Original articles

Effects of carbon-coated coronary stents on the markers of inflammation, thrombin generation and platelet and endothelial activation

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Key words:
Coagulation; Coronary stent; Platelets; Thrombosis.

Background. **The effects of stent carbon coating on the activation of inflammatory and endothelial cells and of coagulation were assessed in patients undergoing coronary artery stent implantation.**

Methods. **Forty-four consecutive patients with stable angina and an isolated significant stenosis in a native coronary vessel undergoing stent implantation were randomized to a carbon-coated stent (Carbostent, n = 23) or an uncoated stent with a similar design (Multilink, n = 21). The markers of inflammation, of hemostasis and of platelet and endothelial activation were determined before and 6, 24, 48 and 72 hours after the procedure.**

Results. **Procedural success was achieved in all cases and no patient presented with major in-hospital adverse events. In both the Carbostent and Multilink groups, the median (interquartile range) plasma levels of C-reactive protein significantly increased after the procedure ($p < 0.001$ and $p = 0.002$ vs baseline levels, respectively), reaching a peak at 48 hours, without any difference between groups ($p = 0.76$). Similarly, in both groups the plasma levels of fibrinogen, thrombin-antithrombin III complexes, prothrombin fragments F1+2, plasminogen activator inhibitor-1, soluble E-selectin, soluble P-selectin and von Willebrand factor significantly increased after the procedure (all $p < 0.05$ vs baseline values), without any difference between groups (all p = NS).**

Conclusions. **This study confirms that the markers of inflammation, of endothelial and platelet activation and of thrombin generation significantly increase after successful coronary artery stent implantation. More importantly, it demonstrates that carbon coating does not modify the biologic response of the vessel wall to stent implantation.**

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Introduction

Coronary artery stent implantation is followed by the activation of inflammatory and endothelial cells and of coagulation[1-5] which, at least partially, account for the acute complications and late restenosis. Experimental *in vitro* and *in vivo* studies suggest that carbon-coated stents might limit these detrimental effects[6-10]. It is still unknown, however, whether these beneficial effects of carbon-coated stents occur also in humans. Thus, we set up a prospective trial of the effects of carbon coating on the markers of inflammation, of thrombin generation and of endothelial activation in which consecutive patients with stable angina and single-vessel coronary artery disease were randomized to Carbostent (Sorin Biomedica, Saluggia-VC, Italy) or ACS Multilink stent (Advanced Cardiovascular Systems, Guidant, Santa Clara, CA, USA) implantation.

Methods

Patient population. The study population consisted of 44 consecutive patients with stable angina and an isolated significant stenosis in a native coronary vessel undergoing stent implantation. The exclusion criteria were acute myocardial infarction, a previous stented lesion, a reference vessel diameter < 2.5 mm and intercurrent inflammatory or neoplastic conditions likely to be associated with an acute-phase response. Patients were randomized to Carbostent

(21 men and 2 women aged 48 to 75 years, mean 61 years) or Multilink (17 men and 4 women aged 37 to 77 years, mean 62 years) stent implantation. Blood samples for the determination of the plasma levels of C-reactive protein (CRP), fibrinogen, thrombin-antithrombin III complexes (TAT), prothrombin fragments F1+2, plasminogen activator inhibitor-1 (PAI-1), soluble E-selectin, soluble P-selectin and von Willebrand factor were drawn from an antecubital vein before the procedure (1 hour after an intravenous cannula was inserted and kept patent by saline infusion), at 6, 24, 48 (at this time only CRP and fibrinogen were assessed) and 72 hours after the procedure. The blood samples were then centrifuged at 2000 rpm and 4°C. Plasma samples were aliquoted in polypropylene tubes and kept frozen at -80°C until assayed. All patients gave written informed consent for participation in the study which was approved by the Institutional Ethics Committee.

Stent implantation procedure. Aspirin (325 mg) was administered 1 day before the procedure and continued indefinitely. Ticlopidine (250 mg) was given orally within 1 hour of the procedure and then twice a day for 4 weeks after the procedure. Intravenous heparin was used during the procedure to maintain an activated clotting time of 250 to 300 s and, having completed sheath removal, was discontinued. In all patients, ioversol (Optiray 320, Mallinckrodt Medical, St. Louis, MO, USA) was used as a contrast agent. No patient received abciximab or thrombolytic agents before or during the procedure.

