

# Collateral Circulation in Chronic Total Occlusions – An Interventional Perspective

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**Abstract:** Human coronary collaterals are inter-coronary communications that are believed to be present from birth. In the presence of chronic total occlusions, recruitment of flow via these collateral anastomoses to the arterial segment distal to occlusion provide an alternative source of blood flow to the myocardial segment at risk. This mitigates the ischemic injury. Clinical outcome of coronary occlusion ie. severity of myocardial infarction/ischemia, impairment of cardiac function and possibly survival depends not only on the acuity of the occlusion, extent of jeopardized myocardium, duration of ischemia but also to the adequacy of collateral circulation. Adequacy of collateral circulation can be assessed by various methods. These coronary collateral channels have been used successfully as a retrograde access route for percutaneous recanalization of chronic total occlusions. Factors that promote angiogenesis and further collateral remodeling ie. arteriogenesis have been identified. Promotion of collateral growth as a therapeutic target in patients with no suitable revascularization option is an exciting proposal.

**Keywords:** Arteriogenesis, chronic total occlusion, collateral, collateral flow index, percutaneous intervention.

## INTRODUCTION

Coronary collaterals have been found even in newborn hearts [1]. The extensive channels were repeatedly found to persist into adulthood. These channels appear ‘cork-screw’ with diameters mostly in the range of 40 to 200  $\mu\text{m}$  but can reach up to 800 $\mu\text{m}$  in coronary artery disease with lengths ranging from 1 - 2 cm to 4 - 5 cm.

In post-mortem studies, William Fulton demonstrated ubiquitous presence of these arterial anastomoses even in normal hearts [2, 3]. Extensive superficial and deep inter-coronary anastomoses were seen, particularly abundant in the interventricular septum and in the subendocardial plexus of the left ventricle.

Collateral arteries are more abundant in the left than in the right ventricle and are uncommon in the subepicardial territory in man.

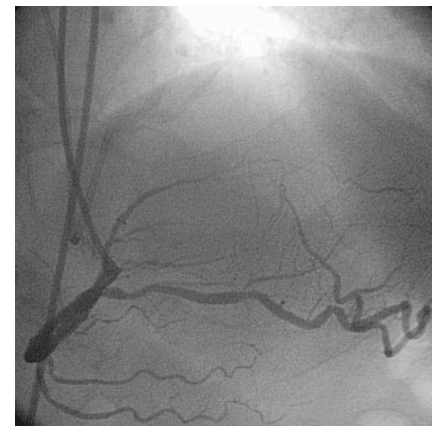
Zoll *et al.* [4] demonstrated collaterals in 46% of 1050 post-mortem adult hearts. The prevalence increased from 9% in normal hearts to 63% in specimens with significantly obstructive coronary artery disease (CAD) and up to 95% when chronic total coronary occlusions (CTOs) were present.

In humans, increased presence of functional pre-formed coronary collaterals in the absence of coronary artery disease (CAD) is predicted by low resting heart rate (not pharmacologically reduced) and absence of hypertension [5].

## ANATOMY AND PHYSIOLOGY OF CORONARY COLLATERALS

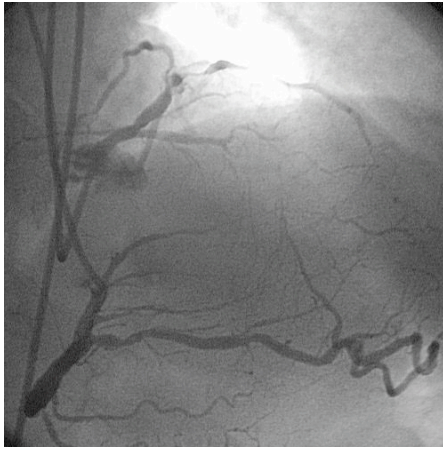
Interventionalists performing coronary angiography are well acquainted with the findings of coronary collaterals in the presence of chronic total occlusions (Figs. 1 and 2).

