Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 59, No. 8, 2012
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2011.10.894

Transient Impairment of Vasomotion Function After Successful Chronic Total Occlusion Recanalization

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Objectives The aim of our study was to assess coronary vasomotion after successful revascularization of chronic total occlusion (CTO).

Background It is largely unknown whether the recovery of anterograde flow after CTO recanalization with drug-eluting stent implantation affects vascular function in distal coronary segments.

Methods One hundred consecutive CTOs successfully treated with drug-eluting stents underwent coronary diameter measurement after intracoronary nitroglycerin injection 5, 20, and 35 mm distal to the stented coronary segment using 3-dimensional quantitative coronary angiography. In a subgroup of 14 patients, coronary vasomotion was tested in distal segments: incremental atrial pacing for endothelium-dependent cases; and intracoronary nitroglycerin injection for endothelium-independent cases. In another subgroup of 13 patients, distal vessels were assessed by intracoronary ultrasounds.

Results Vessel diameters significantly increased at follow-up as compared to baseline values (2.0 ± 0.52 mm vs. 2.25 ± 0.50 mm, 1.76 ± 0.49 mm vs. 2.05 ± 0.58 mm, 1.54 ± 0.53 mm vs. 2.04 ± 0.58 mm, at each segment analyzed; $p < 0.001$). At baseline, distal segments failed to respond to both endothelium-dependent and -independent stimuli. At follow-up, atrial pacing induced vasoconstriction, whereas nitroglycerine administration resulted in significant vasodilation ($p < 0.05$). Intracoronary ultrasounds failed to show changes of the cross-sectional area of distal segments at follow-up angiography.

Conclusions Recanalization of CTO is followed by a hibernation of vascular wall at distal coronary segments that fail to respond to endothelium-dependent and -independent stimuli. Distal vessel diameter increases over time in the absence of positive remodeling and in spite of persistent endothelial dysfunction. This severe impairment of vasomotor tone after CTO reopening suggests that intracoronary ultrasound assessment is of paramount importance for the selection of stent size. (J Am Coll Cardiol 2012;59:711–8) © 2012 by the American College of Cardiology Foundation

Chronic total occlusion (CTO) pathophysiology is not fully elucidated yet; some studies suggest that occlusion is probably caused by thrombus and lipid-rich cholesterol esters that are replaced over time by collagen and calcium deposition (1). Experimental models showed endothelial cell necrosis in response to vessel ligation (2), whereas more recent models suggest that the endothelium might retain viability guiding the subsequent development of CTO, including CTO neo-revascularization, which occurs within the lumen and in various layers of the vessel wall, by the release of paracrine substances (3,4).

It is uncertain whether after CTO recanalization the recovery of anterograde reverses endothelial dysfunction, thus promoting vasodilation and positive remodeling.

The aim of the present clinical study was to investigate the distal coronary vessel after successful percutaneous coronary intervention (PCI) of CTO using drug-eluting stents, assessing both vasomotion and remodeling.

Methods

Study population. All patients undergoing PCI of CTO at our hospital between October 2005 and October 2008 were screened for enrollment in this prospective study. Patients were eligible for inclusion if procedural success was achieved, defined as angiographic success (final residual stenosis less than 30%, with TIMI [Thrombolysis In Myo-

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Manuscript received May 31, 2011; revised manuscript received September 13, 2011, accepted October 17, 2011.

Abbreviations and Acronyms

ANCOVA = analysis of covariance
CTO = chronic total occlusion
EEM = external elastic membrane
IC = intracoronary
ICUS = intracoronary ultrasound
PCI = percutaneous coronary intervention
QCA = quantitative coronary angiography
RVD = reference vessel diameter
SMC = smooth muscle cell
TIMI = Thrombolysis In Myocardial Infarction

cardial Infarction] flow grade ≥2) in the absence of procedural cardiac adverse events and restenosis at follow-up. Exclusion criteria were: life expectancy (<2 years), low left ventricular ejection fraction (<40%), significant lesions in left main coronary artery (≥30% of luminal diameter). Angiographic follow-up was scheduled at 9 to 12 months for all patients who consented to participate in the study. Patients who underwent repeat angiography in the absence of restenosis and/or of adverse events during follow-up represented the final study population.

The study was performed according to the Declaration of Helsinki and World Health Organization guidelines. The study was carried out at the Clinical Division of Cardiology of Ferrarotto Hospital, University of Catania. The ethics committee approved the entire protocol including pacing and intravascular ultrasound substudies, and all patients gave written informed consent for coronary angiography and the endothelial function test.

