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Flow velocity and predictors of a suboptimal coronary flow velocity reserve after coronary balloon angioplasty

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On behalf of the DEBATE investigators

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Aims This study was conducted to analyse flow velocity parameters and predictors of a suboptimal coronary flow reserve (<2·5) following balloon angioplasty.

Methods Two hundred and twenty-five patients underwent sequential intracoronary Doppler as part of the DEBATE I study. Of these, 183, with complete angiography and Doppler at the 6-month follow-up, were included. Univariate and multivariate logistic analysis was performed to identify independent predictors of post-procedural suboptimal coronary flow reserve, defined as coronary flow reserve <2·5.

Results Forty-eight per cent (n=88) of the patients achieved a suboptimal coronary flow reserve. These patients had higher baseline velocities ($cm.s^{-1}$) before balloon angioplasty (18 ± 9 vs 14 ± 6, P=0·004), after balloon angioplasty (22 ± 11 vs 14 ± 5, P<0·001) and at follow-up (19 ± 9 vs 16 ± 6, P=0·011) than the optimal coronary flow reserve group. Although the suboptimal group had lower hyperaemic velocities ($cm.s^{-1}$) after balloon angioplasty than the optimal group (42 ± 17 vs 49 ± 16, P=0·008), these velocities became similar at follow-up. Increasing age (odds ratio, OR 1·071, P=0·0002), female gender (OR 2·52, P=0·014) and increasing pre-procedural baseline average peak velocities (OR 1·056, P<0·001) were found to be independent predictors of a suboptimal coronary flow reserve following balloon angioplasty.

Conclusion A suboptimal coronary flow reserve was associated with (1) a chronically elevated baseline average peak velocity (2) a transient deficit in the hyperaemic average peak velocity (3) the elderly, and female gender.
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Introduction

Coronary flow velocity reserve has been used in the catheterization laboratory to assess the changes in coronary blood flow after balloon angioplasty[1]. The DEBATE I clinical trial suggested that the risk of clinical and angiographic restenosis is significantly lower in patients with optimal balloon angioplasty results defined as a coronary flow reserve ≥2·5 and a residual percentage diameter stenosis ≥35%, than in patients not fulfilling these criteria[2]. However, this combined end-point is not met in more than 50% of patients due to a suboptimal coronary flow reserve[3–5]. Elevation of baseline flow, insufficient augmentation of the hyperaemic flow or a combination of both are accepted explanations for a suboptimal coronary flow reserve. Little is known about acute and long-term flow velocity

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changes in patients achieving or not achieving the optimal coronary flow reserve after balloon angioplasty. Understanding the mechanisms and predictors of a post-procedural suboptimal coronary flow reserve appears to be important for clinical decision making, e.g. when considering strategies for provisional stenting.

Therefore, the aims of the study were to analyse the baseline and hyperaemic flow velocity changes immediately after balloon angioplasty and at the 6-month 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 balloon angioplasty and sequential Doppler flow velocity assessment were included. Patients without complete angiographic and Doppler follow-up (n=42) were excluded from our analysis. The overall remaining population (n=183) was divided into two groups according to a post-procedural coronary flow reserve cut-off value of 2·5. A value lower than 2·5 was considered as suboptimal.

Angioplasty procedure and flow velocity assessment

Balloon angioplasty was performed according to conventional methods. A 0·014-inch Doppler tipped guidewire was used as the primary angioplasty guidewire (FloWire, Endosonics, Rancho Cordova, CA, U.S.A.[6]. Measurements of coronary flow velocity and calculation of coronary flow reserve have been previously described in detail. Determination of the end-point of the angioplasty procedure was based on angiographic criteria (diameter stenosis <50% in any angiographic view) only.

