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# Assessment of Coronary Collateral Circulation in Patients with Chronic Total Occlusion: The Functional Relevance and Estimate the Quality of the Distal Run-offs

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## Abstract

**Background:** The purpose of this article is to investigate the functional relevance of coronary collateral circulation and estimate the quality of the distal run-offs in patients with coronary chronic total occlusion (CTO).

**Methods:** We analyzed the 267 consecutive patients who underwent PCI for CTO. In 119 patients, the distal portion of total occlusion was filled with ipsilateral collateral connections (ipsilateral group), and in 103 patients, it was filled with contralateral collateral connections (contralateral group). The target vessel diameter and dilatation rates of the groups were evaluated and compared for the echocardiographic parameters.

**Results:** The principal finding in this study is that mean value of the target vessel diameter beyond occlusion was significant higher in the contralateral group than in the ipsilateral group ($p<0.05$). The LVEF values before PCI in the contralateral group were significantly higher than in the ipsilateral group. However, Increase in LVEF after PCİ were significantly higher in the ipsilateral group than contralateral group ($p<0.05$).

**Conclusion:** Our study results concerning contralateral circulation in patients with CTO have shown less negative vessel remodelling after CTO. We also showed that the increases of LVEF after PCI, the ipsilateral group had significant increases compared with the contralateral group.

**Keywords:** Chronic total occlusion; Collateral circulation; Coronary intervention; Vasodilatation

## Introduction

Coronary chronic total occlusions, (CTOs) are common occurrences associated with significant morbidity and adverse outcomes [1]. They represent 10% of the lesions treated by percutaneous coronary intervention (PCI) [2]. Despite the benefits of PCI for CTO with regard to mortality and morbidity, it is associated negatively with greater radiation exposure, the need for a larger amount of contrast media, and longer procedure times. This is especially true when compared with interventions for non-CTO lesions. Additionally, it carries a significant risk for vessel dissection and perforation [3,4]. Therefore, patient selection plays a vital role due to the current low success rate and high complication risk of PCI for CTO.

There are many collateral vessels that connect the various coronary arteries in the normal human heart [5], but coronary collateral vessels are not visible angiographically unless there is total or near total occlusion [6]. These vessels are an important alternative source of blood flow when the main coronary arteries fail to supply enough blood, and they also may help protect the myocardium in patients with coronary artery disease [7]. Well-developed collateral circulation has even been suggested to have a favorable impact on infarct size [8], ventricular function, and ventricular aneurysm formation [9]. Beyond the clinical benefits, collateral vessels play an important role in the decision to undergo CTO intervention. Coronary angiography is an inadequate method for estimating the burden of atherosclerotic disease in an artery fed by collaterals. While sometimes the quality and diameter of the distal vessel is better than expected, this is not often the case. Conventional invasive coronary angiography also does not provide information on plaque composition, occlusion length, and the quality of distal run-offs [10,11].

To be sure, the functional relevance of coronary collateral vessels has been a matter of debate for many years: therefore, the purpose of this article is to investigate the functional relevance of coronary collateral circulation in the ipsilateral and contralateral arteries and estimate the quality of distal run-offs in patients with CTO of the coronary artery.

## Methods

### Study design and patient population

The study was approved by the institutional ethics committee and consent was obtained from all patients for participation in the study. All patients also gave their informed consent for the collection of detailed clinical data. In our study, we analyzed the prospectively entered data of 267 consecutive patients who underwent PCI for CTO in 285 lesions at hospital between December 2010 and November 2011. The indication for PCI was determined by the presence of stable angina and the demonstration of viable myocardium or silent ischemia in the territory of the occluded vessel. Twenty-nine patients were excluded because of unsuccessful CTO intervention. Patients whose angiographic

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image quality was poor, those who did not obtain a thrombolysis in myocardial infarction (TIMI) flow grade 3 due to dissection of the distal vascular bed by a guidewire, and those with more than one coronary occlusive lesions were also excluded. Collateral pathways were determined via angiography as in the study by David C. Levin in which pathways and functional significance of the coronary collateral circulation [5]. Two independent observers defined and categorized the collaterals according to the extent of epicardial coronary artery filling that was indicated. Patients with Rentrop's collateral grade [12] II and III were included in the statistical analysis. A total of 222 patients formed the study group. In 119 patients, the distal portion of total occlusion was filled with ipsilateral collateral connections (ICC) (ipsilateral group), and in 103 patients, it was filled with contralateral collateral connections (CCC) (contralateral group). Echocardiographic assessment of left ventrical ejection fraction (LVEF) was performed before PCI and one month after CTO recanalization. The LVEF was then compared with the pre- and post-recanalization values, both for the ipsilateral and contralateral groups and was calculated using the Simpson method. The values between the groups were then compared.