By convention, a total coronary artery occlusion of perceived or known duration of 3 months or longer are labeled as chronic occlusions [6]. However, some of these pre-formed collaterals could be recruited immediately following occlusions (eg. transient balloon occlusion). But with increased chronicity of an occlusion, these small arteriole collaterals undergo remodeling to become muscular arteries, like that of epicardial coronary arteries [7, 8]. This process is termed arteriogenesis.



**Fig. (1).** LAD CTO with retrograde filling of distal LAD from RPDA.

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**Fig. (2).** LAD CTO – bicornary injection – delineates the CTO segment.

With the formation of larger muscular arteries, the number of collaterals decrease, a process termed “pruning”. As per physics of flow (Hagen Poiseuille law), a larger artery confers less flow resistance and hence, is more efficient for blood flow as opposed to small collaterals with high vascular resistance even though the numbers of the latter may be more [9].

The time course of the development of these collaterals is controversial. Smaller ones may be formed within 10-15 days [10].

Rentrop *et al.* described presence of collateral circulation in 27% (74 of 272) of patients undergoing acute medical intervention (streptokinase and/or nitroglycerin) for acute myocardial infarction. Repeat angiography 10-14 days later, showed that the prevalence of angiographically visible collateral arteries in patients whose infarct-related artery never recanalised increased from 33 to 90% [11]. In those who had successful and sustained reperfusion at 10-14 days, the prevalence of collaterals decreased from 38% to 7% [10].

Collateral flow can develop regardless of the viability of the area perfused i.e. viability is not a pre-requisite to its development [12]. The main stimulus for collateral development is the pressure gradient across the trans-arterial connections [13].

Diabetic patients may have less potential for collateral formation [14]. Reduced expression of vascular endothelial growth factor (VEGF) and hypoxia inducible factor (HIF-1 $\alpha$ ) [15] as well as attenuated monocytes cellular response to VEGF-A [16] may be explanations for this observation.

There are also genetic links that determine the extent of pre-existing collateral network as well as development of functional collateral circulation [17-19].

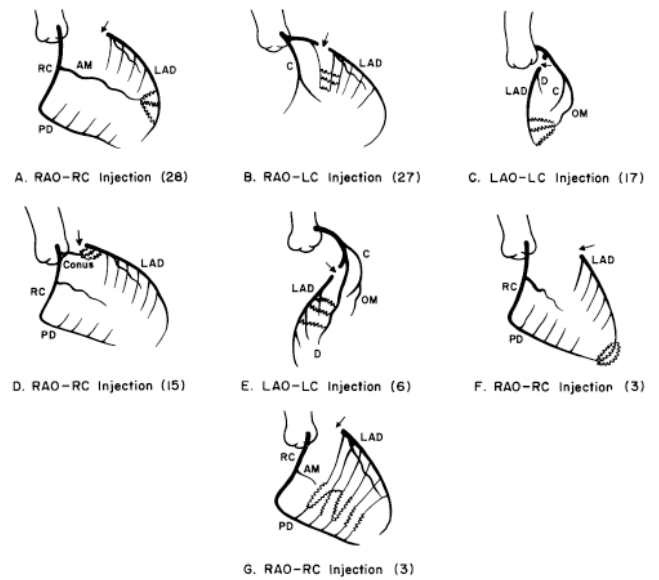
In 1974, David Lewin published an extensive map of 22 different collateral pathways. These are categorized into four types: septal, atrial, branch-branch in ventricular free walls, and trans-lesion bridging [20].

In the presence of a CTO, collateral perfusion to the segment beyond the occlusion often comes from multiple

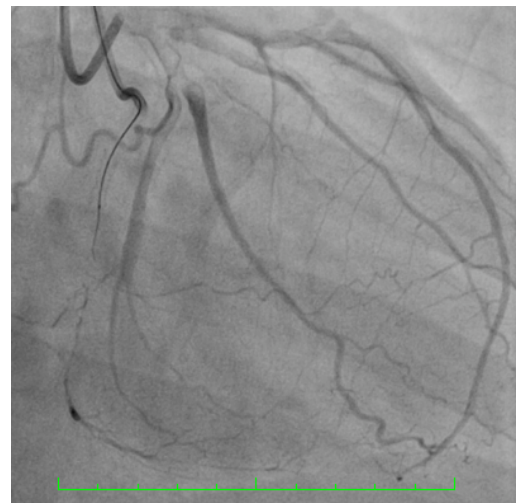
pathways [21]. For example, in the case of a left anterior descending artery occlusion, parallel septal collaterals from the right posterior descending artery, epicardial branches of the right ventricular branches and collaterals from the posterolateral branches of the left circumflex artery often co-exist (Figs. 3 and 4).

