Microvascular Dysfunction in the Immediate Aftermath of Chronic Total Coronary Occlusion Recanalization

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Immediate effects on microvascular function in recanalized CTOs

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Abstract

Objectives

The aim of this study was to compare microvascular resistance under both baseline and hyperaemic conditions immediately after PCI of a CTO with an unobstructed reference vessel in the same patient

Backgorund

Microvascular dysfunction has been reported to be prevalent immediately after CTO PCI. However previous studies have not made comparison with a reference vessel. Patients with a CTO may have global microvascular and/or endothelial dysfunction, making comparison with established normal values misleading.

Methods

After successful CTO PCI in 21 consecutive patients, coronary pressure and flow velocity were measured at baseline and hyperaemia in distal segments of the CTO/target vessel and an unobstructed reference vessel. Haemodynamics including hyperaemic microvascular resistance(HMR), basal microvascular resistance(BMR) and instantaneous minimal microvascular resistance at baseline and hyperaemia were calculated and compared between reference and target/CTO vessels.

Results

After CTO PCI, BMR was reduced in the target/CTO vessel compared with the reference vessel: 3.58mmHg/cm/s vs. 4.94mmHg/cm/s, difference -1.36mmHg/cm/s(-2.33 to -0.39,p=.008). We did not detect a difference in HMR: 1.82mmHg/cm/s vs. 2.01mmHg/cm/s, difference -0.20(-0.78 to 0.39,p=.49). Instantaneous minimal microvascular resistance correlated strongly with length of stented segment at baseline (r=0.63,p=.005) and hyperaemia (r=0.68,p=.002).

Conclusions

Basal microvascular resistance is reduced in a recanalized CTO in the immediate aftermath of PCI compared to an unobstructed reference vessel; however hyperaemic microvascular resistance appears to be preserved. A longer stented segment is associated with increased microvascular resistance.

Introduction

Even in the absence of flow-limiting epicardial coronary disease, an intact microvascular vasodilatory reserve is important in preventing myocardial ischaemia under stress[1] and is associated with improved prognosis[2]. Transient target vessel microvascular dysfunction can occur in a proportion of patients in the immediate aftermath of PCI of non-occlusive coronary disease[3,4] and has been reported to be more frequent in patients who have undergone PCI to a CTO[5,6]. Microvascular function in epicardially diseased vessels is related to unobstructed reference vessels in the same patient[7], so the increased prevalence of microvascular dysfunction in this setting may simply reflect the greater burden of disease in patients with CTOs and represent a global phenomenon of microvascular or endothelial dysfunction.

Microvascular resistance in the immediate aftermath of CTO PCI is not well described with respect to the now well established combined pressure and flow indices of microvascular resistance[8]. In addition, previous studies examining the effect of PCI to a CTO on microvascular function and coronary physiology have examined the target vessel, but not made comparison with a reference vessel[5,6,9]. The aim of this study was to describe the immediate effect of CTO PCI on the coronary microvasculature distal to the occlusion in comparison with an unobstructed reference vessel in the same patient. Using instantaneous measures of microvascular resistance we aimed to measure instantaneous minimal microvascular resistance to estimate maximal microvascular dilatation at rest and hyperaemia. We also investigated whether there was a relationship between post-PCI microvascular resistance and pre-PCI measures of collateral perfusion as well as procedural factors which might influence post-PCI microvascular resistance such as length of stented segment and means of CTO recanalization.

Methods

Study population

21 patients who underwent successful PCI to a CTO for symptoms of angina (Canadian Cardiovascular Society (CCS) class 1-3) were recruited consecutively in a single tertiary centre between July 2013 and June 2014. A CTO was defined as complete coronary occlusion of ≥3 months duration with TIMI grade 0 flow[10]. The presence of viable myocardium in the CTO territory was confirmed in all patients by myocardial perfusion scintigraphy(n=16, 76%), dobutamine stress echocardiography(n=1, 5%) or by the absence of a wall motion abnormality by echocardiography or left ventricular angiography without additional confirmation(n=4, 19%). Exclusion criteria were inability to provide consent, >1 occluded vessel, disease of >50% angiographic severity in both other major epicardial coronary arteries, 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 200μg bolus of intra-coronary

glyceryl trinitrate(GTN), iso-centred coronary angiograms of both non-target vessels were taken.