Quantitative angiographic measurement

Angiographic measurements were done prior to balloon angioplasty, after balloon angioplasty and at the 6-month follow-up. Quantitative assessment of reference diameter, minimal lumen diameter and diameter stenosis was performed using multiple projections by an independent core laboratory (Cardialysis, BV) utilizing CAAS II analysis software (Pie Medical, Maastricht, The Netherlands).

Statistical analysis

Continuous variables are expressed as mean ± 1 SD. 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 analysed using chi-squared or Fisher's exact test when appropriate. Univariate and multivariate logistic regression analysis was performed to search for independent predictors of suboptimal coronary flow reserve result. All *P* values were two-tailed, with statistical significance indicated by a value of *P*<0·05.

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
Hypercholesterolaemia	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 (35)	68 (72)	
Class III/IV	43 (47)	27 (28)	
Unstable angina	47 (54)	53 (56)	ns

Values are given as mean ± 1 SD or as number of patients (proportion of patients %).
CFR=coronary flow reserve.
CAD=Coronary artery disease.
CCS=exertional angina was categorized according to the classification system of the Canadian Cardiovascular Society.

Results

Baseline patient characteristics

Patient's baseline characteristics are summarized in Table 1. Eighty-eight (48%) patients experienced a suboptimal coronary flow reserve lower than 2·5. This group was older and had a higher proportion of females.

Angiographic data

Angiographic lesion characteristics and serial quantitative data are summarized in Table 2. Similar minimal lumen diameter and diameter stenosis were observed among the suboptimal and optimal coronary flow reserve group prior to balloon angioplasty, after balloon angioplasty and at the 6-month follow-up. The suboptimal coronary flow reserve group showed a trend towards a lower reference diameter.

Changes in coronary flow velocity over time

Serial coronary flow velocity measurements are given in Table 3. After balloon angioplasty, coronary

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 (5) fup	44 ± 14	44 ± 16	ns

Values are given as mean ± 1 SD 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.
CFR=coronary flow reserve.
LAD=left anterior descending coronary artery; LCX=left circumflex coronary artery; RCA=right coronary artery; Pre=preprocedural; Post=post-procedural; Fup: 6-month follow-up.

flow reserve improved in both groups. The suboptimal coronary flow reserve group showed a lower diastolic blood pressure after balloon angioplasty than the optimal coronary flow reserve group. In the suboptimal coronary flow reserve group, baseline average peak velocities values were consistently higher than in the optimal coronary flow reserve group (prior to balloon angioplasty, after balloon angioplasty and at follow-up) whereas the hyperaemic response was diminished after balloon angioplasty.

Association between angiography and coronary flow reserve

Analysis of minimal lumen diameter and coronary flow reserve measurements showed no correlation after balloon angioplasty (r=0·02, *P*=ns), whereas before angioplasty and at follow-up a significant relationship was observed. The Pearson correlation between these two parameters prior to balloon angioplasty was r=0·491 (*P*<0·001) and r=0·513 (*P*<0·001) at the 6-month follow-up (Fig. 1).

Predictors of post-procedural coronary flow reserve

Multivariate logistic regression analysis revealed increasing age (OR 1·071, 95% CI 1·033–1·110, *P*=0·0002), female gender (OR 2·52, 95% CI 1·204–5·291, *P*=0·014) and increasing pre-procedural baseline average peak velocities (OR 1·056, 95% CI 1·013–1·100, *P*<0·001) to be independent predictors of the post-procedural coronary flow reserve results. Reference diameter, post-procedural minimal lumen diameter, hyperaemic average peak velocities before balloon angioplasty, post-procedural diastolic blood pressure and heart rate were included in the model but did not predict a suboptimal result. When compared with patients with an adequate coronary flow reserve, patients with a coronary flow reserve <2·5 were associated with a higher rate of target vessel revascularization (35% vs 22%, *P*=0·036), recurrence of symptoms at 30 days (20% vs 12%, *P*=0·018) and positive stress test results at 30 days (19% vs 8%, *P*=0·038).

