmann J, Baumgart D, Ge J, et al. Hyperaemic flow response as an indicator of microembolic events during percutaneous coronary interventions. *Eur Heart J*. 2000;21:514. Abstract.
14. Kern MJ, Dupouy P, Drury JH, et al. Role of coronary artery lumen enlargement in improving coronary blood flow after balloon angioplasty and stenting: a combined intravascular ultrasound Doppler flow and imaging study. *J Am Coll Cardiol*. 1997;29:1520–1527.
15. Haude M, Baumgart D, Welge D, et al. Intracoronary Doppler and quantitative coronary angiography-derived predictors of major adverse cardiac events after stent implantation. *Circulation*. 2001;103:1212–1217.
16. Kern MJ, Bach RG, Mechem CJ, et al. Variations in normal coronary vasodilatory reserve stratified by artery, gender, heart transplantation and coronary artery disease. *J Am Coll Cardiol*. 1996;28:1154–1160.
17. Austin RE Jr, Aldea GS, Coggins DL, et al. Profound spatial heterogeneity of coronary reserve. Discordance between patterns of resting and maximal myocardial blood flow. *Circ Res*. 1990;67:319–331.
18. Carlier SG DC, Kern MJ. Intracoronary Doppler and pressure monitoring. In: Topol EJ, ed. *Textbook of Interventional Cardiology*. 3rd ed. Philadelphia: Saunders; 1998:748–781.