Frequency of Myocardial Infarction and Its Relationship to Angiographic Collateral Flow in Territories Supplied by Chronically Occluded Coronary Arteries

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Background—Despite complete interruption of antegrade coronary artery flow in the setting of a chronic total occlusion (CTO), clinical recognition of myocardial infarction is often challenging. Using cardiac MRI, we investigated the frequency and extent of myocardial infarction in patients with CTO, and assessed their relationship with regional systolic function and the extent of angiographic collateral flow.

Methods and Results—We included 170 consecutive patients (median age, 62 years) with angiographically documented CTO. Regional late gadolinium enhancement and wall motion score index were assessed by cardiac MRI with the use of a 17-segment model. Angiographic collateral flow was assessed by the collateral connection grade and the Rentrop score. Evidence of previous myocardial infarction was found in 25% of patients by ECG Q waves, in 69% by regional wall motion abnormality, and in 86% of patients by late gadolinium enhancement. Increased angiographic collateral flow was associated with a lower frequency of Q waves on ECG, and a lower regional wall motion score index, late gadolinium enhancement volume (%), and degree of late gadolinium enhancement transmurality (all P<0.001), as well.

Conclusions—The frequency of myocardial infarction in territories subtended by CTO is significantly higher than previously recognized. The degree of myocardial injury downstream epicardial CTO is inversely correlated with the degree of angiographic collaterals. (Circulation. 2013;127:703-709.)

Key Words: cardiac MRI ■ chronic total occlusion ■ coronary collateral vessel

Contrast enhanced cardiac MRI (CMR) enables direct visualization of infarcted myocardium and has become the gold standard for quantification of myocardial infarct size.13 We hypothesized that the prevalence of MI in patients with CTO is higher than previously known.9–12 We investigated the frequency and extent of MI measured by CMR in patients with CTO. The results were compared with ECG, left ventricular (LV) regional wall motion, and the extent of angiographic collateral flow.

Methods

Patients

From January 2007 to December 2011, we prospectively screened 217 consecutive patients who had undergone clinically indicated coronary angiography and were found to have a CTO in at least 1 major epicardial coronary artery. Patients with >50% stenosis in the left main artery were excluded, as were those with acute coronary syndrome within 90 days of enrollment, decompensated heart failure, or contraindications to CMR. Patients with previous revascularization (n=38) were also excluded because of the potential confounding of periprocedural myocardial injury.13 CMR was performed within 2 weeks of coronary angiography (median interval period of 2 days). Finally, patients with potential nonischemic causes of myocardial injury (n=6) and poor CMR images (n=3) were also excluded. Thus,
the remaining 170 patients made up the study cohort (Figure 1). The institutional review board committee approved the study protocol, and all patients provided written informed consent to participate in the study.

**Clinical History and Electrocardiography**

The presence of previous MI on 12-lead ECG was defined as the presence of pathological Q waves involving ≥2 contiguous leads according to the third universal definition of MI.14 Because ECG is known to underestimate the prevalence of MI in patients with CTO, 3,10,15 we also evaluated a history of ischemic symptoms consistent with MI.

**Coronary Angiography**

Coronary angiography was performed by the use of standard techniques. CTO was defined by the presence of a coronary artery stenosis causing complete interruption of antegrade flow in a major epicardial coronary artery or minimal contrast penetration through the lesion without distal vessel opacification (Thrombolysis in Myocardial Infarction grade 0–1 flow).1 Because patients with acute coronary syndromes within 90 days of enrollment were excluded, the presence of a total occlusion on coronary angiography was assumed to be chronic (at least 3 months). Retrograde collateral filling of the vessel distal to a CTO was assessed by experienced interventional cardiologists blinded to other clinical and imaging data. The diameter and angiographic flow of collateral vessels was semiquantitatively assessed by the use of the collateral connection grade (CC0=no continuous connection, CC1=continuous threadlike connection, CC2=continuous, small branchlike connection) and the Rentrop classification (class 0=no visible filling of collaterals, class 1=filling of side branches, class 2=partial filling of epicardial segment of the occluded vessel, class 3=total filling of epicardial segment).6,17 The presence of well-developed angiographic collaterals was defined as a collateral connection grade=2 and Rentrop score=3.