Interventional procedures. All patients received intravenous hydration with 1 ml/kg/h of saline the day before and after PCI. At the beginning of the procedure, patients received intravenous unfractionated heparin (100 IU/kg) to maintain activated clotting time higher than 300 s, activated clotting time was measured every 30 min and, if required, additional boluses of unfractionated heparin were administered during the procedures. No glycoprotein IIb/IIIa inhibitors were administered. Expert operators performed the procedures. CTO revascularization strategies were left to the operators' discretion. All procedures were performed via the femoral route, using double coronary cannulation. Several guidewire strategies were used including single-wire technique, parallel-wire technique, intravascular ultrasound–guided wiring technique, and retrograde wiring through collaterals with its refinements (such as pure retrograde wiring, kissing wiring, knuckle, CART [controlled antegrade retrograde tracking], and reverse CART techniques), as previously described (5). In several cases, the Crosser system (Bard Peripheral Vascular Inc., Tempe, Arizona) was used as previously shown (6). Drug-eluting stents only were implanted. Notably, no vasoactive drugs, including nitroglycerine and adenosine, were administered during the procedures. As a final procedural stage, in all patients, at least 2 orthogonal coronary angiograms were obtained after intracoronary (IC) administration of nitroglycerine (200 μg total dose); the same projections were then used at follow-up after IC administration of the same dose of nitrates.

Coronary vasomotor study protocol. To assess endothelium-dependent coronary vasomotion, a pacing study was performed in a subgroup of patients. In these patients, all vasoactive drugs were discontinued at least 24 h before catheterization except for sublingual nitroglycerin, which was allowed up to 1 h before the index or repeat angiography. Long-acting beta-blockers were stopped 48 h before the study. Before IC nitrate administration, a 5-F bipolar pacing wire (St. Jude Medical, St. Paul, Minnesota) was placed against the high lateral right atrial wall, using the femoral vein route, at the end of both index and repeat angiographies. After control conditions were established, rapid atrial pacing was conducted with steps of 20 beats/min increase above baseline heart rate for 2 min, until reaching the final pacing rate of 150 beats/min. The pacing protocol was interrupted in cases of angina or when atrioventricular Wenckebach block occurred. In this latter case, atrioventricular Wenckebach block was not treated with intravenous atropine so as not to influence coronary vasomotion and blood flow responses. Angiograms were obtained at baseline and at the end of a 2-min period at each pacing rate, within beats after ending the highest pacing step. Finally, the endothelium-independent vasomotor response was evaluated with administration of IC nitroglycerine bolus 200 μg, immediately before coronary angiography.

Quantitative coronary angiography. Analysis of quantitative coronary angiography (QCA) was performed by the institutional core laboratory (Ferrarotto Hospital, University of Catania, Catania, Italy) using the CardiOp-B system (Paeion Medical Ltd., Rosh Hayin, Israel). The system includes a software package that runs on off-the-shelf hardware and performs a 3-dimensional reconstruction of the obstructed vessel as well as provides quantitative cross-section information combining two 2-dimensional angiographic projections (7). One experienced technician blinded to the patients' identities and outcomes, performed offline quantitative analysis of angiographic data using end-diastolic images selected from each of the different projections. After calibration using a catheter-based scaling factor, the operator marked the proximal and distal reference points in addition to a third point, which is used as an anchor between different images. At this stage, the software is able to create a 3-dimensional reconstruction of coronary vessel. Using the software's tool, traditional QCA parameters, including reference vessel diameter (RVD), minimal lumen diameter, and diameter stenosis, were obtained, at 5, 20, and 35 mm distal to the distal stent edge (8,9). The intraobserver variability of our technician for RVD measurement is 0.94.

Assessment of coronary remodeling. In another subgroup of patients intracoronary ultrasound (ICUS) was also performed at the end of both index and repeat angiography. Patients with at least a 35-mm distal coronary segment suitable for ICUS examination were included in this suba-

nalysis. ICUS was performed after IC administration of 200 μg of nitroglycerin, using the Galaxy system (Boston Scientific, Fremont, California), using a 40-MHz, 2.6-F rapid exchange probe (Atlantis-Pro, Boston Scientific). Image acquisition using automated transducer pullback at 0.5 mm/s was performed from at least 35 mm distal to the distal stent edge retrograde to the aorto-ostial junction. Offline analysis was performed with a commercially available program for computerized planimetry (EchoPlaque, INDEC System, Mountain View, California). ICUS images were analyzed by side-by-side viewing in post-procedure and follow-up studies. Review of landmarks and pullback speed, frame-by-frame comparison for matching segments, and digitization of images were carried out by 2 expert operators of our core laboratory. The intraclass coefficients for interobserver variability of measurement of plaque and vessel volumes in our laboratory are 0.98 and 0.99, respectively. Interpolation of the lumen and external elastic membrane contours was performed according to an acoustic quantification method and a nonlinear algorithm, respectively, as previously described (10). At every 5-mm axial length segment from the distal stent edge, lumen diameter, external elastic membrane (EEM) diameter, and lumen and EEM cross-sectional areas were measured. The EEM was measured at the leading edge of the adventitia. A total of 107 cross sections were analyzed in the segment of interest at post-procedure and follow-up evaluations. Comparisons were made between the post-intervention and follow-up data.