Carbostent and Multilink are both balloon-expandable, stainless steel, tubular stents with a multicellular design and similar stent thickness. The former has a unique turbostatic carbon coating with physical and biologic properties equivalent to those of pyrolytic carbon[11] and is available in 9-, 15-, and 25-mm lengths. The Multilink stent has been described in detail previously[12,13]. Stent deployment was performed according to standard technique using the femoral approach. Predilation with a conventional balloon ≥ 2.5 mm in diameter was performed at the operator's discretion. The appropriate stent size was selected to achieve a stent to artery ratio of 1.1:1 and the stent was deployed together with the stent delivery balloon at 8 atm. After deployment, additional inflations at high pressure (> 10 atm) with a non compliant balloon were used to achieve a residual stenosis < 10%.

Clinical and angiographic assessment. Procedural success was defined as a residual coronary stenosis < 10% in the worst of two orthogonal views, as assessed by quantitative analysis (Medis Medical Imaging Systems)[14], by normal run-off of the contrast medium (TIMI flow grade 3) in the stented vessel with no evidence of haziness or filling defects, and by the absence of death, myocardial infarction and the need for further revascularization procedures during hospitalization.

Laboratory assays. All the laboratory procedures were performed in duplicate by technicians who were unaware of the study design, purpose and results.

Markers of inflammation. CRP (mg/l) was immunologically determined by an immunoturbidimetric method (Roche Unimate 3 CRP, Milan, Italy). The normal upper reference value for CRP with this method is 5 mg/l[15]. Fibrinogen (mg/dl) was determined according to the method of von Clauss[16].

Hemostatic markers. Commercially available enzyme-linked immunosorbent assays were used to assess plasma concentrations of TAT (ng/ml), prothrombin fragments F1+2 (nmol/l) (Dade Behring, Marburg, Germany), and PAI-1 (ng/ml) (Bender MedSystems, MedSystem Diagnostics GmbH, Vienna, Austria).

Markers of platelet and endothelial activation. Commercially available enzyme-linked immunosorbent assays were used to assess plasma concentrations of soluble E-selectin (μg/l), soluble P-selectin (μg/l) (R&D Systems, Minneapolis, MN, USA) and von Willebrand factor (KU/l) (Boehringer Mannheim, Milan, Italy).

Statistical analysis. Patients were randomized according to a computer-generated random code. We calculated the size of the sample necessary to achieve 80% statistical power at a two-sided significance level of 0.05. The calculated sample size was based on previous reports showing that about 60% of stable patients have elevated CRP levels (> 5 mg/l) 72 hours after stent implantation[2,5]. On the assumption that Carbostent implantation would reduce the percentage of patients with persistently elevated CRP levels after the procedure to 20%, we set a goal of 44 patients for the study. Comparisons between the Carbostent and Multilink groups were performed using unpaired Student's t-tests for continuous variables and χ^2 tests or Fisher exact tests, as appropriate, for categorical variables. CRP and prothrombin fragments F1+2 values were log transformed and expressed as the median and interquartile range in brackets because of their skewed distribution. Serial changes in laboratory markers were evaluated by repeated measure analysis of variance for intra and intergroup comparisons followed by *post hoc* Scheffè F tests. Data are expressed as mean ± SD, unless otherwise indicated. Values of $p < 0.05$ were considered statistically significant. All statistical analysis was performed using StatView (version 5.0) for Windows 8.0 (SAS Institute Inc., Cary, NC, USA).

Results

Baseline characteristics. The baseline clinical characteristics are shown in table I. There were no significant differences in age, sex, risk factors and medical treatment.

Table I. Baseline clinical characteristics.

