The Haemodynamic Effects of Collateral Donation to a Chronic Total Occlusion: Implications for Patient Management

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Abstract

Physiological lesion assessment in the form of Fractional Flow Reserve (FFR) is now well established for the purpose of guiding multi-vessel revascularization. Chronic total coronary occlusions are frequently associated with multi-vessel disease and the collateral dependent myocardium distal to the occlusion is often supplied by a collateral supply from another epicardial coronary artery. The haemodynamic effect of collateral donation upon collateral donor vessel flow may have important implications for the vessel's FFR; rendering it unreliable at predicting ischaemia should the CTO be revascularized. As a consequence, in the setting of multi-vessel disease, optimal revascularization strategy might be altered. There is a paucity of work in the medical literature directly examining this phenomenon. We endeavoured to review the existing literature related to it, to summarise from current knowledge of coronary physiology what is known about the potential effects of CTO revascularization on both collateral flow and collateral donor vessel physiology, and to highlight where further studies might inform practice.

Introduction

The human coronary circulation in both health and in disease consists of a complex pre-existing anastamotic network rather than functional end-arteries. If an epicardial vessel is occluded, there is an associated gradual increase in diameter of these anastamotic collateral branch connections over time[1,2], through which the distal segment of the occluded vessel is filled(figure 1).

This coronary collateral supply can be sufficient to preserve resting left ventricular systolic function in spite of complete coronary occlusion, and in animal models has been shown to be sufficient to prevent ischaemia under stress[3–6]. In the presence of a chronic total coronary occlusion (CTO), if the collateral dependent myocardium is perfused by retrograde collateral branches, as is frequently the case, coronary physiology in the collateral donor vessel could be altered. If this effect is sufficiently large, the haemodynamic importance of a donor vessel coronary stenosis could change. The presence of a CTO may therefore result in flow limitation and myocardial ischaemia in coronary arterial territories remote from the occluded vessel. If so, the additional ischaemia generated by a CTO, relieved on recanalization might even help to explain (in addition to the apparent detrimental effect of a concomitant CTO in the event of STEMI[7,8]) the frequent finding in published cohort studies of a survival benefit associated with successful CTO recanalization[9], which is absent in clinical trials of PCI of non-occlusive lesions versus medical therapy[10]. If this phenomenon results in important changes to physiological stenosis measurement indices such as the Fractional Flow Reserve (FFR), then as the evidence base for their use to guide revascularization grows (as seems inevitable), the need to understand it will become

increasingly important. The purpose of this article is to review what we know about coronary physiology related to this phenomenon, its importance, and to highlight where further studies might inform our practice.

FFR and the effect of a change in donor vessel flow

The FFR is the ratio of the maximum myocardial blood flow in the presence of a coronary stenosis to the maximum myocardial blood flow in the absence of that stenosis[11]. Maximal myocardial blood flow is achieved by pharmacological vasodilatation, most commonly using adenosine given either intravenously or intra-coronary. It is dependent upon multiple morphologic determinants of resistance related to the stenosis, the extent of perfusion territory, and the presence of collateral myocardial blood flow.

The FAME study showed a clinical benefit in the use of physiological lesion assessment in the form of FFR to guide PCI in multi-vessel disease[12]. Patients randomised to treatment by FFR guided PCI (in which a lesion was treated if the FFR was $\leq$0.8) had a significant reduction in the composite primary endpoint of death, non-fatal myocardial infarction and repeat revascularisation at 1 year compared with those treated by angiographically guided PCI. At 2 year follow up, there was a significant difference in a composite of the harder end-points of death or myocardial infarction, favouring the FFR guided group[13]. The FAME II study showed a large increase in urgent revascularization if treatment by PCI of lesions with an FFR $\leq$0.8 was deferred[14].

Although FFR is reported to be independent of changing haemodynamics[15], it is intimately related to total coronary flow through a stenosis[16,17]. Whilst PCI of a lesion remote from a vessel in which there is a stenosis will have no effect upon the characteristics of that stenosis, it would be expected to change the extent of collateral myocardial blood flow

donated by the remote vessel. If the remote vessel makes a significant collateral contribution to the treated vessel, the mass of myocardium the vessel perfuses may reduce, along with flow through the stenosis and as a consequence we might expect the FFR to increase. This is particularly relevant when considering the effect of a CTO on a remote vessel as the myocardium distal to a CTO is by definition entirely collateral dependent. In addition, the angiographic degree of collateralisation is such that one might expect the influence on the remote/donor vessel(s) flow and FFR if a CTO is recanalized to be large. It has been suggested that the large increase in coronary flow through collateral donor vessels as a result of the additional flow through the collateral bed could be enough for minor atherosclerotic irregularities to generate enough resistance to become flow limiting. In support of this, Werner et al measured donor artery FFR prior to recanalization of a CTO in assessing determinants of coronary steal; 18 of 45 patients in whom they reported an FFR measurement had an FFR of <0.8, only 8 of those had a visible lesion in that donor vessel[18].

If the additional flow as a result of donating a collateral supply to collateral dependent myocardium is sufficient to significantly alter donor artery haemodynamics, we would expect an early reversal of the effect once the myocardium is rendered no longer collateral dependent. After CTO angioplasty it has been shown that both flow and pressure-derived recruitable collateral function in the target vessel diminishes rapidly[19,20] (figure 2), and is not significantly different at 24 hours post PCI from the value taken at a mean time of just 48 minutes[19].

