Functional assessment of intermediate lesions of collateral donor artery in chronic total coronary occlusions

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ABSTRACT

Introduction and objectives: The strategy of the percutaneous treatment of patients with multivessel disease associated with chronic total coronary occlusion (CTO) lesions is not well defined. Also, the functional significance of lesions located in the collateral donor artery has not been fully addressed. Using the fractional flow reserve (FFR) the objective was to evaluate the amount of ischemia related to the angiographically intermediate stenosis of collateral donor vessels before and immediately after successful percutaneous coronary intervention (PCI) of a CTO. Also, to assess any changes operated in the amount of ischemia using cardiovascular magnetic resonance imaging prior to the PCI and at 1-month follow-up.

Methods: Prospective pilot study including 14 patients with stable angina and a CTO receiving collateral circulation from a blood vessel with intermediate stenosis (50%-70% diameter stenosis measured using quantitative angiography). In order to indicate recanalization by PCI all patients were referred for magnetic resonance assessment of the presence of myocardial viability.

Results: Seven (50%) of the 14 patients included showed FFR values ≤ 0.80 before the PCI. FFR measures of the donor artery significantly increased after the revascularization of the CTO (0.75 [0.73-0.78] vs 0.83 [0.81-0.84]; \( P = 0.017 \)). Eventually, only 3 patients showed hemodynamically significant FFR values after the recanalization of CTO requiring further revascularization. There was a tendency towards a reduction of the number of ischemic segments (2.5 [0-4] vs 0 [0-0.25]; \( P = 0.066 \)) assessed using magnetic resonance imaging before and after the PCI. No major adverse cardiovascular events were reported at the 2-year follow-up.

Conclusions: Our data suggest that FFR measurements in intermediate stenoses of collateral donor vessels of a CTO may be misleading. Therefore, the strategy of focusing primarily on the revascularization of the CTO and then on the assessment of the intermediate lesion in a collateral donor vessel may be recommended.

Keywords: Chronic total coronary occlusion. Collateral donor vessel. Fractional flow reserve. Cardiovascular magnetic resonance imaging.

Evalúación funcional de lesiones intermedias en arterias donantes de colaterales en oclusiones totales crónicas

RESUMEN

Introducción y objetivos: La estrategia de tratamiento percutáneo de los pacientes con enfermedad multivaso y oclusión total crónica (OTC) no está bien definida. La importancia funcional de las lesiones localizadas en arterias donantes de colaterales no se ha abordado por completo. Nuestro objetivo fue evaluar mediante reserva fraccional de flujo (RFF) la cantidad de isquemia dependiente de una lesión angiográfica intermedia en un vaso donante de colaterales antes y después de la recanalización de la OTC, y valorar el cambio en la cantidad de isquemia por resonancia magnética cardíaca (RMC) antes y 1 mes después de la recanalización.

Métodos: Estudio piloto prospectivo en 14 pacientes con angina estable y una OTC que recibía circulación colateral de un vaso con una estenosis intermedia (50-70% por angiografía coronaria cuantitativa). Para indicar la recanalización, todos los pacientes presentaban viabilidad miocárdica por RMC.

Resultados: De los 14 pacientes, 7 (50%) evidenciaron una RFF ≤ 0,80 antes de la recanalización. Los valores medios de RFF de la arteria donante aumentaron significativamente tras la recanalización de la OTC [0,75 [0,73-0,78] frente a 0,83 [0,81-0,84]; \( p = 0,017 \)]. Solo 3 pacientes mostraron valores de RFF hemodinámicamente significativos después de la recanalización de una OTC que requirió recanalización adicional. Hubo una tendencia hacia una reducción del número de segmentos isquémicos [2,5 [0-4] frente a 0 [0-0,25]; \( p = 0,066 \)] evaluados por RMC antes y después del intervencionismo. No se observaron eventos cardiacos adversos mayores durante el seguimiento de 2 años.