**Cardiac MRI**

A 1.5T scanner (Magnetom Avanto, Syngo MR; Siemens Medical Solutions, Germany) was used. Cine images of the LV myocardium were acquired by using a steady-state free-precession sequence with 8 to 10 contiguous short-axis slices and a slice thickness of 6-mm and 4-mm gaps. Late gadolinium enhancement (LGE) was imaged by contiguous short-axis image acquisition of 10 to 12 slices.

The infarct gray zone was defined as pixels with <50% of maximal signal intensity of remote noninfarcted myocardium, which was measured automatically and manually corrected when needed.18,19 The transmurality of LGE (0%, 1%–24%, 25%–49%, 50%–74%, 75%–100%) and regional wall motion abnormality (RWMA) score (normal=1, hypokinetic=2, akinetic=3, dyskinetic=4, aneurismal=5) were assessed in each segment of LV 17-segment model.21
Assignment of LV segments to the vessel with CTO was defined based on the American Heart Association scientific statement. The global LV LGE volume (%), and the regional LGE transmurality and wall motion score index, as well, in vessels with or without angiographic CTO were determined and compared with the presence of Q wave and angiographic extent of collateral flow.

Statistical Analysis
All analysis was done on a per-patient basis if not indicated otherwise. Data were not normally distributed, and nonparametric statistics were applied. Continuous variables are shown as the median with first and third quartiles in parentheses. Continuous and categorical variables were compared by the Mann-Whitney U or χ² test. Reclassification rate between diagnostic modalities was calculated by using the Pencina reclassification index. SPSS version 19.0 was used. A 2-tailed P<0.05 was considered statistically significant.

The inter- and intraobserver agreement of CMR and angiographic scores was assessed from 21 randomly selected cases. The Cohen κ was 0.81 and 0.82 for collateral connection grade, 0.73 and 0.81 for Rentrop classification, 0.75 and 0.83 for wall motion score, and 0.80 and 0.87 for LGE transmurality. The limits of agreement of the LGE volume (%) were −2.1±7.4% and 2.6±6.4% by Bland-Altman analysis, respectively.

Results
Clinical Characteristics
The Table summarizes the clinical characteristics of the study cohort. The median age of our study population was 62 (interquartile range, 55–70) years, and 89% of patients were male. The majority of patients had angina (61%). Fifty-eight percent of patients did not have a documented clinical history of ischemic symptoms consistent with previous MI.

Frequency of MI by Clinical History, ECG, and CMR
The frequency of previous MI was strikingly different based on clinical and imaging criteria. It was found only in 25% of patients by pathological Q waves on ECG, in 42% by previous ischemic symptom consistent with MI, and in 69% by the presence of RWMA. However, 86% of patients had evidence of LGE by CMR. Representative cases showing discrepancies between these diagnostic modalities are shown in Figure 2A through 2D.

Relationship Between Angiographic Collateral Flow, Presence of Q waves on ECG, Regional Wall Motion, and Transmurality of LGE
We investigated whether LGE transmurality or RWMA are specific to the presence of Q waves or LV segments assigned to vessels with CTO. The degree of LGE transmurality, LGE volume (%), and wall motion score index were higher in patients with Q waves on ECG (all P<0.001; Figure 3A

