###### The Impact of Chronic Total Occlusion (CTO) Percutaneous Coronary Intervention (PCI) Upon Donor Vessel Fractional Flow Reserve and Instantaneous Wave-Free Ratio: Implications For Physiology-Guided PCI in Patients With CTO

Shah R. Mohdnazri, MB BCh a,b, Grigoris V. Karamasis, MD a,b, Firas Al-Janabi, MBBS

a,b, Christopher M. Cook, MBBS c, James Hampton-Till, BSc, PhD b, Jufen Zhang, PhD b

, Rasha Al-Lamee, MBBS c, Jason N. Dungu, MBBS, PhD a, Swamy Gedela, MBBS a, Kare H. Tang, MBBS a, Paul A. Kelly, MBBS, MD a, Justin E. Davies, MBBS, PhD c,

John R. Davies, MBBS, PhD a,b, Thomas R. Keeble, MBBS, MD a,b

a The Essex Cardiothoracic Centre, Basildon and Thurrock University Hospitals NHS Foundation Trust, UK

b Anglia Ruskin University, Chelmsford, UK

c Imperial College London, London, UK

Funding source

This study received research grant support from Philips Volcano and Terumo Corporation. J.E.D. is a British Heart Foundation fellow. C.M.C. (MR/M018369/1) is a Medical Research Council fellow.

Conflict of Interest

J.E.D. is a co-inventor of iFR technology. C.M.C. and R.A.L. have conducted teaching sessions on behalf of Volcano Philips.

Word Count: 4359 words

**Running title:** The impact of CTO PCI on collateral donor vessel physiology.

Corresponding author:

Dr Thomas Keeble, BSc MBBS MRCP MD

Department of Cardiology, The Essex Cardiothoracic Centre, Basildon and Thurrock University Hospitals NHS Foundation Trust, Basildon, SS16 5NL, United Kingdom.

E-mail: Thomas.keeble@btuh.nhs.uk Telephone: +44 1268 524900

Fax number: +44 1268 394802

Abstract

**Objectives** To investigate the immediate and medium term impact of right coronary artery (RCA) chronic total occlusion (CTO) percutaneous coronary intervention (PCI) upon collateral donor vessel physiological indices.

**Background** CTO PCI influences collateral donor vessel physiology, making the indication and / or timing of donor vessel revascularization difficult to determine.

**Methods** In patients with CTO of the RCA; resting Pd/Pa, iFR and FFR were measured in donor vessels pre-CTO PCI, immediately post and at 4 month follow-up. Collateral FFR (FFR*coll*) was measured at the same time points.

**Results** 34 patients were recruited and 28 of them completed follow up. The mean age was 62±10 years old. In the predominant donor vessel immediately post successful PCI, FFR and Pd/Pa did not change significantly (FFR: 0.76±0.12 to 0.75±0.13, *p*=0.267; Pd/Pa: 0.89±0.07 to 0.90±0.07, *p*=0.109). iFR increased significantly (0.86±0.10 to 0.88±0.10, *p*=0.012) immediately after the index procedure. At 4 months follow-up, there was a statistically significant increase in Pd/Pa, iFR and FFR (0.03±0.05 *p*=0.006, 0.04±0.06 *p*=0.003, and 0.02±0.06 *p*=0.047 respectively) compared to baseline. FFR*coll* remained unchanged immediately post PCI (0.31±0.10 vs. 0.34±0.11 *p* =0.078) compared to baseline, but was significantly reduced to 0.19 ± 0.07 at 4 months follow-up (*p*<0.0001).

**Conclusion** Successful recanalization of a RCA CTO resulted in a modest yet significant increase in the predominant donor vessel coronary pressure-derived indices immediately

post CTO PCI in the case of iFR and at 4 month follow-up for resting Pd/Pa, iFR and FFR compared to baseline, accompanied by a concomitant reduction in collateral function. (250 words)

**Keywords:** chronic total occlusion, collateral circulation, fractional flow reserve, instantaneous-wave-free ratio, pressure.

Condensed abstract:

In order to investigate the impact of right coronary artery (RCA) chronic total occlusion (CTO) PCI; and the influence of collateral regression upon collateral donor vessel physiological indices, we prospectively measured resting Pd/Pa, instantaneous wave-free ratio (iFR) and fractional flow reserve (FFR) in donor vessels pre-CTO PCI, immediately post and at 4 month follow-up. Collateral FFR (FFR*coll*) was measured at the same time points.

Successful recanalization of a RCA CTO lead to improvement in predominant donor vessel physiology immediately post CTO PCI in the case of iFR and at 4 months follow- up for resting Pd/Pa, iFR and FFR.

(98 words)

Abbreviations and Acronyms

|  |  |
| --- | --- |
| CABG | Coronary artery bypass graft surgery |
| CC | Collateral connections |
| CMR | Cardiac magnetic resonance imaging |
| CTO | Chronic total occlusion |
| FFR | Fractional flow reserve |
| FFR*coll* | Collateral fractional flow reserve |
| iFR | Instantaneous wave-free ratio |
| Pa | Aortic Pressure |
| Pd | Distal local pressure |
| Pv | Central venous pressure |
| QCA | Quantitative coronary angiography |

**Introduction**

Approximately 1 in 4 patients with obstructive coronary artery disease undergoing coronary angiography have at least one chronic total occlusion (CTO) (1). In the presence of angiographically intermediate lesions in non-CTO arteries, decisions regarding revascularization strategy are challenging. Coronary physiology assessment helps identify ischaemia and guide revascularization decision-making. Fractional flow reserve (FFR) is the current gold standard for the functional assessment of lesion severity in stable patients with single or multi-vessel disease (2,3). The instantaneous wave-free ratio (iFR) is a resting pressure derived index that has been proposed as an alternative for the assessment of coronary stenosis severity (4). Its clinical outcomes in guiding PCI were non-inferior to FFR in two recent large randomised control trials (5, 6).

