Original Article

Impact of Stenting and Oral Sirolimus on Endothelium-Dependent and Independent Coronary Vasomotion

Rósley Weber Alvarenga Fernandes[1,2], João Miguel Dantas[2], Dinaldo Cavalcanti Oliveira[2], Hiram Grando Bezerra[2], Fabio Sandoli Brito Jr.[2], Valter C. Lima[1,2]

Hospital São Paulo - SPDM - Universidade Federal de São Paulo[1]; Hospital do Rim e Hipertensão[2], São Paulo, SP, Brazil

Abstract

Background: There is no consensus regarding the impact of stenting on long-term endothelial function. There have been reports of increased endothelial dysfunction with sirolimus-eluting stents as compared to bare metal stenting (BMS).

Objective: This study aims to assess the impact of BMS and the effect of oral sirolimus on endothelial function.

Methods: Forty-five patients were randomized into three groups: BMS + high-dose oral sirolimus (initial dose of 15 mg, followed by 6 mg/day for four weeks); BMS + low-dose sirolimus (6 mg followed by 2 mg daily for four weeks); and BMS without sirolimus. Changes in vasoconstriction or vasodilation in a 15 mm segment starting at the distal stent end in response to acetylcholine and nitroglycerin were assessed by quantitative angiography.

Results: The groups had similar angiographic characteristics. The percent variation in diameter in response to acetylcholine was similar in all groups at the two time points (p = 0.469). Four hours after stenting, the target segment presented an endothelial dysfunction that was maintained after eight months in all groups. In all groups, endothelium-independent vasomotion in response to nitroglycerin was similar at four hours and eight months, with increased target segment diameter after nitroglycerin infusion (p = 0.001).

Conclusion: The endothelial dysfunction was similarly present at the 15 mm segment distal to the treated segment, at 4 hours and 8 months after stenting. Sirolimus administered orally during 4 weeks to prevent restenosis did not affect the status of endothelium-dependent and independent vasomotion. (Arq Bras Cardiol 2012;98(4):290-299)

Keywords: Stents, coronary vessels; endothelium; sirolimus.

Introduction

Despite the greater effectiveness and safety of stenting as compared to balloon angioplasty, there is no consensus regarding the effect of stenting on endothelial-dependent vasomotricity. Caramori et al[1] have observed more pronounced long-term endothelial dysfunction with coronary artery stenting than balloon angioplasty or directional atherectomy. In contrast, Maier et al[2] reported preserved endothelial function in segments located proximally and distally to the stent.

The advent of drug-eluting stents (DES) has underscored the importance of this topic especially after reports of worsened endothelial dysfunction as compared to bare metal stenting (BMS) [3-6]. Worsened endothelial dysfunction and greatly impaired endothelial stent strut coverage have been strongly related to late and very late DES thrombosis, among other factors[7-9]. In fact, this serious DES safety issue has led to assessment of improved technology, affecting both the need and type of polymer and the type of drug[10-16].

The primary endpoint of this study was to measure the degree of change on endothelial function following BMS implantation and evaluate the effect of oral sirolimusto prevent in-stent intimal hyperplasia on the BMS endothelial function response.

Methods

From April 2003 to March 2004, patients treated with percutaneous coronary intervention (PCI) with BMS were enrolled in this study. Inclusion criteria were coronary artery disease and clinical indication for elective coronary stenting, target vessel reference diameter ≥ 2.5 mm, and successful interventional procedure according to the AHA/ACC/SCAI 2005 Guideline Update for PCI[17]. An Express® stent (Boston Scientific Corp, Natick, MA) was used in all interventions. The Research Ethics Committee at the Universidade Federal de São Paulo approved the protocol. The study was conducted in accordance with the provisions of the Declaration of Helsinki.

Exclusion criteria were impossibility of discontinuing the use of nitrate or calcium channel blockers in the 48 hours

Mailing Address: Rósley Weber Alvarenga Fernandes •
Rua Dr. Nogueira Martins, 282 / 142 – Saúde – 04143-020 – São Paulo, SP - Brazil
E-mail: rosley@uol.com.br, muniz_tessari@uol.com.br
Manuscript received May 25, 2011; revised manuscript received June 06, 2011; accepted december 01, 2011.

before angioplasty, coronary spasm after stenting, uncontrolled hypertension, second and third-degree atrioventricular block, severe aortic stenosis, pregnancy, chronic obstructive pulmonary disease, acute or chronic renal failure (creatinine > 1.5 mg/dL), functional class III and IV heart failure, acute or chronic infectious disease, left main coronary artery shorter than 10 mm.

Patients were randomized into three groups. Group 1 (BMS + high-dose sirolimus) received an initial sirolimus dose of 15 mg, followed by 6 mg/day during four weeks. Group 2 (BMS + low-dose sirolimus) received an initial sirolimus dose of 6 mg, followed by 2 mg daily during four weeks. Group 3 (BMS without sirolimus therapy) was the control group. Sirolimus was administered orally to patients in groups 1 and 2, with the initial dose given on the day before PCI. In these patients, sirolimus whole blood concentration (WBC) was monitored weekly with the aim of achieving a concentration of 10-20 ng/mL and 5-10 ng/mL, respectively, in each group.

Study protocol and evaluation of vasomotor function

Two evaluations were performed in the first four hours after stent implantation and the second eight months later. A 15-mm segment starting at the distal stent border was arbitrarily defined as the target segment. This segment was analyzed by off-line quantitative coronary angiography (QCA) and intravascular ultrasound (IVUS). PCI and IVUS were performed using standard techniques.

