Clinical research

The natural history of myocardium awaiting revascularisation in patients with impaired left ventricular function

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Aims Our aim was to follow changes in myocardial function and physiology in patients awaiting coronary artery bypass surgery (CABG) and relate changes to post-revascularisation functional response.

Methods and results In 21 patients with CAD and LV dysfunction, myocardial glucose utilisation (MGU) and blood flow (MBF) were measured with positron emission tomography using F-18-fluorodeoxyglucose and oxygen-15-labelled water. Left ventricular function, MGU, and MBF were re-assessed after one year, immediately prior to CABG. At baseline, dysfunctional myocardium displayed a reduction in MGU, hyperaemic MBF, and coronary vasodilator reserve (CVR) compared to normally functioning muscle. In the year preceding CABG, the overall wall motion score index increased (2.09 ± 0.65 vs. 2.3 ± 0.7, \( p < 0.0001 \)) and the LV ejection fraction decreased (30.6 ± 11.1% vs. 27.3 ± 11.5%, \( p < 0.001 \)). LVEF fell in 14 patients (28.7 ± 9.4 vs. 23.8, \( p < 0.001 \)). Aggregate regional wall motion worsened in 15 patients. In contrast to myocardium displaying stable function at echocardiography, myocardium with evidence of deterioration showed a parallel decrease in hyperaemic MBF and CVR (1.57 ± 0.67 vs. 1.19 ± 0.7 ml/min/g, \( p = 0.004 \) and 1.9 ± 0.75 vs. 1.33 ± 0.6, \( p = 0.005 \), respectively). Such myocardium displayed attenuated recovery postoperatively (21/68 [31%] LV segments) versus ‘waiting-time’ stable myocardium (98/169 [58%], \( p = 0.0002 \)).

Conclusion Delayed revascularisation in ischaemic left ventricular impairment results in declining function and a reduced likelihood of contractile improvement.

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Introduction

Surgical revascularisation confers a prognostic benefit in patients with coronary artery disease (CAD), impaired left ventricular (LV) function, and evidence of myocardial ischaemia. Patients with LV dysfunction and...
myocardial viability may also represent a population that gains a survival advantage with revascularisation. In such patients, little is known about the natural history of ischaemic heart disease between time of diagnosis and revascularisation. Experimental work has demonstrated a temporal progression from myocardial stunning to a state of hibernation in which the myocyte displays reduced contractility, despite near-normal resting blood flow and maintained metabolism. Delay in revascularisation of such myocardium may be detrimental due to progressive myocyte loss and attenuation of functional recovery.

Previous under-provision of surgical coronary revascularisation and subsequent waiting times of a year or more in the United Kingdom provided a unique opportunity to investigate the temporal nature of myocardial function, metabolism, and perfusion in patients with left ventricular dysfunction awaiting coronary artery surgery. The aim of this study was to follow changes in myocardial function, blood flow, and metabolism in patients with chronic ischaemic LV dysfunction awaiting coronary artery bypass grafting (CABG).

Methods

Patient population

Twenty-one patients with left ventricular dysfunction (LV ejection fraction [LVEF] <50%) due to CAD (>75% luminal diameter stenosis) amenable to surgical revascularisation were studied following entry onto a single surgeon’s CABG waiting list. CABG was recommended according to standard clinical criteria. Percutaneous revascularisation alone was not deemed suitable for any of the patients. Chronic LV dysfunction was confirmed by transthoracic echocardiography (TTE). Mean echocardiographic LV ejection fraction (LVEF) was 30.6 ± 11.1% (SD). All patients had at least two viable anterior LV wall segments (preserved contractile reserve at dobutamine echocardiography). All patients were breathless and most had angina but none had decompensated heart failure. Patient recruitment occurred between July 1999 and August 2000. Patient characteristics are listed in Table 1. The cardiac surgical unit involved in this study performs 600–800 coronary procedures annually (5% with LVEF <30%).

Study design

This was a prospectively designed, observational study of patients on a CABG waiting list who had been referred from local cardiology units to the regional cardiothoracic centre for surgical coronary revascularisation. At study entry, baseline myocardial blood flow (MBF), hyperaemic MBF, and coronary vasodilator reserve (CVR) were measured by positron emission tomography (PET) using oxygen-15 labelled water (H₂¹⁵O). Myocardial glucose uptake (MGU) was measured with PET using 2-[¹⁸F]fluoro-2-deoxy-D-glucose (FDG). The PET studies were repeated after one year, in the 2-week period prior to CABG. Global and regional LV function was assessed by TTE at baseline as well as immediately before and 6 months after CABG. All medications remained unchanged over the preoperative and postoperative period. A schematic diagram of the study time points is presented (Diagram 1). The local Research Ethics Committees of both the surgical and PET centres approved the protocol. All patients gave fully informed written consent.

