

**EDITORIAL COMMENT**

**Myocardial Circulation Distal to Chronic Total Occlusions**

A Brighter Light at the End of the Tunnel*  
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The role of collateral circulation is at the core of the discussion over the net benefit of chronic total occlusion (CTO) recanalization in patients with stable coronary artery disease. Myocardial viability beyond a CTO would have been unthinkable without the pioneer work of Gregg et al. (1) in instrumented dogs, demonstrating the importance of a steady build-up in distal coronary pressure in response to progressively tighter coronary stenosis and its protective effect in complete vessel occlusion. Coronary angiography, introduced 25 years after their research, revealed the extraordinary prevalence of collateral development as an adaptive response of the human heart to occlusive coronary disease. Blood supply in the myocardium subtended by a chronically occluded vessel has been customarily estimated by combining angiography with ischemia-detection techniques. However, many physicians feel that, in most CTO cases with a well-developed collateral circulation, there is little room for clinical worsening and, therefore, revascularization can be safely avoided.

In the human heart, collaterals develop through arteriogenesis, that is, through the recruitment of pre-formed and pre-existing interarterial anastomoses driven by pressure gradient generated by vessel narrowing or occlusion (2). These connections determine the anatomical arrangement of collateral circuits, both in terms of regional and transmural distribution. Remodeling of intercoronary connections in response to shear forces, causing conduit enlargement and angiographic visualization, constitutes the basis for the qualitative classification of collateral connections proposed by Werner et al. (3) (Table 1) that correlates better with distal driving pressure than the widely used Rentrop grading of distal vessel opacification. From a practical point of view, expert CTO operators also learned that coronary connection (CC) 2 collaterals, the largest connections in Werner’s scale, provide the most accessible route for retrograde CTO recanalization.

With the availability of pressure and flow guidewires, a great deal of information has been obtained on collateral function within the complex hydraulic circuits and shifting resistances of myocardial beds in CTO and collateral-donor vessels (3-4). In this issue of *JACC: Cardiovascular Interventions*, Brugaletta et al. (5) report valuable observations obtained from a different angle in the coronary vasculature distal to a CTO. After successful CTO recanalization, the investigators performed measurements of flow velocity and vascular responses to acetylcholine (Ach) and nitrate challenge, demonstrating that distal epicardial vessels exhibit endothelial and smooth muscle cell (SMC) dysfunction, with intensive vasoconstriction response to Ach. The study population was understandably small given the complexity of the study and, although it has to be envisaged as a hypothesis-generating study, the observations fit nicely in the overall picture drafted by other researchers.

It must be remembered that the presence of ischemia in patients with CTOs has been mainly attributed to a mismatch between collateral blood supply and myocardial demand, without considering that downstream vascular dysfunction might be an additional factor contributing to generate ischemia. This study demonstrates that, distal to a CTO, some regulatory responses of myocardial circulation are deeply altered, and that key domains of coronary microcirculation where endothelial cells play a major role in myocardial blood flow regulation may be actively implicated in the generation of myocardial ischemia. This is the case of arterioles with diameters between 120 and 150 μm, in which vasodilation is driven by endothelial cell–mediated responses to increases in shear stress. Under normal conditions, this ensures that vasodilation of these arterioles is coupled to myogenic vasodilation of smaller (30- to 60-μm) arterioles, triggered directly by metabolic stimuli. In the context of severe endothelial dysfunction distal to the CTO, vasodilation of metabolically controlled arterioles in response to exercise, paradoxically, would be followed by upstream vasoconstriction of larger arterioles and decreased blood supply (6,7).

Interestingly, the abnormal responses in myocardial circulation documented by Brugaletta et al. (5) were related to the quality of coronary connections (CC1 or CC2 grade), but not to the commonly used Rentrop classification. In vessels with a CTO and CC1 collaterals, a 6-fold decrease in blood flow was documented during Ach challenge, whereas this was much lower in vessels

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with CC2 collaterals. Why are CC2 collaterals more protective against vascular dysfunction? The fall in intracoronary pressure distal to a coronary stenosis seems to play an important role in the genesis of endothelial dysfunction, structural microcirculatory remodeling, and abnormal vasoreactivity (6). Although Brugaletta et al. (5) did not measure coronary wedge pressure in their patients, we know from the original study by Werner et al. (3) that there is an association between CC grading and distal coronary pressure (3), with significantly higher values in their study (54 mm Hg) than in CTOs with CC0 and CC1 collaterals (35 and 41 mm Hg, respectively). In addition to that, restoration of antegrade flow by CTO recanalization is likely to trigger endothelial responses after long periods of reversed flow and low shear stress.