Figure 2. Representative cases showing discrepancies between diagnostic modalities. Clinical cases showing discrepancies between ECG, RWMA, and LGE in patients with CTO. Coronary angiography of each case is shown in online-only Data Supplement Movies I through VIII. A, A case of proximal LAD total occlusion (blue arrow) showing no Q waves and no RWMA. Left ventricular ejection fraction (LVEF)=61%. No LGE was identified. B, A case of mid-LAD total occlusion (blue arrow) showing no Q waves and no RWMA. LVEF=64%. However, subendocardial LGE was identified (pink arrow). LGE mass=9.6 g. C, A case of mid-LAD total occlusion and distal LCX stenosis. There were no pathological Q waves on the ECG. LVEF=58%. CMR showed LGE involving the anteroseptal wall. D, A case of mid-LAD total occlusion (blue arrow) and proximal LCX stenosis. Q waves in anterior leads were identified. CMR showed mildly dilated LV cavity, systolic dysfunction (LVEF=45%), and hypokinesia of anterior to apical wall. Extensive LGE is seen from the midventricular anterior to apical segments but not in basal inferolateral segments. CMR indicates cardiac MRI; LAD, left anterior descending artery; LCX, left circumflex artery; LGE, late gadolinium enhancement; and RWMA, regional wall motion abnormality.
Figure 3. Relationship between angiographic collateral flow, presence of Q waves on ECG, regional wall motion, and transmurality of LGE. *(P<0.001 by Mann-Whitney U or χ² test). A, The frequency of transmural MI was significantly lower in patients without Q waves than in patients with Q waves. The frequency of LGE transmurality (0%, 1%–25%, 25%–49%, 50%–74%, 75%–100%) was as follows: in patients without Q waves, 18.8% (n=24), 25.8% (n=33), 29.7% (n=38), 19.5% (n=25), and 6.3% (n=8); in patients with Q waves, 0% (n=0), 4.8% (n=2), 16.7% (n=7), 40.5% (n=17), and 38.1% (n=16) (P<0.001 by χ² test). B, LGE volume was significantly lower in patients without Q waves than in patients with Q waves, 5.7% (1.7%–12.8%) versus 19.1% (13.4%–26.1%) (P<0.001 by Mann-Whitney U test). In box plots, the top, middle line, and bottom of the box represent the 75th, 50th, and 25th percentile. The whiskers represent the highest and lowest values that are not outliers or extreme values, which are >1.5 times the interquartile range and shown as separate circles. C, Patients with Q waves in ECG showed significantly higher WMSI in comparison with patients without Q waves. WMSI of LV segments assigned to vessels with CTO: 2.00 (1.54–2.23) versus 1.11 (1.00–1.50); WMSI of LV segments assigned to vessels without CTO: 1.30 (1.13–1.51) versus 1.00 (1.00–1.10). P<0.001 by Mann-Whitney U test, both. D, Consistent correlation between LGE transmurality and regional WMSI is shown. Note the overall higher LGE transmurality and WMSI in LV segments assigned to vessels with CTO compared to the other LV segments. The WMSI of LV segments assigned to vessels with CTO according to the LGE transmurality was as follows: 1.00 (1.00–1.00), 1.00 (1.00–1.20), 1.30 (1.08–1.57), 1.79 (1.40–2.14), 2.18 (1.85–2.54). The WMSI of the other LV segments according to the LGE transmurality was as follows: 1.00 (1.00–1.00), 1.00 (1.00–1.00), 1.04 (1.00–1.25), 1.23 (1.10–1.48), and 1.45 (1.14–1.87). P<0.001 by Kruskal-Wallis and Jonckheere-Terpstra test, all. E, Well-developed collaterals were defined by collateral connection grade 2 and Rentrop class 3 collateral flow (n=82). Poorly developed collaterals were defined by collateral connection grade <2 or Rentrop class <3 collateral flow (n=88). The frequency of Q waves was significantly lower in patients with well-developed collaterals in comparison with patients with poorly developed collaterals: 12.2% (n=10) versus 36.4% (n=32) (P<0.001 by χ² test). F, The frequency of transmural MI was significantly lower in patients with well-developed collaterals than in patients with poorly developed collaterals. In patients with well-developed collaterals, LGE transmurality 0% was 28.0% (n=23), 1% to 24% was 23.2% (n=19), 25% to 49% was 29.3% (n=24), 50% to 74% was 12.2% (n=10), and 75% to 100% was 7.3% (n=6); in patients...
through 3C). Likewise, regional wall motion score index was higher in LV segments subtended by CTO than in vessels without CTO, and in LV segments with higher degrees of transmural scar on LGE, as well (Figure 3C and 3D). The presence of well-developed angiographic collaterals distal to a CTO was associated with a lower frequency of ECG with Q waves, and lower regional LGE transmurality and volume (%) and wall motion score index (all \( P < 0.001 \); Figure 3E through 3H), as well. The detailed results are listed in online-only Data Supplement Table).

**Discussion**
To the best of our knowledge, our study is the first to show that a myocardial scar, as defined by contrast-enhanced CMR, in territories subtended by upstream CTO is much more common than previously known.\(^1\) Consistent with previous experimental and clinical data,\(^24,25\) we showed that the presence of well-developed angiographic collaterals distal to CTO was associated with a lower frequency and transmurality of previous MI, suggesting a protective role of timely developed collaterals distal to a CTO.