Several cases have been reported in which marked changes in non-target vessel FFR have occurred after PCI of a CTO[21–25]. Each case reported pre and post-PCI measurement of

donor vessel FFR and involved PCI of either 1 or 2 CTOs. An impressive increase in FFR of 0.12 in 4 cases and 0.09 in another were reported, crossing the treatment threshold from <0.80 to ≥0.80 in 3 of the 5 cases. Although the change in FFR in these cases seems remarkably consistent, it is important to remember that these are individual published cases. The only attempt thus far to investigate this phenomenon systematically found a much more variable change in FFR[26]. In 14 cases, two of which involved PCI of 2 CTOs, mean change in FFR was an increase of 0.04 with a wide 95% confidence interval of the difference of 0.001–0.079, the standard deviation of the difference was 0.062[27]. The wide confidence interval would suggest that a larger study would be useful to give a more precise estimate of the change. The standard deviation however, implies that there is considerable variability to the change of FFR post CTO PCI, and that we cannot assume there will be a large increase in donor vessel FFR. It also highlights the utility of further studies which might identify features of donor vessel anatomy or haemodynamics which might predict a larger change in FFR.

The haemodynamic changes we predict and describe make the assumption of successful CTO recanalization without additional haemodynamic effects. In recent years CTO PCI has developed considerably with greater success rates[28], this is in part the development of alternative approaches to CTO PCI, including dissection re-entry and retrograde approaches. The effects in the short and longer term of dissection re-entry techniques, which tend to involve longer stented segments, greater disruption of the vascular architecture, and a greater tendency for side branch occlusion upon haemodynamics and microvascular function are not well described. Any effect on the microvasculature is likely to be transient[29], however if the recanalization technique results in side branch occlusion, it may be that a proportion of myopcardium perfused by the lost branch remains collateral

dependent. This could result in a smaller effect on the collateral donor vessel. Although a retrograde approach often results in a damaged collateral vessel, if we expect them to regress after CTO recanalization anyway[19,20], it seems likely that haemodynamics would be a long-term effect on haemodynamics.

The need to understand the influence of a CTO on non-target vessel flow and FFR

It is now generally accepted that when presented with multi-vessel disease, we should aim for complete rather than incomplete revascularisation[30]. There is some evidence which supports the suggestion that complete revascularisation is associated with prognostic benefit[31,32]. In a large registry using New York State's Percutaneous Coronary Intervention Reporting System, 11294 patients with multi-vessel disease, treated by PCI were followed up for 18 months[32]. Incomplete revascularization, performed in 69% of patients, was associated with increased mortality and those with two unattempted vessels including a CTO were at highest risk.

There is good evidence of a clinical benefit if FFR is used to guide multi-vessel angioplasty with clear thresholds to determine treatment. However, there is real doubt as to the effect of recanalization of a CTO on non-target vessel haemodynamics. If the intention of treatment is that of complete revascularization, at present we cannot be certain if a lesion with an FFR of <0.8 in a non-target vessel would still have an FFR of <0.8 once the occluded vessel is recanalized. The concern, is that should CTO revascularization render a vessel's FFR above the treatment threshold of 0.8, the results of the FAME trial[12] would suggest that angioplasty of that vessel would be associated with adverse clinical outcomes. If the intention is to treat by PCI, the simple solution is to open the CTO and then re-assess the FFR of the other vessels. However we do not always have that luxury, in patients with three-

vessel coronary disease coronary artery bypass graft surgery (CABG) has been shown to have superior long-term outcomes compared with PCI, an effect which appears to be greater with increasing angiographic complexity[33] and with concomitant diabetes[34,35]. A vessel with a haemodynamically ambiguous lesion, the FFR of which is <0.8, but might move above that treatment threshold once myocardium receiving collaterals from it is revascularized, could be the difference between CABG and PCI being the most appropriate treatment. A haemodynamically ambiguous lesion would not necessarily be of low angiographic complexity, and the need to treat it might alter the long-term outcomes which can be achieved with angioplasty. What is becoming increasingly clear is that our ability to identify flow limiting lesions by angiography alone is limited[36,37] and knowledge of the FFR frequently changes management strategy[37–39].

There is less evidence for a clinical benefit for the use of FFR to guide coronary artery bypass graft placement than for angioplasty, but the occlusion rate is higher for grafts placed on haemodynamically non-significant lesions[40](figure 3). In a large retrospective cohort study, FFR guided graft placement was associated with a lower number of grafts, lower rate of angina and also a lower rate of graft failure than angiography guided graft placement, there was however, no difference in the 1ry clinical composite end-point of death, myocardial infarction or target vessel revascularization[41].

A CTO is present in approximately one fifth of patients with significant coronary disease on coronary angiography[42]. If we consider assessment by FFR to guide revascularization best practice, then the presence of a CTO, which may or may not alter the physiological significance of stenoses in the accompanying vessels is prevalent and there is therefore an uncertainty about the reliability of the FFR in a sizeable subset of patients.

Relationship between pressure and flow

A particular coronary stenosis or vessel segment will have a characteristic relationship between coronary flow velocity and the associated pressure gradient. That relationship is described by the equation $\Delta P = FV + SV^2$ where ΔP is the pressure drop in mmHg, V is the coronary flow velocity in cm/sec, 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[43,44]. The equation 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).

A vessel with a mild stenosis can accommodate a much larger increase in flow velocity before there is a given pressure gradient than a more severe stenosis. The FFR is dependent upon this flow velocity/pressure gradient relationship. Excluding other factors, it seems likely that the change in FFR of a vessel donating blood to collateral dependent myocardium on recanalization of an accompanying CTO might be dependent on the vessel's flow velocity/pressure gradient curve and the degree to which there is a change in flow.

Using pressure sensor tipped wires in combination with Doppler tipped wires it is possible to plot instantaneous flow velocity against pressure gradient as described in animal models by Gould, in clinical practice[45–47]. This was initially performed with separate Doppler and pressure tipped wires, but can now be performed with a combined wire (Volcano ComboWire, Volcano Corporation, San Diego, California)[47]. As in Gould's original work, coronary pressure gradient (defined as aortic pressure, measured from the guiding catheter minus distal coronary pressure, measured from the pressure wire) is plotted against coronary flow in mid-diastole, excluding the diastolic upstroke in coronary flow. During mid-

diastole, compressive forces of the ventricle are minimal so coronary flow is only related to the severity of the lesion and to the driving pressure, theoretically minimizing any contribution other than resistance to flow across the stenosis to the flow-pressure gradient relationship. The technique takes measurements from a resting state, intermediate hyperaemia and maximal hyperaemia and produces curves very similar to those produced by Gould(figure 6).

