Value of intracoronary Doppler for guiding percutaneous interventions

De waarde van intracoronaire Doppler bij percutane interventies

PROEFSCHRIFT

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Part I

Overview of the Thesis

This thesis attempts to further clarify some of the issues regarding the use of the absolute and relative CFVR. In addition, we search for a more accurate parameter of luminal narrowing.

Chapter II, III and IV, report the various flow velocity patterns observed prior to, after and at 6 month follow-up percutaneous interventions.

The development of coronary artery dissections is a frequent observation following balloon angioplasty. However, very little data is available about the degree of conduit obstruction expected in vessels with moderate dissections. In an attempt to describe the coronary blood flow characteristics in patients with dissections, we utilized various Doppler-derived parameters collected from the DEBATE I and II databases (Chapter V and VI).

Due to the limitations encountered when guiding an intervention with the absolute CFVR, we explored the value of coronary blood flow velocity acceleration at the stenotic site for predicting clinical and angiographic outcomes (Chapter VII and VIII).

Shear stress (the friction force exerted by the blood flow towards the coronary endothelium) has been linked to the pivotal mechanism involved in the restenosis process: 1) vascular remodeling 2) neointimal proliferation. In Chapter IX, we study the prognostic value of the post-procedural averaged shear stress for predicting the clinical and angiographic outcome following balloon angioplasty.

Chapter 1

INTRODUCTION

Following the rapid developments in computer software directed towards the

anatomical assessment of coronary arteries by quantitative coronary angiography

(QCA), interventional cardiologist felt that the anatomical information obtained was

sufficient for clinical decision-making. However, further down the line, it became

clear that QCA presented some limitations especially in patients with diffuse coronary

artery atherosclerosis. In addition, the presence of haziness at the dilated area

precluded an accurate estimate of the acute angioplasty results. The latter was further

supporter by a lack of correlation observed between the QCA and coronary

physiological data following an intervention.

Thanks to the pioneer work of Lance Gould and his team, who established the

relationship between the coronary blood flow resistance and the severity of the

conduit obstruction, the understanding of coronary physiology and its assessment had

rapidly evolved. Furthermore, technical improvements have allowed the development

of miniaturized pressure and Doppler transducers, mounted on 0.014-in. guidewire,

These small devices did not exert a significant effect in coronary fluid dynamics,

which permitted an accurate physiological evaluation of percutaneous interventions at

the catheterization laboratory.

Intracoronary Doppler technique

The Doppler angioplasty guidewire is 0.014" 175 cm long flexible and steerable guidewire with a floppy shapeable distal end mounting a 12-15 MHz piezoelectric transducer at the tip (Cardiometrics Inc, Mountain View, CA). The sample volume is located at a distance of 5.2 mm from the transducer and has an approximate width of 2.25 mm due to divergent ultrasound beam so that a large part of the flow velocity profile is included in the sample volume also in case of eccentric positions of the Doppler guidewire. After real-time processing of the quadrature audio signal a fast-Fourier transform algorithm is used to increase the reliability of the analysis, the Doppler system calculates and displays on-line several spectral variables including the instantaneous peak velocity and the time-averaged (mean of 2 beats) peak velocity. The flow velocity measurements obtained with this system have been validated in vitro and in an animal model using simultaneous electromagnetic flow measurements for comparison. Mean flow velocity is calculated as time-averaged peak velocity/2, assuming a fully developed flow velocity profile.

The Doppler guidewire can be used to assess the severity of the lesion to be treated before angioplasty or stent implantation. During balloon dilatation, the Doppler guidewire is left in place distal to the lesion in order to continuously record the Doppler signal and monitor the development of collateral flow, the restoration of flow after balloon deflation, the phase of post-occlusive reactive hyperemia and, incidentally, the development of flow limiting complications. Immediately after the inflation, the balloon is withdrawn into the guiding catheter in order to avoid the residual obstruction of flow due to the presence of the deflated balloon across the

lesion. The rapid flow velocity increase in the phase of post-occlusion reactive hyperemia can be used to assess the adequacy of lumen enlargement post-angioplasty immediately after deflation of the balloon.

Intracoronary Doppler parameters

Diastolic-Systolic Velocity Ratio

In contrast with flow characteristics of other arterial beds, the epicardial coronary blood flow has a predominant diastolic pulsatility pattern. During systole, myocardial contraction elevates the resistance of the coronary microcirculation translating into a diminished systolic blood flow. On the other hand, a greater systolic blood flow component is observed at the distal portion of the right coronary artery, in which lower compressive forces are observed compared to the left coronary circulation. During severe narrowing of an epicardial artery, the diastolic blood flow reduces whereas the systolic component of the coronary blood flow increase in an attempt to maintain an adequate myocardial perfusion. The latter may be related to changes in the intramyocardial volume. Several animal and human studies have described a reduction of the diastolic/systolic velocity ratio (DSVR) at the presence of a significant stenosis, in which a normalization of the DSVR was seen following balloon dilatation. This observation led to the use of the DSVR for the assessment of a stenosis and for guidance of percutaneous interventions. However, this ratio has shown to have some caveats: 1) it is associated with a high variability, 2) changes in contractility would directly affect the ratio results, 3) a significant overlap was observed when comparing it to pre-procedural QCA or non-invasive testing data. Furthermore, at the DEBATE trial, DSVR carried no additive prognostic value when compared to the combination of the absolute CFVR and QCA data.

No-Reflow Phenomenon

In patients with transmural myocardial infarction, unsuccessful reperfusion is not always related to the presence of a persistent conduit obstruction, but also due to abnormalities of the coronary microcirculation. The occurrence of the no-reflow phenomenon following reperfusion therapies represents a good example of the latter. The no reflow phenomenon may result from microvascular damage, as suggested by myocardial contrast echocardiography performed in patients with TIMI grade 2 flow after PTCA. The mechanism for this was suggested by an animal study, which found that ischemia resulted in the release of cytokines, especially interleukin-1, which stimulated the production of plasminogen activator inhibitor-1 and collagen by cardiac microvascular endothelial cells. This resulted in impaired fibrinolysis and predisposed to the persistence of microvascular thrombi. Other possible mechanisms for the no reflow phenomenon are residual stenosis or diffuse alpha-adrenergic macrovascular and microvascular vasoconstriction, which impair myocardial blood flow and perfusion.

The differentiation between residual stenosis or microvascular damage as a cause for TIMI grade 2 flow has important implications for therapy and left ventricular functional recovery. Hence, in patients with TIMI II flow after primary angioplasty, the presence of a short diastolic deceleration time plus a systolic retrograde flow and/or a very low systolic flow velocity is strongly suggestive of no reflow phenomenon (Table I).

Table I. Coronary flow patterns in patients with TIMI II flow after primary PTCA

	DSVR	DDT	Systolic flow reversal	TIMI Flow with stenting
Residual stenosis	+	+++	Present	Increase
No Reflow	+++	+	Absent	No Change

DDT: indicates diastolic deceleration time.

Thus, the DSVR might also be helpful for deciding whether to further dilate and/or implant a stent versus undergoing measures directed towards the improvement in microvascular function (adenosine, glicoproteins IIb/IIIA inhibitors, verapamil, nitroglycerin)

Proximal-to-Distal Flow Velocity Ratio

In epicardial normal arteries, a modest increase in flow velocity is observed from proximal to distal, inversely proportional to the reduction in total cross-sectional area. This physiological pattern is distorted with the presence of significant stenosis. Proximal to the stenosis, the blood flow is partially deviated to lower resistance branches, translating into a reduction in flow velocity from proximal to distal. This observation led to the utilization of the proximal-to-distal flow velocity ratio for the hemodynamic evaluation of coronary lesion. In one study, this ratio was around 1.1 ± 0.2 in angiographically normal coronary arteries and 2.4 ± 0.7 in patients with significant stenosis. Similar to the DSVR ratio, normalization was observed after coronary angioplasty. However, significant overlap was observed between patients

with limiting and non-limiting coronary lesions. Furthermore, absence of side-branches between the site of the proximal and distal measurements renders this parameter rather useless, since both flow velocities would be equal.

Absolute Coronary Flow Velocity Reserve

A) Intermediate lesion assessment

The absolute coronary blood flow velocity reserve (CFVR) is defined as the ratio of hyperemic to resting coronary blood flow velocity. In one study analyzing 150 angiographically normal arteries in patients with chest pain syndromes, the CFVR was approximately 2.9±0.6, whereas in angiographically normal arteries of patients with single vessel disease was found to be 2.6±0.95. In that study no significant differences were seen between the LAD, LCX or RCA territories.

In several single-center studies and one multicenter trial, a CFVR<2.0 was reported to be strongly correlated with myocardial stress perfusion defects whether assessed by 2D echocardiography or nuclear imaging. In those studies, the presence of an abnormal CFVR had a high sensitivity (86% to 92%), specificity (89% to 100%) and predictive accuracy (89% to 100%) for myocardial perfusion deficits. Several studies have confirmed that in patients with intermediate lesions and CFVR >2.0 a percutaneous intervention could be safely postponed. Nevertheless, the absolute CFVR is not only affected by the epicardial conduit size but also by the integrity of the coronary microcirculation. In a recent data reported by a Dutch group, the microvascular resistance (mean blood pressure / adenosine-induced hyperemic flow) was shown to be a primary determinant of the concordance between the absolute CFVR>2.0 and the FFR>0.75. Thus, in patients with discordant CFVR and FFR, a significantly higher microvascular resistance was found compared to patients with

concordant values. Thus, one could argue that a low CFVR might be associated with perfusion defects not only because of significant conduit obstruction but also due to microvascular dysfunction. This issue remains important since patients with a non-significant obstruction and severe microcirculatory dysfunction might benefit from therapies directed towards improvement of the endothelial dependent and independent microcirculatory function.

B) Doppler-Guided Angioplasty

The aim of the DEBATE trial was to identify a Doppler-derived flow parameter, which would be able to predict the clinical and angiographic long-term outcome. A total of 225 patients underwent sequential intracoronary Doppler assessment prior to and after balloon angioplasty and again at 6-month follow-up. In that study, logistic regression analysis demonstrated that the combination of CFVR and a residual diameter stenosis identifies the best subset group of patients. Thus, the subset of patients with best outcome was those with a CFVR >2.5 and a DS% <35%. When that subset group was compared to the other 3 groups (DS% >35% with or without a CFVR<2.5, DS% <35% with a CFVR<2.5), a significant lower restenosis (16% vs. 41%, p=0.002) and TLR rate (16% vs. 34%, p=0.002) was found at 6-month follow-up. Another interesting finding was that the CFVR was lower in those experiencing early events (2.73 vs. 2.22, p<0.05).

Therefore, this landmark study established for the first time that physiological data carried important prognostic value following a percutaneous intervention. Nevertheless, there are some caveats regarding the use of the absolute CFVR for the assessment of the degree of residual stenosis: 1) the need for an adequate vasodilatation by the coronary microcirculation, 2) its strong dependency on blood

pressure and heart rate changes and 3) the presence of an inappropriate elevation of

resting blood flow velocity potentially underestimating the CFVR results.

Several alternative uses of the absolute CFVR have also been reported in the literature

such as acethylcholine-induced CFVR as a surrogate of the endothelial-dependent

microcirculatory function, following acute myocardial infarction as a marker

myocardial integrity and prognosis, for the detection of cardiac rejection. However,

for the purpose of this book, we will focus only on the CFVR results following

percutaneous interventions.

Relative Coronary Flow Velocity Reserve: a more lesion-specific physiological
evaluation

A) Intermediate lesion assessment:

 Since CFVR is similar at the three major vessel territories, concomitant evaluation of

the target and a non-treated normal vessel (CFVR target/reference ratio) would

exclude for abnormalities in CFVR due to hemodynamics or microvascular disease.

This ratio, the relative CFVR, is claimed to be more lesion-specific than just the

absolute CFVR. Baumgart et al. compared the absolute and relative CFVR to the

Fractional flow reserve (FFR, calculated as the ratio of the absolute distal coronary

pressure and aortic pressures measured during maximal hyperemia) in 24 coronary

lesions ranging from 40% to 95%. In that study, only the FFR and the relative CFVR

showed a strong correlation to percent area of stenosis. Furthermore, a close linear

relationship was found between the relative CFVR and the FFR. However, Piek's

group did not duplicate these results. They found that the pre-procedural relative

CFVR was not more useful than absolute CFVR. One may argue that the populations

were different between the two groups: in Baumgart et al, 18/21 patients had single

vessel disease whereas in Piek et al, the great majority had multivessel disease. Maybe

patients with one vessel disease are more suitable candidates whenever making

clinical decisions based on the relative CFVR.

B) Doppler-Guided Angioplasty

To the best of my knowledge, only one study has been reported showing the predicted

value of the relative CFVR following percutaneous interventions. In that study, 99

stented patients followed for 6 months underwent sequential Doppler measurements

of the target and an angiographically normal reference vessel after balloon angioplasty

and stent implantation. The cut-off value for the absolute and relative CFVR was 2.7

and 0.88, respectively. The sensitivity, specificity, negative and positive predictive

value for both cut-off values are depicted in table II.

Table II.

Parameter	Cut-off Value	Sensitivity	Specificity	PPV	NPV
MLD (mm)	2.65	72%	79%	43%	93%
% stenosis	11%	83%	61%	32%	94%
CFVR	2.7	83%	75%	43%	95%
RCVR	0.88	78%	84%	52%	94%

RCFVR: indicates relative CFVR, PPV and NPV: positive and negative predictive

value.

It appears from this study that patients with CFVR > 2.7 or a relative CFVR >0.88 are

at very low risk of MACE.

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Part *II*

Doppler Flow Velocity Characteristics

Chapter 2

Flow Velocity and Predictors of a Suboptimal Coronary Flow Velocity Reserve After Coronary Balloon Angioplasty

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Introduction

Coronary flow velocity reserve (CFR) has been used in the catheterization laboratory to assess the changes in coronary blood flow after balloon angioplasty (BA)(1). The DEBATE I clinical trial suggested that the risk of clinical and angiographic restenosis is significantly lower in patients with optimal BA results defined as a CFR ≥2.5 and a residual percentage diameter stenosis (DS) ≥35%, than in patients not fulfilling these criteria(2). However, this combined endpoint is not met in more than 50% of patients due to a suboptimal CFR(3-5). An elevation of baseline flow, insufficient augmentation of the hyperemic flow or a combination of both are accepted explanations for a suboptimal CFR. Little is known about acute and long-term flow velocity changes in patients achieving or not achieving the optimal CFR after BA. Understanding the mechanisms and predictors of a post-procedural suboptimal CFR appears to be important for clinical-decision making, e.g. considering strategies of provisional stenting.

Therefore, the aim of the study was to analyze the baseline and hyperemic flow velocity changes immediately after BA and at 6 months follow-up and to search for independent predictors of a suboptimal result.

Methods

Patient Selection

The methods of the DEBATE trial have been previously described(2). In summary, 225 patients undergoing BA and sequential Doppler flow velocity assessment were included. Patients without complete angiographic and Doppler follow-up (n=42) were

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excluded from our analysis. The overall remaining population (n=183) was divided into 2 groups according to a postprocedural CFR cut-off value of 2.5. A value lower than 2.5 was considered as suboptimal result.

Angioplasty Procedure and Flow Velocity Assessment

BA was performed according to conventional methods. A 0.014-in Doppler tipped guidewire was used as the primary angioplasty guidewire (FloWire, Endosonics, Rancho Cordova, CA)(6). Measurements of flow velocity (average peak velocity, APV) at rest (b-APV) and on maximal hyperemia (h-APV) were performed distal to the lesion prior to BA, after BA and at 6 months follow-up. Maximal hyperemia was induced by an intracoronary bolus injection of adenosine 12 μgr for the right coronary artery and 18 μgr for the left coronary artery system. The CFR was calculated as ratio between maximal flow velocity during the peak effect of the adenosine injection and the basal flow velocity (h-APV / b-APV). Determination of the end point of the angioplasty procedure was based on angiographic criteria (DS<50% in any angiographic view), only.

Quantitative Angiographic Measurement

Angiographic measurements were done prior to BA, after BA and at 6 months follow-up. Quantitative assessment of reference diameter (RD), minimal lumen diameter (MLD) and diameter stenosis (DS) was performed using multiple projections by an independent core laboratory (Cardialysis, BV) utilizing CAAS II analysis software (Pie Medical, Mastricht, The Netherlands)[Reiber, 1985 #551; Reiber, 1985 #433].

Statistical Analysis

Continuous variables are expressed as mean ± 1SD. Differences within these variables before and immediately after PTCA were evaluated by paired Student's t-test. Differences between subgroups of patients were evaluated by unpaired Student's t-test. Categorical data were analyzed using chi-square or Fisher's exact test when appropriate. Univariate and multivariate logistic regression analysis was performed to search for independent predictors of a suboptimal CFR result. All p-values were two-tailed, with statistical significance indicated by a value of $p < 0.05$.

Results

Baseline Patients Characteristics

Patients' baseline characteristics are summarized in Table 1. 88 (48%) Patients experienced a suboptimal CFR lower than 2.5. This group had higher age and a higher proportion of females.

Angiographic Data

Angiographic lesion characteristics and serial quantitative data are summarized in Table 2. Similar MLD and DS were observed among the suboptimal and optimal CFR group prior to BA, after BA and at 6 months follow-up. The suboptimal CFR group showed a trend towards lower RD.

Changes in Coronary flow Velocity Over Time

Serial coronary flow velocity measurements are given in Table 3. After BA, both groups improved their CFR. The suboptimal CFR group showed a lower diastolic blood pressure after BA than the optimal CFR group. In the suboptimal CFR group, b-APV values were consistently higher than in the optimal CFR group (prior to BA,

after BA and at follow-up) whereas the hyperemic response was diminished after BA (figure 1).

Association Between Angiography and CFR

Analysis of MLD and CFR measurements showed no correlation after BA (R=0.02, p=NS), whereas before angioplasty and at follow-up a significant relationship was observed. The Pearson correlation between these 2 parameters prior to BA was r=0.491 (p<0.001) and r=0.513 (p<0.001) at 6 months follow-up (Figure 2).

Table 1. Baseline Characteristics

	CFR < 2.5 n=88	CFR >2.5 n=95	p-value
Age (years)	61±9	58±10	0.002
Male sex	58(67)	85(88)	0.001
Cardiovascular risk factors			
Current smoking	18(21)	28(29)	NS
Diabetes mellitus	11(13)	11(11)	NS
Hypercholesterolemia	56(48)	54(57)	NS
Hypertension	32(36)	27(28)	NS
Family history of CAD	40(46)	49(51)	NS
Previous myocardial infarction	15(17)	19(20)	NS
Exertional angina (CCS*)			NS
Class I/II	35(53)	68(72)	
Class III/ IV	43(47)	27(28)	
Unstable angina	47(54)	53(56)	NS.

Values are given as mean±1SD or as number of patients (proportion of patients %).

CCS: Exertional angina was categorized according to the classification system of the Canadian Cardiovascular Society, CAD: Coronary artery disease

Table 2. Angiographic Characteristics and Quantitative Data

		CFR < 2.5 n=88	CFR >2.5 n=95	p-value
Lesion location	LAD	40(45)	46 (48)	NS
	LCX	27(31)	21 (23)	
	RCA	21(24)	28 (29)	
Type of lesion †	A	11(13)	11(12)	NS
	B	76(86)	83(87)	
	C	1(1)	1(1)	
Reference diameter (mm)		2.79±0.51	2,90±0.42	0.093
Minimal lumen diameter (mm) pre		1.04±0.30	1.09±0.34	NS
Diameter stenosis (%)	pre	62±9	62±9	NS
Minimal lumen diameter (mm) post		1.76±0.40	1.80±0.37	NS
Diameter stenosis (%)	post	37±9	37±8	NS
Minimal lumen diameter (mm) fup		1.56±0.52	1.56±0.52	NS
Diameter stenosis (%)	fup	44±14	44±16	NS

Values are given as mean±1SD or as number of patients (proportion of patients %).

†   Classification according to the American College of Cardiology/American Heart Association task force on the assessment of diagnostic and therapeutic cardiovascular procedures.

LAD: Left anterior descending coronary artery, LCX: Left circumflex coronary artery, RCA: Right coronary artery, Pre: Pre-procedural, Post: Postprocedural, Fup: 6- Month follow-up

Table 3. Serial Coronary Flow Data

		CFR <2.5 (n=88)			CFR≥2.5 (n=95)		
		Pre-BA	Post-BA	Follow-up	Pre-BA	Post-BA	Follow-up
HR	(bpm)	71± 12	69±13 †	67.9±11	70±12	68±12†	67±11
DBP	(mmHg)	71±11	70±11	73±11	74±11	74±11*	74±12
SBP	(mmHg)	132±22	128±22	133±21	129±22	125±22	128±22
b-APV	(cm/sec)	17±8	22±9 †	20±11	15±7 *	15±5*	16±7*‡
h-APV	(cm/sec)	25±15	43±16 †	43±20	25±16	50±17† *	44±18‡
CFR		1.43±0.56	1.95±0.35 †	2.34+0.90‡	1.71±0.73 *	3.42±0.76† *	2.84±1.01*‡

Values are given as mean±1 SD. HR: Heart rate, DBP: Diastolic blood pressure,

SBP: Systolic blood pressure, b-APV: Baseline average peak velocity, h-APV: Hyperemic average peak velocity, *p<0.05 vs. CFR<2.5;   † p<0.05 vs pre-BA;   ‡ p<0.05 vs post-BA

Predictors of Post-Procedural CFR

Multivariate logistic regression analysis revealed increasing age (OR 1.071, 95% CI 1.033 to 1.110, p=0.0002), female gender (OR 2.52, 95% CI 1.204 to 5.291, p=0.014) and increasing pre-procedural b-APV (OR 1.056, 95% CI 1.013 to 1.100, p<0.001) as independent predictors of the post-procedural CFR results. Reference diameter, postprocedural MLD, h-APV before BA, postprocedural diastolic blood pressure and heart rate were included in the model but did not predict a suboptimal result.

Discussion

The major finding of this study is that a postprocedural suboptimal CFR is related to the combination of a transient deficit in hyperemic APV response and a chronically elevated baseline APV.

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Several studies have previously described the changes observed in baseline and maximal velocities following BA(4,5,7). However, only one study stratified the patients according to the CFR (< or > 2.5) in an attempt to identify the mechanism responsible for a suboptimal result. In that paper, the authors described a transient elevation of b-APV as the only cause for impairment of CFR(4). However, that study is limited due to the relatively small sample size (n=56). In contrast with that study, in our analysis, the suboptimal CFR group was associated with a transient deficit in h-APV and a persistent elevation in b-APV (before BA, after BA and at 6 months follow-up) when compared to the optimal group.

Baseline Velocities and Suboptimal Results

In our study, patients with suboptimal CFR results were found to be older than the optimal group. Czernin et al. described in healthy elderly volunteers an elevated flow at rest and similar hyperemic flow than in the control group(8). Elderly people usually present conditions associated with high oxygen consumption, such as high blood pressure, decreased arterial distensibility and ventricular hypertrophy, which could lead to a higher baseline flow. Since we found no significant differences in post-procedural MLD between the optimal and suboptimal group, we could assume that an enhanced baseline flow expected in the suboptimal group would also translate into higher baseline flow velocity. The latter might partially explain the persistent elevation of b-APV found in patients with suboptimal CFR results.

Although a linear relationship between heart rate and resting flow has already been described(9), no relationship between heart rate and baseline flow velocity was found in our study.

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Adenosine-Induced Maximal Velocities Following BA

Several reports have shown that the presences of a significant hemodynamic obstruction in coronary blood flow, microvascular dysfunction or the combination of both are the main reasons for a diminished h-APV(10-13).

Although similar MLD and DS were found in both groups, a lower CFR was found in the suboptimal group throughout the study period. The latter discrepancy between anatomy and CFR could be related to differences in the ability to fully vasodilate in response to adenosine infusion. In contrast with our results, Kern et al. reported a strong relationship between the residual epicardial obstruction assessed by IVUS and postprocedural CFR(7). However, the authors reported no relationship when comparing CFR and QCA data after BA, possibly due to the inaccuracy of QCA in assessing the functional gain following a percutaneous intervention.

Recently, we reported a strong association between the target and reference vessel CFR(14), showing no improvement in CFR with additional stent implantation in patients with impaired reference CFR in spite of significant enlargement of the epicardial lumen, suggesting that a great deal of the post-procedural CFR results are dependent on the microvascular function rather than on the anatomical gain. Temporary microvascular dysfunction has been associated in the literature to alpha-adrenergic discharge(13), platelet-aggregates embolization(15) and microvascular stunning.

Smoothening of the epicardial luminal surface or healing of residual dissections might also be responsible for the elevation of the h-APV at 6-month follow-up. This controversy could have been clarified by the assessment of the relative CFR (target vessel CFR divided by the adjacent angiographically normal vessel CFR)(16).

