Does a well developed collateral circulation predispose to restenosis after percutaneous coronary intervention?
An intravascular ultrasound study

Authors
Divaka Perera (MRCP)
Pieter Postema (MSc)
Rizwan Rashid (BSc)
Sundip Patel (MRCP)
Lucy Blows (MRCP)
Michael Marber (PhD)
Simon Redwood (MD)

Affiliations
Cardiovascular Division
Rayne Institute
St Thomas' Hospital Campus
King’s College London
UK
(DP, SP, LB: Specialist Registrars in Cardiology; PP: Medical Student; RR: Radiographer; MM: Head of Cardiology; SR: Consultant Interventional Cardiologist)

Correspondence to
Dr Simon Redwood
Department of Cardiology
St Thomas’ Hospital
London SE1 7EH, UK
T: +44 20 7188 1066
F: +44 20 7410 3527
E: Simon.Redwood@gstt.nhs.uk

Word Count: 2538 (excluding abstract, references, figures, tables)

Keywords: Collateral Flow Index, Intravascular Ultrasound, Restenosis
Percutaneous coronary intervention

The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, an exclusive licence (or non exclusive for government employees) on a worldwide basis to the BMJ Publishing Group Ltd to permit this article (if accepted) to be published in HEART and any other BMJPL products and sublicences such use and exploit all subsidiary rights, as set out in our licence (http://heart.bmjournals.com/misc/ifora/licenceform.shtml)
ABSTRACT

Objective: To evaluate whether a well-developed collateral circulation predisposes to restenosis after percutaneous coronary intervention (PCI).

Design: Prospective observational study

Patients and Setting: 58 patients undergoing elective single vessel PCI in a tertiary referral interventional cardiac unit in the UK

Methods: Collateral flow index (CFI) was calculated as \((P_w-P_v)/(P_a-P_v)\), where \(P_a\), \(P_w\), \(P_v\) = aortic, coronary wedge and central venous pressure during maximal hyperaemia. Collateral supply was considered poor (CFI<0.25) or good (CFI≥0.25).

Main Outcome measures: In-stent restenosis six months after PCI, classified as neointimal volume ≥25% stent volume on intravascular ultrasound (IVUS) or minimum lumen area ≤50% stent area (IVUS) or minimum lumen diameter ≤50% reference vessel diameter on quantitative coronary angiography (QCA).

Results: Patients with good collaterals had more severe coronary stenoses at baseline (90 +/- 11% vs. 75 +/- 16%, p<0.001). Restenosis rates were similar in poor and good collateral groups (35% vs. 43%, p=0.76 diameter restenosis, 27% vs. 45%, p=0.34 area restenosis and 23% vs. 24%, p=0.84 volumetric restenosis) and there was no correlation between CFI and diameter, area or volumetric restenosis (\(r^2<0.1\) for each). By multivariate analysis, stent diameter, stent length, >10% residual stenosis and smoking history were predictive of restenosis.

Conclusion: A well-developed collateral circulation does not predict an increased risk of restenosis following PCI.
INTRODUCTION

The potential of coronary collaterals to abrogate myocardial ischemia and limit infarction has long been established(1;2). Similarly, a well-developed collateral circulation appears to predict an improved clinical outcome following percutaneous coronary intervention. When a dichotomous Collateral Flow Index (CFI) threshold of 0.25 is used to distinguish between good and poor collateral supply, patients with inadequate collateral protection have been shown to have a 4 to 8-fold increase in the rate of death, MI or unstable angina following percutaneous coronary intervention (PCI), compared to those with adequate collaterals(3;4). In contrast to the beneficial association between coronary collaterals and clinical sequelae, the impact of collateral flow at the time of PCI on subsequent restenosis remains controversial. Several retrospective studies have suggested that good collateral flow is a risk factor for restenosis(5-7) and it has been postulated that this may be due to reduced antegrade flow in the target vessel due to competitive flow via persistent collateral channels. More recent reports have failed to reproduce these findings(8;9).