Quantitative coronary angiography (QCA) was performed, and the target vessel diameter (TVD) beyond occlusion was calculated before wire crossing (TVD1) and after stent implantation (TVD2) by two experienced cardiologists. The groups were also compared according to their dilatation rates (TVD2-TVD1).

## Definitions

Collateral blood vessels are vascular connections linking parallel arteries without an intervening capillary bed. The contralateral collaterals in our study were defined and determined by the extent of epicardial coronary artery filling via the collaterals with contrast medium from the contralateral side while the ipsilateral collaterals were determined similarly but with contrast medium from the ipsilateral side. Collaterals formed among them or through their own branches of the left anterior descending (LAD) and circumflex (Cx) arteries were considered ipsilateral collaterals. Coronary collateral circulation was graded according to the following Rentrop classifications: grade 0: no visible collaterals, grade 1: the filling of the side branch via collateral vessels without a visible epicardial coronary artery, grade 2: the incomplete filling of the epicardial coronary artery, and grade 3: the complete filling of the epicardial coronary artery. Chronic total occlusion is defined by the Euro CTO Club as "a lesion with a TIMI grade 0 flow within the occluded segment and angiographic or clinical evidence or high likelihood of an occlusion duration ≥ 3 months" [13]. Angiographic success was defined by the same group as "a restoration of TIMI flow grade 3 in the target vessel after stent implantation and a residual stenosis<15% by visual estimation" [14].

## Coronary angiographic technique and procedural characteristics

Coronary angiography was performed using Judkin's technique, with the transfemoral approach being preferred. Unfractionated heparin was used to maintain an activated clotting time (ACT) ≥ 300 sec. during the procedure. The antegrade approach was used in 218 patients while only four patients underwent the retrograde approach. Intracoronary isosorbide dinitrate was injected to examine coronary collateral circulation before the guidewire crossing, and the reference vessel diameter was calculated before the wire crossing (TVD1) and after stent implantation (TVD2) by two experienced cardiologists.

## Statistical analysis

The data was analyzed using the Statistical Package for the Social Sciences (SPSS) software for Windows version 13.0 (SPSS Inc., Chicago, Illinois, USA). Continuous variables were expressed as mean ± standard deviation, and categorical variables were expressed as a percentage. A p value<0.05 was considered statistically significant. A chi-square test was used for the comparison of qualitative data. The reference vessel diameter and dilatation rates of the groups were evaluated using the Mann Whitney U test and Wilcoxon test. Student's t-test was used to compare the echocardiographic parameters.

## Results

This study included 222 patients who had total occlusion of a coronary vessel (153 men and 69 women, mean age 61.5 ± 11.3 years). The LAD coronary artery was occluded in 74 patients, the left Cx artery in 47, and the right coronary artery (RCA) in 101. The various demographic and clinical characteristics of the patients, which were similar in the two groups, are summarized in table 1. However, the number of target coronary arteries varied greatly between the two groups, and the incidence of diabetes was significantly higher in the contralateral group than in the ipsilateral group (p=0.001) table 1.

The number of pathways which were visualized is shown in table 2. The majority of collateral circulation of the LAD and Cx arteries was ipsilateral, but in the RCA, contralateral was more common. There was a larger number of target vessels of the LAD and Cx in the ipsilateral group than in the contralateral group (p=0.001). On the other hand, an increase occurred in the number of target vessels of the RCA in the

| | Ipsilateral group n:119 (%) | Contralateral group n:103 (%) | P |
|---|---|---|---|
| Age (years) | 63.5 ± 10.7 | 61.9 ± 11.5 | 0.301 |
| Sex (M, n (%) | 40 (67.2%) | 73 (70.9%) | 0.558 |
| Hypertension, n (%) | 37 (67.2%) | 37 (69.8%) | 0.776 |
| Diabetes mellitus, n (%) | 28 (23.5%) | 57 (45.6 %) | 0.001 |
| Hyperlipidemia, n (%) | 57 (47.5%) | 46 (44.7%) | 0.629 |
| Smoking, n (%) | 52 (43.7%) | 36 (35.0%) | 0.184 |
| Previous CABG, n (%) | 12 (10.9%) | 8 (7.5%) | 0.683 |
| Previous stent, n (%) | 28 (25.4%) | 32 (30.1%) | 0.503 |
| Target coronary artery, n (%) | | | |
| LAD | 44(59.5) | 30(40.5%) | <0.001 |
| RCA | 38 (37.6 ) | 63(62.4%) | |
| Cx | 37 (78.7) | 10 (21.3%) | |

