Coronary revascularisation for postischaemic heart failure: how myocardial viability affects survival

D Pagano, M E Lewis, J N Townend, P Davies, P G Camici, R S Bonser

Abstract

Objective—To assess the impact of revascularisation of viable myocardium on survival in patients with postischaemic heart failure.

Methods—35 patients (mean (SD) age 58 (7) years) with severe heart failure (New York Heart Association (NYHA) functional class ≥ III), mean left ventricular ejection fraction (LVEF) 24 (7)% (range 10–35%), and limited exercise capacity (peak oxygen consumption (VO₂) 15 (4) ml/kg/min) were studied. 21/35 patients had no angina. Myocardial viability was assessed with quantitative positron emission tomography and the glucose analogue 18F-fluorodeoxyglucose (FDG) (viable segment = FDG uptake ≥ 0.25 pmol/min/g) in all patients before coronary artery bypass grafting. Patients were divided into two groups: group 1, ≥ 8 viable dysfunctional segments (mean 12 (2), range 8–15); and group 2, < 8 viable dysfunctional segments (mean 3.5 (3), range 0–7). The two groups were comparable for age, sex, NYHA class, LVEF, and peak VO₂.

Results—Two patients died perioperatively and seven patients died during follow up (mean 33 (14) months). All deaths were from cardiac causes. Kaplan-Meyer survival analysis showed 86% survival for group 1 patients versus 57% for group 2 (p = 0.03). Analysis by Cox proportional hazard model revealed three independent factors for cardiac event free survival: presence of ≥ 8 viable segments (p = 0.006); preoperative LVEF (p = 0.002); and patient age (p = 0.01).

Conclusion—Revascularisation for postischaemic heart failure can be associated with good survival, which is critically dependent upon the amount of viable myocardium.

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Keywords: heart failure; myocardial viability; hibernating myocardium; survival

Although coronary artery disease is the most common cause of heart failure, accounting for up to 60% of cases,¹ the role of coronary revascularisation for the treatment of this condition is unknown. The dated randomised trials of coronary surgery excluded patients with heart failure symptoms (New York Heart Association (NYHA) functional class > II). The coronary artery surgery study registry showed an equally poor five year survival rate of 23% for patients with predominant symptoms of heart failure treated medically or surgically.² It is now clear that left ventricular dysfunction caused by coronary artery disease is not always an irreversible process. Areas of dysfunctional myocardium subtended by a stenotic coronary artery may retain viability and regain contractile function with restoration of blood flow. This phenomenon has been termed “myocardial hibernation”.³ As left ventricular function is an important determinant of prognosis,⁴ this concept raises the possibility that patients with coronary artery disease, heart failure, and hibernating myocardium may gain prognostic benefit from coronary revascularisation. This is particularly relevant in view of the limited availability of cardiac transplantation.

We have previously shown that the presence of a significant amount of viable dysfunctional myocardium (at least 8/16 left ventricular segments) is associated with significant improvements (> 5%) in left ventricular ejection fraction (LVEF) in patients with postischaemic heart failure six months after coronary artery bypass grafting (CABG).⁵ We aimed to assess the impact of revascularisation of viable myocardium on survival in a cohort of patients with postischaemic heart failure.

Methods

PATIENT POPULATION

The patients for this study were recruited from those referred to our hospital for investigation of heart failure, or consideration for CABG or heart transplantation. Inclusion criteria were: chronic (> 6 months) heart failure (NYHA class ≥ III); sinus rhythm; multivessel coronary artery disease; and impaired left ventricular systolic function with at least one dysfunctional left ventricular wall subtended by a stenotic coronary artery amenable to surgical revascularisation. Exclusion criteria were: myocardial infarction within six months; decompensation of heart failure within three months; the presence of more than moderate mitral valve regurgitation, as assessed by transthoracic echocardiography; and the presence of left ventricular aneurysm. Over an 18 month period 39 consecutive patients (35 male and four female, mean (SD) age 58 (7) years, range 41–72 years) met the entry criteria. Fourteen patients suffered with symptoms of heart failure and effort angina, and 25 patients had symptoms of heart failure but no angina. CABG was performed in all 14 patients with angina irrespective of the viability study
findings and in 21/25 patients without angina. Four patients in the latter group, in whom no evidence of viability could be found by positron emission tomography (PET), did not undergo CABG and underwent cardiac transplantation or continued medical treatment. Thus, 35 patients undergoing CABG constituted the population of this study.

All 35 patients had suffered at least one myocardial infarction (range 1–3) and the mean time of the most recent was 30 (14) months (range 12–60 months) before the study period. Eleven patients were diabetic (four insulin dependent) and five patients had a history of hypertension. The preoperative ECG showed Q wave infarction in at least one myocardial territory in all the patients (two territories in nine patients). All patients were receiving maximal medical treatment for heart failure including angiotensin converting enzyme (ACE) inhibitors (35), diuretics (25), and digoxin (7) at the time of recruitment. The patients with angina were also receiving nitrates (14) and calcium channel blockers (3).