Recanalization of a CTO reduces the myocardial mass perfused by a collateral donor vessel and a number of previously published cases and case series have reported a significant improvement in FFR measured in the donor artery (7-13). A recent study of a small cohort of left and right coronary CTOs demonstrated a modest but significant increase in FFR immediately after CTO PCI in the predominant collateral donor vessel associated with a reduction in donor coronary flow (14).

The aims of this study were to serially assess the physiological impact of RCA CTO PCI and the influence of collateral regression upon donor vessel coronary physiology indices (resting Pd/Pa, iFR and FFR) pre, immediately post-CTO PCI and at 4 month follow-up. We selected RCA CTOs, as this is the most common CTO found (1) and functional assessment of LAD disease in the presence of an RCA CTO has increased clinical significance, as it can be the determinant between percutaneous and surgical

revascularization. We hypothesised that donor vessel coronary physiology indices will improve following successful CTO PCI and at follow-up.

Methods

*Study patients*

40 consecutive patients scheduled for RCA CTO PCI with symptomatic stable angina were recruited at our institution from October 2015 to November 2016. All patients had an RCA total occlusion with duration ≥3 months, evidence of viability and / or ischaemia in the CTO territory as shown by non-invasive cardiac imaging. 92% of patients had perfusion cardiac magnetic resonance imaging (CMR) performed prior to the CTO PCI. All patients had spontaneously visible collaterals from a contralateral donor artery. Patients with previous CABG, > 1 CTO and significant LMS disease were excluded. The study was approved by the local ethics committee (15/EE/0269) and all patients provided written informed consent prior to the procedure.

*CTO PCI*

PCI to RCA CTO was performed with standard interventional techniques. Dual arterial access was used as per standard practice in CTO PCI. Femoral venous access was obtained for central administration of adenosine and measurement of central venous pressure (Pv) using a 5-F Pigtail catheter. CTO recanalization strategy was at the operator’s discretion, following the hybrid algorithm (15). A procedure was considered successful when achieving TIMI flow grade 3 with <30% angiographic residual stenosis in the CTO vessel. All patients had third-generation drug-eluting stents (Ultimaster DES, Terumo Corp, Japan) and were discharged on dual antiplatelet therapy with a duration of at least one year.

*Study protocol and coronary physiology measurements*

To begin with physiological measurements were performed in the collateral donor vessels (LAD and Cx). ECG, heart rate, aortic pressure (Pa), and distal coronary pressure (Pd) were recorded continuously and digitally stored throughout all the phases of the study. Philips Volcano consoles and wires (s5i and PrimeWire Prestige PLUS pressure guide wire; Philips Volcano Corporation, San Diego, California) were used for haemodynamic measurements. Three hundred (300) mcg intra-coronary (IC) Nitro-glycerine followed by saline flush was administered through the guide catheter prior to every physiological measurement. Measurements in donor vessels were performed simultaneously using 2 pressure wires. After normalization at the tip of the guide catheter, the pressure wire was advanced so the pressure sensor was positioned at least 3 reference vessel diameters beyond the stenosis or in the distal segment of the vessel in cases with no angiographic apparent stenosis or a diffusely diseased vessel. Baseline resting Pd/Pa was recorded for 5 seconds. iFR measurement was fully automated. FFR was calculated as (Pd - Pv) / (Pa - Pv) under maximum steady state hyperaemia. Hyperaemia was achieved with intravenous adenosine administered centrally through a femoral vein at a dose of 140 mcg/kg/min as an intravenous infusion. Once FFR measurements were completed, the pressure guide wire was pulled back to the guide catheter and assessed for drift of the Pd/Pa recording. In the presence of drift (> ±0.02), measurements were repeated; otherwise the operator would proceed to CTO PCI.

Once a guidewire was successfully placed at the distal true lumen of the RCA CTO and without restoring the antegrade flow, an over-the-wire microcatheter was advanced distal to the occlusion. The guidewire was exchanged with a pressure wire positioned distal to

the occluded segment in a relatively disease-free area to measure the pressure-derived fractional collateral blood flow index. The collateral FFR (FFR*coll*) was calculated using the following equation FFR*coll* = Qc/QN = (Pw-Pv)/(Pa-Pv) during maximum hyperaemia (16,17), (Pw = wedge pressure / pressure distal to occlusion. Pv = central venous pressure and Pa = aortic pressure). Following the measurements, the occlusion was dilated and treated by stent implantation. After successful revascularization of the RCA, measurements in the donor vessels were repeated as performed pre-RCA CTO PCI.

At follow-up, angiographic findings and physiological indices (resting Pd/Pa, iFR and FFR) measurements in the donor vessels were repeated as performed pre-RCA CTO PCI. Measurements of collateral function at the follow-up procedure were performed with balloon occlusion in the revascularized RCA CTO artery at the site of previous occlusion.

*CTO characteristics*

The CTOs were graded using the J-CTO system by two blinded experienced CTO operators (18).

*Angiographic assessment of collateral donor arteries*

At least 2 different projections differing >30° were recorded for each assessed lesion. QCA analysis was performed in optimal projections using quantitative coronary angiography software (Philips Allura, The Netherlands). The guide catheter filled with contrast medium was used as a calibrating device. Minimum lumen diameter, percent diameter stenosis, lesion length, and reference lumen diameter were measured.

*Angiographic assessment of collateral circulation*

At least 2 different projections differing >30° were recorded for assessment of collateral circulation. Donor artery dominancy and collateral contribution to the occluded artery segment was assessed angiographically by the two experienced CTO operators using the Rentrop grading classification and collateral connections grading system as previously described (19, 20).

The predominant collateral donor artery was defined as the artery making the largest collateral contribution to the occluded artery segment. The minor collateral donor artery was the artery contributing the least number of collaterals to the occluded artery segment.

*Statistical analysis*

Continuous variables are presented as mean ± standard deviation. Categorical variables are expressed as frequency and proportion. The paired t-test was used for the primary analysis to compare pre- and post-CTO PCI and pre and follow up physiological measurements. Scatter plots and Pearson’s correlation coefficients or Spearman’s correlation coefficients were used to assess the relationship between two variables as appropriate. The level of statistical significance was set at *p* = 0.05 with two tails. Statistical analysis was carried out using SPSS 20 software (SPSS Inc., Chicago, Illinois).