Abbreviation: M: male; CABG: coronary artery by-pass grafting; LAD: Left anterior descending artery; Cx: Circumflex artery; RCA: Right coronary artery

**Table 1:** Baseline demographic and clinical characteristics of the study patients.

| | Number/% |
|---|---|
| **Contralateral RCA** | 63 |
| 1. LAD artery to posterior descending branch of the RCA via the ventricular septal branches | 25/39.6 |
| 2. Distal circumflex artery to distal RCA artery | 23/36 |
| 3. Obtuse marginal branch of the circumflex artery to posterior left ventricular branch of RCA | 10/15.8 |
| 4. Distal LAD artery around the cardiac apex to posterior descending branch of the RCA | 3/4.7 |
| 5. Distal circumflex artery or its left atrial circumflex branch to A-V node branch of the RCA | 2/3.1 |
| **Ipsilateral RCA** | 38 |
| 1. Proximal acute marginal or conus branch of the RCA to a more distal acute marginal branch | 13/34.2 |
| 2. Kugel's artery passes from either the proximal right or left coronary artery down along the anterior margin of the atrial septum to anastomose with the A-V node branch of the distal RCA | 8/21.0 |
| 3. Acute marginal branch of the RCA to posterior descending branch of the RCA via the diaphragmatic surface of the right ventricle | 7/18.4 |
| 4. Sinoatrial node branch of the RCA around the lateral wall of the left atrium to the left atrial circumflex branch; then to the distal RCA | 5/13.1 |
| 5. Right ventricular branch of the LAD artery to acute marginal branch of the RCA | 5/13.1 |
| **Contralateral LAD** | 30 |
| 1. Acute marginal branch of the RCA to the LAD artery | 7/23.3 |
| 2. Conus branch of the RCA to the LAD artery | 8/26.6 |
| 3. Posterior descending branch of the RCA around the cardiac apex to the LAD artery | 3/10.0 |
| 4. Posterior descending branch of the RCA to LAD artery via the ventricular septal branches | 12/40.0 |
| **Ipsilateral LAD** | 44 |
| 1. Proximal ventricular septal branch of the LAD artery to a more distal septal branch | 25/56.8 |
| 2. Obtuse marginal branch of the circumflex artery to the LAD artery | 15/34.0 |
| 3. Diagonal branch of the LAD artery to the distal LAD artery | 4/9.0 |
| **Contralateral Cx** | 10 |
| 1. Distal RCA to the distal circumflex artery | 5/50 |
| 2. Posterior left ventricular branch of the RCA to the obtuse marginal branch of the circumflex artery | 5/50 |
| **IpsilateralCx** | 37 |
| 1. Left atrial circumflex branch to the distal circumflex artery | 17/45.9 |
| 2. Proximal obtuse marginal branch of the circumflex artery to a more distal obtuse marginal branch | 14/37.8 |
| 3. Diagonal branch of the LAD artery to the obtuse marginal branch of the circumflex artery | 6/16.2 |

Abbreviation: LAD: Left anterior descending artery; Cx: Circumflex artery, RCA: Right coronary artery

**Table 2:** Collateral pathways.

contralateral group that was markedly greater than in the ipsilateral group.

The mean value of TVD beyond occlusion, which was calculated before TVD1 and after TVD2, is shown in table 3. The mean value of TVD1 in the contralateral group was significantly higher than in the ipsilateral group (1.56 ± 0.59 mm and 1.33 ± 0.57 mm, respectively, p=0.003). The mean value of TVD after PCI in the contralateral group was much greater than in the ipsilateral group (2.22 ± 0.64 mm and 1.94 ± 0.59 mm, respectively, p=0.000). While there was a more representative escalation in the mean value of TDV2 in the ipsilateral and contralateral groups than in the TVD1. The coronary dilatation ratio of the target vessels was 0.61 ± 0.44 mm after coronary recanalization in the ipsilateral group and 0.66 ± 0.55 mm in the contralateral group. These dilatation ratios were insignificant between two groups (p>0.05).