Echocardiography

Regional myocardial function was assessed using a 16-LV-segment model. LVEF was calculated using Simpson’s rule. Regional wall motion abnormality was graded 1–5 (where 1 = normal and 5 = dyskinetic). The wall motion score index was calculated (sum of LV segment scores/number of segments evaluated in each patient). A segment was considered to have recovered contractile function following CABG or to have deteriorated if there was a reduction or increase of at least one grade in the regional wall motion score, respectively. One cardiologist performed and analysed all echocardiograms. The intraobserver agreement for the assessment of wall motion was 0.88 (kappa agreement test). The mean difference in LVEF between two separate measurements was 1 ± 0.6% and was not significant (p = 0.4). An independent cardiologist later reviewed all the TTE studies, yielding an interobserver agreement of 0.82.

Positron emission tomography

All PET (ECAT 931-08/12, Siemens/CTI Inc, USA) studies were performed during euglycaemic hyperinsulinaemic glucose clamp. After transmission scanning, the blood pool was imaged (oxygen-15 labelled carbon monoxide). Resting MBF was measured using intravenous H₂¹⁵O. Hyperaemic MBF was measured following intravenous adenosine administration (140 μg/kg/min). The coronary vasodilator reserve (CVR) was calculated as hyperaemic/resting MBF. Once stable glycaemia was achieved, 185 MBq of FDG was administered followed by a multislice dynamic emission scan. Continuous blood sampling allowed for the estimation of plasma-to-whole blood ratios of radioactivity, thus facilitating subsequent kinetic modelling.

PET data analysis

PET data were reconstructed employing standard algorithms. Subsequent images were analysed with MATLAB (The MathWorks...}

Table 1: Patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N (%)</th>
</tr>
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<tr>
<td>Age, mean ± SD (years)</td>
<td>60.5(7.7)</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>19/2</td>
</tr>
<tr>
<td>Angina, n (%)</td>
<td>15(71)</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>13(62)</td>
</tr>
<tr>
<td>Dyspnoea, n (%)</td>
<td>21(100)</td>
</tr>
<tr>
<td>NYHA class</td>
<td>II:11; III:10</td>
</tr>
<tr>
<td>Coronary anatomy [3, 2, and 1-vessel disease]</td>
<td>18.2.1</td>
</tr>
<tr>
<td>Risk factors [n (%)]</td>
<td></td>
</tr>
<tr>
<td>Current smokers</td>
<td>5(24)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>8(38)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>7(33)</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>15(71)</td>
</tr>
<tr>
<td>Cholesterol, mean ± SD (mmol/L)</td>
<td>5.1 ± 1.2</td>
</tr>
<tr>
<td>Medications [n (%)]</td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>20(95)</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>13(62)</td>
</tr>
<tr>
<td>Statins</td>
<td>21(100)</td>
</tr>
<tr>
<td>Nitrates</td>
<td>14(66)</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>15(71)</td>
</tr>
<tr>
<td>Oral hypoglycaemics</td>
<td>4(19)</td>
</tr>
<tr>
<td>Insulin</td>
<td>3(14)</td>
</tr>
</tbody>
</table>
Inc., MA, USA) software. Sixteen myocardial regions of interest (ROIs) corresponding with TTE segmentation9 were drawn within the left ventricular myocardium and projected onto the dynamic H215O images to obtain tissue activity curves. Regional MBF (ml/min/g) and tissue fraction (TF, the fraction of tissue within a ROI that exchanges water rapidly and is therefore viable) were calculated using single-tissue-compartment tracer kinetic models.

Basal MBF data were corrected for rate pressure product (MBFcorr = MBF/RPP x 104). Tissue FDG time-activity curves were analysed by linearised approach using the same 16 myocardial ROIs.7,10 MGU data (µmol/g/min) were corrected for partial volume effect using the extravascular volume measurement obtained from the C15O and transmission scans.9

Surgical technique

Coronary artery surgery was performed in a standard manner using cardiopulmonary bypass. Cold-blood cardioplegia was used in all cases. Cardiopulmonary bypass (56 [16] min) and aortic clamp (29 [15] min) times did not vary significantly between patients. The median number of grafts applied was three (range 2-4). All patients received a pedicled left internal mammary artery graft (LIMA) to the LAD. Strenuous efforts were made to reinstitute all preoperative medications prior to hospital discharge. No patient was commenced on new vasoactive medication prior to follow-up TTE at 6 months.

