Percutaneous Treatment of Chronic Total Coronary Occlusions Improves Regional Hyperemic Myocardial Blood Flow and Contractility

Insights From Quantitative Cardiovascular Magnetic Resonance Imaging

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Objectives We sought to investigate temporal changes in contractility and hyperemic and resting myocardial blood flow (MBF) in dependent and remote myocardium after percutaneous coronary intervention (PCI) of chronic total occlusions (CTOs) by using cardiovascular magnetic resonance (CMR) imaging.

Background Data about the physiological consequences of revascularization of CTOs are limited. The use of CMR allows investigation of the regional effects of revascularization on MBF and left ventricular contractility.

Methods We prospectively recruited 3 patient groups: 17 patients scheduled for CTO PCI, 17 scheduled for PCI of a stenosed but nonoccluded coronary artery (non-CTO), and 6 patients with CTO who were not scheduled for revascularization. All patients undergoing PCI underwent CMR imaging ≤24 h before PCI, with repeat CMR imaging 24 h and 6 months after PCI. Each CMR scan consisted of cine, perfusion, and delayed enhancement imaging. Regional hyperemic and resting MBF, wall thickening, and transmural extent of infarction were calculated.

Results In both intervention groups, hyperemic MBF in treated segments increased 24 h after PCI compared with baseline: CTO group, 2.1 ± 0.2 ml/min/g versus 1.4 ± 0.2 ml/min/g (p < 0.01); non-CTO group, 2.5 ± 0.2 ml/min/g versus 1.6 ± 0.2 ml/min/g (p < 0.01). This improvement persisted 6 months after PCI (p ≤ 0.01 for both groups). Contractility in treated segments was improved at 24 h and 6 months after CTO PCI but only at 6 months after non-CTO PCI. In both intervention groups, treated segments no longer had reduced MBF or contractility compared with remote segments. In patients with untreated CTO segments, MBF and wall thickening did not improve at follow-up.

Conclusions Successful CTO PCI increases hyperemic MBF as early as 24 h after the procedure, with a greater and earlier improvement in regional contractility than after non-CTO PCI, despite a greater likelihood of irreversible injury in CTO segments. (J Am Coll Cardiol Intv 2008;1:44–53) © 2008 by the American College of Cardiology Foundation
Chronic total coronary occlusions (CTOs) remain a major challenge in percutaneous coronary intervention (PCI). New procedural technologies and techniques, including the retrograde approach, have improved success rates (1) and heralded increased interest in strategic approaches. Concomitantly, the use of drug-eluting stents has reduced restenosis and reocclusion (2,3) and the need for revascularization (4). Surprisingly, data about the physiological consequences of successful opening of a CTO are limited and heterogeneous. Studies assessing left ventricular (LV) ischemia in the territory subtended by the occluded vessel or in remote myocardium. Changes observed in patients after CTO PCI were compared with changes in patients with angina undergoing PCI of nontotally occluded coronaries and CTO patients managed medically. We hypothesized that hyperemic MBF in the territory subtended by the CTO would increase after successful PCI and result in improved regional wall thickening. Furthermore, we anticipated that observed changes in patients undergoing CTO PCI might be greater in magnitude than those occurring after treatment of nontotally occluded vessels.

Methods

The Oxford Research Ethics Committee approved this study. All participants gave written informed consent.

Patient population. A total of 17 consecutive patients with angina and/or objective evidence of inducible myocardial ischemia in the relevant territory who were scheduled for PCI of a native coronary CTO were recruited prospectively. Stone et al. (21) defined CTO as a lesion compromise resulting in either Thrombolysis In Myocardial Infarction (TIMI) flow grade 0 or 1, with a likely duration of >3 months. Two other groups of patients were recruited prospectively: 17 consecutive patients with angina scheduled for PCI of a single stenosed but not occluded coronary artery and 6 consecutive patients with a documented CTO who were managed with medical therapy and were not scheduled for revascularization. Predetermined exclusion criteria were the standard contraindications to magnetic resonance imaging (MRI).

CMR imaging time points. All patients undergoing PCI underwent an initial CMR scan <24 h before PCI, with repeat imaging 24 h and 6 months later. Each scan consisted of cine, perfusion, and delayed enhancement imaging. Patients not scheduled for revascularization were scanned twice, 6 months apart, using the same imaging protocol. A clinical review was performed at each visit.

