

Collateral Donor Artery Physiology and the Influence of a Chronic Total Occlusion on Fractional Flow Reserve

Andrew Ladwiniec, MA MRCP; Michael S Cunningham, BMedSci MD MRCP; Jennifer Rossington, BSc MRCP; Adam N Mather, BMedSci MD MRCP; Albert Alahmar, MRCP; Richard M Oliver, DM FRCP; Sukhjinder S Nijjer, MRCP; Justin E Davies PhD MRCP; Simon Thackray, MD MRCP; Farquod Alamgir, MRCP; Angela Hoye, MRCP PhD

Address: Department of Academic Cardiology,
Daisy Building,
Castle Hill Hospital
Castle Road,
Hull, UK
HU16 5JQ

Tel: +44 1482 461776

Fax: +44 1482 461779

E-mail: andrew.ladwiniec@nhs.net

Total word count: 6,012

Subject codes: [7]Chronic ischemic heart disease

[24]Catheter-based coronary interventions: stents

[29]Coronary imaging: angiography/ultrasound/Doppler/CC

Abstract

Background: The presence of a concomitant chronic total coronary occlusion (CTO) and a large collateral contribution might alter the fractional flow reserve (FFR) of an interrogated vessel, rendering the FFR unreliable at predicting ischaemia should the CTO vessel be revascularized and potentially affecting the decision regarding optimal revascularization strategy. We tested the hypothesis that donor vessel FFR would significantly change following percutaneous coronary intervention (PCI) of a concomitant CTO.

Methods and Results:

In consecutive patients undergoing PCI of a CTO, coronary pressure and flow velocity were measured at baseline and hyperaemia in proximal and distal segments of both non-target vessels, before and after PCI. Haemodynamics including FFR, absolute coronary flow and the coronary flow velocity-pressure gradient relation were calculated. After successful PCI in 34 of 46 patients, FFR in the predominant donor vessel increased from 0.782 to 0.810(difference 0.028(0.012-0.044,p=.001)). Mean decrease in baseline donor vessel absolute flow adjusted for rate-pressure product: 177.5 to 139.9ml/min(difference -37.6(-62.6 to -12.6, p=.005)), mean decrease in hyperaemic flow: 306.5 to 272.9ml/min(difference -33.5(-58.7 to -8.3, p=.011)). Change in predominant donor vessel FFR correlated with angiographic(%) diameter stenosis severity ($r=0.44$, $p=.009$) and was strongly related to stenosis severity measured by the coronary flow velocity-pressure gradient relation($r=0.69$, $p<.001$).

Conclusions: Recanalization of a CTO results in a modest increase in the FFR of the predominant collateral donor vessel associated with a reduction in coronary flow. A larger increase in FFR is associated with greater coronary stenosis severity.

Key words: -Angina, stable

-collateral circulation

-coronary disease

-physiology

-pressure

Introduction

The presence of a chronic total coronary occlusion (CTO) is a strong predictor of treatment strategy¹ and is found in almost one in five patients with significant coronary artery disease on angiography². In the presence of a CTO, collateral blood supply originating from a major epicardial vessel other than the occluded vessel is usually present and is often sufficient to maintain resting perfusion and contractility in the collateral dependent myocardium³. In this setting, we would expect coronary flow to be increased relative to the same vessel in the absence of collateral donation. Restoration of antegrade flow by PCI of a CTO has been shown to be associated with a rapid reduction in received collateral supply in the treated vessel^{4,5} and is likely to be coupled by an associated rapid reduction in flow in the collateral donor vessel amounting to the flow donated to the collateral dependent myocardium prior to PCI.

In the setting of both single and multi-vessel coronary disease, randomised trials support the use of fractional flow reserve to guide PCI⁶⁻⁸ with an established treatment threshold of ≤ 0.8 ^{7,8}. Revascularization strategy based upon angiographic assessment is frequently altered by FFR assessment⁹. Although FFR is reported to be independent of changing haemodynamics¹⁰, it is intimately related to total coronary flow through a stenosis

which in turn is related to perfused myocardial mass¹¹. In keeping with this, there have been a number of reports of large increases in collateral donor vessel FFR associated with PCI of a concomitant CTO and therefore reduction in perfused myocardium^{12–16}. However, there is inherent variability to FFR measurement¹⁰, and therefore selective reporting and publication bias might have exaggerated the magnitude (or even presence) of this phenomenon in the reported cases.

The purpose of this study is to serially investigate the changes in collateral donor vessel physiology, before and after successful PCI of a CTO and to test the hypothesis that there will be an associated significant change in collateral donor vessel FFR.

Methods

Study patients

Forty-seven patients scheduled for PCI to a CTO for symptoms of angina (Canadian Cardiovascular Society (CCS) class 1-3) were recruited consecutively in a single tertiary centre between January 2013 and June 2014. A CTO was defined as complete coronary occlusion of ≥ 3 months duration with TIMI grade 0 flow¹⁷. Exclusion criteria were inability to provide consent, >1 occluded vessel, prior CABG with any patent grafts, left main stem stenosis considered to be haemodynamically significant and contra-indications to adenosine. Patient's usual medications were continued and they were asked to abstain from caffeine for 48 hours prior to the procedure.

Ethics

The study protocol was approved by the local research ethics committee (12/YH/0360). All subjects provided written informed consent.

Catheter laboratory protocol

Dual arterial access was used for all procedures. Femoral venous access was obtained for central administration of adenosine and measurement of central venous pressure (CVP) at the beginning and end of the procedure using a catheter positioned in the right atrium. Patients were anti-coagulated with 100 U/kg of unfractionated heparin to maintain an activated clotting time of >300 seconds. After a 200mcg bolus of intra-coronary glyceryl trinitrate (GTN), iso-centred coronary angiograms of both non-target vessels were taken.

A dual sensor pressure-velocity 0.014" intracoronary wire (Combwire, Volcano Corp, San Diego, CA)¹⁸ was connected to a ComboMap console (Volcano Corp) and used for haemodynamic measurements. The wire was normalised to aortic pressure at the tip of the catheter, advanced to the distal segment of each non-target vessel and manipulated to obtain a good Doppler trace. After administration of 100mcg intra-coronary GTN, once the hyperaemic response had settled, continuous recordings from the ComboMap were taken. Hyperaemia was achieved by central venous administration of adenosine at 140 mcg/kg/minute. Once steady state hyperaemia had been reached and a continuous recording of ≥ 20 beats taken, adenosine infusion was ceased. The Combwire was withdrawn into the segment of the vessel proximal to any major side-branches and measurements repeated as described. Samples were recorded at 200Hz and stored on disk for offline analysis.

After initial haemodynamic recordings, PCI of the CTO was undertaken at the discretion of the treating interventional cardiologist using an antegrade or retrograde approach. Once access to the vessel lumen distal to the point of occlusion was achieved, prior to restoration of antegrade flow, a microcatheter was placed into the distal vessel to facilitate delivery of the ComboWire. The ComboWire was positioned in a vessel segment angiographically free of a significant stenosis, then baseline and hyperaemic measurements taken as described. PCI success was defined as stenting of the target vessel with <30% residual stenosis and thrombolysis in myocardial infarction (TIMI) grade III flow.

If PCI was successful, non-target vessel haemodynamic measurements were repeated as described pre-procedure, including repeated CVP measurement.

Recorded data was analysed using dedicated custom software (Study Manager, Academic Medical Center, University of Amsterdam, The Netherlands; and a Matlab(Mathworks Inc., Natick, Massachusetts) environment for wave-intensity analysis, Imperial College London, UK).