Usually, the bulk of the perfusion comes from the larger of the collaterals as the larger vessels have the least flow resistance. Some of the parallel collateral channels are therefore ‘invisible’ angiographically but operators of the retrograde percutaneous intervention technique are sometimes able to ‘serendipitously’ navigate dedicated guidewires through these unseen tracks [22, 23].

Interestingly, these collaterals appear not to be prone to atherosclerosis [8].



**Fig. (3).** Examples of collateral pathways with LAD artery occlusion [9].



**Fig. (4).** RCA CTO - Multiple parallel septal collateral channels and also distal epicardial collaterals from LAD to Right posterolateral branch.

## CLASSIFICATION AND ASSESSMENT OF CORONARY COLLATERAL CIRCULATION

There are a number of ways to classify coronary collateral circulation [24].

1. Interventionalists are familiar with the angiography-based Rentrop classification.

Angiographic Classification of Coronary Collateral Circulation:

### Rentrop classification [25]

Grade 0	No visible filling of any collateral channel.
Grade 1	Filling of the side branches of the infarct-related artery.
Grade 2	Partial filling of the epicardial vessel of the infarct-related artery.
Grade 3	Complete collateral filling of the epicardial vessel.

There are a number of factors that affect the angiographic visualization of collaterals eg. speed of injection, contrast concentration, catheter size and spatial resolution of angiographic systems (of up to 100  $\mu\text{m}$  only).

2. A more recently described angiographic classification describes the size of the collateral connections.

Collateral connection (CC) grades-size based classification [26].

CC0	No continuous connection between donor and recipient artery
CC1	Continuous, threadlike connection
CC2	Continuous, side branch-like size throughout its course

The adequacy of collateral circulation can be assessed with these few methods:

### 1. Collateral Flow Index (CFI)

First described by Pijls *et al.* [27], this allows a quantitative assessment of the adequacy of collateral circulation (Fig. 5). In the initial papers, a value of  $\leq 23\%$  predicts presence of inducible ischemia during balloon inflation and it could predict future ischemic events [28].

Collateral supply should be assessed during maximal coronary hyperemia which is best achieved by systemic intravenous infusion of adenosine (140 mcg/kg/min). In a large cohort of stable CAD patients undergoing PCI, a CFI of  $< 0.25$  predicts likelihood of ischaemia during balloon occlusion [30].

A higher CFI value correlates with the development of hemodynamically significant obstructive lesion. Hence, in the presence of CTO, the occluded vascular bed has a higher CFI compared to those without [31].

CFI of  $\geq 25\%$  is a threshold that is required to prevent myocardial ischemia and limit infarct size during coronary occlusion [32].