During intracoronary infusion of acetylcholine, heart rate and frequency, blood pressure, changes in ST-T segment, and oxygen saturation (digital oximetry) were continuously monitored. Acetylcholine was infused for 2 minutes with a syringe pump (IP 680, Samtronic do Brasil, São Paulo, Brazil) at 1.25 mL/min and 0.625 mL/min into the left and right coronary arteries, respectively, in the following sequence: control (saline 0.9%); incremental doses of acetylcholine (Ach): 10^{-6} mol/L (0.036 mg/mL), 10^{-5} mol/L (0.36 mg/mL), and 10^{-4} mol/L (3.6 mg/mL); recontrol (0.9% saline); and 300 mg nitroglycerine.

Endothelial dysfunction was arbitrarily defined as less than 5% vasodilation or any degree vasoconstriction.

Quantitative coronary analysis (QCA)

Off-line quantitative coronary angiography was carried out with the Cardiovascular Measurement System 5.0, Medis, Neunen, The Netherlands. The target segment diameter was measured during the control and other stages. The percent variation in target segment mean diameter as compared to the control measurement was the end-point used to determine endothelium-dependent (response to acetylcholine) and independent (response to nitroglycerin) vasomotion. An observer who was blinded to the group to which the patient had been randomized performed the measurements.

Intracoronary ultrasound (IVUS)

IVUS imaging was performed immediately after stent placement and following intracoronary nitroglycerine administration. The measurements were performed according to the recommendations of the American College of Cardiology and the European Society of Cardiology[18]. The images were obtained using a mechanical system (Galaxy II, Boston Scientifc Corp, Natick, MA). A transducer positioned at least 15 mm distally from the stent was automatically pulled back at a constant speed of 0.5 mm/s. Only artifact-free images were analyzed. Atlantis SR™ Pro 40 MHz or Ultra Cross 30 MHz (Boston Scientific Corp, Natick, MA) catheters were used. To correct variability resulting from the use of various catheters, calibration equations were applied[19]. Off-line analysis to determine cross-sectional areas and derived volumes was performed with appropriate software (QIVA, Pie Medical BV, Maastricht, The Netherlands). All data were evaluated by the investigator in chief and reviewed by two additional observers blinded to the groups to which the patient had been randomized.

Statistical analysis

The sample size was calculated based on the in-stent restenosis study primary endpoint which was the IVUS stent obstruction volume at eight-month follow-up. The calculation led to 45 patients (15 patients per group) in order to provide 80% statistical power ($b = 0.2$) to detect a 40% reduction in the primary end-point (from 30 ± 15% in the control group to 18 ± 15% in the two drug groups), with a 5% probability of type 1 error ($a = 0.05$). Therefore, for the endothelial dysfunction assessment, the study individuals were just the handy population target.

Continuous variables were expressed as mean ± standard deviation (SD). To study the behavior of numeric variables for each group in time, taking into consideration the association between the measurements obtained for each single patient, repeated measures analysis of variance (ANOVA) was employed. To investigate the association between continuous variables, dispersion graphs were plotted and Pearson's linear correlation was calculated. Categorical variables were expressed as percent values. The association between the variables of interest was verified using Fisher's exact test. Significance was established as $p < 0.05$.

Results

Baseline characteristics and clinical events during follow-up

From the 45 patients randomized, 39 fulfilled the inclusion criteria for the vasomotricity study protocol. Six were excluded from the study: three for having severe coronary artery spasm after stenting, two for having short left main coronary artery and one patient withdrew informed consent.

Thirty-nine patients underwent endothelial function testing four hours after stenting and 36 patients eight months later. Three patients were not available for the second evaluation: two died suddenly of an unknown cause four months after PCI. The third patient was excluded due to severe in-stent restenosis associated with severe chest pain during the coronary angiography. There were no significant differences between the groups in terms of indication for angioplasty, treated artery and type of lesion according to the ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention classification[17]. Baseline patient's clinical characteristics are in Table 1.

Table 1 - Baseline Patient's Characteristics, Quantitative Angiographic and IVUS data

	Group 1 (10-20 ng/ml)	Group 2 (5-10 ng/ml)	Group 3 (control)
Age (years)	55 ± 8	52 ± 7	54 ± 10
Gender (M/F)	9/6 (60% / 40%)	10/5 (67% / 33%)	9/6 (60% / 40%)
Medical History			
Diabetes mellitus	5 (33%)	5 (33%)	4 (31%)
Current smoker	11 (73%)	10 (67%)	5 (38%)
Hypertension	14 (93%)	14 (93%)	13 (100%)
Hypercholesterolemia	5 (33%)	5 (33%)	6 (46%)
Prior MI	2 (13%)	2 (13%)	5 (38%)
Clinical presentation			
Stable Angina	6 (40%)	4 (27%)	9 (69%)
Unstable Angina	2 (13%)	2 (13%)	3 (31%)
Recent MI	4 (27%)	9 (60%)	3 (31%)
Treated Vessel			
LAD	8 (53%)	7 (47%)	7 (54%)
Left Circumflex	1 (7%)	1 (6%)	1 (8%)
RCA	6 (40%)	7 (47%)	5 (38%)
Lesion Type			
A/B1	9 (60%)	7 (47%)	10 (77%)
B2/C	6 (40%)	8 (53%)	3 (23%)
Baseline Angiography			
Lesion length (mm)	16.81 ± 4.33	15.95 ± 7.17	13.19 ± 4.85
Reference diameter (mm)	2.8 ± 0.55	2.98 ± 0.59	2.95 ± 0.34
MLD (mm)	1.10 ± 0.25	1.14 ± 0.45	1.27 ± 0.38
Diameter stenosis (%)	60.70 ± 10.06	61.05 ± 13.73	56.18 ± 14.98
Post procedure Angiography			
Reference diameter (mm)	3.17 ± 0.43	3.22 ± 0.45	3.17 ± 0.05
Acute gain (mm)	1.76 ± 0.42	1.78 ± 0.39	1.68 ± 0.14
In-Stent MLD (mm)	2.86 ± 0.38	2.92 ± 0.52	2.96 ± 0.52
In-Stent Diameter stenosis (%)	10.2 ± 10	7 ± 7	6.7 ± 6.6
8-Months Angiographic F-Up*			
Reference diameter (mm)	2.91 ± 0.4	3.01 ± 0.53	2.78 ± 2.31
In-Stent MLD(mm)	2.04 ± 0.74	2.15 ± 0.74	1.62 ± 0.50
In-stent Diameter stenosis (%)	31.4 ± 21.9	30.8 ± 18.5	35.6 ± 23.3
I-stent Late loss (mm) ‡	0.83 ± 0.7	0.78 ± 0.64	1.34 ± 0.45
Binary Restenosis	1(7%)	4(27%)	5(42%)
8-Months IVUS Follow-up*			
Stent volume (mm^3)	214.4 ± 69.4	212 ± 87.4	153 ± 91.1
Lumen volume (mm^3)&	138.21 ± 63	142.34 ± 72.7	68.8 ± 45
NIH volume (mm^3)	66 ± 56.3	65.6 ± 41.4	66.4 ± 57.9
Obstruction volume (%)§	35.3 ± 22.6	33.2 ± 16.5	54.6 ± 16.0