Discussion

The major finding of this study is that a post-procedural suboptimal coronary flow reserve is related to a

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 (beats.min^{-1})	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.s^{-1})	17 ± 8	22 ± 9†	20 ± 11	15 ± 7*	15 ± 5*	16 ± 7*‡
h-APV (cm.s^{-1})	25 ± 15	43 ± 16†	43 ± 20	25 ± 16	50 ± 17†*	44 ± 18‡
CFR	1·43 ± 0·56	1·95 ± 0·35†	2·34+0·9‡	1·71 ± 0·73*	3·42 ± 0·76†*	2·84 ± 1·01*‡

Values are given as mean ± 1 SD.
CFR=coronary flow reserve; BA=balloon angioplasty; HR=Heart rate; DBP=diastolic blood pressure; SBP systolic blood pressure; b-APV=baseline average peak velocity; h-APV=hyperaemic average peak velocity; Pre=pre-procedural; Post=post-procedural.
**P*<0·05 vs coronary flow reserve <2·5; †*P*0·05 vs pre-balloon angioplasty; ‡*P*<0·05 vs post-balloon angioplasty.

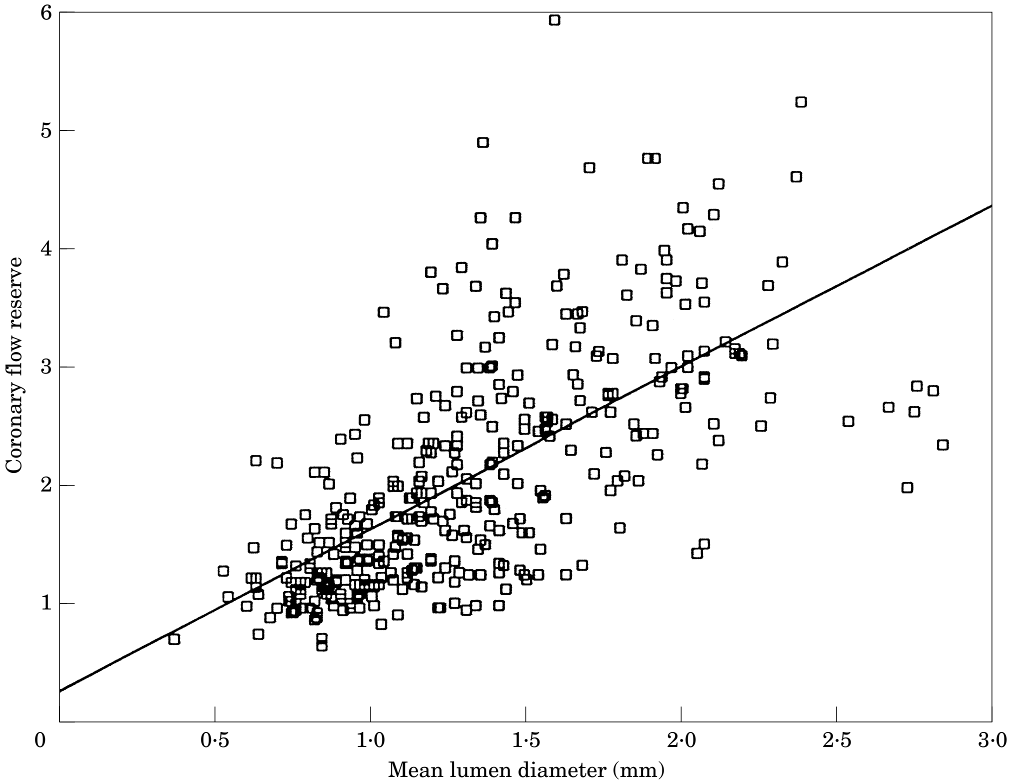

Figure 1 **Coronary flow reserve and mean lumen diameter at 6-months follow-up.**

combination of a transient deficit in hyperaemic average peak velocity response and a chronically elevated baseline average peak velocity.