Results

Out of the 40 consecutive patients recruited, 34 patients underwent successful RCA CTO PCI. 28 patients completed measurements pre, immediately post and at 4 (±1.2) months follow-up after the index procedure.

Baseline demographics, angiographic and procedural details are outlined in (**Table 1**). Overall, the mean age was 62 ± 10 years old and 88% of the patients were male. Average LVEF was 51% and area of ischemia measured by CMR was 13.6 +/- 5%. LAD was the predominant donor in 88% of the cases with a mean maximum stenosis of 41 +/- 12.6%.

*Physiological Indices pre and immediately post CTO PCI*

The mean Pd/Pa, iFR and FFR values and their change immediately post-CTO PCI are illustrated in **Figure 1**. FFR in the predominant donor vessel did not change significantly immediately post-CTO PCI (0.76 ± 0.12 vs. 0.75 ± 0.13, p=0.267) (**Table 2**). There was no statistical significant change in resting Pd/Pa (0.89 ± 0.07 vs. 0.90 ± 0.07, p=0.109), while iFR increased from 0.86 ± 0.10 to 0.88 ± 0.10 (p=0.012). In the minor donor vessel, there were no significant changes in resting Pd/Pa, iFR and FFR (0.98 ± 0.04 vs. 0.99 ± 0.03, p=0.534, 0.97 ± 0.06 vs. 0.98 ± 0.04, p=0.152, 0.89 ± 0.07 vs 0.89 ± 0.07, p=0.183

respectively) (**Table 2**).

*Physiological Indices at follow up*

28 out of 34 patients completed follow-up measurements at 4 (± 1.2) months post-index procedure. All 28 patients had patent stents in the CTO vessel with TIMI 3 flow. At follow-up, the mean FFR in the previously predominant collateral donor vessel was 0.79, significantly increased compared to pre-CTO recanalization (0.76, p = 0.047). Similarly resting Pd/Pa increased from 0.89 to 0.92 (p = 0.006) and iFR from 0.86 to 0.90 (p = 0.003) (**Figure 2A**). The was no significant change in minor donor vessel Pd/Pa, iFR and FFR at follow-up compared to pre-CTO PCI (0.98 vs 0.98, p=0.816, 0.97 vs. 0.97, p =

0.523 , 0.89 vs. 0.90, p=0.399 respectively) (**Figure 2B**). The overall temporal changes

for Pd/Pa, iFR and FFR for predominant and minor donor vessels are outlined in (**Figure 3**).

*Regression of collateral vessels*

During the index procedure, we measured FFR collateral in 31 out of 34 patients. Mean FFR collateral was 0.31 ± 0.10 prior to CTO PCI and did not change significantly immediately after the procedure (0.34 ± 0.10, p = 0.078) (**Figure 4A**). At 4 months follow-up, complete angiographic collateral regression was observed in 23 patients out of 28 patients. The mean FFR collateral measured during balloon occlusion in RCA was

* 1. ± 0.07, demonstrating a significant decrease compared to the index procedure (*p* < 0.0001), suggestive of significant collateral regression (**Figure 4C**).

*Correlations of changes in physiological indices*

There was no relationship demonstrated between the changes in the physiological indices (Pd/Pa, iFR and FFR) pre- and post-CTO PCI with the severity of donor vessel stenosis measured by QCA, pre-PCI CTO FFR collateral, change in FFR*coll* or percentage ischaemia in RCA territory measured by CMR (**Supplementary Table 1**). At follow-up, there was a statistically significant correlation between the changes in Pd/Pa and iFR with donor vessel stenosis measured by QCA, and between the change in FFR with the change in overall CC grading and the predominant CC grading compared to baseline (**Figure 5 and Supplementary Table 2**).

Discussion

To our knowledge, this is the first study to evaluate the immediate and medium-term impact of successful RCA CTO PCI on donor vessel physiology using resting and hyperaemic coronary pressure-derived indices. Our main findings are as follows:

1. Percutaneous revascularisation of an RCA CTO leads to a modest improvement in predominant donor vessel physiological indices (Pd/Pa, iFR and FFR),
2. The time point at which iFR and FFR detected changes in donor vessel physiology differed, with the improvement in predominant donor vessel physiology detectable immediately after CTO PCI with iFR. In contrast FFR measurements did not change immediately post-CTO PCI but a significant change in FFR was observed at follow-up procedure,
3. The collateral function index remained unchanged immediately post-PCI, but decreased significantly at follow-up.

In the presence of a CTO, the coronary artery providing the main collateral vessel supplies blood not only to its one myocardial territory, but also to the territory of the chronically occluded artery. As FFR is dependent on the amount of tissue to be perfused (21), theoretically a non-ischaemic FFR for a given lesion and myocardial territory can become ischaemic if the perfused territory increases in the presence of a CTO in another vessel. A number of case reports and case series have described a significant increase in FFR in the collateral donor vessel after recanalization of a CTO (7-13), but selective reporting and publication bias might have exaggerated the extent or even presence of this

phenomenon. Recently, Ladwiniec *et al* measured coronary pressure and flow velocity in the non-CTO vessels pre and immediately post-successful PCI in 34 RCA, LAD and Cx CTOs (14). They found an increase in FFR in the predominant donor vessel by 0.028 accompanied by a reduction in baseline and hyperaemic blood flow. The authors concluded that the observed reduction in donor vessel coronary flow is related to a reduction in collateral donation and perfused myocardial mass. Our study supports these findings as it shows a consistent but modest increase in all pressure-derived indices with a concomitant reduction in collateral function at follow-up.