The protocol for coronary haemodynamic assessment is summarised in **figure 1**. A dual sensor pressure-velocity 0.014" intracoronary wire (Combowire XT 9500, Volcano Corp, San Diego, CA)[8], with pressure and Doppler sensors at its tip, was connected to a ComboMap console (Volcano Corp) and used for haemodymamic measurements. 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 normalised to aortic pressure at the tip of the catheter alongside the microcatheter, removed, and passed through the microcatheter into the occluded segment and positioned in a vessel segment angiographically free of a significant stenosis. After administration of 100µg GTN in the vessel donating collaterals to the CTO vessel and once any hyperaemic response had settled, continuous recordings from the ComboMap were taken. Hyperaemia was achieved by central venous administration of adenosine at 140µg/kg/minute. Once steady state hyperaemia had been reached and a continuous recording of $\geq$20 beats taken, adenosine infusion was ceased. Samples were recorded at 200Hz and stored on disk for offline analysis.

PCI success was defined as stenting of the target vessel with <30% residual stenosis and thrombolysis in myocardial infarction(TIMI) grade III flow. After successful PCI, The Combowire was normalised to aortic pressure at the tip of the catheter, advanced to the distal segment of the target vessel at the point of measurement in the occluded segment prior to PCI and manipulated to obtain a good Doppler trace. After administration of 100µg intra-coronary GTN, once the hyperaemic response had settled, continuous recordings from the ComboMap were taken as described. Haemodynamic measurements were then

repeated in each non-target vessel as described for the target vessel post-PCI, including repeated CVP measurement.

Recorded data was analysed using dedicated custom software (Study Manager, Academic Medical Center, University of Amsterdam, The Netherlands).

Angiographic assessment

Maximal non-target vessel diameter stenosis(%) was 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 was identified, vessel collateral connection(CC) grade[11] and modified Rentrop score[12] were assessed by two independent observers blinded to haemodynamic measurements and agreed by consensus.

The non-target vessel selected as the reference vessel was selected based upon an angiographic diameter stenosis severity of <50%. Where possible, the non-target vessel making the smallest collateral contribution to the CTO was selected.

Data analysis

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 under hyperaemic conditions and basal microvascular resistance(BMR) as Pd/APV under baseline conditions. FFR was calculated as (Pd-CVP)/Pa-CVP), using mean pressures taken over 5 cardiac cycles at stable hyperaemia[13]. Coronary flow reserve (CFR) was calculated as APV at steady state hyperaemia divided by APV at baseline, measured over 5 cardiac cycles.

In addition, we also investigated the instantaneous minimal microvascular resistance which was calculated by sampling instantaneous flow velocity and Pd from 25% into the diastolic period (taken from the dicrotic notch to the ECG R-wave), stopping at the onset of the qrs complex) over three beats. It is during this period in the cardiac cycle that the absolute value and the variance of microvascular resistance have been shown to be minimal[14]. Instantaneous minimal microvascular resistance was then calculated as the mean Pd/mean IPV taken during this period**(figure 2).**

Collateral flow index (CFI_p) 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.

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. Using 10 repeated baseline measurements and 10 repeated hyperaemic measurements, the coefficient of variation for instantaneous minimal microvascular resistance was 12.8%. If just repeated baseline measurements were assessed it was 11.5% and if only hyperaemic measurements were assessed it was 14.0%.

Statistical analysis

Stata v.12(StataCorp, College Station, Texas) was used for statistical analysis. Continuous values are expressed as means±SD, or median(25^{th} percentile-75^{th} percentile) as appropriate. 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 the 21 patients who underwent successful CTO PCI, mean age was 60.9±10.9 years, 18 (86%) were male and mean LV ejection fraction was 57.3±10.2%. Median estimated duration of occlusion was 54 weeks (30-87) and all patients had Rentrop[12] ≥2 and CC[11] ≥1 grade collateralisation. Drug-eluting stents were used for all procedures. Demographics, angiographic and procedural details are summarized in **Table 1**.