Several studies have previously described the changes observed in baseline and maximal velocities following balloon angioplasty[4,5,7]. However, only one study stratified the patients according to coronary flow reserve (< 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 baseline average peak velocities as the only cause for impairment of coronary flow reserve[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 coronary flow reserve group was associated with a transient deficit in hyperaemic average peak velocities and a persistent elevation in baseline average peak velocities (before balloon angioplasty, after balloon angioplasty and at the 6 month follow-up) when compared with the optimal group.

Baseline velocities and suboptimal results

In our study, patients with suboptimal coronary flow reserve results were found to be older than the optimal group. Czernin *et al.* described, in healthy elderly volunteers, an elevated flow at rest but a hyperaemic flow similar to that of 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 minimal lumen diameter between the optimal and suboptimal groups, 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 in baseline average peak velocities found in patients with suboptimal coronary flow reserve 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.

Adenosine-induced maximal velocities following balloon angioplasty

Several reports have shown that the presence of a significant haemodynamic obstruction in coronary blood flow, microvascular dysfunction, or the combination of both, is the main reason for a diminished hyperaemic average peak velocities[10–13].

Although similar minimal lumen diameter and diameter stenosis were found in both groups, a lower coronary flow reserve was found in the suboptimal group throughout the study period. The latter discrepancy between anatomy and coronary flow reserve could be related to differences in the ability to vasodilate fully in response to adenosine infusion. In contrast with our results, Kern *et al.* reported a strong relationship between the residual epicardial obstruction assessed by intravascular ultrasound and post-procedural coronary flow reserve[7]. However, the authors reported no relationship when comparing coronary flow reserve and quantitative coronary angiography data after balloon angioplasty, possibly due to the inaccuracy of quantitative coronary angiography in assessing functional gain following a percutaneous intervention.

Recently, we reported a strong association between the target and reference vessel coronary flow reserve[14]. No improvement was found in coronary flow reserve with additional stent implantation in patients with impaired reference coronary flow reserve in spite of significant enlargement of the epicardial lumen. This suggests that many post-procedural coronary flow reserve results are dependent on microvascular function rather than on anatomical gain. Post-ischaemic macro- and microvascular constriction have been associated in the literature to an increase in alpha-adrenergic vasoconstrictor tone[13], platelet-aggregate embolization[15] and microvascular stunning.

Smoothing of the epicardial luminal surface or healing of residual dissections might also be responsible for the elevation of the hyperaemic average peak velocities at the 6-month follow-up. This controversy could have been clarified by the assessment of the relative coronary flow reserve (target vessel coronary flow reserve divided by the adjacent angiographically normal vessel coronary flow reserve[16].

Limitations

The technical limitations of intracoronary Doppler assessment have been described extensively. In our study, quantitative coronary angiography was used to assess the anatomical gain. However, quantitative coronary angiography could over-estimate the actual functional luminal dimensions. Therefore, intra-coronary ultrasound imaging, or the measurement of the residual trans-stenotic pressure gradient in maximal hyperaemia would have helped to assess the degree of luminal enlargement achieved following balloon angioplasty. It would also have excluded the presence of dissections missed by the angiography in the suboptimal group as a likely cause of residual obstruction[17].

Conclusion

In our study, a post-procedural suboptimal coronary flow reserve was related to a chronically elevated baseline average peak velocity and a transient inability to mount an adequate hyperaemic response. Elderly and female patients as well as patients with elevated pre-procedural baseline average peak velocities are associated with a suboptimal coronary flow reserve. The presence of an impaired post-procedural coronary flow velocity reserve warrants further close monitoring of patients as it is associated with a worse short- and long-term clinical outcome, particularly during the first 24 h after the procedure. The latter endorses the concept of provisional stenting.

Further studies, combining intra-coronary assessment of coronary flow velocities and pressure, should be designed for a better understanding of the different coronary flow impairments following balloon angioplasty.

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