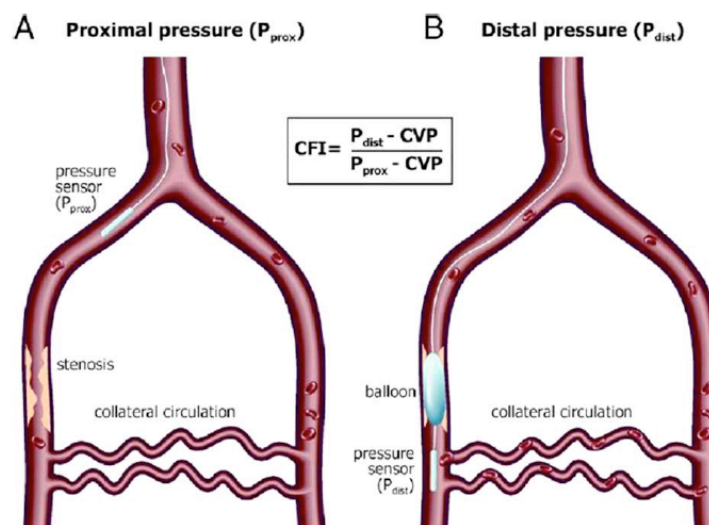
### 2. Intracoronary ECG lead

Using the coronary angioplasty or coronary pressure guidewire as an ECG lead, presence of ST-segment elevation  $> 0.1\text{mV}$  is used as a tool for detection of ischemia at the region of interest [33]. In fact, a strong inverse relationship between CFI and the intracoronary occlusive ECG ST-segment shift (elevation or depression) during coronary occlusion has been described. A good collateral perfusion with  $\text{CFI} \geq 0.217$  can be accurately detected with an ST-segment shift of  $\leq 0.1\text{mV}$  [34].

3. Presence of angina during balloon occlusion is a crude way of determining presence of ischaemia owing to inadequate collateral support.

4. Myocardial perfusion imaging with  $^{99\text{m}}\text{Tc}$ -Sestamibi scan can be used to quantify collateral circulation by assessment of the extent of ischemia [35].

5. Myocardial contrast echocardiography (MCE) is a tool that may allow the demonstration of spatial extent of perfusion from collateral circulation by selectively injecting soni-



**Fig. (5).** Measurement of collateral flow index (CFI) requires measurements of mean aortic pressure or proximal pressure (P<sub>prox</sub>), mean distal coronary pressure (P<sub>dist</sub>) and central venous pressure (CVP) [29].

cated microbubbles into the donor artery [36]. However, direct intra-arterial injection of these contrast agents are not FDA approved.

Realtime non-invasive assessment of collateral supply using MCE and systemic administration of contrast is feasible. In one series, a close relationship between the pressure-derived CFI and absolute collateral-derived myocardial blood flow (MBFc) measured by echocardiography in 32 PCI cases was demonstrated [37].

Non-invasive MCE demonstrates the importance of collateral circulation to predict potential for LV function recovery post-myocardial infarction [38, 39].

6. Washout collaterometry [40]. Following injection of contrast into the coronary artery immediately before coronary balloon occlusion, the number of heart beats needed to wash out the angiographic medium is calculated. Washout time of  $\leq 11$  heart beats accurately predicts adequacy of collaterals sufficient to prevent ischemia.

### CLINICAL IMPORTANCE OF CORONARY COLLATERAL CIRCULATION

During acute coronary occlusion, collaterals are recruited to mitigate regional myocardial hypoperfusion and ischemia.

Interventionalists are well aware of ischemic manifestations during angioplasty balloon inflation eg. chest pain, ischemic ST-segment depressions. However, there are many patients who do not manifest such ischemia and every patient is different in his/her ischemic duration thresholds. These differences may be accounted for by the presence of collateral circulation.

Antoniucci *et al.* found at least grade 2 Rentrop's collateral circulation in 23% of 1164 patients undergoing primary PCI [41].

In experimental occlusion of coronary artery with angioplasty balloon of 100 individuals, the flow provided by collateral circulation is 18% of baseline flow – as measured by collateral flow index, CFI. During this 1 minute coronary occlusion time, about 25% of individuals do not develop angina pectoris and 20% do not develop intracoronary ECG signs of ischemia [42].

In the setting of acute ST-elevation myocardial infarction (STEMI), collateral circulation have the following potential beneficial effects:

1. Reduction of infarct size. This was seen in pre-clinical animal studies [43] as well as in human studies. Human studies demonstrated lower peak serum creatine kinase (CK) levels post-STEMI in patients with collateral circulation compared to those without [44]. Following anteroseptal MI, presence of well developed collateral minimised infarct size and predicted more viable myocardium [45]. One MRI study showed that collateral circulation reduced transmural-ity of infarction but not the extent of lateral boundaries of infarct area [46]. Microvascular obstruction is also less extensive in the presence of well-developed collateral circulation [47].