Characteristics	Carbostent (n=23)	Multilink stent (n=21)	p
Age (years)	60.7 ± 8.9	61.5 ± 10.6	0.78
Sex (M/F)	21/2	17/4	0.40
Previous myocardial infarction	9 (39%)	6 (29%)	0.46
Risk factors			
Hypertension	8 (35%)	10 (48%)	0.39
Hypercholesterolemia*	16 (70%)	15 (71%)	0.89
Diabetes mellitus	2 (9%)	5 (24%)	0.17
Current smoking	8 (35%)	10 (48%)	0.39
Medical treatment			
Nitrates	16 (70%)	17 (81%)	0.38
Antiplatelet drugs	23 (100%)	21 (100%)	1
Statins	10 (43%)	8 (38%)	0.72
Beta-blockers	10 (43%)	6 (29%)	0.30
ACE-inhibitors	7 (30%)	10 (48%)	0.24
Calcium channel blockers	12 (52%)	10 (48%)	0.76

Values are expressed as mean ± SD or number (percent of total). * total cholesterol > 200 mg/dl.

Baseline angiographic and procedural characteristics. There were no significant differences in the lesion location and lesion type (Table II). Procedural success was achieved in all cases. The mean stent length in the Carbostent group and in the Multilink group was 11.5 ± 4.1 and 12.3 ± 3.3 mm respectively (p = 0.50). An optimal acute angiographic result was achieved in all cases, with a final minimal lumen diameter of 2.85 ± 0.47 and 2.97 ± 0.44 mm respectively (p = 0.37). No patient developed major in-hospital adverse events. No patient exhibited abnormal levels of the creatine kinase and creatine kinase-MB enzymes or new pathologic Q waves. One patient in each group developed a hematoma at the puncture site (4 vs 5%, p = 0.90) and the median hospital stay was similar for both groups (4.2 ± 0.5 vs 4.1 ± 0.5 days, p = 0.67).

Table II. Baseline angiographic and procedural characteristics.

Characteristics	Carbostent (n=23)	Multilink stent (n=21)	p
Stented artery			
LAD	6 (26%)	8 (38%)	0.58
LCX	11 (48%)	7 (33%)	
RCA	6 (26%)	6 (29%)	
Type of lesion (B, C)*	16 (70%)	14 (67%)	0.84
Ejection fraction (%)	56.4 ± 9.0	57.5 ± 9.2	0.69
Lesion length (mm)	10.1 ± 3.1	10.3 ± 2.1	0.85
Predilation balloon size (mm)	2.8 ± 0.3	2.8 ± 0.3	0.90
Predilation balloon pressure (atm)	6.1 ± 1.0	5.6 ± 2.0	0.20
Dissections after predilation	4 (9%)	3 (7%)	0.80
Stent length (mm)	11.5 ± 4.1	12.3 ± 3.3	0.50
Stent size (mm)	3.4 ± 0.3	3.5 ± 0.4	0.26
Maximum inflation pressure (atm)	11.2 ± 2.1	11.7 ± 1.7	0.35
Direct stenting	10 (43%)	10 (48%)	0.78
Procedural success	23 (100%)	21 (100%)	1
Preprocedure			
Minimal lumen diameter (mm)	0.93 ± 0.43	1.0 ± 0.46	0.60
Reference diameter (mm)	2.96 ± 0.50	3.09 ± 0.50	0.39
% diameter stenosis	68.4 ± 13.7	67.8 ± 13.4	0.89
Postprocedure			
Minimal lumen diameter (mm)	2.85 ± 0.47	2.97 ± 0.44	0.37
Reference diameter (mm)	3.02 ± 0.50	3.15 ± 0.50	0.39
% diameter stenosis	5.5 ± 2.7	5.2 ± 3.1	0.80

Values are expressed as mean ± SD or number (percent of total). LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; RCA = right coronary artery. * according to the system of the American College of Cardiology/American Heart Association Task Force on the Assessment of Diagnostic and Therapeutic Cardiovascular Procedures.