A novel finding in this study demonstrates that the change in donor vessel physiology, particularly in FFR, does not occur immediately, but does so over a more prolonged time course. In the case of FFR, contrary to the results of Ladwiniec *et al* we did not find any difference in the predominant donor vessel FFR measurements immediately post-PCI. However, at 4 month follow-up we observed a similar modest increase in FFR by 0.03. The difference between the timing of FFR change could potentially be explained by the process of collateral regression. Early clinical studies on collateral function in CTO have suggested rapid regression after successful CTO PCI (22-25). More recent work has shown that collateral function remains relatively unchanged immediately (26) and for at least 24 hours post-PCI (27). Furthermore, animal models suggest that the collateral circulation does not diminish for several weeks after recanalization (28,29). In any case as anatomic re-modelling of well-developed collaterals requires sufficient time (30), a rapid decrease in functional capacity seems unlikely. A recent study that defined the anatomy of angiographic visible collaterals identified 45 different patterns of coronary connections (31). In the case of the RCA, 1 out of 4 CTOs had bridging collaterals and 14.5% epicardial collaterals from the LAD (31). The high degree of anatomical variance could

potentially explain the different patterns in functional regression. In our study, which included only RCA CTOs, FFR collateral remained unchanged immediately after successful PCI. However, at 4 months there was a significant decrease that provides a potential mechanism for the concurrent increase in FFR.

In contrast to FFR, resting indices showed bigger changes immediately post-PCI. Resting Pd/Pa showed a numerical but not statistically significant increase of 0.01 (final increase at 4 months follow-up of 0.03). iFR significantly increased by 0.02 showing no further significant increase at follow-up. These results are interesting but they require further investigation, as any explanation would remain speculative. In any case the difference with FFR probably depicts the different physiological principles between resting and hyperaemic indices and the fact that they may represent different aspects of myocardial ischemia (32).

We did not find statistically significant relationships between the change in any of the three different indices (resting Pd/Pa, iFR and FFR) in the predominant donor vessel pre and post CTO-PCI with donor vessel disease severity, FFR collateral or percentage of ischaemia in RCA territory. Our sample size was probably too small to detect any significant relationship between these indices and a larger sample size including LAD CTOs may potentially be able to reveal associations. Furthermore, overall disease severity in the major donor vessel was low as the mean maximum stenosis was 41 ± 12%. Finally, mean percentage of ischemia as measured with CMR was 14%. It is possible a higher ischaemic burden would have provided a significant correlation.

Clinical implications

CTO is a common finding in patients with coronary artery disease and with contemporary PCI techniques can be readily treated with a high degree of success and low complication rates (33). Functional assessment of co-existing lesions in non-CTO vessels is of great importance as it can be the determinant between subsequent percutaneous or surgical revascularization. Our study shows that in predominant collateral donor vessels there is an increase in pressure derived physiological indices if measured in a staged fashion post- CTO PCI. Although this increase is modest it can be important when a binary cut-point is used to guide revascularization. At the four-month follow-up of our cohort, 18% of FFR cases in the predominant donor vessel crossed the treatment threshold of 0.80 when compared with pre-CTO PCI, thereby changing the classification of the lesion from haemodynamically significant to haemodynamically insignificant. In the case of iFR the percentage was 25% (using an ischaemic cut off of 0.89). These results should be taken into account when physicians are using invasive physiological measurements in the presence of a CTO.

*Study limitations*

Our study is not without limitations. It is a single centre study, involving a small number of patients. The study is limited to RCA CTOs, for clinical reasons as mentioned earlier and in order to provide a more consistent and uniform cohort. However, the myocardial mass supplied by the LAD is much greater, so the physiological changes in donor and collateral vessels supplying an LAD CTO might be bigger. The mean follow-up in our study was medium-term at 4 months so these collaterals may further regress and influence the coronary pressure-derived measurements if they were measured at a later stage. Nevertheless, medium-term follow-up limits the possibilities for significant disease

progression in the donor vessels. Finally, the exact location of the pressure wire sensor is critical to make serial comparisons of the coronary physiological measurements and despite special care taken to measure at identical points during the post-PCI and follow- up studies, inaccuracy may have occurred during these measurements. However, as the observation of improvement is in all three (resting Pd/Pa, iFR and FFR) indices with concomitant reduction of collateral function, the observed changes can be considered genuine.

Conclusion

Successful recanalization of an RCA CTO results in a modest yet significant increase in predominant donor vessel coronary pressure-derived indices (resting Pd/Pa, iFR and FFR) at 4-month follow-up with a concomitant reduction in collateral function. In the case of iFR a significant increase happens immediately post CTO PCI. These results have implications for physiological coronary lesion assessment in the presence of a CTO, the timing of the assessment and subsequent revascularisation in this setting.

Clinical perspectives

**What is known?**

CTO is common and is present in 1/4 of all patients with obstructive coronary artery disease. Coronary physiology guided-PCI with FFR and iFR improve outcome. However, in the presence of a CTO, donor vessel FFR is influenced by the collateralisation to the CTO territory making the decision-making process for complete revascularisation challenging. The physiological impact of CTO PCI and the influence collateral regression

upon donor vessel resting indices (Pd/Pa and iFR), and the influence of further collateral regression on donor vessel measurements are unknown.

What is new?

Successful recanalization of a RCA CTO leads to improvement in predominant donor vessel physiology immediately post CTO PCI in the case of iFR and at 4 months follow- up for resting Pd/Pa, iFR and FFR. At four months, functional significance lesion classification changed in 25 % for iFR and 18 % with FFR to defer donor vessel revascularisation. Collateral FFR did not regress immediately post-CTO PCI but reduced significantly at 4 months follow-up.

What is next?

Incorporate coronary flow measurement in order to better understand and examine the potential mechanism between iFR and FFR temporal changes. Future studies with larger sample size, multicentre studies with longer follow-up duration and clinical outcomes.

Acknowledgements

We would like to thank all the cardiac catheter laboratory and research department staff at the Essex Cardiothoracic Centre for their commitment and support.