Statistical analysis

All data are expressed as means ± SD. χ² was used to compare dichotomous outcomes related to TTE change over the preoperative period. Repeated measures ANOVA was used to compare baseline and repeat PET data, with log transformation of data if not normally distributed. Unpaired data were compared using Student’s unpaired t test. A value of p < 0.05 was considered significant.

Results

No patients suffered an acute coronary syndrome or worsening symptoms of heart failure between baseline assessment and CABG, therefore coronary angiography was not repeated preoperatively. One patient died before postoperative day 30.

Myocardial function (echocardiography)

Overall, in the year prior to CABG the wall motion score index (WMSI) increased (2.09 ± 0.65 vs. 2.3 ± 0.7, p = 0.0001) and LVEF decreased (30.6 ± 11.1% vs. 27.3 ± 11.5%, p < 0.001). WMSI (1.76 ± 0.7, p = 0.0001 vs. baseline) and LVEF (38.215%, p = 0.0008 vs. baseline) improved following revascularisation (Fig. 1). LVEF fell in 14 patients (28.7 ± 9.4 vs. 23.8 ± 8.3, p < 0.0001) and remained stable in 7. When comparing baseline to postoperative LVEF, patients with a fall in LVEF over the waiting period displayed a trend towards reduced absolute improvement in function compared to those with stable LVEF (delta LVEF 6.3% vs.10%). On a per-patient basis, aggregate regional wall motion was unchanged in 6 patients but worsened in the remaining 15 (Fig. 2).

Three hundred thirty one and 315 LV segments were visualised at the baseline and 6-month postoperative TTEs, respectively (16 segments were discounted due to 1 early postoperatively death). Of 243 dysfunctional LV segments, 119 (49%) showed improved function following CABG (hibernating myocardium). When comparing baseline to postoperative segmental function, improvement was less likely in segments displaying echocardiographic deterioration over the preoperative waiting period (χ² = 13.2, p = 0.0002) (Fig. 3).

Sixty-eight of the LV segments with contractile deterioration over the preoperative waiting period could be assessed postoperatively. When comparing regional function just prior to CABG with 6 months postoperatively, 12 (17%) showed no contractile improvement. A proportion of such segments may have shown improvement at a further delayed assessment. Likewise, some may not have improved due to infarction over the preoperative wait or during CABG (Fig. 4).

Myocardial blood flow and metabolism (positron emission tomography)

Paired PET studies were separated by 354 ± 23 days. The patients’ haemodynamic and metabolic conditions were similar at the two study points (Table 2). Paired PET data were available for analysis in 323 (96%) out of a possible
336 LV segments. Of the 217 dysfunctional segments at baseline assessment, 174 (80%) met the PET-FDG definition of viability (i.e., MGU >0.25 \( \mu \text{mol/g/min} \)).

Segmental analysis according to functional changes over waiting time for CABG

Myocardial segments with TTE evidence of functional deterioration over the surgical waiting period showed a parallel decrease in hyperaemic MBF and CVR (1.57 ± 0.67 vs. 1.19 ± 0.7 ml/min/g, \( p = 0.004 \)) and 1.33 ± 0.6 vs. 1.33 ± 0.6, \( p = 0.005 \) respectively) (Fig. 5(a)). Resting MBF (0.80 ± 0.22 vs. 0.85 ± 0.29 ml/min/g, \( p = 0.6 \)), tissue fraction (0.59 ± 0.13 vs. 0.60 ± 0.20, \( p = 0.59 \)), and MGU (0.40 ± 0.18 vs. 0.42 ± 0.20 \( \mu \text{mol/g/min} \), \( p = 0.38 \)) remained unchanged.

PET-derived parameters vs. baseline and postoperative function

Dysfunctional myocardium displayed reduced MGU, hyperaemic MBF, CVR and tissue fraction compared to myocardium with normal baseline function. Confirmed hibernating segments revealed a similar pattern, as did dysfunctional myocardium that did not improve post-CABG. Tissue fraction was significantly higher in hibernating compared to non-recovering, dysfunctional myocardium.
myocardium. Resting MBF was no different between groups (Table 3).

Discussion

This study provides a unique insight into the natural history and pathophysiology of ischaemic heart disease and left ventricular dysfunction. Until recently, waiting times between initial assessment and subsequent coronary surgical revascularisation were very long in the United Kingdom. Such delays in revascularisation provided a unique opportunity to examine the natural history of myocardial function, metabolism, and perfusion in patients with chronically dysfunctional myocardium due to CAD.