Inflammatory markers. The pre and postprocedural values of inflammatory markers in the Carbostent and Multilink groups are shown in table III. Preprocedural levels of the inflammatory markers CRP and fibrinogen were similar in the Carbostent and Multilink groups [2 mg/l (2 to 4.5) vs 2 mg/l (2 to 7.7), p = 0.48, and 423 ± 98 vs 438 ± 139 mg/dl, p = 0.68, respectively]. In both groups, the plasma levels of CRP increased significantly after the procedure (p < 0.001 and p = 0.002 vs baseline levels, respectively), peaking at 48 hours [9.6 mg/l (2.8 to 19.7) and 7.7 mg/l (3.6 to 15.1) respectively], without any difference between groups (p = 0.76). At 72 hours, the plasma levels of CRP were still elevated (> 5 mg/l) in 12 (52%) patients in the Carbostent group and in 12 (57%) patients in the Multilink group (p = 0.74). Fibrinogen levels also increased in both groups (p = 0.02 and p = 0.002 vs baseline levels, respectively), without any difference between groups (p = 0.80).

Hemostatic markers and markers of platelet and endothelial activation. The pre and postprocedural values of the hemostatic markers and markers of platelet and endothelial activation in the Carbostent and Multilink groups are shown in tables IV and V. The preprocedural levels of the hemostatic markers (TAT, prothrombin fragments F1+2, PAI-1) and of the markers of platelet and endothelial activation (soluble E-selectin, soluble P-selectin and von Willebrand factor) were similar in the Carbostent and Multilink groups. In both groups, all increased significantly (all p < 0.05) after the procedure, but without any difference between groups (all p = NS).

Table III. Levels of the inflammatory markers.

	Carbostent (n=23)	Multilink stent (n=21)	p
C-reactive protein (mg/l)			
Baseline	2.0 (2 to 4.5)	2.0 (2 to 7.7)	
6 hours	2.0 (2 to 5)	2.0 (2 to 11.4)	
24 hours	3.1 (2 to 12.5)	4.0 (2 to 14.5)	0.76
48 hours	9.6 (2.8 to 19.7)*	7.7 (3.6 to 15.1)*	
72 hours	8.0 (3.3 to 26.8)*	8.0 (2.3 to 23.9)*	
Fibrinogen (mg/dl)			
Baseline	423 ± 98	438 ± 139	
6 hours	432 ± 130	467 ± 125	
24 hours	446 ± 111	480 ± 125	0.80
48 hours	463 ± 105	488 ± 138**	
72 hours	477 ± 99**	491 ± 140**	

Values are expressed as median (interquartile range) or mean ± SD. * p < 0.01 vs baseline values; ** p < 0.05 vs baseline values.

Table IV. Levels of the hemostatic markers.

	Carbostent (n=23)	Multilink stent (n=21)	p
TAT (ng/ml)			
Baseline	16.2 ± 4.7	17.3 ± 4.8	
6 hours	21.6 ± 6.2*	21.2 ± 6.6*	
24 hours	22.0 ± 6.0*	22.2 ± 5.2*	0.34
72 hours	21.2 ± 4.7*	19.8 ± 5.6*	
Prothrombin fragments F1+2 (nmol/l)			
Baseline	1.9 (1 to 2.8)	1.4 (1 to 3.1)	
6 hours	4.8 (3.5 to 11.6)**	3.6 (2 to 8.2)**	
24 hours	4.0 (2.1 to 9.1)**	5.7 (2 to 7.3)**	0.40
72 hours	5.7 (2.7 to 9.7)**	3.1 (1.9 to 6.2)**	
PAI-1 (ng/ml)			
Baseline	23.2 ± 5.8	23.3 ± 5.7	
6 hours	29.6 ± 6.1**	29.1 ± 5.7**	
24 hours	31.4 ± 7.9**	28.6 ± 4.5**	0.40
72 hours	27.9 ± 4.8**	26.7 ± 6.4**	

Values are expressed as median (interquartile range) or mean ± SD. PAI-1 = plasminogen activator inhibitor-1; TAT = thrombin-antithrombin III complexes. * p < 0.01 vs baseline values; ** p < 0.05 vs baseline values.

Table V. Levels of the markers of platelet and endothelial activation.