Angiographic assessment

Maximal non-target vessel diameter stenosis(%) and proximal non-target vessel diameters (at the point of proximal haemodynamic measurement) measured in two orthogonal views were calculated by two independent observers using quantitative coronary angiography(QCA)(GE Centricity CA1000, GE Healthcare) using the guiding catheter luminal diameter as reference. Mean values from both observers were used for analysis. The non-target vessel making the largest collateral contribution (the predominant collateral donor vessel), vessel collateral connection(CC) grade¹⁹ and modified Rentrop score²⁰ were assessed by two independent observers blinded to haemodynamic measurements and

agreed by consensus. The non-target vessel donating angiographically least/no collaterals to the occluded segment was considered the minor collateral donor vessel.

Data analysis

FFR was calculated as $(Pd-CVP)/Pa-CVP$, using mean pressures taken over 5 cardiac cycles at stable hyperaemia²¹. An FFR of ≤ 0.80 was considered haemodynamically significant. Flow velocity was measured in cm/s, mean values are expressed as average peak velocity (APV) and instantaneous values as instantaneous peak velocity (IPV). Hyperaemic microvascular resistance (HMR) was calculated as Pd/APV and hyperaemic stenosis resistance (HSR) as $(Pa-Pd)/APV$, both measured over five beats at stable hyperaemia. Absolute coronary flow was estimated as $(\pi \times \text{proximal vessel radius}^2) \times (\text{proximal vessel APV}/2)$ ^{22,23}. As resting absolute myocardial blood flow is closely related to rate pressure product (RPP), values for resting absolute coronary flow were divided by the respective $RPP/10,000$ ²⁴. Coronary flow reserve (CFR) was calculated as APV at steady state hyperaemia divided by APV at baseline, measured over 5 cardiac cycles.

Fractional collateral flow reserve was calculated as for FFR, with Pd measured in the occluded segment of the artery, prior to restoration of antegrade flow. Collateral flow velocity reserve was calculated as for CFR with flow velocities in the occluded segment measured at rest and steady state hyperaemia.

The diastolic flow-velocity pressure gradient relation (DFV-PGR) describes the relationship between pressure and flow for a given stenosis or vessel segment^{25,26}. It was calculated using continuous recordings of 30 cardiac cycles measured in the distal vessel from baseline through to maximal hyperaemia²⁷. Instantaneous pressures and flow

velocities were extracted from the Study Manager programme and Pa timings corrected to adjust for any time delay with respect to Pd. Instantaneous flow velocities from mid-diastole (after the diastolic upstroke in coronary flow velocity) to atrial activation (identified by the beginning of the p-wave on ECG) were plotted against instantaneous pressure gradient (Pa-Pd). DFV-PGR was then calculated using Stata v.12 (StataCorp, College Station, Texas), fitting the quadratic linear regression equation: $\Delta P = (F \times IPV) + (S \times IPV^2)$ where ΔP is the pressure gradient in mmHg, F is the coefficient of pressure loss due to viscous friction and S is the coefficient of pressure loss due to flow separation or localized turbulence downstream from the stenosis^{25,26}. The peak slope was defined as the gradient of the fitted values over the highest 10cm/s of measured IPV.

Wave intensity represents the rate of energy per unit area transported by travelling waves in arteries and is derived from phasic changes in local pressure and flow velocity. The blood pressure and Doppler velocity recordings were filtered with a Savitzky-Golay filter²⁸ and ensemble averaged using the ECG R-wave for timing. Wave intensity was calculated from simultaneous baseline pressure and flow measurements taken in the proximal non-target vessels over 20 cardiac cycles. The change in pressure was separated into wave components originating from the proximal vessel and from the microvasculature assuming the density of blood to be 1050 kg/m³, and estimating wave speed using the sum of squares method^{29,30}. Cumulative wave energy was calculated for each wave by measuring the area under the curve. Coronary flow is predominantly diastolic and is proportional to perfused myocardial mass¹¹. Because we were interested in the mechanism of any change in donor vessel flow, we focused our analysis on the change in cumulative wave intensity of the backwards expansion wave (BEW).

Measurement repeatability

Based upon analysis of 26 repeated flow measurements at baseline and hyperaemia without any intervening treatment, coefficient of variation for average peak coronary flow velocity measurements was 17.4%. Analysis of 10 repeated measurements taken from repeated adenosine infusions gave a coefficient of variation for FFR, CFR and HMR of 3.6%, 19.7% and 8.6% respectively.

Statistical analysis

Stata v.12(StataCorp) was used for statistical analysis. Continuous values are expressed as means \pm SD, or median(25th percentile-75th percentile) as appropriate. Assuming a standard deviation of the difference(SDD) of 0.04 and success rate of CTO PCI of 70%; for the study to have 80% power to detect a two-tailed change in FFR of 0.02, we estimated that 48 participants were required with procedural success in 33. Continuous variables were compared using a paired t-test or Wilcoxon signed-rank test. Correlations were quantified using Pearson's correlation coefficient. Probability values were 2-sided, and values of $p < .05$ considered significant.

Results

Of 47 patients recruited, 34 underwent successful CTO angioplasty, completed the study protocol and were included in analysis. One was excluded because of significant left main stem disease found at the time of PCI not apparent on initial angiography. The presence of viable myocardium in the CTO territory was confirmed in all patients by myocardial perfusion scintigraphy($n=26$, 76.5%), dobutamine stress echocardiography($n=1$, 2.9%) or by the absence of a wall motion abnormality by echocardiography or left ventricular angiography without additional confirmation($n=7$, 20.6%). Drug-eluting stents

were used for all procedures. Demographics, angiographic and procedural details are shown in **Table 1**.

Haemodynamic indices

Mean time in minutes from restoration of antegrade flow in the CTO vessel to post-PCI FFR measurement was 70.1 ± 23.1 for the predominant donor vessel and 71.5 ± 25.3 for the minor donor vessel. Pre and post-procedural haemodynamic measurements for the predominant and minor donor vessels are detailed in **Table 2**.

Pre-procedural predominant donor vessel FFR measured 0.782 ± 0.117 , which increased to 0.810 ± 0.095 after CTO angioplasty (difference 0.028, 95% CI 0.012 to 0.044, $p = .001$). We found no significant difference in the minor donor vessel. Individual FFR measurements are detailed in Figure 1. The treatment threshold for the predominant donor vessel was crossed from ≤ 0.8 to > 0.8 in 4 patients (11.8%), however 4 patients also crossed in the opposite direction from an FFR of > 0.8 to ≤ 0.8 .

Coronary flow

Satisfactory flow measurements were obtained in 32 of 34 subjects completing the study protocol. Changes in baseline and hyperaemic absolute coronary flow are depicted in Figure 2. Predominant donor vessel absolute coronary flow under baseline conditions, adjusted for RPP was 177.5 ± 87.2 ml/min pre-procedure, and reduced to 139.9 ± 68.2 ml/min post-procedure (difference -37.6 ml/min, 95% CI -62.6 to -12.6 , $p = .005$). Predominant donor vessel hyperaemic absolute coronary flow also reduced, pre-procedure: 306.5 ± 149.0 ml/min; post-procedure: 272.9 ± 151.1 ml/min (difference -33.5 ml/min, 95% CI -58.7 to -8.3 ml/min $p = .011$). We found no statistically significant difference in baseline or

hyperaemic absolute coronary flow in the minor donor vessel. There was no statistically significant difference in the absolute size of reduction in coronary flow in the predominant donor vessel at baseline compared with hyperaemia (difference 4ml/min, 95% CI -29.6 to 37.7ml/min, $p=.60$). There was also no statistically significant change in mean CFR or HSR in either the predominant donor vessel or minor donor vessel.