During the year preceding CABG, two thirds of our patients experienced a fall in LVEF and approximately one quarter of LV segments in these patients showed either new-onset contractile dysfunction or further deterioration in established wall motion abnormality. All but 6 patients had one or more LV segments with contractile deterioration over this period.

Reduced LVEF is an indicator of poor prognosis in patients with CAD. The deterioration in regional wall motion seen in our patients translated into a significant fall in LVEF prior to surgery, thus potentially increasing operative risk. Furthermore, there was a reduced chance of improvement in LV function following surgery in such patients, which might adversely influence long-term survival. However, only a small proportion of the LV segments that displayed contractile deterioration over the preoperative waiting period failed to improve at all following surgery, thus suggesting a low rate of silent infarction in such myocardium. The prevailing contractile deterioration is thus more likely to have been due to worsening stunning/hibernation.

The onset of new myocardial dysfunction and the deterioration in prevailing wall motion abnormalities was associated with a decline in hyperaemic MBF but stable resting MBF. One may hypothesise that the progression of CAD at the epicardial and microvascular level resulting in repetitive stunning may have played a significant role in such worsening function. Early investigation of such patients is thus mandatory in order to avoid progressive, untreated myocyte decline and the potential associated increased risk of major cardiac events.

At variance with other studies, in our patient cohort there was no mortality during the preoperative
waiting period. However, our population was a medically treated, surgically eligible group with viable myocardium rather than a non-randomised group undergoing surgical revascularisation or medical therapy depending upon physician preference with its potential selection biases.

Chronically dysfunctional, ischaemic myocardium can improve function following revascularisation. Such myocardium has been termed 'hibernating'. Previous studies have demonstrated that the quantum of dysfunctional, but viable myocardium prior to revascularisation determines the magnitude of recovery in LV function and symptomatic improvement. In our study, hibernating LV segments exhibited a decrease in glucose uptake during the waiting time for CABG. This phenomenon may be due to a fall in myocyte mass and/or altered myocardial glucose handling. Baseline hyperaemic MBF in hibernating myocardium was reduced compared to normally functioning myocardium but did not fall further over the preoperative waiting time. This suggests that the response to microvascular dilatation in hibernating myocardium is exhausted. Worsening dysfunction in myocardium with such blunted vasodilator reserve is most likely associated with advancing ultrastructural change and loss of myocyte contractile elements.

Our data suggest that in hibernating myocardium the myocardial tissue fraction (an index of the balance between structurally intact myocytes and fibrosis) lies in an intermediate range between normally functioning and non-recovering tissue. Relatively preserved tissue fraction appears to act as a discriminator in the identification of hibernating and irrecoverably dysfunctional myocardium.

At variance with previous data, our study shows that MGU in hibernating myocardium is similar to that in non-recovering dysfunctional myocardium. Potential recovery of function may be more accurately identified if the residual myocardial metabolic activity and degree of myocardial degeneration/fibrosis are considered in tandem. Residual viable myocytes may subsequently display increased affinity for glucose, thus preserving total regional MGU. Moreover, such myocardium may not easily be defined as either 'viable' or 'non-viable' but may be an admixture of stunned yet viable myocytes within a matrix of fibrosis. In order to decrease partial volume effects, MGU data are presented following correction for extravascular volume and this can in itself correct partially for intrinsic myocardial scarring. We are currently assimilating the PET data presented with the addition of 35 further patients with CAD and LV dysfunction that underwent PET viability examination (not paired studies) and subsequent CABG, in order to review viability threshold criteria.

In accordance with other studies, we suggest that resting MBF measured with H$_{2}$O is similar in normally functioning, confirmed hibernating and dysfunctional, but non-recovering myocardium. However, the heterogeneity of resting MBF in both normal humans and animals makes assumptions about blood flow that are difficult to clarify. Nevertheless, hibernation is associated with a profound limitation in flow reserve. Data

**Table 2** Comparisons of initial with repeat PET haemodynamic and metabolic data

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline PET</th>
<th>Repeat PET</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting RPP</td>
<td>7114 ± 1789</td>
<td>7145 ± 1803</td>
<td>0.76</td>
</tr>
<tr>
<td>Fasting glucose (mmol/L)</td>
<td>6.4 ± 3.8</td>
<td>6.7 ± 2.5</td>
<td>0.25</td>
</tr>
<tr>
<td>Fasting FFA (meq/ml)</td>
<td>0.91 ± 0.42</td>
<td>1.01 ± 0.52</td>
<td>0.22</td>
</tr>
<tr>
<td>Glucose (clamped) (mmol/L)</td>
<td>5.7 ± 1.9</td>
<td>5.6 ± 1.7</td>
<td>0.12</td>
</tr>
<tr>
<td>FFA (clamped) (meq/ml)</td>
<td>0.23 ± 0.13</td>
<td>0.25 ± 0.22</td>
<td>0.24</td>
</tr>
<tr>
<td>Body mass index</td>
<td>29.7 ± 6.0</td>
<td>29.4 ± 5.8</td>
<td>0.87</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>5.1 ± 1.2</td>
<td>5.0 ± 1.2</td>
<td>0.8</td>
</tr>
</tbody>
</table>

