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## The Enhanced Vasoreactivity of the Culprit Lesion in Unstable Angina is Associated with an Increased Local Release of Endothelin-1

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An increased tissue endothelin-1 (ET-1) immunoreactivity has been demonstrated at the site of the culprit lesion (CL) in patients with unstable angina (UA) thus suggesting that ET-1 may be involved in the abnormal vasoreactivity of the CL in UA. The aim of this study was to establish whether an enhanced local release of ET-1 is involved in the pathogenesis of the enhanced vasoreactivity of the unstable plaque in patients with UA. We studied 9 patients with UA and 9 patients with stable angina (SA) with a single proximal lesion of the left anterior descending coronary artery. Luminal diameter of the CL and of the proximal, middle and distal normal-appearing coronary segments were measured by quantitative coronary angiography at baseline, during cold pressor test (CPT) and after intracoronary administration of nitroglycerine (NTG). ET-1 levels were measured in blood samples obtained proximally and distally to the coronary CL before and after successful stent implantation. During CPT, the CL in patients with UA constricted more than that of patients with SA (percent reduction compared with baseline  $-25 \pm 8$  vs  $-8 \pm 10$  %,  $p = 0.0007$ ). After NTG, the CL in patients with UA dilated more than that of patients with SA (percent increase compared with baseline  $48 \pm 21$  vs  $22 \pm 7$  %,  $p = 0.0028$ ). The uninvolved proximal, middle and distal coronary artery segments had similar changes during CPT and after NTG in patients with UA and SA. Baseline proximal and distal ET-1 levels before stenting were similar in patients with UA and SA ( $1.29 \pm 0.08$  vs  $1.24 \pm 0.20$  pmol/L,  $p = 0.54$  and  $1.27 \pm 0.20$  vs  $1.25 \pm 0.23$ ,  $p = 0.79$  respectively). After stenting, proximal and distal ET-1 levels significantly increased compared to baseline values both in patients with UA and SA ( $1.88 \pm 0.11$  vs  $1.40 \pm 0.16$  pmol/L,  $p = 0.0001$  and  $1.89 \pm 0.18$  vs  $1.5 \pm 0.30$  pmol/L,  $p = 0.003$  respectively); however, the relative increase was greater in UA than in SA patients ( $45 \pm 6$  vs  $14 \pm 16$  %,  $p = 0.001$  and  $51 \pm 23$  vs  $22 \pm 12$  %,  $p = 0.0035$  respectively). The enhanced potential to release ET-1 might be responsible, at least in part, for the enhanced vasoreactivity of the CL in patients with UA. *J Clin Basic Cardiol* 2002; 5: 87–92.

**Key words:** endothelin, culprit lesion, unstable angina

The active atherosclerotic coronary lesion represents the patho-morphological substrate of unstable angina [1–3] and is characterized functionally by an abnormal vasoconstrictor response to different provocative stimuli [4–7]. Previous studies have also shown an increased tissue endothelin-1-like immunoreactivity at the site of the unstable atherosclerotic plaque [8]. The goal of the present study was to establish whether an enhanced local release of endothelin-1 (ET-1), the most potent endogenous vasoconstrictor [9], is involved in the pathogenesis of the enhanced vasoreactivity of the unstable plaque.

### Materials and Methods

#### Patients

Nine consecutive patients (6 men, mean age  $58 \pm 11$  years) with unstable angina (class IIIB according to Braunwald criteria) and 9 consecutive patients (6 men, mean age  $64 \pm 12$  years) with chronic stable angina (class II–III of the Canadian Cardiovascular Society), who underwent elective coronary artery stent implantation within 24 hours of coronary angiography, were enrolled for this study. The angiographic inclusion criterion was the presence of a newly diagnosed, isolated stenosis of the proximal portion of the left anterior descending coronary artery (defined as a reduction of  $> 50$  % of the luminal diameter, as measured by quantitative computerised angiography, extending  $< 18$  mm in length in a vessel  $> 3$  mm in

diameter). Angiographic exclusion criteria included total coronary occlusion, ostial lesion, major branching of the vessel within the target lesion, severe tortuosity of the proximal portion of the epicardial vessel, and left ventricular ejection fraction  $< 50$  %. Clinical exclusion criteria included previous myocardial infarction, uncontrolled hypertension, peripheral vascular disease, and significant endocrine, hepatic, renal or inflammatory disease. Written, informed consent was obtained from every patient.