CMR protocol. Patients were asked to abstain from all competitive adenosine antagonists for at least 24 h before each CMR scan with a 1.5-T clinical MRI scanner (Siemens Sonata, Erlangen, Germany). Steady-state free-precession cine images (repetition time 3.0 ms; echo time 1.5 ms; flip angle 60°) were acquired in long- and short-axis views covering the entire LV (22).

After an adenosine infusion (140 µg/kg/min) lasting 4 min (less if angina was provoked), a gadolinium-based contrast agent (Gadodiamide, Omniscan, GE Healthcare, Milwaukee, Wisconsin) was administered intravenously at a dose of 0.04 mmol/kg body weight (injection rate, 6 ml/s), followed by a saline flush. Perfusion imaging (repetition time 2.2 ms; echo time 1.0 ms; flip angle 18°) was performed every cardiac cycle during first pass, using a T1-weighted fast (spoiled) gradient echo sequence in 3 short-axis imaging planes representing the basal, midventricular, and apical myocardial segments (23). The rest perfusion study was started >15 min after discontinuation of adenosine.

After rest perfusion imaging, a further dose of 0.045 mmol/kg gadodiamide was administered, giving a total dose of 0.125 mmol/kg before delayed enhancement imaging, as previously described (24,25).

PCI protocol: interventional strategy. All patients were preloaded with aspirin and clopidogrel >24 h before the procedure and received intravenous heparin, either 5,000 U
or 70 U/kg at initiation. We performed the CTO procedures by using the antegrade approach. Collaterals were graded according to the angiographic classification proposed by Werner et al. (26). Contralateral injection to define the distal vessel was used when collateral flow was substantial. Predominantly polymer-coated wires were used, including the Cross-it 150 (Guidant, Boston Scientific, Natick, Massachusetts) and the Shinobi (Cordis, Johnson & Johnson, Miami Lakes, Florida). Stents were deployed at high pressure (minimum 12 atm). Troponin I was routinely measured before and 12 h after the procedure in all patients. Patients receiving drug-eluting stents were prescribed aspirin indefinitely and clopidogrel for at least 6 months.

**CMR post-processing.** Data were analyzed, blinded to the patient identity, clinical status, and coronary angiogram. For regional analysis, all cine, perfusion, and delayed enhancement images were matched with the use of anatomical landmarks. The LV was divided according to the American Heart Association segmentation model (27), and the coronary angiogram was used to define affected myocardial segments. Because the most apical segment can be affected by partial volume effects, it was excluded from the analysis. We defined “CTO segments” as those myocardial segments subtended by the CTO. “Remote segments” were defined as those myocardial segments that satisfied all of the following criteria: not subtended by a coronary stenosis of ≥50%, not revascularized, and free of hyperenhancement (HE) on delayed enhancement imaging.

Global LV function, end-diastolic, end-systolic, and stroke volume indexes (ml/m²), and ejection fraction (%) were determined by planimetry of the short-axis cine images. For regional wall thickening assessment, cine MRI was evaluated quantitatively with the use of automated computer software (QMass, version 6.2.1, Medis, Medical Imaging Solutions, Leiden, the Netherlands) to determine systolic wall thickening (%) by a modified centerline method (28). Wall thickening was calculated by: (end-systolic wall thickness – end-diastolic wall thickness)/end-diastolic wall thickness × 100%.

Quantitative perfusion analysis was performed as previously described (11). Absolute MBF was determined for each myocardial segment in ml/min/g by deconvolution of signal intensity curves, with an arterial input function measured in the LV blood pool (19), taking into account the delay in the arrival of contrast (20,29). Values for resting MBF were divided by the respective rate-pressure product/10,000 (30). In the study by Wang et al. (31), hyperemic MBF in adults with no coronary artery calcification was $3.31 \pm 0.77$ ml/min/g (95% confidence interval $1.77$ to $4.85$ ml/min/g). Calculated values for MBF exceeding 5 ml/min/g were excluded from the analysis.