Microvascular assessment

Mean time in minutes from restoration of antegrade flow in the CTO vessel to post-PCI microvascular assessment was 54.4±20.1 for the CTO/target vessel and 68.9±21.2 for the reference vessel. Post-PCI haemodynamic indices for the CTO vessel and reference vessel are detailed in **Table 2.** We did not demonstrate a significant difference in HMR, however BMR was significantly lower in the target vessel compared with the reference vessel: difference -1.36mmHg/cm/s(-2.33 to -0.39, p=.008). Although not well established, if an HMR is ≤2.0 is considered normal[15], 14(67%) patients had a 'normal' target vessel HMR and 14(67%) patients had a 'normal' reference vessel HMR post CTO PCI. If a CFR of ≥2 is considered normal[1,2,7,16], 6(29%) patients had a 'normal' target vessel CFR and 10(48%) had a 'normal' reference vessel CFR.

Figure 2 depicts an example of the calculation of minimal instantaneous microvascular resistance at baseline and at hyperaemia. **Figure 3** shows individual measurements for target/CTO and reference vessels. Under baseline conditions, instantaneous minimal microvascular resistance in the recently recanalized CTO vessel measured in mmHg/cm/s was 2.57±1.13 and was significantly lower when compared with a

paired unobstructed reference vessel, which measured 3.40±1.26; difference -0.83 (95% CI -1.62 to -0.04, p=.04). We did not detect a statistically significant difference in minimal instantaneous microvascular resistance between target and reference vessels at hyperaemia**(table 2).** The reduction in minimal instantaneous microvascular resistance as a result of adenosine infusion was greater in the reference vessel: 2.10±1.07mmHg/cm/s than the target vessel: 1.26±0.68mmHg/cm/s; difference 0.84(95% CI 0.23 to 1.45, p=.009).

Determinants of post-PCI microvascular function

Any determinant of microvascular resistance should be related to the maximal vasodilatory capacity under either baseline or hyperaemic conditions, and therefore the minimal instantaneous microvascular resistance. We therefore examined the relationship between minimal instantaneous microvascular resistancve and invasively derived indices of pre-PCI collateral perfusion to the occluded segment, as well as length of stented segment (as a possible predictor of procedural microvascular injury).

It was possible to measure invasive indices of collateral function distal to the occlusion, prior to PCI in 19 of 21 patients, of which one was measured through a retrograde approach (CFI_p : 0.50, Collateral flow velocity reserve: 1.02). We found no correlation between microvascular indices in the target vessel and invasive measures of collateral perfusion measured distal to the occlusion**(figure 4)**.

Target vessel minimal instantaneous microvascular resistance at both baseline and hyperaemia strongly correlated with length of stented segment in millimetres: baseline r=0.63, p=.005; hyperaemia r=0.68, p=.002 **(figure 5)**. A similar relationship was found using mean values of microvascular resistance: BMR r=0.58, p=.005; HMR r=0.58, p=.005. There was no relationship between minimal instantaneous microvascular resistance and length of stented segment in the reference vessel: baseline r=0.21, p=.36; hyperaemia r=0.36, p=.11

Discussion

By conventional values of microvascular normality the results of this study, consistent with previous studies[5,6], suggest that microvascular dysfunction is prevalent amongst recently recanalized CTOs. By the same definitions, this study demonstrates that high prevalence extends to global coronary microvascular dysfunction amongst patients with a CTO. We demonstrate that the microvasculature distal to a recently recanalized CTO behaves differently to the microvasculature in an angiographically unobstructed reference vessel in the same patient. In particular, the microvascular resistance under baseline conditions is lower in the recanalized CTO vessel relative to the reference vessel, however maximal vasodilatory capacity in response to adenosine appears to be preserved. There is a strong association between length of stented segment and increased microvascular resistance both under baseline conditions and in response to adenosine infusion. We were not able to demonstrate any relationship between invasively derived indices of collateralisation prior to recanalization of the CTO and target vessel microvascular resistance post PCI.

Prevalance of microvascular dysfunction

If a CFR <2 is used to define microvascular dysfunction, 71% of CTO vessels had abnormal microvascular function after PCI. A larger study by Werner et al reported a CFR of <2 in 46% of a total of 120 patients[6]. However, by the same definition 53% of patients in our study had microvascular dysfunction (CFR<2) in an angiographically unobstructed reference vessel. Werner reported that in a sizeable proportion of patients (26% of 120) CFR did not return to ≥2 at 5 month follow up[6]. Our results would suggest that these patients are likely to have had global coronary microvascular dysfunction, possibly in conjunction with diffuse but non-obstructive atheroma and had it been measured, would also have had a CFR <2 in a reference vessel at the time of PCI.