Limitations

The technical limitations in intracoronary Doppler assessment have been described in extense. In our study, QCA was used to assess the anatomical gain. However, QCA could overestimate the actual functional luminal dimensions. Therefore, intracoronary ultrasound (IVUS) imaging or the measurements of the residual transtenotic pressure gradient on maximal hyperemia (FFR) would have helped to assess the degree of luminal enlargement achieved following BA as well as to exclude the presence of dissections missed by the angiography in the suboptimal group as a likely cause of residual obstruction(17).

In our study, we did not assess if an attenuated hyperemic response would have improved with the additional application of Yohimbine infusion. This is especially important since the superimposed infusion of Yohimbine after intracoronary injection of adenosine has proved to increase an already suspected maximal hyperemic response(18).

Summary

In our study a postprocedural suboptimal CFR was related to a chronically elevated b-APV and a temporary inability to mount an adequate hyperemic response. Elderly and female patients as well as patients with elevated pre-procedural b-APV are associated with a suboptimal CFR. Further studies combining intracoronary assessment of coronary flow velocities and pressure should be designed for a better understanding of the different coronary flow impairments following BA.
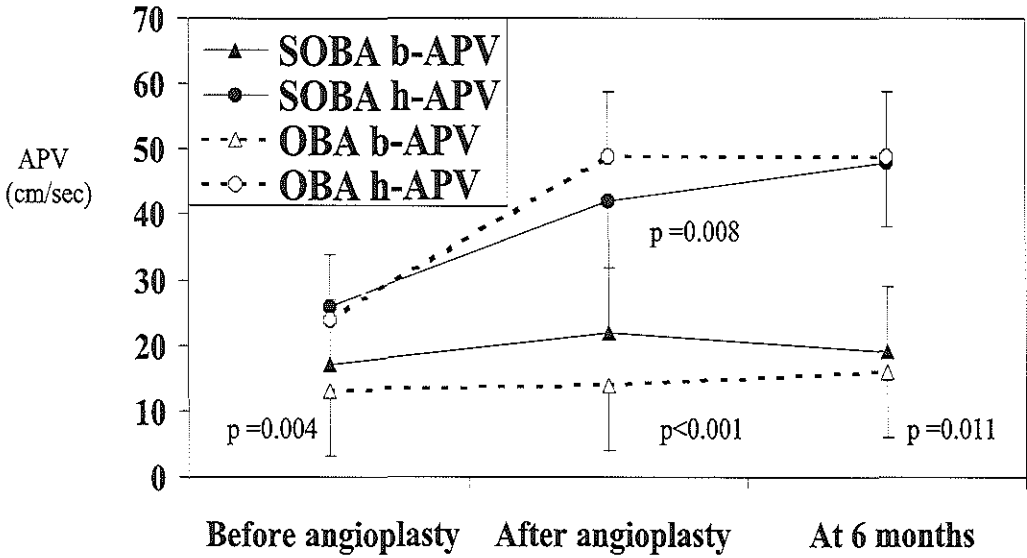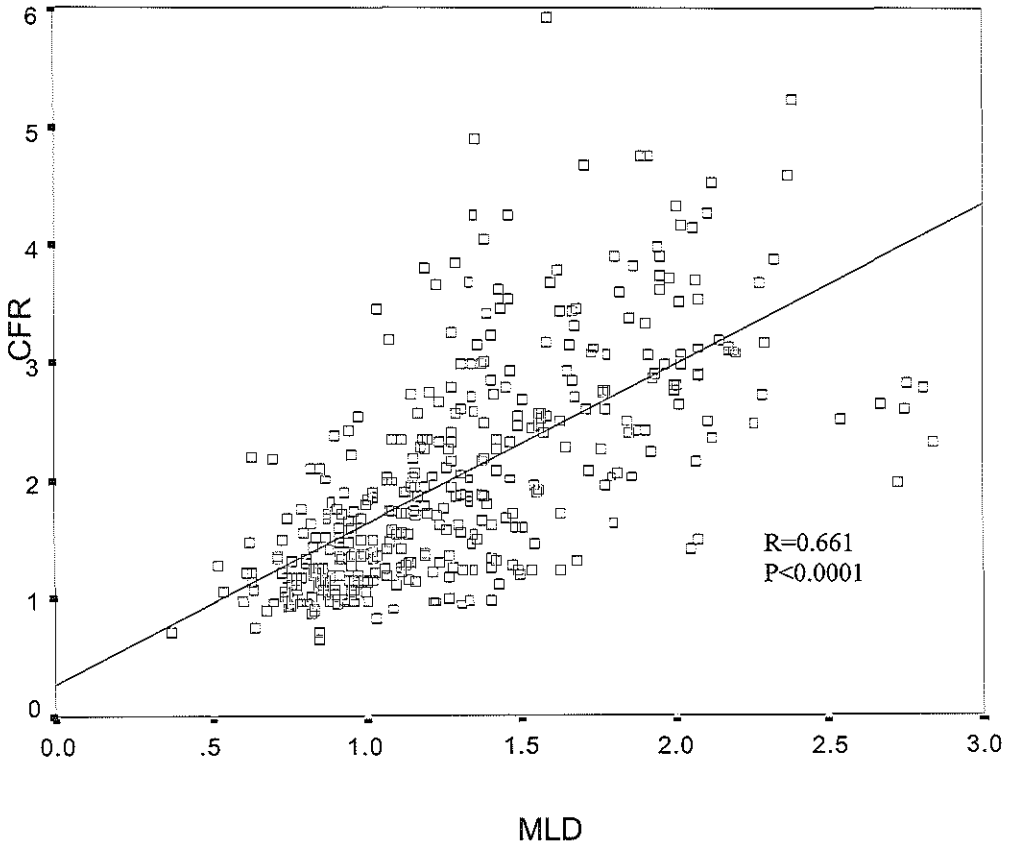
Figure 1

Figure 2

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Coronary Flow Velocity Reserve After Percutaneous

Interventions is Predictive of Peri-procedural Outcome

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ABSTRACT

Background: Analysis of the post-procedural coronary flow velocity changes has shown heterogeneous results. We endeavored to quantify the 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 DEBATE II study, 379 patients undergoing balloon angioplasty were randomized to additional stent implantation (n=187) or no further treatment (n=192). All patients were evaluated according to their coronary flow velocity reserve (CFVR) results ($\geq$2.5 and < 2.5) after angioplasty and again at the end of the catheterization procedure. A CFVR <2.5 after PTCA was associated with an elevated baseline blood flow velocity in both the target artery and reference artery. The only independent predictors of an optimal CFVR after angioplasty were the CFVR before angioplasty [odds ratio (OR) 2.041, 95% confidence intervals (CI) 1.297-3.212, p=0.002] and at the non-treated vessel (OR 2.66, 95%CI 1.83-3.85, p<0.001). 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 1 at year follow-up (OR 2.17, 95% CI 1.22 to 3.85, p=0.008). After excluding 30 days MACE, no differences in MACE at 1year follow-up was observed between the patients with and without a CFVR <2.5 at the end of the procedure.

Conclusions: A low post-procedural CFVR was associated with a worse peri-procedural outcome, related to microcirculatory disturbances, while there was no significant difference at late follow-up.

Keywords: angiography; intracoronary Doppler; microcirculation

CONDENSED ABSTRACT

The prognostic value and determinants of the postprocedural coronary flow velocity reserve (CFVR) was investigated in 379 patients enrolled in the DEBATE II trial. A CFVR <2.5 (suboptimal) after PTCA was characterized by an elevated baseline blood flow velocity in both the target artery and the reference artery. A suboptimal CFVR was correlated with a low pre-procedural and reference CFVR. A low postprocedural CFVR predicted major cardiac events (MACE) at 30 and 360 days follow-up. Thus, the low post-procedural CFVR was associated with a worse peri-procedural outcome, related to microcirculatory disturbances, while there was no significant difference at late follow-up.

INTRODUCTION

Coronary flow velocity reserve (CFVR) has been used in the catheterization laboratory to assess the physiological stenosis significance and the changes in coronary blood flow after balloon angioplasty[1]. The Debate I trial has recently demonstrated that the recurrence of clinical events following angioplasty was markedly larger in patients with CFVR <2.5 (24% vs. 12%)[2].

The Debate II clinical trial was designed to test the value of a stategy of provisional stenting, defined as stenting only when suboptimal angiographic and CFVR results were observed after angioplasty, as compared to a strategy of elective stenting. In patients of the DEBATE II study, in whom the CFVR had been monitored throughout the procedure, we analyzed the clinical predictive value of the 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 amenable for stent implantation were eligible for the DEBATE II trial. Patients with total coronary occlusion, 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 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 QCA guided coronary angioplasty (n=521). Patients without Doppler data available (n=13) or undergoing bailout stenting (n=129) were excluded from the guided-angioplasty group.

Regardless of the CFVR results after balloon angioplasty, these remaining 379 patients underwent a second randomization to additional stenting (n=187) or no further treatment (n=192). For 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 (CFVR ≥2.5; n=240) and suboptimal (CFVR <2.5; n=139). In contrast to the DEBATE II study protocol, in the present study, QCA data following 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 pre-set criteria.

Optimal CFVR and QCA were defined as ≥2.5 and a percentage diameter stenosis <35%, respectively. An 'optimal (QCA and CFR) result' was expected to be achieved by upsizing the balloon and/or increasing the inflation pressure. Bail-out stenting was allowed in the following situations: a residual stenosis of more than 50 percent, dissection type D, E or F, persistent myocardial ischemia along with a dissection type C, drop in Thrombolysis in Myocardial Infarction (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 coronary flow velocity reserve were assessed. Hereafter, and irrespective of these measurements, the second randomization was performed.

Quantitative Coronary Angiography

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

CFVR measurement

A 0.014" Doppler guide wire (Cardiometrics FloWire®; EndoSonics, Rancho Cordoba, CA, USA) 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 µg/kg/min) of adenosine. Target vessel Doppler measurements were performed prior to and after angioplasty and again following stent implantation. In addition, Doppler measurements of an adjacent angiographically normal vessel (less than 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 non-treated vessel CFVR[4]. The CFVR was considered normalized when the relative CFVR ≥0.8 [5,6].

Endpoints

For the Debate II study, the efficacy endpoint was a composite of major adverse cardiac events within twelve months of the procedure and included: death from any cause, non-fatal myocardial infarction and percutaneous or surgical target lesion revascularization. Myocardial infarction 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 twelve-lead electrocardiogram and a complete physical examination. No follow-up angiogram was performed unless clinically indicated.

Statistical Analysis

Continuous variables are expressed as mean ± standard deviation, and differences between groups of patients were studied using the unpaired Student's t-test or one-way analysis of variance, whichever was appropriate. Categorical variables are presented as percentages and differences between groups are evaluated using the Fisher's exact test, Chi Square or long-rank test whenever appropriate. Odds ratio and 95 percent confidence intervals 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, angiographic with (model 1) or without Doppler-derived data (model 2) 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 follow-up. All statistical tests were 2-tailed and significance was stated at the 0.05 level.

RESULTS

Baseline Characteristics

Table I illustrates the baseline characteristics of the overall study population. From the overall population (n=379), 240 patients appeared to have an optimal CFVR after the intervention, defined as a CFVR ≥2.5, whereas 139 patients did not meet this criterion. Patients with an optimal CFVR result appeared to be slightly younger, with a lower percentage of female patients. No significant differences in drug treatment prior to the procedure (aspirin, beta 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 group, respectively).

Coronary flow data in the optimal and suboptimal CFVR groups

As shown in Table II, patients with a CFVR ≥2.5 following PTCA had a lower b-APV (18±9 vs. 22±9, $p < 0.05$) and a higher h-APV (48±18 vs. 43±18, $p < 0.05$) 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 vs. 2.45±0.60, p<0.001), due to a lower b-APV in the reference artery (14±7 vs. 21±9, p<0.05). Relative CFVR was lower in patients with a CFVR <2.5 after completion of the procedure (0.81±0.25 vs. 1.01±0.34, p<0.001). No difference was seen in the angiographical result of the intervention between the two groups. Patients with UA had lower CFVR values in the reference and target artery after PTCA than patients with stable anginal complaints (2.73±0.78 versus 2.93±0.77 and 2.53±0.79 versus 2.74±0.80, respectively; both p<0.05). 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 to 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±6IU/L; p=0.011).

Multivariate predictors of an optimal CFVR after balloon angioplasty

The patients with optimal CFVR results after balloon angioplasty were younger (58±10 vs. 61±11, p<0.05), had a lower female gender proportion (20 vs. 33%, p=0.005) and baseline heart rate (66±11 vs. 70±12, p=0.001) as well as higher diastolic blood pressure (75±16 vs. 72±13, p=0.022) than the suboptimal CFVR group. The optimal group presented with a higher baseline CFVR in the target (1.73±0.62 vs. 1.37±0.39, p<0.0001) and at the reference artery (3.09±0.72 vs. 2.50±0.64, p<0.0001) compared to 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 III). However, after including Doppler-derived data, an elevated diastolic blood pressure and the CFVR values before angioplasty and at the non-treated vessel were found to be the only independent predictors of an optimal balloon CFVR. (Table III)

Multivariate predictors of an optimal CFVR after stent implantation

Patients with optimal CFVR results following stent implantation were younger (56 ± 10 vs. 60 ± 11, p=0.024), had a lower smoker proportion (53 vs. 70%, p=0.017) and presented with higher diastolic blood pressure (76 ± 13 vs. 71 ± 12, p=0.024) than the suboptimal group. Moreover, a higher CFVR at baseline (1.70 ± 0.68 vs. 1.37 ± 0.33, p<0.0001), following angioplasty (2.59 ± 0.69 vs. 1.89 ± 0.50, p<0.0001) and at the reference vessel (3.11 ± 0.83 vs. 2.41 ± 0.56, p<0.0001) was consistently found in the optimal when compared to the suboptimal stent CFVR group.

In addition, the optimal stent group had a greater proportion of eccentric lesions than in the suboptimal group (45 vs. 26 %, p=0.011, respectively). 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 following stent implantation (table IV). After including Doppler-derived variables, the absence of eccentric lesions, elevated values of diastolic blood pressure, CFVR values before angioplasty and at the reference vessel were found to be independent predictors of an optimal stent CFVR result (Table IV).

Independent predictors of early and late clinical outcome

During the first 30 days, the event-free survival was 98% for all patients, 99% (n=1) for those with a CFVR ≥2.5 and 96% (n=7) for those with a CFVR<2.5 (p=0.024). All these early events occurred during the first 24 hours (1 death, 4 repeat angioplasty and 3 periprocedural myocardial infarction).

The one-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.

The estimated hazard ratio for MACE at 30 days and at one year for a CFVR<2.5 as compared with a CFVR ≥2.5 was 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% vs. 85%, p=0.139).

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 DS was found to be an independent predictor of MACE at 1-year follow-up (OR 1.04, 95% CI 1.01 to 1.06, p=0.003).

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 event. A low CFVR after PTCA is determined by the CFR before PTCA in the reference artery, suggestive of pre-

existing microvascular disturbances as a cause of the low CFVR. Furthermore, the association with elevated CK and CK-MB values suggest that micro-embolization may also be operative to 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 the b-APV as a contributing factor for a low post-procedural CFVR. Several mechanisms have been postulated for this finding such as: 1) epicardial vasoconstriction[8] 2) delay in the recovery of autoregulation[1] 3) distal embolization of microparticles[9] 4) post-occlusive hyperemia. Our data show that a low CFVR after PTCA is determined by the CFVR before PTCA and CFVR of the reference artery. This phenomenon may be related to several clinical conditions associated with microvascular abnormalities (e.g. diabetes mellitus, left ventricular hypertrophy, diffuse atherosclerotic disease). Furthermore, our results show elevated CK and CK-MB levels in patients with an impaired CFVR after PTCA. This suggests that micro-embolization may serve as an alternative explanation for the observed microcirculatory disturbances.

Animal and human data have shown an enhanced coronary flow following miocroembolization [10,11]. This phenomenon appears 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 have been associated with higher CPK values than patients without hyperemia[13]. Equivalent with those findings, we found a significant difference of cardiac enzyme levels between the patients with an optimal and suboptimal post-procedural CFVR value, as stated.

In our study, also a low hyperemic response was also responsible for a suboptimal CFVR after balloon angioplasty. The latter has been previously reported, 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 post-procedural CFVR results. Therefore, a combination of microvascular dysfunction and the severity of the residual stenosis appear to explain a post-angioplasty suboptimal CFVR result. Following stent implantation, normalization of the CFVR appears to be primarily dependent on the integrity of the microcirculatory function.

Impaired CFVR following 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 days 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 post-procedural CFVR was associated with a worse peri-procedural outcome, while there was no significant difference at late follow-up.

Although the methods used for the evaluation of the clinical outcome was different between our study and DEBATE I, an agreement in acute results was observed between both studies. In DEBATE I, a post-procedural CFVR <2.5 was associated with a higher recurrence of angina (25% vs. 12%, p=0.19) and a greater proportion of

patients with objective evidence of ischemia (21% vs. 8%, p=0.018) at one-month follow-up compared to their counterparts.

It is conceivable that the elevated risk of early events observed in patients with an impaired post-procedural CFVR was not only related to the residual stenosis geometry but to microvascular alterations. A low CFVR after PTCA, as an independent predictor of clinical outcome, was determined by the CFVR before PTCA and CFVR of the reference artery, as stated before. This suggests that pre-existing 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 micro-embolization may serve as an alternative explanation for the observed microcirculatory disturbances and consequent worse clinical outcome.

Recent data showed that the relative CFVR appears 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]. Moreover, 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[15]. However, in the present study, multivariate analysis showed that a low relative CFVR was not associated with an enhanced risk of cardiac events neither following angioplasty nor stent implantation. these contrasting results might be explained by differences in population size. In the latter study, the authors included 150 patients, whereas a total of 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 patients[17].

LIMITATIONS

Limitations in Doppler measurements have been extensively described [18].

In the present study, transtenotic guidewire pressure-derived FFR was not routinely performed. In patients with a low relative CFVR, FFR could have helped us verify the presence of a significant residual conduit obstruction and further understand the role of the post-procedural relative CFVR in the guidance of a percutaneous intervention. The post-hoc nature of our analysis prevents us from drawing definitive conclusion and a prospective evaluation is warranted to further confirm our results. Furthermore, this study only included patients with one vessel disease and normal left ventricle function.

CLINICAL IMPLICATIONS

After balloon angioplasty, an impaired absolute CFVR was due to microcirculatory abnormalities and a significant residual anatomical obstruction whereas after stenting it was primarily related to a persistent elevation in the baseline velocity. The presence of an impaired post-procedural CFVR warrants more closely monitoring of patients as it is associated with a worse short-term clinical outcome, in particularly during the first 24 hours after the procedure. The latter endorses the concept of provisional stenting.

Reference CFVR

Figure 1

Days since Randomization
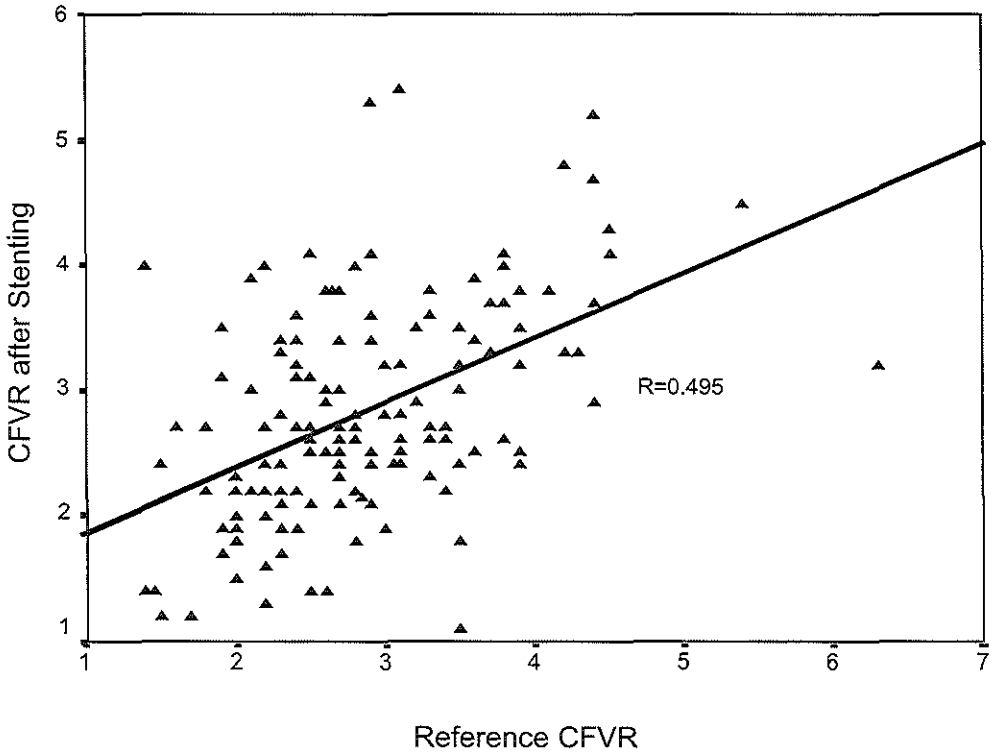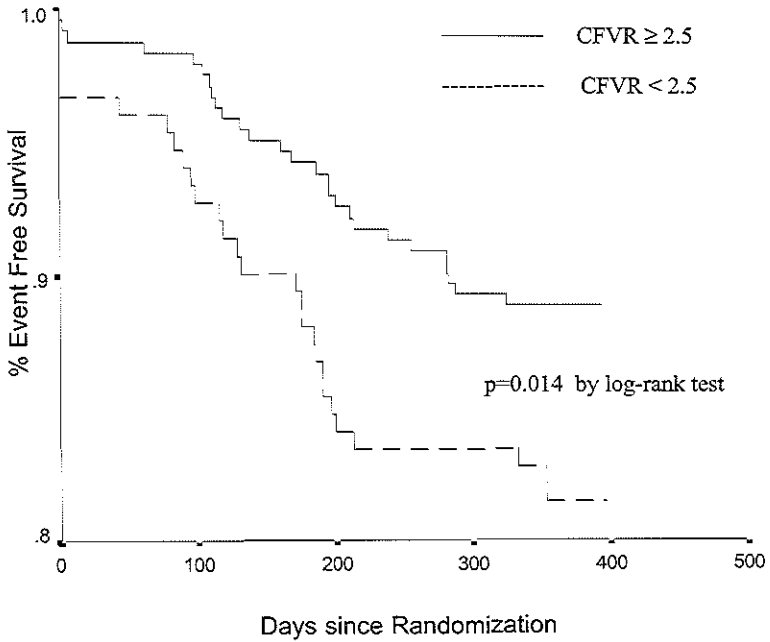
Figure 2

Table I. Baseline characterisitcs of the patients with a CFVR ≥2.5 (Group E) and <2.5 (Group F) at the end of the procedure.

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

CCS indicates Canadian Cardiovascular Society

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Table II. Doppler-derived data of the patients with and without a low CFVR after additional stenting

	Group A (n=240)			Group B (n=139)		
	Reference	Before PTCA	After PTCA	Reference	Before PTCA	After PTCA
DS (%)		68±11	15±11*		70±11	16±11*
Relative CFR		0.60±0.27	1.01±0.34*†		0.58±0.18	0.81±0.25*
CFR	3.10±0.77†	1.71±0.64†	3.12±0.62*†	2.45±0.60	1.47±0.36	1.90±0.37*
b-APV	14±7†	14±7	18±9*†	21±9	15±8	22±9*
h-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 group F.

Group A and B: indicates CFVR ≥ or < 2.5 at the end of the procedure. Reference: Reference vessel, b- and h-APV: baseline and hyperemic average peak velocities; DS: percentage diameter stenosis

Table III. Multivariate predictors of an optimal CFVR following angioplasty

	Clinical data alone		Clinical and Doppler data	
	Hazard ratio		Hazard ratio	
Variables*	(95% CI)	P value	(95% CI)	P value
Unstable angina	0.45 (0.23 to 0.90)	0.02		
Diastolic blood pressure	1.04 (1.01 to 1.07)	0.002	1.04 (1.01 to 1.08)	0.012
CFVR			8.88 (2.72 to 28.8)	0.003
Ref CFVR			5.91 (2.76 to 12.6)	<0.001

* Gender, diabetes, hypertension, previous myocardial infarction or revascularization, functional angina baseline heart rate, systolic blood pressure and diameter stenosis, lesion characteristics (angulation, calcification, bifurcation, contour) were not independent predictors. CFVR: indicates measurements performed before angioplasty; Ref CFVR: measurements performed at the non-treated vessel.