#### Study protocol

Patients were brought into cardiac catheterization laboratory in the fasting state and all cardiovascular medications had been discontinued for  $> 10$  hours with the exception of aspirin (325 mg) and ticlopidine (250 mg bid) which were started before the procedure and sublingual nitrates if needed. At the beginning of the procedure, 10000 IU of heparin were administered intra-arterially; when needed supplemental doses were then given to maintain an activated clotting time  $\geq 250$  seconds.

#### Angiographic assessment

The optimal view for visualizing the culprit lesion was selected, and this view was maintained throughout the study. In all patients, ioversol (Optiray 320, Mallinckrodt Medical, St. Louis, USA) was used as a contrast agent. After the baseline arteriogram a cold pressor test was performed. The patient

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placed a hand and forearm in a basin containing a slurry of ice water for 90 seconds and a second arteriogram was taken at 80 seconds. After five minutes, intracoronary nitroglycerine (400 µg in 2 ml of saline) was administered as a bolus and, after 30 seconds, a third arteriogram was taken. Quantitative analysis was performed by two experienced technicians who were unaware of the study protocol with the use of the Automated Coronary Analysis System (Philips, Best, The Netherlands). End-diastolic cine frames were selected and identifiable branching points were used for localizing the proximal, middle and distal normal-appearing coronary segments. Measurements included the minimal lumen diameter of the culprit lesion, the proximal luminal diameter (uninvolved vessel proximal to the culprit lesion), the middle luminal diameter (uninvolved vessel between the first and last diagonal branch) and the distal luminal diameter (uninvolved vessel distal to the last diagonal branch). All measurements were obtained for arteriograms taken at baseline, during cold pressor test and after nitroglycerine administration. Ninety-one (of the 216) randomly selected measurements were reanalyzed by two blinded observers. The mean of the difference between measurements was  $0.05 \pm 0.09$  ( $p = 0.74$ ).

#### Plasma endothelin-1 assessment

Baseline blood samples were obtained from coronary artery segment distal and proximal to the site of the coronary stenosis by using a coronary drug-delivery catheter (Tracker-325 Vascular Access System, Target Therapeutics, Fremont, CA, USA) positioned about 10–15 mm distally and 10–15 mm proximally to the stenosis. During sampling the guide wire was withdrawn. The same sampling procedure was repeated immediately after stent implantation. Circulating ET-1 levels were assessed as previously described [10]. Briefly, each plasma sample was injected into a C18 octyldecylsilane column (Pharmacia, Uppsala, Sweden), activated with 0.1 % trifluoroacetic acid. The eluate (derived from two aliquots of 2.5 ml plasma) was then freeze-dried, reconstituted in starting high performance liquid chromatography (HPLC) buffer and eluted by reverse by reverse-phase HPLC over 70 minutes using a linear gradient of 15–75 % acetonitrile/0.1 % trifluoroacetic acid in distilled water. The chromatographic

separation of plasma eluates identified a single peak of ET-1, perfectly corresponding to the elution position of human ET-1 standard and of  $^{125}\text{I}$ -ET-1. Fractions corresponding to ET-1 were collected each minute and evaporated before reconstitution in assay buffer (50 mmol/L phosphate buffer, pH 7.4, containing 0.9 % NaCl, 0.04 %  $\text{NaN}_3$ , and 0.3 % bovine serum albumin). ET-1 immunoreactivity was assayed on reconstituted samples by radioimmunoassay, using a rabbit anti-ET-1 antibody (Peninsula Laboratories, Belmont, CA),  $^{125}\text{I}$ -ET-1 (Peninsula), and human ET-1 (Peptide Institute, Osaka, Japan) as standard. Inter-assay and intra-assay variations were 6 % and 8 % respectively. Cross-reactivity of the ET-1 antibody with ET-2 and ET-3 was < 7 %, according to the supplier. Serum vascular endothelial growth factor concentrations (VEGF) measured by sensitive chemiluminescence enzyme immunoassay [11] (Akiyoshi, Tokyo, Japan), and vascular cell adhesion molecule 1 (VCAM-1) plasma levels, assessed by commercially available monoclonal antibody-based ELISA method [12] (R & D Systems, Minneapolis, MN, USA) were also obtained. Arterial blood samples for the assessment of ET-1, VEGF and VCAM-1 were also obtained from the femoral artery at baseline and immediately after stent implantation.