Statistical analysis. The sample size was calculated considering the results of QCA analysis; therefore, assuming a 0.45-mm standard deviation of RVD, a total sample size of 87 analyzed lesions was estimated to detect a difference of 0.2 mm between index and repeat angiography RVDs at each coronary segment analyzed, with 95% of statistical power and a beta error equal to 0.36. Taking into the account a dropout rate of 40%, the sample size was set at 135 lesions. The dropout rate was predicted based on the expected incidence of restenosis and failed QCA assessment. For the vasomotor tone assessment, it was estimated that a sample size of 13 patients was needed to detect with 95% of statistical power and assuming a difference of 0.35 mm in coronary RVD between the maximal pacing and IC nitroglycerine administration at each segment studied. Continuous variables were analyzed for a normal distribution with the Kolmogorov-Smirnov test and presented as mean ± SD or as median and interquartile range if a normal distribution was present or not, respectively. Student *t* test or Mann-Whitney *U* test were used for comparison of continuous variables as appropriate. Categorical variables are expressed as frequencies and percentages. Categorical variables were tested by means of the chi-square test or Fisher exact test when at least 25% of values showed an expected cell frequency below 5. A 2-tailed p value <0.05 was considered to indicate a statistically significant difference for all the analyses performed. No corrections were made in cases of multiple CTO lesions in the same patients.

A repeated measure analysis of covariance (ANCOVA) model was used to compare the changes of RVD at each coronary segment analyzed (5 mm, 20 mm, and 35 mm) at index and repeat angiography, using as covariates diabetes, stent type, and the diameter of the distal stent implanted. One-way analysis of variance was used to test the differences in diameter variation between the analyzed segments. Spearman correlation test was used to show the relationship between the baseline vessel diameter (measured at distal stent edge) and the percentage of diameter variation. Another ANCOVA model was use to compare index procedure ICUS results (measured at each 5 mm, from the distal stent edge until 35 mm) with those obtained at follow-up. Statistical analysis was performed using a SPSS software (version 16.0, SPSS Inc., Chicago, Illinois).

Results

During the study period, 210 patients with 234 CTO lesions were screened; among these, 87 patients with 100 CTO lesions constituted the final study population. Study population and study protocol flow charts are shown in Figures 1 and 2, respectively. Baseline clinical characteristics of patients are reported in Table 1 and lesion angiographic characteristics are in Table 2. The average of contrast load administration per patient was 387± 223 cc.

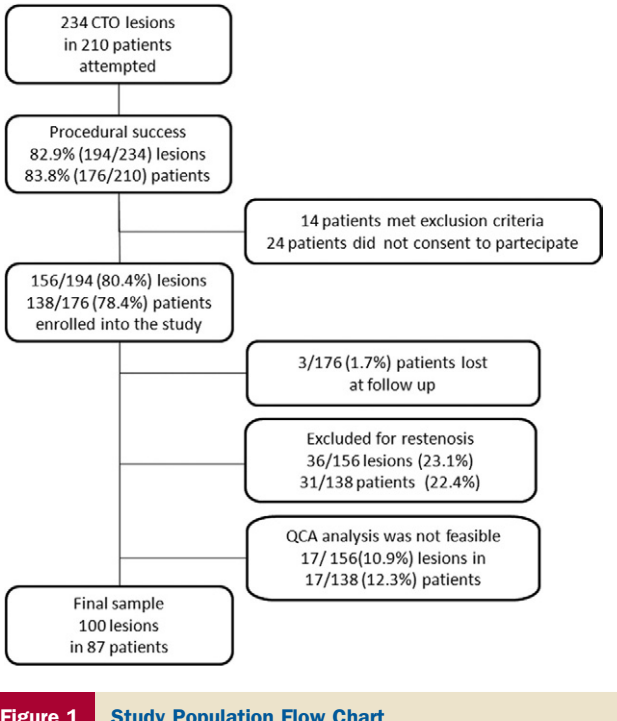

Figure 1 Study Population Flow Chart

The final sample of the study is represented by 100 chronic total occlusions (CTO) lesions successfully revascularized in 87 patients. QCA = quantitative coronary angiography.