Table IV. Multivariate predictors of an optimal CFVR following stent implantation

Variables*	Clinical data alone Hazard ratio (95% CI)	P value	Clinical and Doppler data Hazard ratio (95% CI)	P value
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
CFVR			8.83 (2.83 to 27.56)	0.001
Ref CFVR			7.46 (3.37 to 16.53)	< 0.001

*Age, gender, history of diabetes, hypertension, smoking, previous myocardial infarction or revascularization,

Functional angina class, baseline heart rate, systolic blood pressure and diameter stenosis, lesion characteristics

(angulation, calcification, bifurcation, contour) were not independent predictors. For abbreviations see table III.

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Chapter 4

Spontaneous Long-term Normalization of Impaired Coronary Flow Reserve after Successful Balloon Angioplasty: The Effect of Age and Diabetes Mellitus

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Submitted

Objectives. We sought to identify patients with spontaneous long-term normalization of impaired CFVR after successful balloon angioplasty to assess a better selection of patients that may benefit from adjunctive coronary stent implantation.

Background. Impaired coronary flow reserve (CFVR <2.5) after successful balloon angioplasty is a predictor of major adverse cardiac events (MACE) during 6 months follow-up. However, spontaneous normalization of impaired CFVR after balloon angioplasty may occur.

Methods. Distal CFVR was measured before and after balloon angioplasty and at 6 months follow-up in 183 patients studied with single vessel disease using a Doppler guide wire. Normalized CFVR at follow-up was defined by its best cutoff value for MACE. MACE was defined as death, myocardial infarction or target lesion revascularization.

Results. Of the patients studied, 88 patients (48%) demonstrated an impaired CFVR (<2.5) after balloon angioplasty. Impaired CFVR normalized at follow-up (CFVR >2.0) in 52 patients (59%), which was related to a better clinical outcome as compared to patients with CFVR < 2.0 at follow-up (MACE: 4% vs. 72%, $p < 0.0001$). Multiple logistic regression analysis revealed diabetes mellitus and aging (>60 yrs) as independent predictors for unchanged impaired CFVR at follow-up. Patients with impaired CFVR after balloon angioplasty, without diabetes and age >60 yrs, demonstrated less MACE at follow-up as compared to those with diabetes and/or age >60 yrs (21% vs. 56%; $p < 0.0001$).

Conclusions. Spontaneous long-term normalization of CFVR (‡2.0) occurs in 59% of patients with impaired CFVR (<2.5) after successful balloon angioplasty, that is associated with favorable clinical outcome. Diabetes mellitus and aging are independent predictors of unchanged impaired CFVR (<2.0).

Keywords: angioplasty   blood   flow   aging   diabetes   restenosis

Abbreviations List

PTCA   = percutaneous transluminal coronary angioplasty

B-APV   = baseline average peak velocity

H-APV   = hyperemic average peak velocity

CFVR   = coronary flow velocity reserve

MACE   = major adverse cardiac events

TLR   = target lesion revascularization

DEBATE   = Doppler End Points Balloon Angioplasty Trial Europe

DESTINI   = Doppler End Point Stenting International Investigation

Introduction

The incidence of restenosis (30-50%) following successful conventional balloon angioplasty may be reduced by coronary stent implantation due to its favorable effect on epicardial remodeling following PTCA. However, neo-intima proliferation is more pronounced after stent implantation as compared with balloon angioplasty, which is difficult to treat in case of diffuse in-stent restenosis. These considerations have led to a revival of conventional balloon angioplasty (1). The clinical outcome following balloon angioplasty may be improved using intravascular ultrasound imaging (2,3) or intracoronary physiological parameters (4-7) for guidance of the procedure. A recent published observational multicenter trial, DEBATE- I (4), revealed two predictors of a better long-term clinical outcome after successful balloon angioplasty in patients with single vessel disease; i.e. diameter stenosis <35% combined with distal coronary flow velocity reserve (CFVR) >2.5 after balloon angioplasty. These combined predictors identify patients with a low recurrence of symptoms, a low target lesion revascularization rate and a low restenosis rate. Patients with a hemodynamic residual lumen obstruction after balloon angioplasty showing an impaired CFVR may benefit from additional stent implantation (6-11). However, several studies demonstrated a spontaneous normalization of impaired coronary flow velocity reserve during follow-up (12-15). The aim of the present study is to identify clinical, angiographic and hemodynamic factors that are associated with spontaneous normalization of impaired CFVR following balloon angioplasty and to evaluate its relationship with clinical outcome.

Methods

<u>Patient selection</u>

The study population of the DEBATE-I trial consisted of 297 patients undergoing balloon angioplasty of a single lesion in a major native coronary artery. Exclusion criteria were multivessel disease, previous transmural myocardial infarction in the perfusion area of the vessel to be dilated, acute myocardial infarction less than 1 week before PTCA, total coronary occlusion, presence of left bundle-branch block, or second- to third degree atrioventricular block, open bypass graft distal to the lesion to be dilated, and use of alternative or additional interventional treatments (directional or rotational atherectomy, stent implantation, etc.). All patients gave witnessed written informed consent, and the interstitutional review boards of all participating centers approved the study.

For a variety of reasons, described in detail elsewhere (4), distal CFVR was measured in only 225 patients after successful balloon angioplasty. The study population consisted of 183 patients in whom blood flow measurements were completed after balloon angioplasty and at 6 months follow-up. Major adverse cardiac events (MACE) at 6 months follow-up were defined as death, myocardial infarction or target lesion revascularization.

<u>Quantitative coronary angiography</u>

All patients received heparin and acetyl salicylic acid as premedication before angioplasty. At least two cineangiograms, in orthogonal directions, were obtained before coronary angioplasty and repeated after successful balloon angioplasty

(diameter stenosis <50%) and at follow-up in the same directions. Intracoronary nitroglycerin 0.1 to 0.3 mg or isosorbide dinitrate 1 to 3 mg was administered to achieve maximal coronary vasodilatation. All cinefilms were sent to an independent core laboratory, which was blinded to the clinical and Doppler flow velocity results. Matched views and frames were selected for off-line quantitative analysis. A computer-assisted analysis system was used (CAAS II system, Pie Medical Data). Automatic edge detection of the luminal dimensions (MLD and reference diameter) and video densitometry analysis (minimal luminal cross-sectional area) were performed by use of the guiding catheter filled with contrast as a scaling factor. Restenosis was defined as a diameter stenosis >50% at follow-up.

Intracoronary blood flow velocity analysis

All coronary blood flow velocity measurements with the Doppler angioplasty guidewire (FloWire, Endosonics) were performed as previously described (16). After on-line assessment of the baseline average peak velocity (APV), hyperemia was induced by administration of an intracoronary bolus of adenosine (12 g in the right coronary artery; 18 g in the left coronary artery). Baseline and adenosine-induced hyperemic coronary blood flow velocity measurements were performed at the same location, verified by coronary angiography, distal to the dilated segment at follow-up. CFVR was defined as the ratio of the adenosine induced hyperemic/baseline APV. An impaired CFVR after balloon angioplasty was defined as a CFVR <2.5 (4,14). Normalized CFVR at follow-up was defined by using the calculated best cut-off value for MACE at follow-up.

Statistics

Continuous variables were expressed as mean–1SD. Differences between continuous variables were evaluated using the unpaired Student's t test or Mann-Whitney-U test. Receiver operating characteristic (ROC) analysis was used to assess the best cut-off value of CFVR at follow-up for MACE. The best cut-off values of ROC curves were used to translate continuous variables into dichotomous variables for logistic analysis. The exact test for 2 x 2 tables was used to compare dichotomous variables. Variables with a p-value < 0.1 after univariate logistic analysis was entered in a multivariate analysis. This multivariate analysis was performed by means of stepwise logistic regression. Statistical analysis was performed with SPSS software for Macintosh (version 6.1.1, SPSS Inc., Chicago, Illinois). A p-value < 0.05 was considered statistically significant.

Results

Patients

A total of 88 of 183 patients (48%) demonstrated an impaired CFVR (2.5) after successful balloon angioplasty. ROC analysis revealed a CFVR at follow-up of 2.0 as the best cut-off value for the absence of MACE at follow-up in patients with impaired CFVR after successful balloon angioplasty. A total of 52/88 patients (59%) with initially impaired CFVR directly after balloon angioplasty demonstrated a spontaneous normalization (CFVR ‡2.0) at 6 months follow-up (Fig. 1). The better clinical outcomes of these patients as compared to those without a normalization of impaired CFVR at follow-up are depicted in Table 1. No death or myocardial infarction occurred during the 6 months observational period.

The percentage diameter stenosis after successful balloon angioplasty, earlier mentioned as an independent angiographic predictor for MACE (4), did not influence the clinical outcome in patients with normalized CFVR at follow-up; ie, 96% of these patients remained free of MACE (Fig. 2). However, patients without normalized CFVR at follow-up (CFVR <2.0) and a diameter stenosis >35% after balloon angioplasty demonstrated a lower incidence of MACE than patients with DS>35% after balloon angioplasty (p = 0.04, Fig. 2).

Predictors of normalized CFVR

Univariate analysis of all patient characteristics, angiographic and hemodynamic variables resulted in the following variables showing a significant difference between patients with normalized CFVR and those without; i.e. age, diabetes mellitus, percentage area stenosis (AS) after balloon angioplasty, cross sectional area (CSA) after balloon angioplasty and CFVR after balloon angioplasty (Table 2). ROC analysis demonstrated the best cutoff values of the above mentioned continuous variables age (>60 yrs; 2 = 6.30, p = 0.01), AS before PTCA (>80%; 2 = 3.80, p = 0.01), CSA after PTCA (<3.08; 2 = 2.27, p = 0.13) and CFVR after PTCA (<1.95; 2 = 2.29, p = 0.13). Both forward and backward stepwise logistic regression analysis revealed the following model of independent predictors for spontaneous normalization of impaired CFVR: Logit P= -1.72 + 1.89 (absence of diabetes) + 0.94 (age 60 yrs). The overall accuracy of this regression equation was 89%.

Influence of diabetes and aging on clinical outcome

The presence or absence of diabetes in patients with impaired CFVR after balloon angioplasty did not show a significant difference in clinical (MACE 6/11 vs. 22/77; p

= 0.08 and recurrence of angina 7/11 vs. 32/77; p = 0.18) and angiographic outcome (restenosis 5/11 vs. 24/77; p = 0.36). The effect of aging (†60 yrs vs. >60 yrs) on clinical outcome (MACE 9/41 vs. 19/47; p = 0.06 and recurrence of angina 26/44 vs. 13/44; p = 0.007) was more apparent as on angiographic outcome (restenosis 15/46 vs. 14/42; p = 0.88). When both independent predictors were combined, a worse clinical outcome was demonstrated in diabetics and/or older patients (>60 years) with impaired CFVR after balloon angioplasty (Table 3, Group II + III + IV) as compared to those †60 years old and without diabetes (Table 3, Group I). The angiographic outcome (restenosis) was not influenced by diabetes and aging (Table 3).

Influence of diabetes and aging and normalized CFVR.

Diabetes Mellitus. A total of 11 diabetic patients in the overall DEBATE-I population demonstrated impaired CFVR. Impaired CFVR in diabetic patients was related to an impaired hyperemic-APV as compared to non-diabetic patients (Table 4). Hyperemic-APV did not change at follow-up despite a more pronounced late lumen loss as compared to the non-diabetic patient group (0.43–0.41 mm vs. 0.15–0.41 mm, p < 0.05). In contrast, an impaired CFVR after balloon angioplasty in non-diabetic patients was due to an increase in baseline-APV, while CFVR at follow-up increased in association with a decrease in baseline-APV (Table 4). There was no difference in the occurrence of hypertension between patients with or without diabetes (36% vs. 50%, p = 0.51).

Age. Between the patient groups with and without normalization of impaired CFVR both baseline and hyperemic blood flow velocity before and after balloon angioplasty were similar in those younger and older than 60 years (Table 5). Moreover, baseline blood flow velocity increased after balloon angioplasty in both patient groups.

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Age. Between the patient groups with and without normalization of impaired CFVR both baseline and hyperemic blood flow velocity before and after balloon angioplasty were similar in those younger and older than 60 years (Table 5). Moreover, baseline blood flow velocity increased after balloon angioplasty in both patient groups.

However, this increased baseline blood flow velocity normalized at follow-up only in patients †60 years old while hyperemic blood flow velocity remained unchanged resulting in a significant increase in CFVR at follow-up (Table 5).

Discussion

The findings of the present study demonstrate a spontaneous long-term normalization of CFVR in 59% of the patients with impaired CFVR after balloon angioplasty. Normalized CFVR ‡2.0 at follow-up was associated with good clinical and angiographic outcomes. These clinical outcomes were not influenced by angiographic results (DS%) directly after balloon angioplasty. Diabetes mellitus and aging were independent negative predictors for normalization of initially impaired CFVR after successful balloon angioplasty. Patients >60 years showed a steady high baseline-APV at follow-up, while diabetics showed a consistent impaired hyperemic-APV at follow-up, both resulting in an unchanged impaired CFVR. Patients with impaired CFVR after balloon angioplasty, without diabetes and †60 years old demonstrated 20% MACE at follow-up, approaching the 16% MACE observed in the original presentation of the DEBATE-I study in patients with a diameter stenosis †35% in combination with a CFVR >2.5 after balloon angioplasty.

Impaired CFVR after successful PTCA

Numerous studies described a frequent occurrence of impaired CFVR after successful balloon angioplasty, varying between 30-61% of their patient population depending their definition of impaired CFVR (cut-off values between 2.0 and 3.0) (12,14,15,17). In this study, 48% of the patients studied demonstrated impaired CFVR after balloon angioplasty, which concurs with previous studies. The majority of our patients (59%)

demonstrated a spontaneous normalization of impaired CFVR that may be explained by a transient state of a high baseline-APV and/or a transient low hyperemic-APV directly after balloon angioplasty. Several clinical studies demonstrated impaired CFVR after PTCA due to a transient increase in resting blood flow (13-15,18). Several mechanisms have been postulated for the transient increase in baseline flow velocity after balloon angioplasty, such as epicardial vasoconstriction at the site of the Doppler guidewire tip mediated by a myogenic response and/or neural mechanisms (19,20), the influence of drug therapy (21,22) or a prolonged hyperemic response after balloon occlusion. A temporary impaired adenosine-induced hyperemic response may be explained by several mechanisms; i.e., remodeling of a residual lumen obstruction (23), differences in drug therapy, platelet activation, micro-embolization of platelet aggregates (24), release of platelet-mediated vasomotor products that occur after angioplasty-induced medial injury (25), and ischemic-induced desensitization for exogenous adenosine.

This is the first study evaluating factors associated with spontaneous normalization of impaired CFVR after balloon angioplasty. Both aging and diabetes showed to be negative predictors for normalization of CFVR.

Age. Aging was associated with a stabilized high baseline-APV at follow-up, which in combination with a normal hyperemic-APV at follow-up, resulted in an unchanged impaired CFVR at follow-up. This high baseline-APV may be explained by an increase in systolic blood pressure and heart rate in rest due to an age-related intimal thickening of the large arteries and decline in the compliance of the vascular system. These increases in systolic blood pressure and heart rate would be expected to elevate myocardial oxygen demand and, consequently, blood flow at rest (26,27). However, indexes of cardiac work at rest in the present study did not differ between the age-

determined patient groups (Table 5) that are not consistent with earlier mentioned studies. Furthermore, increases in endogenous adenosine release at rest are described in aged animals, which may explain increased blood flow at rest. However, this hypothesis includes a process of desensitization of the vascular smooth muscle for exogenous adenosine resulting in a lower adenosine-induced hyperemic-APV, which was not observed in the aged patients of the present study. Moreover, impaired angiogenesis is an important age-related and also diabetes-related factor that may induce an increase in baseline-APV (28,29). Impaired angiogenesis during ischemic coronary disease lowers the capillary density of the ischemic myocardium (30), which results in a relative higher oxygen demand that induces an increase in blood flow at rest and, consequently, a decrease in CFVR (31).

Diabetes

In this study, impaired CFVR after balloon angioplasty in diabetics is due to a lower hyperemic-APV as compared with non-diabetics with impaired CFVR after balloon angioplasty. This finding was consistent with the results of other studies, which demonstrated a reduced hyperemic myocardial perfusion by positron emission tomography or invasive Doppler-wire measurements in diabetics without a history of coronary artery disease (32-34). Reduced hyperemic myocardial blood flow in diabetics may be related to a more diffuse state of atherosclerosis and microvascular disease undetectable by angiography (35,36). Moreover, the abnormal endothelium-dependent vasodilatation in diabetics is supported by several mechanisms such as: abnormalities in signal transduction, reduced synthesis of EDRF, accelerated inactivation of nitric oxide, transport barriers such as thickened basement membranes, and generation and release of competing vasoconstrictor substances.

In this study, aging >60 yrs and the presence of diabetes demonstrated no recovery of impaired CFVR at follow-up due to different disorders in the regulatory mechanism of coronary vasomotor tone, and these patients are, therefore, prone to adverse clinical events.

Diabetes and aging related to clinical outcome in patients with impaired CFVR after balloon angioplasty.

In the DEBATE-I study (4), impaired CFVR after successful balloon angioplasty may occur in 48% of the patients treated. According original article of the DEBATE-I study, these patients are prone to long-term adverse outcomes and, therefore, subject to additional stent implantation. However, the present study provides the clinic predictive tools to select a high-risk patient cohort with impaired CFVR after balloon angioplasty and long-term adverse outcomes. This cohort of patients exist of patients with impaired CFVR in combination with diabetes and/or >60 years of age. These patients showed 41% MACE at follow-up and, therefore may benefit from additional stent implantation. Contrary, a total of 39 (44%, Table 3) patients with impaired CFVR after balloon angioplasty were 60 years old and no diabetic. These patients showed 21% MACE which almost equalizes the outcome of 16% in patients of the DEBATE-I study with DS <35% and CFVR>2.5 after balloon angioplasty (4). So, a selected group of 44% of the patients with impaired CFVR after balloon angioplasty may maintain from abundant stent implantation.

Moreover, the strong association between improved CFVR and MACE in the present study enlightened the pivotal role of hemodynamic measurements as CFVR, relative CFVR (distal CFVR/CFVR of a normal reference vessel) or pressure derived fractional flow reserve to predict particularly clinical and not angiographic outcomes.

Study limitations

Intracoronary blood flow velocity assessment is a sensitive technique for the detection of alterations in coronary blood flow, but this method is also prone to technical failures, and accurate measurements depend on the time, skill, and experience of the cardiologist.

Two different cut-off values for CFVR were used in this article; ie, 2.5 after balloon angioplasty and 2.0 at follow-up. Because of the gap between these two cutoff values, 3 patients showed a "normalization" of their impaired CFVR during follow-up while their CFVR decreased during follow-up (Fig. 1). However, the cut-off value 2.5 for CFVR after balloon angioplasty was determined in patients with single vessel disease (DEBATE-I trial (4)), which may agree with a relative CFVR of 0.80 with a mean CFVR of approximately 3.1 in the reference vessel (14). In patients with multivessel disease a lower cut-off value of 2.0 (DESTINI trial (7)) may be used because of lower CFVR values in the reference coronary artery due to a more extended diffuse coronary artery disease (15). Moreover, this is the first study that determined a cutoff value for CFVR at long-term follow-up in patients treated with balloon angioplasty. This value of 2.0 is the same as the diagnostic cutoff value of CFVR before coronary intervention.

The site of the repeated blood flow velocity measurements was determined by angiography, although this method for making repeated measurements may have been a contributing factor in the variations noted.

In the present study, intravascular ultrasound analysis was not performed to evaluate the role of remodeling in the normalization process of the CFVR; therefore, this entity cannot be ruled out.

It is recognized that the DEBATE-I study was not designed to evaluate the effect of diabetes on vasomotor tone, a factor limiting the strengths of our conclusions. Potential information as type and duration of diabetes, diabetic medication, glycemic control, presence of autonomic neuropathy, grade of retinopathy and left ventricular function were not registered. Moreover, this study did not perform histological and echocardiographic measurements to evaluate the capillary density and presence of diabetic cardiomyopathy.

An important issue missing is the measurement of the CFVR in an adjacent angiographic normal coronary artery to calculate the relative coronary flow velocity reserve. Several studies demonstrated also high percentages impaired CFVR values in the angiographic normal coronary artery after balloon angioplasty or stent implantation (15,17). It is this feature that may distinguish between global abnormalities in the regulation of coronary vascular tone versus blood flow abnormalities restricted to the cardiac vascular bed of the dilated coronary artery.

Clinical implications

The DEBATE-I study demonstrated a reduced number of MACE in patients with a diameter stenosis 35% and CFVR >2.5 directly after balloon angioplasty, which legitimized provisional stent implantation in patients with impaired CFVR after balloon angioplasty. However, the present study demonstrated a spontaneously normalization of CFVR associated with good clinical outcomes in 59% of the patients with impaired CFVR, who otherwise were subject to stent implantation. This normalization of impaired CFVR occurs independently from the diameter stenosis after balloon angioplasty.

According their clinical outcome, additional stent implantation may be abundant in patients with impaired CFVR after balloon angioplasty, 60 years old and without diabetes showed. In contrary, diabetics and elderly with impaired CFVR after successful balloon angioplasty did not show an improved CFVR at follow-up and were prone to worse angiographic and clinical outcomes. Adjunctive stent implantation in these patients remains neither questionable as it may not lower high resting blood flow values nor improve impaired hyperemic blood flow values in patients with diffuse microvascular coronary disease. Therefore, additional measurements of relative CFVR, pressure-derived fractional flow reserve or intravascular ultrasound dimensions are necessary to differentiate between residual lumen obstruction (suitable for stent implantation) and generalized microvascular disease.

Appendix
The following investigators and institutions participated in the DEBATE study. The number enrolled at each center is given in parentheses.
J.J. Piek, K.T.Koch: Academic Medical Center, Amsterdam, Netherlands (40); E. Schroeder, O. Gurn , P. Chenu: Clinique Universitaire de Mont-Godinne, Yvoir, Belgium (33); C.Vrints: Universitair Ziekenhuis Antwerpen, Belgium (30); C. di Mario, R. Gil, P. Nierop, P.W. Serruys: Thoraxcenter Rotterdam, Netherlands (28); P. Probst, G. Porenta: Kardiologische Universitätsklinik Wien, Austria (25); G. Hendrickx, B. de Bruyne, W. Wijns: Onze Lieve Vrouwe Kliniek Aalst, Belgium (24); C. Hanet: Clinic Universitaire St Luc, Brussels, Belgium (20); E. Fleck, E. Wellnhofer, H. Sauer: Deutsches Herzzentrum Berlin, Germany (17); R. Erbel, M. Haude, D. Baumgart: Universität Essen, Germany (15); E. Verna: Ospedale di Circolo, Varese, Italy (13); V. Voudris, A. Manginas: Onassis Cardiac Surgery Center, Athens, Greece (12); H. Geschwind: CHU Henri Mondor, La Creteil, France (10); V. M_hlberger, N. Moes, G. Friedrich: Universitätsklinik fur Innere Medizin Innsbr_ck, Austria (9); H. Emanuelsson: Sahlgrenska Hospital G teborg, Sweden (9); L. Campolo, G. Danzi: Ospedale Niguarda Ca'Granda,Milano, Italy (6); P. den Heijer, H. Peels; Academisch Ziekenhuis Groningen, Netherlands (6).
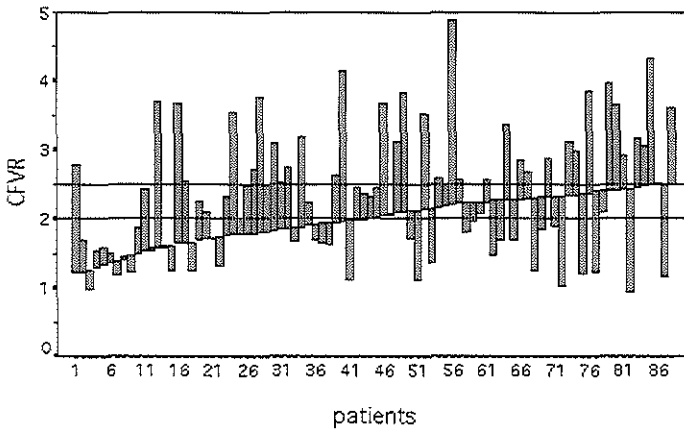
Figure 1. Individual changes of coronary flow velocity reserve (CFVR) during 6 months

follow-up (bars) in patients sorted by their impaired CFVR after successful balloon angioplasty

Figure 2. The percentage diameter stenosis (DS) after successful PTCA did not correlate with normalization of impaired coronary flow velocity reserve (CFVR) at follow-up (p = 0.19). DS after PTCA did not influence major adverse cardiac events (MACE) in patients with normalized CFVR at follow-up. However, patients without normalized CFVR at follow-up (CFVR <2.0) and a DS ó35% after PTCA demonstrated a lower incidence of MACE than patients with DS >35% after PTCA (p = 0.04).