#### References

1. Tsai TT, Stanislawski MA, Shunk KA, et al. Contemporary Incidence, Management, and Long-Term Outcomes of Percutaneous Coronary Interventions for Chronic Coronary Artery Total Occlusions: Insights From the VA CART Program. J Am Coll Cardiol Intv 2017 May 8;10(9):866-875.
2. Windecker S, Kolh P, Alfonso F, et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J 2014 Oct 1;35(37):2541-2619.
3. Patel MR, Dehmer GJ, Hirshfeld JW, Smith PK, Spertus JA. ACCF/SCAI/STS/AATS/AHA/ASNC/HFSA/SCCT 2012 Appropriate Use Criteria for Coronary Revascularization Focused Update: A Report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons, American Association for Thoracic Surgery, American Heart Association, American Society of Nuclear Cardiology, and the Society of Cardiovascular Computed Tomography. J Am Coll Cardiol 2012 2/28;59(9):857-881.
4. Sen S, Escaned J, Malik IS, et al. Development and validation of a new adenosine- independent index of stenosis severity from coronary wave-intensity analysis: results of the ADVISE (ADenosine Vasodilator Independent Stenosis Evaluation) study. J Am Coll Cardiol 2012 Apr 10;59(15):1392-1402.
5. Davies JE, Sen S, Dehbi H, et al. Use of the Instantaneous Wave-free Ratio or Fractional Flow Reserve in PCI. N Engl J Med 2017 03/18; 2017/03.
6. Götberg M, Christiansen EH, Gudmundsdottir IJ, et al. Instantaneous Wave-free Ratio versus Fractional Flow Reserve to Guide PCI. N Engl J Med 2017 03/18; 2017/03.
7. Melikian N, Cuisset T, Hamilos M, De Bruyne B. Fractional flow reserve — The influence of the collateral circulation. Int J Cardiol 2009 3/6;132(3):e109-e110.
8. Iqbal MB, Shah N, Khan M, Wallis W. Reduction in myocardial perfusion territory and its effect on the physiological severity of a coronary stenosis. Circ Cardiovasc Interv 2010 Feb 1;3(1):89-90.
9. Kurisu S, Mitsuba N, Ishibashi K, et al. A pitfall of fractional flow reserve associated with the presence of collateral circulation. Intern Med. 2011;50:2811–2813.
10. Sachdeva R, Uretsky BF. The effect of CTO recanalization on FFR of the donor artery. Catheter Cardiovasc Interv 2011 Feb 15;77(3):367-369.
11. Matsuo H, Kawase Y. Physiological impact of CTO recanalization assessed by coronary pressure measurement: A case report. Catheterization and Cardiovascular Interventions 2013;82(4):E459-E464.
12. Sachdeva R. Reversal of ischemia of donor artery myocardium after recanalization of a chronic total occlusion. Catheterization and cardiovascular interventions 2013;82(4):E453.
13. Tigen K, Durmus E, Sari I. Recanalization of a total occlusion with marked retrograde collateral supply: Impact of collateral circulation on fractional flow reserve measurements of donor artery. J Invasive Cardiol 2014;26(6):E70-E75.
14. Ladwiniec A, Cunnington MS, Rossington J, et al. Collateral Donor Artery Physiology and the Influence of a Chronic Total Occlusion on Fractional Flow Reserve. Circulation: Cardiovascular Interventions 2015 April 01;8(4).
15. Brilakis ES, Grantham JA, Rinfret S, et al. A percutaneous treatment algorithm for crossing coronary chronic total occlusions. J Am Coll Cardiol Intv 2012 Apr;5(4):367-79.
16. Pijls NH, van Son JA, Kirkeeide RL, De Bruyne B, Gould KL. Experimental basis of determining maximum coronary, myocardial, and collateral blood flow by pressure measurements for assessing functional stenosis severity before and after percutaneous transluminal coronary angioplasty. Circulation 1993 Apr;87(4):1354-1367.
17. Pijls NHJ, Willem Bech GJ, El Gamal MIH, et al. Quantification of recruitable coronary collateral blood flow in conscious humans and its potential to predict future ischemic events. J Am Coll Cardiol 1995 6;25(7):1522-1528.
18. Morino Y, Abe M, Morimoto T, et al. Predicting successful guidewire crossing through chronic total occlusion of native coronary lesions within 30 minutes: the J-CTO (Multicenter CTO Registry in Japan) score as a difficulty grading and time assessment tool. J Am Coll Cardiol Intv 2011 Feb;4(2):213-221.
19. Rentrop KP, Thornton JC, Feit F, Van Buskirk M. Determinants and protective potential of coronary arterial collaterals as assessed by an angioplasty model. Am J Cardiol 1988 Apr 1;61(10):677-684.
20. Werner GS, Ferrari M, Heinke S, et al. Angiographic assessment of collateral connections in comparison with invasively determined collateral function in chronic coronary occlusions. Circulation 2003 Apr 22;107(15):1972-1977.
21. Leone AM, De Caterina AR, Basile E, et al. Influence of the amount of myocardium subtended by a stenosis on fractional flow reserve. Circ Cardiovasc Interv 2013 Feb;6(1):29-36.
22. Petronio AS, Baglini R, Limbruno U, et al. Coronary collateral circulation behaviour and myocardial viability in chronic total occlusion treated with coronary angioplasty. Eur Heart J 1998;19:1681–7.
23. Werner GS, Richartz BM, Gastmann O, Ferrari M, Figulla HR. Immediate changes of collateral function after successful recanalization of chronic total coronary occlusions. Circulation 2000;102: 2959–65.
24. Werner GS, Emig U, Mutschke O, Schwarz G, Bahrmann P, Figulla HR. Regression of collateral function after recanalization of chronic total coronary occlusions: a serial assessment by intracoronary pressure and Doppler recordings. Circulation 2003;108:2877–82.
25. Zimarino M, Ausiello A, Contegiacomo G, et al. Rapid decline of collateral circulation increases susceptibility to myocardial ischemia: the trade-off of successful percutaneous recanalization of chronic total occlusions. J Am Coll Cardiol 2006 Jul 4;48(1):59-65.
26. Lee JH, Kim C, Kim N, et al. Coronary Collaterals Function and Clinical Outcome Between Patients With Acute and Chronic Total Occlusion. J Am Coll Cardiol Intv 2017 3/27;10(6):585-593.
27. Perera D, Kanaganayagam GS, Saha M, Rashid R, Marber MS, Redwood SR. Coronary collaterals remain recruitable after percutaneous intervention. Circulation 2007 Apr 17;115(15):2015-2021.
28. Khouri EM, Gregg DE, McGranahan GM Jr. Regression and reappearance of coronary collaterals. Am J Physiol 1971;220:655–61.
29. Fujita M, McKown DP, McKown MD, Franklin D. Coronary Collateral Regression in Conscious Dogs. Angiology 1990 08/01; 2017/05;41(8):621-630.
30. Helisch A, Schaper W. Arteriogenesis: the development and growth of collateral arteries. Microcirculation. 2003 Jan;10(1):83-97.
31. McEntegart MB, Badar AA, Ahmad FA, et al. The collateral circulation of coronary chronic total occlusions. EuroIntervention. 2016 Apr 8;11(14):e1596-603.
32. Hwang D, Jeon KH, Lee JM, et al. Diagnostic Performance of Resting and Hyperemic Invasive Physiological Indices to Define Myocardial Ischemia: Validation With 13N- Ammonia Positron Emission Tomography. J Am Coll Cardiol Intv 2017 Apr 24;10(8):751-760.
33. Patel VG, Brayton KM, Tamayo A, et al. Angiographic success and procedural complications in patients undergoing percutaneous coronary chronic total occlusion interventions: a weighted meta-analysis of 18,061 patients from 65 studies. J Am Coll Cardiol Intv 2013 Feb;6(2):128-36.

