Effects of Selective $\alpha_1$- and $\alpha_2$-Adrenergic Blockade on Coronary Flow Reserve After Coronary Stenting

Luisa Gregorini, MD; Jean Marco, MD; Bruno Farah, MD; Monique Bernies, MD; Carlo Palombo, MD; Michaela Kozáková, MD; Irene M. Bossi, MD; Bernard Cassagneau, MD; Jean Fajadet, MD; Carlo Di Mario, MD; Remo Albiero, MD; Massimo Cugno, MD; Adalberto Grossi, MD; Gerd Heusch, MD

Background—Coronary flow reserve (CFR) is not normalized shortly after coronary stenting. We hypothesized that $\alpha$-adrenergic coronary vasoconstriction acts to limit CFR.

Methods and Results—We assessed flow velocity by Doppler wires and cross-sectional area by angiography in 46 patients undergoing coronary culprit lesion stenting (81±4% stenosis). Hyperemia was induced by adenosine (24 $\mu$g IC or 140 $\mu$g/kg per minute IV) before and after stenting. Finally, either the $\alpha_1$-antagonist urapidil (10 mg IC) or the $\alpha_2$-antagonist yohimbine (3 mg IC) was randomly combined with adenosine. In 8 subjects with angiographically normal coronary arteries, CFR was increased from 3.21±0.30 to 3.74±0.43 by yohimbine and to 4.58±0.65 by urapidil, respectively ($P=0.0001$). Patients were divided according to the cutoff of CFR ≥3.0 (n=18) or <2.5 (n=28). Revascularization per se did not change CFR. However, 15 minutes after stenting, CFR decreased to 2.05±0.55 from CFR 3.64±0.58, whereas in patients with CFR 2.39±0.51, it remained unchanged. Yohimbine improved CFR to 3.26±0.42 and to 3.41±0.58 in patients with >3.0 and <2.05±0.55 baseline CFR, respectively. Urapidil improved CFR to 3.52±0.30 and 3.98±1.07, respectively.

Conclusions—Urapidil and yohimbine attenuated the CFR impairment occurring after revascularization by increasing both the epicardial vasodilator effect of adenosine and the blood flow velocity, thus suggesting that the adrenergic system plays an important role in limiting the capacity of the coronary circulation to dilate. (Circulation. 2002;106:2901-2907.)

Key Words: adenosine ■ blood flow ■ microcirculation ■ nervous system, sympathetic ■ receptors, adrenergic, alpha

After stenting, coronary flow reserve is not immediately normalized.1–3 We have recently shown that angioplasty and stenting induce a diffuse $\alpha$-adrenergic coronary vasoconstriction in the epicardial vessels and in the microcirculation that acts to limit coronary blood flow and contractile function.4–6 Such $\alpha$-adrenergic coronary vasoconstriction was antagonized by intracoronary phen tolamine and intravenous urapidil, a selective $\alpha_1$-antagonist. $\alpha$-Adrenergic microvascular coronary constriction is predominantly mediated by $\alpha_2$-adrenoceptors in dogs7,8 and in humans.9,10 Therefore, in the present study, we analyzed the effects of selective $\alpha_1$- and $\alpha_2$-antagonists on the recovery of coronary flow reserve (CFR) in patients after stenting. We divided patients according to the cutoff value of CFR >3.0 or <2.5, because a value >3.0 is considered normal in clinical practice.1–3
Doppler guidewire tip was used to calculate coronary blood flow.

of the procedure. The cross-sectional area (CSA) measured at the

either by the transfemoral (25% of cases) or the transradial approach

Coronary stenting was performed in our patients both to reduce

Adenosine (Ade) was given intracoronary (24-μg IC bolus) or intravenously (140 μg/kg per minute for 5 minutes). Patients and subjects with apparently normal coronary arteries were randomized to receive urapidil (U) or yohimbine (Yo). CFR was calculated by dividing hyperemic by baseline blood flow. In each condition, an angiogram (angio) was performed to obtain the cross-sectional area.