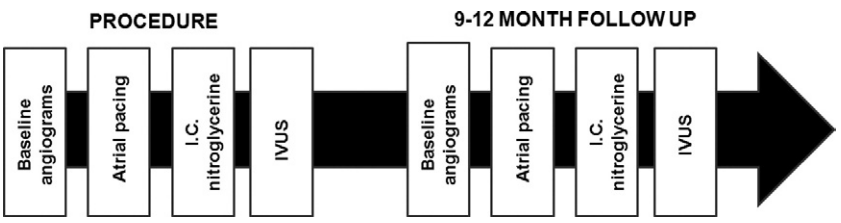

Figure 2 Study Protocol Flow Chart

Angiograms were obtained at the end of chronic total occlusion percutaneous coronary intervention procedure (baseline) and at the end of a 2-min period at each pacing rate. After that, the endothelium-independent vasomotor response was evaluated with administration of an intracoronary (IC) nitroglycerine bolus of 200 μg, immediately before coronary angiography. Finally, intravascular ultrasound (IVUS) assessment was performed. The same protocol was executed at angiographic follow-up.

Assessment of vessel diameter changes. Repeat angiography was performed in all patients after 11.7 ± 2.8 months. Comparing post-procedure and follow-up angiograms, a significant increase of RVD was observed at each analyzed coronary segment (2.0 ± 0.52 mm vs. 2.25 ± 0.50 mm, 1.76 ± 0.49 mm vs. 2.05 ± 0.58 mm, 1.54 ± 0.53 mm vs. 2.04 ± 0.58 mm, respectively, at 5, 20, and 35 mm distal to stent edge; all $p < 0.001$). A higher RVD at follow-up was confirmed by ANCOVA analysis ($p < 0.001$) (Fig. 3). Diabetes, stent type, and distal stent diameter were included in the ANCOVA model as covariates, but only distal stent diameter was related to RVD changes ($p = 0.02$). No differences were observed by stratifying percentage RVD variations according to diabetes status and type of implanted stent (Fig. 4). A significant negative linear correlation was found between vessel diameter measured at the distal stent edge and percentage RVD change at follow-up ($r = -0.5$, $p < 0.001$) (Fig. 5).

Assessment of endothelium-dependent and -independent vasomotion. Assessment of vasomotor tone was carried out in 15 patients, but 1 patient was excluded for the occurrence of restenosis at angiographic follow-up, thus 14 patients, 4 with type 2 diabetes, underwent assessment of endothelium function. Sirolimus-eluting stents were implanted in 8 patients and paclitaxel-eluting stents in the remaining 6 patients. Table 3 reports mean vessel diameter assessed at baseline, at peak pacing, and after IC administration of nitroglycerine at both index and repeat angiography. At index angiography, neither pacing nor nitroglycerine modified vessel diameters (Fig. 6A). In contrast, at follow-up, atrial pacing resulted in significant vasoconstriction (Fig. 6B). Vasoconstriction observed during pacing was similar in the presence or absence of diabetes (−7.2 ± 16.2% vs. −9.3 ± 6.4%, respectively; $p = 0.7$) and with different stent types (−10.4 ± 11.1% vs. −6.4 ± 7.1%, $p = 0.5$ for sirolimus- and paclitaxel-eluting stents, respectively). Of note, vasoconstriction was greater in proximal than in distal segments (−14.1 ± 10.4%, 10.7 ± 11.4%, and −8.7 ± 9.5% at 5 mm, 20 mm, and 35 mm, respectively; $p = 0.001$).

Intracoronary nitroglycerine administration resulted in significant vasodilation in all 3 segments (Fig. 6B).

Assessment of coronary remodeling. Post-procedural and follow-up ICUS was performed in 13 patients; 2 patients were excluded for stent restenosis at follow-up. No differences were found in the EEM cross-sectional areas between index and repeat angiography for segments assessed from 5 to 35 mm distal to the stent (3.62 ± 0.94 mm^2 vs. 3.70 ± 0.85 mm^2, 6.74 ± 3.30 mm^2 vs. 6.70 ± 2.38 mm^2, 6.04 ±

Table 1 Patients Characteristics (N = 87)

Age, yrs	60.3 ± 6.5
Male	81 (93.1)
Hypertension	62 (71.3)
Diabetes	25 (28.7)
Hyperlipidemia	71 (81.6)
Smoking	57 (65.5)
Family history of coronary artery disease	45 (51.7)
Statins	78 (89.6)
ACE inhibitors	69 (79.3)
Beta-blockers	61 (70.1)
Nitrates	49 (56.3)
Calcium antagonist	22 (25.3)

Values are mean ± SD or n (%).
ACE = angiotensin-converting enzyme.

