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EDITORIAL COMMENT

Chronic Total Occlusions

A Benign Entity or a "Perfect Storm" of Road Closures Waiting to Occur…?*

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London becomes Europe's gridlock capital.
"You cannot build any more roads in London,
so now it is about managing that congestion."
—Financial Times, 2015 (1)

Coronary blood flow may be regarded as a series of major roads supplying traffic to all key districts of a city. When rush hour ensues (akin to significant physical activity), demand on the roads increases exponentially. If the road infrastructure is suitably developed, the city roads cope, and traffic gridlock is averted. If, however, some of the major roads have a temporary reduction in the number of lanes because of roadworks (akin to, say, a coronary stenosis), the city continues to cope with the ensuing rush-hour traffic, albeit with more congestion (akin to angina). Enhanced traffic management systems (e.g., smart roads/traffic lights, akin to antianginals) may be sufficient to avoid heavy congestion. As the number of roadworks (coronary stenoses) increases, more severe traffic congestion occurs during rush hour (worsening angina), and the chances of traffic gridlock—when traffic flow exceeds capacity and the cars stop moving (akin to an ischemic malignant arrhythmia and/or cardiac arrest)—increases exponentially.

Yet, drivers (and coronary blood flow) are resourceful: if there is heavy traffic congestion, they find alternative routes to reach their destination along smaller roads (akin to coronary collateral vessels [2]). Now, let us add to this scenario major road closures, short term due to a road traffic accident (akin to an acute myocardial infarction [AMI]), or long term due to, say, prolonged engineering works (akin to a chronic total occlusion [CTO]). In the short-term situation, a major road closure may be better tolerated if other smaller roads (collateral vessels) link to other major roads, and there are fewer major road works/road closures (akin to bystander coronary artery stenoses/occlusions) elsewhere. The analogy here is of an acutely occluded left anterior descending coronary artery (LAD) that is well collateralized to the right coronary artery (RCA). In this scenario, the patient would have a smaller infarct size, because infarct size is inversely related to the extent of collateral supply when corrected for coronary artery occlusion time and area at risk (2). Moreover, the absence of angiographic collateral vessels distal to an acutely occluded coronary artery can occur in up to one-quarter of patients and in itself is strongly associated with an early occurrence of cardiogenic shock (3).

Conversely in the same clinical situation, what if there was a CTO to the RCA that had been medically managed with a couple of antianginal medications? An acutely occluded LAD would result in loss of blood flow to both the LAD and RCA territories. If the RCA territory was viable—noting that approximately one-half of patients with a CTO have an absence of a prior myocardial infarction (4)—the result would be a higher likelihood of cardiogenic shock ensuing (5). Adding to this latter scenario is the presence of bystander coronary artery disease (CAD). On the one hand, more bystander CAD would mean the acute blockage of the LAD would be less tolerated (particularly in the presence of 1 or more CTOs); on the other hand, more bystander CAD implies a greater plaque

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burden and substantially greater risk of an AMI occurring in the first place. A concept that lends support from a COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) substudy (6) and a prospective registry quantifying plaque burden using computed tomography (7). Both studies demonstrated that the global atherosclerotic CAD burden to be a much more consistent predictor of AMI and cardiac death compared with myocardial ischemia alone.

Now, going back to the city analogy, what if some areas of the city hit economic decline and became depopulated (akin to, say, infarcted myocardium), but the major roads (and collateral vessels) from this region to the more populated areas remained opened? Exactly the same scenario would exist here in terms of traffic flow and risk of gridlock as described previously. For example, a revascularized CTO to the RCA, irrespective of whether it supplies infarcted tissue or not, would still prove vital to provide collateral vessels to the LAD—particularly if the LAD became acutely occluded and/or was diffusely diseased and not amenable to revascularization—to limit the size of the infarct and/or prevent ischemia-driven malignant arrhythmias, raising the specter that CTOs may not be as benign as once thought, even if the supplied myocardial territory is not viable….