HMR did increase after CTO PCI in the predominant donor vessel; pre-procedure: 1.92 ± 0.71 mmHg/cm/s, post-procedure 2.47 ± 1.35 mmHg/cm/s (difference 0.55 mmHg/cm/s, 95% CI 0.12 to 0.99, $p=.014$); there was no statistically significant change in the minor donor vessel.

It was possible to measure coronary flow velocity distal to the point of occlusion in 30 patients, 4 of which through a retrograde approach. Mean collateral flow velocity reserve measured 1.09 ± 0.25 (excluding retrograde measurements: 1.08 ± 0.26). We found no correlation between change in predominant donor vessel FFR and invasive measures of collateral perfusion measured distal to the occlusion; fractional collateral flow reserve: $r=-0.08$, $p=.66$, collateral flow velocity reserve: $r=-0.10$, $p=.62$; or change in coronary flow velocity at the point of FFR measurement: $r=0.11$, $p=.55$. In the predominant donor vessel, there was a trend to a smaller reduction in flow in more severe stenoses measured by DFV-PGR ($r=0.33$, $p=.068$). We did find a relationship between maximal angiographic stenosis severity in the predominant donor vessel and change in FFR in the predominant donor vessel: $r=0.44$, $p=.009$ (Figure 3).

Figure 4 shows an example of measurement and calculation of the DFV-PGR. There was a strong correlation between peak DFV-PGR slope in the predominant donor vessel and change in predominant donor vessel FFR; $r=0.69$, $p<.001$ (Figure 5).

Wave intensity analysis

Wave intensity analysis was performed in 32 of 34 patients using measurements taken from the proximal non-target vessels prior to any major branch; figure 6 shows typical examples. In the predominant donor vessel, mean cumulative wave energy of the BEW decreased from $79.7 \pm 44.3 \times 10^5 \text{ Jm}^{-2}\text{s}^{-2}$ before PCI to $65.3 \pm 43.6 \times 10^5 \text{ Jm}^{-2}\text{s}^{-2}$ after PCI (difference $-14.3 \times 10^5 \text{ Jm}^{-2}\text{s}^{-2}$, 95% CI -25.9×10^5 to -2.9×10^5 , $p=.016$). We found no statistically significant difference in the minor donor vessel; Pre-PCI: $71.9 \pm 39.9 \times 10^5 \text{ Jm}^{-2}\text{s}^{-2}$, post-PCI: $67.1 \pm 42.3 \times 10^5 \text{ Jm}^{-2}\text{s}^{-2}$ (difference $-4.8 \times 10^5 \text{ Jm}^{-2}\text{s}^{-2}$, 95% CI -18.5×10^5 to 9.0×10^5 , $p=.49$). Change in cumulative wave energy correlated with change in resting coronary flow, unadjusted for RPP: $r=0.43$, $p=.014$.

Discussion

Our findings support the hypothesis that in a patient with a CTO, measurement of the FFR in an artery providing collateral supply to the myocardium beyond the occlusion is significantly lower than it would otherwise be in the absence of the CTO. Our estimate of the size of the effect in a group of unselected patients is smaller than suggested by case reports of the phenomenon¹²⁻¹⁶. A number of our findings are suggestive of a possible physiological mechanism and reasons for variation in size of change, they are as follows: (1) there is an associated reduction in absolute coronary flow and increase in HMR; (2) the reduction in coronary flow is associated with a reduction in size of the BEW; (3) the magnitude of reduction in flow is similar at baseline and hyperaemia; (4) change in FFR is strongly related to donor vessel coronary stenosis severity; (5) there is no demonstrable association between invasive indices of collateral function and change in FFR.

Effect size

The increase in predominant donor vessel FFR associated with CTO PCI of approximately 0.03 is consistent with a smaller study examining the same phenomenon^{31,32} however case reports suggest the expected increase should be closer to 0.10¹²⁻¹⁶. This may be because measurement and re-measurement of an index such as the FFR is vulnerable to confounding by regression to the mean. If measurements are considered as a whole and not selected based upon their values, regression to the mean will not influence overall effect size. However individual measurement changes are much more likely to involve a contribution by regression to the mean³³. It can be estimated that the SDD of repeated FFR measurements is 0.032 and coefficient of repeatability 0.063⁶; this measurement variability is sufficient for regression to the mean to explain the disparity if the case reports are subject to selective reporting and/or publication bias. In addition, there appears to be a greater change in FFR in more severely diseased vessels. Including angiographically unobstructed vessels is likely to have reduced our effect size. However it has been suggested that the phenomenon exists in unobstructed vessels³⁴ and the mean pre-PCI FFR in the predominant donor vessel was 0.78, close to the widely practiced treatment threshold of 0.80 at which the phenomenon is most relevant.

Reduction in donor vessel flow

A likely explanation for the change in predominant donor vessel FFR is the associated reduction in absolute coronary flow (figure 2) and increase in HMR. Previous studies have shown a rapid reduction in recruitable collateral flow distal to the point of occlusion after CTO PCI^{4,5}, we have shown a reduction in coronary donor vessel flow at a similar interval. The absence of this finding in the vessel donating no/fewer collaterals suggests the change

is related to reduced collateral donation. A generalised effect of PCI on microvascular function seems less likely, whether mediated through an adrenergic effect³⁵ or through myocardial stunning and an elevation in left ventricular end-diastolic pressure^{36,37}. An alternative mechanism that may work in synergy with the reduction in flow is that collateral contribution to distal pressure in the donor vessel might increase once the CTO is recanalized in the reverse direction to collateral flow prior to PCI.

The mechanism of a reduction in donor vessel flow

In support of the hypothesis that the observed reduction in donor vessel coronary flow is related to a reduction in collateral donation and perfused myocardial mass, we demonstrate a reduction in the size of the BEW in the predominant collateral donor vessel associated with CTO PCI. Moreover, the size of that reduction is related to the size of reduction in flow. A predominant pattern of 6 coronary waves measured by wave intensity analysis has been described. The BEW, caused by the relief of myocardial microcirculatory compression in early diastole, is responsible for the large increase seen in coronary flow in early diastole³⁰ (figure 6). Increased left ventricular contractility is associated with an increase in the size of the early backwards compression wave (eBCW)³⁸. The size of the BEW, being driven by the reverse of the mechanism of the eBCW is likely to be related to the mass of myocardium relaxing in early diastole. A reduction in its size associated with a change in flow supports the hypothesis that a change in donor vessel antegrade flow is related to reduced collateral donation, rather than an increase in received collateral supply.

We describe a similar fall in predominant donor vessel absolute flow after CTO PCI at baseline and hyperaemia. This is consistent with the fall in coronary flow being the component of pre-PCI flow donated to the collateral dependent myocardium. Flow in well

collateralised occluded vessel segments responds to an arteriolar vasodilatory stimulus in a similar fashion to flow beyond a severe stenosis³⁹. The microcirculation beyond a severe stenosis is already maximally vasodilated, so a further vasodilatory stimulus is unlikely to increase flow⁴⁰. Coronary flow distal to a CTO can actually diminish with adenosine infusion (a coronary flow reserve of <1), a phenomenon known as coronary steal^{34,41}. The mean collateral flow velocity reserve measured in the occluded segment in this study was 1.09, with coronary steal evident in 9 patients (26%). The small relative proportion of donor vessel absolute flow attributable to the collateral circulation at hyperaemia may explain the relatively small increase in FFR.