The LVEF values are shown in table 4. These were higher before PCI in the contralateral group than in the ipsilateral group (47.6 ± 8.1 and 45.6 ± 7.1, respectively, p=0.049). The values after PCI were also higher in the contralateral group (50.0 ± 8.1 and 48.7 ± 6.9, p=0.152). There were greater increases of LVEF values in the ipsilateral group than in contralateral group (2.9 ± 1.9 and 2.3 ± 2.1, respectively, p=0.024). Additionally, there was a more detectable gain in the LVEF values after PCI for CTO in RCA patients in the ipsilateral group than for the contralateral patients. Furthermore, the LVEF values after PCİ for CTO in the LAD and CX patients increased more in the ipsilateral group than in the contralateral group.

## Discussion

The principal finding in this study is that mean value of the target vessel diameter (TVD1 and TVD2) beyond occlusion was significant higher in the contralateral group than in the ipsilateral group (p<0.05), but there was no significant difference in the coronary dilatation ratio between the two groups (p>0.05). The LVEF values before PCI in the contralateral group were significantly higher than in the ipsilateral group. However, the increases of LVEF after PCI were significantly higher in the ipsilateral group than contralateral group (p<0.05).

Successful recanalization for CTO of the coronary arteries has been associated with improved survival, improved left ventricular systolic function, reduced angina, and increased exercise capacity [3,15]. In these patients, the presence of collateral circulation may decrease the infarct area and reduce the incidence of left ventricular aneurysm formation [16]. Good coronary collateralization have recently been described to predict the risk for restenosis but also to reduce the mortality risk [17,18]. Meier et al. showed that the coronary collateralization has a relevant protective effect in patients with coronary artery diseases [18]. Patients with a high collateralization have a 36% reduced mortality risk compared with patients with low collateralization [18]. Collateral coronary blood flow depends on the equality of between the coronary artery perfusion pressure and flow resistance in the coronary bed [19]. Anatomically, collateral arteries serve as contralateral or ipsilateral conduits [20]. Many studies have investigated the functional relevance of coronary collateral circulation [21,22], but our attempts to find studies about the functional relevance of the anatomical differentiation of coronary circulation were fruitless.

Standard coronary angiography has been the gold standard for the diagnosis of coronary artery disease. However, coronary angiography demonstrates only vessel stenosis and the severity of coronary atherosclerosis. It cannot provide information concerning occlusion length, and quality of distal run-offs [10]. But a well-developed coronary collateral circulation may permit for the angiographic evaluation

| | İpsilateral group | Contralateral group | p |
|---|---|---|---|
| Increase in TVD | 0.61 ± 0.44 | 0.66 ± 0.55 | 0.813 |
| TVD1 (mm) | 1.33 ± 0.57 | 1.56 ± 0.59 | 0.003 |
| TVD2 (mm) | 1.94 ± 0.59 | 2.22 ± 0.64 | 0.000 |
| P | 0.000 | 0.000 | |

Abbreviation: TVD: Target vessel diameter; TVD1: Target vessel diameter before guidewire crossing; TVD2: Target vessel diameter after recanalization

**Table 3:** The angiographic characteristics of the groups.

| | İpsilateral group | Controlateral group | P |
|---|---|---|---|
| LVEF before PCI (%) | 45.6 ± 7.1 | 47.6 ± 8.1 | 0.049 |
| LVEF after PCI (%) | 48.7 ± 6.9 | 50.0 ± 8.1 | 0.152 |
| Increase in LVEF after PCI | 2.9 ± 1.9 | 2.3 ± 2.1 | 0.024 |
| Increase in LVEF in LAD patients | 2.9 ± 2.0 | 2.3 ± 1.2 | 0.182 |
| Increase in LVEF in RCA group | 3.6 ± 2.1 | 2.4 ± 2.3 | 0.007 |
| Increase in LVEF in Cx group | 2.3 ± 1.2 | 2.1 ± 2.8 | 0.714 |

Abbreviation: LVEF: Left ventricular ejection fraction; PCI: Percutaneous coronary intervention; LAD: Left anterior descending artery; Cx: Circumflex artery; RCA: Right coronary artery

**Table 4:** Ejection fraction before and one month after recanalization of coronary artery patients with chronic total occlusion.

the segments of vessel beyond the occlusion [23]. A difference in the definitions of contralateral or ipsilateral circulation may help to treatment modality decisions regarding the treatment of CTO. This may effect to patient outcomes.