Furthermore, in patients with impaired left ventricular ejection fraction (LVEF), the clinical consequences of an AMI (even a small one) would be more profound, because the myocardial reserve is substantially lower than normal, with a greater risk of cardiogenic shock and mortality. A concept that lends support from the long-term follow-up of the STITCH (Surgical Treatment of Ischemic Heart Failure) study (8), which demonstrated in subjects with more advanced ischemic cardiomyopathy, more extensive CAD, and worse myocardial dysfunction and remodeling, that a net longer-term (10-year) prognostic benefit was evident for CABG compared with optimal medical therapy, despite the short-term (30-day) mortality risk being higher with CABG. Although the bypass graft passivating the coronary vessels against future AMI is the most plausible mechanism for the longer-term benefit in the STITCH study, one should not underestimate the potential value of percutaneous-based CTO revascularization in ischemic cardiomyopathy, particularly if unsuitable or too high risk for conventional CABG given the potential dependency all epicardial vessels have on each other through collateral vessels (2). Conversely, whether there would be a short- to medium-term disadvantage for PCI in the setting of severely impaired LVEF (as occurs with CABG) is entirely credible, due to the potential risk of periprocedural necrosis having an adverse prognostic impact, given the poor myocardial reserve these patients have. A hypothesis that is supported by the single-arm ORBIT II (Evaluate the Safety and Efficacy of OAS in Treating Severely Calcified Coronary Lesions) study, which demonstrated an increased shorter-term (1-year) mortality in patients with severely impaired LVEF (compared with preserved LVEF) who underwent PCI with adjunctive orbital atherectomy for calcified coronary lesions (9).

Pulling all of this together, more complete revascularization (10), or at least staying within the realms of reasonable incomplete revascularization (11), including that related to CTOs, appears justified to prevent the "perfect storm" of vessel closures that would result in "gridlock," that is, cardiogenic shock as a result of an AMI, and death.

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To this increasingly complex field comes an interesting study (VACTO secondary substudy [12] in this issue of *JACC: Cardiovascular Interventions*) examining the association of CTOs with ventricular arrhythmias secondary to ischemic cardiomyopathy requiring implantable cardioverter defibrillator (ICD) therapy (antitachycardia pacing or shock). Strikingly, both impaired LVEF and CTOs (present in approximately one-half of the subjects [215 of 425]) were independently associated with appropriate ICD therapy, despite adjustment for all recorded confounding factors. Although the possibility of residual confounding remains, the fact that stable CAD was solely examined (with AMI patients excluded) implies that even if the CTO patients had greater plaque burden (as seems likely), and therefore carried a higher risk of a future AMI, this would not account for both CTO and LVEF remaining independent predictors of ICD therapy (without any described collinearity), and raises the possibility of another mechanism beyond AMI.

Notably in the CTO subjects, impaired LVEF (<40%; $p = 0.042$), impaired renal function (estimated glomerular filtration rate <60 ml/min; $p = 0.023$), and better collateral flow (Rentrop 3; $p = 0.093$) were independently associated with appropriate ICD therapy. In addition, a greater number of ICD therapies were evident with increasing number of CTOs, especially in the context of multivessel disease, compared with single or multivessel disease without CTOs. Although the potential confounding association of CTOs with a greater burden of myocardial scar is plausible, the fact that the presence of collateral vessels somewhat paradoxically increased the frequency of ICD therapies, implies that the collateral vessels (either bridging or supplying another vessel)

may be sufficient to keep the myocardial territory viable, but be insufficient to prevent ischemia-driven arrhythmias (i.e., traffic gridlock) during physical activity. Indirect evidence to support this hypothesis comes from a large Korean registry, which demonstrated a longer-term prognostic benefit in successfully revascularized CTO patients with a well-developed collateral circulation (compared with medical therapy) (13). Unfortunately, the present study (12) is limited in that it does not have enough recorded ischemia and viability data to support this hypothesis. It should, however, come as no surprise that the presence of a CTO (in addition to renal dysfunction and a lower LVEF) was independently associated with adverse long-term mortality.

Perhaps a greater understanding of the interdependency of all the major epicardial vessels on each other, and its association with the overall plaque burden and LVEF, may improve our understanding of the importance of revascularization of CTOs in both viable and, more controversially, nonviable myocardial territories. The most striking finding from this study is the apparent independent association of CTOs with life-threatening arrhythmias in patients with ischemic cardiomyopathy, with the suggestion that maintaining the viability of myocardial territories through collateral vessels is insufficient, and that untreated CTOs may actually fuel ischemia-driven malignant arrhythmias and ultimately have an adverse impact on long-term mortality. If future trials targeted these higher-risk patients, then perhaps one day, we may show the potential prognostic impact of CTO revascularization in appropriately selected patients. To quote Albert Einstein, "everything should be made as simple as possible, but not simpler" (14); when trying to understand CTOs and their potential importance in revascularization, this appears to follow the same logic.

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