**Frequency of LGE and RWMA**
CTO is presumed to originate from the organization of thrombi developed in the context of a nonfatal MI. However, objective evidence of myocardial injury has been documented in up to 50% of patients in most clinical studies.\(^1,3–6,9–12\) The frequency of abnormal ECGs displaying Q waves is consistent with this notion. However, the use of CMR imaging in our study revealed a significantly higher frequency of MI: 86% in our study patients. On the other hand, 14% of our patients did not show LGE, and all had normal ECGs. Nonetheless, LGE may not be detected in areas of very small myocardial injury.\(^7,26–28\) Hence, our data suggest that most myocardial territories distal to a CTO contain varying degrees of myocardial scar.

Although some degree of LGE was found in 86% of patients, an associated RWMA was found only in 69% of them. However, most patients with a RWMA showed LGE transmurality \( >25\% \), which is consistent with the notion of a threshold phenomenon governing the relationship between scar burden and regional systolic function.\(^21\) The varying extent of transmural injury explains, at least in part, some of the apparently incongruent results between the frequency of LGE and regional function. In these patients, a RWMA may also represent viable but stunned or hibernating myocardium owing to inadequate coronary flow reserve.\(^29–31\)

**Coronary Collaterals and Transmurality of MI**
We found that the presence of well-developed collateral vessels was inversely correlated with the degree transmural injury and was also associated with a lower frequency of abnormal ECG with Q waves. Indeed, the frequency of transmural infarct defined by LGE transmurality \( \geq 50\% \) was 19% in patients with well-developed collaterals, whereas it was 49% among those with poorly developed collateral vessels (Figure 3F).

Human coronary arteries are not functionally end arteries, but, instead, they are interconnected by a rich network of collateral vessels.\(^32\) It is estimated that approximately one fourth of individuals have functional collateral vessels able to reduce or prevent myocardial ischemia induced by brief abrupt reduction of antegrade flow.\(^28,33\) The size and transmural extent of MI is determined by coronary artery occlusion time, the extent of myocardium at risk, and the degree of collateral blood flow at the time of coronary occlusion.\(^34\) Therefore, increased collateral flow to a territory suddenly deprived of its natural antegrade flow should ameliorate the extent of transmural myocardial necrosis and attenuate LV dysfunction.\(^35–37\) Indeed, well-developed collateral circulation reduces the infarct size in ST-elevation MI and the long-term mortality in patients with stable angina, as well.\(^38–49\)

**Limitations**
Our findings represent a single-center experience. The duration of CTO was likely heterogeneous. Our definition of previous MI was retrospective and predicated on the presence of ischemic symptoms and Q waves on ECG, which may not be completely accurate.\(^1\) Our result was derived from a population with a high prevalence of multivessel disease and need of revascularization and may not be translated to populations with less severe disease. The physiological consequence of collateral vessels was not interrogated by assessment of stress testing. We followed standardized but empirical assignment of coronary arteries to specific myocardial segments, which may be discordant especially for non–left anterior descending artery vessels.\(^46\) Patient-specific coronary artery and myocardial mapping would be required for a more refined evaluation.\(^37\)

**Conclusions**
Most patients with chronic coronary artery occlusions show evidence of previous MI. The transmural extent of myocardial injury and the presence of regional LV dysfunction are inversely related with the degree of angiographic collaterals. Our results are consistent with a protective role of collateral blood flow against myocardial damage related to CTO.

**Disclosures**
None.

**References**


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CLINICAL PERSPECTIVE

Despite totally occluded coronary by heavy atherosclerotic burden, previous myocardial infarction (MI) has been documented only in one half of patients with chronic total occlusion by clinical history or the recently published third universal definition of MI. In this study, cardiac magnetic resonance (CMR) late gadolinium enhancement imaging revealed the footprint of previous MI in most of patients with chronic total occlusion. Hence, most patients with chronic total occlusion should be regarded as having experienced type 1 spontaneous MI. In addition, patients with well-developed collateral vessels showed lesser infarct size and better regional wall motion. This finding suggests a protective role of collateral development against myocardial damage related to chronic total occlusion. Promotion of coronary collateral growth or arteriogenesis, which can be facilitated by physical exercise or cytokine therapy, may be a promising preventive therapy that is protective from the future MI and salvages myocardium even in the complete absence of natural anterograde coronary artery flow.
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### Table I. Relationship between Angiographic Collateral Flow, Q waves on ECG, Regional Wall Motion, and Transmurality of Late Gadolinium Enhancement according to Coronary Artery