Data are presented as number (relative percentages) or mean value ± SD; 8-month follow-up available for 12 patients in group 1 due to 1 death in the fourth month. ‡ p 0,027 G1;G2 vs G3 / & p 0.017 G1; G2 vs G3 / § p 0.015 G1; G2 vs G3. ANOVA-BONFERRONI; MI - Myocardial infarction; NIH - Neointimal hyperplasia; LAD - Left anterior descending artery; RCA - Right coronary artery; M.L.D - Minimum luminal diameter; A/B1 & B2/C - Classification of ACC/AHA.

Baseline and 8-Month Angiographic and IVUS Follow-Up Data

Groups were well matched with respect to baseline quantitative angiographic and IVUS data (Table 1). At follow-up, percent diameter stenosis and minimal lumen diameter were not different among groups, at the same time in-stent late lumen loss was significantly lower in groups 1 and 2 than in the control group 3 (p = 0.027). Additionally, IVUS analysis demonstrated that obstruction volume was lower in groups 1 and 2 than in group 3 (p=0.015). There were no significant differences between groups 1 and 2 with regard to angiographic and IVUS parameters at follow-up.

Response to acetylcholine

In group 1, vasomotor function was evaluated in 14 patients at four hours after stenting. Twelve patients underwent a second evaluation eight months later. Response to high-dose acetylcholine (10^{-4} mol/L) was -2.36 ± 10.86% and -4.63 ± 10.53% vasoconstriction at four hours and eight months, respectively (p = 0.469). In group 2, both evaluations were performed in 12 patients. Response to high-dose acetylcholine (10^{-4} mol/L) was -5.98 ± 12.62% and -4.42 ± 14.64% vasoconstriction at four hours and eight months, respectively (p = 0.469). In group 3, four-hour evaluation was performed in 13 patients and eight months evaluation in 12. Target segment diameter after high-dose acetylcholine infusion (10^{-4} mol/L) was -1.0 ± 7.38% and +0.10 ± 5.97% at four hours and eight months, respectively (p = 0.469).

In the three groups, vasoconstriction response to an acetylcholine dose of 10^{-4} mol/L was significantly higher compared to doses of 10^{-5} mol/L and 10^{-6} mol/L (Table 2). Table 2 and Figure 1 show that the percent variation in diameter (endothelium-dependent vasomotor function) in all groups was similar at the two time points (p = 0.469). At four hours after stenting, the target segment presented an endothelial dysfunction that was maintained after eight months in all three groups.

Response to nitroglycerin

In the three groups, endothelium-independent vasomotor response was similar at four hours and eight months. Target segment diameter increased from 2.18 ± 0.47 mm to 2.53 ± 0.45 mm at four hours (p = 0.001) and from 2.10 ± 0.41 mm to 2.42 ± 0.46 mm (p = 0.001) after eight months (Table 3 and Figure 2).

Mean target segment diameter for the three groups was 2.71 ± 0.52 mm immediately after stenting, while patients were still under the effect of nitroglycerin. Four hours later, after the effect of nitroglycerin had subsided, a 19% reduction in diameter was observed, to 2.18 ± 0.47 mm (p = 0.001). After evaluation of endothelial function, these patients again received the same nitroglycerin dose and an increase in diameter was observed, to 2.54 ± 0.45 mm. There was endothelium-independent vasodilation, however of less intensity than that observed immediately after stenting. After administration of acetylcholine, the target segment's mean diameter, with the same nitroglycerin dose, was smaller than the mean diameter observed immediately after stenting (p = 0.001) (Figure 3).

Endothelial dysfunction, risk factors and use of medication

Endothelial dysfunction was not correlated with any of the variables evaluated among the three groups such as diabetes, arterial hypertension, dyslipidemia and smoking. The statin usage rate was very high for all three groups, 85%, 100%, 76%, respectively.

Intravascular ultrasound evaluation of endothelial dysfunction and plaque volume (PV) in the target segment

PV was 58.23 ± 34.65 mm^3 and 59.67 ± 38.88 mm^3 at four hours and eight months after stenting, respectively (p = 0.173). PV normalized by target segment length was 4.34 ± 2.60 mm^3/mm and 4.53 ± 2.94 mm^3/mm four hours and eight months after stenting, respectively (p = 0.096). Taking into consideration the overall group of 39 patients, PV distally to the stent, at the target segment, was not correlated to endothelium-dependent vasomotor dysfunction as evaluated with acetylcholine (10^{-4} mol/L). No correlation was observed between PV normalized by segment length and vasomotor response to acetylcholine (10^{-4} mol/L), with a Pearson correlation coefficient of 0.17 [95% CI (-0.17 - 0.48)] four hours after stenting and 0.23 [95%CI (-0.11 - 0.52)] at eight months, respectively (Figure 4).