2. The preservation of myocardium from the reduced infarct area, ensures higher residual cardiac function (left ventricular ejection fraction) – which is a great prognostic indicator [48].
3. In addition, decreased myocardial death reduces associated mechanical complications eg. cardiogenic shock [49], myocardial rupture [50] or ventricular aneurysm [51] formation. The reduction of cardiogenic shock translates to improved survival rates [52].
4. Presence of coronary collaterals maintains viability for a longer period of time [53]. This may extend the time buffer for successful reperfusion be it with thrombolysis or primary PCI [54].

### CHRONIC CAD AND COLLATERAL CIRCULATION

Majority of studies correlated improved survival in the presence of well-developed collateral circulation in chronic CAD patients.

Using collateral flow index (CFI) to determine adequacy of collateral circulation, cumulative 10-year survival rates (from all-cause and cardiac mortality) were 71% and 88%, respectively, in patients with low CFI and 89% and 97% in the group with high CFI ( $p = 0.04$ ,  $p = 0.01$ , respectively) [55].

The primary author, Dr. Meier of this paper and other co-authors, later performed a meta-analysis of 12 studies with 6,529 stable CAD or acute MI patients. High collateralization was associated with less mortality especially in the stable CAD group (RR 0.59; CI 0.39-0.89;  $p = 0.012$ ) [56].

### COLLATERAL CIRCULATION IN CHRONIC TOTAL OCCLUSIONS [57]

Development of collateral circulation to the territory of occluded artery is related to the distribution extent of the donor artery [58], microvascular function [59], chronicity of occlusion [60] and left ventricular function.

The collateral circulation may be bidirectional [61].

Despite the development of large collateral channels in CTO, this alternative supply may be sufficient at rest but this is not so during demand periods eg. exercise [62, 63].

Pressure changes and coronary flow velocity distal to CTO are significantly impaired (ie. FFR  $< 0.75$ ) during stress provocation with systemic adenosine infusion [64].

### PERCUTANEOUS RECANALISATION OF CHRONIC TOTAL OCCLUSIONS(CTOs)

Percutaneous coronary intervention (PCI) of CTOs remain one of the most challenging procedures for interventional cardiologists. Successful recanalization rates have improved to  $>80\%$  in many reported series and may be in excess of 90% in the hands of CTO masters. In addition to refinement of techniques and devices (eg. CTO wires, IVUS guidance, support catheters, etc) , one other important advance has been the introduction of retrograde approach for wire crossing of CTO). This essentially uses the 'back door' to pass the guidewire from the donor ar-

tery via collateral channels to penetrate the distal CTO cap.

This is an option in cases of antegrade crossing failure. Collateral channel crossing with a guidewire is successfully achieved in 73% to 87% of cases in experienced hands [65, 66].

Collateral channels can be as large as 800 $\mu$ m (0.031") [3]. Only those > 100 $\mu$ m are visible angiographically. Specialised polymer jacket wires eg. non-tapered 360 $\mu$ m (0.014") eg. Fielder FC<sup>®</sup> (Asahi Intecc, Japan), 360  $\mu$ m (0.014") Whisper<sup>®</sup> (Abbott Vascular, USA) or tapered wires 230 $\mu$ m (0.009") eg. Fielder XT<sup>®</sup> (Asahi Intecc, Japan) are device options designed to cross these channels.

The guidewires' collateral crossing is supported by microcatheters. One of the most successful support catheter is the Corsair<sup>®</sup> (Asahi Intecc, Japan). It's atraumatic tip is a tapered soft cone of 0.016" (420 $\mu$ m) profile. The distal shaft diameter is 870 $\mu$ m (2.6 Fr / 0.034") and the proximal shaft diameter is 930 $\mu$ m (2.8Fr / 0.037"). The kink-resistant tungsten braiding and distal hydrophilic polymer coating enables crossing of tortuous micro-channels. Finecross<sup>®</sup> Terumo, Japan is another micro-catheter that may be used in contemporary PCI for collateral tracking. It has an outer diameter of 600 $\mu$ m (1.8Fr; 0.024").