Keywords: Chronic total coronary occlusion. Collateral donor vessel. Fractional flow reserve. Cardiovascular magnetic resonance imaging.
INTRODUCTION

The prevalence of chronic total coronary occlusions (CTO) is around 16% to 52% in patients with significant coronary artery disease on the angiography.1 In the presence of a CTO, collateral blood supply is often enough to maintain resting perfusion and contractility in the collateral-dependent myocardium.2 Restoration of antegrade flow by the percutaneous coronary intervention (PCI) of a CTO is associated with a rapid reduction in the collateral supply received in the treated vessel.3 Randomized trials support the use of fractional flow reserve (FFR) to guide the PCI with an established treatment threshold of ≤ 0.8.4-8 Although the FFR is reported to be independent of hemodynamic changes,9 it is intimately related to total coronary flow through a stenosis, which in turn is related to perfused myocardial mass.10 In keeping with this, there have been several reports of normalization of FFR values from collateral donor vessel after successful recanalization of a CTO.11 By removing nutrient flow to the collateralized territory by CTO recanalization, the collateral network almost immediately increased its resistance, thus favoring flow to the donor territory during maximal hyperemia.12 In patients with Rentrop grade-2 or grade-3 collateral flow, the FFR value of the donor artery increased at least 0.10 after revascularization of the recipient artery. However, the FFR value did not change significantly in patients with Rentrop grade-0 or grade-1 collateral flow following revascularization. This suggests that well-developed collateral circulation might overestimate the FFR value in the donor artery with mild stenosis.13 The assessment of myocardial-perfusion through cardiovascular magnetic resonance imaging (CMR) is a noninvasive imaging modality for the detection of coronary artery disease with a high degree of concordance with the FFR for ischemia detection.14-16

Also, the CMR has emerged as robust and reproducible method to assess the ischemia and viability of the myocardium related to the CTO.17-19 The MR-INFORM trial showed that in patients with stable angina and risk factors for coronary artery disease, the CMR of myocardial perfusion was associated with a lower incidence of coronary revascularization compared to the FFR and was noninferior to the FFR regarding major adverse cardiovascular events [all-cause mortality, non-fatal myocardial infarction or target-vessel revascularization] at 12 months.20 However, it is uncertain whether opening a CTO can modify the amount of ischemia related to an angiographically intermediate lesion of the collateral donor vessel. It could also be possible to diagnose microvascular dysfunction using CMR.21

Therefore, in this pilot study, using the FFR we assessed changes in the amount of ischemia related to the angiographically intermediate stenosis of collateral donor vessel before and immediately after the successful PCI of a CTO. We also tried to determine any changes in the amount of ischemia using the CMR prior to the PCI and 1 month after recanalization.

METHODS

In this prospective pilot study, we included patients with stable angina and CTO with collateralization of the distal vascular bed, and collateral donor vessel with a single angiographically intermediate lesion [50%-70% diameter stenosis by quantitative coronary angiography]. In order to indicate recanalization through PCI all patients were referred for CMR evaluation to assess the presence of myocardial viability. During the procedure, the FFR of the donor vessel was measured before the PCI of the CTO (figure 1). Only with FFR values ≤ 0.80, the measure was reassessed after the procedure (figure 2). A second CMR was performed 1 month after the index PCI. All patients gave their informed consent, the local ethics committee approved the study, and all procedures were performed in accordance with the Helsinki Declaration. The study population was clinically followed for 2 years. The rate of major adverse cardiovascular events was established. This was defined as a composite of all-cause mortality, non-fatal acute myocardial infarction (AMI), clinically-driven target vessel revascularization or rehospitalization due to unstable or progressive angina according to Braunwald Unstable Angina Classification. The exclusion criteria were: prior IAM; failed recanalization of the CTO, inability to obtain signed written informed consents; severity of valvular heart disease; acutely uncomplicated chronic heart failure; asthma or obstructive sleep apnea; high risk of bleeding; known hypersensitivity or contraindication to aspirin; nursing subjects; patients with pacemakers/implantable cardioverter-defibrillators.