If the definition of an HMR >2 is used to define microvascular dysfunction, we found a lower prevalence of 33% in CTO vessels. Interestingly, the prevalence of an HMR >2 was also 33% in reference vessels. We did not find a statistically significant difference in HMR or instantaneous minimal microvascular resistance between target/CTO and reference vessels. It might be argued that the increased prevalence of reference vessel microvascular dysfunction is due to a global effect of PCI[17–19], however we have recently shown that in the non-target vessel donating least/no collaterals there is little change in indices of microvascular function before and after CTO PCI[20].

The HMR and CFR measure different aspects of the microvasculature. HMR measures the microvasculature's maximal vasodilatory capacity, which does not seem to be reduced relative to a reference vessel. Except for in the event of idiosyncratic peri-procedural microvasculature insult, maximal vasodilatory capacity appears to return to what is normal for the patient immediately after CTO PCI. This is consistent with previous findings that hyperaemic absolute coronary flow in the CTO myocardial segment is no different at 24 hours compared with 6 months post PCI[21]; and maximal coronary flow velocity is no different immediately after PCI compared with at 5 months follow-up[6].

CFR incorporates baseline flow and therefore basal microvascular tone. The most striking abnormality we demonstrate of the behaviour of the CTO/target vessel microvasculature relative to the reference vessel microvasculature is the significant relative reduction in basal microvascular resistance.

Reduced basal microvascular tone

We report a significant reduction in BMR, minimal basal instantaneous microvascular resistance and the relative reduction in microvascular resistance in response to adenosine (as a result of lower basal microvascular resistance) in a recently recanalized CTO vessel compared with an unobstructed reference vessel **(Table 2 & figure 4).** This is in

keeping with previous reports of increased coronary flow velocity immediately after CTO PCI[5,6], and is likely to represent impairment of the normal auto-regulatory mechanisms of the microvasculature to regulate coronary flow. Although collateral vessels are frequently sufficient to preserve myocardial viability[22], they are seldom (if ever) sufficient to prevent ischaemia under stress[23,24]. This is most likely because the microvasculature distal to a CTO is in a state of maximal vasodilatation in order to preserve basal myocardial perfusion, and is unable to dilate any further[25–27]. Both endothelium dependent and independent vasodilatation have been shown to be impaired in CTO vessels in the immediate aftermath of PCI[9,28], and return to normal at follow-up[28]. It is likely that the state of reduced basal microvascular tone that we demonstrate is related to the endothelial dysfunction of a chronically under-perfused vessel and we would expect it to normalise at a similar interval post-PCI. This state of reduced basal microvascular tone results in increased coronary flow under baseline conditions and therefore increased pressure gradient across any epicardial stenosis. Notwithstanding the dysfunctional nature of vasodilatory mechanisms in the recanalized epicardial segment of a CTO, optimization of the result using iFR[14], a pressure based index of stenosis severity measured under baseline conditions, is therefore likely to lead to an erroneous result given the (most likely transient) increased basal flow. In the absence of microvascular embolization however, hyperaemic indices of stenosis severity are likely to be unaffected.

Relationship with pre-PCI collateral perfusion

We have not identified a relationship between indices of collateral perfusion prior to CTO PCI and target vessel/CTO microvascular resistance after PCI**(figure 4)**. A previous study demonstrated greater coronary endothelial dysfunction in the recently recanalized segment of CTOs in patients who had previously had less well collateralised occluded segments as assessed by the CC grade[9]. However, this finding may have reflected individual patient's

ability to form collaterals by arteriogenesis, which is an endothelium dependent process[22]. One might imagine that improved collateral perfusion prior to recanalization might result in less marked microvascular abnormalities post-recanalization. The effect of other variables, in particular the length of the stented segment on microvascular resistance makes this difficult to investigate further in such a small patient population.

Relationship with length of stented segment

We demonstrate a strong relationship between length of stented segment and microvascular resistance both at baseline and hyperaemia with higher microvascular resistance associated with a longer stented segment(**figure 4)**. It seems likely that this is related to increased risk of micro-embolization and microvascular injury as the treated segment increases in length. The finding is consistent with a previous study which demonstrated increased risk of peri-procedural myocardial infarction (MI4a) with a longer stented segment in non-occlusive disease[29]. Contemporary techniques of dissection/re-entry tend to result in longer stented segments, but also involve greater disruption to the vascular architecture than a lumen-lumen approach which could conceivably lead to more distal embolization. The greater vascular disruption of the dissection re-entry approach might explain this finding; however the same trend with stent length seems to occur amongst the lumen-lumen group. In either case, it would appear that a dissection re-entry approach (usually involving a longer stented segment) is associated with peri-procedural microvascular impairment which may not be apparent angiographically (all study patients had TIMI III flow at the time of haemodynamic measurement). It remains to be seen if this finding has any implication with respect to clinical outcomes.