Discussion

Bare Metal Stent and vasomotor function

Caramori et al[1] were pioneers in the evaluation of endothelial function in patients submitted to PCI with three techniques (balloon angioplasty, directional atherectomy and stenting). To evaluate endothelial function six months after PCI, those authors used intracoronary acetylcholine infusion. They observed more severe endothelial dysfunction with stenting as compared to other techniques.

Maier et al[2] reported vasodilation in the proximal and distal portions of the stented segment (+8% and +11%, respectively) in response to exercise 10 months after stenting, showing normal coronary vasomotion. Monnink et al[20] observed that 30 patients with ischemia on the stress test had vasoconstriction in response to acetylcholine in the distal segment more frequently six months after stenting.

The conflicting findings reported by Maier et al[2] and Caramori et al[1] have been attributed to the different methods used to evaluate endothelial function (physical exercise and intracoronary infusion of acetylcholine). However, Gordon et al[21] have concluded that the two methods are equivalent. Maier et al[2] have also suggested that the variation could be explained by differences in the severity of coronary atherosclerosis between the small samples analyzed (12 patients in the study by Caramori et al[1] and 14 in the study by Maier et al[2]). To investigate this aspect, in this study we measured PV distally to the stent using IVUS. Contrary to the hypothesis raised by Maier et al[2], we did not observe a relationship between PV and response to intracoronary infusion of acetylcholine. The three studies share the limitation of not having evaluated vasomotor endothelial function before stenting and not having evaluated the distal

Table 2 - Percent diameter variation in response to intracoronary acetylcholine infusion

Group	4 hours			8 months		
	A6	A5	A4	A6	A5	A4
1						
Mean	-0.12	-0.06	-2.36	-0.14	-2.66	-4.63
SD	4.89	7.29	10.86	7.27	4.90	10.53
Minimum	-6.66	-16.55	-21.91	-14.23	-8.43	-29.7
Maximum	9.08	8.79	13.76	11.64	8.16	9.49
2						
Mean	0.11	-1.23	-5.98	-2.53	-1.45	-4.42
SD	4.34	3.91	12.62	6.79	7.81	14.64
Minimum	-7.91	-8.40	-37.20	-21.87	-21.0	-33.7
Maximum	5.39	4.06	7.25	5.21	5.96	11.96
3						
Mean	0.77	0.81	-1.00	-0.25	0.92	0.10
SD	4.66	6.38	7.38	4.31	3.80	5.97
Minimum	-7.64	-10.04	-15.71	-9.99	-4.35	-11.9
Maximum	7.63	9.94	10.64	4.54	7.57	10.12
Total						
Mean	0.25	-0.13	-3.02*	-0.97	-1.06	-2.99†‡
SD	4.55	6.01	10.39	6.18	5.79	10.88
Minimum	-7.91	-16.55	-37.20	-21.87	-21.0	-33.7
Maximum	9.08	9.94	13.76	11.64	8.16	11.96

*A4 - 10-4 mol/L acetylcholine; A5 - 10-5 mol/L acetylcholine; A6 - 10-6 mol/L acetylcholine; * p = 0.022 (A4 vs. A5 and A6 – at 4 hours); SD - standard deviation, †p = 0.022 (A4 vs. A5 and A6 measurement at 8 months); ‡p = 0.469 (A4 at 4 hours vs. A4 at 8 months).*

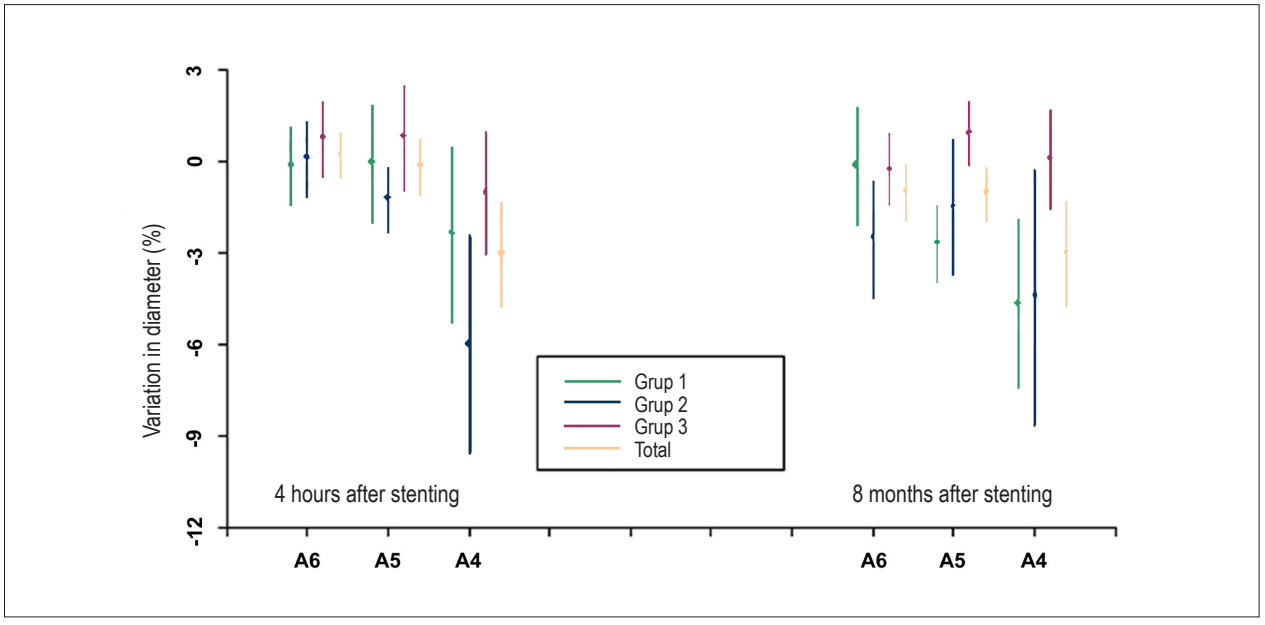

Figure 1 - *Percent variation in diameter (endothelium-dependent vasomotor function).*