Much of this controversy may relate to the methodology used in these studies. In early reports, the collateral circulation was characterised by coronary wedge pressure(5) or angiographically visible channels(6), which are imprecise techniques and have largely been superseded. All these studies have relied on a dichotomous angiographic definition of restenosis(7-9), which is relatively insensitive and thus may obscure potentially important associations. Furthermore, in many of these reports, angiographic follow-up was limited to symptomatic patients, which in turn may have introduced substantial bias. We have carried out a prospective study to evaluate the potential association between collateral flow and restenosis, using gold-standard techniques to characterise both processes.
METHODS

Patients: 58 consecutive patients (aged 60 +/- 9 years, 76% male) undergoing single vessel elective PCI were studied. Patients with high-grade coronary lesions and chronic total coronary occlusions (CTO) (TIMI 0 or I flow, duration of occlusion ≥4 weeks) were recruited and those who had undergone previous PCI or coronary bypass surgery were excluded from the study. The protocol was approved by the local research ethics committee and written informed consent was obtained from each subject at enrolment.

Coronary Intervention: Coronary Angiography and PCI were carried out via the femoral route using a 6 or 8F guiding catheter. Patients were pre-treated with Aspirin and Clopidogrel and unfractionated Heparin was administered to maintain an ACT>250s during the procedure. An intra-coronary bolus of one milligram of Isosorbide Dinitrate was administered before diagnostic angiography with further boluses during the procedure. The lesion was crossed directly with a Pressurewire® (Radi® Medical Systems, Sweden) in most instances. In the case of CTOs, the lesion was crossed with a conventional guidewire and the Pressurewire® inserted via an exchange catheter. Predilation followed by stent deployment was mandated by the protocol and patients requiring drug-eluting stents were excluded from the study. PCI was performed by a single operator (SR) during the study.

Quantification of Collateral Supply: Following calibration and equalisation to aortic pressure, the tip of a 0.014inch pressure-sensing guidewire (Pressurewire®) was advanced beyond the lesion to measure distal coronary pressure. CFI was measured as previously described(10;11), by simultaneous measurement of aortic, right atrial and coronary wedge pressures (P_a, P_v, P_w respectively) where CFI=(P_w-P_v)/(P_a-P_v). P_w was assessed following at least 90s of balloon occlusion and abolition of antegrade flow was confirmed by contrast angiography. P_a was measured via the guide catheter and P_v via the tip of a diagnostic catheter, which was inserted into the right atrium via the femoral vein. All measurements were carried out during maximal hyperaemia induced by an intravenous infusion of Adenosine at 140µg/kg/min.

Characterisation of Coronary Lesion: Angiograms of the target vessel were obtained in at least two orthogonal projections. Images were analysed off-line using Discovery™ software (Quinton Instrument Co., USA) which utilises an edge-detection technique (CorTrek application). Dimensions of the guide catheter were used to calibrate the system. Normal reference segments were identified proximal and distal to the lesion, and minimum lumen diameter (MLD), reference vessel diameter, percentage diameter stenosis and lesion length recorded in each case. Fractional Flow Reserve (FFR) was calculated as previously described(10;11).
**Intravascular Ultrasound**: At 6-month follow-up, stented vessel segments were examined with a mechanical IVUS catheter (Atlantis Plus™ 40 MHz, Boston Scientific) using automated pullback at 0.5 mm per second. Images were obtained via a Clearview® or Galaxy® system (Boston Scientific) and analysed offline, using Indec™ software. The stented segment was analysed in cross-sectional slices at intervals ≤0.5mm and lumen, stent boundaries, and external elastic lamina were delineated using a contour tracing method. A computer-based contour detection program (Echoplaque™) was used for automated 3D reconstruction of the stented segment from serial cross-sectional slices. Volumetric stent obstruction was calculated as neointimal volume/stent volume x100. Incomplete stent apposition was recorded.