The amount of delayed HE in the LV was quantified using dedicated software (Matlab, version 6.5, MathWorks, Natick, Massachusetts). Hyperenhanced pixels were defined (32), and computer-assisted planimetry was used to delineate the area of HE (25). Transmural extent of infarction (TEI) in each myocardial segment was calculated by dividing the hyperenhanced area by the total area of that segment and scored using a 5-point scoring system: no HE, grade 0; 1% to 25% HE, grade 1; 26% to 50% HE, grade 2; 51% to 75% HE, grade 3; and 76% to 100% HE, grade 4. Any myocardial segment with TEI <25% was considered viable (18,32).

**Statistical analysis.** Statistical analysis was performed with SPSS (version 14.0, SPSS Inc., Chicago, Illinois) and the R software (R: A language and environment for statistical computing, R Foundation for Statistical Computing, Vienna, Austria), using the library for linear mixed effects models developed by Pinheiro and Bates (33). Deviation from normality was tested with the Shapiro-Wilk test. Continuous variables are presented as mean ± standard error of the mean when normally distributed, or median (interquartile range) when not normally distributed. Categorical variables were compared with chi-square statistics.

Linear mixed effects models were used to analyze: 1) changes in hyperemic MBF, corrected resting MBF, and wall thickening in follow-up examinations, relative to baseline; 2) the differences in these variables at any time point between segments subtended by a stenosed coronary artery and remote segments; and 3) the differences between patient groups. The 3 CMR examination times (baseline, 24 h, and 6 months) and whether myocardial segments were subtended by a stenosed vessel or remote to the stenosis were encoded as categorical variables in the fixed effects specification, allowing for an interaction between examination time and myocardial segment location. The presence and transmurality of HE was graded on the aforementioned 5-point scale, and polynomial contrasts for HE grade were used to test whether MBF and wall thickening changed with HE grade.

The random effects were first modeled as a random intercept by subject, with uniform correlation structure for measurements within each patient. Random intercepts led to a significantly better fit than models without random effects ($p < 0.0001$ for log-likelihood ratio test). To determine more complex correlation structures for the repeated measurements, we considered nested models to fit the same data and then used a log-likelihood ratio test to determine whether added terms in the random effects specification fit the data significantly better. Nesting of examination time within subjects significantly improved the fit to the data. Relaxing the assumption of compound symmetry for the correlation structure to allow for a general positive–definite matrix did not improve the fits. Tests were 2-sided and significance was accepted at $p < 0.05$.

**Results**

**Patient population.** Baseline characteristics are shown in Table 1. Participants were predominantly male. There were no significant differences in clinical risk factor profile or
Angiography and intervention. Visible collaterals (collateral connection grade >0 [26]) were present more often in patients with CTO lesions, compared with those with non-CTO lesions (74% vs. 0%; p < 0.01) (Table 2). The operator successfully opened the CTO in 15 of 17 (88%) cases, and all non-CTO lesions were treated successfully. Two-vessel PCI was performed in 1 patient who was originally scheduled for PCI of a single stenosed but not occluded coronary artery. Drug-eluting stents were used in 13 of 15 successful CTO cases and 9 of 17 non-CTO PCI cases. There was no difference in the occurrence of post-procedural troponin I elevation (24%) or new myocardial HE (18%) between the 2 intervention groups.

**Effect of intervention on morbidity and mortality.** A significantly greater proportion of patients undergoing CTO PCI had less angina at 6 months, compared with those managed medically (76% vs. 17%; p < 0.05) (Table 1). No patient in any of the groups had suffered death, myocardial infarction, or unstable angina by follow-up (mean duration after first scan, 17 ± 4 months). One patient who had failed CTO PCI underwent coronary bypass surgery a few months after the 6-month CMR scan, and 2 patients with CTO in the medically treated group were later referred for revascularization.

**Effect of intervention on myocardial blood flow. PATIENTS UNDERGOING CTO PCI.** At baseline, resting MBF was lower in CTO segments compared with remote segments (1.2 ± 0.1 ml/min/g/[mm Hg beats/min] vs. 1.3 ± 0.1 ml/min/g/[mm Hg beats/min]; p < 0.05). Similarly, baseline hyperemic MBF was reduced in CTO segments compared with remote segments (1.4 ± 0.2 ml/min/g vs. 2.4 ± 0.2 ml/min/g; p < 0.01). Both resting and hyperemic MBF in CTO territories decreased significantly with HE of adenosine at follow-up (n = 3). All images were of sufficient quality for analysis, and no images were excluded.

### Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Medication</th>
<th>CTO PCI (n = 17)</th>
<th>Non-CTO PCI (n = 17)</th>
<th>CTO But No PCI (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>14 (82%)</td>
<td>14 (82%)</td>
<td>5 (83%)</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>65 ± 3</td>
<td>63 ± 3</td>
<td>61 ± 8</td>
</tr>
<tr>
<td>CCS class at baseline (0/1/2/3/4)</td>
<td>1/2/7/2/5</td>
<td>3/5/8/1/0</td>
<td>2/1/3/0/0</td>
</tr>
<tr>
<td>CCS class at 6 months follow-up</td>
<td>5/8/3/1/0</td>
<td>11/2/4/0/0</td>
<td>2/1/1/2/0</td>
</tr>
<tr>
<td>Improvement in CCS class at 6-month follow-up</td>
<td>13 (76%)</td>
<td>11 (65%)</td>
<td>1 (17%)</td>
</tr>
</tbody>
</table>

### Table 2. Coronary Angiography and Intervention

<table>
<thead>
<tr>
<th>Total number of tackled lesions</th>
<th>CTO PCI (n = 17)</th>
<th>Non-CTO PCI (n = 17)</th>
<th>CTO But No PCI (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of successful procedures</td>
<td>15 (88%)</td>
<td>17 (100%)</td>
<td>N/A</td>
</tr>
<tr>
<td>LAD lesion</td>
<td>5 (29%)</td>
<td>12 (67%)</td>
<td>1 (13%)</td>
</tr>
<tr>
<td>LCX lesion</td>
<td>4 (24%)</td>
<td>1 (6%)</td>
<td>2 (25%)</td>
</tr>
<tr>
<td>RCA lesion</td>
<td>8 (47%)</td>
<td>5 (28%)</td>
<td>5 (63%)</td>
</tr>
<tr>
<td>Collateral connection grade</td>
<td>6/9/2</td>
<td>n/a</td>
<td>0/4/2</td>
</tr>
<tr>
<td>Troponin elevation after PCI</td>
<td>4 (24%)</td>
<td>4 (24%)</td>
<td>N/A</td>
</tr>
<tr>
<td>New hyperenhancement after PCI</td>
<td>3 (18%)</td>
<td>3 (18%)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Values are presented as number (%) or mean ± standard error of the mean.
ACE = angiotensin-converting enzyme; CCS = Canadian Cardiovascular Society; CTO = chronic total occlusion; HE = hyperenhancement; MI = myocardial infarction; PCI = percutaneous coronary intervention.

medication prescribed between the 3 patient groups. No patient had had previous coronary artery bypass surgery. Across all 3 groups, in 6 of 27 (22%) patients who gave no history of previous myocardial infarction, the initial CMR scan detected myocardial HE. At baseline, the odds ratio for HE in a myocardial segment was greatest in medically managed patients (1.6; p = 0.1), followed by patients scheduled for CTO PCI (1.2; p < 0.01) and lowest in patients scheduled for non-CTO PCI (1.1;877; p < 0.01). The odds of HE in a myocardial segment were significantly lower in patients scheduled for non-CTO PCI (1.2; p < 0.01). Both resting and hyperemic MBF were reduced in CTO segments compared with remote segments (1.4 ± 0.2 ml/min/g vs. 2.4 ± 0.2 ml/min/g; p < 0.01). Both resting and hyperemic MBF in CTO territories decreased significantly with HE of adenosine at follow-up (n = 3). All images were of sufficient quality for analysis, and no images were excluded.
grade, with a decrease of 0.6 ± 0.1 ml/min/g/(mm Hg beats/min/10^4) for each linear increment in HE grade for resting MBF (p < 0.01) and a decrease of 0.7 ± 0.2 ml/min/g for each linear increment in HE grade for hyperemic MBF (p < 0.01 for linear trend) (Fig. 1).