The study protocol is shown in Figure 1. In all patients the baseline CFR was obtained in duplicate with intracoronary bolus injection of 24 μg adenosine.13 CFR measurements were repeated 3 minutes after coronary stenting and 15 minutes later, when coronary vasoconstriction and LV dysfunction had been previously documented.13–16 Fifteen minutes after stenting in 38 patients, the CFR measurements were repeated to compare the effects of intracoronary adenosine (24-μg bolus) with the intravenous infusion (140 μg/min in 5 minutes). As previously reported,13,14 these doses of adenosine induced identical blood flow velocity responses.

Two ECG leads were continuously recorded. Systolic, diastolic, and mean blood pressures were measured through the guiding catheter at the coronary ostium.

Protocol

Coronary blood flow velocity (CBFV) was measured as average peak velocity in centimeters per second (APV) using a Doppler-tipped guidewire of 0.014-inch diameter with a 12-MHz piezoelectric ultrasound transducer at its tip (Cardiometrics JOMED).11 The guidewire was positioned in a distal epicardial vessel (2.34±0.22-mm diameter) at the beginning of the procedure and left in place until the end of the study. APV was continuously recorded, because the Doppler guidewire was only shortly disconnected for insertion of balloons or stents.

Coronary blood flow velocity reserve (CFR) was calculated as the ratio of maximal coronary flow velocity to baseline flow velocity with the search option of the maximal hyperemic APV that is supplied with the Cardiometrics software. A blinded reader measured offline the peak effect on flow velocity induced by contrast medium (meglumine ioxaglate, 6 g/kg per minute for 5 minutes). Patients and subjects with apparently normal coronary arteries were randomized to receive urapidil (10 mg, Ebrantil, 50-mg vials, Byk Gulden)5,6 and the selective α1-antagonist yohimbine (3 mg, Streuli G & Co)5,6 in randomized sequence on top of or before intravenous adenosine. Urapidil and yohimbine were diluted in 3 mL saline. A second bolus of 3 mL saline was given to wash the guiding catheter. In the 28 patients with a basal CFR <2.5, the α1-antagonist urapidil was injected 5 minutes before adenosine instead of on top of adenosine to test the effect of the drug on basal APV. We have previously observed that urapidil (10 mg IC) achieves maximal coronary dilation 5 to 8 minutes after intracoronary injection.16 Accordingly, the adenosine infusion (140 μg/kg per minute over 5 minutes) was started 5 minutes after urapidil injection and after measuring the effects induced by urapidil per se on blood flow velocity and coronary diameters.

Warm saline as vehicle or angiographic contrast media17 per se has a vasodilator action when injected into the coronary circulation. Accordingly, in our patients, we evaluated the changes in blood flow velocity induced both by contrast medium (meglumine ioxaglate, 6

minutes before the procedure. In all patients, the baseline flow velocity measurements were repeated at the end of the revascularization procedure (60 minutes) to investigate the time effect.

Angiographic Analysis Methods

Automatic contour detection was performed in duplicate in the catheterization laboratory and offline by quantitative angiography, as previously described.4–6 An angiogram was performed at each step of the procedure. The cross-sectional area (CSA) measured at the Doppler guidewire tip was used to calculate coronary blood flow.

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Two ECG leads were continuously recorded. Systolic, diastolic, and mean blood pressures were measured through the guiding catheter at the coronary ostium.

Patients received an intracoronary bolus of both the selective α1-antagonist urapidil (10 mg, Ebrantil, 50-mg vials, Byk Gulden)3,6 and the selective α1-antagonist yohimbine (3 mg, Streuli G & Co)5,6 in randomized sequence on top of or before intravenous adenosine. Urapidil and yohimbine were diluted in 3 mL saline. A second bolus of 3 mL saline was given to wash the guiding catheter. In the 28 patients with a basal CFR <2.5, the α1-antagonist urapidil was injected 5 minutes before adenosine instead of on top of adenosine to test the effect of the drug on basal APV. We have previously observed that urapidil (10 mg IC) achieves maximal coronary dilation 5 to 8 minutes after intracoronary injection.16 Accordingly, the adenosine infusion (140 μg/kg per minute over 5 minutes) was started 5 minutes after urapidil injection and after measuring the effects induced by urapidil per se on blood flow velocity and coronary diameters.
respectively. 17 The intracoronary injection of 3 mL saline on /H11006
2.219 cm/s or 5.6
4.2%,
minutes after stenting was 0.03
/H11006
intracoronary and intravenous adenosine in 38 patients 15
The mean difference in blood flow velocity responses to
Coronary Blood Flow Velocity
Coronary Stenting
Patients with CFR
Coronary Blood Flow Velocity