Calculating diastolic flow-pressure gradient curves is relatively cumbersome when in FFR we have a validated means of identifying ischaemia which is simpler, more reproducible[46] and is associated with benefits in clinical outcome. What they add however, is a means of identifying the relationship between pressure gradient and flow in an individual vessel segment and allow us to predict the change in pressure gradient for a given change in flow velocity. It could even be that the characteristics of the slope could provide a means of identifying lesions which are likely to alter in haemodynamic importance after a change in subtended myocardium, such as PCI of a concomitant CTO.

Another possible explanation for a difference between patients with differing donor vessel lesion severity and how the change in FFR with concomitant CTO PCI might vary is that the contribution of collateral flow to distal pressure appears to be greater with more severe stenoses[48]. It is not known whether recruitable collateral function is improved in the non-target vessel after PCI of a CTO. If it is, the vessels (with more severe stenoses) which depend on collateral flow to a greater extent might see a larger change in distal perfusion and therefore FFR.

Flow to the collateral dependent myocardium

The change in remote, non-target vessel FFR post CTO PCI will be dependent upon the size of the change in flow, and therefore flow velocity across any stenosis. The magnitude of that change has not been studied, but the behaviour of the collateral dependent myocardium at rest and hyperaemia has been studied extensively.

The extent of collateralisation to an occluded segment can be readily assessed angiographically by the Rentrop grade[49], a measure of retrograde filling of the occluded vessel where: grade 0=no collaterals; grade 1=side branch filling of the recipient artery without filling of the main epicardial artery; grade 2=partial filling of the main epicardial recipient artery; and grade 3=complete filling of the main epicardial recipient artery. It might be expected that a higher Rentrop collateral filling grade would reflect greater collateral perfusion, however it has not been shown to be related to invasive functional measures of collateral perfusion[50]. An alternative angiographic collateral grading system exists in the collateral connection (CC) grade[50]where: grade 0=no continuous connection between donor and recipient vessels, CC1=threadlike continuous connection and CC2=side branch–like connection. Pressure and flow derived measures of collateral function have been shown to be greater in those with CC2 collaterals. It might be that CTOs perfused via CC2 grade collaterals would have a greater predicted change in collateral donor vessel flow and FFR FFR on recanalization of a CTO.

Studies of collateral function under stress in man have demonstrated a consistent finding of a distal collateral supply seldom sufficient to prevent myocardial ischaemia under stress[51–54]. It should be borne in mind that all studies in man are confounded in that the study participants had sufficient symptoms to present to a cardiologist and undergo angiography, and in most cases revascularisation. Nevertheless, it seems unlikely that there is a

population of patients with chronically occluded coronary arteries which behave differently to those studied, in any case, the study participants represent the very patients that present to us in clinical practice and in whom we must translate these results into best treatment.

With respect to the influence on donor vessel haemodynamics, the importance of the almost universal presence of inducible ischaemia in the collateral dependent myocardium is that the additional flow in collateral donor vessels as a result of a CTO is less than we would expect the flow through the CTO vessel to be should it be patent. Indeed, recanalization of a CTO by PCI has been shown to result in an approximate 50% increase in absolute regional hyperaemic myocardial blood flow at 24 hours measured by cardiovascular magnetic resonance imaging, which was unchanged at 6 months[55]. Hyperaemic flow to the collateral dependent myocardium is therefore only approximately two thirds of expected, and this additional flow is often shared between two collateral donor coronary arteries and also antegrade collateral branches originating from the occluded vessel.

The response of the flow to the collateral dependent myocardium during Adenosine stress is also unpredictable. Early clinical work involving patients undergoing coronary artery bypass graft surgery showed that augmentation of coronary flow beyond an angiographically well collateralized occlusion is no better than that beyond an 80-90% coronary stenosis[53]. In a positron emission tomography study, Uren et al showed that vessels with 80-90% stenoses tend to have a coronary vasodilatory reserve of approximately 1, the microvasculature being already maximally dilated to maintain resting perfusion and therefore unable to dilate further in response to vasodilators[56]. The behaviour of chronically occluded vessels appears to be similar[53,57,58], however perfusion to the collateral dependent myocardium frequently diminishes with vasodilator stress, a phenomenon known as coronary steal. The

mechanism of coronary steal is a fall in perfusion pressure at the origin of collateral vessels due to increased resistance to flow during hyperaemia, as there is a proportionally greater increase in conductance (or reduction in resistance) of the microvascular bed of the donor vessel myocardium relative to the low and fixed conductance of the collateral dependent myocardium, flow and perfusion actually falls during hyperaemia, rather than increases as we would usually expect[59].

Coronary steal

The phenomenon of coronary steal has been reported to occur in a very high proportion of well collateralised myocardial beds using positron emission tomography[57]. The conditions considered to be necessary for coronary steal to occur are: 1) there is sufficient resistance in the donor vessel to cause a pressure drop during hyperaemia; 2) resistance of the collateral vessel is not negligible; and 3) The microvascular resistance of the collateral dependent myocardium is fixed and lacks vasodilatory reserve[18,59]. The phenomenon has been investigated by Werner and colleagues, using the definition of coronary steal as a fall in coronary flow velocity over and above what would be expected by measurement variation measured by intra-coronary Doppler wire during Adenosine infusion[18,58]. Using this definition, approximately one third of patients with a CTO exhibit steal, one third have no significant change and one third have an increase in flow during adenosine infusion. Werner showed that either a significant fall in pressure in the donor artery during Adenosine infusion (defined as an FFR of <0.8) or a lack of vasodilatory reserve in the collateral dependent myocardium, in addition to well-developed collateral vessels, was necessary for coronary steal to occur. From the same studies it was also concluded that coronary steal could not occur in patients with large ($\geq$0.5mm) collateral vessels, however this was based

on the absence of steal in only 3 patients. For coronary steal to occur, there has to be an alternative myocardial bed for flow to be redirected to, it should not occur to collateral flow through bridging collaterals. It is possible therefore, that the relative contribution of antegrade collateral flow and retrograde collateral flow changes during adenosine infusion, with a larger antegrade and diminished retrograde contribution.