The percutaneous coronary intervention

The PCI was performed using bilateral femoral artery access and 7-Fr sheaths and guide catheters. Anticoagulation was achieved with 100 U/Kg of unfractionated heparin to maintain activated clotting times of 250-300 msec. All the procedures on the CTO were performed using the antegrade wire escalation technique. All patients were treated with drug-eluting stent implantation. The J-CTO score was calculated for each CTO lesion and assessed taking the following parameters into consideration: occlusion...
Figure 1. Example of chronic total coronary occlusion (CTO) of right coronary artery (panel A, yellow arrows) with collateralization of distal vascular bed, and left main and left anterior descendent artery (LAD) as the collateral donor vessel shows an angiographically intermediate lesion (panel B, yellow circles). During the procedure, the fractional flow reserve (FFR) of the donor vessel was measured before the percutaneous coronary intervention of the CTO (panel C).

Figure 2. Example of the recanalization of chronic total coronary occlusion (CTO) of the right coronary artery (panel A) with left anterior descendent artery (LAD) as the collateral donor vessel shows an angiographically intermediate lesion (panel B, yellow circles). Panel C: after the CTO repermeabilization, the fractional flow reserve (FFR) value of the LAD increased (FFR value = 0.91).

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length, stump morphology, presence of calcification, presence of
tortuosity and prior attempt to open the CTO.\textsuperscript{22} Collateral flow
was graded in accordance with Rentrop collateral flow classification.\textsuperscript{23} Procedural success was achieved as achievement of residual
post-PCI stenosis < 30\% in the target lesion associated with TIMI
grade-3 flow without mortality, IAM or new lesion revascularization
during the index hospitalization.

**Assessment using fractional flow reserve**

To measure FFR in the intermediate coronary lesions a 0.014-inch
pressure-monitoring guidewire (Prime Wire Volcano Therapeutics,
Inc, Rancho Cordova, CA, United States) was used. After calibration
of both the aortic and wire pressures, the FFR wire was
advanced until the tip of the guiding catheter. Equalization of both
pressures was performed. Then, the wire was advanced and positioned
distally at least 15 mm from the stenotic lesion followed by the
administration of 0.2 mg of nitroglycerin to avoid any form of
epicardial vasoconstriction. Maximal hyperemia was induced
through the IV infusion of adenosine [180 μg/kg/min]. After
reaching the steady state we measured the FFR as the ratio
between mean distal coronary pressure and mean aortic pressure.
Values < 0.80 were considered significant from the hemodynamical
standpoint. After FFR measurement and under maximal hyperemia, the pressure wire was pulled back until the sensor
was close to the tip of the guiding catheter to make sure that no
drift had occurred.

**Cardiovascular magnetic resonance imaging**

All CMR studies were performed using a General Electric Signa
HDxT 1.5-T scanner equipped with an 8-channel coil and cardiac-dedicated software. Perfusion studies were conducted using a
gradient-echo turbo-field sequence prescribed in the left ventricular
short-axis orientation, at the basal, mid-ventricular and apical levels after 4 min of IV administration of adenosine
(Atepo-din) at a dose of 180 μg/kg/min and simultaneous administration
of 0.1 mmol/kg of gadobutrol (Gadovist, Bayer Hispania) at a 5 mL/s rate. The functional and volumetric assessment of the left ventricle (LV) was conducted using the conventional Steady State Free Precession (SSFP) cine sequence, prescribed in sequential short-axis slices, and encompassing the entire LV and
the 2-, 3-, and 4-chamber views. The typical temporal and in-plane spatial resolution of these images was 40 ms and
1.4 × 1.4 mm, respectively. Rest perfusion images were obtained at least 10 min after the stress perfusion study using the same
sequence, location, and contrast injection protocol. Ten minutes
after administering the dose of gadolinium for the rest perfusion study, late gadolinium-enhanced images were obtained using a
segmented inversion-recovery spoiled gradient echo sequence in the
same location and identical spatial resolution as the cine images.
To calculate left ventricular ejection fraction (LVEF), the LV mass and left ventricular end-systolic and end-diastolic
volumes, the endocardial and epicardial borders were manually
traced at end-systole and end-diastole in the cine short-axis images using a dedicated software package (ReportCard, GE).
The regional wall motion analysis was performed by visual
grating of the cine images according to the 17-segment model
proposed by the American Heart Association.\textsuperscript{27} The pre- and
post-PCI image analysis was conducted by 2 independent experi-
enced operators masked to the patient’s coronary anatomy and the
PCI results; the disparities in their evaluation were resolved by
consensus with a third independent operator. The appropriate
allocation between the involved myocardial segments and the
correspondent coronary anatomy in each case was evaluated
according to previously reported criteria.\textsuperscript{11}