#### Statistical analysis

Data are expressed as mean  $\pm$  1 standard deviation. Two-tailed unpaired *t*-test was used to analyze differences in luminal diameter at baseline and after each intervention and ET-1, VEGF and VCAM-1 plasma levels between the unstable and stable angina groups before and after coronary stenting. Within each group, two-tailed paired *t*-test was used to analyze differences in luminal diameter compared to baseline after each intervention and ET-1, VEGF and VCAM-1 plasma levels before and after coronary stenting. Differences between groups were considered to be significant at a *p* value < 0.05.

## Results

### Haemodynamic results

Baseline systemic mean blood pressure was similar in patients with unstable and stable angina ( $115 \pm 11$  vs  $120 \pm 17$  mmHg,  $p = 0.466$ ). During cold pressor test and after intracoronary injection of nitroglycerine, blood pressure had similar changes in both groups ( $133 \pm 10$  vs  $138 \pm 24$  mmHg,  $p = 0.602$  and  $101 \pm 12$  vs  $109 \pm 11$  mmHg,  $p = 0.145$  respectively) and the differences were significant compared with baseline values ( $p < 0.002$ ). Baseline heart rate was similar in patients with unstable and stable angina ( $70 \pm 8$  vs  $68 \pm 7$  beats per minute,  $p = 0.566$ ). During cold pressor test and after intracoronary injection of nitroglycerine, heart rate had similar changes in both groups ( $81 \pm 7$  vs  $78 \pm 9$  beats per minute,  $p = 0.68$  and  $80 \pm 6$  vs  $77 \pm 8$  beats per minute,  $p = 0.44$  respectively) and the differences were significant compared with baseline values ( $p < 0.02$ ).

### Angiographic results

At baseline, the luminal diameter of the culprit lesion and of uninvolved

**Table 1.** Luminal diameter (mm) of culprit lesion at baseline and following each intervention

Subjects	Baseline	CPT	Change %	NTG	Change %
<b>Unstable Angina</b>					
1	0.94	0.71	-24	1.31	39
2	1.76	1.32	-25	2.21	26
3	0.55	0.40	-27	0.97	76
4	0.59	0.45	-24	0.95	61
5	1.14	0.85	-25	1.54	35
6	0.57	0.47	-18	1.01	77
7	1.54	1.10	-29	1.90	23
8	1.10	0.67	-39	1.45	32
9	0.67	0.60	-10	1.10	64
Mean $\pm$ SD	$0.98 \pm 0.44$	$0.73 \pm 0.31^\dagger$	$-25 \pm 8^*$	$1.38 \pm 0.44^\dagger$	$48 \pm 21^*$
<b>Stable Angina</b>					
1	1.15	0.94	-18	1.31	14
2	0.86	0.67	-22	0.99	15
3	0.81	0.83	-2	1.10	36
4	1.35	1.23	-9	1.57	16
5	0.79	0.71	-10	0.97	23
6	0.62	0.59	-5	0.78	26
7	1.03	0.93	-10	1.23	19
8	0.77	0.84	-9	0.98	27
9	1.10	1.05	-5	1.30	18
Mean $\pm$ SD	$0.94 \pm 0.23$	$0.87 \pm 0.20^\dagger$	$-8 \pm 10^*$	$1.14 \pm 0.24^\dagger$	$22 \pm 7^*$

CPT: cold pressor test; NTG: intracoronary nitroglycerine; \*: significantly different unstable vs stable angina; †: significantly different vs baseline

proximal, middle and distal coronary segments were similar in patients with unstable and stable angina ( $0.98 \pm 0.44$  vs  $0.94 \pm 0.23$  mm,  $p = 0.80$ ;  $3.77 \pm 0.65$  vs  $3.87 \pm 0.79$  mm,  $p = 0.76$ ;  $2.58 \pm 0.63$  vs  $2.53 \pm 0.72$  mm,  $p = 0.88$ ;  $1.65 \pm 0.54$  vs  $1.57 \pm 0.43$  mm,  $p = 0.74$ , respectively). During cold pressor test the luminal diameter of the culprit lesion diminished in both patients with unstable ( $p = 0.001$ ) and stable angina ( $p = 0.036$ ); however, the luminal diameter reduction was greater in the former group ( $0.73 \pm 0.31$  vs  $0.87 \pm 0.20$  mm, absolute reduction  $0.25 \pm 0.15$  vs  $0.08 \pm 0.1$  mm, percent reduction compared with baseline  $-25 \pm 8$  vs  $-8 \pm 10$  %,  $p = 0.0007$ ) (Fig. 1A and Tab. 1). After intracoronary injection of nitroglycerine, the luminal diameter of the culprit lesion dilated in both patients with unstable ( $p = 0.001$ ) and stable angina ( $p = 0.001$ ); however, the luminal diameter dilation was greater in the former group ( $1.38 \pm 0.44$  vs  $1.14 \pm 0.24$  mm, absolute increase  $0.38 \pm 0.4$  vs  $0.19 \pm 0.05$  mm, percent increase compared with baseline  $48 \pm 21$  vs  $22 \pm 7$  %,  $p = 0.0028$ ) (Fig. 1A and Tab. 1).