RPP, rate pressure product; FFA, free fatty acids. (Clamped = measurement taken at plateau of hyperinsulinaemic euglycaemic clamp.)
from animal models suggest that in the absence of fibrosis the phenomena of myocardial stunning and hibernation represent a continuum. In patients with multivessel disease and prior myocardial infarction, it is less clear-cut. Hibernating myocardium may show normal resting MBF measured with PET and $H_2^{15}$O due to a complex interaction between myocardial microinfarction and chronic hypoperfusion admixed with chronically stunned myocytes.

### Study limitations

One year is a short period in the overall natural history of CAD and postischaemic myocardial dysfunction, but our study is the first to document changes in myocardial physiology over such a clinically relevant period. PET-FDG reproducibility remains undefined, however rigorous attention to standardisation of glycaemia and suppression of free fatty acids (glucose clamp) has reduced the heterogeneity in MGU seen during PET under fasting conditions. The reproducibility of MBF measurements using $H_2^{15}$O is good (reproducibility coefficient 0.17 ml/min/g).

One cardiologist initially performed and analysed the echocardiograms, however, both intra and interobserver agreement was good at post hoc analysis. Graft attrition cannot be excluded, as postoperative angiography was not performed. We chose the 6-month postoperative echocardiography as the investigation time point but recognise that further recovery of function may occur later. Other studies with similarly timed postoperative assessment have demonstrated a prevalence of hibernating myocardium equivalent to ours. The time course of segmental functional recovery is progressive and follows a monoexponential time course with a median time constant of 23 days (range 6–78).

### Conclusions

In summary, during a one-year wait for CABG, patients with CAD and impaired LV contractility exhibited a decline in function accompanied by pathophysiological changes indicative of disease progression. Such a decline attenuates myocardial functional recovery. Whether earlier operation would have led to greater improvement cannot be directly inferred from this data. Nevertheless, as revascularisation may be the single treatment option

### Table 3

<table>
<thead>
<tr>
<th>Index</th>
<th>Normal TTE function at baseline</th>
<th>All dysfunctional</th>
<th>Hibernating</th>
<th>Dysfunctional with no improvement post-CABG</th>
</tr>
</thead>
<tbody>
<tr>
<td>MGU ($\mu$mol/min/g)</td>
<td>0.52 ± 0.20 (103)</td>
<td>0.43 ± 0.21 $^b$ (220)</td>
<td>0.43 ± 0.22 $^a$ (119)</td>
<td>0.42 ± 0.21 $^b$ (77)</td>
</tr>
<tr>
<td>Resting MBF (ml/min/g)</td>
<td>0.81 ± 0.23 (102)</td>
<td>0.82 ± 0.24 (215)</td>
<td>0.81 ± 0.25 (115)</td>
<td>0.82 ± 0.22 (76)</td>
</tr>
<tr>
<td>Hyperaemic MBF (ml/min/g)</td>
<td>1.63 ± 0.63 (41)</td>
<td>1.31 ± 0.70 $^b$ (108)</td>
<td>1.28 ± 0.62 $^a$ (52)</td>
<td>1.33 ± 0.82 (42)</td>
</tr>
<tr>
<td>CVR</td>
<td>2.30 ± 0.79 (40)</td>
<td>1.53 ± 0.70 $^b$ (107)</td>
<td>1.50 ± 0.64 $^a$ (52)</td>
<td>1.52 ± 0.84 (41)</td>
</tr>
<tr>
<td>TF</td>
<td>0.66 ± 0.11 (104)</td>
<td>0.58 ± 0.13 $^c$ (220)</td>
<td>0.60 ± 0.14 $^b$ (115)</td>
<td>0.55 ± 0.11 (77)</td>
</tr>
</tbody>
</table>

Number in brackets = segment count.

$^a p < 0.01$ vs. normal function at baseline.

$^b p < 0.0002$ vs. normal function at baseline.

$^c p = 0.006$ vs. dysfunctional with no improvement post-CABG.
available to limit functional decline, it should be under-
taken as promptly as possible following initial assessment.

References