Table 3 - Diameter of target segment (mm): control (C), recontrol (RC) and after nitroglycerin intracoronary infusion (NTG)

Group	4 hours			8 months		
	C	RC	NTG	C	RC	NTG
1						
Mean	2.17	2.19	2.50	2.01	1.99	2.24
SD	0.39	0.39	0.44	0.36	0.33	0.35
Minimum	1.52	1.50	1.70	1.60	1.60	1.85
Maximum	2.86	2.89	3.12	2.53	2.50	2.93
2						
Mean	2.17	2.20	2.58	2.22	2.22	2.60
SD	0.48	0.48	0.44	0.48	0.51	0.49
Minimum	1.23	1.35	1.87	1.56	1.53	1.95
Maximum	3.12	3.28	3.45	3.00	2.98	3.29
3						
Mean	2.21	2.21	2.53	2.06	2.07	2.40
SD	0.57	0.54	0.51	0.39	0.37	0.48
Minimum	1.46	1.46	1.81	1.49	1.53	1.60
Maximum	3.26	3.20	3.61	2.75	2.72	3.08
Total						
Mean	2.18*	2.20	2.53†	2.10‡‖	2.09	2.42§
SD	0.47	0.46	0.45	0.41	0.41	0.46
Minimum	1.23	1.35	1.70	1.49	1.53	1.60
Maximum	3.26	3.28	3.61	3.00	2.98	3.29

*C - control; RC – recontrol; NTG - nitroglycerin; SD - standard deviation, *p = 0.918 (control vs. recontrol at 4 hours); †p = 0.001 (NTG at 4 hours vs. control at 4 hours); ‡p = 0.918 (control vs. recontrol at 8 months); §p = 0.001 (NTG 8 months vs. control 8 months); ‖p = 0.015 (Control at 8 months vs. control at 4 hours).*