to 8 mL) and by vehicle saline. Saline was injected intracoronary both at baseline and on top of intravenous adenosine infusion.
Statistical Analysis
Results are expressed as mean±SD. One- or two-way ANOVA for repeated measures was performed with the commercially available package SPSS version 11.0 (SPSS Inc). To assess statistical significance between controls and patients, Scheffé F tests were applied, and a value of P<0.05 was considered significant. Covariance analysis was used to account for different baseline cross-sectional areas. Agreement between the two observers’ readings was evaluated estimating the consistent bias between measurements, as recommended by Bland and Altman.18
Results
Coronary Stenting
Patients with CFR >3.0 and <2.5 had an 80±3% and 82±6% diameter stenosis, respectively (NS). No residual in-stent stenosis was present after coronary stenting.
Adverse Adenosine Effects
Adenosine infusion induced atrial fibrillation in 2 patients and transient complete AV block in 5. These patients were not included in the study.
Coronary Blood Flow Velocity
The mean difference in blood flow velocity responses to intracoronary and intravenous adenosine in 38 patients 15 minutes after stenting was 0.03±2.219 cm/s or 5.6±4.2%, respectively.17 The intracoronary injection of 3 mL saline on top of intravenous adenosine infusion elicited an additional 19.9±7.5% increase in APV (P<0.05). This increase was limited to the injection time and lasted 2.9±1.5 seconds. The intracoronary injection of saline in the absence of adenosine elicited an APV increase of 27.4±8.2% (P<0.05). The effect lasted for 5.4±1.5 seconds.
Before revascularization, APV was 11.1±5.0 and 14.7±4.7 cm/s in patients with CFR >3.0 and CFR <2.5, respectively (P<0.05, Table 1). Soon after balloon deflation, a short-lasting hyperemia was observed. Hyperemic APV was 46±8.0 and 32.6±3.6 cm/s, respectively. Three minutes after balloon deflation, APV decreased to 12.3±5.1 (P=NS versus before percutaneous coronary intervention [PCI]) and to 26.8±5.5 cm/s (P=0.001 versus before PCI). These values were unchanged at the end of the study, when the effect of drugs had vanished.
In the group with CFR <2.5, in which urapidil was injected before adenosine, urapidil decreased APV to 20.7±4.7 cm/s (P=0.001 versus 3 minutes stenting), whereas the adenosine infusion given on top of urapidil’s peak effect potentiated the hyperemia, reaching 65.6±19.1 cm/s.
When urapidil was injected before adenosine in control subjects, no major changes in APV were observed. In both patient groups, yohimbine superimposed on top of adenosine additionally potentiated the effect of adenosine alone (P=0.001).
Cross-Sectional Area
Before revascularization, adenosine significantly increased epicardial CSA from 4.9±0.9 to 5.5±0.9 mm² and from 3.0±1.1 to 3.5±1.2 mm² in patients with CFR >3.0 and <2.5, respectively. Also in controls, adenosine significantly increased CSA from 5.7±1.0 to 7.2±1.1 mm² and from 5.5±0.4 to 6.2±0.5 mm² in subjects with CFR 4.77±0.58 (P=0.0001) and with CFR 3.10±0.35 (P<0.05), respectively. When yohimbine was superimposed on top of adenosine, CSA increased from 4.4±1.2 to 5.0±1.2 mm² and from 2.9±1.7 to 3.9±1.8 mm² (P=0.0001) in patients with CFR >3.0 and <2.5, respectively. Also, in controls who underwent the full drug protocol, yohimbine increased CSA from 5.5±0.4 to 6.5±0.3 mm² (P=0.0001). As previously reported,5,6 urapidil increased coronary CSA from 4.4±1.2 to 5.7±1.4 mm² and from 2.9±1.7 to 4.0±1.7 mm² in the 2 groups of patients, respectively. When adenosine was super-