	Carbostent (n=23)	Multilink stent (n=21)	p
P-selectin (μg/l)			
Baseline	42.6 ± 13.1	44.1 ± 15.2	
6 hours	49.1 ± 17.1*	50.2 ± 16.3*	
24 hours	48.4 ± 19.6*	52.6 ± 19.9*	0.76
72 hours	48.1 ± 19.2*	49.6 ± 18.3*	
von Willebrand factor (KU/l)			
Baseline	1.4 ± 0.5	1.5 ± 0.5	
6 hours	1.6 ± 0.5**	1.8 ± 0.5**	
24 hours	1.8 ± 0.5**	1.8 ± 0.5**	0.78
72 hours	1.9 ± 0.5**	2.0 ± 0.5**	
E-selectin (μg/l)			
Baseline	56.1 ± 19.9	57.0 ± 16.6	
6 hours	75.6 ± 36.3**	75.5 ± 31.7**	
24 hours	81.7 ± 44.3**	76.5 ± 29.2**	0.68
72 hours	88.9 ± 40.5**	81.1 ± 37.0**	

Values are expressed as mean ± SD. * $p < 0.05$ vs baseline values; ** $p < 0.01$ vs baseline values.

Discussion

Stent implantation with an appropriate antiplatelet regimen has reduced the incidence of early thrombotic events and restenosis after percutaneous coronary interventions[17,18]. Yet, 10-30% of patients undergoing coronary artery stent implantation still exhibit restenosis due to neointimal proliferation[17,18]. As recent experimental *in vitro* and *in vivo* studies have suggested that carbon coating provides a high thromboresistance and an excellent biocompatibility[6-10], we sought to simultaneously assess the changes in inflammation, hemostasis, and platelet and endothelial activation after coronary implantation of carbon-coated and uncoated stents and to evaluate whether such changes were affected by carbon coating. The Carbostent is a new balloon-expandable, stainless steel, tubular stent with a multicellular design and unique turbostatic carbon coating, which has been recently shown to be associated with the absence of stent thrombosis, a very high procedural success rate and a low rate of angiographic restenosis and clinical related events[19,20]. The Multilink stent is another balloon-expandable, stainless steel, tubular stent with a multicellular design and no carbon coating which has already been tested in several clinical trials[12,13].

The inflammatory changes were assessed by measuring the plasma levels of CRP, a very sensitive marker of the inflammatory response[21], and of fibrinogen, an acute-phase reactant and a key coagulation factor[22]. Hemostatic changes were assessed by measuring the plasma levels of TAT and of the prothrombin fragments F1+2, respectively markers of thrombin generation and function[23], and the plasma levels of PAI-1, previously shown to predict restenosis after coronary angioplasty[24]. Platelet and endothelial activation were assessed by measuring the plasma levels of soluble P-selectin, which is not significantly affected by aspirin and ticlopidine[25,26], and of von Willebrand factor and soluble E-selectin, which have been shown to reflect early endothelial damage[27,28].

This study confirms that the markers of inflammation, of platelet and endothelial activation and of thrombin generation significantly increase after successful coronary artery stent implantation, thus indicating potential pathways leading to in-stent restenosis in spite of procedural success and optimal medical treatment. More importantly, our study shows that these changes are independent of whether patients undergo Carbostent or Multilink stent implantation, thus suggesting that they are not affected by carbon coating. Of note, as the study was powered to detect a 40% reduction in the percentage of patients with persistently elevated serum levels of CRP after Carbostent implantation, with a statistical power of 80% at an α level of 0.05, it is unlikely that significant differences between the two groups would have emerged had the number of patients enrolled been increased. The discrepancy between our results and the favorable results obtained with carbon-coated stents in experimental *in vitro* and *in vivo* studies[6-10] highlights how difficult it is to extrapolate experimental findings to humans with coronary artery disease. In the clinical setting, the biologic response of the vessel wall to stent implantation depends on the combination of the histologic composition of the plaque, the stent properties (mainly the stent thickness) and the consequent arterial injury[29-31]. In conclusion, carbon coating does not affect the inflammatory and hemostatic responses and the endothelial and platelet activation occurring after coronary artery stent implantation. However, the impact of carbon-coated stents on restenosis remains to be evaluated in larger clinical trials, taking into account the promising results obtained with the new drug-eluting stents[32].

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