Table 2 Lesions and Procedural Characteristics

CTO culprit artery	
Left anterior descending	31 (31)
Right coronary artery	49 (49)
Left circumflex artery	20 (20)
CTO duration, months	37.2 ± 47.9
Lesion length >40 mm	37 (37)
Moderate/severe calcification	29 (29)
Tortuosity of occluded segment	33 (33)
Blunt stump	53 (53)
Number of stents implanted	2.8 ± 1.4
Length of implanted stent, mm	61.3 ± 27
SES use	51 (51)
PES use	37 (37)
ZES use	12 (12)

Values are n (%) or mean ± SD. Lesions, n = 100.
CTO = chronic total occlusion; PES = paclitaxel-eluting stent(s); SES = sirolimus-eluting stent(s); ZES = zotarolimus-eluting stent(s).

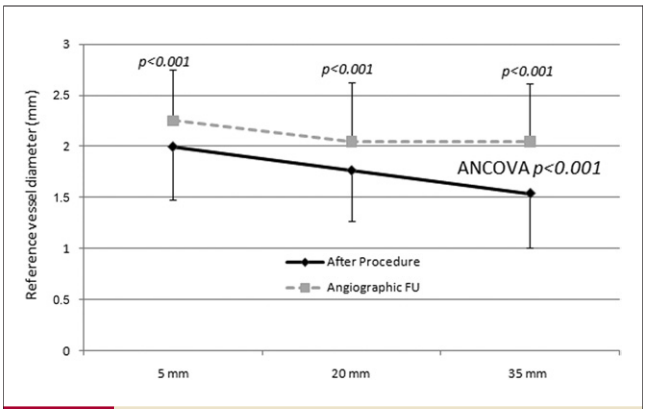

Figure 3 Comparison of RVDs

Comparison of reference vessel diameters (RVDs) at each coronary segment assessed between index procedure **(black line)** and at 9- to 12-month angiographic follow-up (FU) **(gray line)**. ANCOVA = analysis of covariance.

3.09 mm^2 vs. 6.96 ± 2.70 mm^2, 6.7 ± 4.2 mm^2 vs. 7.7 ± 4.2 mm^2, 7.37 ± 3.61 mm^2 vs. 6.78 ± 1.12 mm^2, 8.75 ± 3.75 mm^2 vs. 9.17 ± 3.15mm^2, and 7.40 ± 3.92 mm^2 vs. 7.05 ± 4.10 mm^2, respectively; all p = NS). ANCOVA model confirmed lack of differences (Fig. 7). No significant differences were also observed in lumen diameter, EEM diameter, and intimal hyperplasia (Table 3).

Discussion

To the best of our knowledge, this is the first study to investigate systematically coronary vessels distal to CTO after successful recanalization (11). Coronary CTO represents a unique in vivo pathophysiological model, in which alterations of segments distal to the occlusion are mainly determined by severe shear stress reduction. Indeed, in the distal coronary segments, the reduction of shear stress results in lesser endothelial release of vasodilators, in particular of nitric oxide (12) and greater release of vasoconstrictors, in particular endhotelin-1, thus favoring vasoconstriction (13). Moreover, the endothelium promotes the proliferation of "noncontractile" smooth muscle cells (SMCs) into the intima and structural alteration of extracellular matrix. Vasoconstriction and entrenchment through tissue reorganization have been identified as the 2 consecutive phases of inward arterial remodeling (14). Of note, inward (or constrictive) remodeling and plaque mass represent the most important factors determining the severity of coronary luminal stenosis (15). In this study, immediately after successful CTO recanalization, coronary segments distal to the implanted stent failed to respond to both nitrates (a nonendothelium-dependent stimulus) and atrial pacing (an endothelium-dependent stimulus). At follow-up, distal segments dilated in response to nitrates; accordingly, distal vessel diameter, assessed after nitrates, was considerably greater at follow-up than immediately after drug-eluting stent implantation. The increase of distal vessel diameter was not associated with outward remodeling as assessed by ICUS. Notably, atrial pacing at follow-up was associated with vasoconstriction, thus suggesting persistent endothelium-dependent dysfunction.

The improvement of distal vessel diameter size detected at follow-up after CTO recanalization can theoretically be explained by 3 different mechanisms: 1) impaired endothelium-dependent and/or -independent vasomotion immediately after CTO recanalization (hibernated vascular wall) and/or an intense vasoconstriction that improves at follow-up; 2) positive remodeling; or 3) a combination of both.