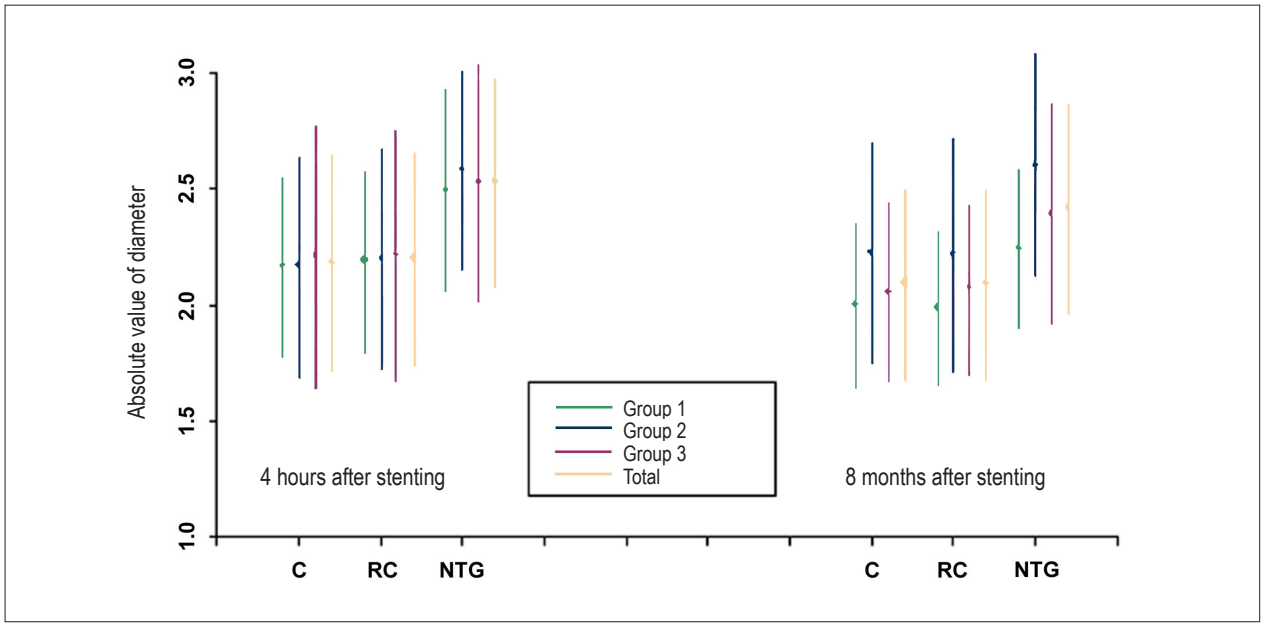

Figure 2 - *Groups in response to nitroglycerin.*

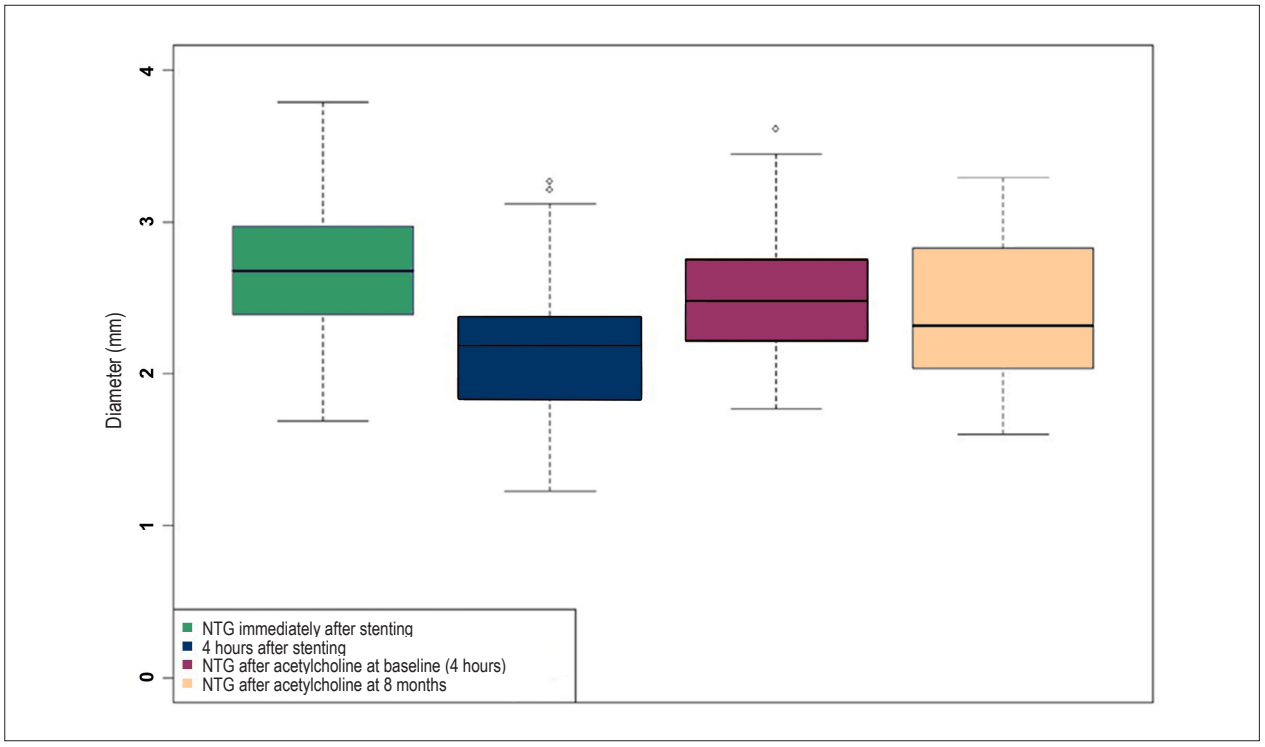

Figure 3 - *39 patients in response to nitroglycerin.*

segment with IVUS.Four hours after stenting, we observed endothelial dysfunction characterized by -3% vasoconstriction in response to a higher concentration of acetylcholine (A4) in the 15mm section distally from the stent. IVUS findings in this target segment reveal the presence of atherosclerotic plaque in all the sections evaluated. In fact, Mintz et al[22] had already reported atherosclerotic plaque shown by IVUS in 93.2% of angiographically normal reference segments. The finding of atherosclerotic plaque associated with underlying endothelium with normal vasomotor function has also been reported by Nishimura et al[23].

As Caramori et al[1], we employed the same methodology to evaluate endothelium-dependent vasomotor function. Nevertheless, different results were observed: those authors state that the PCI is implicated in long-term endothelial dysfunction, with stenting being associated with greater severity, while we do not believe that the endothelial dysfunction observed at eight months was caused by the stents, especially because it was already present four hours after stenting.

The maintenance of endothelial dysfunction that we observed with BMS may be of clinical relevance when considering drug eluting stents[24]. Several reports have shown that DES may be associated with severe endothelial dysfunction[7-9]. This fact has led to improved technology associated to DES with biodegradable and biocompatible polymers[14,15] and drugs with fewer side-effects on the endothelium[13]. There are recent new stents without polymers and drugs eluted directly into the face of the abluminal stent[16].

Oral Sirolimus and vasomotor function

Among the oral drugs used to control vascular proliferative response after coronary angioplasty, the sirolimus showed the most promising results[25-27]. Arruda et al[28] observed that patients with kidney transplant in a regular immunosuppression regimen who were submitted to angioplasty had only moderate in-stent intimal proliferation. Soon after that, the same group reported that the use of oral sirolimus was associated with a small amount of in-stent intimal proliferation[29]. On the other hand, the effect of oral sirolimus on coronary vasomotion had not been described. We employed oral sirolimus to control in-stent intimal proliferation, a measure that did not affect the status of endothelium-dependent and independent vasomotor function.

Limitations

Ethical considerations precluded us from testing coronary endothelial function in patients with severe stenosis before treating them with stenting. Epicardial coronary vessels with tight stenosis may occlude acutely with acetylcholine infusion. Therefore, we cannot be sure that the status of endothelial function four hours after the procedure had not been acutely modified by stenting. This may be the greatest limitation of this study.

Also, these patients use to take a number of drugs that have beneficial effects on endothelial function, especially the statins. They are so effective on lowering cardiovascular events rate that it would be unethical to discontinue them, even temporarily. They may have attenuated endothelial dysfunction[30,31].