The total number of study participants was small with a low rate of diabetes. We have therefore not been able to examine clinical characteristic such as smoking,

hypertension and diabetes that might be related to microvascular dysfunction as previously reported[5].

Limitations

This is a single centre study, with a small number of patients. However, it is the first to make comparison of microvascular resistance after CTO PCI in the target and an unobstructed reference vessel. The study population had a preponderance of right coronary CTOs and the reference vessel was more commonly a branch of the left coronary artery. Although this could have introduced confounding into our results, it does not seem plausible that it could account for our major findings.

By Protocol, target/CTO vessel haemodynamics were assessed earlier than the reference vessel, with a mean interval of 14.5 minutes between measurements. Although it would be preferable to have taken measurements at the same interval after restoration of antegrade flow, we consider it unlikely to have altered our results.

We did not incorporate collateral flow into our calculation of microvascular resistance. However it has been shown previously that in vessels with an FFR >0.60, the effect of collateral flow on HMR is minimal[30]. All interrogated vessels in this study had an FFR well in excess of 0.60.

Where possible we selected the vessel angiographically donating least/no collaterals to the CTO vessel. Receipt of collaterals rapidly diminishes after CTO PCI[31,32] and collateral donation falls at a similar interval with little effect on the microvasculature of the non-target vessel donating least/no collaterals [20]. It is plausible that the presence of minimal collaterals may have had some effect on our measurements, however we consider it unlikely to have altered our results significantly.

We would imagine that microvascular resistance under baseline conditions in the CTO/target vessel would increase to a level similar to the reference level after an interval.

However, we did not repeat assessments at follow-up and further studies would be required to confirm and describe this.

Conclusions

Microvascular resistance under baseline conditions is reduced in a recanalized CTO in the immediate aftermath of PCI when compared to an unobstructed reference vessel; however hyperaemic microvascular resistance appears to be similar. Although microvascular dysfunction is common in CTO vessels after recanalization, the dysfunction appears to be abnormal autoregulation of microvascular tone (or a continued hyperaemic response to coronary occlusion in spite of recent recanalization) with a preserved maximal vasodilatory capacity. A longer stented segment is associated with increased microvascular resistance both under baseline conditions and at hyperaemia. The abnormal microvascular conditions in this setting should be considered prior to considering physiological lesion assessment in the immediate aftermath of CTO PCI.

Clinical implications

Microvascular resistance under baseline conditions remains abnormally low approximately 1 hour after recanalization of a CTO, but maximal vasodilatory capacity appears to remain unchanged. If phyisiological lesion assessment is considered in this setting, the use of 'resting' indices such as iFR are likely to overestimate lesion severity due to relative hyperaemia. Longer stented segments and dissection re-entry techniques may be associated with greater microvascular injury, larger studies are required to investigate this further and establish any clinical significance.

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Disclosures

None.

