Effects of coronary revascularisation on myocardial blood flow and coronary vasodilator reserve in hibernating myocardium

D Pagano, F Fath-Ordoubadi, K J Beatt, J N Townend, R S Bonser, P G Camici

Abstract
Objective—Previous studies have suggested that resting myocardial blood flow is within normal limits in most chronically dysfunctional left ventricular segments which improve function after coronary artery revascularisation (hibernating myocardium). The aim of this study was to assess myocardial blood flow and coronary vasodilator reserve in hibernating myocardium before and after coronary revascularisation.

Patients and methods—30 patients with multivessel coronary disease undergoing coronary revascularisation (21 patients with bypass grafting and nine with coronary angioplasty), and 21 age and sex matched healthy volunteers (controls). Myocardial blood flow (MBF, ml/min/g) was measured by positron emission tomography using oxygen-15 water at rest and after dipyridamole (MBFdip, 0.56 mg/kg in four minutes). Coronary vasodilator reserve was calculated as MBFdip/MBF. Regional wall motion was assessed with echocardiography.

Results—Before revascularisation there were 48 remote and 275 dysfunctional myocardial segments, of which 163 (59%) improved function after revascularisation (hibernating). In hibernating segments coronary vasodilator reserve before revascularisation was significantly lower than in remote segments (1.97 (0.7), p < 0.0001) and controls (3.2 (1.5), p < 0.0001). In hibernating segments, myocardial blood flow remained unchanged after revascularisation (0.94 (0.3) vs 0.95 (0.3) ml/min/g, p = 0.3) while coronary vasodilator reserve increased (1.47 (0.7) vs 1.98 (1.0), p < 0.0001). Myocardial blood flow was similar in remote, hibernating segments before and after revascularisation and in controls.

Conclusions—This study confirms that myocardial blood flow at rest in hibernating myocardium is within normal limits in most segments, and that hibernating myocardium is characterised by an impaired coronary vasodilator reserve which improves significantly after coronary revascularisation. (Heart 2001;85:208–212)

Keywords: hibernating myocardium; myocardial blood flow; heart failure; positron emission tomography

Chronic post-ischaemic left ventricular dysfunction in myocardium subtended by a stenotic coronary artery can be improved by revascularisation. This phenomenon of reversible dysfunction has been termed “myocardial hibernation”.1,2 It has been hypothesised that hibernation is an “adaptation” to chronic reduction in resting myocardial blood flow secondary to coronary artery stenosis.3 However, this is contentious as many studies have suggested that basal myocardial blood flow is not significantly reduced even in the presence of severe coronary artery stenoses,4 while there is a progressive reduction of coronary vasodilator reserve with increasing stenosis severity.5 It has also been demonstrated that, in the majority of cases, baseline myocardial perfusion in chronically dysfunctional myocardium which recovers function after revascularisation is similar to that of myocardium with normal contractile function in the same patients6 and to that of normal healthy subjects. Furthermore, non-infarcted, collateral dependent dysfunctional myocardium has normal resting myocardial perfusion but a reduced coronary vasodilator reserve compared to ischaemic but normally functioning segments.7

Our study aimed to assess non-invasively regional myocardial blood flow and coronary vasodilator reserve in hibernating myocardium before and after coronary revascularisation using positron emission tomography (PET), and to compare them with regions with normal contractile function subtended by a normal coronary artery (remote regions) and myocardium of healthy subjects.

Methods

STUDY POPULATION
The patient population consisted of 30 subjects (28 males; mean (SD) age 56 (10) years) with coronary artery disease (> 6 months) undergoing coronary artery bypass grafting (CABG, 21 patients) or percutaneous transluminal coronary angioplasty (PTCA, nine patients). All patients were in sinus rhythm and had suffered at least one (range 1–3) Q wave myocardial infarction 30 (14) months before the study. Seven patients were diabetic and five were hypertensive. The left ventricular ejection fraction (LVEF) was 30 (11)%. Patients were receiving treatment with angiotensin converting enzyme (ACE) inhibitors (20 patients), diuretics (15 patients), digoxin (5 patients), nitrates (10 patients), calcium channel blockers (13 patients), and β blockers (9 patients). All medical treatment was withdrawn at least 24 hours before the study day both at baseline and follow
Table 1  Myocardial blood flow and coronary vasodilator reserve in hibernating segments