Table I. Differences in long-term clinical outcomes (restenosis, ischemia/angina, MACE) between patients with normalized CFVR (>2.0) and those without normalized CFVR (<2.0) at follow-up

	CFVR <2.0 (n=36)	CFVR ‡2.0 (n=52)	Sensitivity	Specificity	P-value
Recurrent AP	26 (72%)	13 (26%)	67%	80%	<0.0001
Restenosis	23 (64%)	6 (12%)	77%	78%	<0.0001
MACE	26 (72%)	2 (4%)	93%	83%	<0.0001

MACE: major adverse cardiac events, similar to target lesion revascularization,
AP = angina pectoris; CFVR = coronary flow velocity reserve.

Table 2. Univariate analysis of the baseline characteristics between patients with and without normalization of a postprocedural impaired CFVR at follow-up.

	CFVR at FU 2.0 (n=52)	CFVR <2.0 (n=36)	P-value
Patient characteristics			
Male	35 (67%)	25 (69%)	0.83
Age (yrs)	60–9	64–7	0.03
Current smoker	13 (25%)	5 (14%)	0.20
Diabetes Mellitus	2 (4%)	9 (25%)	0.006
Hypertension	17 (33%)	14 (39%)	0.55
Unstable angina	25 (48%)	23 (64%)	0.14
Dyslipidemia	26 (50%)	21 (58%)	0.44
Hx Myocardial Infarction	11 (21%)	4 (11%)	0.22
Hx Family	25 (48%)	16 (44%)	0.67
Previous PTCA	6 (12%)	5 (14%)	0.74
Beta-blockers	30 (58%)	18 (50%)	0.48
Ca-antagonists	6 (12%)	2 (6%)	0.28
Nitrates	36 (69%)	27 (75%)	0.56

Table 3. Angiographic and hemodynamic characteristics between patients
with (n=52) and without (n=36) normalization of an impaired CFVR at follow-up

Variables	CFVR ≥2.0	CFVR<2.0		P-value
RCA/LAD/ LCx	15,17,20	9, 17,10		0.71
Collaterals	5 (10%)	1 (3%)	0.20	
TIMI-flow 2	7 (13%)	2 (6%)		0.20
Lesion type ACC 1/2/3	8/43/1	4/32/0		0.58
Lesion length (mm)	8.11–2.40	7.56–2.03		0.27
Reference Diameter (mm)	2.79–0.42	2.79–0.54		0.97
DS before PTCA (%)	63–9	61–8		0.13
AS before PTCA (%)	84–10	79–12		0.05
DS after PTCA (%)	36–10	37–7		0.60
AS after PTCA (%)	46–16	48–16		0.73
Heart rate (bpm)	72–12	70–11		0.56
MAP (mm Hg)	91–15	93–12		0.40
B-APV before PTCA	16–8	17–7		0.60
H-APV before PTCA	25–16	22–11		0.32
CFVR before PTCA	1.5–0.5	1.3–0.4		0.14
B-APV after PTCA	21–11	23–9		0.48
H-APV after PTCA	43–16	43–18		0.85
CFVR after PTCA	2.1–0.3	1.9–0.4		0.06

RCA = right coronary artery, LAD = left anterior descending, LCx = left circumflex,

TIMI = trombolysis in myocardial infarction, DS = diameter stenosis,

MLD = minimal lumen diameter, AS = area stenosis, MAP = mean aortic pressure,

B-APV and H-APV = baseline and hyperemic average peak velocity.

Table 4. The effect of diabetes and aging on hemodynamic, angiographic and clinical outcome during 6 months follow-up in patients with impaired CFVR after balloon angioplasty.

Group	I (n=39)	II (n=38)	III (n=2)	IV (n=9)	II+III+IV (n=49)
Age	<60	>60	<60	>60	
DM	0	0	1	1	
CFVR ≥2.0	30 (77%)	20 (53%)	0 (0%)	2 (22%)*	22 (45%)*
MACE (=TLR)	8 (21%)	14 (37%)	1 (50%)	5 (56%)*	20 (41%)*
Recurrent AP	11 (29%)	18 (58%)*	1 (50%)	6 (67%)*	25 (51%)*
Restenosis	13 (33%)	11 (30%)	1 (50%)	4 (44%)	16 (33%)

* $p < 0.05$ as compared with group I. Abbreviations as in previous tables, DM: diabetes mellitus.

Table 5. Influence of diabetes on hemodynamics measured before, after balloon angioplasty and at follow-up in patients with impaired CFVR directly after balloon angioplasty.

	Absence of diabetes (n=75)			Diabetes (n=11)		
	before PTCA	after PTCA	follow-up	before PTCA	after PTCA	follow-up
HR (bpm)	71–12	68–12	68–12	73–10	70–9	68–10
SBP (mm Hg)	131–21	126–21*	133–20	141–31	142–28	134–23
DBP (mm Hg)	71–12	69–10*	73–11	76–13	77–14	71–10
MAP (mm Hg)	91–13	88–12*	93–12	98–17	98–17	92–13
HRxMAP (x10)	647–164	601–155	633–156	719–183	690–145	624–84
DS (%)	63–8*	37–9	43–14	57–7	35–7	46–15
MLD (mm)	1.03–0.27	1.76–0.35	1.61–0.45	1.13–0.27	1.82–0.33	1.40–0.4
B-APV (cm/s)	17–8	22–10	19–8	15–8	19–6	21–11
H-APV (cm/s)	24–14	44–17*	44–20	20–17	34–10	33–19
CFVR	1.4–0.5	2.0–0.3*	2.4–0.9*	1.2–0.3	1.8–0.4	1.7–0.5

* $p < 0.05$ as compared to diabetics, $p < 0.05$ as compared to previous measurement. Abbreviations as in previous table.

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Part III

Coronary Artery Dissections and Physiology

Chapter 5

Angiographic and Clinical Outcome of Mild to Moderate Nonocclusive Unstented

Coronary Artery Dissections and the Influence on Coronary Flow Reserve

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Angiographic and Clinical Outcome of Mild to Moderate Nonocclusive Unstented Coronary Artery Dissection and the Influence on Coronary Flow Velocity Reserve

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Limited data are available regarding the angiographic healing rate and physiologic impact of coronary artery dissections. Therefore, we studied the impact of coronary dissections on coronary flow velocity and outcome as well as their healing rate at 6-month follow-up balloon angioplasty. Of 297 patients who underwent balloon angioplasty, 225 underwent intracoronary Doppler measurements and 184 had Doppler and angiographic assessment at 6-month follow-up. Dissections were scored by an independent core lab (Cardialysis BV) and divided in 4 groups: mild (types A to B), moderate (type C), severe (D to F), and patients without dissections. Severe dissections (types D to F) were excluded from the analysis. Clinical, angiographic, and Doppler data were compared among the remaining 3 patient groups. From the 67 dissections detected after balloon angioplasty, only 3 (4.5%) remained unhealed at follow-up. Immediately after balloon angioplasty, the moderate dissection group was associated with a lower coronary flow velocity reserve than the patients with mild (2.16 ± 0.60 vs 2.82 ± 1.00, p = 0.037) or no dissections (2.16 ± 0.60 vs 2.71 ± 0.88, p = 0.046), respectively. In addition, higher recurrence of angina at 30 days was observed in the moderate group rather than in the mild group (5 [50%] vs 8 [16%], p = 0.0160) and in the patients without dissections (11 [12%], p = 0.007). After standard balloon angioplasty, the occurrence of unhealed dissections is a rare phenomenon. An impaired coronary flow reserve was observed after the development of nonocclusive type C dissections, which was associated with a worse short-term outcome. ©2000 by Excerpta Medica, Inc.

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Coronary artery dissection ranges are observed angiographically in up to 50% of cases after balloon angioplasty.[1,2] Although stenting has ended the era of urgent surgical revascularization for coronary dissections impairing distal perfusion,[3] most mild to moderate dissections are still left untreated, due to adequate distal filling.Previous studies have shown that mild to moderate angiographic dissections do not increase the risk of major adverse cardiac events or the restenosis rate at 6-month follow-up.[4,5] The low rate of clinical and angiographic events may be due to the healing of nearly all dissections with time, although the true frequency of healing remains ill-defined.Also of potential prognostic importance is the impact of the different types of dissections on coronary physiology. Therefore, we investigated the coronary flow velocity reserve of the different types of unstented dissections after balloon angioplasty and the percentage of healing at 6-month follow-up.

METHODS

The methods and results of the Doppler Endpoints Balloon Angioplasty Trial Europe (DEBATE) have been previously described.[6] Briefly, in 297 patients who underwent balloon angioplasty of a single lesion in a major native coronary artery because of chest pain and/or other documented signs of ischemia (electrocardiographic, scintigraphic, or echocardiographic) at rest or with exertion, a Doppler guidewire was used to measure basal and maximal hyperemic average peak velocities proximal and distal to the stenosis before and after angioplasty. For a variety of reasons, such as bail-out stenting and protocol violation (Figure 1), the recording of distal coronary flow reserve was not obtained in 72 of the 297 patients initially enrolled. Only angiographic criteria (diameter stenosis <50% in any angiographic view) were used to determine the end point of the angioplasty procedure. Flow velocity measurements recorded during the procedure were not used for guidance of the intervention, although the investigators were not blinded to the Doppler results.

Follow-up procedures: Within 4 ± 2 weeks after the initial angioplasty procedure, the patient's anginal status was determined with the Canadian Cardiovascular Society angina classification.When possible, a symptom-limited bicycle stress test was also performed
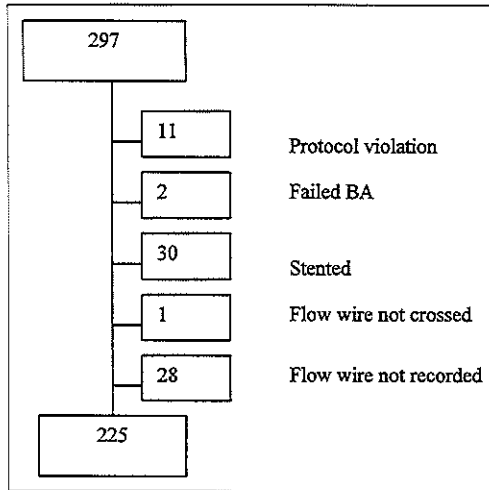
FIGURE 1. Flow chart of the initial study enrollment and those eligible for clinical, angiographic, and Doppler follow-up. BA = balloon angioplasty.

	Any Dissection	A	B	C	D	E	F
Initial group (n = 297)	119	50	46	16	4	2	1
Enrolled group (n = 225)	84	36	37	11	—	—	—
Follow-up group (n = 183)	67	30	29	8	—	—	—

TABLE I Dissection Rate of the Initial and Final Enrollment and the Group With Angiographic and Doppler Data Available at Follow-Up

after withdrawal of all antianginal medication. At 6 months (± 4 weeks), the patient's anginal status was re-evaluated, a repeat stress test was performed, and quantitative angiography (with the same set of matched views obtained during the angioplasty procedure) was performed. The criteria for reintervention were based on the presence of a percentage diameter stenosis of >50% in a patient with either symptoms or signs of ischemia. Flow velocity assessment at the time of recatheterization was not used in the decision-making process.

Quantitative angiographic measurement: At least 2 cine angiograms, in orthogonal projections, were obtained before coronary angioplasty and repeated after angioplasty in the same projections. All cine films were sent to an independent core laboratory, which was blinded to the clinical and the Doppler information. Matched views and frames were selected for off-line quantitative analysis. A computer-assisted analysis system was used (CAAS II system, Pie Medical Data, Maastricht, The Netherlands). Automatic edge detection of the luminal dimensions and reference diameter were performed by use of the guiding catheter filled with contrast as a scaling factor.

Dissection evaluation: Nonocclusive dissection incidence and grading was determined by an independent core lab (Cardyalisis BV) blinded to flow results and clinical outcome according to the National Heart, Lung, and Blood Institute classification[7]: type A (small radiolucent area within the vessel), B (nonpersisting extravasation of contrast), C (persisting contrast medium extravasation), D (spiroid filling defect with delayed but complete distal flow), E (persistent filling defect with delayed anterograde flow), or F (filling defect with total occlusion). Patients with type D, E, or F dissections or any type of dissections associated with a Thrombolysis In Myocardial Infarc-

tion (TIMI) flow grade <3, or with symptoms and/or signs of ischemia were excluded from the analysis. Most of these patients received bail-out stenting.

We divided the patients into 3 groups: types A to B dissection (mild), type C dissection (moderate), and patients without dissections. A comparison of the baseline characteristics, and clinical and angiographic outcome as well as the coronary flow reserve results after balloon angioplasty and at 6-month follow-up between the 3 groups was performed.

Flow velocity measurement: During the angioplasty procedure, the Doppler flow velocity spectra were recorded continuously on videotape. The Doppler ultrasound instrument (FloMap, Cardiometrics, Mountain View, California) calculates and displays on-line several spectral variables, including the time-averaged peak velocity (normalized to the cardiac cycle), the average systolic peak velocity, and the ratio of the average diastolic to average systolic peak velocities. The following ratios were also computed: coronary flow reserve, calculated as the ratio between time-averaged peak velocity during the peak effect of the adenosine injection (hyperemic average peak velocity) and the baseline time-averaged peak velocity.

Statistical analysis: The Student's t and chi-square tests were performed when appropiate for the comparison of the clinical, angiographic, and Doppler-derived data between the 3 groups.

RESULTS

Table I illustrates the dissection rate of the 297 patients initially screened in our study, the 225 patients who underwent Doppler measurements after balloon angioplasty, and the 184 patients who underwent angiographic and Doppler measurements at 6-month follow-up. In this latter group, 67 dissections were present after balloon angioplasty and only 3 (4.5%) persisted at follow-up. Of these 3 patients, 1 underwent repeat balloon angioplasty of the target lesion due to restenosis accompanied by recurrence of symptoms; the other 2 patients had no restenosis and were event free at 6 months.

Patient characteristics: Patient baseline characteristics are shown in Table II. All patients had single-vessel disease. All 3 groups had similar clinical and angiographic baseline characteristics. Heart rate and diastolic and systolic blood pressure did not differ significantly between the 3 groups.

Angiographic and clinical outcome in the different dissection types: Clinical and angiographic data are summarized in Table III. All 3 groups had comparable

TABLE II Baseline Characteristics of the Patients With and Without Dissections

	A–B Dissection (n = 73)	C–D Dissection (n = 11)	No Dissection (n = 141)
Age (yrs ± SD)	59 ± 8	54 ± 10	59 ± 10
Men	44 (78%)	6 (72%)	72 (78%)
Unstable angina	28 (48%)	4 (50%)	50 (54%)
TIMI flow grade			
2	52 (90%)	6 (72%)	86 (93%)
3	6 (10%)	2 (27%)	6 (7%)
Type of lesion			
A	7 (12%)	2 (25%)	11 (12%)
B	50 (86%)	6 (75%)	81 (88%)
C	1 (2%)	–	–
Reference diameter (mm ± SD)	2.89 ± 0.59	2.86 ± 0.65	2.84 ± 0.41
Lesion length (mm ± SD)	8.44 ± 2.34	9.38 ± 2.28	7.87 ± 2.40

TABLE III Clinical and Angiographic Outcome at Six-Month Follow-Up

	A–B Dissection (n = 59)	C–D Dissection (n = 80)	No Dissection (n = 116)
Restenosis	17 (31%)	1 (12%)	32 (35%)
Angina at 30 d	8 (16%)	4 (50%)*	11 (12%)
Angina at 6 mo	22 (38%)	1 (12%)	39 (42%)
TLR	15 (26%)	0 (0%)	26 (28%)

*p <0.05 for type A to B versus C–D; p <0.05 no dissections versus type C–D.
TLR = target vessel revascularization.

major adverse cadiac events, restenosis, and recurrence of symptoms at 6-month follow-up. The patients with type C dissections had significantlyhigher recurrence of angina at 30 days compared with the other patient groups (Table III). Of the 4 patients (50%) with type C dissections who experienced recurrence of angina at 30 days, 3 of 4 (75%) had positive bicycle stress tests. All 4 patients were managed medically, experiencing no major adverse cardiac events or restenosis at 6 months. None of these 4 patients had persistent dissections at follow-up.

Coronary flow velocity according to dissection type: Coronary flow velocity data are shown in Table IV. The patients with type A to B dissections and the patients without dissections had comparable coronary flow reserve after balloon angioplasty, whereas the patients with type C dissections had significantly lower coronary flowreserve after balloon angioplasty when compared with the other 2 groups.

The coronary flowreserve at follow-up was similar in all groups (see Table IV). Figure 2 illustrates a case of a patient who developed type C dissection after balloon angioplasty, resulting in an impaired coronary flowreserve that improved at 6-month follow-up.

DISCUSSION

Our study is the firstone to evaluate the coronary flowvelocity profileof patients with various types of coronary artery dissections, demonstrating a temporary coronary flowreserve impairment in patients with moderate dissections as well as healing of most coronary dissections at 6-month follow-up. Cappeletti et al[8] have recently documented a percentage of healing of 63% (31 of 49) at 6-month follow-up. The discrepancy with our results (95.5% vs 63%) could be due to differences in study design: in our study, coronary dissections were reviewed off-line by Cardialysis core lab, whereas in the Capelletti et al[8] study the dissection grade was assessed online by the principal operators.

As with previous studies,[4,5,9] no correlation was found between restenosis and the presence of dissections. Although no difference in clinical events at 6 months was detected between the 3 groups, the recurrence of angina at 30 days was statistically higher in patients with type C dissections compared with the A to B types and the control group. This findingwas further supported by the significantlylower coronary flow reserve observed in the type C group compared with the other 2 groups, potentially explaining the higher incidence of ischemic complications usually found shortly after the procedure in patients experiencing more severe dissections.[7,10,11] In the present study, the limited number of patients with type C dissections who experienced early recurrence of angina prevented us from drawing definitiveconclusions about the exact incidence and pathophysiologic mechanism responsible for the early recurrence in symptoms. However, in the patients with early recurrence of angina, all previously positive stress tests became negative at follow-up, dissections healed, restenosis was not observed, and patients experienced improved symptoms on medical therapy. All these factors may indicate that a temporary disturbance in coronary flow had an impact on the early recurrence of angina in those patients who developed type C dissections.

Although a disturbance in coronary blood flow velocity was found in the moderate dissection group, it did not appear to be due to a residual obstruction as demonstrated by similar hyperemic velocities in all groups. Furthermore, a lack of improvement in hyperemic velocities at follow-up in patients with type C dissections, despite the absence of unhealed dissections or restenosis, argues against a significantresidual obstruction in flow.

Moreover, the equalization of coronary blood flow at follow-up in all groups supports the concept that dissections are likely to influence the coronary flow and clinical outcome after balloon angioplasty, but only in the short term.

In agreement with previous studies, we found a temporary elevation in the baseline average peak velocity as a cause for an impaired coronary flowreserve after balloon angioplasty[12,13] in the moderate dissection group that could be related to a delay in the recovery of autoregulation,[14] cholesterol embolization,[15,16] or postocclusive hyperemia.

Study limitations: Measurements of transstenotic pressure gradients on maximal hyperemia were not performed; these measurements would have helped to exclude the presence of residual anatomical obstruction as the cause for the temporary disturbance in coronary flow.

TABLE IV Procedural and Follow-Up Angiographic and Doppler Flow Data

	A-B Dissection Type		C-D Dissection Type		No Dissection	
	Post-BA	FU-BA	Post-BA	FU-BA	Post-BA	FU-BA
b-APV (cm/s)	18 ± 7	21 ± 13	24 ± 10*†	19 ± 11	18 ± 9	17 ± 7
h-APV (cm/s)	46 ± 15	46 ± 20	48 ± 13	48 ± 9	47 ± 18	42 ± 19
CFR (±SD)	2.82 ± 1.00	2.52 ± 0.93	2.16 ± 0.60*†	2.86 ± 0.87	2.71 ± 0.88	2.55 ± 1.52
DS% (±SD)	37 ± 7	42 ± 13	40 ± 9	40 ± 12	36 ± 9	43 ± 15
MLD (mm ± SD)	1.85 ± 0.42	1.61 ± 0.37	1.71 ± 0.35	1.68 ± 0.38	1.80 ± 0.32	1.53 ± 0.50
Acute gain (mm ± SD)	0.75 ± 0.29		0.71 ± 0.24		0.71 ± 0.33	
Late loss (mm ± SD)	0.20 ± 0.37		0.10 ± 0.53		0.26 ± 0.44	

*p <0.05 for type A to B versus type C to D; †p <0.05 for no dissections versus type C to D.
b-APV = baseline average peak velocity; CFR = coronary flow reserve; DS% = percentage of diameter stenosis; h-APV = hyperemic average peak velocity; MLD = minimum luminal diameter.
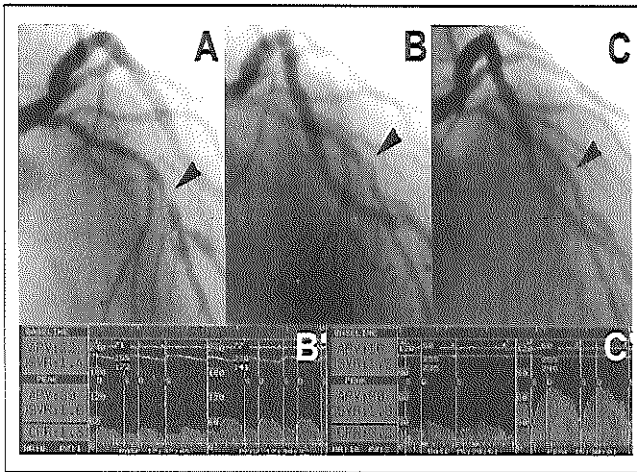
FIGURE 2. Angiographic and physiologic data of a patient before *(A)* and after *(B)* development of a type C dissection associated with an impaired coronary flow velocity reserve (B'). The follow-up angiogram shows complete healing of the moderate dissection *(C)* and an improvement in coronary flow velocity reserve (C').

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Chapter 6

Uncomplicated Moderate Coronary Artery Dissections after Balloon Angioplasty

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.

Uncomplicated moderate coronary artery dissections after balloon angioplasty: good outcome without stenting

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Abstract

Objective—To study the relation between moderate coronary dissections, coronary flow velocity reserve (CFVR), and long term outcome.

Methods—523 patients undergoing balloon angioplasty and sequential intracoronary Doppler measurements were examined as part of the DEBATE II trial (Doppler endpoints balloon angioplasty trial Europe). After successful balloon angioplasty, patients were randomised to stenting or no further treatment. Dissections were graded at the core laboratory by two observers and divided into four categories: none, mild (type A-B), moderate (type C), severe (types D to F). Patients with severe dissections (n = 128) or without available reference vessel CFVR (n = 139) were excluded. The remaining 256 patients were divided into two groups according to the presence (group A, n = 45) or absence (group B, n = 211) of moderate dissection.

Results—Following balloon angioplasty, there was no difference in CFVR between the two groups. At 12 months follow up, a higher rate of major adverse cardiac events was observed overall in group A than in group B (10 (22%) v 23 (11%), p = 0.041). However, the risk of major adverse events was similar in the subgroups receiving balloon angioplasty (group A, 6 (19%) v group B, 16 (16%), NS). Among group A patients, the adverse events risk was greater in those randomised to stenting (odds ratios 6.603 v 1.197, p = 0.046), whereas there was no difference in risk if the group was analysed according to whether the CFVR was < 2.5 or ≥ 2.5 after balloon angioplasty.

Conclusions—Moderate dissections left untreated result in no increased risk of major adverse cardiac events. Additional stenting does not improve the long term outcome.

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Keywords: coronary dissection; intracoronary Doppler; angioplasty

Coronary artery dissection is observed angiographically in up to 50% of cases after balloon angioplasty.[1][2] Although coronary stenting has greatly curbed the need for urgent surgical revascularisation for dissections that impair distal perfusion, it remains to be established whether moderate dissections with unimpaired flow and a good epicardial lumen would benefit from additional stenting. Previous studies have shown that mild to moderate angiographic dissections do not increase the risk of major adverse cardiac events or restenosis rate at a six months follow up after balloon angioplasty.[3][4] However, limited data are available on the impact of stenting on the short and long term clinical outcome after the development of moderate dissections.

We investigated the relation between dissection after balloon angioplasty and coronary flow velocity reserve, and the impact of stenting on the subsequent clinical outcome in patients treated by balloon angioplasty or stenting in the DEBATE II trial (Doppler endpoints balloon angioplasty trial Europe).

Methods

PATIENTS

Patients scheduled to undergo angioplasty because of stable or unstable angina pectoris or documented myocardial ischaemia, caused by a single de novo coronary stenosis less than 25 mm long and potentially amenable to stent implantation, were eligible for the DEBATE II trial. Those with total coronary occlusions, ostial lesions, bifurcated lesions, lesions in a previously bypassed vessel, lesions in an extremely tortuous vessel, or lesions containing thrombus 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 in the previous week. The study was carried out according to the principles of the Declaration of Helsinki, and all patients provided written informed consent.