Compared with baseline, resting MBF did not change significantly in treated segments after PCI. In contrast, 24 h after PCI, hyperemic MBF in treated segments increased compared with baseline (2.1 ± 0.2 ml/min/g vs. 1.4 ± 0.2 ml/min/g; p < 0.01) (Fig. 1). This improvement in hyperemic MBF persisted at 6 months after PCI (2.1 ± 0.2 ml/min/g vs. 1.4 ± 0.2 ml/min/g; p < 0.01) (Fig. 2). These increases in hyperemic MBF at 24 h and 6 months remained significant after simultaneous adjustment of hyperemic MBF by HE grade. After successful CTO PCI, there was no longer reduced hyperemic or resting MBF in the treated segments, compared with remote segments, at 24 h and 6 months after PCI. In remote segments, there was no significant change in either hyperemic or resting MBF at 24 h and 6 months after PCI when compared with baseline.

**PATIENTS UNDERGOING PCI OF NON-CTO LESIONS.** At baseline, resting MBF in the culprit territories was lower than in remote segments (1.2 ± 0.1 ml/min/g/[mm Hg beats/min/10^4] vs. 1.3 ± 0.1 ml/min/g/[mm Hg beats/min/10^4]; p < 0.01). Hyperemic MBF was also lower in territories subtended by a stenosis compared with remote segments (1.6 ± 0.2 ml/min/g vs. 2.2 ± 0.2 ml/min/g; p < 0.01).

Resting MBF did not change significantly in treated segments after PCI, relative to baseline. In contrast, 24 h after PCI, hyperemic MBF in treated segments increased compared with baseline (2.5 ± 0.2 ml/min/g vs. 1.6 ± 0.2 ml/min/g; p < 0.01). As in patients who underwent CTO PCI, this improvement in hyperemic MBF persisted at 6 months after PCI (2.4 ± 0.2 ml/min/g vs. 1.6 ± 0.2 ml/min/g; p < 0.01). These increases in hyperemic MBF at 24 h and 6 months remained significant after simultaneous adjustment of hyperemic MBF by HE grade. Both 24 h and 6 months after PCI, the differences in hyperemic and resting MBF between treated segments and remote seg-
ments were no longer significant. The improvement in hyperemic MBF in treated segments was not significantly different between patients undergoing CTO PCI or PCI of non-CTO lesions. This remained true after adjustment by baseline hyperemic MBF. As in patients who underwent CTO PCI in remote segments, there was no significant change in either hyperemic or resting MBF at 24 h and 6 months after PCI compared with baseline.

**PATIENTS WITH MEDICALLY MANAGED CTO.** At baseline, CTO segments had significantly worse resting MBF compared with remote segments (1.2 ± 0.2 ml/min/g/[mm Hg beats/min/10^4] vs. 1.4 ± 0.2 ml/min/g/[mm Hg beats/min/10^4]; p < 0.01). Hyperemic MBF was also lower in CTO segments compared with remote segments (0.9 ± 0.2 ml/min/g vs. 1.6 ± 0.2 ml/min/g; p < 0.01). At baseline, there was no significant difference between hyperemic or resting MBF in CTO segments in this patient group and hyperemic or resting MBF in segments subtended by a stenosis to be tackled in the 2 intervention groups.

Resting MBF did not improve in either CTO segments or remote segments at 6-month follow-up. CTO segments continued to have lower resting MBF than remote segments at 6-month follow-up (0.8 ± 0.2 ml/min/g/[mm Hg beats/min/10^4] vs. 1.0 ± 0.2 ml/min/g/[mm Hg beats/min/10^4]; p < 0.01).

There was no improvement in hyperemic MBF at 6-month follow-up, compared with baseline, in CTO segments or remote segments (Fig. 3), which remained true after simultaneous adjustment of hyperemic MBF by HE grade. We found that CTO segments continued to have lower hyperemic MBF than remote segments at 6-month follow-up (0.9 ± 0.2 ml/min/g vs. 1.4 ± 0.3 ml/min/g; p < 0.01). In addition, CTO segments in this patient group had significantly lower hyperemic MBF compared with treated CTO segments in the intervention group (0.9 ± 0.2 ml/min/g vs. 2.1 ± 0.2 ml/min/g; p < 0.01).