The change in FFR is related to stenosis severity

We report an association between predominant donor coronary stenosis severity and change in FFR in the predominant donor vessel associated with CTO PCI, assessed both angiographically and haemodynamically (figures 3&5). Although functional stenosis severity assessment by angiography is limited, it is independent of individual variation in measurement of FFR and therefore the relationship with pre/post measurement should not be confounded by regression to the mean³³.

The DFV-PGR describes the pressure gradient as a result of overall lesion severity, encompassing lesion length, diameter stenosis and induced turbulence as coronary flow velocity changes (figure 4). The slope of the curve is independent of the absolute difference in Pd and Pa and so in addition to describing the effect of a change in flow on pressure based physiological lesion indices, it should also be less susceptible to confounding by regression to the mean compared with indices dependent upon absolute values of Pa and Pd. The observed strong association between a steeper predominant donor peak DFV-PGR

slope and a greater change in predominant donor FFR (figure 5) is supportive of the hypothesis that any change in pressure gradient (and therefore FFR) is related to reduced flow.

Relation of change in FFR and indices of collateral function in the occluded segment

The absence of a relationship between the change in predominant donor flow and measured indices of collateral function is surprising. It may be that overall collateral dependent myocardial mass is more important than the measurement of collateral function for a given myocardial mass. This could be evaluated by comparing LAD with non-LAD CTOs, but would require a study population larger than reported here. The absence of a correlation between change in predominant donor vessel flow and change in predominant donor FFR may reflect an interaction between the effect of donor vessel stenosis severity on collateral flow and the effect of the change of flow. Coronary steal, and therefore reduced collateral flow at hyperaemia, is more prevalent if a collateral donor vessel has a lower FFR³⁴. We report a trend towards a smaller change in hyperaemic flow associated with CTO PCI in predominant donor vessels with more severe stenoses. A smaller change in flow may therefore be associated with a steeper DFV-PGR slope, masking any relationship.

Clinical implications

This study confirms that the presence of a CTO is associated with a lower FFR in the predominant collateral donor vessel than if the CTO were absent. The change is smaller than might be expected and is closely related to lesion severity such that greater changes are largely confined to stenoses of severities that remain below the treatment threshold of ≤ 0.8 in spite of a large increase in FFR. The number of patients in the study population that cross

the treatment threshold is small. A small number have also crossed the FFR treatment threshold in the opposite direction to that expected, most likely because of measurement variation and possibly short term PCI related effects upon the microvasculature. When planning multi-vessel revascularization in the presence of a concomitant CTO, physiological lesion assessment by FFR is reliable. If measurements are close to the current established treatment threshold of ≤ 0.80 , a probable small increase in FFR should be considered when deciding upon treatment strategy.

Limitations

This is a single centre study, and the number of patients with a significant lesion in the predominant donor vessel was small. The study population had a preponderance of right coronary CTOs, with fewer LAD CTOs. This is a reflection of practice and is in keeping with other publications in the field, but may have reduced the size of the observed effect.

Measurements were repeated early after PCI, therefore transient procedural related changes such as microvascular dysfunction due to distal embolization, catecholamine release³⁵, left ventricular stunning^{36,37} or a hyperaemic stimulus related to side-branch occlusion may have influenced donor vessel physiology. However, if the observed effect were due to transient global effects of PCI, we would expect a similar effect on the vessel donating no/less collaterals angiographically. In addition, other than the hyperaemic effect of side branch occlusion, these mechanisms would result in a larger reduction in donor vessel flow and larger increase in FFR. Given the smaller than expected change we observed, it seems unlikely that these additional mechanisms are contributing greatly to the overall change, however they may have contributed to individual variation.

Conclusions

Recanalization of a CTO results in a modest increase in the FFR of the collateral donor vessel associated with a reduction in coronary flow. The magnitude of the change is closely related to lesion severity such that the largest changes are observed across stenoses which remain haemodynamically significant in spite of a large increase in FFR. In vessels with less severe stenoses, the effect is likely to be so small that it is masked by variations in physiology both related and unrelated to PCI as well as measurement variation.

Funding Sources

This study was funded by a grant provided by The Hull & East Yorkshire Cardiac Trust Fund.

Disclosures

None.

References

1. Christofferson RD, Lehmann KG, Martin G V, Every N, Caldwell JH, Kapadia SR. Effect of chronic total coronary occlusion on treatment strategy. *Am J Cardiol.* 2005;95:1088–91.
2. Fefer P, Knudtson ML, Cheema AN, Galbraith PD, Osherov AB, Yalonetsky S, Gannot S, Samuel M, Weisbrod M, Bierstone D, Sparkes JD, Wright GA, Strauss BH. Current perspectives on coronary chronic total occlusions: the Canadian Multicenter Chronic Total Occlusions Registry. *J Am Coll Cardiol.* 2012;59:991–7.
3. Bache RJ, Schwartz JS. Myocardial blood flow during exercise after gradual coronary occlusion in the dog. *Am J Physiol.* 1983;245:H131–8.
4. Zimarino M, Ausiello A, Contegiacomo G, Riccardi I, Renda G, Di Iorio C, De Caterina R. 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;48:59–65.
5. Werner GS, Richartz BM, Gastmann O, Ferrari M, Figulla R. Immediate Changes of Collateral Function After Successful. *Circulation.* 2000;102:2959–2965.
6. Bech GJ, De Bruyne B, Pijls NH, De Muinck ED, Hoorntje JC, Escaned J, Stella PR, Boersma E, Bartunek J, Koolen JJ, Wijns W. Fractional flow reserve to determine the appropriateness of angioplasty in moderate coronary stenosis: a randomized trial. *Circulation.* 2001;103:2928–34.
7. Tonino PAL, De Bruyne B, Pijls NHJ, Siebert U, Ikeno F, Van't Veer M, Klauss V, Manoharan G, Engstrøm T, Oldroyd KG, Ver Lee PN, MacCarthy PA, Fearon WF. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med.* 2009;360:213–24.
8. De Bruyne B, Pijls NHJ, Kalesan B, Barbato E, Tonino PAL, Piroth Z, Jagic N, Möbius-Winkler S, Mobius-Winckler S, Rioufol G, Witt N, Kala P, MacCarthy P, Engström T, Oldroyd KG, Mavromatis K, Manoharan G, Verlee P, Frobert O, Curzen N, Johnson JB, Jüni P, Fearon WF. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. *N Engl J Med.* 2012;367:991–1001.
9. Curzen N, Rana O, Nicholas Z, Golledge P, Zaman A, Oldroyd K, Hanratty C, Banning A, Wheatcroft S, Hobson A, Chitkara K, Hildick-Smith D, McKenzie D, Calver A, Dimitrov BD, Corbett S. Does routine pressure wire assessment influence management strategy at coronary angiography for diagnosis of chest pain?: the RIPCORDER study. *Circ Cardiovasc Interv.* 2014;7:248–55.
10. De Bruyne B, Bartunek J, Sys SU, Pijls NH, Heyndrickx GR, Wijns W. Simultaneous coronary pressure and flow velocity measurements in humans. Feasibility,