STUDY OBJECTIVES AND DESIGN

The primary objective of the DEBATE II trial was to compare the cost-effectiveness of elective stent implantation (primary stenting) with balloon angioplasty guided by quantitative coronary angiography and Doppler flow velocity measurements. Stent implantation was permitted for bail out situations or whenever an "optimal result" could not be achieved. The secondary objective was to evaluate differences in benefits of additional stenting in patients with and without an optimal result. Thus a double randomisation was required. The first randomisation (1:5) allocated 620 patients to

either primary stenting (n = 97) or guided balloon angioplasty (n = 523). All patients in the guided balloon angioplasty group who did not require bail out stenting (n = 395) underwent a second randomisation to additional stenting or termination of the procedure. For the purpose of our analysis, we selected from the latter 395 patients all those (n = 256) in whom a reference vessel coronary flow velocity reserve (CFVR) measurement was available, and divided them according to the presence or absence of moderate type C dissections (fig 1).

GUIDED BALLOON ANGIOPLASTY
Doppler flow measurements
Target vessel Doppler measurements were performed before and after balloon angioplasty and again following additional stent implantation. It was also a requirement to perform a Doppler assessment of the CFVR of an adjacent angiographically non-diseased reference vessel (< 30% diameter stenosis). A 0.014 inch (0.36 mm) Doppler guide wire (Cardiometrics FloWire; EndoSonics, Rancho Cordova, California, USA) was advanced distal to the lesion, and velocity recordings were obtained under basal and hyperaemic conditions. Maximum hyperaemia was induced by adenosine, either by an intracoronary bolus injection (12 µg for the right coronary artery and 18 µg for the left coronary artery) or by intravenous infusion (140 µg/kg/min). Absolute CFVR was calculated as the ratio of hyperaemic to baseline time averaged peak velocity. Relative

Guided balloon angioplasty
n = 523

Patients without ref CFVR
n = 139

Bail-out stenting
n = 128

Type C
n = 45

Non-type C
n = 211

Balloon group
n = 32

Stent group
n = 13

Balloon group
n = 100

Stent group
n = 111

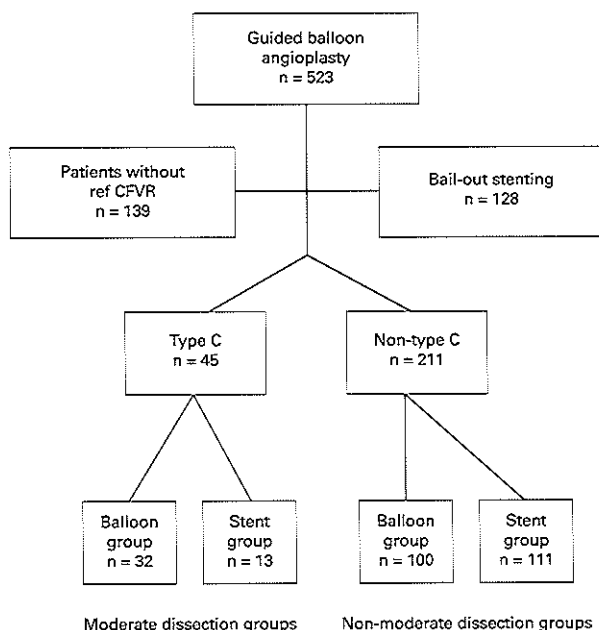Moderate dissection groups   Non-moderate dissection groups

Figure 1   Study population. All patients allocated to the guided balloon angioplasty group of the DEBATE II trial who did not require bail out stenting formed the population for our substudy (395 patients). Of these, 139 had no data of the reference vessel coronary flow velocity reserve available and were therefore excluded from further analysis. The remaining 256 patients underwent a second randomisation to additional stenting or termination of the procedure. We analysed these patients depending on the presence (group A) or absence (group B) of uncomplicated "moderate" dissections.

CFVR was calculated as the ratio of the absolute CFVR to the non-diseased reference vessel CFVR.

Quantitative coronary angiography
Intracoronary glyceryl trinitrate 0.1–0.3 mg or isosorbide dinitrate 1–3 mg was given to achieve maximum coronary vasodilatation. At least two cineangiograms were performed before the angioplasty or stenting procedure and were repeated in the same projections afterwards. Quantitative angiography was performed using a standardised protocol described previously.[5 6]

Definition of an "optimal" result
An "optimal" result (on quantitative angiography and coronary flow reserve determination) was defined as a diameter stenosis of < 35% and a coronary flow reserve of > 2.5,[7] and was achieved by upsizing the balloon or increasing the inflation pressure, or both, if necessary.

BAIL OUT STENTING
Bail out stenting was allowed in the following situations: a residual stenosis of more than 50%; dissection of type D, E, or F; persistent myocardial ischaemia along with a dissection type C; a fall in thrombolysis in myocardial infarction (TIMI) flow grade of at least one grade; or TIMI grade 0 or 1.

SECOND RANDOMISATION
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 coronary flow velocity reserve were assessed. Thereafter, and irrespective of these measurements, the second randomisation was performed.

DISSECTION EVALUATION
Intimal dissection incidence and grading was determined by an independent core laboratory (Cardialysis BV) classification,[1] blinded to Doppler flow results and clinical outcome, according to the National Heart, Lung, and Blood Institute (NHLBI) classification:
● type A: small radiolucent area within the vessel;
● type B: no persisting extravasations of contrast;
● type C: persisting contrast medium extravasations;
● type D: spiral filling defect with delayed but complete distal flow;
● type E: persistent filling defect with delayed antegrade flow;
● type F: filling defect with total occlusion.
Dissections were clinically divided into "mild" dissections (type A or B), "moderate" dissections (type C without signs or symptoms of ischaemia), or "severe" dissections (type C with symptoms or signs of ischaemia plus types D to F). The patient population was analysed on the basis of the presence (group A) or absence (group B) of uncomplicated moderate dissections.

EFFICACY END POINTS

For the DEBATE II study, the efficacy end point was a composite of major adverse cardiac events within 12 months after the procedure and included the following: death from any cause, non-fatal myocardial infarction, and percutaneous or surgical target lesion revascularisation. After hospital discharge, patients were seen at the outpatient clinic at one, six, and 12 months. 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 analysis of variance, as appropriate. Categorical variables are presented as percentages, and differences between groups were evaluated using the χ^2 test or Fisher's exact test. Multivariate logistic regression analysis was used to study the value of the clinical, angiographic, and Doppler derived data to predict major adverse cardiac events at the 12 months follow up. Odds ratios and 95% confidence intervals (CI) are presented. The Breslow-Day test was used to assess the homogeneity of odds ratios between subgroups. The

log rank test was applied to study differences in event-free survival between subgroups at the 12 months follow up. All statistical tests were two tailed, and significance was assumed at $p < 0.05$.

Results

From 523 patients randomised to the guided angioplasty group in the DEBATE II trial, 128 underwent bail out stenting because of severe dissections. All the remaining patients (n = 395), irrespective of the presence or absence of a moderate dissection, underwent a second randomisation to additional stenting or to halting the procedure. Of these 395 patients, 139 were excluded from our analysis because no reference CFVR measurements were available. The remaining 256 patients were divided into two groups according the presence (group A, n = 45) or absence (group B, n = 211) of uncomplicated moderate dissections (fig 1).

BASELINE CHARACTERISTICS

Patients' baseline characteristics are summarised in table 1. Patients in group A were older and had a smaller proportion of smokers than those in group B.

Lesion characteristics are given in table 2. Group A had a greater proportion of calcified lesions than group B. Both groups had similar vessel size (mean (SD): 2.93 (0.43) mm v 3.03 (0.59) mm, group A v group B, respectively (NS)). In group B, 110 of the 211 patients (53%) had no dissection, whereas 101 (47%) showed "mild" dissections.

Stent length was similar in both groups (16.3 mm v 15.6 mm in groups A and B, respectively; p = 0.64).

CORONARY DISSECTION SEVERITY AND CORONARY FLOW

For both groups, baseline and hyperaemic averaged peak velocity values before and after the procedure are given in fig 2. The preinterventional hyperaemic response was slightly impaired in the group A patients randomised to stenting. After balloon angioplasty, both groups showed similar baseline and hyperaemic averaged peak velocity values. In patients randomised to additional stent implantation, no differences in baseline and hyperaemic averaged peak velocities were seen.

Absolute and relative CFVR values are given in table 3. Before and after balloon angioplasty, absolute CFVR was similar in the patient population as a whole. However, in the subgroup randomised to stenting, the absolute CFVR was lower in group A than in group B. As the non-diseased reference vessel CFVR was also significantly lower in group A than in group B (2.43 (0.71) v 2.91 (0.78), p < 0.001), the resulting relative CFVR after stent implantation was similar in the two groups.

CORONARY DISSECTION SEVERITY AND CLINICAL OUTCOME

Complete follow up data were obtained in all patients. Thirty three cardiac events occurred. There were five deaths (one in group A and four in group B) and six myocardial infarcts

Table 1   Baseline characteristics of the patients according to dissection score following balloon angioplasty

Characteristic	Dissection		p Value
	Type C (group A) (n=45)	Nonetype A-B (group B) (n=211)	
Age (years) (mean (SD))	62 (11)	57 (11)	0.011
Female sex	33 (73%)	157 (74%)	NS
Diabetes mellitus	3 (7%)	23 (11%)	NS
Family history	21 (47%)	73 (35%)	NS
Hypertension	14 (31%)	86 (41%)	NS
Hypercholesterolaemia	21 (47%)	117 (55%)	NS
Smoking	23 (51%)	145 (69%)	0.014
CCS functional class			NS
I	3 (9%)	8 (7%)	
II	19 (56%)	61 (50%)	
III	11 (32%)	46 (38%)	
IV	1 (3%)	6 (5%)	
Unstable angina*	11 (32%)	89 (42%)	NS

Values are n (%) unless stated.
CCS, Canadian Cardiovascular Society; type C, moderate dissection; type A-B, very minor dissection.
*Patients with unstable angina were excluded from the analysis of the CCS functional class.

Table 2   Lesion characteristics in the two subgroups

Characteristic		Dissection		p Value
		Type C (group A) (n=45)	Nonetype A-B (group B) (n=211)	
Eccentricity	Yes	31 (69%)	125 (60%)	
	No	15 (31%)	85 (40%)	NS
Length	< 10 mm	23 (51%)	95 (49%)	
	≥ 10 mm	22 (49%)	92 (47%)	NS
Accessibility	No tortuosity	43 (93%)	180 (86%)	
	Moderate tortuosity	3 (6%)	28 (13%)	
	Excess tortuosity	0	2 (1)	NS
Angulation*	None	41 (89%)	185 (88%)	
	Moderate	5 (11%)	25 (12%)	
	Severe bend point	0	0	NS
Calcification	Little or none	39 (85%)	198 (94%)	
	Moderate to heavy	7 (15%)	12 (6%)	0.026

Values are mean (%).
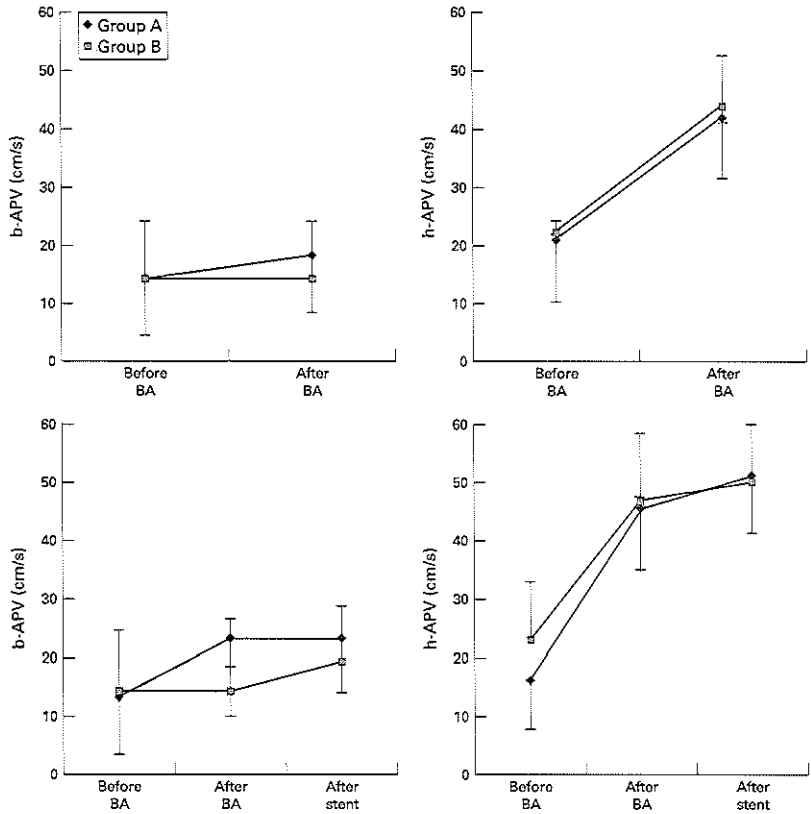*None, < 45°; moderate, > 45° to 90°; severe, > 90°.

Figure 2 Baseline (b-APV) and hyperaemic (h-APV) average peak velocities before and after the procedure in group A and group B. Upper panels show the subgroup randomised to stopping the procedure after balloon angioplasty (BA); lower panels show the subgroup randomised to further stent implantation (stent).

(one in group A and five in group B). At 12 months, the rate of target lesion revascularisation and major adverse cardiac events was higher in group A than in group B (table 4). Event-free survival at 12 months was 78% in group A *v* 89% in group B (p = 0.041).

All variables for which univariate analysis yielded a significant difference (age, smoking, degree of lesion calcification) were entered into the multivariate logistic model as potential predictors of major adverse cardiac events,

along with the presence of moderate dissections. The presence of moderate dissections was the only independent predictor of major adverse cardiac events (odds ratio 2.42; 95% CI, 1.06 to 5.57; p = 0.036).

IMPACT OF STENTING ON MODERATE DISSECTIONS

Among group A patients, those randomised to stent implantation had a higher rate of major adverse cardiac events than those randomised to stopping the procedure (31% *v* 19%). The Breslow-Day test for homogeneity of odds ratios between the two patient subgroups was significant, showing a higher risk of major adverse cardiac events at 12 months of follow up in the stent arm (odds ratios 6.603 *v* 1.197, p = 0.046). The CFVR (< 2.5 *v* > 2.5) before second randomisation did not affect the long term outcome (odds ratios 3.617 *v* 1.410, p = 0.287).

Discussion

The main findings of our study are that uncomplicated moderate dissections after balloon angioplasty left untreated had a good long term clinical outcome. In agreement with these results, several angioplasty studies have described a lack of association between the

Table 3   Coronary flow velocity data

	Group A		Group B	
	Stent group (n=13)	Balloon group (n=32)	Stent group (n=111)	Balloon group (n=100)
DS before BA (%)	76 (7)	69 (11)	68 (10)†	68 (11)
DS after BA (%)	23 (8)	23 (7)	22 (10)	21 (8)
DS after stenting (%)	7 (9)	–	8 (8)	–
CFVR before BA	1.29 (0.32)*	1.55 (0.52)	1.64 (0.61)	1.64 (0.60)
CFVR after BA	2.04 (0.59)*	2.65 (0.95)	2.50 (0.74)	2.50 (0.73)
CFVR after stenting	2.33 (0.87)	–	2.88 (0.30)†	–
RCFVR before BA	0.57 (0.21)	0.57 (0.19)	0.60 (0.25)	0.58 (0.21)
RCFVR after BA	0.86 (0.17)	1.00 (0.28)	0.89 (0.27)	0.89 (0.27)†
RCFVR after stenting	0.97 (0.24)	–	1.02 (0.30)	–
Reference CFVR	2.43 (0.71)*	2.83 (0.81)	2.91 (0.78)†	2.90 (0.75)

Values are mean (SD).
*p < 0.05 *v* balloon group A; †p < 0.05 *v* same subgroup in group A.
BA, balloon angioplasty; CFVR, coronary flow velocity reserve; DS, percentage diameter stenosis; group A, patients with moderate dissections; group B, patients with no or minimal dissection; RCFVR, relative CFVR.

Table 4   Clinical outcome at 30 days and 12 months of follow up in the group as a whole and in the two subgroups

	Whole group (n=256)			Stent group (n=124)			No further treatment group (n=132)		
	Dissection Nonetype A-B (group B) (n=111)	Type C (group A) n=45	p Value	Dissection Nonetype A-B (group B) (n=111)	Type C (group A) (n=13)	p Value	Dissection Nonetype A-B (group B) (n=100)	Type C (group A) (n=32)	p Value
MACE (30 days)	5 (5%)	3 (7%)	NS	2 (2%)	2 (15%)	0.054	3 (2%)	1 (3%)	NS
MACE (12 month)	23 (11%)	10 (22%)	0.041	7 (6%)	4 (31%)	0.002	16 (16%)	6 (19%)	NS
TLR (12 month)	14 (7%)	8 (17%)	0.016	3 (3%)	4 (31%)	< 0.001	11 (11%)	4 (13%)	NS

Values are n (%).
MACE, major adverse cardiac events; TLR, target lesion revascularisation.

presence of a moderate dissection and the long term clinical outcome.[8–10] Previous three dimensional intracoronary ultrasound data from our group have shown that the presence of intimal dissection is associated with a greater total vessel volume at long term follow up, probably owing to favourable remodelling.[11] It is conceivable that the development of a more deeply seated injury reduces vessel wall strength, thereby predisposing to favourable remodelling.

Overall, the patients with moderate dissections had a worse outcome than those with no or minimal dissections. This probably reflects the findings in the stented subgroup, which had a higher risk of major adverse cardiac events than the group with moderate dissections but without additional stenting. Although stents were placed according to the DEBATE II protocol and not to the operator's preference, the small sample size (n = 13) prevents us from drawing any firm conclusions. While coronary stenting after the development of moderate dissections has proved to reduce the acute complication rate, there is no established long term clinical benefit of additional stenting in patients with uncomplicated moderate dissection (TIMI 3 flow and absence of signs or symptoms of angina). Recent reports have shown that coronary stent implantation causes more severe injury and a greater inflammatory response, as well as worse endothelial dysfunction, than plain balloon angioplasty.[12–15] It is conceivable that the combination of a deep arterial injury associated with a moderate dissection and the implantation of a metallic body may cause a synergistic proliferative response.[16] In patients with moderate dissections, preventing favourable remodelling might offset the beneficial stent scaffolding effect. The latter could be particularly important as these patients are expected to develop an enhanced neointimal response.[16 17]

Our group has previously reported a temporary reduction in absolute coronary flow reserve in patients who developed uncomplicated moderate dissections.[18] This reflected a transient increase in the baseline velocity. Therefore the reduced coronary flow reserve values did not translate into a greater residual stenosis and obstruction of coronary blood flow. In the present study, we used the relative CFVR—a more reliable index of persistent conduit obstruction than the absolute CFVR[19]—and found similar values between the two groups. The latter results indicate that without signs or symptoms of ischaemia and the presence of TIMI 3 flow, no significant

obstruction to coronary blood flow should be expected in patients experiencing mild to moderate dissections.

Although the use of long or multiple stents has recently been reported to be associated with a greater restenosis risk,[20–22] in our study similar lengths and numbers of stents per patient were used in the two groups, so this is unlikely to be a confounding factor.

LIMITATIONS
The limited number of patients with moderate dissections prevents us from drawing definitive conclusions. However, this is the largest prospective study investigating a selected population of patients who developed uncomplicated moderate dissections and underwent randomisation to additional stenting or no further treatment, and in whom post-procedural Doppler flow data and one year follow up data were available.

CONCLUSIONS
Moderate dissections left unstented do not have an adverse clinical outcome. Additional stenting does not appear to be of benefit.

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Part IV

Stenotic Flow Velocity Acceleration and outcome

Chapter 7

Value of coronary stenotic flow velocity acceleration in prediction of

angiographic restenosis following balloon angioplasty

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Introduction

Numerous studies have shown that quantitative angiographic assessment after balloon angioplasty (BA) is a poor predictor of immediate and long-term outcome[1,2]. This limitation of angiography has prompted clinicians to use alternative methods for the functional assessment of angioplasty results. After the introduction of a Doppler angioplasty guidewire the continuous measurement of blood flow velocity during routine angioplasty has been shown to be clinically useful[3-5]. A recent multicentric clinical trial, DEBATE I, suggested that a coronary flow velocity reserve greater than 2.5 combined with a residual percentage diameter stenosis (DS) lower or equal to 35% after BA predicted a 16% restenosis rate at 6 months follow-up[6]. However, the coronary flow velocity reserve is dependent on the status of the coronary microcirculation and hemodynamic parameters such as heart rate and blood pressure[7]. In addition, a recent study has reported a lack of further improvement in coronary flow velocity reserve and maximal adenosine-induced flow velocity after additional stent implantation in patients who underwent intracoronary ultrasound-guided BA despite substatial luminal gain[8]. These limitations prompted us to evaluate other Doppler parameters such as the maximal stenotic flow velocity (SV) and the presence of stenotic flow velocity acceleration (aSV), both dependent on the theory of the continuity equation. The presence of aSV has been reported to be a very accurate marker of a significant stenosis[9,10]. Following successful angioplasty, the presence of aSV would suggest insufficient luminal enlargement. The purpose of our study was to examine the impact of aSV on the long-term angiographic results.

Methods

Coronary Doppler flow measurement protocol

The methods of the DEBATE trial have been previously described [6]. In short, 225 patients undergoing successful angioplasty of a single lesion were included. Baseline and hyperemic average peak velocities measurements were performed proximal and distal to the lesion using a 0.014-inch Doppler tipped guidewire. For distal measurements, a distance from the stenosis of at least 5 times the vessel diameter was chosen to avoid pre-stenotic acceleration of flow or post-stenotic turbulence, both of which may influence local velocities. Following distal measurements, pullback into the lesion site was performed. Whenever the investigators detected a clinically significant aSV, a thorough documentation of SV measurements was attempted. aSV was defined as acceleration in the stenotic coronary flow velocity of 50% or greater compared to the baseline velocity assessed at a reference site of the target vessel. According to Caiati et al[9], acceleration in coronary flow velocity of 50% at the stenotic site is highly sensitive (92%) and specific (100%) for diagnosing significant stenosis (diameter stenosis >50 %).

Measurements were performed before and 15 minutes after treatment. The patients were divided into 2 groups according to the presence or absence of aSV. Any patient with SV measurements complicated by technical failure was excluded from the study.

Balloon Angioplasty and Quantitative Angiographic Measurement

BA was performed in a conventional manner. At least two cineangiograms, in orthogonal projections, were obtained before, after and at 6 months follow-up in the same projections. Intracoronary nitroglycerin (0.1 to 0.3 mg) or isosorbide dinitrate (1 to 3 mg) was administered to achieve maximal coronary vasodilatation. All cinefilms were sent to an independent core laboratory (Cardialysis, Netherlands), which was blinded to the clinical and the Doppler information. Matched views and frames were selected for off-line quantitative analysis. A computer-assisted analysis system was used (CAAS II system, Pie Medical Data). Automatic edge detection of the luminal dimensions (minimun luminal diameter -MLD and reference diameter -RD)

were performed by use of the empty guiding catheter as a scaling factor. Restenosis was defined as binary angiographic restenosis with a diameter stenosis (DS) >50% at 6 months follow-up.

Statistics

Values are reported as means ± SD. Comparison between groups was performed using paired and unpaired Student's t-tests when appropriate. Clinical, angiographic and Doppler-derived variables that had demonstrated statistical significant difference among the patients with and without aSV were included in the multivariate logistic regression model to identify predictors of angiographic restenosis. A p-value of <0.05 was considered significant. In search for a diagnostic cut-off value of SV, a receivers operating characteristics curve analysis was constructed and the area under the curve is reported which is representative of the diagnostic power of the variable cut-off value. Sensitivity and specificity, positive and negative predictive value of the best cut-off variable were calculated.

Results

Baseline Data and Procedural Results

From the 225 patients enrolled in the DEBATE I trial, 202 had angiographic follow-up. A total of 77/202 patients had documented aSV whereas 125 did not experience aSV. From the 77 patients, 23 were excluded from the analysis due to technical limitations in the accurate measurement or recording of SV.
The baseline clinical data of the remaining aSV (n=54) and non-aSV (n=125) groups is summarized in Table I. Patients with aSV were older and had higher proportion of unstable angina than the patients without aSV. (Table I).

Quantitative Coronary Angiographic and Coronary Flow Velocity Data

DS, MLD and coronary flow velocity reserve values were similar prior to and after balloon angioplasty between the 2 groups. (Table II).
Among the aSV group, 27 patients had measurements performed before, after angioplasty and at 6-month follow-up. In those patients, a reduction in SV was seen after angioplasty from 194±74 cm/sec to 90±43

cm/sec (p<0.0001), which parallel with a change in DS from 60±8% to 37±8% (p<0.0001).