<table>
<thead>
<tr>
<th></th>
<th>Pre-revascularisation</th>
<th>Post-revascularisation</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MBF (ml/min/g)</td>
<td>0.92 (0.30)</td>
<td>0.95 (0.32)</td>
<td>0.29</td>
</tr>
<tr>
<td>MBF-corr (ml/min/g)</td>
<td>0.94 (0.34)</td>
<td>0.95 (0.27)</td>
<td>0.88</td>
</tr>
<tr>
<td>MBF-dip (ml/min/g)</td>
<td>1.31 (0.65)</td>
<td>1.86 (1.0)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>CVR</td>
<td>1.40 (0.66)</td>
<td>2.0 (1.0)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>CVR-corr</td>
<td>1.47 (0.66)</td>
<td>1.95 (1.0)</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

All values are mean (SD).

Figure 1  Perfusion data on 163 hibernating myocardial segments before (baseline) and after coronary revascularisation. MBF: myocardial blood flow; MBF-dip, post-dipyridamole myocardial blood flow; CVR, coronary vasodilator reserve. ***p < 0.0001.

Table 2  Myocardial blood flow and coronary vasodilator reserve in remote segments

<table>
<thead>
<tr>
<th></th>
<th>Pre-revascularisation</th>
<th>Post-revascularisation</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MBF (ml/min/g)</td>
<td>0.91 (0.20)</td>
<td>0.86 (0.25)</td>
<td>0.29</td>
</tr>
<tr>
<td>MBF-corr (ml/min/g)</td>
<td>0.96 (0.28)</td>
<td>0.89 (0.36)</td>
<td>0.15</td>
</tr>
<tr>
<td>MBF-dip (ml/min/g)</td>
<td>1.89 (0.84)</td>
<td>1.84 (0.80)</td>
<td>0.68</td>
</tr>
<tr>
<td>CVR</td>
<td>2.1 (1.0)</td>
<td>2.2 (1.0)</td>
<td>0.86</td>
</tr>
<tr>
<td>CVR-corr</td>
<td>1.97 (0.70)</td>
<td>2.2 (1.2)</td>
<td>0.10</td>
</tr>
</tbody>
</table>

All values are mean (SD).

See table 1 for key to abbreviations.
Simultaneous comparison of more than two sets of data was made using one way analysis of variance, followed by the Tukey-Kramer test to identify the source of variation. Significance was assumed for a probability value of $p < 0.05$ (two tailed).

**Results**

**Left Ventricular Functional Outcome**

A total of 431 left ventricle segments were assessed by PET and echocardiography. Of these, 48 manifested normal contractile function and were subtended by a normal coronary artery (remote regions) and 383 segments were subtended by a stenotic (> 70%) coronary artery. Of these 383 segments, 370 were revascularised. Nine segments were excluded because of restenosis of the subtending vessel three months after PTCA. Of the remaining 361 revascularised segments, 275 were dysfunctional and 86 had normal baseline wall motion. At follow up 163/275 (59%) of dysfunctional segments improved contractile function (hibernating segments) while dys-function in the remaining 112 segments remained unchanged. The global LVEF increased from 30 (11)% to 37 (10)% ($p = 0.0002$). LVEF remained unchanged after PTCA (41 (12%) v 43 (10%), $p = 0.16$) and improved after CABG (24 (7%) v 33 (9%), $p = 0.0004$).

**Myocardial Blood Flow and Coronary Vasodilator Reserve**

**Controls**

In the normal subjects, blood flow was homogeneously distributed in the different ventricular regions, and the mean baseline myocardial blood flow was 0.99 (0.21) ml/min/g, increasing to 3.1 (1.3) ml/min/g after dipyridamole, giving a coronary vasodilator reserve of 3.2 (1.5). The rate–pressure product was 8037 (1798). After correction for the rate–pressure product, myocardial blood flow was 1.03 (0.29) ml/min/g and coronary vasodilator reserve was 3.2 (1.6).

**Patients**

In the patients the rate–pressure product before revascularisation was 9337 (2250) and after revascularisation was 8443 (1749) ($p = 0.1$ v controls and pre-revascularisation). In the hibernating segments the baseline myocardial blood flow was unchanged after revascularisation while there was a significant increase in the post-dipyridamole myocardial perfusion and the coronary vasodilator reserve (table 1, fig 1). In the remote regions there were no changes in baseline and post-dipyridamole myocardial blood flow and coronary vasodilator reserve after revascularisation (table 2).
Effects of coronary revascularisation on hibernating myocardium

COMPARISON OF THE THREE GROUPS

The baseline myocardial blood flow values before and after revascularisation in hibernating, remote, and control segments were not significantly different (fig 2).