- reproducibility, and hemodynamic dependence of coronary flow velocity reserve, hyperemic flow versus pressure slope index, and fractional flow reserve. *Circulation*. 1996;94:1842–9.
11. Pijls NHJ, Van Son JAM, Kirkeeide RL. 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;87:1354–1367.
 12. Melikian N, Cuisset T, Hamilos M, De Bruyne B. Fractional flow reserve--the influence of the collateral circulation. *Int J Cardiol*. 2009;132:e109–10.
 13. 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;3:89–90.
 14. Sachdeva R, Uretsky BF. The effect of CTO recanalization on FFR of the donor artery. *Catheter Cardiovasc Interv*. 2011;77:367–9.
 15. Kurisu S, Mitsuba N, Ishibashi K, Kato Y, Dohi Y, Nishioka K, Kihara Y. A Pitfall of Fractional Flow Reserve Associated with the Presence of Collateral Circulation. *Intern Med*. 2011;50:2811–2813.
 16. Matsuo H, Kawase Y. Physiological impact of CTO recanalization assessed by coronary pressure measurement: a case report. *Catheter Cardiovasc Interv*. 2013;82:E459–64.
 17. Di Mario C, Werner GS, Sianos G, Galassi AR, Büttner J, Dudek D, Chevalier B, Lefevre T, Schofer J, Koolen J, Sievert H, Reimers B, Fajadet J, Colombo A, Gershlick A, Serruys PW, Reifart N. European perspective in the recanalisation of Chronic Total Occlusions (CTO): consensus document from the EuroCTO Club. *EuroIntervention*. 2007;3:30–43.
 18. Siebes M, Verhoeff BJ, Meuwissen M, de Winter RJ, Spaan JAE, Piek JJ. Single-wire pressure and flow velocity measurement to quantify coronary stenosis hemodynamics and effects of percutaneous interventions. *Circulation*. 2004;109:756–62.
 19. Werner GS, Ferrari M, Heinke S, Kueth F, Surber R, Richartz BM, Figulla HR. Angiographic assessment of collateral connections in comparison with invasively determined collateral function in chronic coronary occlusions. *Circulation*. 2003;107:1972–7.
 20. Rentrop KP, Cohen M, Blanke H, Phillips RA. Changes in collateral channel filling immediately after controlled coronary artery occlusion by an angioplasty balloon in human subjects. *J Am Coll Cardiol*. 1985;5:587–92.
 21. Vranckx P, Cutlip DE, Mcfadden EP, Kern MJ, Mehran R. Coronary Pressure-Derived Fractional Flow Reserve Measurements: Recommendations for Standardization,

- Recording, and Reporting as a Core Laboratory Technique. Proposals for Integration in Clinical Trials.*Circ Cardiovasc Interv.*2012;5:312–317.
22. Labovitz AJ,Anthonis DM,Cravens TL,Kern MJ. Validation of volumetric flow measurements by means of a Doppler-tipped coronary angioplasty guide wire. *Am Heart J.*1993;126:1456–61.
 23. Chou TM,Sudhir K,Iwanaga S,Chatterjee K,Yock PG. Measurement of volumetric coronary blood flow by simultaneous intravascular two-dimensional and Doppler ultrasound: validation in an animal model.*Am Heart J.*1994;128:237–43.
 24. Czernin J,Muller P,Chan S,Brunken RC,Porenta G,Krivokapich J,Chen K,Chan A,Phelps ME,Schelbert HR. Influence of age and hemodynamics on myocardial blood flow and flow reserve.*Circulation.*1993;88:62–69.
 25. Gould KL. Pressure-flow characteristics of coronary stenoses in unsedated dogs at rest and during coronary vasodilation.*Circ Res.*1978;43:242–253.
 26. Young DF,Cholvin NR,Roth AC. Pressure drop across artificially induced stenoses in the femoral arteries of dogs.*Circ Res.* 1975;36:735–743.
 27. Marques KMJ, Van Eenige MJ, Spruijt HJ, Westerhof N, Twisk J, Visser CA, Visser FC, Koen MJ. The diastolic flow velocity-pressure gradient relation and dp v50 to assess the hemodynamic significance of coronary stenoses.*Am J Physiol Heart Circ Physiol.*2006;291:H2630–H2635.
 28. Savitzky A,Golay M. Smoothing and differentiation of data by simplified least squares procedures.*Anal Chem.*1964;36:1627–1639.
 29. Parker KH. An introduction to wave intensity analysis. *Med Biol Eng Comput.*2009;47:175–188.
 30. Davies JE,Whinnett ZI,Francis DP,Manisty CH,Aguado-Sierra J,Willson K,Foale RA,Malik IS,Hughes AD,Parker KH,Mayet J. Evidence of a dominant backward-propagating “suction” wave responsible for diastolic coronary filling in humans, attenuated in left ventricular hypertrophy.*Circulation.*2006;113:1768–78.
 31. Ladwiniec A,Hoye A. Change in donor artery fractional flow reserve after recanalization of a chronic total occlusion: Not as Impressive as Some Might Have Us Believe. *Catheter Cardiovasc Interv.*2014;83:1190–1.
 32. Sachdeva R,Agrawal M,Flynn SE,Werner GS,Uretsky BF. Reversal of ischemia of donor artery myocardium after recanalization of a chronic total occlusion.*Catheter Cardiovasc Interv.*2013;458.
 33. Bland JM,Altman DG. Regression towards the mean.*Br Med J.*1994;308:1499.

34. Werner GS, Fritzenwanger M, Prochnau D, Schwarz G, Ferrari M, Aarnoudse W, Pijls NHJ, Figulla HR. Determinants of coronary steal in chronic total coronary occlusions donor artery, collateral, and microvascular resistance. *J Am Coll Cardiol*. 2006;48:51–8.
35. Gregorini L, Marco J, Farah B, Bernies M, Palumbo C, Kozakova M, Bossi I, Cassagneau B, Fajadet J, Di Mario C, Albiero R, Cugno M, Grossi A, Heusch G. Effects of Selective alpha1- and alpha2-Adrenergic Blockade on Coronary Flow Reserve After Coronary Stenting. *Circulation*. 2002;106:2901–2907.
36. Kass DA, Midei M, Brinker J, Maughan WL. Influence of coronary occlusion during PTCA on end-systolic and end-diastolic pressure-volume relations in humans. *Circulation*. 1990;81:447–460.
37. Westerhof N, Boer C, Lamberts RR, Sipkema P. Cross-Talk Between Cardiac Muscle and Coronary Vasculature. *Physiol Rev*. 2006;86:1263–1308.
38. Sun Y-H, Anderson TJ, Parker KH, Tyberg J V. Effects of left ventricular contractility and coronary vascular resistance on coronary dynamics. *Am J Physiol Heart Circ Physiol*. 2004;286:H1590–5.
39. Flameng W, Schwarz F, Hehrlein FW. Intraoperative evaluation of the functional significance of coronary collateral vessels in patients with coronary artery disease. *Am J Cardiol*. 1978;42:187–92.
40. Uren N, Melin J, De Bruyne B. Relation between myocardial blood flow and the severity of coronary-artery stenosis. *N Engl J Med*. 1994;330:1782–1788.
41. Werner GS, Surber R, Ferrari M, Fritzenwanger M, Figulla HR. The functional reserve of collaterals supplying long-term chronic total coronary occlusions in patients without prior myocardial infarction. *Eur Heart J*. 2006;27:2406–12.