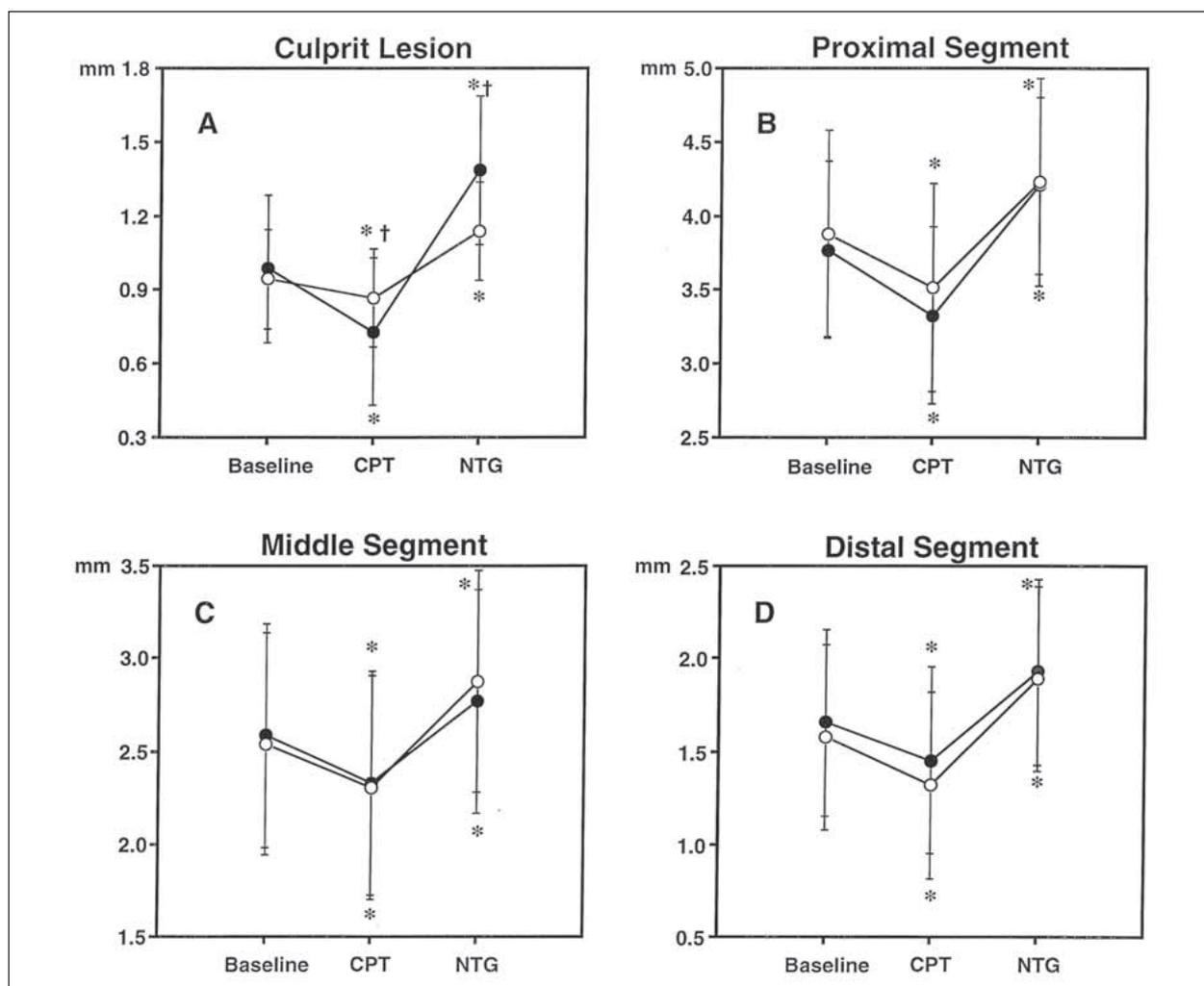
The normal appearing proximal, middle and distal coronary segments had similar changes during cold pressor test and after intracoronary injection of nitroglycerine in both patients with unstable and stable angina (Fig. 1B–D).