#### Figure legends

Figure 1: Change in Predominant and Minor Donor Vessel Pre and Post-CTO PCI.

**(A)** Change in predominant donor vessel pressure-derived indices pre and post-CTO PCI for individual stenoses. **(B)** Change in minor donor vessel pressure-derived indices pre and post-CTO PCI for individual stenoses.

FFR = fractional flow reserve; iFR = instantaneous wave-free ratio; PCI = percutaneous coronary intervention; Pd/Pa = Resting distal local pressure / aortic pressure.

Figure 2: Change in Predominant and Minor Donor Vessel Pre-CTO PCI and at Follow-up.

1. Change in predominant donor vessel pressure-derived indices pre-CTO PCI and at follow-up for individual stenoses. **(B)** Change in minor donor vessel pressure-derived indices pre-CTO PCI and at follow-up for individual stenoses.

Abbreviations as in Figure 1.

Figure 3: Mean Change in Donor Vessel Pressure-Derived Indices Pre and Post- CTO PCI and at Follow-up.

* 1. Predominant donor vessel. **(B)** Minor donor vessel NS = non significant; other abbreviation as in Figure 1.

Figure 4: Collateral Fractional Flow Reserve (FFR*coll*) Pre, Post-CTO PCI and at Follow-up.

**(A)** Mean and individual changes pre and post-PCI. **(B)** Individual changes pre, post-PCI and at follow-up (n=25). **(C)** Temporal changes in collateral FFR (n=25).

FFR*coll* = Collateral Fractional Flow Reserve; other abbreviation as in Figure 1 and 3.

Figure 5: Relationships With Change in Predominant Donor Vessel Pressure- Derived Indices at 4 Months Follow-up and Pre-CTO PCI.

**(A)** Angiographic diameter stenosis (DS) % on QCA. **(B)** Change in overall Rentrop classification grading and change in FFR. **(C)** Change in overall collateral classification (CC) grading and change in FFR. **(D**) Change in predominant donor vessel (PDV) Rentrop classification grading and change in FFR. **(E)** Change in PDV CC grading and change in FFR. **(F)** Change in PDV CC size grading and change in FFR.

Figure 1.

**A**

**Pd/Pa**

#### Predominant Donor Vessel

**iFR**

**FFR**

0.89 ± 0.07 vs 0.90 ± 0.07

Δ 0.012 (-0.003 to 0.027) p=0.109

0.86 ± 0.10 vs 0.88 ± 0.10

Δ 0.024 (0.006 to 0.043) p=0.012

0.76 ± 0.12 vs 0.75 ± 0.13

Δ - 0.013 (-0.035 to 0.010) p=0.267

**1.0**

**0.8**

**0.6**

**0.4**

Pre-PCI Post-PCI

**1.0**

**0.8**

**0.6**

**0.4**

Pre-PCI Post-PCI

**1.0**

**0.8**

**0.6**

**0.4**

Pre-PCI Post-PCI

## B

**Pd/Pa**

#### Minor Donor Vessel

**iFR**

**FFR**

0.98 ± 0.04 vs. 0.99 ± 0.03

Δ 0.003 (-0.007 to 0.013) p=0.534

0.97 ± 0.06 vs 0.98 ± 0.04

Δ 0.010 (-0.004 to 0.025) p=0.152

0.89 ± 0.07 vs 0.89 ± 0.07

Δ - 0.008 (-0.021 to 0.004) p=0.183

**1.0**

**1.0**

**1.0**

**0.8**

**0.8**

**0.8**

**0.6**

**0.6**

**0.6**

**0.4**

Pre-PCI Post-PCI

**0.4**

Pre-PCI Post-PCI

**0.4**

Pre-PCI Post-PCI

Figure 2.

**A**

**Pd/Pa**

0.89 ± 0.07 vs. 0.92 ± 0.05

Δ 0.025 (0.008 to 0.043) p=0.006

**Predominant Donor Vessel**

iFR

0.86 ± 0.10 vs. 0.90 ± 0.07

Δ 0.039 (0.014 to 0.064) p=0.003

FFR

0.76 ± 0.12 vs. 0.79 ± 0.11

Δ 0.023 (0.0003 to 0.046) p=0.047

**1.0**

**1.0**

**1.0**

**0.8**

**0.8**

**0.8**

**0.6**

**0.6**

**0.6**

**0.4**

Pre-PCI Follow-up

**0.4**

Pre-PCI Follow-up

**0.4**

Pre-PCI Follow-up

# B

Pd/Pa

**Minor Donor Vessel**

**iFR**

**FFR**

0.98 ± 0.04 vs. 0.98 ± 0.03

Δ 0.002 (-0.014 to 0.017) p=0.816

0.97 ± 0.07 vs. 0.97 ± 0.06

Δ 0.008 (-0.016 to 0.031) p=0.523

0.89 ± 0.07 vs. 0.90 ± 0.08

Δ 0.008 (-0.011 to 0.028) p=0.399

**1.0**

**1.0**

**1.0**

**0.8**

**0.8**

**0.8**

**0.6**

**0.6**

**0.6**

**0.4**

Pre-PCI Follow-up

**0.4**

Pre-PCI Follow-up

**0.4**

Pre-PCI Follow-up

Figure 3.