<table>
<thead>
<tr>
<th>TABLE 1. Coronary Flow Reserve</th>
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<td>Time</td>
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Between groups: †P<0.05 vs ≥3.0 CFR, ‡P<0.05 vs CFR <2.5, §P<0.05 vs Controls. Within groups: ∗P<0.05, ††P=0.001, ‡‡P=0.0001.
imposed on top of urapidil, the vasodilator effects were combined and consequently greater. In fact, CSA was increased to 6.2 ± 1.6 and 4.9 ± 2.1 mm² in patients with basal CFR >3.0 and <2.5, respectively. The vasodilator effect of urapidil combined with adenosine was present also in controls, and CSA increased from 5.5 ± 0.4 to 7.5 ± 0.6 mm² (Table 1).

**Coronary Blood Flow**

Blood flow changes induced by adenosine were significantly greater in patients with CFR >3.0 than in patients with CFR <2.5. Three minutes after revascularization, adenosine significantly improved flow, but 15 minutes later this hyperemia was reduced, reaching the lowest value observed during the study (Table 1). The reduction in blood flow paralleled the previously observed vasoconstriction and reduction in LV function.**4–6** Both α₁- and α₂-adrenergic blockers, combined with adenosine, increased CBF.

**Coronary Flow Reserve**

In controls with CFR 4.77 ± 0.58, two consecutive CFR measurements during the protocol duration were reproducible with CFR 4.67 ± 0.85 and 4.81 ± 0.87, respectively. Reproducible were also the measurements obtained in controls with CFR 3.10 ± 0.35, who were subsequently given α-antagonists (Table 1). Coronary revascularization left CFR unchanged in patients, whereas 15 minutes later, when postischemic LV dysfunction is described to occur,**5,6** in patients with CFR >3.0 it decreased from 3.55 ± 0.54 to 2.05 ± 0.55 (P=0.0001). Yohimbine and urapidil combined with adenosine restored almost normal values in both groups of patients (Figures 2 and 3 and Table 1). In control subjects, CFR was increased from 3.21 ± 0.30 to 4.58 ± 0.65 by urapidil and to 3.74 ± 0.43 by yohimbine, respectively.

**Hemodynamics**

The changes in blood pressure and in heart rate are reported in Table 2. Adenosine transiently reduced systolic blood pressure and mean pressure when given alone and when combined with α-adrenergic blockade. Yohimbine and adenosine did not reduce SBP in patients and controls with >3.0 CFR. No heart rate changes were observed, except when α₁-blockers were combined with adenosine.

**Discussion**

In the present study, α₁- and α₂-adrenergic blockade combined with adenosine exerted an additional vasodilation and, counteracting the α-adrenoceptor–mediated vasoconstriction, normalized coronary flow reserve. Several mechanisms are hypothesized to play a role in the CFR decrease observed after coronary stenting. The ischemia induced by balloon inflations and the stretch of the artery elicit a reflex**19** sympathetic increase of α-adrenergic constrictor tone, leading to an increase previously described in animals**19,20** and in humans.**4–6,9,10** Both α₁- and α₂-adrenergic receptors are present in the human coronary circulation, with α₂-adrenoceptors predominant in the microcirculation.**4–6,9,10** Also, in the present study, selective blockade of α₁- and α₂-adrenergic receptors had different effects on conduit and resistance vessels. In fact, urapidil mainly dilated conduit coronary arteries and even decreased blood flow velocity in patients with CFR <2.5 in the absence of adenosine. Yohimbine increased blood flow mainly by increasing the flow velocity over that observed with adenosine alone, thus indicating an additional vasodilatation of the microcirculation.**7,8** Urapidil combined with adenosine acted by increasing both epicardial CSA and hyperemic APV (Table 1). Our data are in agreement with the functional distribution of α₁- and α₂-adrenergic receptors along the coronary tree previously described in animal models.**7,8**

**Coronary Blood Flow Velocity**

Baseline APV was lower in patients with CFR >3.0 than in patients with a CFR<2.5 in all conditions. Soon after coronary stenting, a short-lasting hyperemia was observed in
all patients. This hyperemia was greater in patients with CFR >3.0. As previously reported by other authors, baseline APV was increased after revascularization. Indeed, the higher baseline coronary blood flow velocity was in part responsible for the CFR reduction in our patients with CFR <2.5. Such APV increase might be the consequence of distal embolization of plaque debris after the manipulation of the plaque.