**Study Protocol**: Patients were assigned to two groups based on CFI at the time of PCI: good (CFI≥0.25) and poor (CFI<0.25) collateral supply(3). Follow-up angiography and IVUS were carried out six months after PCI and three dichotomous classifications of restenosis were examined: neointimal volume ≥25% stent volume on IVUS, minimum lumen area (MLA) ≤50% of stent area on IVUS, MLD ≤50% of reference vessel diameter on QCA. In patients with restenosis, target vessel revascularisation (TVR) was based on clinical status. Investigators were blinded to CFI and patient characteristics during IVUS and QCA analysis.

**Statistical analysis**: Data are presented as mean +/- standard deviation, unless otherwise specified. Between-group categorical variables were compared by a Chi Square test (with Yates’ correction where appropriate) and continuous variables by a Mann-Whitney test, at a significance level of 5%. Baseline variables found to correlate with restenosis in a univariate analysis (p<0.10) were assessed by a multiple logistic regression model. Analyses were carried out using Statview® 5.0 software.

Previous studies have demonstrated binary angiographic restenosis rates of 85% and 45% in patients with good and poor collateral flow respectively(7). Anticipating lower restenosis rates on account of systematic follow-up (30% in the poor collateral group), a sample size of 50 would have 80% power (α=5%) to detect the magnitude of difference found by Wahl et al. Using volumetric IVUS analysis, a sample of 50 provides sufficient power to detect even smaller differences in restenosis rates than previously shown(12).
RESULTS

CFI was 0.22 +/- 0.11 at the time of PCI; 25 patients had poor and 33 had good collateral supply. Compared to those with poor collaterals, patients with good collaterals had more severe coronary stenoses at baseline (90 +/- 11% vs. 75 +/- 16%, p<0.001) and included a higher proportion of chronic total occlusions (CTO) (48% vs. 6%, p<0.001). Left ventricular ejection fraction was higher in patients with poor collaterals (68 +/-10% vs. 60 +/-11%, p=0.002). Baseline characteristics were otherwise similar in both groups (Table 1).

Follow-up was completed in 50 patients, 189 +/- 32 days following PCI. Eight patients, who were asymptomatic at follow-up, declined further investigation. The latter group had a higher final MLD (3.1 +/- 0.6 vs. 2.5 +/- 0.5mm, p=0.003) but baseline characteristics of those who declined follow-up were otherwise similar to the group who underwent follow-up angiography. CFI in the two groups was 0.22 +/- 0.12 and 0.22 +/- 0.11 respectively (p=0.85).

Angiographic follow-up: At six months, MLD on QCA was 42% +/- 23% of reference vessel diameter, with no significant differences between poor and good collateral groups (38 +/- 21% vs. 47 +/- 26%, p=0.33) (Figures 1,2). The binary in-stent restenosis rate was 35% in patients with poor collaterals and 43% in those with good collaterals (p=0.76). Baseline CFI was similar in patients who had binary angiographic restenosis and those who did not (0.21 +/- 0.12 vs. 0.23 +/- 0.11, p=0.68). The degree of lesion stenosis at baseline was positively correlated with CFI (r²=0.33, p<0.001) but there was no correlation between CFI and the degree of restenosis at 6 months (r²=0.03, p=0.27).