<table>
<thead>
<tr>
<th>Location of CTO</th>
<th>LAD (N=73)</th>
<th>LCX (N=29)</th>
<th>RCA (N=68)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Frequency of LGE transmurality</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0%</td>
<td>No Q wave</td>
<td>27.5 (14)</td>
<td>11.5 (3)</td>
</tr>
<tr>
<td>1-24%</td>
<td>No Q wave</td>
<td>27.5 (14)</td>
<td>34.6 (9)</td>
</tr>
<tr>
<td>25-49%</td>
<td>No Q wave</td>
<td>23.5 (12)</td>
<td>30.8 (8)</td>
</tr>
<tr>
<td>50-74%</td>
<td>No Q wave</td>
<td>15.7 (8)</td>
<td>15.4 (4)</td>
</tr>
<tr>
<td>75-100%</td>
<td>No Q wave</td>
<td>5.9 (3)</td>
<td>7.7 (2)</td>
</tr>
<tr>
<td><strong>LGE volume%</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0%</td>
<td>No Q wave</td>
<td>5.6 (0.0 – 13.3)</td>
<td>4.7 (2.0 – 11.9)</td>
</tr>
<tr>
<td>1-24%</td>
<td>No Q wave</td>
<td>21.4 (14.3 – 24.8)</td>
<td>17.7 (12.9 – 18.4)</td>
</tr>
<tr>
<td><strong>Frequency of ECG Q wave</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q wave</td>
<td>W/D collaterals</td>
<td>7.9 (3)</td>
<td>15.4 (2)</td>
</tr>
<tr>
<td>No Q wave</td>
<td>P/D collaterals</td>
<td>54.3 (19)</td>
<td>6.3 (1)</td>
</tr>
<tr>
<td><strong>Frequency of LGE transmurality</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0%</td>
<td>W/D collaterals</td>
<td>31.6 (12)</td>
<td>23.1 (3)</td>
</tr>
<tr>
<td>1-24%</td>
<td>P/D collaterals</td>
<td>5.7 (2)</td>
<td>15.4 (2)</td>
</tr>
<tr>
<td>25-49%</td>
<td>W/D collaterals</td>
<td>23.7 (9)</td>
<td>46.2 (6)</td>
</tr>
<tr>
<td>50-74%</td>
<td>P/D collaterals</td>
<td>17.1 (6)</td>
<td>25.0 (4)</td>
</tr>
<tr>
<td>75-100%</td>
<td>W/D collaterals</td>
<td>21.3 (8)</td>
<td>7.7 (1)</td>
</tr>
<tr>
<td><strong>LGE volume%</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>W/D collaterals</td>
<td>5.3 (0.0 – 14.9)</td>
<td>8.9 (0.7 – 15.3)</td>
<td>5.0 (7.2 – 11.0)</td>
</tr>
<tr>
<td>P/D collaterals</td>
<td>14.3 (6.2 – 23.6)</td>
<td>4.7 (2.3 – 11.6)</td>
<td>11.8 (5.3 – 23.6)</td>
</tr>
<tr>
<td><strong>WMSI of LV assigned to CTO</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>W/D collaterals</td>
<td>1.000 (1.000 – 1.589)</td>
<td>1.200 (1.000 – 1.500)</td>
<td>1.200 (1.000 – 1.600)</td>
</tr>
<tr>
<td>P/D collaterals</td>
<td>1.571 (1.000 – 2.143)</td>
<td>1.250 (1.025 – 1.950)</td>
<td>1.400 (1.100 – 2.000)</td>
</tr>
</tbody>
</table>

Results are shown as median (1st quartile – 3rd quartile) or frequency % (n). W/D, well-developed; P/D, poorly developed. p-value between No Q wave and Q wave groups, or W/D collaterals and P/D collaterals are shown. * p-value by Chi-square test, ** p-value by Mann-Whitney U test.
Legend for movie files

Each movie is coronary angiography of representative cases shown in Figure 2

CAG_A_LAD_xvid.avi: Case A, left coronary artery
CAG_A_RCA_xvid.avi: Case A, right coronary artery
CAG_B_LAD_xvid.avi: Case B, left coronary artery
CAG_B_RCA_xvid.avi: Case B, right coronary artery
CAG_C_LAD_xvid.avi: Case C, left coronary artery
CAG_C_RCA_xvid.avi: Case C, right coronary artery
CAG_D_LAD_xvid.avi: Case D, left coronary artery
CAG_D_RCA_xvid.avi: Case D, right coronary artery