**Effect of intervention on regional wall thickening. PATIENTS UNDERGOING CTO PCI.** In patients scheduled for CTO PCI, CTO segments had significantly worse wall thickening at baseline compared with remote segments (64 ± 5% vs. 82 ± 6%; p < 0.01). This remained true after simultaneous adjustment of wall thickening by HE grade. Absolute wall thickening decreased by 38 ± 7% for each linear increment of HE grade (p < 0.01). After successful CTO PCI, compared with baseline, wall thickening in treated segments improved at 24 h (73 ± 4% vs. 64 ± 5%; p = 0.06) and 6 months (77 ± 5% vs. 64 ± 5%; p < 0.05) (Fig. 4). These improvements at 24 h and 6 months were significant after simultaneous adjustment of wall thickening by HE grade (p < 0.05 and < 0.01, respectively).
Both 24 h and 6 months after PCI, the differences in wall thickening between treated segments and remote segments were no longer significant.

An improvement in absolute wall thickening of $\frac{11}{10} \%$ was less likely in segments with greater TEI before PCI ($p < 0.01$ for trend). The absolute improvement in wall thickening between baseline and 24 h after PCI was $19 \frac{9}{10} \%$ ($p < 0.05$) for each increment of HE grade at baseline, with simultaneous adjustment by wall thickening at baseline. Six months after successful CTO PCI, a significantly greater proportion of viable segments had an absolute improvement in wall thickening of $\frac{11}{10} \%$, compared with nonviable segments, that is, 46 of 70 (66%) versus 5 of 15 (27%); $p < 0.05$.

**PATIENTS UNDERGOING PCI OF NON-CTO LESIONS.** In patients scheduled for non-CTO PCI, there was no significant difference in wall thickening between territories subtended by a stenosis and remote segments at any of the 3 examination time points. In these patients, treated segments had higher wall thickening only at 6 months, relative to baseline ($73 \pm 3\%$ vs. $66 \pm 4\%$; $p < 0.05$).

**PATIENTS WITH MEDICALLY-MANAGED CTO.** At baseline, CTO segments in this patient group had significantly worse wall thickening compared with remote segments ($42 \pm 7\%$ vs. $68 \pm 7\%; p < 0.01$) and CTO segments in those scheduled for PCI ($42 \pm 7\%$ vs. $64 \pm 5\%; p < 0.05$). At 6-month follow-up, wall thickening of CTO segments did not change relative to baseline, and CTO segments in this patient group continued to have significantly worse wall thickening compared with remote segments ($35 \pm 7\%$ vs. $61 \pm 7\%; p < 0.01$) and compared with treated CTO segments in the intervention group ($35 \pm 7\%$ vs. $77 \pm 5\%; p < 0.01$).

**REMOTE SEGMENTS.** There was no significant difference in wall thickening of remote segments among all 3 patient groups at any time point and no significant change in wall thickening in remote segments at follow-up in any of the patient groups.

**Ventricular volumes and function.** At all imaging time points, there were no significant differences in LV end-diastolic, end-systolic, or stroke volume indexes or ejection fraction between the CTO PCI group and the other 2 patient groups. Ejection fraction was well preserved in all groups. There was no significant change in LV volume indexes or ejection fraction over the 6 months across all 3 patient groups.

## Discussion

This study demonstrates that successful PCI of CTO significantly increases hyperemic MBF as early as 24 h after...
procedure, an effect that is maintained at 6 months. Furthermore, the magnitude of this improvement in hyperemic MBF is similar to that observed after PCI of nontotally occluded arteries. Regional wall contractility in the territory subtended by the CTO returns towards normal within the same time frame, with no difference between CTO segments and remote segments at 24 h after PCI. In contrast, although successful PCI of nontotally occluded arteries also significantly increases hyperemic MBF 24 h and 6 months after procedure, regional contractility in treated segments only improved significantly at 6 months. These clear benefits after CTO PCI might be considered surprising because, in this study, patients with CTO were more likely to have irreversibly injured myocardium, compared with patients with nontotally occluded arteries, and this may have limited benefit from PCI.