Coronary vasomotion at the site of atherosclerotic plaques and in coronary microcirculation reflects an elusive but important link between coronary atherosclerosis and the clinical manifestations of myocardial ischemia (16,17). In our study, the lack of response to atrial pacing suggests impairment of endothelium-dependent regulatory mechanisms. The endothelium plays a key role in the control of vasomotor tone through the nitric oxide–dependent and

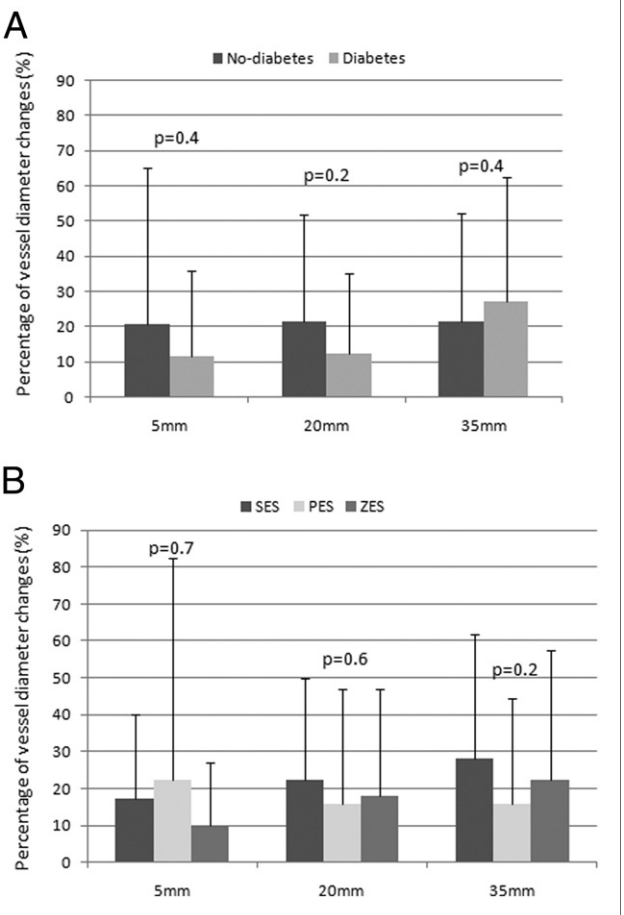

Figure 4 Percentage of Vessel Diameter Changes

Percentage of vessel diameter changes at 9- to 12-month angiographic follow-up according to diabetes status **(A)** and drug-eluting stent type **(B)**. PES = paclitaxel-eluting stent(s); SES = sirolimus-eluting stent(s); ZES = zotarolimus-eluting stent(s).

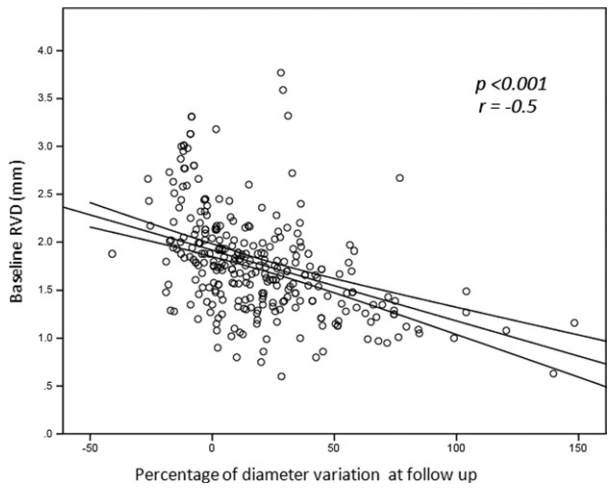

Figure 5 **Linear Correlation Between Baseline Vessel Diameter and Percentage of Diameter Variation**

Scatter dot plot reporting the negative linear correlation between baseline vessel diameter and percentage of diameter variation at follow-up. RVD = reference vessel diameter.