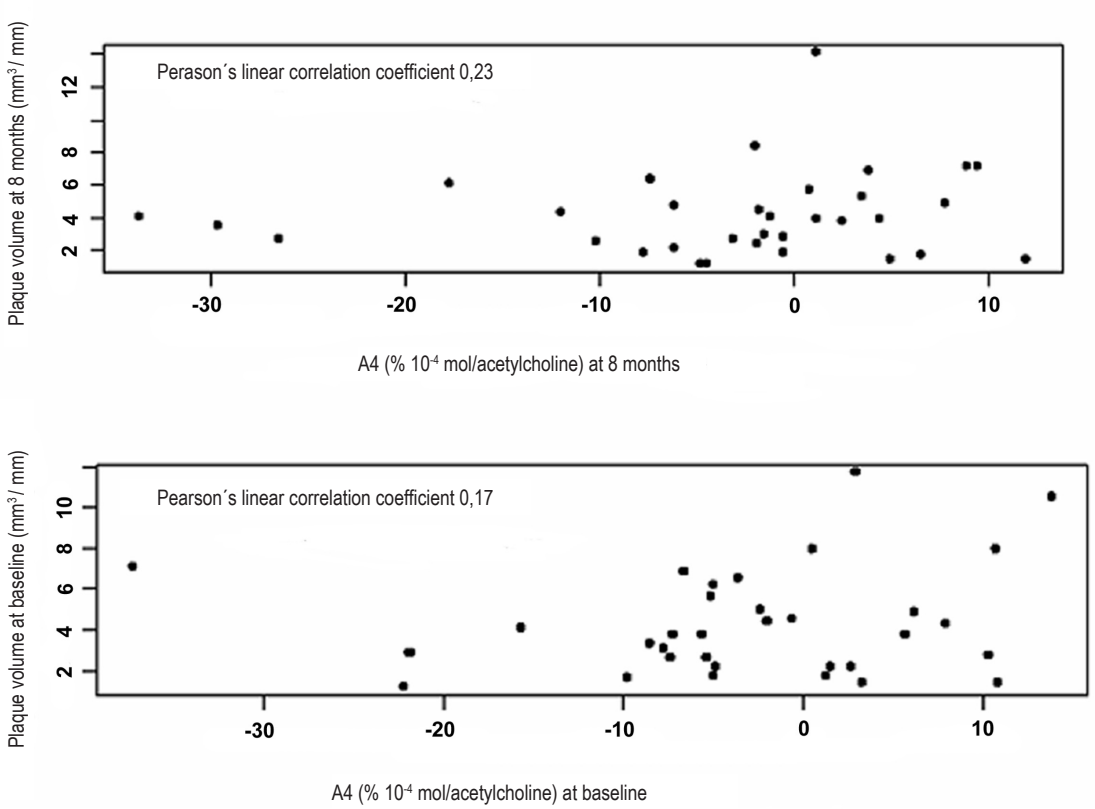

Figure 4 - *Correlation of PV with the response to acetylcholine.*

As to the relatively small sample size, it could be a concern because it was calculated based on the expected in-stent intimal response measured by IVUS. But this is unlikely, because most of the human coronary endothelial interventional studies typically include no more than a few dozen individuals and successfully detect differences between study groups[32,33].

Conclusions

Endothelial function status was not affected by BMS stenting. Furthermore, even significantly lowering in-stent intimal hyperplasia, orally administered sirolimus did not affect coronary endothelial dependent and independent response.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

This study was partially funded by CAPES.

Study Association

This article is part of the thesis of doctoral submitted by Rósley Weber Alvarenga Fernandes, from Universidade Federal de São Paulo.

References

1. Caramori PR, Lima VC, Seidelin PH, Newton GE, Parker JD, Adelman AG. Long-term endothelial dysfunction after coronary artery stenting. J Am Coll Cardiol. 1999;34(6):1675-9.
2. Maier W, Windecker S, Kung A, Lutolf R, Eberli FR, Meier B, et al. Exercise-induced coronary artery vasodilation is not impaired by stent placement. Circulation. 2002;105(20):2373-7.
3. Togni M, Windecker S, Cocchia R, Wenaweser P, Cook S, Billinger M, et al. Sirolimus-eluting stents associated with paradoxic coronary vasoconstriction. J Am Coll Cardiol. 2005;46(2):231-6.
4. Hofma SH, van der Giessen WJ, van Dalen BM, Lemos PA, McFadden EP, Sianos G, et al. Indication of long-term endothelial dysfunction after sirolimus-eluting stent implantation. Eur Heart J. 2006;27(2):166-70.

5. Fuke S, Maekawa K, Kawamoto K, Saito H, Sato T, Hioka T, et al. Impaired endothelial vasomotor function after sirolimus-eluting stent implantation. Circ J. 2007;71(2):220-5.

6. Obata JE, Kitta Y, Takano H, Kodama Y, Nakamura T, Mende A, et al. Sirolimus-eluting stent implantation aggravates endothelial vasomotor dysfunction in the infarct-related coronary artery in patients with acute myocardial infarction. J Am Coll Cardiol. 2007;50(14):1305-9.

7. Virmani R, Guagliumi G, Farb A, Musumeci G, Grieco N, Motta T, et al. Localized hypersensitivity and late coronary thrombosis secondary to a sirolimus-eluting stent: should we be cautious? Circulation. 2004;109(6):701-5.

8. Joner MJ, Finn AV, Farb A, Mont EK, Kolodgie FD, Ladich E, et al. Pathology of drug-eluting stents in humans. J Am Coll Cardiol. 2006;48(1):193-202.

9. Finn AV, Nakazawa G, Joner M, Kolodgie FD, Mont EK, Gold HK, et al. Vascular responses to drug-eluting stents importance of delayed healing. Arterioscler Thromb Vasc Biol. 2007;27(7):1500-10.

10. Hamilos M, Sarma J, Ostojic M, Cuisset T, Sarno G, Melikian N, et al. Interference of drug-eluting stents with endothelium-dependent coronary vasomotion: evidence for device-soecific responses. Circ Cardiovasc Intervent. 2008;1(3):193-200.

11. Pendyala LK, Yin X, Li J, Chen JP, Chronos N, Hou D. The first-generation drug-eluting stents and coronary endothelial dysfunction. JACC Cardiovasc Interv. 2009;2(12):1169-77.

12. Joner M, Nakazawa G, Finn AV, Quee SC, Comeman L, Acampado E, et al. Endothelial cell recovery between comparator polymer-based drug-eluting stents. J Am Coll Cardiol. 2008;52(5):333-42.

13. Barber U, Mehran R, Sharma SK, Brar S, Yu J, Suh JW, et al. Impact of the everolimus-eluting stent on stent thrombosis: a meta-analysis of 13 randomized trials. J Am Coll Cardiol. 2011;58(15):1569-77.

14. Ahmed TAN, Bergheanu SC, Stijnen T, Plevier JWM, Quax PHA, Jukema W. Clinical performance of drug-eluting stents with biodegradable polymeric coating: a meta-analysis and systematic review. Eurointervention. 2011;7(4):505-16.

15. Granillo-Rodrigues A, Rubilar B, Granillo-Rodriguez G, Rodriguez AE. Advantages and disadvantages of biodegradable platforms in drug-eluting stents. World J Cardiol. 2011;3(3):84-92.