From the point of view of considering the effect of a CTO on the physiology of the collateral donor vessel, the association between a lower donor vessel FFR and coronary steal may have important consequences. Although donor vessels with a lower FFR may be more sensitive to a change in flow, their tendency for coronary steal, or a lower flow reserve in the collateral dependent myocardium would suggest that the relative increase in hyperaemic donor artery flow as a consequence of the presence of a CTO would also be reduced, compared with a donor vessel with a higher FFR. Accordingly, one might expect a smaller change in donor vessel flow if the starting donor vessel FFR is lower and possibly therefore a smaller expected increase in FFR after CTO recanalization. On the other hand, the presence of diffuse disease in the collateral donor vessel would be likely to be associated with a reduced coronary flow reserve[60]. The relative proportion of donor vessel flow attributable to the collateral dependent myocardium might therefore be increasedand the effect on FFR greater.

Collateral dependent myocardial mass

The major driver of the large upstroke in coronary flow during early diastole, and therefore the predominant driver of coronary flow, is the negative pressure (or suction) generated by the relief of myocardial microcirculatory compression in early diastole[61]. This suction effect can be quantified by means of wave intensity analysis. 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. A predominant pattern of 6 coronary waves measured by wave intensity analysis has since been described[61], and the effect of myocardial microcirculatory compression in systole and relaxation in early diastole can be estimated by the magnitude of the early backward compression wave(eBCW) and the backward expansion wave (BEW) respectively(figure 6). The size of the eBCW has been shown to be greater with increasing myocardial contractility[62]. Accordingly, one would expect that with increasing downstream contracting myocardial mass the eBCW would also increase in size. The size of the BEW and consequently the size of the diastolic upstroke in coronary flow, being driven by the reverse of the mechanism of the eBCW, is therefore also likely to be related to the mass of myocardium relaxing in early diastole. The increased flow generated by a greater contracting myocardial mass provides an explanation why stenoses subtending a greater myocardial mass but with similar angiographic severities have been shown to have a significantly lower FFR[63]. Similarly, an inverse relationship between FFR and left ventricular ejection fraction has been demonstrated[64].

A corollary of the inverse relationship between perfused, contracting myocardial mass and FFR, is that the quantitative change in perfused myocardial mass in a collateral donor vessel as a result of CTO PCI is likely to be related to the change in donor vessel FFR. This would apply to the absolute myocardial mass and also the collateral dependent mass relative to the myocardial mass in the ordinary perfusion territory of the collateral donor vessel. One might expect the largest changes to occur in large collateral dependent coronary territories (such as that distal to a proximally occluded LAD), predominantly collateralised by a small vessel such as a non-dominant circumflex artery.

Vessel diameter is related to perfused myocardial mass[65], in the absence of ectasia in the donor vessel, the larger the donor vessel diameter, the smaller any change in FFR might be. Given the limited visualisation of the occluded vessel segment distal to a CTO and the likely reduction in diameter as a result of a chronic reduction in flow, the use of vessel diameter in the occluded segment is unlikely to be useful.

Viability of the collateral dependent myocardium

We would expect the increase in flow in a donor vessel associated with the additional supply of collateral dependent myocardium to be related to the collateral dependent myocardium's mass. We would therefore also expect there to be a similar relationship with the influence upon the FFR. If myocardium is infarcted or non-viable, then flow is very low indeed[66], however viable myocardium in the same territory has preserved microvascular function[67], it is likely that the territory can therefore be considered smaller and the change in flow related to the mass of viable myocardium. It is not clear whether coronary steal would be more likely in this situation.

Inherent variability in FFR measurement

As with all measurements, there is inherent variability to the measurement of FFR. The often quoted coefficient of variation, based upon 15 repeated measurements under baseline conditions is 4.8%[15], which is far superior to coronary flow reserve(10.5%). Put into context, this equates to a standard deviation of the difference between repeated measurements of 0.045 and, assuming the difference is unrelated to initial FFR, a coefficient of repeatability of 0.088(figure 7). The largest study of FFR repeatability comes from the DEFER trial[68]. In patients enrolled in the trial, FFR measurements were taken twice within

a 10 minute interval. The mean absolute difference was reported as 0.03, with a standard deviation of 0.02. There was also no apparent association between the value of the FFR and the measurement variability.

FFR measurement is highly reproducible, but we have grown to practice with that assumption in mind, such that clinical decisions are sometimes made based upon margins of as little as 0.01. Based upon the reported absolute difference from DEFER, we can estimate a standard deviation of the difference of 0.032, and a coefficient of repeatability of 0.063, which means 95% of repeat measurements will be within 0.063 of the initial measurement. It is therefore not particularly unusual for repeat FFR measurements taken within 10 minutes of one another, to differ by as much as 0.06 despite no action taken in the interim. If FFR is measured and re-measured after a longer interval, with a CTO angioplasty in the intervening period, even if the angioplasty has no direct effect itself, it would be reasonable to assume that the standard deviation of the difference might be larger than 0.032. The problem of publication bias in case reports is well recognised[69], and if a large change in FFR is encountered in the expected direction (even if a large proportion of the change is due to simple measurement variability), it is more likely to be published than one in the unexpected direction, which when repeated has regressed towards the mean[70,71].