In fact, Hori et al have previously described in dogs that acute embolization of the coronary microcirculation by microspheres and subsequent release of adenosine into adjacent nonembolized vessels is responsible for hyperemia. In the past, distal embolization was considered an uncommon phenomenon both in angioplasty and in coronary stenting procedures. More recently, the use of protective intravascular

**TABLE 2. Blood Pressure and Heart Rate**

<table>
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<tr>
<th>Time</th>
<th>Condition</th>
<th>SBP</th>
<th>DBP</th>
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<th>HR</th>
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<td>73±4</td>
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<tr>
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<td>Adenosine</td>
<td>104±11</td>
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Between groups: †P<0.05 vs Controls.
Within groups: *P<0.05.
filters has confirmed that an unsuspected amount of plaque debris can be retrieved after revascularization. In support of the hypothesis that distal microembolization is responsible for the sustained hyperemia occurring after coronary stenting, urapidil administered 5 minutes before adenosine significantly attenuated the APV increase measured after coronary stenting. The α₁-adrenergic blocker urapidil may share with prazosin the capacity of inhibiting adenosine release and accordingly decrease APV. The APV increase was greater in patients with unstable angina and lower baseline CFR, whereas the patients with >3.0 CFR who had a more stable clinical situation and likely a more stable plaque had only a minor APV increase. Unstable plaques are known to be frequently ulcerated and more inclined to embolize. These findings support the idea of coronary microembolization.

In our study, the combination of urapidil and high doses of exogenous adenosine significantly dilated the coronary circulation. Apparently, when in the presence of exogenous adenosine, urapidil’s effect on endogenous adenosine release becomes negligible; the blockade of α₁-adrenergic coronary vasoconstriction prevails in both epicardial conduit vessels and in the microcirculation.

Both the baseline APV decrease and the CSA increase improved the coronary flow reserve (Figures 2 and 3 and Table 1). In subjects with apparently normal coronary arteries, a minor APV reduction was observed with urapidil injection (from 10.8 ± 2.5 to 8.4 ± 1.6 cm/s), whereas the combination of urapidil and adenosine induced an increase in CFR. This effect is in agreement with the observation of Lorenzoni et al in healthy human volunteers with positron emission tomography. In this study, the α₁-adrenoceptor antagonist doxazosin led to a 30% to 40% increase in dipyriramole-induced hyperemia, thus suggesting that also in a normal setting α₁-mediated coronary vasoconstriction limits dipyriramole-hyperemia. These data in humans are in agreement with a previous study in dogs demonstrating a tonic α₁-mediated vasoconstrictor tone that limited hyperemia by 30%. A greater vasoconstrictor effect is likely to occur in the presence of ischemia or of distal embolization, when the α₁-mediated constrictor tone is increased.

The effect of yohimbine on top of adenosine is expected, because coronary blood flow was previously reported to be increased in animal studies with high doses of yohimbine. Although all of our patients were pretreated with the full doses of anticoagulants and antplatelets, the sustained vasodilation may also have reduced platelet microaggregates in arterioles or leukocyte plugging. The impaired production of NO by the atherosclerotic endothelium, i.e., of a vasodilator mechanism that competes with α₁- and α₂-adrenergic constrictions and contributes to the vasodilator effect of adenosine, likely also plays a role in the observed CFR reduction.

Conclusions and Perspective

In patients undergoing coronary revascularization, an additional increase in coronary blood flow can be obtained by superimposition of α₁- or α₂-adrenergic blockade on top of adenosine, and coronary reserve is normalized. Whether the effects of α-blockade in patients undergoing revascularization are actually greater than in controls depends on the parameter used. Coronary reserve in patients undergoing revascularization remains somewhat, although not significantly, lower than in controls, whereas the increment in coronary reserve by α-blockade is clearly greater (Figure 2). Certainly, the functional importance of α-adrenergic coronary vasoconstriction in patients during revascularization is greater than in controls, as previously evidenced by the α-blockade–associated improvement in contractile function. The more long-term functional consequences of peri-interventional α-blockade remain to be determined.

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References

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