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Figures

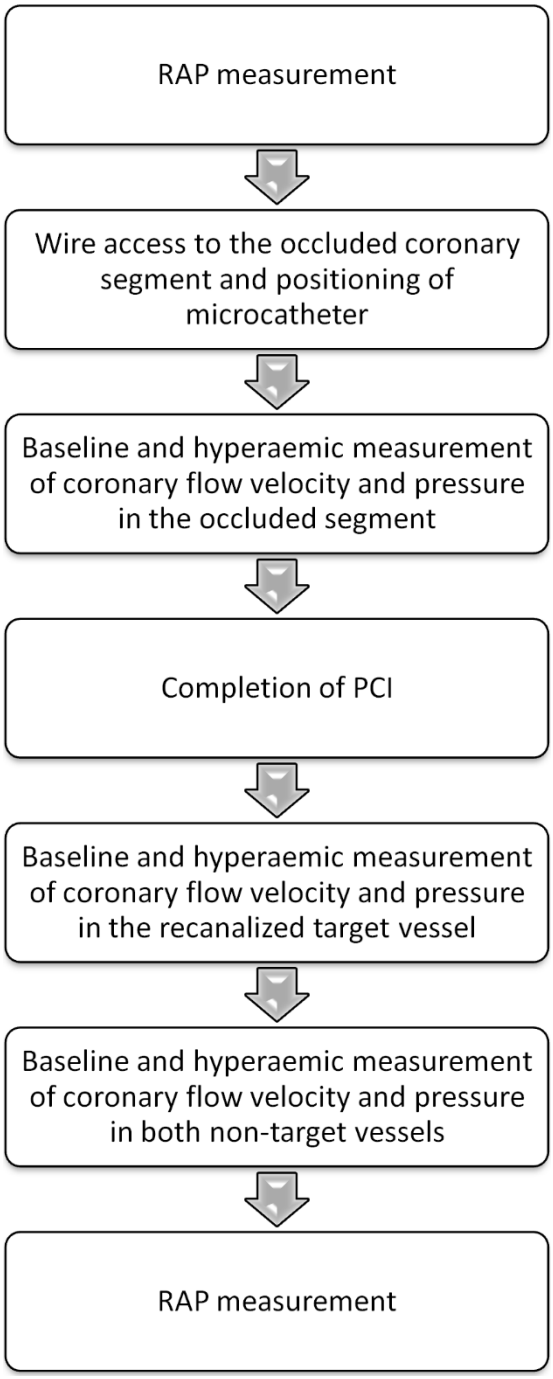

Figure 1.

Flowchart summarizing the order of haemodynamic measurements taken as part of the study protocol. RAP = right atrial pressure.