16. Tada N, Virmani R, Grant G, Barlett L, Black A, Clavijo C, et al. Polymer-free biolimus A9-coated stent demonstrates more sustained intimal inhibition, improved healing, and reduced inflammation compared with a polymer-coated sirolimus-eluting cypher stent in a porcine model. Circ Cardiovasc Interv, 2010;3(2):174-83.

17. Smith SC Jr, Feldman TE, Hirshfeld JW Jr, Jacobs AK, Kern MJ, King SB 3rd, et al. ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update the 2001 Guidelines for Percutaneous Coronary Intervention). J Am Coll Cardiol. 2006;47(1):e1-121.

18. Mintz GS, Nissen SE, Anderson WD, Bailey SR, Erbel R, Fitzgerald PJ, et al. American College of Cardiology Clinical Expert Consensus Document on Standards for Acquisition, Measurement and Reporting of Intravascular Ultrasound Studies (IVUS). A report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. J Am Coll Cardiol. 2001;37(5):1478-92.

19. Schoenhagen P, Sapp SK, Tuzcu EM, Magyar WA, Popovich J, Boumitri M, et al. Variability of area measurements obtained with different intravascular ultrasound catheter systems: Impact on clinical trials and a method for accurate calibration. J Am Soc Echocardiogr. 2003;16(3):277-84.

20. Monnink SH, Tio RA, Veeger NJ, Amoroso G, van Boven AJ, van Gilst WH. Exercise-induced ischemia after successful percutaneous coronary intervention is related to distal coronary endothelial dysfunction. J Investig Med. 2003;51(4):221-6.

21. Gordon JB, Ganz P, Nabel EG, Fish RD, Zebede J, Mudge GH, et al. Atherosclerosis influences the vasomotor response of epicardial coronary arteries to exercise. J Clin Invest. 1989;83(6):1946-52.

22. Mintz GS, Painter JA, Pichard AD, Kent KM, Satler LF, Popma JJ, et al. Atherosclerosis in angiographically "normal" coronary artery reference segments: an intravascular ultrasound study with clinical correlations. J Am Coll Cardiol. 1995;25(7):1479-85.

23. Nishimura RA, Lerman A, Chesebro JH, Ilstrup DM, Hodge DO, Higano ST, et al. Epicardial vasomotor responses to acetylcholine are not predicted by coronary atherosclerosis as assessed by intracoronary ultrasound. J Am Coll Cardiol. 1995;26(1):41-9.

24. Hamasaki S, Tei C. Effect of coronary endothelial function on outcomes in patients undergoing percutaneous cornary intervention. J Cardiol. 2011;57(3):213-38.

25. Hausleiter J, Kastrati A, Mehilli J, Vogeser M, Zohlnhofer D, Schuhlen H, et al. Randomized, double-blind, placebo-controlled trial of oral sirolimus for restenosis prevention in patients with in-stent restenosis: the Oral Sirolimus to Inhibit Recurrent In-stent Stenosis (OSIRIS) trial. Circulation. 2004;110(7):790-5.

26. Rodriguez AE, Rodriguez Alemparte M, Vigo CF, Fernandez Pereira C, Llaurado C, et al. Role of oral rapamycin to prevent restenosis in patients with de novo lesions undergoing coronary stenting: results of the Argentina single centre study (ORAR trial). Heart. 2005;91(11):1433-7.

27. Jung JH, Min PK, Kim JY, Park S, Choi EY, Ko YG, et al. Systemic immunosuppressive therapy inhibits in-stent restenosis in patients with renal allograft. Catheter Cardiovasc Interv. 2006;68(4):567-73.

28. Arruda JA, Costa MA, Brito FS Jr, Tedesco H, Barbosa AH, Ribeiro EP, et al. Effect of systemic immunosuppression on coronary in-stent intimal hyperplasia in renal transplant patients. Am J Cardiol. 2003;91(11):1363-5.

29. Brito FS Jr, Rosa WC, Arruda JA, Tedesco H, Pestana JO, Lima VC. Efficacy and safety of oral sirolimus to inhibit in-stent intimal hyperplasia. Catheter Cardiovasc Interv. 2005;64(4):413-8.

30. Pasceri V, Patti G, Nusca A, Pristipino C, Richichi G, Di Sciascio G, ARMYDA Investigators. Randomized trial of atorvastatin for reduction of myocardial damage during coronary intervention: results from the ARMYDA (Atorvastatin for Reduction of MYocardial Damage during Angioplasty) study. Circulation. 2004;110(6):674-8.

31. Mood GR, Bavry AA, Roukoz H, Bhatt DL. Meta-analysis of the role of statin therapy in reducing myocardial infarction following elective percutaneous coronary intervention. Am J Cardiol. 2007;100(6):919-23.

32. Anderson TJ, Meredith IT, Yeung AC, Frei B, Selwyn AP, Ganz P. The effect of cholesterol-lowering and antioxidant therapy on endothelium-dependent coronary vasomotion. N Engl J Med. 1995;332(8):488-93.

33. Mancini GB, Henry GC, Macaya C, O'Neill BJ, Pucillo AL, Carere RG, et al. Angiotensin-converting enzyme inhibition with quinapril improves endothelial vasomotor dysfunction in patients with coronary artery disease: the TREND (Trial on Reversing ENdothelial Dysfunction) study. Circulation. 1996;94(3):258-65.

April 2012

In the original article "Impact of Stenting and Oral Sirolimus on Endothelium-Dependent and Independent Coronary Vasomotion", consider as correct the keywords "Stents, coronary vessels, endothelium sirolimus".

In the original article "The Influence of ACE Genotype on Cardiorespiratory Fitness of Moderately Active Young Men", consider as correct the keywords "Angiotensin-converting enzyme; I/D polymorphism; VO_2max, middle-distance running".