### Stent implantation

Stent implantation was successful in all patients. A pre-mounted stent delivery system (Multilink Rx Duet, Guidant Advanced Cardiovascular System, Inc, Temecula, CA, USA) was used in all patients without predilatation. In 10 patients (5 with unstable and 5 with stable angina) a 18 mm stent was used; in two patients (1 with unstable and 1 with stable angina) a 8 mm stent was implanted; in the remaining 6 patients a 13 mm stent was deployed. Angiographic and procedural data are reported in Table 2.

### Endothelin-1, vascular endothelial growth factor and vascular cell adhesion molecule 1 plasma levels

Proximal and distal ET-1 plasma levels before stent implantation were similar in both patients with unstable and stable angina ( $1.29 \pm 0.08$  vs  $1.24 \pm 0.2$  pg/ml,  $p = 0.54$  and  $1.27 \pm 0.20$  vs  $1.25 \pm 0.23$  pg/ml,  $p = 0.79$ , respectively) (Fig. 2). After stent implantation, proximal and distal ET-1 plasma levels significantly increased compared to baseline both in unstable ( $p = 0.001$  and  $p = 0.001$ , respectively) and stable angina ( $p = 0.042$  and  $p = 0.004$ , respectively) patients; however, the increase both in the proximal and distal coronary site was higher in the former group ( $1.88 \pm 0.11$  vs  $1.40 \pm 0.16$



**Figure 1.** Plot of the luminal diameter of the coronary stenosis (A) and of the proximal (B), middle (C) and distal (D) angiographically normal-appearing coronary segments at baseline, during cold pressor test (CPT) and after intracoronary nitroglycerine administration (NTG). Black circles indicate patients with unstable angina and white circles indicate patients with stable angina. \*: significantly different vs baseline; †: significantly different unstable vs stable angina.

pmol/L, absolute increase  $0.40 \pm 0.039$  vs  $0.19 \pm 0.046$  pmol/L, percent increase  $45 \pm 6$  vs  $14 \pm 17$  %,  $p = 0.001$  and  $1.89 \pm 0.18$  vs  $1.5 \pm 0.3$  pmol/L, percent increase  $51 \pm 23$  vs  $21 \pm 13$  %,  $p = 0.0035$ , respectively) (Fig. 2).

Proximal and distal VEGF plasma levels before stent implantation were similar in both patients with unstable and stable angina ( $33 \pm 19$  vs  $27 \pm 7$  pg/ml,  $p = 0.34$  and  $32 \pm 21$  vs  $27 \pm 14$  pg/ml,  $p = 0.54$ , respectively). After stent implantation, proximal and distal VEGF plasma levels significantly increased compared to baseline values both in unstable ( $p = 0.005$  and  $0.03$ , respectively) and stable angina ( $p = 0.02$  and  $p = 0.03$ , respectively) patients; however, the increase in the proximal and distal coronary site was similar in both groups ( $53 \pm 25$  vs  $43 \pm 15$  pg/ml, percent increase  $73 \pm 61$  vs  $69 \pm 64$  %,  $p = 0.89$  and  $44 \pm 26$  vs  $51 \pm 33$  pg/ml, percent increase  $70 \pm 13$  vs  $110 \pm 16$  %,  $p = 0.56$ , respectively).

Proximal and distal VCAM-1 plasma levels before stent implantation were similar in both patients with unstable and stable angina ( $353 \pm 81$  vs  $321 \pm 65$   $\mu$ g/L,  $p = 0.40$  and  $328 \pm 82$  vs  $289 \pm 60$   $\mu$ g/L,  $p = 0.29$ , respectively). After stent implantation, proximal and distal VCAM-1 plasma levels significantly increased compared to baseline values both in patients with unstable ( $p = 0.01$  and  $p = 0.04$ , respectively) and stable ( $p = 0.008$  and  $p = 0.0015$ ) angina; however, the relative increase in the proximal and distal coronary site was similar in both groups ( $390 \pm 101$  vs  $353 \pm 59$   $\mu$ g/L, percent increase  $10 \pm 7$  vs  $11 \pm 9$  %,  $p = 0.78$  and  $340 \pm 72$  vs  $326 \pm 58$   $\mu$ g/L, percent increase  $6 \pm 14$  vs  $14 \pm 11$  %,  $p = 0.22$ , respectively).