Tables

Table 1. Baseline Characteristics, Angiographic, and Procedural Details

Demographics(n=34)	
Male, n(%)	27(79.4)
Age	60.8±9.6 y
Left ventricular ejection fraction(%)	56.2±11
Estimated occlusion duration(weeks)	53(30-104)
CCS class I/II/III/IV	8/20/6/0
Previous PCI, n(%)	9(26.5)
Previous myocardial infarction, n(%)	10(29.4)
Hypertension, n(%)	6(17.7)
Diabetes Mellitus, n(%)	5(14.7)
Current smoker, n(%)	10(29.4)
Angiographic details	
CTO vessel(RCA/LCx/LAD)	21/4/9
Predominant donor vessel(RCA/LCx/LAD)	10/11/13
Rentrop collateral grade(1/2/3)	0/12/22
Predominant donor vessel CC grade(0/1/2)	0/18/16
Minor donor vessel CC grade(0/1/2)	17/15/2
Predominant donor vessel stenosis severity(%)	39.1(25.2-47.7)
Minor donor vessel stenosis severity(%)	39.4(26.8-46.1)
Procedural details	
Number of stents 1/2/3/4/5	6/11/10/6/1
Length of stent(mm)	74.5(44-101)
Means of recanalization	
Antegrade lumen-lumen, n(%)	19(55.9)
Antegrade dissection re-entry, n(%)	9(26.5)
Retrograde lumen-lumen, n(%)	3(8.8)
Retrograde dissection re-entry, n(%)	3(8.8)

PCI indicates percutaneous coronary intervention; ACE-inhibitor, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; RCA, right coronary artery; LCx, left circumflex artery; LAD, left anterior descending artery

Table 2. Haemodynamic assessment pre and post CTO PCI

	Pre-procedure	Post procedure	Difference (95% CI)	p-value
CVP (mmHg)	5.6±2.9	6.1±3.1	0.5 (-1.7 to 0.7)	p=.39
MAP (mmHg)	121.7±18.8	124.2±19.7	-2.5 (-9.9 to 4.9)	p=.50
Heart rate (beats/minute)	69.7±12.4	70.4±11.2	-0.6 (-3.5 to 2.3)	p=.67
Predominant donor vessel				
FFR	0.782±0.117	0.810±0.095	0.028 (0.012 to 0.044)	p=.001
Baseline flow (ml/min)*	177.5±87.2	139.9±68.2	-37.6 (-62.6 to -12.6)	p=.005
Hyperaemic flow (ml/min)†	306.5±149.0ml	272.9±151.1	-33.5 (-58.7 to -8.3)	p=.011
CFR†	2.24±0.93	2.33±0.78	0.10 (-0.24 to 0.44)	p=.57
HMR (mmHg/cm/s)†	1.92±0.71	2.47±1.35	0.55 (0.12 to 0.99)	p=.014
HSR (mmHg/cm/s)†	0.50±0.37	0.50±0.30	-0.002 (-0.09 to 0.09)	p=.95
Minor donor vessel				
FFR	0.808±0.104	0.813±0.110	0.005 (-0.015 to 0.023)	p=.63
Baseline absolute flow (ml/min)*†	157.6±80.3	141.4±98.1	-16.2 (-43.3 to 11.0)	p=.23
Hyperaemic flow (ml/min)†	274.4±147.7	270.6±185.3	-3.7 (-29.9 to 22.4)	p=.77
CFR†	2.25±0.67	2.24±0.72	-0.01 (-0.24 to 0.27)	p=.91
HMR (mmHg/cm/s)†	2.28±0.95	2.47±1.32	0.19 (-0.11 to 0.49)	p=.20
HSR (mmHg/cm/s)†	0.48±0.28	0.54±0.43	0.06 (-0.03 to 0.15)	p=.20

CI indicates confidence interval; CVP, central venous pressure; MAP, men aortic pressure; FFR fractional flow reserve; CFR, coronary flow reserve; HMR, hyperaemic microvascular resistance; HSR, hyperaemic stenosis resistance. *adjusted for rate pressure product. †Satisfactory flow measurements were obtained in 32 patients

Figures

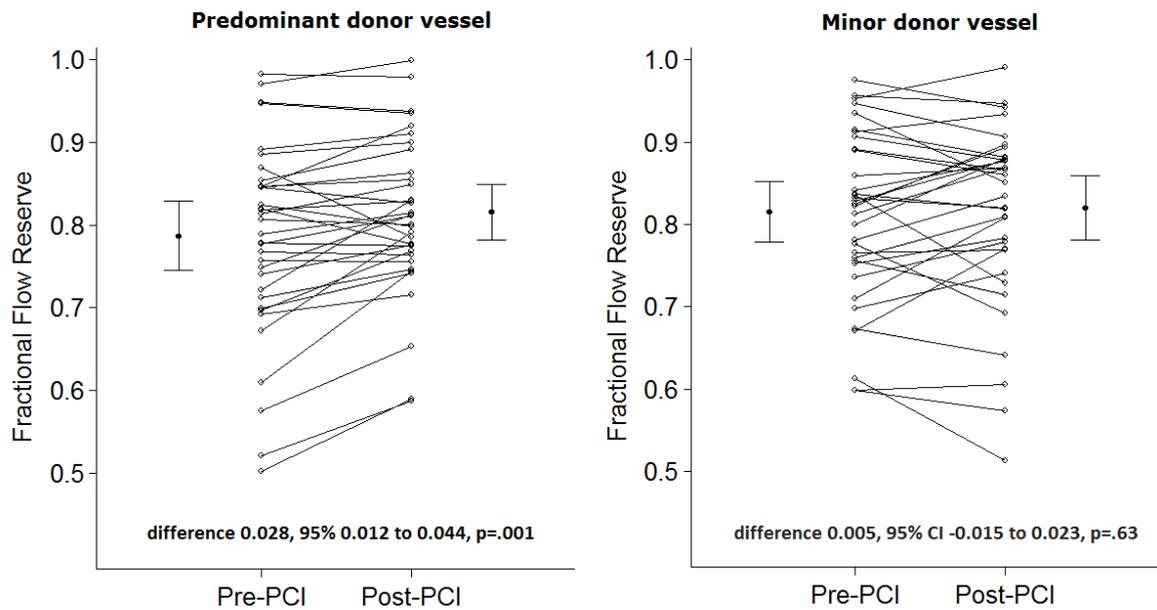


Figure 1. The change in non-target vessel FFR before and after CTO PCI. Mean values are presented either side of the link-plots, error-bars represent 95% confidence intervals.



Figure 2. Mean absolute coronary flow pre and post-PCI at baseline (adjusted for RPP) and hyperaemia for the predominant donor vessel (left) and the minor donor vessel (right).