Conclusions

At present, when confronted with a chronic total coronary occlusion in the setting of multi-vessel disease, there is real uncertainty as to how large the influence of collateral donation is upon physiological lesion assessment indices on the collateral donor vessel. The existing literature we can base our decision making on includes case reports (which are likely to be subject to publication bias), one small study which reported a change with a very wide

confidence interval and also inferences from our knowledge of coronary physiology. An understanding of the magnitude of the change in the index after PCI of the CTO, the mechanism of any change and the factors which influence that change would inform our revascularization strategy in a sizeable subset of patients with multi-vessel disease. This can only realistically be achieved by further study of the phenomenon in the clinical setting.

Figure captions

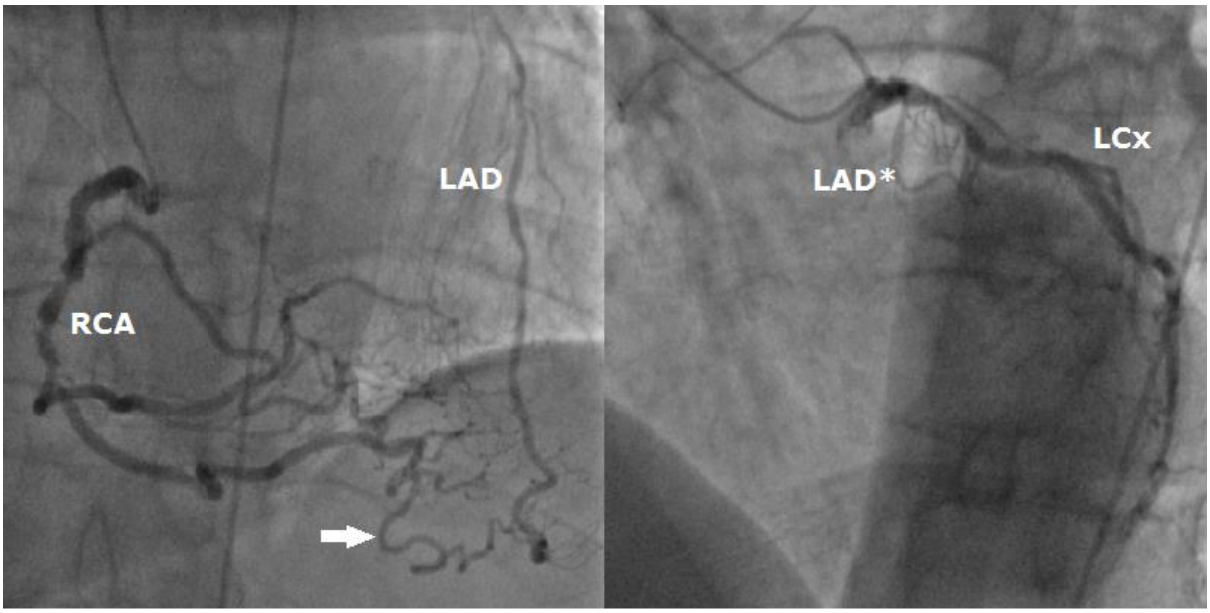

Figure 1. Left: Coronary angiogram demonstrating filling of the left anterior descending artery (LAD) by retrograde collateral branches arising from the right coronary artery (RCA), which have developed as a result of chronic occlusion of the left anterior descending artery. The arrow highlights the largest of these. Right: Coronary angiogram of the left coronary artery in the same projection as that for the right coronary artery (left). The LAD is completely occluded to antegrade flow at the point of the asterisk. The left circumflex artery (LCx) is also shown)