IVUS follow-up: At six months, MLA on IVUS was 6.0 +/- 2.8 mm², with an MLA ≤4mm² in 12% and 40% respectively of the poor and good collateral groups (p=0.06). The binary restenosis rate (for MLA ≥50% stent area) was 27% and 45% in each group (p=0.34). Even a more conservative threshold (MLA≥60% stent area) did not reveal significant differences in restenosis rates between poor and good collateral groups (12% vs. 20%, p=0.71). Furthermore, there was no correlation between area stenosis at follow-up and CFI at baseline (r²=0.02, p=0.31) (Figure 3a). On volumetric analysis, neointimal volume was 51 +/- 59 mm³ vs. 62 +/- 48 mm³ (p=0.22) and degree of stent obstruction was 19 +/- 8% vs. 23 +/- 11% (p=0.31) respectively in the poor and good collateral groups (Figure 2). The binary volumetric restenosis rate was 23% in the poor collateral and 24% in the good collateral group (p=0.84). Baseline CFI was similar in patients who had binary volumetric restenosis and those who did not (0.25 +/- 0.10 vs. 0.22 +/- 0.12, p=0.37). There was no correlation between volumetric stent obstruction and CFI at baseline (r²=0.06, p=0.10) (Figure 3b).
**FFR at follow-up:** There was no significant difference in the haemodynamic severity of restenosis assessed by FFR in patients with poor and good collateral supply (0.83 +/- 0.07 vs. 0.86 +/- 0.08 respectively, p=0.41). There was a trend towards a positive correlation between FFR at follow-up and CFI at baseline ($r^2=0.17$, p=0.08).

**Predictors of Restenosis:** By univariate analysis, stent length $\geq$20mm, stent diameter $\leq$3mm and residual stenosis $>10\%$ were predictive of binary QCA restenosis; baseline stenosis severity and smoking history were predictive of binary volumetric restenosis; baseline stenosis severity, CTO and stent length $\geq$20mm were predictive of binary area restenosis. CFI was neither a predictor of restenosis on univariate analysis nor on multivariate logistic regression analysis (Figure 4).

**Target vessel revascularisation:** The 6 month TVR rate was 7% in the whole cohort, two patients undergoing further PCI and two undergoing coronary artery bypass surgery. CFI at the time of PCI was 0.27 +/- 0.14 in patients who had subsequent TVR, but the difference in TVR rates in the poor and good collateral groups was not statistically significant (3% vs. 12%, p=0.42). On univariate analysis, stent diameter $\leq$3mm was weakly related to TVR ($r=0.29$, p=0.03) but none of these variables were predictive of TVR in a multivariate regression model.
DISCUSSION

Despite substantial technical advances in recent years, restenosis after PCI continues to be the major limitation of this procedure. It affects approximately 30% of coronary lesions treated with bare-metal stents(13), with rates approaching 60% following recannalisation of chronic total occlusions(14). Interestingly, collateral flow at the time of PCI has emerged as one of many factors that may predict the development of subsequent restenosis. Although a biologically plausible mechanism has not been demonstrated, it has been proposed that collateral flow may play a causal role in promoting restenosis, in a manner analogous to the progression of atherosclerosis in native coronary arteries proximal to insertion of an aorto-coronary bypass graft(15;16). Alternatively, collateral flow may merely be a marker for another established risk factor for restenosis, such as the morphology or chronicity of a coronary lesion(17). Robust methods of characterising both the collateral circulation and the restenotic process are central to unravelling this putative association.

Many of the methodological difficulties posed by characterising the collateral circulation according to coronary wedge pressure(5;6) or angiographically visible channels(18) have been overcome by the use of CFI, which is currently the accepted clinical standard for quantifying collateral flow(10). However, even recent studies that have used CFI have yielded conflicting results. Wahl et al reported that patients with symptomatic restenosis had a higher CFI at the time of PCI (0·26 +/- 0·14 vs. 0·12 +/- 0·09, p<0·0001)(7). The actual incidence of restenosis in this population is unclear, as follow-up was only available in one third of the patients studied. Conversely, Werner et al found that patients with restenosis had similar baseline CFIs to those who did not(9). This study was restricted to patients with CTOs and as such, was notable for the excellent collateral flow demonstrated in all patients (with relatively few possessing a CFI<0.25) which limits the comparison of restenosis in good and poor collateral groups. In addition to the methodological issues listed above, some of the contradictory results may have arisen from the reliance of these studies on a dichotomous angiographic threshold for detection of restenosis. Although ≥50% diameter stenosis has traditionally been the working definition of restenosis, the limitations of angiography in delineating neointimal hyperplasia and the superiority of IVUS are well established(19-21). The improved sensitivity of IVUS allows detection of more subtle differences in restenosis rates in small samples, particularly when three-dimensional volumetric measurements are performed(12;22).