One of the interesting aspects of using CTO as a research model during percutaneous coronary intervention (PCI) is that, unlike in nonocclusive stenoses, the microcirculation in the dependent myocardium is not affected by transient episodes of ischemia during balloon occlusion. This is certainly one of the strengths of the present study. It could be argued that CTO recanalization implies a higher vascular wall damage than nonoccluded vessels, and, therefore, that microcirculation could be impaired due to distal embolization of plaque debris. However, whereas this might affect indexes such as coronary flow reserve or coronary resistance indexes, it is unlikely that this might influence distal endothelial responses to flow. A more complex issue is whether downstream elution of antiproliferative drugs from the recently implanted stents may constitute a cause of endothelial dysfunction; although, this would not explain the differences noted in the responses to Ach challenge in patients with CC1 and CC2 collaterals. Another major issue that deserves further research is whether the abnormalities revert over time after CTO recanalization or if these or other effects can be observed in the donor vessels. Angiographic follow-up of patients with successfully treated CTOs often reveal that vessel diameter was much larger than immediately after the procedure; future research will probably show whether this runs in parallel with an improvement in endothelial and SMC function. It is unknown if pharmacological treatment could contribute to normalizing endothelial function in patients with CTO and if this might result in benefit for patients with a chronically occluded artery.

What are the practical implications of these findings? As discussed, a frequent argument to justify not treating a CTO is that the patient is already protected by collateral support to the myocardium and, therefore, myocardial ischemia is unlikely. This study shows, once again, that angiography is a deceiving tool, and that collateral filling does not allow physiological assessment. We have now learned that coronary circulation in the myocardium subtended by a chronically occluded artery is deeply abnormal and that, far from being a passive receptor of collateral blood supply, is a potential primary cause of ischemia. Second, pre-existing coronary occlusion has been identified as a major determinant of death in patients with acute myocardial infarction undergoing primary PCI (8). This occurred not only in the most evident and serious cases where the infarct culprit vessel was the collateral donor artery. The study by Brugaletta et al. (5) provides a new potential explanation for the excess of mortality in patients with CTOs by showing the existence of dysfunctional myocardial circulation in a nonculprit territory. A third practical aspect is the abnormal vasoreactivity of distal coronary segments frequently faced by CTO operators immediately after opening the vessel, which persists despite nitrate administration. This paper provides the first direct evidence that this is likely to be the result of endothelial and SMC dysfunction. Operators should be aware of this phenomenon and reconsider ad hoc treatment of distal coronary stenoses immediately after CTO recanalization.

Finally, it would be wrong to infer from this study that CC2 collaterals indicate myocardial viability in CTOs, and, therefore, that they can be used as an index to decide treatment. Because arteriogenesis is not triggered by ischemia but by pressure gradients across the pre-existing coronary connection, collaterals may develop in the presence of nonviable myocardium. This is a key difference with a frequently confounded phenomenon, angiogenesis, which is driven by ischemia but accounts only for a small percentage of blood supply to myocardium in CTOs (2). The patients included in the study of Brugaletta et al. (5) were treated on the grounds of documented myocardial viability and ischemia, and this certainly continues to be the right way to set the indication for CTO recanalization.

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REFERENCES


Table 1. Qualitative Angiographic Classification of CC

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<tr>
<th>CC</th>
<th>Description</th>
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<tbody>
<tr>
<td>CC0</td>
<td>no continuous connection</td>
</tr>
<tr>
<td>CC1</td>
<td>threadlike continuous connection</td>
</tr>
<tr>
<td>CC2</td>
<td>side branch–like connection</td>
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Data based on Werner et al. (3).

CC = collateral connection.


Key Words: arteriogenesis ■ chronic total occlusion ■ collateral connection ■ coronary collaterals ■ endothelial dysfunction.