* + 1. **Predominant Donor Vessel**

**1.0**

**0.8**

**overall p=0.009 overall p=0.002**

Pd/Pa iFR FFR

**overall p=0.012**

**0.6**

Pre-PCI

Post-PCI

Follow-up

Pre-PCI

Post-PCI

Follow-up

Pre-PCI

Post-PCI

Follow-up

* + 1. **Minor Donor Vessel**

**overall p=NS overall p=NS**

**overall p=NS**

**1.0**

**0.8**

Pd/Pa iFR FFR

**0.6**

Pre-PCI

Post-PCI

Follow-up

Pre-PCI

Post-PCI

Follow-up

Pre-PCI

Post-PCI

Follow-up

Figure 4.

**A**

**0.8**

0.31(±0.10) vs.0.34(±0.11)

p=0.078

**B**

**0.8**

Δ0.028(-0.003to0.060)

**C**

###### 0.8

**p< 0.0001**

FFR

**p= NS**

**p< 0.0001**

**Overall pvalue< 0.0001**

*coll*

##### Pre-PCI

###### 0.6

**FFR*coll***

**0.4**

**0.6**

**0.4**

**FFR*coll***

**0.6**

###### 0.4

**FFR*coll***

FFR*coll*Post-PCI FFR*coll* atfollow-up

###### 0.2

**0.2**

**0.2**

###### 0.0

Pre-PCI Post-PCI

**0.0**

Pre-PCI Post-PCI Follow-up

**0.0**

Figure 5.

**A**

**0.3**

**Change in Pressure Indices**

**0.2**

**0.1**

**B C**

ChangeinPd/Pa ChangeiniFR ChangeinFFR

Pd/Pa r = 0.40 ; p = 0.04 iFR r = 0.48 ; p = 0.01 FFR r = 0.16 ; p = 0.43

**0.3**

**0.2**

*r* = - 0.20

*p* = 0.31

**0.1**

**0.0**

**-0.1**

**0.3**

**0.2**

*r* = - 0.50

*p* = 0.10

**0.1**

**0.0**

**-0.1**

**Change in FFR**

**Change in FFR**

**0.0**

**-0.1**

**0 20 40 60 80**

**Diameter stenosis (DS) on QCA (%)**

**-4 -3 -2 -1 0**

**Change in overall Rentrop grading**

**-4 -3 -2 -1 0**

**Change in overall CC grading**

**D E**

**0.3**

**0.3**

**0.2**

*r* = - 0.11

*p* = 0.60

**0.1**

**0.0**

**-0.1**

**0.2**

**Change in FFR**

**Change in FFR**

**0.1**

**F**

*r* = - 0.46

**0.3**

**0.2**

*r* = - 0.45

*p* = 0.02

**0.1**

**0.0**

**-0.1**

*p* = 0.02

**Change in FFR**

**0.0**

**-0.1**

**-4 -3 -2 -1 0**

**Change in PDV Rentrop grading**

**-4 -3 -2 -1 0**

**Change in PDV CC grading**

**-4 -3 -2 -1 0**

**Change in PDV collateral size**

### Tables

Table 1: Baseline demographics, angiographic and procedural details

**n (%) or mean ± SD**

**Demographic** (n=34)

Male 30 (88.2)

Age (years) 61.76 ± 10.53

Previous MI 21 (61.8)

Previous PCI 14 (41.2)

Hypertension 22 (64.7)

Hypercholesterolaemia 24 (70.6)

Diabetes mellitus 9 (26.5)

Current smoker 7 (20.6)

Angina Duration (months) 39.88 ± 65.58

Estimated duration of CTO (weeks) 221.38 ± 397.30

Angina CCS Class (1/2/3/4) 4(11.8) / 12(35.3) / 17(50.0) /

1(2.9)

LVEF on CMR (%) 51.26 ± 19.61

RVEF on CMR (%) 51.76 ± 23.37

Ischaemia in RCA territory on CMR (%) 13.65 ± 5.00

Angiographic Characteristics

CTO Vessel (RCA) 34 (100)

CTO length (mm)

J-CTO Score (0/1/2/3/4)

34.59 ± 25.70

7(20.6) / 5(14.7) / 8(23.5) /

10(29.4) / 4(11.8)

Predominant donor vessel (LAD / LCx) 30 (88) / 4 (12)

Predominant donor vessel stenosis on QCA (%) 41.43 ± 12.59

Minor donor vessel stenosis on QCA (%) 35.06 ± 13.72

|  |  |
| --- | --- |
| Overall Rentrop Classification grading |  |
| Pre-CTO PCI (0/1/2/3) | 0(0.0) / 0(0.0) / 2(5.9) / 32(94.1) |
| Post-CTO PCI (0/1/2/3) | 3(8.8) / 25(73.5) / 6(17.6) / 0(0.0) |

Overall Collateral Connection Classification grading

Pre-CTO PCI (0/1/2/3) 0 (0.0) / 3(8.8) / 22(64.7) / 9(26.5)

Post-CTO PCI (0/1/2/3) 23(67.6) / 10(29.4) / 0(0) / 1(2.9)

Procedural details

No of stents in RCA CTO (1/2/3/4/5) 8/7/9/8/2 Length of stented segment (mm) 71.41 ± 30.17 Technique of recanalisation

Antegrade Lumen-Lumen 19 (0.56)

Antegrade Dissection Re-entry 4 (0.12)

Retrograde Lumen-Lumen 2 (0.06)

Retrograde Dissection Re-entry 9 (0.26)

Procedural time (mins) Radiation (cGycm/2)

197.29 ± 52.53

29132.65 ± 34974.37

Table 1 legend:

MI = myocardial infarction; PCI = percutaneous coronary intervention; CTO = chronic total occlusion; CCS = canadian cardiovascular society; LVEF = left ventricular ejection fraction; CMR= cardiac magnetic resonance imaging; RVEF = right ventricular ejection fraction; RCA = right coronary artery; LAD = left anterior descending artery; LCx = left circumflex artery; QCA = Quantitative coronary angiography.