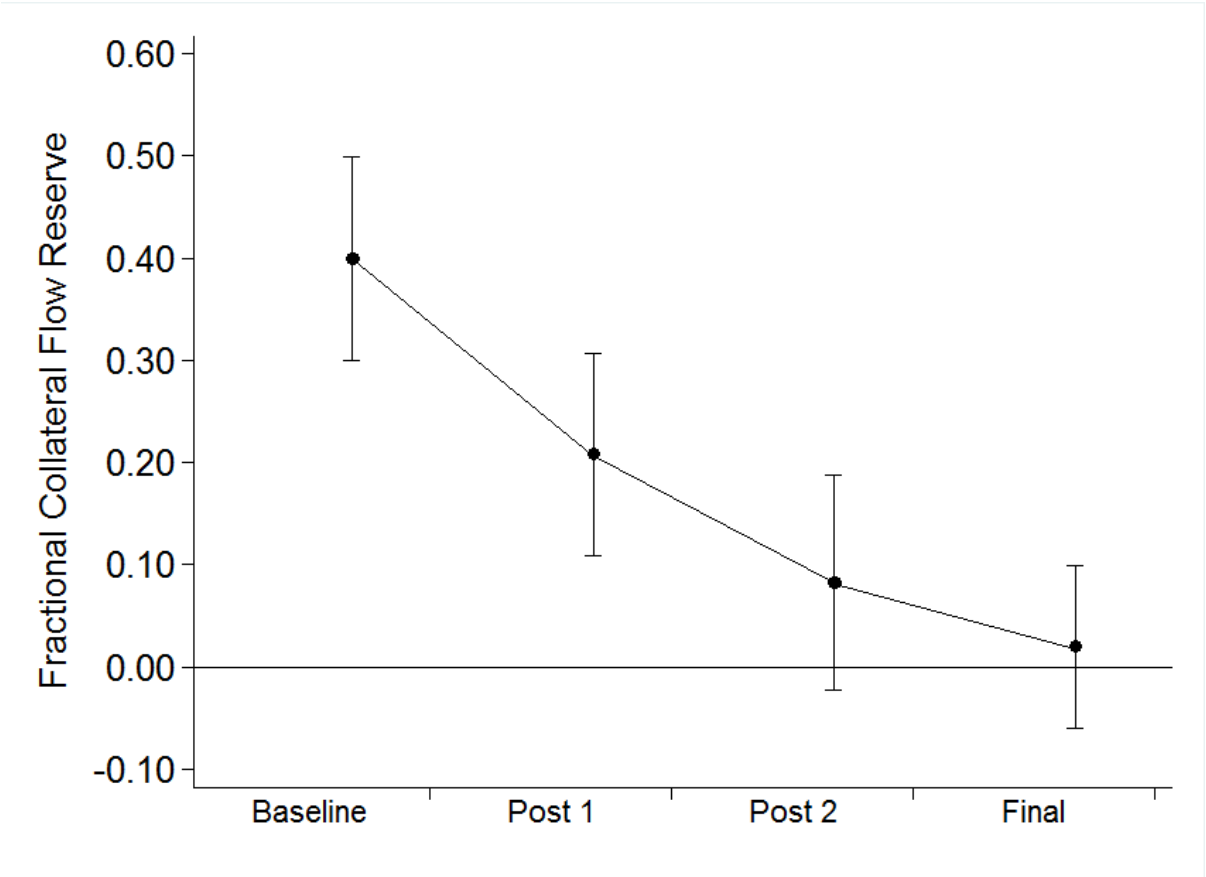

Figure 2. Data taken from Zimerano et al[20]. Changes in target vessel fractional collateral flow reserve after PCI of chronic total occlusions. Fractional collateral flow reserve (FFR_{coll}) diminished significantly at Final measurement, measured by protocol approximately 34 minutes after restoration of antegrade flow in the CTO vessel. FFR_{coll} = myocardial FFR – coronary FFR. Coronary FFR = (distal pressure-wedge pressure)/(aortic pressure-wedge pressure), myocardial FFR = (distal pressure-central venous pressure)/aortic pressure-central venous pressure). Error bars represent 1 standard deviation.

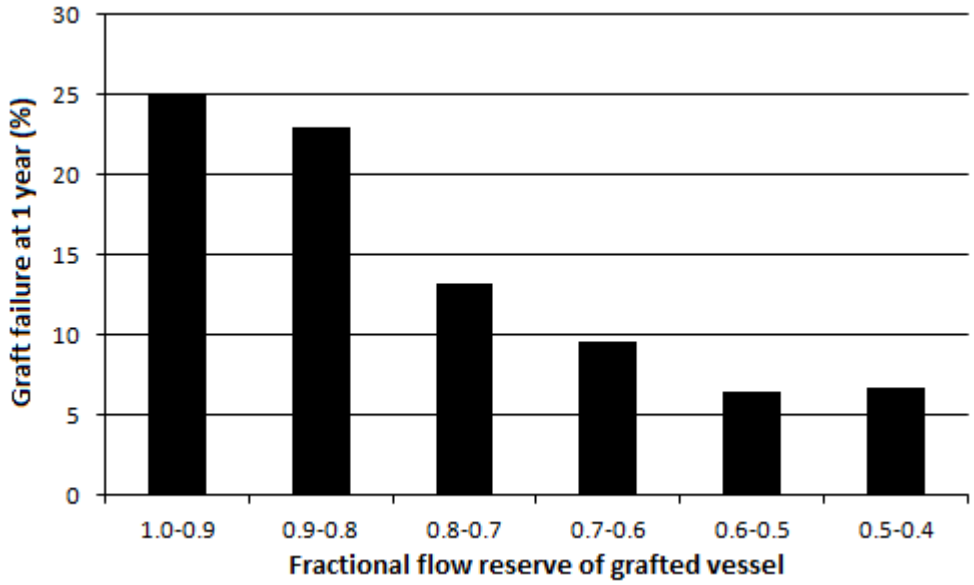

Figure 3. Data taken from Botman et al[40]. % graft occlusion at 12 months post CABG by pre-operative FFR.