To identify hibernating segments with abnormally low baseline myocardial blood flow before revascularisation, a cut-off of 0.45 ml/min/g which corresponds to the mean myocardial blood flow of controls (corrected for RPP) minus 2 SD, was used. Only 10/163 (6%) hibernating segments had myocardial blood flow lower than this threshold before revascularisation (fig 3).

All pre and post-revascularisation perfusion parameters for hibernating, remote, and control segments are compared in figs 4 and 5.

Discussion

The main finding of this study is that revascularisation of hibernating myocardium is associated with an increase in coronary vasodilator reserve, while the baseline myocardial blood flow remains unchanged. Furthermore, our data show that in more than 90% of hibernating segments the myocardial blood flow before revascularisation is within normal range while the coronary vasodilator reserve is significantly lower than in remote regions (in the same patients) and the myocardium of healthy subjects (controls). Previous studies have also demonstrated that the myocardial blood flow of hibernating segments is similar to that of remote regions or healthy control subjects.15 16

Furthermore, Vanoverschelde and colleagues demonstrated in a small and selected group of patients that the pre-revascularisation coronary vasodilator reserve is reduced in dysfunctional myocardium proved to be hibernating by post-revascularisation contractile improvement.12 Our study confirms and expands these findings by providing post-revascularisation data on myocardial blood flow and coronary vasodilator reserve.

Our findings suggest that chronic post-ischaemic left ventricular dysfunction is not necessarily caused by a chronic reduction in resting blood flow (hibernation in its classical definition), but may be related to a reduction in coronary vasodilator reserve. Reduced coronary vasodilator reserve may result in stress induced left ventricular dysfunction. There is evidence both in animals and humans that this left ventricular dysfunction persists in the post-ischaemic period despite absence of irreversible damage and in the presence of normal or near normal myocardial blood, and has been termed myocardial stunning.17 18 In these cases, chronic ventricular dysfunction may be the result of repetitive episodes of imbalance between the supply and demand for oxygen caused by either a temporary increase in myocardial demands (that is, exercise inducible ischaemia) or by oscillations in the blood supply (that is, unstable coronary plaques). Repeated episodes of myocardial ischaemia, occurring during daily life activity, have been documented in patients with chronic stable coronary artery disease.19 These authors demonstrated myocardial stunning.17 18

In our study, both the coronary vasodilator reserve of left ventricle segments subtended by an angiographically normal coronary vessel and with normal contractile function (remote regions), and that of hibernating segments after revascularisation, was significantly lower than the coronary vasodilator reserve of controls. These findings are consistent with previous studies demonstrating an abnormal coronary vasodilator reserve in patients with coronary artery disease, even in regions subtended by normal epicardial coronary vessels.20 21 Although the mechanism underlying this phenomenon remains unknown, others have explained it as a manifestation of microvascular endothelial dysfunction which affects patients with coronary artery disease.22

STUDY LIMITATIONS

In this study we assessed myocardial blood flow, coronary vasodilator reserve, and regional left ventricular function at a single postoperative time point. Serial temporal studies of these parameters could have provided some insight into the time course of improvement in coronary vasodilator reserve and left ventricular function. Although our study demonstrates that hibernating myocardium is associated with a reduced coronary vasodilator reserve, because of the resolution limitations of the current PET scanners we were unable to measure epicardial and endocardial myocardial blood flow and coronary vasodilator reserve, and thus ascertain the implications of these data for the pathophysiology of hibernation. The choice of 0.45 ml/min/g as a lower limit of normal myocardial blood flow is arbitrary and reflects the difficulty of defining normal myocardial blood flow. Studies have demon-
strated the significant heterogeneity of myocardial blood flow in normal subjects.27 28


Effects of coronary revascularisation on myocardial blood flow and coronary vasodilator reserve in hibernating myocardium

D Pagano, F Fath-Ordoubadi, K J Beatt, J N Townend, R S Bonser and P G Camici

*Heart* 2001 85: 208-212
doi: 10.1136/heart.85.2.208

Updated information and services can be found at:
http://heart.bmj.com/content/85/2/208

*These include:*

**References**
This article cites 26 articles, 12 of which you can access for free at:
http://heart.bmj.com/content/85/2/208#BIBL

**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

- Clinical diagnostic tests (4779)
- Drugs: cardiovascular system (8842)
- Echocardiography (2127)

**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/