Using CFI to determine collateral support and IVUS to document restenosis, we have demonstrated that the degree of collateral flow at the time of PCI is not predictive of subsequent restenosis. In particular, similar binary restenosis rates were found in patients with poor and good collateral flow, using three different classifications of restenosis based on IVUS and QCA. Furthermore, no correlation was observed between baseline collateral flow and any of the
continuous parameters reflecting neointimal hyperplasia. On the other hand, several established risk factors(13;23;24) were found to be predictive of in-stent restenosis in the current study, including residual diameter stenosis after PCI and the use of smaller and longer stents.

It seems clear that a well-developed collateral circulation should not be considered a risk factor for restenosis after PCI. On the other hand, we have shown that good collateral flow tends to be associated with higher grade coronary lesions and chronic total occlusions, which do augur an increased likelihood of restenosis(17). The concept of competitive flow via collateral channels following PCI is simplistic, as flow down these conduits is passive and likely to be minimal once the pressure gradient across the collateral bed is abolished. However, these channels may remain recruitable if this pressure gradient is subsequently re-established due to acute coronary occlusion, which may underlie the improved clinical outcome observed in well-collateralised patients(3;4). Taken together, a good collateral circulation could probably be regarded as a favourable indicator rather than a contraindication to PCI.

The principal limitation of our study was the relatively small sample size. However, several features of this population make them particularly suitable for prospective evaluation of the potential association between restenosis and collateral flow. Firstly, the inclusion strategy was devised to ensure that a broad spectrum of collateral support was represented in the study population. This was achieved by recruiting patients with non-occlusive lesions as well as CTOs, given that approximately two thirds of the former group have poor collaterals (25) and most of the latter group have good collateral supply(9). The statistical constraints imposed by low numbers were further ameliorated by using intravascular ultrasound, which is a sensitive and reproducible technique for evaluating restenosis. The lower left ventricular ejection fraction in the well-collateralised group may be accompanied by a degree of microvascular dysfunction. Theoretically, the latter could limit the induction of maximal hyperaemia during infusion of Adenosine, which in turn may affect assessment of CFI. However, given the relatively normal left ventricular function in both groups, the actual impact of this difference is likely to be minimal.

**Conclusion**

A well-developed collateral circulation does not predict an increased risk of restenosis following PCI.
COMPETING INTERESTS
None

ACKNOWLEDGEMENTS
Divaka Perera was funded by a fellowship from the Guy’s and St Thomas’ Charitable Foundation, London, UK
References

(1) Reimer KA, Jennings RB. The "wavefront phenomenon" of myocardial ischemic cell death. II. Transmural progression of necrosis within the framework of ischemic bed size (myocardium at risk) and collateral flow. Lab Invest 1979; 40(6):633-644.


(10) Pijls NH, van Son JA, Kirkeeide RL et al. Experimental basis of determining maximum coronary, myocardial, and collateral blood flow by pressure measurements for assessing functional stenosis severity before


(21) Kozuma K, Regar E, Bruining N et al. Sensitivity and specificity of QCA in detecting coronary arterial remodeling after intracoronary brachytherapy: a comparison to serial volumetric three-dimensional intravascular ultrasound