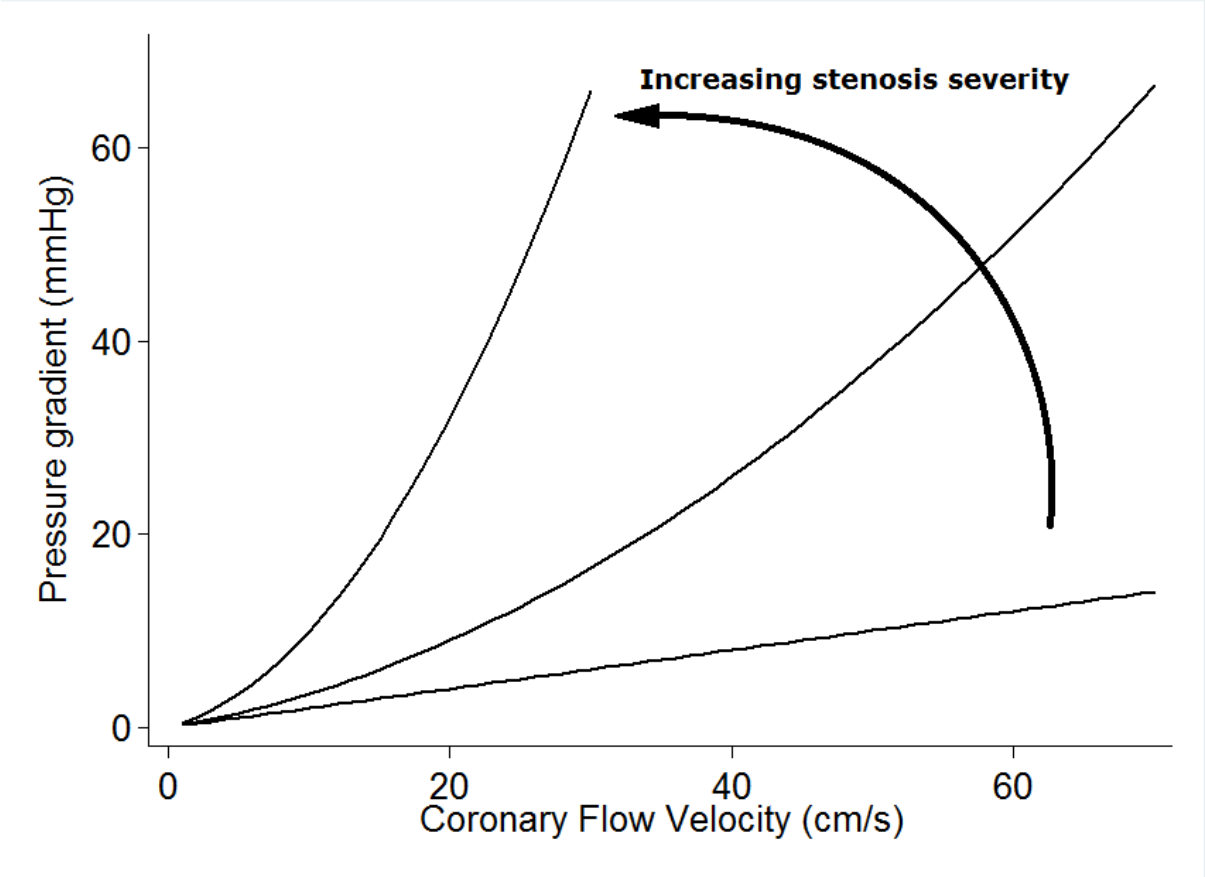

Figure 4. Predicted pressure gradient by stenosis severity described by the equation $\Delta P = FV + SV^2$. As the curves get steeper, stenosis severity increases.

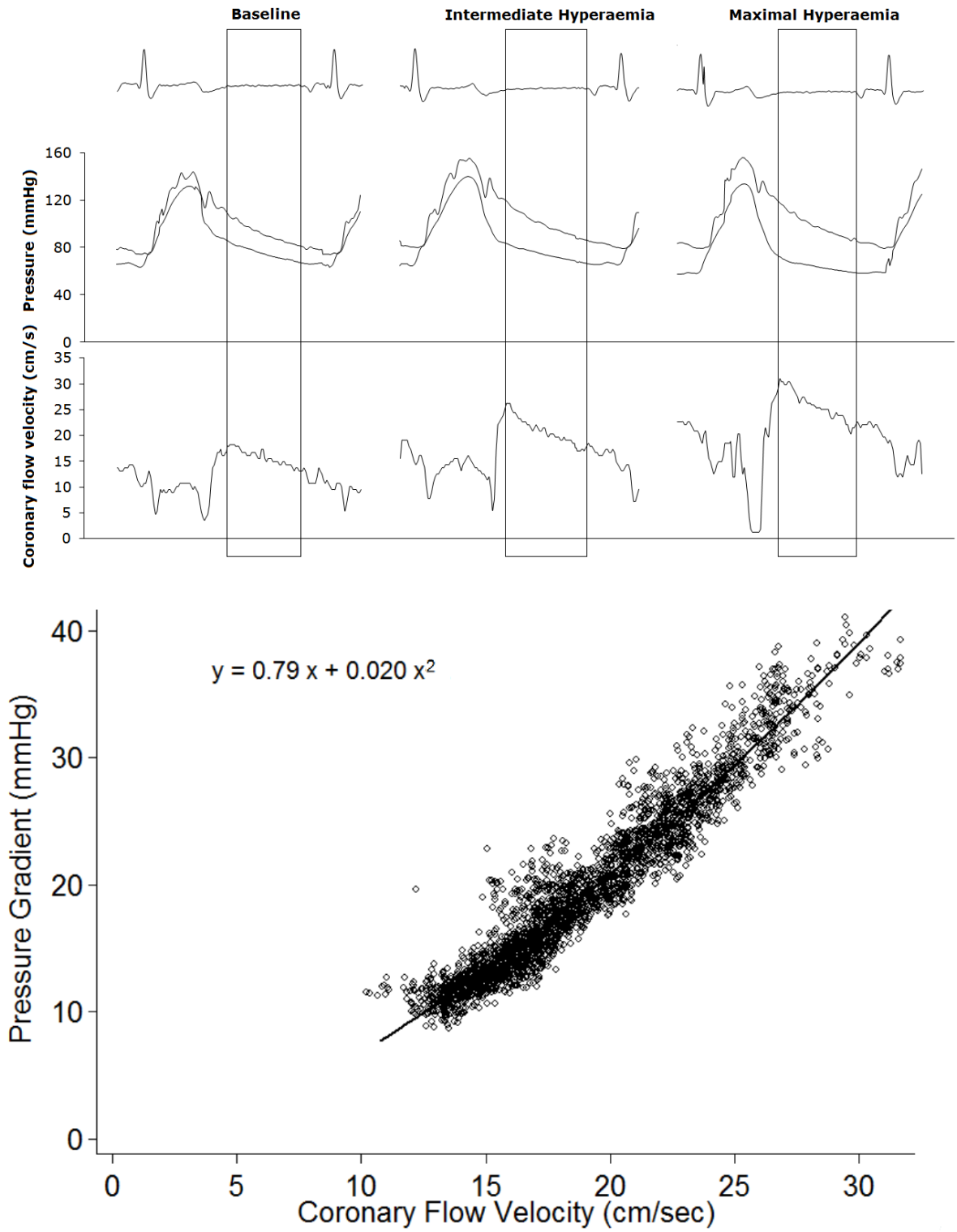

Figure 5. Top panel: example of simultaneous pressure and flow measurement for calculation of diastolic flow-pressure gradient, for each beat measurements are taken during the boxed diastolic periods. Bottom: calculation of the diastolic flow pressure-gradient slope using the formula $\Delta P = FV$

+ SV^2, 30 beats are used from baseline through to maximal hyperaemia, in this case F=0.79 and S=0.020.