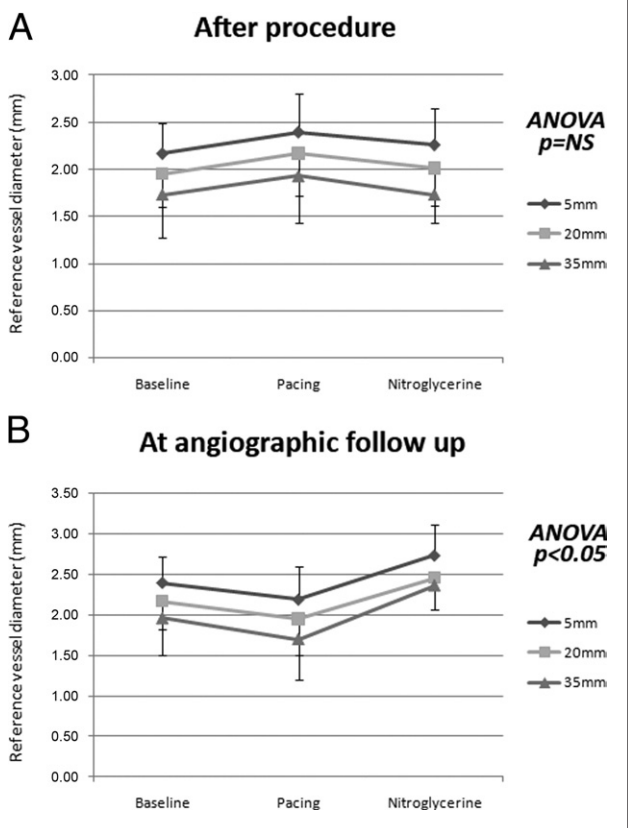

Figure 6 **Results of Endothelium Vasomotion Assessment**

Mean diameter values at baseline, maximal pacing rate, and after intracoronary nitroglycerine administration at each coronary segment assessed, at the time of index procedure **(A)** and at 9- to 12-month angiographic follow-up **(B)**. All the significant p values are reported in Table 3. ANOVA = analysis of variance.

-independent mechanisms. The latter include complex pathways involving diffusible factors and/or the spread of hyperpolarization through myoendothelial gap junction (18). Furthermore, suppression of nitric oxide endothelial production activates tissue transglutaminase, which might induce changes in SMCs, including the assembly of actin filaments, thus controlling SMCs orientation and elongation. As result, these ultrastructural changes might favor the activation of SMCs with a subsequent increase in vasoconstriction (19). Our study's observation that immediately after recanalization distal segments failed to respond to nitrates suggests that a primary alteration of SMCs also is likely to play an important role in this setting. The causes of this primary impairment cannot be deduced by the results of our study. Enhanced Rho-kinase activation leading to SMC contraction might play an important pathogenetic role as shown by Shimokawa and Takeshita (20) in experimental models of coronary spasm as well as in humans. It is worth noting that at follow-up angiography, distal vessels responded to nitrates, thus suggesting recovery of SMC function, whereas they showed vasoconstriction in response to atrial pacing, suggesting persistent endothelial dysfunction. Thus, it would appear that the time course of endothelial and SMC function recovery is different. Persistent endothelial dysfunction might well reflect the persistence of

Table 3 **IVUS Parameters Measured at Each Segment**

	5 mm	10 mm	15 mm	20 mm	25 mm	30 mm	35 mm
After procedure							
Luminal diameter, mm	2.9 ± 1.0	2.5 ± 0.7	2.5 ± 0.7	2.3 ± 0.8	2.5 ± 0.7	2.4 ± 0.9	2.2 ± 0.7
EEM diameter, mm	3.3 ± 0.8	3.0 ± 0.7	2.9 ± 0.7	2.8 ± 0.9	3.0 ± 0.7	3.0 ± 0.7	2.7 ± 0.9
EEM area, mm^2	8.5 ± 1.4	6.8 ± 3.3	6.1 ± 3.1	6.6 ± 4.2	7.4 ± 3.6	8.7 ± 3.7	7.4 ± 3.9
Intimal hyperplasia, mm^2	1.6 ± 0.7	1.4 ± 0.5	0.8 ± 0.3	1.4 ± 1.1	1.4 ± 0.5	1.5 ± 1.2	1.3 ± 0.6
Angiographic follow-up							
Luminal diameter, mm	2.5 ± 0.2	2.4 ± 0.5	2.4 ± 0.5	2.4 ± 0.6	2.7 ± 0.3	3.0 ± 0.8	2.7 ± 0.9
EEM diameter, mm	3.1 ± 0.3	2.9 ± 0.6	2.9 ± 0.6	2.8 ± 0.7	3.2 ± 0.1	3.5 ± 0.5	3.2 ± 0.6
EEM area, mm^2	7.6 ± 0.8	6.7 ± 2.4	7.7 ± 2.7	7.7 ± 3.2	7.8 ± 1.1	9.2 ± 3.1	7.1 ± 4.1
Intimal hyperplasia, mm^2	2.8 ± 1.7	2.1 ± 1.5	2.1 ± 1.8	1.7 ± 1.4	3.2 ± 1.6	2.1 ± 1.4	2.0 ± 1.1

Values are mean ± SD. All differences are not significant.
EEM= external elastic membrane.

