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Value of coronary stenotic flow velocity acceleration in prediction of angiographic restenosis following balloon angioplasty

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Introduction Quantitative angiographic assessment after balloon angioplasty is a poor predictor of immediate and long-term outcome. However, the measurement of blood flow velocity during angioplasty has been proved clinically useful.

Aims To analyse the value of the maximal stenotic flow velocity and the presence of stenotic flow velocity acceleration (aSV) for the long-term outcome after balloon angioplasty.

Methods and Results Patients undergoing single lesion angioplasty within the DEBATE trial were included. aSV was defined as acceleration in the stenotic coronary flow velocity >50% baseline velocity assessed at a reference site of the target vessel. After balloon angioplasty diameter stenosis, minimal lumen diameter (MLD) and coronary flow velocity reserve were similar between the aSV (n=54) and non-aSV group (n=125). At follow-up, the aSV group had a higher restenosis rate (52% vs 30%, $P=0{\cdot}006$) The presence of aSV was the strongest independent predictor of restenosis (OR 3·08, 95% CI 1·35 to 7·05, $P=0{\cdot}008$). The best predictive cut-off value of SV was 101 cm . s^{-1} (sensitivity of 46%, specificity of 81%, positive predictive value of 85% and a negative predictive value of 58%).

Conclusion Following angioplasty, SV appears to be exquisitely sensitive to the changes experienced at the treated area without depending on the status of the microcirculation.

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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-month follow-up[6]. However, the coronary flow velocity reserve is dependent on the status of the coronary microcirculation and haemodynamic 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 substantial 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

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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 hyperaemic average peak velocity 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 five 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 min after treatment. The patients were divided into two 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-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 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-month follow-up.

Table 1 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.

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 a statistically 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 the 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 1. Patients with aSV were older and had a higher proportion of unstable angina than the patients without aSV (Table 1).

Table 2 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 6-month follow-up.

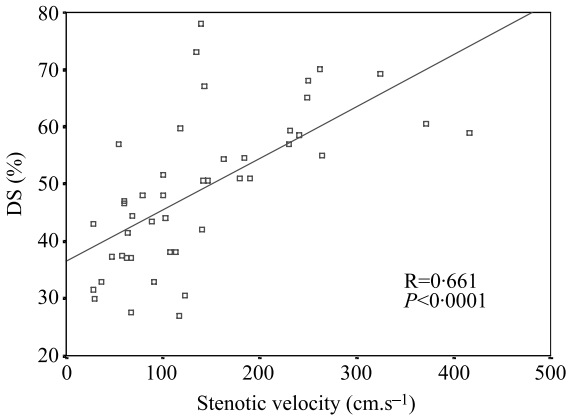

Figure 1 **Relationship between DS and SV at 6-month follow-up.**

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 two groups (Table 2).

Among the aSV group, 27 patients had measurements performed before and after angioplasty and at 6-month follow-up. After angioplasty there was a reduction in SV from 194 ± 74 cm . s^{-1} to 90 ± 43 cm . s^{-1} (P<0·0001), which paralleled 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 (Fig. 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) (Fig. 2).

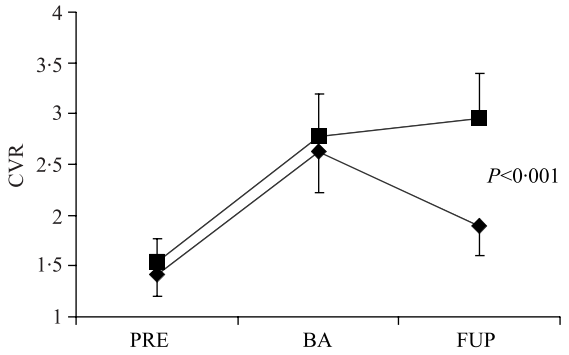

Figure 2 **Coronary flow velocity reserve in restenotic (◆) and non-restenotic (■) patients.**

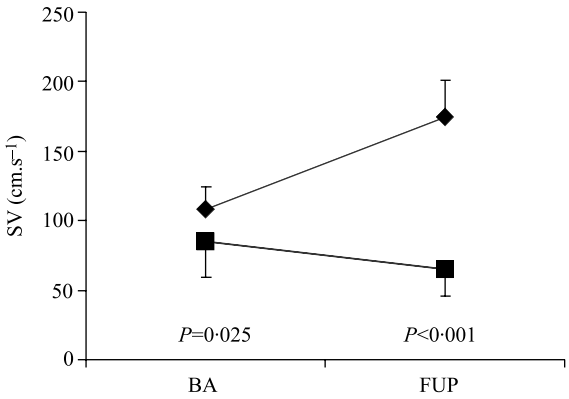

Figure 3 **SV data in restenotic (◆) and non-restenotic (■) patients.**

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 . s^{-1} vs 68 ± 32 cm . s^{-1}, P=0·025) and at follow-up (169 ± 27 cm . s^{-1} vs 64 ± 37 cm . s^{-1}, P<0·0001) than non-restenotic patients (n=9, Fig.3). Moreover, a significant elevation in SV was observed at follow-up in the restenotic patients (from 107 ± 45 cm . s^{-1} to 169 ± 27 cm . s^{-1}, P=0·004) whereas no significant change was found in the non-restenotic patients (from 68 ± 32 cm . s^{-1} to 64 ± 37 cm . s^{-1}, 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).

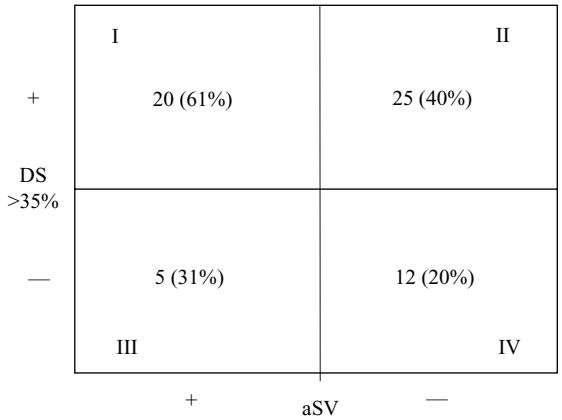

Figure 4 **Number and percent incidence of angiographic restenosis in the four groups identified by the pre-defined presence of stenotic flow velocity acceleration and a residual diameter stenosis cut-off value of 35%. Values are presented in percentages. Group I, n=35, DS≥35% and aSV; group II, n=65,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

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 four subsets. Results of this stratification in relation to restenosis are shown in Fig. 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 favourable 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 two groups (II and III) had an intermediate angiographic outcome (Fig. 4).

When only analysing 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 . s^{-1} (area under the curve 66%, 95% CI 0·516 to 0·809, $P=0·040$). The patients with SV >101 cm . s^{-1} (n=18) presented a significantly higher restenosis rate than patients with SV<101 cm . s^{-1} (72% vs 42%, $P=0·034$). In predicting restenosis, a cut-off value of 101 cm . s^{-1} was associated with a sensitivity of 46%, specificity of 81%, positive predictive value of 85% and a negative predictive value of 58%.

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-month 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 Fig. 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 hyperaemia)[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 of an adequate hyperaemic response.

As previously mentioned, the dependency of the coronary flow velocity reserve on the integrity of the microcirculation is a major limitation when assessing a 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>101 cm . s^{-1} carries a bad angiographic prognosis, justifying adjunctive stenting.

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