**Statistical analysis**

The distribution of continuous variables was assessed by visual
inspection of frequency histograms and using the Shapiro–Wilk
test. Continuous variables were expressed as mean ± standard
deviation (SD) or median with interquartile range [IQR] when they
followed a normal or non-normal distribution, respectively. The
continuous variables were compared using the unpaired Student’s
t test or Mann–Whitney U test and the categorical variables were
compared using the chi-square test or Fisher’s exact test, as appro-
priate. Correlations between variables were conducted using the
Pearson test. The software SPSS 17.0 (SPSS Italy, Florence, Italy)
was used for statistical analyses.

**RESULTS**

We screened 23 patients with stable angina and CTO with collateral-
ization of distal vascular bed, and collateral donor vessel with
angiographically intermediate lesion. We excluded 9 patients who
showed some exclusion criteria. Fourteen patients were finally
included in the study (Figure 3). The clinical characteristics and
angiographic details are shown on Table 1. Seven intermediate lesions
(50\%) of the collateral donor vessels showed FFR values ≥ 0.80 before
the recanalization of the CTO. On average, FFR measures signifi-
cantly increased after CTO revascularization (0.75 [0.73–0.78] vs 0.83
[0.81–0.84]; \( P = .017 \)) (Table 2 and Figure 4). Four patients normalized
their FFR values, while in the other 3 the FFR remained hemody-
namically significant and required subsequent PCI. There was a
tendency towards a reduction of the number of ischemic segments
assessed through CMR before and after the recanalization of the
CTO (2.5 [0–4] vs 0 [0–0.25]; \( P = .066 \)). No differences were found
in other parameters including the number of hypokinetic segments,
left ventricular ejection fraction, left ventricular end-diastolic and
end-systolic volumes; left ventricular mass; and necrotic mass before
and after the PCI (Table 2). In addition, the number of ischemic
segments did not significantly correlate with the FFR values before
or after PCI (\( R^2 = .31, P = .328; R^2 = .68, P = .20 \), respectively).
Finally, no major adverse cardiovascular events were reported
during the 2-year follow-up.
DISCUSSION

These are the main findings of the study: 
a) functional assessment of intermediate lesions located in the collateral donor artery showed significantly lower FFR values than it would have in the absence of collateralized CTOs; 
b) after the recanalization of the CTO, the FFR values of the collateral donor artery normalized in most of patients; 
c) the amount of ischemia assessed through CMR used to decrease after successful CTO recanalization; 
d) no major adverse cardiovascular events were reported in our population at the long-term follow-up.

The FFR is a method used to assess the functional significance of coronary stenosis while taking into account the following parameters: severity of stenosis, myocardial territory and viability, and collateral perfusion. Results from the FAME trial showed that FFR-guided PCI was superior to the angiography-guided PCI at 1 and 2 years in terms of death or AMI and AMI alone. In the FAME 2 trial, the FFR-guided PCI reduced the rate of major adverse cardiovascular events compared to medical therapy alone. To this day, physiology has been proposed to outline which stenoses should be treated in the context of multivessel disease. However, there is uncertainty around what the waiting time is before performing an accurate pressure wire assessment of donor arteries after the successful recanalization of a CTO. Several studies have shown that full collateral regression does not happen immediately after the successful revascularization of a CTO. During embryonic development, collaterals derive either from capillary sprouting or pre-existing arteriolar connections. Collateral growth occurs through 2 major processes: arteriogenesis and arteriolization.