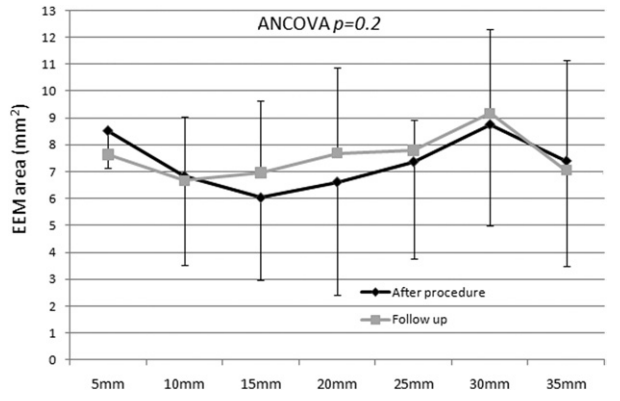

Figure 7 **EEM CSAs**

Comparison of elastic external membrane (EEM) cross-sectional area (CSA) at each coronary segment assessed between index procedures **(black line)** and at 9- to 12-month angiographic follow up **(gray line)**. ANCOVA = analysis of covariance.

risk factors, whereas the early, reversible alteration of SMC function might be more strictly related to the extreme reduction of shear stress associated with CTO. It is interesting to note that administration of iodinated contrast media have complex vasomotor effects especially in CTO PCI procedures where large amounts of contrast are used (21). Similarly, aggressive guidewire manipulation can determine an intense coronary vasoconstriction, which could be a reasonable factor of vessel diameter changes seen at late follow-up.

Notably, diabetes and stent type did not influence vessel diameter changes observed at follow-up. Conversely, the distal stent diameter, and thus the coronary segment distal to it, yielded a significant effect on diameter improvement. This finding might be related to the well-known association between shear stress and vessel diameter (18). Accordingly, a larger vessel diameter in the distal stented segment might increase shear stress, thus facilitating the recovery of endothelial vasodilator function at follow-up. The observation of diverging patterns of vessel diameters in proximal and distal coronary segments in response to nitrates could be explained by the enhanced reactivity of distal epicardial vessels to vasodilators, as shown previously by a study executed in patients with stable angina and obstructive coronary atherosclerosis (22). This phenomenon could be the reason for the observed inverse correlation between baseline RVD and the percentage of vessel diameter changes.

In our study, ICUS shows that positive remodeling does not account for the increase of distal vessel diameter observed at follow-up angiography. Remodeling is a process that determines a change of cross-sectional vessel area in response to atherosclerosis (23). Although the initial response to the formation of an atherosclerotic plaque is an outward positive remodeling, further progression of the atherosclerotic plaque can lead to inward remodeling usually associated with stable plaques, lack of remodeling, or further positive remodeling possibly associated with unstable plaques (24,25). The reasons for these different evolutions are still largely unknown, although it is widely accepted that endothelial cells able to sense changes in shear stress play a critical role. In our study, we did not measure shear stress. It is likely, however, that recanalization of a CTO resulted in a considerable increase in shear stress. Thus, the lack of positive remodeling in our study seems to cast some shadow on the notion that shear stress is a key factor in determining remodeling. It might well be that shear stress is more important in determining remodeling in the presence of atherosclerotic plaques than in segments distal to CTO, which did not necessarily exhibit a large atherosclerotic burden.

Study limitations. This study presents some limitations including the small number of patients, in particular in the substudies on the assessment of endothelial dysfunction and of arterial remodeling. The complexity of CTO recanalization makes it difficult to prolong the procedure with additional pathophysiological studies. Thus, a bias in our study might have been the selection of patients undergoing a faster CTO revascularization. Furthermore, the small number of patients precluded the possibility to carry out an extensive multivariate analysis of the predictors of endothelial dysfunction, SMC dysfunction, and remodeling. The absence of a reasonable standardized timing for the administration of nitroglycerine at the end of the procedure represents another study limitation. Finally, the lack of an appropriate control group of patients treated with long segment stents for not chronically occluded vessels does not permit us to clarify if distal diameter changes are or are not unique to CTO lesions.

Conclusions

Recanalization of CTO is followed by a reversible hibernation of vascular wall at distal coronary segments that are resistant to conventional doses of intracoronary nitrates. The vascular wall dysfunction improves over time, resulting in a larger lumen at follow-up; the improvement appears to be related to recovery of SMC function rather than to improvement of endothelial function or to positive remodeling. The clinical implications of our study are obvious. Indeed, our results indicate that, the size of distal coronary vessel immediately after CTO recanalization might lead to an underestimation of stent size even after intracoronary administration of conventional doses of nitrate. This severe impairment of vasomotor tone after CTO reopening suggests ICUS assessment for the selection of the correct stent size and if the landing zone is of paramount importance, not withstanding that aggressive post-dilation might increase procedural complications in the complex PCI. Our study also shed some light on the complex mechanisms responsible for vasomotion alterations and remodeling suggesting that in this setting: 1) endothelial and smooth muscle

dysfunction have different time courses and, therefore, probably different mechanisms; and 2) changes in shear stress are not the only determinants of remodeling.

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Key Words: chronic total occlusion ■ endothelial ■ percutaneous coronary intervention ■ vasomotion.