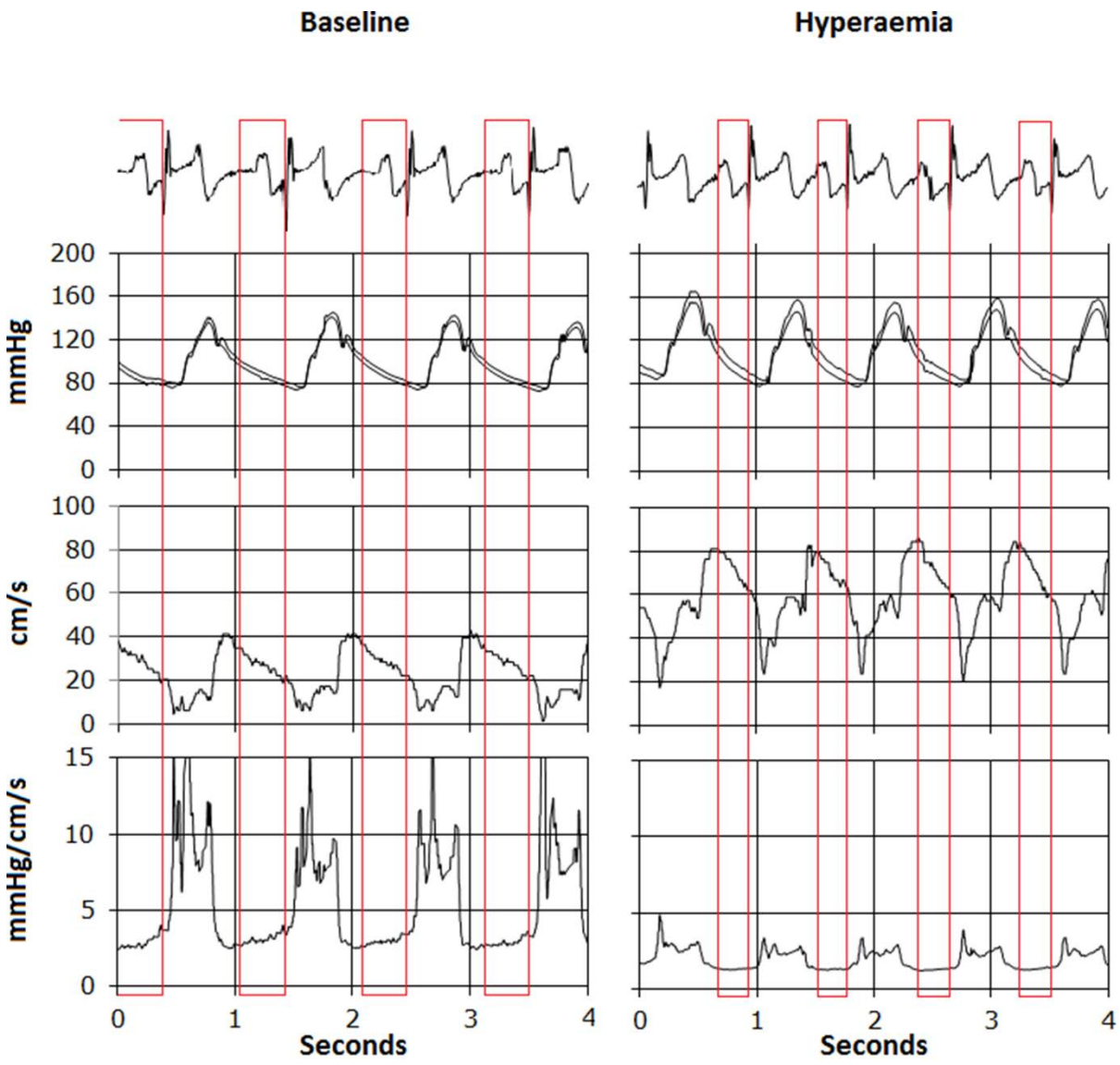

Figure 2.

Assessment of minimal instantaneous microvascular resistance. Coronary haemodynamics measured in a recently recanalized right coronary artery. Instantaneous coronary pressure (top, Pa and Pd), flow velocity (middle) and derived microvascular resistance (bottom) under baseline conditions(left) and at maximal hyperaemia (right). The segments within red boxes represent the sampled period for minimal instantaneous microvascular resistance.

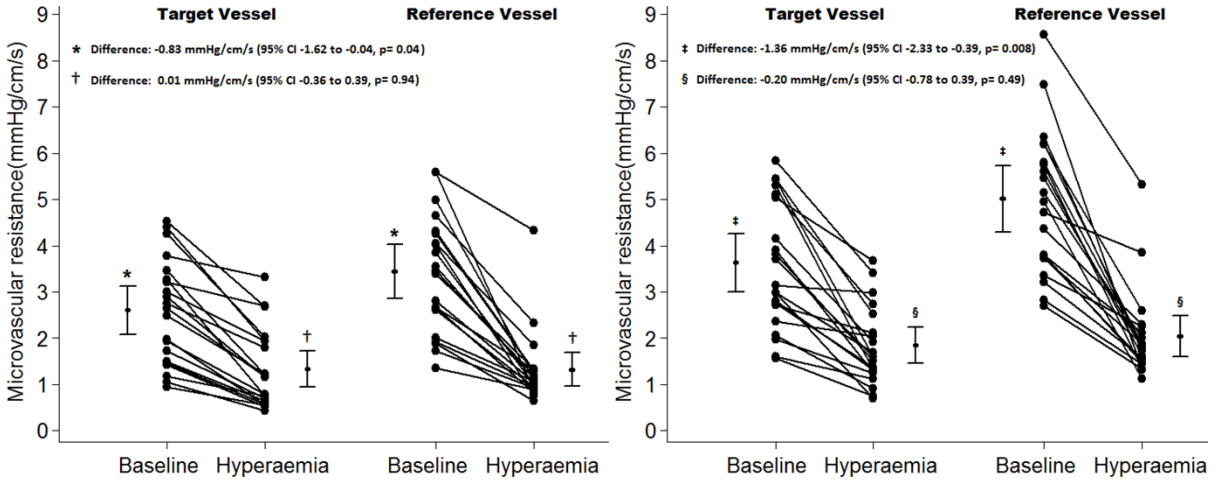

Figure 3.

CTO/target vessel basal and hyperaemic microvascular resistance after PCI**.** Left graph: Instantaneous minimal microvascular resistance at baseline and hyperaemia for the CTO/target vessel (left) and an unobstructed reference vessel (right). Right graph: Using mean values, baseline and hyperaemic microvascular resistance (BMR and HMR) for the CTO/target vessel (left) and an unobstructed reference vessel (right). Error bars represent 95% confidence intervals.