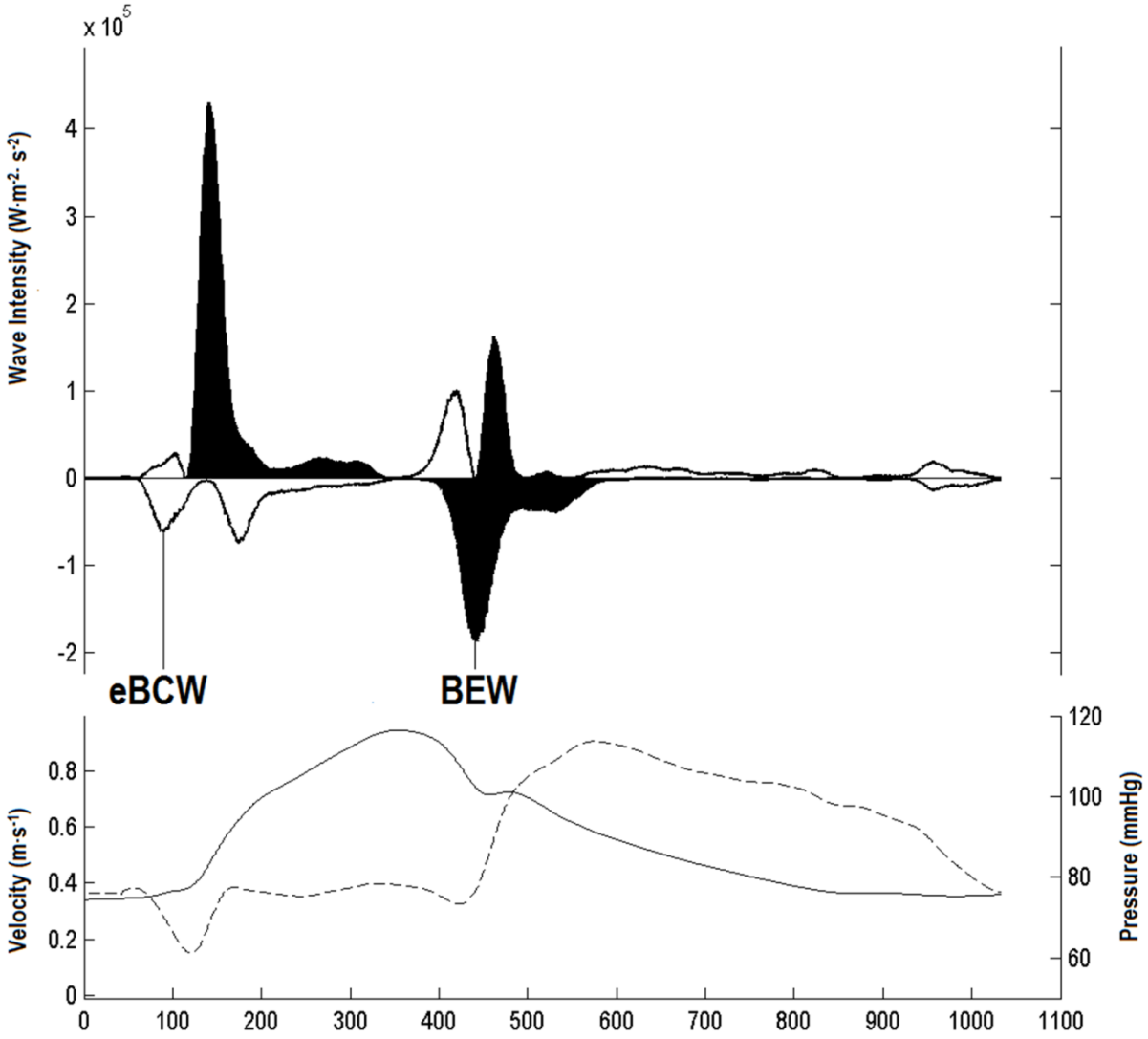

Figure 6. Wave intensity analysis, ensemble averaged coronary pressure (solid line) and flow velocity (dashed line) measured in a non-dominant left circumflex artery in man. Note the diastolic predominance of coronary flow. eBCW= early backward compression wave, BEW=backward expansion wave.

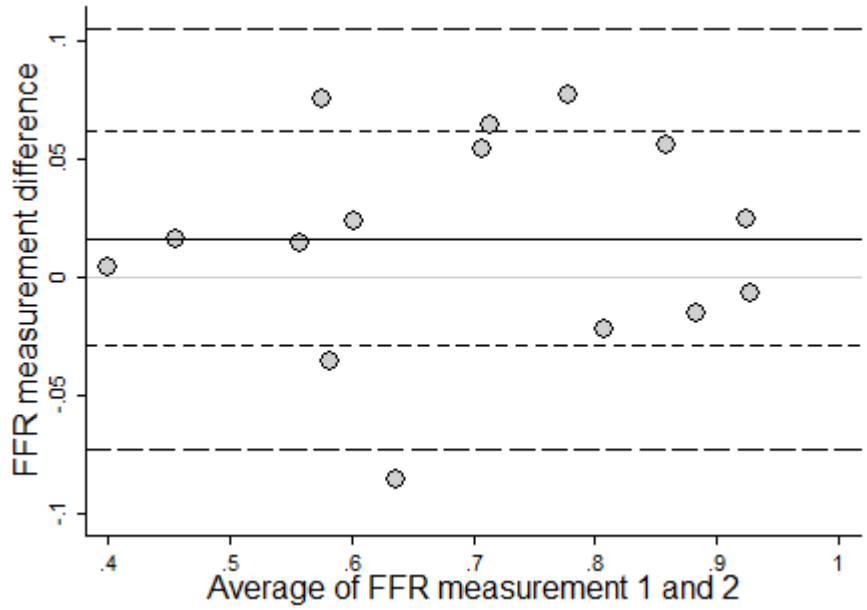

Figure 7. Bland-Altman plot of data taken from De Bruyne et al[15], the black solid horizontal line represents the mean difference between measurements (non-significant), short dashed lines represent one SDD either side of the mean difference and long dashed lines represent limits of agreement.

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