Recanalization of CTOs can relieve angina and reduce the 12-month incidence of cardiac death or myocardial infarction and the need for coronary artery bypass surgery (34). Similarly, patients in this current study undergoing CTO PCI had less anginal symptoms at 6 months compared with those managed medically. In clinical practice, attempting to define which patients with CTO may benefit from revascularization is complex and, when the patient has no symptoms, medical management is the usual strategy (35). In our study, there appear to be almost immediate physiological benefits from successful PCI in patients with CTO and angina. For comparison, our study also documented changes over time in a small number of medically managed patients with CTO, as well as patients undergoing non-CTO PCI. Compared with segments in patients who subsequently underwent revascularization, CTO segments in medically managed patients had significantly lower hyperemic and resting MBF and wall thickening at 6-months follow-up. Medically managed patients were more likely to have extensive myocardial necrosis in the dependent territory at

### Figure 4. Changes in Wall Thickening in Segments Subtended by a Stenosis and Remote Segments in the 3 Patient Groups

Each myocardial segment is represented by a circle at each time point, with larger circles denoting greater TEI. Mean ± standard error of the mean are displayed for each time point. Wall thickening in territories subtended by a CTO decreased significantly with increasing TEI. At baseline, CTO segments had worse contractility than remote segments. After successful CTO PCI, wall thickening in treated segments improved, such that, after simultaneous adjustment of wall thickening by TEI, the differences between treated segments and remote segments were no longer significant at 24 and 6 months after PCI. Improvement in contractility was less likely in segments with greater TEI before PCI. In patients scheduled for non-CTO PCI, wall thickening improved only at 6 months, relative to baseline. There was no change in wall thickening in untreated CTO segments or remote segments. Untreated CTO segments had significantly worse wall thickening than treated CTO segments at 6-month follow-up. *p < 0.01 for comparison with baseline; †p < 0.01 for comparison between stenosed and remote segments at the same time point; ‡p < 0.05 for comparison with CTO PCI group at the same time point. Abbreviations as in Figure 1.
baseline, which probably accounts for their relative lack of anginal symptoms.

Studies using LV angiography to quantify the impact of successful CTO revascularization on LV function have been inconclusive (5–8). We demonstrated improvement in wall thickening confined to revascularized CTO segments and no change in overall ejection fraction after successful CTO PCI, supporting the findings of other recent studies (8,18). However, unlike Baks et al. (18), we found no significant change in volume indexes after PCI, which may reflect a difference in the definition of a CTO occlusion of >6 weeks in the study by Baks et al. (18) and >3 months in Stone et al. (21), with consequent disparity between the respective study populations. It might be that there is greater potential for advantageous ventricular remodeling after successful treatment of more recent coronary occlusions.

Baks et al. (18) demonstrated that the TEI present before PCI predicted the likelihood of later improvement in absolute wall thickening, whereas in patients with a CTO, Muehling et al. (36) found an inverse correlation between TEI and regional wall thickening, as well as both hyperemic and resting MBF at baseline. Our study confirmed the findings of both studies and, furthermore, is the first to quantify and relate changes in myocardial thickening, blood flow, and irreversible injury before and after CTO PCI.

Increased myocardial perfusion reserve index (MPRI) after successful PCI has been demonstrated in a heterogeneous group of patients (37). In this study, semiquantitative measurements of the upslope of signal intensity-time curves were used to derive MPRI, a ratio of hyperemic to resting parameters. This approach has fundamental limitations. For instance, MPRI could be increased by an elevation in hyperemic MBF, a decrease in resting MBF, or both, which cannot be accurately determined by semiquantitative assessment. Furthermore, small alterations in resting perfusion indexes can have a disproportionate effect on MPRI. The model-independent deconvolution method used in our study to quantify MBF allowed us to examine the separate effects of PCI on hyperemic MBF and resting MBF.

This study shows that the improvement in MPRI after successful PCI is caused solely by significant improvements in hyperemic MBF, because resting MBF did not change in either of the 2 intervention groups. In the CTO PCI cohort, this presumably reflects the efficacy of collateral circulation. Failure of this collateral circulation to respond to increased workload is the mechanism of angina. We did not detect perfusion changes at rest or during stress in remote adjoining segments of myocardium, reflecting the ability of a healthy vessel to maintain perfusion to its primarily dependent myocardium.

**Study limitations.** This study was observational and nonrandomized, and there was inevitable bias in selecting which patients should undergo intervention. The sample size of the medically managed group was small, despite the fact that all patients eligible for this group were recruited during the study period.

**Conclusions**

We demonstrate that successful CTO PCI results in a significant, early increase in hyperemic MBF, with a greater and earlier improvement in wall thickening than after PCI of nontotally occluded arteries, despite a greater likelihood of irreversible injury in CTO segments.

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