No significant linear relationship was observed between the DS and the SV immediately after angioplasty while a significant correlation was seen at follow-up. (Figure 1)

Coronary Flow Velocity Reserve, Stenotic Flow Velocity and Restenosis

Among the patients with restenosis at 6 month follow-up (n=66), the coronary flow velocity reserve was similar following the procedure (2.6±0.7 vs. 2.8±1.0, p=0.177) and lower at follow-up (1.9±0.8 vs. 2.9±0.9) when compared to the non-restenotic patients (n=113) (Figure 2).

Among the aSV group in whom SV was also available at follow-up (n=27), the patients who experienced restenosis (n=18) presented higher SV values following the procedure (107±45 cm/sec vs. 68±32 cm/sec , p=0.025) and at follow-up (169± 27 cm/sec vs. 64± 37 cm/sec, p<0.0001) than non-restenotic patients (n=9, Figure 3). Moreover, a significant elevation in SV was observed at follow-up in the restenotic patients (from 107±45 cm/sec to 169± 27 cm/sec , p=0.004) whereas no significant change was found in the non-restenotic patients (from 68±32 cm/sec to 64± 37 cm/sec, p=0.707).

Presence of Stenotic Flow Velocity Acceleration and Restenosis Rate

At follow-up, the aSV group had lower MLD and higher DS, late loss and restenosis rate (52% vs. 30%, p=0.006) than the group of patients without post-procedural SV acceleration. Among the overall group (n=179), the presence of aSV was the strongest independent predictor of restenosis (OR 3.08, 95% CI 1.35 to 7.05, p=0.008). In addition, DS was also an independent predictor of restenosis (OR 1.12, 95% CI 1.06 to 1.18, p<0.0001) whereas age, unstable angina, coronary flow velocity reserve were not.

According to the presence or absence of aSV and a cut-off value of 35% for post-procedural DS, patients were stratified into 4 subsets. Results of this stratification in relation to restenosis are shown in Figure 4. Group I, characterized by the presence of a DS ≥ 35% and the presence of aSV, was associated with the highest restenosis rate. The most favorable subset of patients is characterized by the absence of aSV and a residual DS <35% (Group IV), which was associated with the lowest restenosis rate. The remaining 2 groups (II and III) had an intermediate angiographic outcome. (Figure 4)

When only analyzing the aSV group (n=54), an elevated SV value was the only independent predictor of restenosis (OR, 1.02; 95% CI 1.00 to1.032, p=0.034) whereas DS, MLD and coronary flow velocity reserve were not.

By receivers operating characteristics curve analysis, the best predictive cut-off value of SV was 101 cm/sec (area under the curve 66%, 95% CI 0.516 to 0.809, p=0.040). For the patients with SV >101 cm/sec (n=18) presented a significantly higher restenosis rate than patients with SV<101 cm/sec (72% vs. 42%, p=0.034). In predicting restenosis, a cut-off value of 101cm/sec was associated with a sensitivity of 46%, specificity of 81%, positive predictive value of 85% and a negative predictive value of 58%.

Table I. Baseline Characteristics

Variables	aSV (N=54)	Non-aSV (N=125)	p-value
Age (years)	62±8	58±9	0.006
Female gender	11(18)	32(29)	NS
Diabetes	8(13)	88(8)	NS
Smoking	11(18)	31(28)	NS
Hypercholesterolemia	27(43)	58(53)	NS
Hypertension	19(31)	41(37)	NS
Unstable Angina	42(67)	52(47)	0.013
Previous MI	5 (9)	20 (18)	NS
Previous BA	9(14)	11(10)	NS
RD before BA (mm)	2.96±0.53	2.82±0.43	0.067
DS before BA (%)	63±9	62±9	NS

MI: myocardial infarction, RD: reference diameter DS: diameter stenosis, BA: balloon angioplasty

Table II. Procedural Data

Variables	aSV (N=54)	Non-aSV (N=125)	p-value
Before BA			
CVR	1.55± 0.53	1.57±0.63	NS
MLD (mm)	1.09±0.30	1.05±0.27	NS
After BA			
CVR	2.73±0.93	2.79± 0.92	NS
MLD (mm)	1.84± 0.36	1.77±0.34	NS
Follow-up			
CVR	2.30±0.82	2.75±1.07	0.009
MLD (mm)	1.44±0.49	1.63±0.49	0.010
Late loss (mm)	0.34±0.39	0.16±0.42	0.003

BA: balloon angioplasty; MLD: minimum luminal diameter; CVR: coronary flow velocity reserve, late loss is calculated as the difference between the minimal luminal diameter after the intervention and the diameter at the six-month follow-up.

Discussion

Invasive and non-invasive studies have investigated the feasibility of applying the concept of the continuity equation based on Doppler measurements distal and at the stenosis in an attempt to determine the degree of coronary stenosis [9-12]. In agreement with these studies, we found 1) a strong correlation between the angiographic data and the SV values at 6 months follow-up, 2) higher SV values at follow-up in restenotic compared to non-restenotic patients, 3) a significant reduction in SV values after balloon dilatation whereas

the opposite was found at follow-up in patients experiencing restenosis.

This study is the first describing the relationship between angiographic restenosis and the presence of post-procedural aSV. As illustrated in figure 4, the predictive value of the aSV appears to be complementary to quantitative coronary angiography data. Furthermore, we also found that the higher the SV at the end of the intervention, the greater the likelihood of observing restenosis at 6 month follow-up. Based on the continuity equation, the presence of high post-procedural SV appears to reflect insufficient luminal gain following the intervention, which has been shown to be associated with a greater restenosis risk.

In the catheterization laboratory, the standard assessment of the arterial conductance is performed by measuring the fractional flow reserve (distal coronary pressure divided by aortic pressure at maximal hyperemia)[13]. A recent study has reported the predictive value of the post-procedural fractional flow reserve following angioplasty[14]. Since SV is an indicator of the trans-stenotic gradient, it is not surprising to find that SV carries a strong predictive value. However, in comparison with pressure measurements, the assessment of SV does not require the use of adenosine and is independent on an adequate hyperemic response.

As previously mentioned, the dependency of the coronary flow velocity reserve on the integrity of the microcirculation is a major limitation when assessing the post-procedural residual anatomical obstruction. Following angioplasty, SV appears to be exquisitely sensitive to the changes experienced at the treated area without depending on the status of the microcirculation.

Limitations

The paucity of patients with available SV prevents one from drawing definitive conclusions about the value of this parameter for the assessment of outcome of percutaneous interventions.

Due to technical failure, it was not feasible to measure SV in 30% of patients with aSV. This technical limitation might be overcome by the on-line automatic detection of the flow velocity contour based on the acquisition of the raw Doppler signal and off-line optimal contour detection. These methods are presently being prospectively investigated and should prove to be useful for the assessment of these high jet velocities.

Clinical implications

Identification of aSV and the measurement of the SV appear to be useful invasive tools in the assessment of

angioplasty results and predicting restenosis. Following balloon angioplasty, the presence of aSV alone or in

conjunction with a SV > than 101 cm/sec carries a bad angiographic prognosis, justifying adjunctive

stenting.

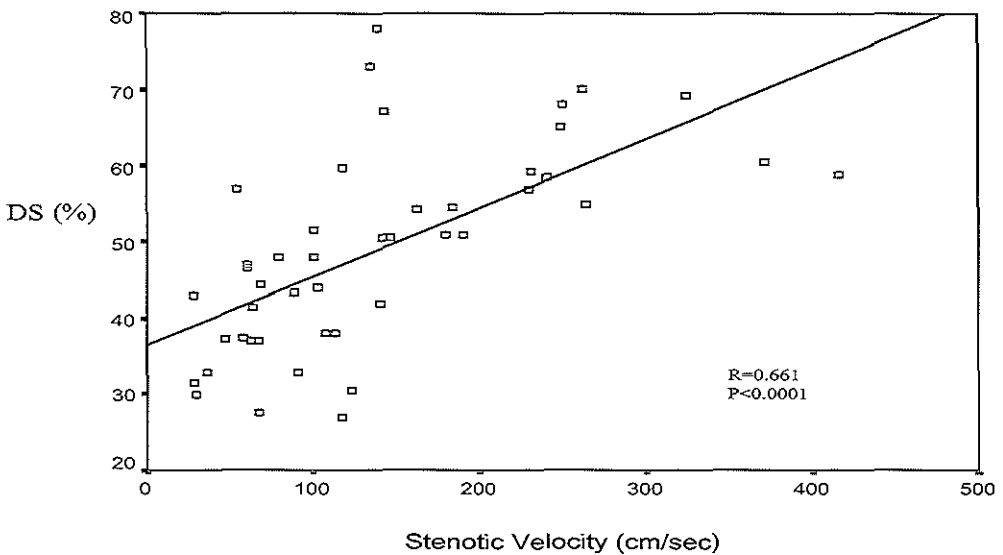Figure 1. Relationship between DS and SV at 6-month follow-up

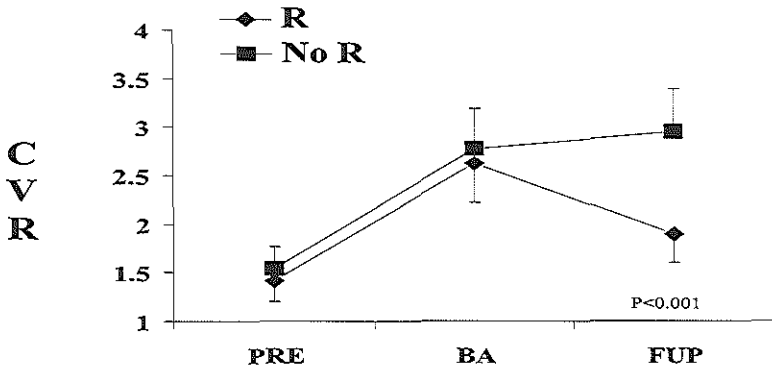Figure 2. Coronary flow velocity reserve in restenotic (R) and non-restenotic (No R) patients.

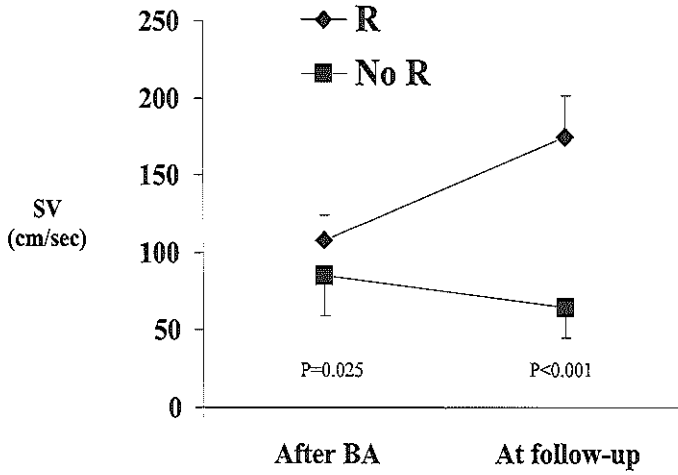Figure 3. SV data in restenotic and non-restenotic patients

Figure 4. Number and percent incidence of angiographic restenosis in the four groups identified by the predefined presence of stenotic flow velocity acceleration and residual diameter stenosis cut-off value of 35%. Values are presented in percentages. Group I, n=35 DS≥35% and aSV; group II, n= 65, DS≥35% and No aSV; group III, n=19, DS<35% and aSV; group IV, n=60, DS<35% and No aSV

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Chapter 8

Value of coronary stenotic flow velocity acceleration on the prediction of long-term improvement in functional status after angioplasty

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Value of coronary stenotic flow velocity acceleration on the prediction of long-term improvement in functional status after angioplasty

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Background The coronary flow velocity acceleration at the stenotic site (SVA), defined as a ≥50% increase in resting stenotic velocity when compared with the reference segment, has been shown to be highly sensitive and specific for the diagnosis of a hemodynamically significant stenosis. In this study, we describe the value of postprocedural SVA for the prediction of a lack of improvement in functional activity at long-term follow-up balloon angioplasty (BA).

Methods We investigated the improvement in functional activity in patients undergoing single native vessel angioplasty and intracoronary Doppler (before BA, after BA, and again at 6-month follow-up) as part of the Doppler Endpoints Balloon Angioplasty Trial Europe (DEBATE) I trial. Lack of improvement was defined as no change in Duke Activity Status Index (DASI) at 6-month follow-up, whereas SVA was defined as ≥50% elevation in resting velocity at the treated area compared with the distal measurement.

Results SVA was found more frequently in patients without improvement in DASI (45% vs 31%, $P = .03$). Similar percent diameter stenosis and coronary flow velocity reserve were observed in patients with and those without improvement in DASI at follow-up. By multivariate regression analysis, the presence of SVA ($P = .029$; odds ratio, 1.97; 95% confidence interval, 1.07 to 3.63) and an elevated DASI at baseline ($P < .001$; odds ratio, 1.05; 95% confidence interval, 1.03 to 1.07) were associated with a lack of improvement at follow-up.

Conclusions The detection of SVA was associated with failure of improvement in functional activity at follow-up after coronary intervention. (Am Heart J 2001;142:81-6.)

The assessment of functional status is the most clinically relevant end point after a percutaneous intervention. However, the factors influencing the functional status after balloon angioplasty (BA) have not been clearly established. Previous studies revealed an association between acute procedural results such as diameter stenosis (DS), minimal luminal diameter (MLD), coronary flow velocity reserve (CFVR), and the angiographic outcome at 6-month follow-up.[1] However, the impact of these acute procedural parameters on the long-term functional status are unknown.

A major limitation of the CFVR is its dependency on the microvascular status,[2] a factor that may lead to an underestimation of the acute hemodynamic gain obtained after an intervention. Conversely, recent data

have shown that the presence of coronary flow velocity acceleration at the stenotic site compared with a reference segment may allow accurate diagnosis of a hemodynamically significant stenosis.[3,4] We hypothesize that the detection of a stenotic flow velocity acceleration after angioplasty may indicate residual hemodynamic conduit obstruction, possibly associated with an absence of functional status improvement at long-term follow-up.

In this study, we analyzed the incidence of the postprocedural stenotic flow velocity acceleration and its potential predictive value for the long-term functional status.

Methods

Patients

All patients enrolled in the Doppler Endpoints Balloon Angioplasty Trial Europe (DEBATE) study were investigated. Details of the DEBATE protocol has been previously described.[1] Briefly, 225 patients undergoing single native coronary angioplasty and sequential intracoronary Doppler measurements were enrolled in the DEBATE study. A total of 225 and 202 patients underwent clinical and angiographic follow-up, respectively. For our current study, we grouped these 225

Table I. Baseline characteristics of the overall population

Characteristics	Total group (n = 225)
Age, y	59 ± 11
Female sex	52 (23)
Diabetes mellitus	23 (10)
Hypercholesterolemia	116 (52)
Previous myocardial infarction	39 (17)
Previous angioplasty	25 (11)
Smoking	57 (25)
Exertional angina	183 (81)
Unstable angina	133 (35)

patients according to the presence or absence of improvement in functional capacity at long-term follow-up.

Quantitative coronary angiographic measurements and balloon angioplasty

Balloon angioplasty was performed in a conventional manner. At least two cineangiograms, in orthogonal projections, were obtained before, after, and at 6-month follow-up in the same projections. Intracoronary nitroglycerin (0.1 to 0.3 mg) or isosorbide dinitrate (1 to 3 mg) was administered to achieve maximal coronary vasodilation. All cinefilms were sent to an independent core laboratory (Cardialysis, The Netherlands), which was blinded to the clinical and the Doppler information. Matched views and frames were selected for off-line quantitative analysis. A computer-assisted analysis system was used (CAAS II system, Pie Medical Data, Maastricht, The Netherlands). Automatic edge detection of the luminal dimensions (MLD and reference diameter) was performed with the use of the empty guiding catheter as a scaling factor. DS was calculated. Restenosis was defined as binary angiographic restenosis (DS > 50%) at 6-month follow-up.

Intracoronary Doppler recording

Baseline and hyperemic average peak velocity measurements were performed proximal and distal to the lesion with a 0.014-inch Doppler tipped guide wire. For distal measurements, a distance from the stenosis of at least 5 times the vessel diameter was chosen to avoid prestenotic acceleration of flow or poststenotic turbulence, both of which may influence local velocities. After distal measurements were made, pullback into the lesion site was performed. According to Caiati et al,[4] the observation of coronary flow velocity acceleration of ≥50% at the stenotic site is highly sensitive (92%) and specific (100%) for the diagnosis of a hemodynamically significant stenosis. Therefore, flow velocity acceleration was defined as an elevation in stenotic coronary flow velocity of ≥50% compared with distal baseline velocities. Measurements were performed before and 15 minutes after treatment.

Activity assessment

Functional status was measured in all 225 patients with the Duke Activity Status Index (DASI), a 12-item scale with total scores ranging from 0 to 58.2 (with higher scores indicating better functional status) that evaluates the ability to perform common activities of daily living.[5,6] Lack of improvement in

DASI was defined as 0% change or reduction in DASI from baseline to 6-month follow-up. Angina pectoris was assessed according to the Canadian Cardiovascular Society (CCS 1-4) and the Braunwald (I-III, A-B) classification.

Statistical analysis

Quantitative data are presented as mean ± SD, whereas qualitative data are presented as frequencies. Continuous variables were compared by means of an unpaired Student t test. Categoric variables were compared by means of Fisher exact test. Stepwise logistic regression was performed to search for independent predictors of a lack of improvement in functional status at follow-up. A value of $P < .05$ was considered statistically significant.

Results

Baseline and procedural data of the study population

Two-hundred twenty-five patients were enrolled. Table I illustrates the baseline characteristics of the study population. After BA, the DS decreased from 62% ± 9% (MLD, 1.06 ± 0.27 mm) to 37% ± 8% (MLD, 1.79 ± 0.34 mm; $P < .001$), whereas the CFVR increased from 1.58 ± 0.60 to 2.72 ± 0.91 ($P < .001$).

In 82 (37%) patients, the presence of coronary flow velocity acceleration of ≥50% at the lesion site was detected.

Functional status at baseline and follow-up

At 1-month follow-up, the DASI increased from 18 ± 14 to 24 ± 15 ($P < .001$) and to 23 ± 18 ($P < .001$ vs before BA) at 6-month follow-up. The functional status of all the patients in the study, as assessed by the DASI, increased by 6.75 units (85%, $P < .0001$) at early follow-up. From baseline to 6-month follow-up, the DASI increased by 5.0 units (58%, $P < .001$), whereas no significant changes in functional status score were seen between early and late follow-up.

Sequential DASI and the presence of angina symptoms (before angioplasty and at 1- and 6-month follow-up) as well as Doppler and quantitative coronary angiography (QCA) measurements (baseline, immediately after angioplasty, and at 6-month follow-up) are shown in Figure 1.

Failure of functional status improvement at long-term follow-up

From the overall population, 129 (56%) patients had an improved DASI at 6-month follow-up, whereas 96 (44%) patients did not. Furthermore, similar risk factor profile (age, sex, diabetes mellitus, hypertension, hypercholesterolemia, smoking, history of a previous angioplasty) was found among the 2 subgroups.

The improvement group had a greater proportion of patients with baseline exertional angina compared with the nonimprovement group (87% vs 76%, $P = .030$).
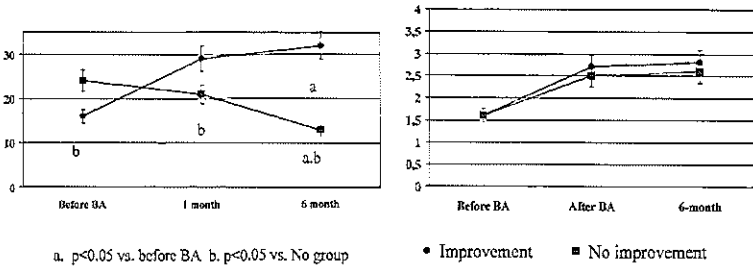
Figure 1
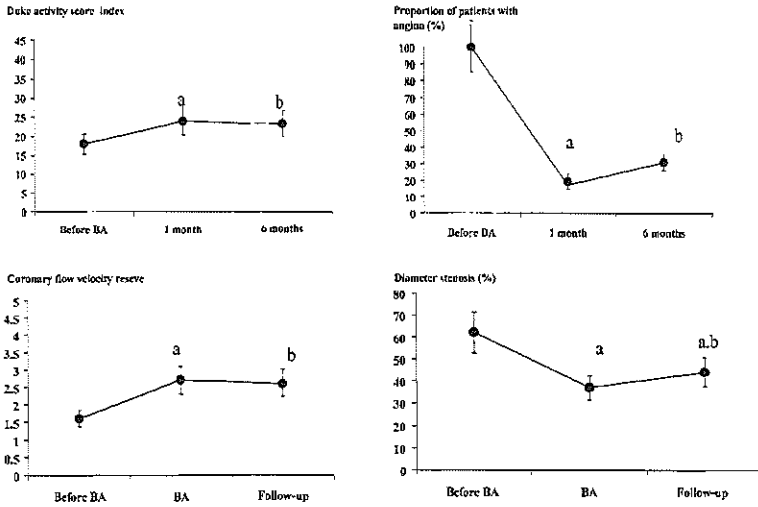
a. p<0.05 vs previous measurement   b. p<0.05 before vs follow-up BA

DASI and proportion of patients with angina symptoms before BA and at 1- and 6-month follow-up; CFVR and percent DS before and after angioplasty and at 6-month follow-up.

Figure 2

Duke activity status index

Coronary flow velocity reserve

a. p<0.05 vs. before BA b. p<0.05 vs. No group

• Improvement   ▪ No improvement

DASI and CFVR in improvement and nonimprovement groups.

Figure 2 illustrates the DASI values at baseline and at 1- and 6-month follow-up of both subgroups. The improvement group had a lower baseline DASI than did the nonimprovement group (Figure 2).

QCA and Doppler-derived data of patients with and those without improvement in functional status at follow-up

Angiographic data of both subgroups are shown in Table II. At follow-up, a greater MLD and a lower DS were found in the improvement group compared with the nonimprovement group (Table II), whereas baseline and postprocedural DS and MLD were found to be similar in both subgroups.

CFVR was similar in both groups before BA, after BA, and at 6-month follow-up (Figure 2). However, postprocedural stenotic flow velocity acceleration was detected more frequently in the nonimprovement group than in the improvement group ($P = .033$, Figure 3).

Figure 3

Flow acceleration
at the stenosis (%)
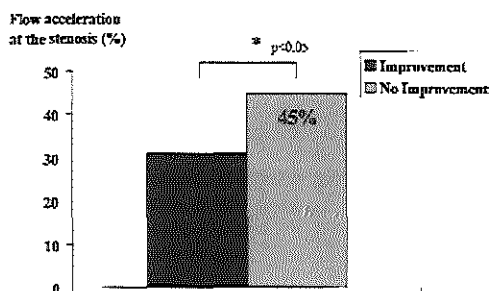
Proportion of patients with postprocedural stenotic flow veloc-
ity acceleration in improvement and nonimprovement groups.

Table II. QCA data of patients with and those without func-
tional improvement at 6-month follow-up

	Improve-ment (n = 129)	No improvement (n = 96)	P value
Reference diameter (mm)	2.84 ± 0.51	2.86 ± 0.45	NS
DS before BA (%)	62 ± 9	63 ± 8	NS
MLD before BA (mm)	1.07 ± 0.30	1.05 ± 0.26	NS
DS after BA (%)	37 ± 9	38 ± 8	NS
MLD after BA (mm)	1.79 ± 0.35	1.78 ± 0.32	NS
DS at 6 mo (%)	42 ± 15	48 ± 16	.007
MLD at 6 mo (mm)	1.63 ± 0.49	1.44 ± 0.49	.010

Predictors of DASI at long-term follow-up

By univariate analysis, the absence of exertional
angina and an elevated DASI at baseline assessment in
addition to the presence of flow velocity acceleration at
the ballooned site were associated with a lack of
improvement in functional status at long-term follow-up
(Table III). Age, sex, hypertension, hypercholes-
terolemia, diabetes mellitus, and previous myocardial
infarction were not independent predictors of a lack of
improvement in functional status at follow-up.

Multivariate logistic regression analysis revealed that
an elevated baseline DASI and the presence of stenosis
flow velocity acceleration were the only independent
predictors of a lack of improvement in functional status
at long-term follow-up (Table III).

After excluding all restenotic patients (n = 72), the
presence of baseline exertional angina (odds ratio, 0.24;
95% confidence interval, 0.62 to 0.96; P = .003) was
retained as the only predictor of no improvement in
functional status at long-term follow-up.

Discussion

From this study, several findings should be men-
tioned: (1) the detection of postprocedural stenotic
flow velocity acceleration predicted a lack of improve-
ment in functional status at long-term follow-up; (2)
standard QCA and Doppler flow measurements failed to
predict the long-term changes in functional status.