There are 2 forms of coronary collaterals. The capillary collaterals and the larger muscular-walled collaterals that develop from pre-existing arterioles through a process called arteriogenesis [67, 68].

Hence, the smaller collateral channels may be stretched/expanded with the passage of the microcatheters. Together with the tortuosity of collaterals and device manoeuvring for collateral tracking, the potential for injury is real especially with the smaller capillary type of collaterals. The risks includes septal hematoma, collateral channel rupture causing pericardial tamponade, equipment entrapment and donor artery injury.

Following successful recanalization of a CTO, collateral circulation regresses and loses its functional ability [69]. However, they remain recruitable rapidly, within minutes if re-occlusion occurs soon after.

Diabetic patients may have less pronounced collateral recruitment compared to non-diabetics early after angioplasty especially when the occlusion had only occurred less than 3 months earlier, a factor that may account for the poorer outcome in these patient subset [70].

With time, the collaterals regress further (up to 5 months) [71]. If the re-occlusion then occurs gradually, these collaterals may recover but for acute occlusions eg. acute myocardial infarction, they may not be recruited early enough for significant myocardial salvage.

However, myocardial infarction occurrence is less common than re-occlusion. It is believed that there are persistent collaterals that protect the post-occluded segment. It could also be that MI is less common because the culprit artery is more likely to reocclude gradually rather than abruptly, hence allowing time for recruitment and development of collateral circulation [10].

There are some suggestions that paclitaxel and rapamycin drugs from drug-eluting stents (DES) may impair the function and development of collaterals. Although, DES improves patency rates after successful revascularization, acute occlusion eg. stent thrombosis may have worse consequences without adequate collateral support [72].

## THERAPEUTIC PROMOTION OF COLLATERAL FORMATION

There are patients that have such extensive CAD especially occlusive and diffuse atherosclerotic disease that there is no revascularization option. With our understanding of the various stimuli for angiogenesis, arteriogenesis and collateral function, the prospect of 'growing' or augmenting collateral circulation is an attractive investigation subject.

Granulocyte macrophage-colony stimulating factor (GM-CSF) in small randomized placebo-controlled trials [73, 74] have been shown to improve collateral function (CFI) in patients with CAD. However, these trials were stopped owing to potential harm by the induction of plaque rupture.

Granulocyte-colony-stimulating factory (G-CSF) has been showed to have similar benefits in enhancing collateral function (CFI) [75].

Increased coronary blood flow and tangential shear stress stimulate arteriogenesis. Hence, physical exercise is a logical physical stimulus to promote functional collateral development. However, exercise therapy failed to increase collateral circulation as assessed by Rentrop's classification in a prospective 1 year trial of 113 patients, despite improvements in CAD severity [76]. The criticism of this paper noted that this angiographic classification is an insensitive way to assess collateral growth and the improvements in the CAD severity may have deterred collateral development.

In another report, following 3-months of cardiac rehabilitation utilizing exercise-based regimen, collateral function improved in CAD patients when compared to a sedentary control group [77].

Augmentation of vascular shear stress via enhance external counter-pulsation (ECCP) to promote collateral function may be the mechanism for some of the positive outcomes of this therapy [78].

## CONCLUSION

Coronary collateral network is present in both normal as well as CAD hearts. They mitigate ischemic insults during acute and chronic coronary events eg. acute myocardial infarction, and after the development of chronic total occlusions. The extent of collateral network depends on acuity of occlusion, duration of ischemia, genetic influence and comorbid states eg. diabetes status. The adequacy of collateral circulation may be assessed and graded anatomically or via functional measurements eg. collateral flow index(CFI). Success of percutaneous recanalization of chronic total occlusions have improved with the use of collateral channels as retrograde access routes for intervention. Knowledge of the collateral anatomy, physiology coupled with the development of appropriate devices and techniques has enabled the conduct of these procedures successfully and safely. Future

research targeting collateral enhancement may provide therapeutic opportunity for patients without revascularization options.

### CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

### ACKNOWLEDGEMENT

Declared none.

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