Table 1. Clinical and angiographic characteristics

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>Patients (n = 14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>67.44 ± 12.9</td>
</tr>
<tr>
<td>Male</td>
<td>12 (85)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>6 (42.8)</td>
</tr>
<tr>
<td>Smoking</td>
<td>2 (14.3)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>10 (71.4)</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>5 (35.7)</td>
</tr>
<tr>
<td>Renal failure</td>
<td>2 (14.3)</td>
</tr>
<tr>
<td>Prior CABG</td>
<td>1 (7.1)</td>
</tr>
<tr>
<td>Medical treatment</td>
<td></td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>5 (35.7)</td>
</tr>
<tr>
<td>Calcium antagonist</td>
<td>2 (14.3)</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>4 (28.6)</td>
</tr>
<tr>
<td>Statins</td>
<td>10 (71.4)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Angiographic characteristics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CTO vessel</strong></td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>2 (14.3)</td>
</tr>
<tr>
<td>LCX</td>
<td>1 (7.1)</td>
</tr>
<tr>
<td>RCA</td>
<td>11 (78.6)</td>
</tr>
<tr>
<td>Calcification</td>
<td>7 (50%)</td>
</tr>
<tr>
<td>Bending &gt; 45 degrees</td>
<td>2 (14.3)</td>
</tr>
<tr>
<td>Tapered</td>
<td>8 (57.1)</td>
</tr>
<tr>
<td>Occlusion length, mm</td>
<td>24.6 [6-43.3]</td>
</tr>
<tr>
<td>Rentrop &gt; 1</td>
<td>13 (92.8)</td>
</tr>
<tr>
<td>J-CTO score &gt; 2</td>
<td>3 (21.4)</td>
</tr>
</tbody>
</table>

| **Collateral donor vessel**  |               |
| LAD                          | 7 (50)        |
| LCX                          | 4 (28.6)      |
| RCA                          | 3 (21.4)      |
| Stenosis degree              | 52 (50-55)    |

Data are expressed as n (%), mean ± standard deviation or median (interquartile range).

Table 2. FFR and CMR measures in the study population

<table>
<thead>
<tr>
<th></th>
<th>Before PCI (n = 7)</th>
<th>After PCI (n = 7)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pd/Pa</td>
<td>0.93 (0.88-0.96)</td>
<td>0.91 (0.89-0.93)</td>
<td>1.0</td>
</tr>
<tr>
<td>FFR</td>
<td>0.75 (0.73-0.78)</td>
<td>0.83 (0.81-0.84)</td>
<td>.017</td>
</tr>
<tr>
<td>IS</td>
<td>2.5 (0.0-4.0)</td>
<td>0.0 (0.0-0.25)</td>
<td>.066</td>
</tr>
<tr>
<td>HS</td>
<td>1.0 (0.0-4.75)</td>
<td>0.0 (0.0-0.50)</td>
<td>.15</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>60.5 (55.0-63.25)</td>
<td>63.5 (54.0-65.25)</td>
<td>.41</td>
</tr>
<tr>
<td>LVEDV, ml</td>
<td>111.3 (102.7-451.1)</td>
<td>109.0 (100.6-139.2)</td>
<td>.50</td>
</tr>
<tr>
<td>LVESV, ml</td>
<td>41.1 (38.6-65.17)</td>
<td>38.9 (35.2-81.4)</td>
<td>.49</td>
</tr>
<tr>
<td>LV mass, gr</td>
<td>83.4 (56.4-92.1)</td>
<td>88.5 (69.1-110.2)</td>
<td>.50</td>
</tr>
<tr>
<td>NM, gr</td>
<td>0.83 (0.3-2.3)</td>
<td>0.92 (0.4-1.5)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

CMR, cardiovascular magnetic resonance imaging; FFR, fractional flow reserve; HS, hypokinetic segments; IS, ischemic segments; LV, left ventricular; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; NM, necrotic mass; Pd/Pa: resting distal coronary pressure to aortic pressure ratio; PCI, percutaneous coronary intervention. Data expressed as median (interquartile range).