The biological composition of CTO changes over time. There is approximately an 80% reduction in the overall size of the vessel after six weeks. The size of the microvessels and the relative blood volume within the CTO began to decrease during the latter, intermediate, and advanced stages of occlusion time [24]. Decreases in flow are also associated with a decrease in lumen diameter, as is seen in lesions that cause CTO [25]. In this study, the mean value of TVD before PCI was 1.33 ± 0.57 mm in the ipsilateral group and 1.56 ± 0.59 mm in the contralateral group ($p<0.05$). This shows that the diameter of target vessels in the collateral group was well preserved. The mean value of TVD after PCI was 1.94 ± 0.59 mm and 2.22 ± 0.64 mm in the ipsilateral and contralateral group, respectively ($p<0.05$). Increases in the diameter of target vessels existed in both groups. The target vessel coronary dilatation ratio was 0.61 ± 0.44 mm after coronary recanalization in the ipsilateral group and 0.66 ± 0.55 mm in the contralateral group. This ratio was insignificant between the two groups ($p>0.05$). Our findings suggest that anatomical differentiation of coronary collaterals was not affected by the increases in the diameter of the target vessels after PCI. However, our study result show that contralateral circulation in patients with CTO have shown less negative vessel remodelling after CTO.

Some studies have shown that there is a negative relationship between collateral development and cardiovascular risk factors related to endothelial dysfunction such as diabetes mellitus, age, hyperlipidemia, and obesity [26]. Endothelial dysfunction prevents the vasoactive effect of a healthy endothelium. Other factors such as nitric oxide and plasma asymmetric dimethylarginine also affect endothelial function and collateral development [27]. Hemodynamic factors that affect contralateral collateral flow contain ipsilateral distal vascular resistance, the severity of contralateral stenosis, and the diameter of the collateralized vascular bed [28]. After successful recanalization of a coronary CTO, most patients experience subjective improvement, and relief of angina has been recorded. This has been documented by exercise testing. Moreover, improvement of left ventricular function after recanalization has been demonstrated [29,30]. Szwoch et al. compared the results of twenty-three patients who underwent recanalization of the LAD or RCA and found an increase in the LVEF in both groups in the post-recanalization analysis [31]. The majority of collateral circulation of the LAD and Cx arteries was ipsilateral. However, in the RCA, it was contralateral. We compared the LVEF before PCI and after PCI, and the contralateral group had better LVEF values than the ipsilateral group at both occasions ($p<0.05$). This is consistent with the study of Szwoch et al. who found significantly lower LVEF values in patients with chronic occlusion of the LAD when compared with the RCA group [31]. We also compared the increases of LVEF after PCİ between the two groups and found that the values in the ipsilateral group had significant increases compared with the contralateral group. Our findings suggest that if the ipsilateral collateral were dominant, early revascularization would be more necessary.

In spite of significant advances in revascularization strategies in recent years, a significant numbers of patients with CTO are excluded from PCI and coronary artery bypass grafting (CABG) due to unsuitable coronary anatomy [19]. Our findings suggest that a correct and unified anatomical definition of collateral coronary circulation may help to decide which patients suitable for revascularization in patients with CTO.

## Study Limitations

The study is the small size and single-center. A second limitation of the study presence of multiple factors that affect endothelial function and vascular dilatation. Also non-invasive coronary multi-detector computed tomography (MDCT) can visualize the distal coronary artery lümen of CTO lesion. But it is expensive and availability is limited. So, there is a need for a cheap and simple marker. Therefore, we used of collateral vessel for predict to size of distal vessel beyond the occlusion. Our findings suggest that anatomical differentiations of coronary collaterals aren't use for prediction. So further studies with larger number of patients are required.

## Conclusion

Our findings suggest that anatomical differentiation of coronary collaterals was not estimated the ratio of the increases in the diameter of the target vessels after PCI. However, our study results concerning contralateral circulation in patients with CTO have shown less negative vessel remodelling after CTO. We also showed that the increases of LVEF after PCI, the ipsilateral group had significant increases compared with the contralateral group. A correct and unified anatomical definition of collateral coronary circulation may help to decide the best strategy for revascularization. Our findings suggest that if the ipsilateral collateral were dominant, early revascularization would be more necessary.

- The target vessel diameter in the distal vessels (beyond the occlusion) to be larger if patients had contralateral collaterals compared to those with ipsilateral collaterals.
- The LV function improved more in the ipsilateral collateral group after PCI.
- Contralateral circulations in patients with CTO have shown less negative vessel remodelling after CTO.

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