Table 1. Clinical and Lesion Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Poor Collaterals CFI &lt; 0.25</th>
<th>Good Collaterals CFI ≥ 0.25</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>33</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>59 ± 9</td>
<td>60 ± 9</td>
<td>0.71</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>73</td>
<td>80</td>
<td>0.74</td>
</tr>
<tr>
<td>Smoking History ( non / ex / current )</td>
<td>43 / 30 / 27</td>
<td>28 / 60 / 12</td>
<td>0.07</td>
</tr>
<tr>
<td>Hypertension</td>
<td>58</td>
<td>40</td>
<td>0.29</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>18</td>
<td>4</td>
<td>0.22</td>
</tr>
<tr>
<td>Previous Myocardial Infarction</td>
<td>21</td>
<td>40</td>
<td>0.21</td>
</tr>
<tr>
<td>LV Ejection Fraction (%)</td>
<td>68 +/- 10</td>
<td>60 +/- 11</td>
<td>0.002</td>
</tr>
<tr>
<td>Target Vessel ( LAD / RCA / Cx )</td>
<td>49 / 24 / 27</td>
<td>56 / 32 / 12</td>
<td>0.36</td>
</tr>
<tr>
<td>Reference Vessel Diameter (mm)</td>
<td>2.85 ± 0.45</td>
<td>2.85 ± 0.72</td>
<td>0.70</td>
</tr>
<tr>
<td>Baseline Diameter Stenosis (%)</td>
<td>75 ± 16</td>
<td>90 ± 11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chronic Total Occlusions</td>
<td>6</td>
<td>48</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stent Length (mm)</td>
<td>19.1 +/- 9.3</td>
<td>25.9 +/- 16.8</td>
<td>0.30</td>
</tr>
<tr>
<td>Stent Diameter (mm)</td>
<td>3.36 ± 0.42</td>
<td>3.25 ± 0.64</td>
<td>0.35</td>
</tr>
<tr>
<td>Final Diameter Stenosis (%)</td>
<td>9 ± 11</td>
<td>10 ± 10</td>
<td>0.74</td>
</tr>
</tbody>
</table>

Data are % or mean +/- SD. Categorical variables compared by Chi Square and continuous variables by Mann-Whitney tests. LAD: left anterior descending artery, RCA: right coronary artery, Cx: circumflex artery.
Figure Legends

Figure 1. Angiographic Restenosis. Cumulative distribution curves for percentage diameter stenosis in patients with good (dashed line) and poor (full line) collateral flow, before and immediately after PCI and at six month follow-up. Patients with good collateral flow had more severe stenoses at baseline but there were no significant differences in diameter stenosis after PCI or at follow-up.

Figure 2. The extent of restenosis on QCA (% diameter stenosis) and IVUS (% area stenosis and % volume stenosis) in poor and good collateral groups (filled and open bars respectively) was not significantly different.

Figure 3. Restenosis on IVUS in relation to CFI. A: maximal neointimal area (in relation to stent area) and B: neointimal volume (in relation to stent volume) had no correlation to baseline CFI.

Figure 4. Predictors of Restenosis. Logistic Regression Model (data are presented as odds ratios and 95% confidence intervals).
$r^2 = 0.02$
$p = 0.31$
$r^2 = 0.06$
$p = 0.10$
Diameter restenosis (QCA)
Stent length ≥ 20mm
Stent diameter ≤ 3mm
Residual stenosis > 10%
Smoking Hx
CTO
CFI ≥ 0.25

Area restenosis (IVUS)

Volumetric restenosis (IVUS)
Does a well developed collateral circulation predispose to restenosis after percutaneous coronary intervention? An intravascular ultrasound study

Divaka Perera, Pieter Postema, Rizwan Rashid, Sundip Patel, Lucy Blows, Michael Marber and Simon Redwood

Heart published online October 10, 2005

Updated information and services can be found at:
http://heart.bmj.com/content/early/2005/10/10/hrt.2005.067322.citation

These include:

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections
Articles on similar topics can be found in the following collections

- Interventional cardiology (2933)
- Clinical diagnostic tests (4779)
- Percutaneous intervention (964)
- Drugs: cardiovascular system (8842)
- Tobacco use (635)

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/