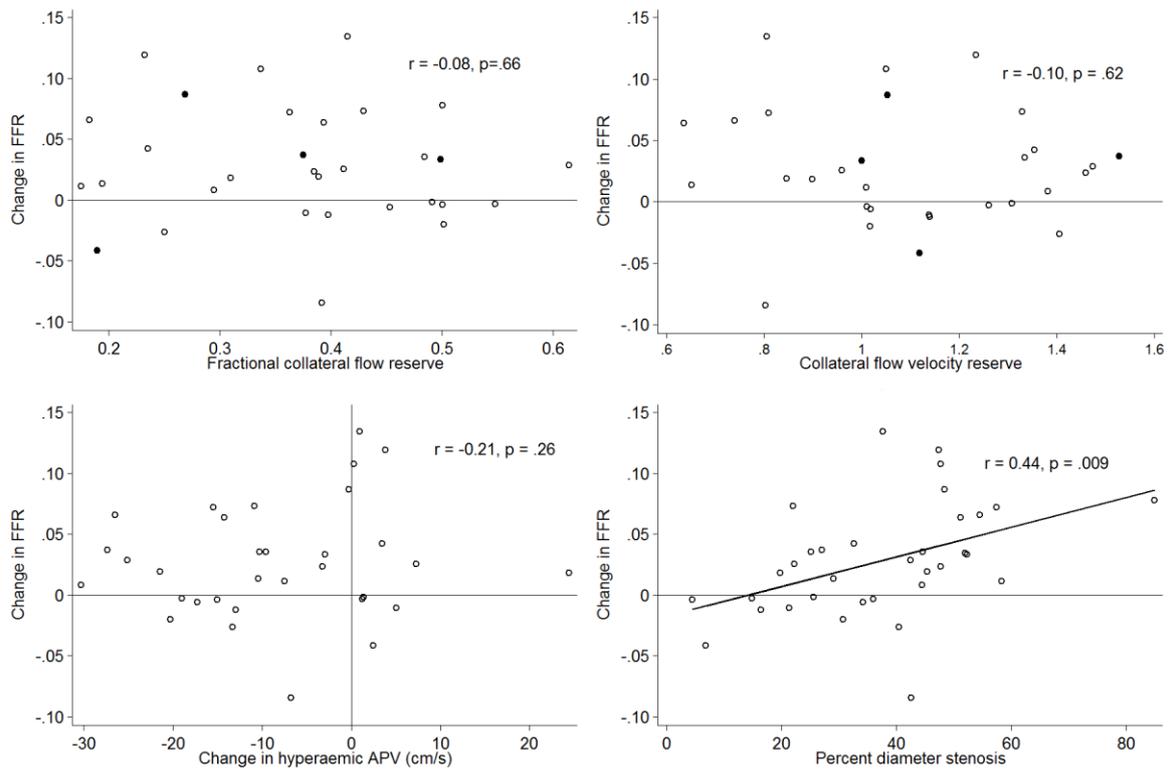


Figure 3. Relationships with change in predominant donor vessel FFR. Top left: fractional collateral flow reserve distal to the chronic occlusion(n=31). Top right: collateral flow velocity reserve distal to the chronic occlusion(n=30). Solid markers represent measures taken by a retrograde approach. Bottom left: change in distal hyperaemic APV(n=32). Bottom right: angiographic(%) stenosis severity(n=34).

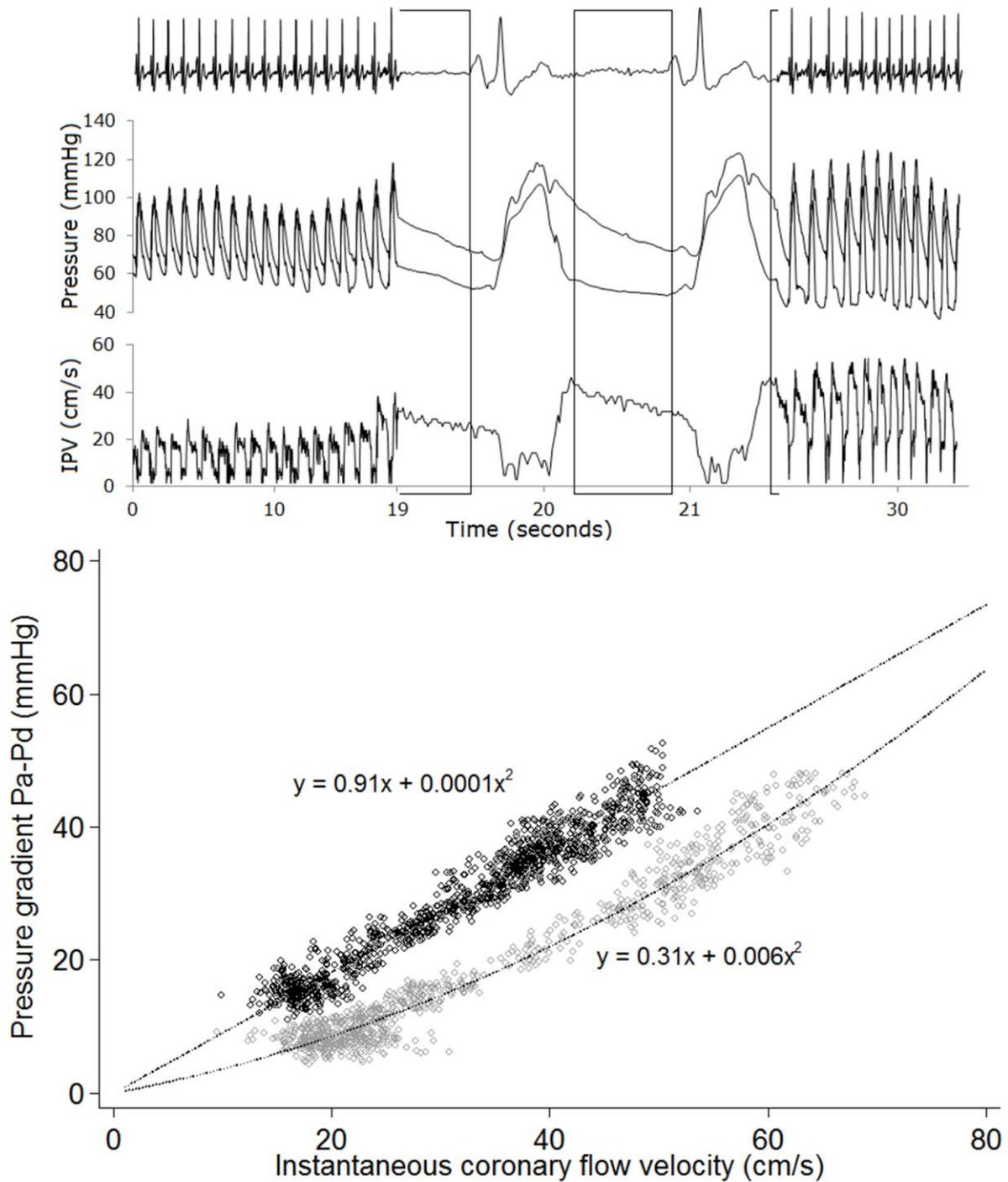


Figure 4. Top panel: simultaneous pressure and flow measurement for calculation of DFV-PGR, measurements are taken during the boxed diastolic periods. Bottom: calculation of the DFV-PGR slope using the formula $\Delta P = FV + SV^2$. In the above example $F=0.91$ and $S=0.0001$ (black circles). Another example is shown with different coefficient values, but a similar peak gradient: $F=0.31$ and $S=0.006$ (grey circles).