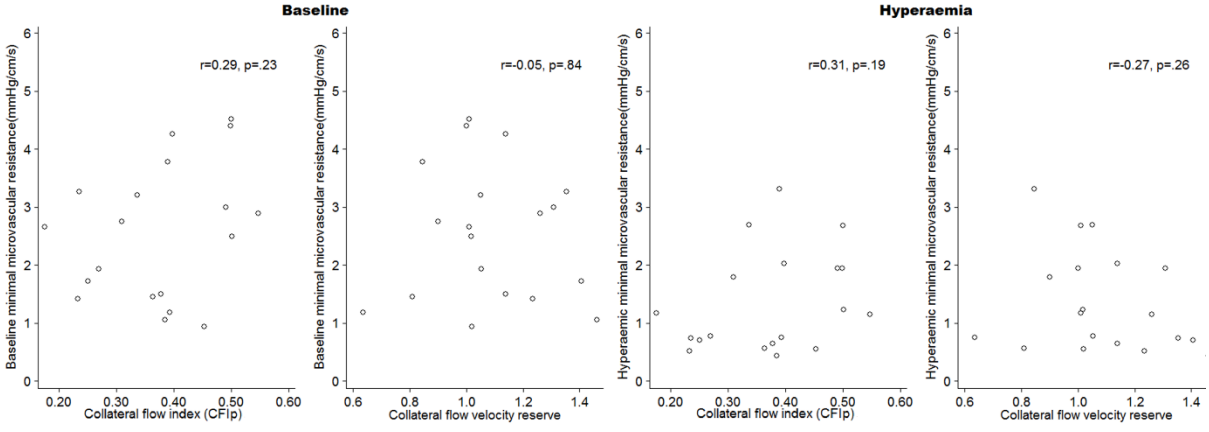

Figure 4.

Relationship between pre-PCI collateral perfusion and post-PCI microvascular resistance CTO/target vessel instantaneous minimal microvascular resistance at baseline (left) and hyperaemia right).

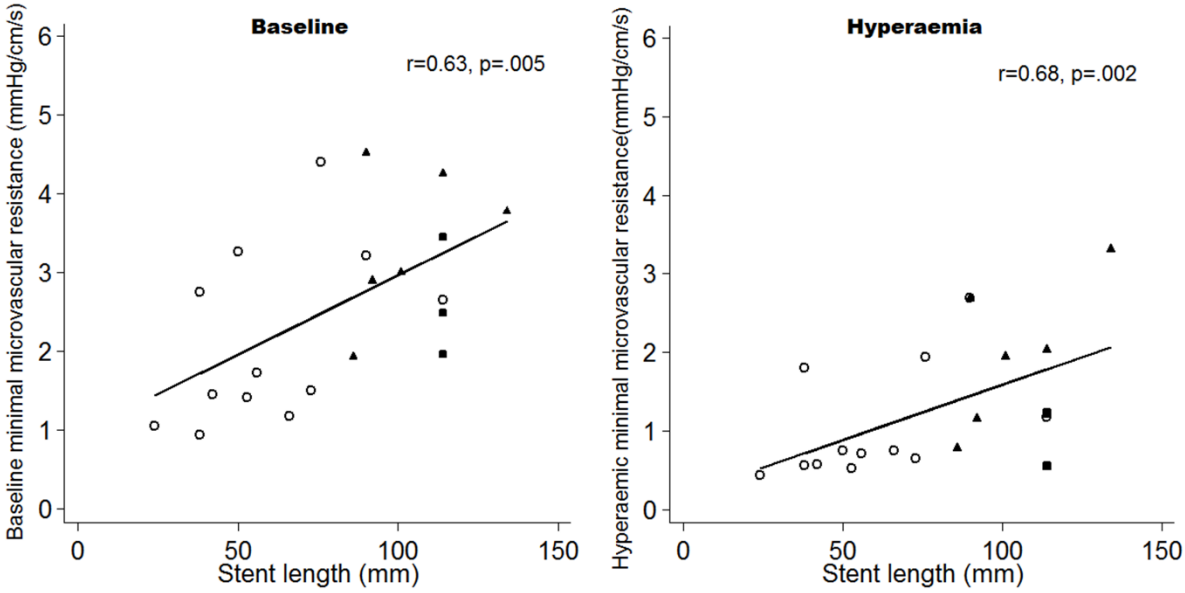

Figure 5.

Relationship between length of stented segment in mm and CTO/target vessel instantaneous minimal microvascular resistance at baseline (left) and hyperaemia (right). Circles represent an antegrade lumen-lumen approach, triangles: antegrade dissection re-entry and squares: retrograde dissection re-entry.