Several studies including DEBATE I have described
the predictive value of postprocedural QCA data for the
prediction of angiographic restenosis.[1,7-9] Despite the
latter, postprocedural QCA data did not predict the
functional status at long-term follow-up. Reports from
our group and others have shown that QCA is not accu-
rate for evaluating the degree of residual hemodynamic
obstruction after an intervention.[2,10-12] Furthermore, in
concert with previous studies,[13-15] we observed that only

62% (n = 43) of the restenotic patients had symptoms of
angina at 6-month follow-up. It is conceivable that post-
procedural QCA data might only predict the long-term
morphologic changes observed at the ballooned site irre-
spective of its hemodynamic significance. In contrast,
the detection of stenotic flow velocity acceleration indi-
cates the presence of a more physiologically significant
residual obstruction, which may also predict significant
physiologic changes observed in the epicardial lumen at
long-term follow-up.

Several reports have described the dependency of
CFVR on the microcirculation.[16-19] The latter is particu-
larly important in patients with diabetes,[20] left ventricu-
lar hypertrophy,[21] or previous myocardial infarction,[22-25]
in whom an inability to mount an adequate hyperemic
response could result in an underestimation of the
actual epicardial luminal gain after a percutaneous
intervention. In addition, a transient elevation in base-
line velocities caused by a delay in the recovery of
microvascular autoregulation,[18] postocclusive hyper-
emic response, or intracoronary nitrates may also trans-
late into a low CFVR. Surprisingly, the improvement in
functional status was not followed by a higher CFVR at
6-month follow-up. This unexpected finding further
supports the concept that the absolute CFVR is a rather
nonspecific anatomic index subjected to severe inher-
ent limitations.

Our study is the first one demonstrating the value of
flow velocity acceleration at the ballooned site for the
prediction of an improvement in functional status at 6-
month follow-up. The presence of coronary flow veloc-
ity acceleration at the end of the procedure may indi-
cate a hemodynamically significant residual stenosis,
possibly explaining its strong predictive value. This
new invasive index presents several advantages. First, it
is independent of hemodynamic variables. Second, it
does not require an adequate hyperemic response.
Third, it may convey specific information regarding
arterial conductance.[3,26,27]

From the current study, whenever stenotic velocity
acceleration is being identified, it appears justified to

Table III. Univariate and multivariate predictors of lack of improvement in functional status at long-term follow-up

Variables	Univariate P value (OR, 95% CI)	Multivariate P value (OR, 95% CI)
Exertional angina	.045 (0.46, 0.22–0.94)	
Baseline DASI	<.001 (1.05, 1.02–1.07)	<.001 (1.05, 1.03–1.07)
SV acceleration	0.033	.029 (1.97, 1.07–3.63)

OR, Odds ratio; CI, confidence interval; SV, flow velocity at the stenosis site.

undergo additional anatomic evaluation in an attempt to rule out residual conduit obstruction and to improve the long-term functional status.

Limitations

In our study, we used Doppler-derived parameters to assess the physiologic changes occurring after balloon dilatation. In patients with postprocedural flow acceleration, the use of transstenotic guide wire pressure-derived fractional flow reserve could have helped us verify the presence of a significant residual conduit obstruction.[28] However, in contrast with the assessment of flow velocity acceleration, fractional flow reserve is dependent on an adequate hyperemic response.

In our study, we did not measure the relative CFVR (the ratio of target vessel CFVR to the CFVR in a normal reference vessel). This index has been advocated for the objective evidence of the functional lesion severity because it is relatively independent of hemodynamic variables.[29,30] However, it is conceivable that alterations in baseline and/or hyperemic velocities immediately after the procedure may also confound the relative CFVR results. Furthermore, its role in the evaluation of the hemodynamic changes occurring after a percutaneous intervention is still undefined.

Stenotic flow velocity acceleration at the end of the angioplasty procedure predicted a failure to improve long-term functional status. The possible impact on therapeutic strategies, however, has not been an objective of this study. Further investigations are needed to elucidate the value of this parameter in guidance of angioplasty procedures such as provisional stenting.

Conclusions

Stenotic flow velocity acceleration at the end of the angioplasty procedure predicted a failure to improve the functional status at 6-month follow-up.

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Part V

Shear Stress and Restenosis

Chapter 9

High shear stress after successful balloon angioplasty is associated with restenosis and target lesion revascularization

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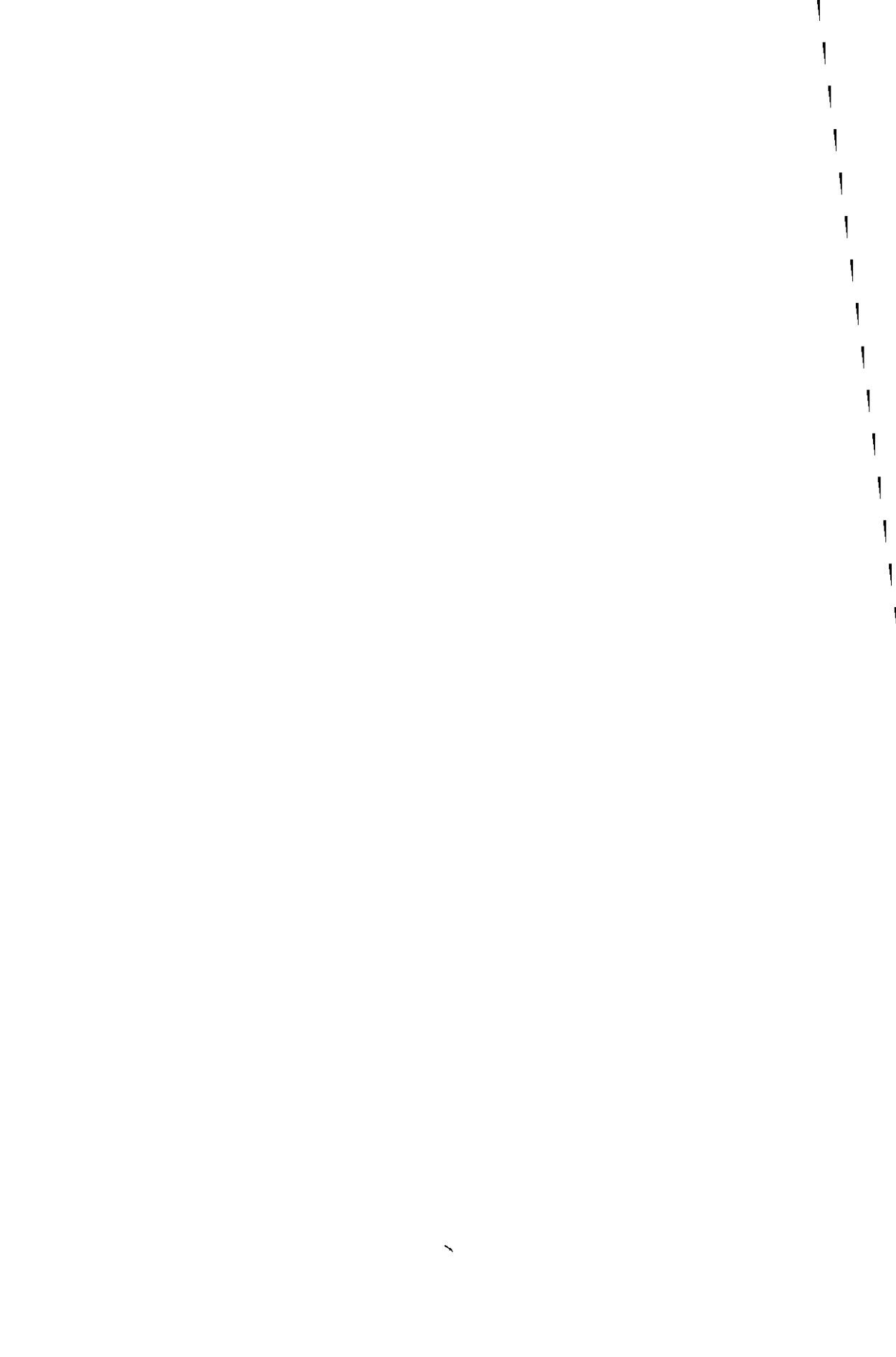
Introduction

Vascular wall shear stress (WSS), the frictional force exerted by the flowing blood on the endothelium of the artery, has repeatedly been implied in the pathogenesis of atherosclerosis and vascular remodeling (1-6). The pathophysiologic mechanisms linking these events are diverse. Abnormal shear stress induces pathways that transmit information to the cell nucleus, where expression of certain genes may occur. The actions initiated by these genes can - amongst others - result in cellular adhesion onto the vascular wall, lipid accumulation, release of vasoactive substances, induction of growth factors and interference with smooth muscle cell proliferatory characteristics (7-18). It has not unequivocally been shown whether rapid changes in shear stress, gradients in shear stress or low, oscillatory shear stress is the main modulator of atherogenesis, although recent evidence points to the latter (19-21).

Although, there is strong scientific evidence that WSS is a key player in the pathophysiology of atherosclerosis (3, 20-21), no evidence for its role in restenosis after balloon angioplasty has been provided. Also, no currently available technique can measure local wall shear stress in vivo on-line. Recently, our group developed a two-step off-line apparatus to assess WSS at numerous finite elements of the luminal surface, combining the newly developed ANGUS (combination of ANGiography and intravascular UltraSound) method (22) with 3-dimensional computational fluid dynamics (23-25). This method, however, remains time consuming, and cannot be used on-line in the catheterization laboratory to evaluate the possible necessity for adjunctive treatment after balloon angioplasty.

Balloon angioplasty is subjected to an undesirable rate of restenosis (26). Prediction of restenosis is conventionally based on consideration of patient characteristics, the targeted lesion and post-procedural angiographic parameters. Although functional parameters such as post-procedural Doppler-derived coronary flow velocity reserve (CFR) or fractional flow

reserve obtained by a sensor tipped guidewire further extend the performance of quantitative

coronary angiography (QCA) in predicting restenosis after PTCA (27-29), the functional

parameter with optimal predictive accuracy is still sought.

However, average WSS may be calculated in vivo for an entire cross-sectional segment of

arteries from the known lumen radius and volume flow rate using the Hagen-Poiseuille

equation (30-31). Volumetric blood flow can be estimated at that site of the vessel by

multiplying Doppler-derived average peak velocity (APV) with cross sectional area (CSA)

assessed by QCA (32,33).

We aimed to introduce the concept of calculation of this average WSS to the clinical setting

and to establish the possible predictive value of post-procedural WSS parameters on

restenosis, target lesion revascularization (TLR) rate and the reoccurrence of angina and/or

positive exercise stress testing after angiographically successful balloon angioplasty.

Methods

Patient selection

Methods of the DEBATE I trial have been described in detail previously (27). In short, 297

patients undergoing successful balloon angioplasty of a single lesion were included. Baseline

and hyperemic flow velocity measurements were performed proximal and distal to the lesion

and at the site of the lesion using a 0.014-inch Doppler tipped guidewire (FloWire,

Endosonics Co., Rancho Cordova, CA, USA). For both proximal and distal measurements, a

distance from the stenosis of at least 5 times the vessel diameter was chosen to avoid

prestenotic acceleration of flow or poststenotic turbulence, both of which may influence local

velocity. This, in turn, would affect the laminar flow conditions, which is an essential

assumption for flow and WSS calculations. The site of the blood flow velocity measurements

was recorded on cinefilm, providing to obtain flow recording in the same position at post-procedure and follow-up. The Doppler data were not used as guidance for the intervention; only angiographic criteria (diameter stenosis [DS] <50% in any angiographic view) were used to determine the end point (successfulness) of the angioplasty procedure. For various reasons as bailout stenting and urgent revascularization, 225 patients were finally enrolled and 202 had a 6-month control coronary angiogram performed, again with the Doppler measurements made at the different sites. The population of these 202 patients formed the subject of our study.

Calculation of wall shear stress

WSS was computed proximal and distal to the lesion and in the lesion, before and after treatment and at 6-month repeat angiogram using the Hagen-Poiseuille formula (30): $WSS = 4\mu Q/\pi R^3$, with μ being blood viscosity, taken to be constant at 0.03 Poise (=0.003 Ns/m^2), Q the volumetric blood flow in ml/sec, and R the radius of the coronary lumen at the site of the flow measurement. Volumetric flow was calculated from blood velocity (assuming parabolic flow) measured with intravascular Doppler using the validated formula (32,33): $Q = CSA \times APV \times 0.5$, where CSA is the cross-sectional area and APV is the baseline (before adenosine administration) average peak velocity. Minimal and reference vessel CSA was measured by videodensitometry with a computer-assisted quantitative coronary angiography analysis system (CAAS II system, Pie Medical Data, Maastricht, The Netherlands). Lumen radius to apply the Hagen-Poiseuille formula was derived from videodensitometric area ($R = \sqrt{CSA/\pi}$) in order to achieve the best approximation of the real lumen dimension (34). In-lesion WSS values ($WSS_{in-lesion}$) were calculated with minimal CSA and the in-lesion velocities, whereas proximal (WSS_{prox}) and distal to the lesion values (WSS_{dist}) were derived from the measured APV at those sites and the reference segment CSA. After replacing the

constants and substituting the equations the final formula used for each calculation was:

$WSS=0.10635 \times APV / \sqrt{CSA}$, and results were expressed in N/m^2.

Follow-up and study endpoints

Quantitative angiography was repeated at the 6-month follow-up visit. Angiographic restenosis was defined as a DS >50% on the follow-up angiogram. The rate for target lesion revascularization (TLR) was determined based on the presence of angiographic restenosis of the remote angioplasty site in a patient with either symptoms or signs of ischemia. The anginal status of the patients was evaluated and, when possible, a symptom-limited bicycle stress test was performed at the 1 month and at 6 months follow-up visits.

Statistical analysis

Values are reported as means ± SD. Analyses were accomplished applying a standard software package (SPSS 9.0, SPSS Inc. Chicago, IL, USA). Comparison between groups of patients in respect to the presence of restenosis was evaluated by unpaired Student's t-tests. Differences within WSS values after the procedure and at follow-up were evaluated by paired Student's t-tests. Univariate and multivariate logistic regression tests were performed to study the diagnostic value of WSS data and other variables to predict angiographic and clinical endpoints. Receiver operator characteristic curve (ROC) analyses were performed to find the optimal (where sensitivity equals specificity) cut-off value of variables.

Results

Comparison of angiographic and Doppler flow measurements

The baseline characteristics of study patients, the procedural and clinical outcomes are detailed elsewhere (27). Seventy-two patients presented with angiographical restenosis at

follow-up and 62 had reintervention during the study period. After the successful initial intervention, distal velocity measurements were obtained in all, at proximal site in 183 and at the site of the minimal lumen diameter with acceptable quality in 56 patients. At follow-up cardiac catheterization distal measurements were taken in 182, at the lesion site in 74 and in 173 vessels proximal to the remote target site. Results of videodensitometric QCA analysis and Doppler study at post-procedure and their comparison in respect to restenosis are given in Table 1. Post-procedural residual minimal CSA, the reference segment CSA and percent area stenosis did not differ between the groups. The APV in-lesion tended to be higher in restenotic lesions than in non-restenotic lesions. The difference was small but significant at the site proximal to the lesion.

Comparison of different WSS values

Table 2 gives the calculated WSS values at pre-, post-procedure and at follow-up at the different locations and their comparison between restenotic and non-restenotic patients. It is seen that the post-procedural WSS_{prox} and $WSS_{in-lesion}$, and $WSS_{in-lesion}$ at follow-up are significantly higher in the group with versus the group without restenosis. Figure 1 shows the results of the paired t-tests performed to compare post-procedural and follow-up WSS values and reveals significant change in the restenosis group (Fig. 1[a]) at the in-lesion location; it increases at follow-up; reflecting the recurrence of lumen obstruction. WSS_{prox} and WSS_{dist} remain in narrow range (0.6-1.4 N/m^2).

Predictive values of WSS measurements on angiographic restenosis and TLR

Bivariate logistic regressions and ROC-curves were applied to establish the prognostic power of post-procedural respective values of WSS to predict the recurrence of restenosis (Table 3) and TLR (Table 4). $WSS_{in-lesion}$ had a good predictive value for angiographic restenosis (ROC

area, 66%, $P<0.05$, Figure 2). The ROC analysis detected an optimal cut-off value of 2.58 N/m^2 above which restenosis could be predicted with a sensitivity and specificity of 62%. WSS_{prox} had a reasonable (ROC area, 62%, $P<0.01$), WSS_{distal} had a modest (ROC area, 60%, $P<0.05$) power to predict TLR. On the other hand, as it is depicted in Table 4, the measured APV at the corresponding reference segments also had a prognostic value for TLR (ROC area, 61%, $P<0.05$ for the proximal and ROC area 59 %, $P<0.05$ for the distal site).

In order to assess any additional independent predictive value of WSS parameters, the results of post-procedural DS and distal CFR measurements as known independent predictors for worse outcome after BA (27) were entered in the multivariate analysis (Table 5). In predicting restenosis DS proved to be an independent predictor (OR = 1.10, $P<0.001$), when added to the respective values of WSS at the reference segments and distal CFR. However, WSS_{prox} was the only independent predictor for TLR (OR = 2.15, $P<0.05$).

Predictive values of WSS measurements on early and late recurrence of symptoms and/or ischemia

The relations between the post-procedural APV, CSA, calculated WSS parameters and the reoccurrence of angina and/or ischemia at 1 and 6 months follow-up were also analyzed. None of the variables had significant predictive power in respect to the 1-month results (data not shown). For predicting late recurrence of symptoms and/or ischemia only WSS_{prox} revealed significant prognostic value (ROC area, 62%, $P<0.05$). However, in the multivariate model it did not prove to be an independent predictor.

Table 1. Comparison of videodensitometric cross-sectional areas, area stenosis and average peak velocities of vessels measured at post-procedure in respect to binary restenosis at 6-month follow-up.

	RESTENOSIS	NO RESTENOSIS	*P*
CSA_{min} (mm^2)	3.2 ± 1.3 (72)	3.5 ± 1.5 (130)	0.105
CSA_{ref} (mm^2)	6.6 ± 1.8 (72)	6.6 ± 2.3 (130)	0.996
AS (%) *	51.8 ± 13.1 (72)	45.6 ± 15.0 (130)	0.107
APV_{prox} (cm/s)	**28.9 ± 14.2 (66)**	**24.6 ± 11.4 (117)**	**0.036**
$APV_{in-lesion}$ (cm/s)	53.6 ± 27.9 (29)	42.4 ± 18.9 (27)	0.089
APV_{distal} (cm/s)	18.1 ± 6.8 (72)	17.4 ± 8.8 (130)	0.505

* Residual diameter stenosis measured with edge detection was <50% for both groups.

CSA_{min} = minimal cross-sectional area, CSA_{ref} = reference segment cross-sectional area, AS = percent area stenosis, APV_{prox}, $APV_{in-lesion}$ and APV_{distal} = average peak velocity at proximal to, at the site of and distal to the targeted lesion.

Values are mean ± SD. Numbers in parentheses indicate the available number of observations. Statistically significant values are in bold.

Table 2. Calculated WSS values at different sites at pre-, post-procedure and at follow-up in respect to binary restenosis at 6-month follow-up.

		RESTENOSIS	NO RESTENOSIS	P
PRE-PROCEDURE	WSS_{prox}	0.97 ± 0.46 (64)	0.89 ± 0.46 (116)	0.225
	$WSS_{in\text{-}lesion}$	16.06 ± 10.3 (17)	10.97 ± 9.2 (33)	0.097
	WSS_{distal}	0.70 ± 0.36 (71)	0.65 ± 0.32 (127)	0.319
POST-PROCEDURE	**WSS_{prox}**	**1.22 ± 0.61 (66)**	**1.05 ± 0.51 (117)**	**0.047**
	$WSS_{in\text{-}lesion}$	**3.61 ± 2.38 (29)**	**2.46 ± 1.39 (27)**	**0.033**
	WSS_{distal}	0.78 ± 0.34 (72)	0.76 ± 0.45 (130)	0.660
FOLLOW-UP	WSS_{prox}	1.06 ± 0.70 (60)	1.06 ± 0.80 (113)	0.973
	$WSS_{in\text{-}lesion}$	**10.51 ± 8.84 (35)**	**3.03 ± 2.05 (39)**	**0.000**
	WSS_{distal}	0.77 ± 0.53 (61)	0.76 ± 0.37 (121)	0.863

WSS_{prox} = wall shear stress proximal to the lesion, $WSS_{in\text{-}lesion}$ = wall shear stress in the lesion, WSS_{dist} = wall shear stress distal to the lesion.

Values are mean ± SD and expressed in N/m^2. Numbers in parentheses indicate the available number of observations. Statistically significant values are in bold.

Table 3. Predictive values of post-procedural WSS, APV and CSA for restenosis at 6 months follow-up. Results of ROC curve analysis and univariate logistic regression tests.

Variable	Cut-off	ROC Area (95% CI)	P-value of the ROC curve	Univariate regression	
				OR	P
WSS$_{prox}$ (183)	0.97	58 (49-66)	0.085	1.72	0.051
APV$_{prox}$ (203)	24.3	59 (50-68)	0.051	**1.03**	**0.030**
WSS$_{in-lesion}$ (56)	**2.58**	**66 (51-80)**	**0.048**	1.42	**0.048**
APV$_{in-lesion}$ (56)	41.0	61 (46-76)	0.156	1.02	0.100
WSS$_{distal}$ (202)	0.69	55 (52-69)	0.216	1.16	0.664
APV$_{distal}$ (225)	16.0	57 (49-65)	0.118	1.01	0.540
CSA$_{min}$ (202)	3.15	56 (48-64)	0.165	0.84	0.119
CSA$_{ref}$ (202)	6.45	53 (44-61)	0.530	1.00	0.996

ROC = receiver operator characteristic, CI = confidence interval, OR = odds ratio.

Numbers in parentheses indicate the available number of observations. Statistically significant values are in bold.

Table 4. Predictive values of post-procedural WSS, APV and CSA for target lesion revascularization rate during 6 months follow-up. Results of ROC curve analysis and univariate logistic regression tests.

Variable	Cut-off	ROC Area (95% CI)	*P*-value of the ROC curve	Univariate regression	
				OR	*P*
WSS$_{prox}$ (183)	**1.00**	**62 (53-71)**	**0.008**	**2.33**	**0.004**
APV$_{prox}$ (203)	**24.6**	**61 (52-70)**	**0.013**	**1.04**	**0.003**
WSS$_{in-lesion}$ (56)	2.70	58 (42-74)	0.324	1.19	0.226
APV$_{in-lesion}$ (56)	40.4	58 (41-75)	0.305	1.02	0.115
WSS$_{distal}$ (202)	**0.71**	**60 (51-69)**	**0.026**	1.90	0.088
APV$_{distal}$ (225)	16.5	**59 (50-67)**	**0.043**	1.03	0.140
CSA$_{min}$ (202)	3.14	56 (48-65)	0.156	0.84	0.139
CSA$_{ref}$ (202)	6.20	46 (37-55)	0.392	1.00	0.506

ROC = receiver operator characteristic, CI = confidence interval, OR = odds ratio.

Numbers in parentheses indicate the available number of observations. Statistically significant values are in bold.

Table 5. Results of multivariate logistic regression of CFR and post-procedural DS with respective WSS values for prediction of restenosis and target lesion revascularization.

	Restenosis			Target lesion revascularization		
	OR	**CI**	*P*-value	**OR**	**CI**	*P*-value
WSS$_{prox}$	1.82	0.98-3.37	0.055	**2.15**	1.17-3.95	**0.014**
CFR	0.93	0.63-1.35	0.690	0.80	0.54-1.19	0.270
DS (%)	**1.10**	1.04-1.13	**0.000**	1.03	0.99-1.08	0.104
WSS$_{in-lesion}$	1.33	0.91-1.95	0.140	1.17	0.85-1.62	0.34
CFR	0.96	0.49-1.88	0.910	0.70	0.35-1.41	0.32
DS (%)	1.05	0.97-1.14	0.250	0.97	0.89-1.05	0.45
WSS$_{distal}$	1.24	0.56-2.76	0.59	1.56	0.78-3.50	0.276
CFR	0.84	0.57-1.23	0.370	0.71	0.48-1.07	0.103
DS (%)	**1.09**	1.05-1.14	**0.000**	1.04	0.99-1.08	0.066

CFR = distal coronary flow reserve, DS = diameter stenosis, OR = odds ratio, CI = 95% confidence interval.

Significant values are in bold.