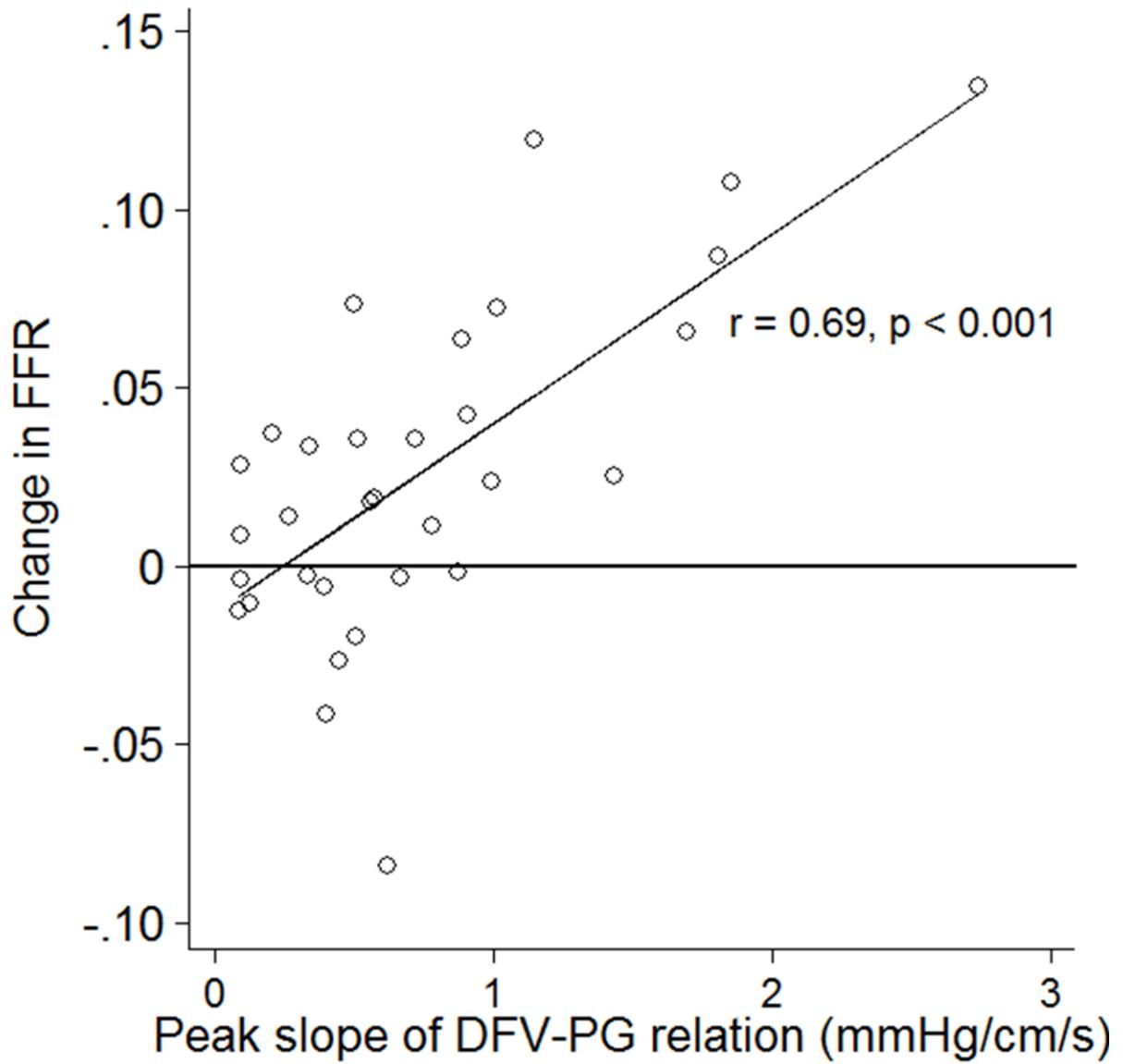


Figure 5. Relationship between peak DFV-PGR and change in predominant donor vessel FFR, before and after CTO PCI(n=32).

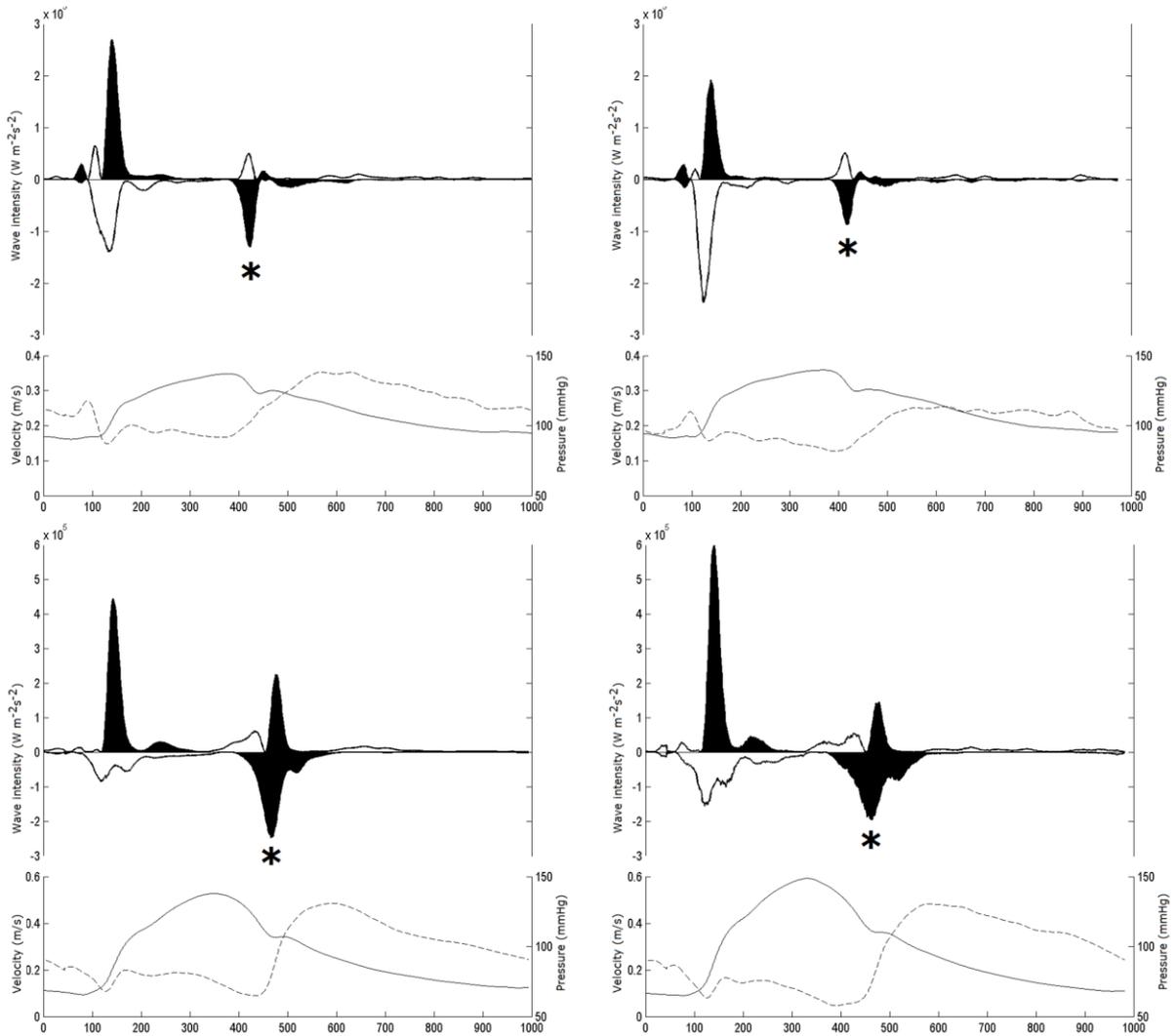


Figure 6. Wave intensity analysis, ensemble averaged coronary pressure (solid line) and flow velocity (dashed line) measured in the proximal predominant donor vessel pre(left) and post(right) PCI of a CTO. Top two panels: proximal RCA donating collaterals to a chronically occluded LAD. Bottom two panels: proximal LAD donating collaterals to a chronically occluded RCA. BEW are asterisked.