Figure 4. Fractional flow reserve (FFR) values of 7 angiographically intermediate lesions in the collateral donor vessels before and after the percutaneous coronary intervention (PCI) of a chronic total coronary occlusion.
Recently, Mohdnazri et al. have showed that the successful recanalization of a right coronary artery CTO resulted in a modest FFR increase of the predominant collateral donor vessel associated with a reduced coronary flow, of a similar magnitude at baseline and maximal hyperemia. Few patients of our study did not show this improvement. The persistence of non-angiographically visible collateral circulation, the presence of microcirculation dysfunction and type of prior collateral circulation grade, and distal embolization or myocardial infarction following PCI recanalization may be potential causes of this lack of improvement. In this regard, in a recent study, measurements repeated shortly after the PCI of a CTO showed transient procedural-related changes like microvascular dysfunction secondary to distal embolization, catecholamine release, left ventricular stunning or hyperemic stimulus related to side-branch occlusion.

Our data suggest that in the setting of CTOs and an angiographically intermediate lesion of the collateral donor vessel, it seems like the FFR measurement may be misleading. Therefore, it seems advisable to postpone the assessment of intermediate stenoses until achieving the successful recanalization of the associated CTO. This approach should avoid overtreating patients who only require the revascularization of their CTOs. On the contrary, if the recanalization of the CTO fails, treating the intermediate stenosis in the donor artery may be necessary to reduce ischemia in this territory. It also still is a good practice to try to re-open the CTO prior to performing any interventions on the donor vessel, due to the risk of extensive acute ischemia in case of troublesome PCI.

Moreover, we did not find any correlations between the amount of ischemia assessed through CMR and the FFR values before or after the PCI. As far as we know, this is the first comparison between CMR and FFR assessment of an angiographically intermediate lesion in a collateral donor vessel related a CTO. Former studies have suggested that the CMR underestimates or that the FFR overestimates the number of ischemic segments in multivessel disease. This discrepancy seems to highlight the poor accuracy of the FFR method in the presence of collaterals involving territories that are from the target lesion to be assessed.

Finally, after treating the patients according to the FFR measures obtained after the PCI of a CTO, no major adverse cardiovascular events were detected at the 2-year follow-up.

**CONCLUSIONS**

The FFR assessment of intermediate stenoses in a collateral donor vessel of a CTO may overestimate the severity of the lesion by increasing the territory at risk. Therefore, the strategy of first focusing on the revascularization of the CTO and then re-assess the intermediate lesion in a collateral donor vessel may be recommended to overcome this pitfall.

**WHAT IS KNOWN ABOUT THE TOPIC?**

- In patients with CTOs, collateral circulation supplied by donor vessels is often seen.
- The progression of atherosclerosis in donor vessels may compromise the coronary circulation of several territories.
- Angiography is not a reliable technique to assess the hemodynamic compromise of an intermediate lesion located in a vessel that provides collateral circulation to a chronically-occluded vessel.

**WHAT DOES THIS STUDY ADD?**

- Patients with positive FFR of donor vessels before the recanalization of a CTO may show significant increases of FFR values (even normalization in most of them too) after successful revascularization of the CTO.
- Also, the revascularization of the CTO may lead to a reduction in the number of ischemic segments assessed through CMR before and after the PCI of the CTO.
- These findings support the strategy of recanalizing the CTO first and then performing the functional assessment of donor artery with intermediate lesions.

**REFERENCES**