Peripheral ET-1, VEGF and VCAM-1 plasma levels before and after stent implantation were similar in both patients with unstable and stable angina.

## Discussion

In this study the culprit lesion of patients with unstable angina exhibited an increased resting tone and an enhanced vasoconstrictor response in comparison with the culprit lesion of patients with stable angina. Furthermore, coronary artery stent implantation at the site of the atherosclerotic lesion was followed by a detectable increase of ET-1, the most potent endogenous vasoconstrictor [9], which was significantly greater at the site of the unstable than at the site of the stable plaque. The enhanced potential to release ET-1 might be responsible, at least in part, for the increased vasoreactivity of the culprit lesion in patients with unstable angina. Of note, the release of VCAM-1 and VEGF following stent implantation was similar in unstable and stable patients.

The intracoronary administration of a high dose of nitroglycerine caused a significant increase of the luminal diam-

eter of the culprit lesion, compared with baseline, both in patients with unstable and stable angina. However, the luminal diameter increase of the stenosis was greater in patients with unstable angina than in patients with stable angina thus indicating an increased resting tone at the site of the unstable plaque. In a previous elegant study, carried out by Bogaty et al. [7] in patients with unstable and stable angina, the intracoronary administration of isosorbide dinitrate caused a similar luminal diameter increase of the stable and unstable plaques. This discrepancy might be due to the utilization of an inadequate dose of nitrates in the study of Bogaty et al. indeed, in that study, the intracoronary administration of 2 mg of isosorbide dinitrate did not affect systemic blood pressure, while in our study the intracoronary administration of 400  $\mu$ g of nitroglycerine resulted in a significant reduction of systemic blood pressure.

The causes of the enhanced resting tone of the unstable plaque cannot be deduced from the results of our study. It might be due to: 1) vasoconstrictors released by an intracoronary thrombus known to be more frequently present at the site of unstable compared to stable plaques [13], 2) vasoconstrictors released by endothelial cells and macrophages activated by inflammatory mediators [14, 15], 3) a primary local alteration of coronary smooth muscle as proposed in patients with variant angina [16].

As previously reported [7], and in our study also, the unstable plaque was hyper-reactive to the constrictor stimulus of the cold pressor test. This latter is known to evoke a systemic neurohumoral response; however, the evidence that the uninvolved coronary segments exhibited similar response in patients with unstable and stable angina supports the concept that the enhanced vasoreactivity is a local plaque-related phenomenon.

Although the mechanisms responsible for the increased vasoreactivity of the unstable atherosclerotic plaque are still poorly understood, a growing body of evidence indicates that ET-1 might play a pivotal role. ET-1 is one of a family of peptides that are potent constrictors of vascular smooth muscle [9]. In addition ET-1 markedly potentiates the constrictor effects of other vasoconstrictor mediators such as catecho-

Table 2. Angiographic and procedural data\*

Variables	Unstable Angina	Stable Angina
Left ventricular ejection fraction (%)	$61 \pm 7$	$59 \pm 9$
Type of lesion (B/C) <sup>†</sup>	6/3	5/4
Length of lesion (mm)	$12 \pm 7$	$11 \pm 7$
Baseline stenosis (%)	$67 \pm 8$	$72 \pm 7$
Max inflation pressure (atm)	$12 \pm 2$	$13 \pm 2$
Total inflation duration (sec)	$39 \pm 24$	$41 \pm 28$
Residual stenosis (%)	$2 \pm 4$	$3 \pm 4$

\*: Plus-minus values are means  $\pm$  1 standard deviation. <sup>†</sup>: Lesions were classified according to the system of the American College of Cardiology/American Heart Association Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures. Differences between groups are not statistically significant.