Table 2: Haemodynamics and coronary pressure assessment pre and post-RCA

|  |  |
| --- | --- |
| **CTO PCI** |  |
|  | **Pre-CTO PCI** | **Post-CTO PCI** | **Difference****(95% CI)** | ***p* Value** |
| **CVP (mmHg)** | 4.82 ± 3.31 | 5.00 ± 3.56 | 0.121 | 0.764 |
| **Mean BP (mmHg)** | 86.50 ± 11.54 | 86.82 ± 14.68 | (-0.695 to 0.937)0.545 | 0.846 |
| **Heart Rate (beats/min)** | 65.38 ± 11.32 | 64.46 ± 13.33 | (-5.124 to 6.215)-0.727 | 0.658 |
| **Predominant Donor Vessel** |  |  | (-4.042 to 2.588) |  |
| Resting Pd/Pa | 0.89 ± 0.07 | 0.90 ± 0.07 | 0.012 | 0.109 |
| iFR | 0.86 ± 0.10 | 0.88 ±0.10 | (-0.003 to 0.027)0.024 | 0.012 |
| FFR | 0.76 ±0.12 | 0.75 ± 0.13 | (0.006 to 0.043)-0.013 | 0.267 |
| **Minor Donor Vessel** |  |  | (-0.035 to 0.010) |  |
| Resting Pd/Pa | 0.98 ± 0.04 | 0.99 ± 0.03 | 0.003 | 0.534 |
| iFR | 0.97 ± 0.06 | 0.98 ± 0.04 | (-0.007 to 0.013)0.010 | 0.152 |
|  |  |  | (-0.004 to 0.025) |  |

FFR 0.89 ± 0.07 0.89 ± 0.07 -0.008

(-0.021 to 0.004)

0.183

Table 2 legend:

CI = confidence interval; CVP = central venous pressure; BP = blood pressure; Pd/Pa = distal local pressure / aortic pressure; iFR = instantaneous wave free ratio; FFR = fractional flow reserve.

Supplementary Materials

**Supplementary Table 1: Relationships with change in predominant donor vessel pressure-derived indices pre and immediately post-RCA CTO PCI**

**Diameter Percent of**

**Stenosis on QCA (%)**

**FFR*coll***

Change in

**FFR*coll***

Ischemia in RCA territory on CMR

**Change in Pd/Pa**

Correlation

Coefficient

-0.04 0.09 -0.11 0.02

p Value

|  |  |  |  |
| --- | --- | --- | --- |
| 0.80 | 0.63 | 0.56 | 0.94 |
| 0.19 | -0.05 | -0.03 | 0.11 |

Change in iFR

Correlation

Coefficient

p Value 0.28 0.79 0.90 0.56

Change in FFR

Correlation

Coefficient

-0.17 0.27 0.05 -0.10

p Value 0.33 0.14 0.80 0.61

Supplementary Table 1 legend:

FFR*coll* = collateral fractional flow reserve; other abbreviations as in Table 1 and 2.

Supplementary Table 2: Relationships with change in predominant donor vessel pressure-derived indices pre-RCA CTO PCI and at follow-up.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **DS on** | **FFR** | **Change** | **Percent** | **Change** | **Change** | **Change** | **Change** | **Change** |
| **QCA** | ***coll*** | **in FFR** | **of** | **in** | **in** | **in PDV** | **in PDV** | **in PDV** |
| **(%)** |  | ***coll*** | **Ischemia** | **Overall** | **Overall** | **Rentrop** | **CC** | **collateral** |
|  |  |  | **in RCA** | **Rentrop** | **CC** | **grading** | **grading** | **size** |
|  |  |  | **territory** | **grading** | **grading** |  |  |  |
|  |  |  | **on CMR** |  |  |  |  |  |
| **Change in** |  |  |  |  |  |  |  |  |  |
| **Pd/Pa** |  |  |  |  |  |  |  |  |  |
| Correlation | 0.40 | -0.06 | -0.11 | -0.13 | -0.10 | -0.24 | 0.00 | -0.21 | -0.27 |
| Coefficient |  |  |  |  |  |  |  |  |  |
| p Value | 0.04 | 0.78 | 0.58 | 0.53 | 0.62 | 0.21 | 0.99 | 0.28 | 0.16 |
| **Change in iFR** |  |  |  |  |  |  |  |  |  |
| Correlation | 0.48 | -0.29 | 0.15 | 0.05 | -0.24 | -0.30 | -0.11 | -0.25 | -0.28 |
| Coefficient |  |  |  |  |  |  |  |  |  |
| p Value | 0.01 | 0.14 | 0.45 | 0.81 | 0.22 | 0.13 | 0.58 | 0.20 | 0.15 |
| **Change in FFR** |  |  |  |  |  |  |  |  |  |
| Correlation | 0.16 | -0.01 | -0.04 | -0.02 | -0.20 | -0.50 | -0.11 | -0.46 | -0.45 |
| Coefficient |  |  |  |  |  |  |  |  |  |
| p Value | 0.43 | 0.95 | 0.83 | 0.94 | 0.31 | 0.10 | 0.60 | 0.02 | 0.02 |

Supplementary Table 2 legend:

DS = diameter stenosis ; PDV= predominant donor vessel ; CC = Collateral Connection; other abbreviations as in Table 1, 2 and supplementary Table 1.