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Discussion

The main findings of the current study are: (1) Higher WSS values measured in-lesion ($WSS_{in-lesion}$) immediately after balloon angioplasty are predictive for restenosis. (2) TLR is predicted by WSS_{prox} and WSS_{dist}. (3) Moreover, after adding known independent predictors such as DS and distal CFR, WSS_{prox} remained the only independent predictor for TLR. These results suggest that the post-balloon angioplasty higher wall shear stress is associated with increased probability of restenosis and/or TLR during the follow-up period. Thus, it is conceivable that WSS, indeed, might contribute to the restenotic process. The method described allow one to calculate on-line the average value of WSS for a particular segment of the coronary artery after angioplasty. This is the first study to report the potential prognostic value of a combined functional and morphologic parameter for the outcome after BA, which does not necessitate administering a provocative agent.

Although some authors put forward the involvement of WSS in the restenosis pathophysiology (35), there is lack of scientific evidence in humans. High shear forces have been shown to induce thrombus formation (36-39), which in turn, through local platelet deposition with the subsequent release of chemotactic and mitogenic factors, such as platelet-derived growth factor and thrombin, may induce restenosis (40). Chow et al. showed that pathological levels of WSS (>3 N/m^2) initiate platelet aggregation (41). Thus, the induction of localized thrombus formation may be the initiating factor for restenosis in our patients. However, higher WSS at post-procedure was not associated with an increase of early recurrence of anginal complaints or exercise-induced ischemia. Cyclic flow variation may be a warning sign for immediate thrombotic vessel closure after angioplasty (42). To examine the possible relation between this phenomenon and the corresponding acute changes in WSS was beyond the scope of the present study.

Although, high average shear stress values for the entire cross-section were calculated in our patient group, no certainty about the spatial distribution of the WSS could be investigated. Indeed, it is possible that next to a high average WSS; regions of low shear stress exist. As previously shown, zones of low WSS can also coexist with flow separation zones inducing strong secondary flows (43). It might be that especially these regions are prone to the evolvement of restenosis: possibly the patients that developed restenosis had more severe vessel injury after PTCA, with more flow separation and more regions of secondary flow and localized slow flow, facts not accounted for by the present angiographic and Doppler evaluation. One might also speculate that turbulent flow across residual stenosis results in low shear stress downstream at the distal site of the lesion (not the site of the distal flow velocity measurement), known to be a preferential part for smooth muscle cell proliferation (44). Moreover, the higher WSS values after the procedure in the restenosis group might be explained by an increased baseline flow after the procedure and/or a less optimal angioplasty result with a lower residual CSA. However, $APV_{in-lesion}$ and CSA_{min} after the procedure did not differ significantly between the two groups. Furthermore, these parameters alone, which were taken for the WSS calculation, did not appear to have any predictive power.

Shear stress values in the arteries tend to attain a baseline value, which seems to be constant throughout the whole arterial vascular tree. Kamiya et al. found this value to be around 1.5 N/m^2 (45). This is in part confirmed by our study, which shows WSS values in the non-diseased parts of the vessels to be between 0.6-1.4 N/m^2. The WSS values found in the lesion seem unreasonably high (up to 20 N/m^2); however Strony et al. showed that WSS could be as high as 100 N/m^2 in severely atherosclerotic arteries (46).

The influence of the higher WSS of the proximal reference segments on late anginal symptoms and TLR is difficult to interpret. But the mechanisms through which WSS exerts its effect are extremely diverse and a substantial interplay between adjacent segments of the

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artery might exist. The mechanical signal provided by laminar shear stress is transmitted to the cellular nuclei, with the induction of certain genes or inhibition of expression of other genes, thereby inducing different pathogenetic events such as the suppression of platelet-derived growth factor (PDGF), monocyte adhesion on the endothelium and influence on the growth process of the endothelial cells (47-49). These molecular events might act not only the treated site of the vessel but also from a certain distance.

Our results are promising, viewing the current strategy of "stent-like balloon angioplasty", which reduces the rate of restenosis (50). Recent data (51) showed that outcome after "provisional stenting" (guided by distal CFR results upon QCA) is comparable to systematic stenting. Application of WSS measurement may eliminate the necessity to administer a vasodilatory agent to measure flow reserve. It appears that having normal values of $WSS_{in-lesion}$ and WSS_{prox} might be translated as good functional and angiographic result after balloon dilatation and are associated with less restenosis and TLR. Thus, unnecessary adjunctive therapy (e.g. stent implantation) after a successful balloon angioplasty might be avoided with the use of these parameters. Only a large, prospective study may clarify the potential of this strategy in comparison with systematic stenting.

Limitations

Important limitations to our study and its findings should be mentioned. The present calculations of shear stress assumes that blood is an incompressible, homogeneous Newtonian fluid at constant temperature, that the coronary arteries are rigid and that the flow is laminar and in steady state (30). In addition, the Hagen-Poiseuille formula ($WSS=4\mu Q/\pi R^{3}$) yields accurate results for a fully developed Poiseuille flow and for an idealized cylindrical stenosis. All these assumptions may be questioned in a coronary artery following balloon angioplasty, with the creation of an irregular vessel wall profile, possible disturbance in blood viscosity

due to clotting factors, and the disappearance of an intact endothelium. It might also be possible that the actual area of flow is different than what the densitometric CSA provided to derive the lumen radius for the Hagen-Poiseuille formula, thus resulting in incorrect values. However, it has been shown that videodensitometric quantitative angiography offers a better correlation to true luminal dimensions after BA or directional coronary atherectomy than edge detection, using intracoronary ultrasound as the gold standard (52, 53).

Furthermore, it cannot be ascertained that the measurements made using a Doppler wire are really accurate (for instance, that the wire was placed in the region of optimal flow after balloon angioplasty), and that the wire itself has no influence on the flow it is measuring, as previously suggested by Back (54). Indeed, flow-measuring techniques perform best when the flow profile is well established, and the tube is straight. In vivo, however, there are curves, bifurcations, luminal enlargements and narrowings, and atheromatous plaques causing flow disturbances and turbulence (43).

Finally, some concern may arise as to the value of these average shear stress measurements. Although heterogeneous responses of neighboring endothelial cells to WSS and high local variations in WSS have been described (55), Zarins et al. showed that average macroscopic shear stress values can be accurately derived from vessel geometry and flow parameters (56,57).

Conclusion

Our study shows that high average WSS after balloon angioplasty might be detrimental in terms of angiographic and functional outcome. WSS, as a combined parameter of anatomy and physiology can be used for the on-line assessment of procedural result in the catheterization laboratory without the need of a provocative agent. Further prospective studies may further assess the prognostic value of this new parameter.
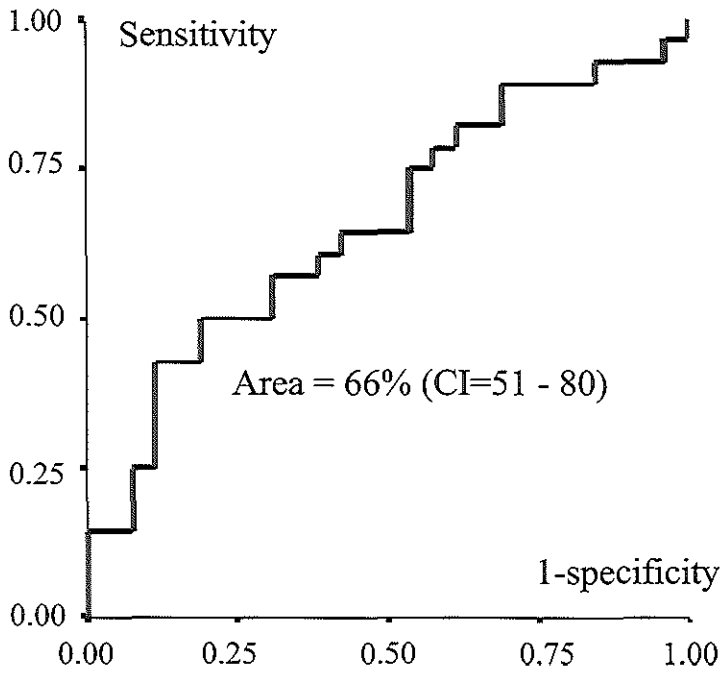
Figure.
Receiver operative characteristics curve showing the best in-lesion post-procedural wall
shear stress cut-off value (2.58 N/m^2) for the presence of restenosis.

Acknowledgements

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Part VI

Summary of the Thesis

Chapter 10a

SUMMARY AND CONCLUSION

The absolute coronary flow velocity reserve, the ratio of hyperemic to basal mean flow velocity, has been used at the cardiac catheterisation for clinical-decision making and for a further understanding of the pathophysiology processes involved in diseases such as variant angina, syndrome X, left ventricular hypertrophy, hypertension, diabetes and acute coronary syndromes.

This index is dependent on the patency of the epicardial conduit and the status of the microvascular circulation. In the absence of epicardial conduit obstruction, the CVR may be abnormal only on the basis of a compromised microcirculation. Therefore, an abnormal CVR cannot differentiate which of the 2 components is responsible for flow impairment. For example, utilizing the DEBATE database, which collected sequential Doppler-derived data (before, after and at 6-month follow-up angioplasty), we were only able to observe a transient impairment in hyperemic velocity in patients with an impaired CFVR. The hyperemic improvement observed in those patients at follow-up was unrelated to geometrical changes experienced at the lesion site. Furthermore, in patients undergoing balloon angioplasty and additional stenting as part of the DEBATE II trial, we further dissected the causes of depressed hyperaemic flow velocity in two: 1) Insufficient luminal enlargement after angioplasty 2) Persistent microvascular dysfunction following adequate stent deployment (Chapter III).

Another caveat encountered when utilizing the post-procedural absolute CFVR is that inappropriate elevations of the resting average peak velocity would falsely diminish the

actual CFVR value. Several authors have previously reported elevations in resting flow velocities as the main cause of an impaired CFVR. These reports only described transient elevations, which could be explained by a delay in the coronary autoregulation. In addition, in-vitro and in-vivo studies have directed the attention to coronary miocroembolization as a cause for transient elevations of the resting blood flow following percutaneous interventions. This response appears to be mediated by adenosine release from microvessels at the microembolized territories. In chapter II, we reported our results from Debate I database showing higher resting blood flow velocities prior to, after and at 6-month follow-up balloon angioplasty in patients with an impaired CFVR when compared to controls. Moreover, we also report an elevation in resting velocity not only in the target but also at the reference vessel (Chapter III). Therefore, it appears from our results that the post-procedural elevation in resting velocity observed on patients with impaired CFVR is a diffuse and a rather permanent phenomenon (Chapter III). The latter appears to be associated with higher systolic blood pressure values, age, and female gender proportion. In addition, higher resting velocities have recently found to be associated with more diffusely atheroschlerotic vessels. It might be possible that an elevated resting velocity is associated with higher risk patient's profile.

Whenever a low absolute CFVR is encountered, an additional measurement of CVR in an adjacent, normal vessel as a reference value (CVR $_{reference}$) can confirm the significance of the coronary lesion and compute the relative CFVR:

$$\text{Relative CVR} = \text{CVR}_{absolute} / \text{CVR}_{reference}$$

Prior to an intervention, this new index has been highly correlated with the hyperaemic transtenotic pressure gradient. However, scant data is available about its prognostic value after an intervention. In chapter III, we report its clinical predictive value, particularly at short term, following balloon angioplasty and stent implantation.

In chapter IV, a detailed analysis of patients with impaired post-procedural CFVR showed that diabetes and increasing age are independent predictors of a lack of normalization of CFVR at 6 month-follow-up.

Post-procedural coronary artery dissections are found in approximately 20 to 40% when assessed by angiography, and up to 80% with IVUS assessment. In chapter V we reported the hemodynamic impact of unstented coronary dissections. We observed that patients with moderate dissections associated with a TIMI 3 flow and no signs or symptoms suggestive of angina had an impaired post-procedural CVFR. However, the latter was mainly due to an inappropriate elevation of the resting average peak velocity. Interestingly, this elevation vanished at follow-up, normalizing the CFVR. Therefore, it appears that moderate dissections do not impose a significant obstruction in coronary blood flow. This concept was further supported by the fact that similar relative CFVR were found in patients with and without moderate dissections (Chapter VI).

In attempt to circumvent the various limitations encountered by our groups and others whenever using the absolute CFVR for clinical-decision making, we decided to search for a more lesion-specific Doppler-derived parameter. We investigated the post-procedural coronary blood flow velocity acceleration at the stenotic site as an index of persistent residual stenosis. The absence of this acceleration predicted a functional improvement following balloon angioplasty (Chapter VII). Moreover, the presence of

stenotic velocity acceleration was strongly associated with a worst angiographic outcome

(Chapter VIII).

The blood flow, by virtue of viscosity, engenders on the luminal surface a frictional force

per unit area known as hemodynamic shear stress. Shear stress inflicted on the healthy

coronary endothelium induces an NO-mediated vasodilatation. Several reports have

shown that the presence of elevated shear stress values inhibit and induces regression of

neointimal formation. Moreover, shear stress has been shown to be a critical determinant

of vessel calibre and the vascular remodelling process. Despite all these data, the impact

of shear stress on the restenosis rate is currently unknown. In order to evaluate the

restenosis rate according to shear stress levels, we analysed the DEBATE database. This

database is rich in angiographic data performed by QCA (minimal luminal area, reference

diameter, diameter stenosis) and videodensitrometry (cross-sectional area) as well as

Doppler-derived data (CFVR, baseline and hyperaemic velocity prior to, after and at 6

month follow-up angioplasty). From these data analysis, we reported that patients with

elevated post-procedural shear stress values at the reference sites are associated with a

worst clinical and angiographic outcome. These apparent paradoxical findings might be

due to the presence of a local turbulent blood flow, which is known to be associated with

an enhanced proliferative and thrombotic response.

Chapter 10b

SAMENVATTING EN CONCLUSIES

Samenvatting en Conclusies

De absolute reserve van de coronaire doorstromingssnelheid, de verhouding van hyperemische tot basale gemiddelde doorstromingssnelheid, wordt bij hartcatheterisatie gebruikt voor klinische besluitvorming en voor beter inzicht van de pathofysiologische processen die betrokken zijn bij ziekten zoals angor Prinzmetal, X syndroom, hypertrofie van het linker ventrikel, hypertensie, diabetes en acute coronair syndromen.

Dit verhoudingscijfer is afhankelijk van de doorgankelijkheid van het epicardiale kanaal en de toestand van de microvasculaire circulatie. Bij afwezigheid van obstructie van het epicardiale kanaal, kan de CVR (*coronary velocity reserve= reserve van de coronaire snelheid*) alleen afwijkend zijn op grond van een in gevaar gebrachte microcirculatie. Bijgevolg, een afwijkende CVR kan niet onderscheiden welke van de 2 componenten verantwoordelijk is voor vermindering van de doorstroming. Bij voorbeeld, bij gebruikmaking van de databank DEBATE, die opeenvolgende Doppler gegevens heeft verzameld (voor, na en bij een vervolg-angioplastiek na 6 maanden), waren wij slechts in staat een kortstondige vermindering in hyperemische snelheid te constateren bij patiënten met een verzwakte CFVR (*coronary flow velocity reserve= reserve van de coronaire doorstromingssnelheid*). De hyperemische verbetering waargenomen bij die patiënten bij de follow-up was niet gerelateerd aan geometrische veranderingen die plaats hadden gehad op de plek van de laesie. Bovendien, bij patiënten die een ballon angioplastiek ondergaan en bij wie een additionele stent wordt aangebracht als onderdeel van de DEBATE II proef, hebben wij verder de twee oorzaken ontleed van de verlaagde hyperemische doorstromingssnelheid: 1) Onvoldoende verwijding van het lumen na angioplastiek 2) Blijvende microvasculaire disfunctie na een adequate ontplooiing van de stent (Hoofdstuk III).

Een andere waarschuwing die men tegen kan komen wanneer men gebruik maakt van de absolute CFVR na de ingreep is dat oneigenlijke verhogingen van de gemiddelde pieksnelheid in rust ten onrechte de actuele CFVR waarde verminderen. Verscheidene auteurs hebben voorheen verhogingen in de doorstromingssnelheden in rust beschreven als de voornaamste oorzaak van

een verminderde CFVR. Deze verslagen beschreven slechts kortstondige verhogingen, die verklaard zouden kunnen worden door een vertraging in de coronaire autoregulatie. Bovendien, in-vitro en in-vivo studies hebben de aandacht gericht op coronaire micro-embolisatie als de oorzaak voor kortstondige verhogingen in rust van de bloedstroom, volgend op percutane interventies. Deze reactie schijnt te worden opgewekt door het vrijkomen van adenosine afkomstig van microvaten in de gebieden waar micro-embolisatie is opgetreden. In Hoofdstuk II beschrijven wij resultaten van de databank DEBATE I, die hogere doorstromingssnelheden van het bloed in rust laten zien voor, na en bij de follow-up ballon angioplastiek na 6 maanden bij patiënten met een verminderde CFVR, vergeleken met de controlewaarden. Bovendien beschrijven wij een verhoging van de snelheid in rust niet alleen in het behandelde gebied maar ook in het referentievat (Hoofdstuk III). Bijgevolg, uit onze bevindingen komt naar voren dat de verhoging na de ingreep in de snelheid in rust, waargenomen bij patiënten met verminderde CFVR, een diffuus en min of meer permanent fenomeen is (Hoofdstuk III). Dit laatste schijnt te moeten worden geassocieerd met hogere systolische waarden van de bloeddruk, leeftijd, en het vrouwelijk geslacht. Bovendien, onlangs is ontdekt dat hogere snelheden in rust in verband gebracht worden met meer diffuse atherosclerotische vaten. Mogelijk dat een verhoogde snelheid in rust verbonden is met het profiel van een patiënt met een hoger risico.

Wanneer een lage absolute CFVR wordt aangetroffen, kan een aanvullende meting van de CVR in een aangrenzend, normaal vat als een referentiewaarde ($CVR_{reference}$) de omvang bevestigen van de coronaire laesie en de relatieve CFVR berekenen:

$$\text{Relatieve CVR} = CVR_{absolute}/ CVR_{reference}$$

Voorafgaand aan een interventie wordt dit nieuwe verhoudingscijfer in hoge mate gecorreleerd aan de hyperemische transstenotische drukgradiënt. Echter, weinig gegevens zijn beschikbaar over de prognostische waarde hiervan na een interventie. In Hoofdstuk III beschrijven we de voorspellende waarde, in het bijzonder op de korte termijn, na ballon angioplastiek en implantatie van een stent.

In Hoofdstuk IV heeft een gedetailleerde analyse van patiënten met verminderde CFVR na de ingreep aangetoond dat diabetes en gevorderde leeftijd onafhankelijke factoren zijn voor de uitblijvende normalisatie van de CFVR bij de follow-up na 6 maanden.

Dissecties van de coronaire arterie na de ingreep zijn gevonden in ongeveer 20 tot 40 % van de gevallen, wanneer de beoordeling plaats vond d.m.v. angiografie, en tot 80 % met de beoordeling d.m.v. IVUS (*intracoronaire vasculaire echografie*). In Hoofdstuk V hebben we de hemodynamische impact beschreven van coronair dissecties zonder het aanbrengen van een stent. We hebben waargenomen dat patiënten met gematigde dissecties, gepaard gaande met een TIMI 3 stroming en geen tekenen of symptomen verdacht voor angina, een verminderde CFVR hadden na de ingreep. Echter, dit laatste was voornamelijk te wijten aan een oneigenlijke verhoging van de gemiddelde pieksnelheid in rust. Interessant was dat deze verhoging verdwenen was bij de follow-up en dat de CFVR genormaliseerd was. Daarom schijnt het dat gematigde dissecties geen significante obstructie vormen in de coronaire bloedstroom. Deze opvatting werd verder gesteund door het feit dat soortgelijke relatieve CFVR's werden gevonden bij patiënten met en zonder gematigde dissecties (Hoofdstuk VI).

In een poging de verscheidene beperkingen te omzeilen, die we ontmoetten bij onze groepen en andere, wanneer we de absolute CFVR gebruikten voor de klinische besluitvorming, hebben we besloten te zoeken naar een parameter meer specifiek gericht op laesie, ontleend aan de Doppler. We onderzochten de acceleratie van de doorstromingssnelheid van het bloed in de coronaire vaten na de ingreep op de plaats van de stenose als een verhoudingscijfer van blijvende rest-stenose. Het uitblijven van deze acceleratie gaf een functionele verbetering aan na de ballon angioplastiek (Hoofdstuk VII). Bovendien, het optreden van acceleratie van de stenotische snelheid werd sterk in verband gebracht met een zeer slecht resultaat van de angiografie (Hoofdstuk VIII).

De bloedstroom, krachtens viscositeit, veroorzaakt aan de oppervlakte van het lumen een wrijvingskracht per oppervlakte eenheid, bekend als de hemodynamische shear stress. Shear stress, uitgeoefend op het gezonde coronaire endotheel, veroorzaakt een vasodilatatie, door middel van NO (*stikstofmonoxyde*). Verscheidene verslagen hebben aangetoond dat de aanwezigheid van verhoogde shear stress waarden een belemmering vormt en leidt tot regressie van neo-intimaal

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herstel. Bovendien, het is aangetoond dat shear stress een kritische beslissende factor is met betrekking tot de doorsnee van het vat en het proces van de vasculaire remodellering. Ondanks al deze gegevens, is de impact van shear stress op de restenose thans onbekend. Om de graad van restenose te evalueren volgens de shear stress niveaus, hebben we de gegevens van de databank DEBATE geanalyseerd. Deze databank bevat zeer vele gegevens over angiografie uitgevoerd door QCA (*kwantitatief coronair angiogram*) (minimaal gebied van het lumen, referentie diameter, diameter stenose) en videodensitrometrie (dwarsdoorsnede van het gebied), evenals gegevens ontleend aan de Doppler (CFVR, grondwaarde en hyperemische snelheid, voor, na en bij een vervolg-angioplastiek na 6 maanden). Op grond van analyse van deze gegevens, hebben we beschreven dat patiënten met verhoogde shear stress waarden na de ingreep op de onderzoeksplaatsen geassocieerd worden met een zeer slecht klinisch en angiografisch resultaat. Deze ogenschijnlijk paradoxale bevindingen zijn mogelijk te wijten aan de aanwezigheid van een lokale turbulente bloedstroom, waarvan bekend is dat die wordt geassocieerd met een verhoogde proliferatieve respons en kans op trombose.

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These sentences are by far more difficult to orchestrate than any of the paper that I have written in this thesis.

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Once I arrived to the Thoraxcenter (TX), I have had an average of 2 months where no official contact with PWS is allowed. That time is purposefully planned for the new fellow to get to know the surroundings and get himself going. In those days, the "senior fellows" were Michael Kutryk, Manel Sabaté, Patrick Kay. I am indebted with all three of them, because they have taught me in what to focus and how to survive in this tough environment. Michael, thanks for your generosity in spending long hours at night discussing cell adhesion, metalloproteinases, stent thrombosis and how to build an ideal stent. I deeply treasure all I have learned from you. Manel, it has been an honor been exposed to such a gentleman like you. I keep very good memories from you laughing at my bad jokes as well as your suggestion about how to design a paper. Patrick, the smallest details in writing are vital for the success in publishing. Thanks my friend for teaching me these tiny and very important details as well as having sharpened my English.

After a while, a tall funny looking guy arrived. I wanted to call him chimney, but I decided to call him from his actual name, Glenn. After a one day, he managed to get know very

well all of the Rotterdam Police Department and us. Average phone calls a day: 27(60%
Dutch, 20% English and 20% French). He was able to work hard and lighten up the tension
of our small-crowed room at the same time. We rapidly became great friends. Thanks my
friend because you show me that pleasure does not impair my scientific production and it
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support.

Marco Aurelio Costa, Brazilian, from Minas Gerais, people from that region are usually
quiet, humble, patient and obedient. Definitely he was not "Minero". I met him one day at
the TX; he entered the fellow's room and introduced himself. I made a quick joke about
soccer and immediately heard a sweet voice coming from a small hand above Marco's
shoulder: "We are tetra champion of the world!!" That was Erica; Marco's wife and biggest
achievement in his life. Beautiful, generous, understanding but together she is as determine
and hard worker as Marco. With them I spent very special moments inside and outside the
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After getting to know the entire fellow clan, I finally met Prof. Serruys. It is difficult for me to try to summarize a man like PWS, but I believe that these are the most salient characteristics of probably the best scientist of interventional cardiologist in the entire world: 1) Availability: always available and receptive for new projects or ideas even from a naïve fellow. 2) No Fear: willingness to take chances and risks, 3) Knowledge and common sense, 4) Metamorphsis: he is able to switch from Mr Jekill to the best listener if required, 5) Bad-bad tennis player. Thanks for teaching me coronary flow, conductance and how to write and think like an interventional cardiologist. I would never forget it.

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After leaving TX, I arrived to Brazil for cardiac training. I could not have finish my thesis without the unconditional support of Drs. Amanda and Eduardo Sousa. Thanks you very much, and I wish this is the beginning of a fruitful friendship.

Those rainy weekends, alone at the TX, the first thing that came my mind when I was feeling lonely was the memory of the mother's smile and the voice of my father telling me

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Curriculum Vitae

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