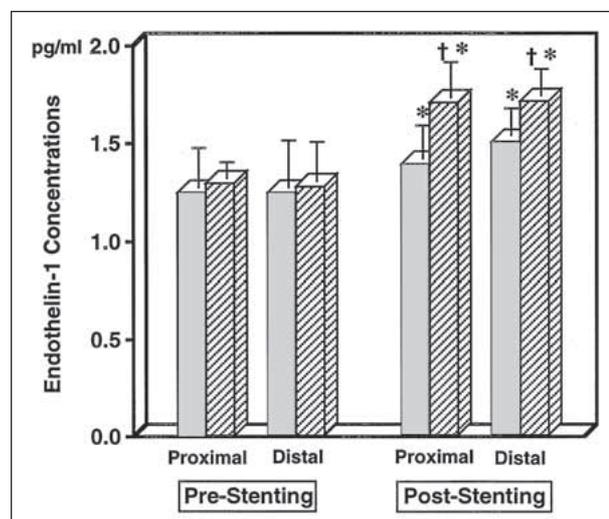


Figure 2. Endothelin-1 levels in blood sampled proximally and distally to the site of dilatation, before (Pre-stenting) and after (Post-stenting) coronary artery stent implantation in patients with stable (shaded bars) and unstable (striped bars) angina. \*: significantly different vs baseline (pre-stenting); †: significantly different unstable vs stable angina.

lamine, serotonin and angiotensin II [17–19] and its release is stimulated by thrombin [20] and inflammatory factors such as interleukin-1 [21]. ET-1 is not only produced by endothelial cells but also by human macrophages [22] and polymorphonuclear leucocytes [23] which appear to be involved in the inflammatory processes at the site of the atherosclerotic unstable plaque. Furthermore, previous experimental studies have demonstrated that oxidatively modified low-density lipoproteins, which accumulate prominently at the site of active atherosclerotic plaques [24], activate human macrophages to secrete immunoreactive ET-1 by activation of protein kinase C [25]. Accordingly, in a previous *in vitro* study [8], Zeiher et al. evaluated the endothelin-1-like immunoreactivity at the site of coronary atherosclerotic lesions obtained by directional coronary atherectomy from patients with stable angina and patients with crescendo and postinfarction angina. These authors found that ET-1 staining grade was significantly greater in patients with acute coronary syndromes compared to that observed in atherosclerotic plaque tissue obtained from patients with stable angina. In addition ET-1 immunostaining was most prominent in the areas with evidence of infiltration by macrophages whose key role in the transition from stable to unstable lesions is well established [14]. In the present study we specifically investigated the local release of ET-1 induced by coronary stent implantation. Baseline plasma ET-1 levels in patients with unstable and stable angina were similar. However, the mechanical stress induced by coronary artery stent implantation caused a release of ET-1, which resulted more markedly at the site of the unstable than at the site of the stable plaque. The ET-1 released during the mechanical stress caused by coronary stent implantation might originate from an internalization of ET-1 produced by endothelial cells [26] or be generated by macrophages or polymorphonuclear leucocytes present in the atherosclerotic plaque [22, 23].

Recently, in a selected group of patients with stable angina, Hasdai et al. [27] showed that the mechanical stress induced by percutaneous transluminal coronary angioplasty caused a release of ET-1 and of the precursor big ET-1 from human atherosclerotic coronary arteries and that the degree of mechanical stress applied correlated with the degree of ET-1 release. In our study, differently from what was reported by Hasdai et al., who found an increase of ET-1 only distally to the dilated atherosclerotic lesion, increased levels of ET-1 after coronary stent implantation were found both distally and proximally to the treated lesion. The increased release of ET-1 at the proximal site may be due to temporary blood stasis during the procedure which is known to cause a release of ET-1 [28] and/or to the persistent stretching of the vessel wall determined by the stent implantation [29]. Of note, in our study, the similar increase at the coronary level of VEGF and VCAM-1 plasma levels observed both in patients with unstable and stable angina and the observation that peripheral ET-1, VEGF and VCAM-1 plasma levels did not change after stent implantation indicates that the increased ET-1 release in patients with unstable angina does not represent a generalised activation of vasoactive peptides.

In conclusion, the enhanced potential to release ET-1, a potent vasoconstrictor of vascular smooth muscle, in patients with unstable angina might, at least partially, be responsible for the increased vasoreactivity of the unstable plaque. Furthermore, as ET-1 production is stimulated by inflammatory mechanisms, the enhanced potential to release ET-1 further supports the role of inflammatory mechanisms in the instabilization of the atherosclerotic plaque. Finally, our results suggest that more selective vasodilators, such as endothelin antagonists, might be much more effective than

the currently available vasodilators in the clinical setting of acute coronary syndromes.

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