The study was approved by the local ethics committee and written informed consent obtained by all patients before the study. The radiation exposure was licensed by the UK administration of radioactive substances advisory committee.

### STUDY PROTOCOL

Selective coronary arteriography was performed in all patients. Patients underwent cardiopulmonary exercise testing, transthoracic echocardiography, PET imaging with 18F-fluorodeoxyglucose (FDG), and radionuclide ventriculography (MUGA) within four weeks before CABG.

### Cardiopulmonary exercise testing

Symptom limited cardiopulmonary exercise testing was performed using a treadmill according to a modified Naughton protocol. Breath by breath ventilatory and gas exchange data were measured using a Morgan Benchmark system (PK Morgan Ltd, Gillingham, Kent, UK). Peak oxygen consumption (VO2) was calculated as the mean of the values recorded during 30 seconds before peak exercise.7 Attainment of the anaerobic threshold was assessed as the point at which carbon dioxide (VCO2) increases disproportionately to VO2 (v-slope method).7 Exercise tests were supervised by a physician unaware of the patients’ clinical details to avoid bias.

### Echocardiography

Segmental left ventricular wall motion was assessed by transthoracic echocardiography (HP Sonos 2500, Hewlett Packard) according to the recommendations of the American Society of Echocardiography.8 The wall motion was graded as 1 (normal), 2 (hypokinetic), 3 (akinetic), and 4 (dyskinetic). The wall motion score index (WMSI) was calculated as the sum of the scores of the left ventricular segments divided by the number of segments evaluated.8 The echo images were analysed by two independent observers blinded to the clinical details and viability details of the patients. In a random subset of 10 patients (160 segments), the interobserver and the intraobserver agreement was assessed using the κ agreement coefficient: interobserver κ = 0.82 (95% confidence interval (CI) 0.69 to 0.95); intraobserver κ = 0.90 (95% CI 0.80 to 1.00).

### PET

The study for the measurement of myocardial glucose utilisation was carried out during hyperinsulaenic euglycaemic clamp with the glucose analogue FDG as described previously.9 Images were resliced in the short axis view and the left ventricle was divided to provide 16 regions of interest comparable to the ones used for echo analysis.9 A dysfunctional segment was considered viable if FDG uptake was \( \geq 0.25 \mumol/min/g \).

### MUGA

All patients underwent radionuclide ventriculography for the assessment of LVEF.9 Analysis was performed by two independent physicians blinded to clinical details including the pre- or postoperative status. The interobserver and intraobserver agreement was assessed in a random subset of 10 patients using a standard method.10 The mean of the differences in LVEF was 0.05 (1.5)% and the 95% limits of agreement were −2.9% to 3%.

### Clinical end point

The end point of the study was major cardiac events defined as cardiac death or transplantation. Cardiac mortality was defined as death.
occuring suddenly or after progressive heart failure deterioration. Information about mode of death was obtained from the patient’s general practitioner and the patient’s family.

**STATISTICAL ANALYSIS**

Data were tested for absence of a Gaussian distribution with the Shapiro-Wilk test. Comparison of means of continuous data was made with the unpaired $t$ test or the Mann-Whitney U test as appropriate. Categorical data were compared using the Fisher’s exact test. Differences in survival between patient groups were compared using Kaplan-Meier survival curves, and significance was determined by the log rank test. The most important predictors of mortality were identified by Cox proportional hazard analysis. Data are expressed as mean (SD). Significance was set at $p < 0.05$.

**Results**

**BASELINE CHARACTERISTICS OF THE PATIENTS**

The age, sex, NYHA functional class, and the number of dysfunctional viable segments revascularised in each patient are shown in table 1. The mean LVEF was 23 (7)% (range 10–37%) and the mean WMSI was 2.2 (0.3). One patient with severe left main coronary artery disease did not undergo exercise testing (patient 19, table 1). Exercise was discontinued because of a combination of chest pain and dyspnoea in 14 patients and dyspnoea alone in 20. Anaerobic threshold was attained in one of 14 patients with angina and in all 20 patients with heart failure symptoms alone. The mean peak VO$_2$ was 15 (4) ml/kg/min (range 7–22 ml/kg/min) (table 1).

**CORONARY ARTERY REVASCULARISATION**

CABG was performed by one surgeon using intermittent aortic cross clamping and induced ventricular fibrillation technique. The quality of the coronary vessels’ subendocardial viable myocardium was good/fair in all but one case (subjective assessment by operating surgeon). The median number of grafts was 3 (range 1–5) and all patients received a pedicled left internal mammary artery graft to the left anterior descending coronary artery. One patient (patient 7, table 1) received incomplete revascularisation because of a poor quality coronary vessel. The mean cardiopulmonary bypass time was 50 (16) minutes and the mean aortic clamp time was 24 (7) minutes.

**FOLLOW UP AND MORTALITY**

Two deaths occurred during the early postoperative period (table 1) because of myocardial failure (overall perioperative mortality 5.7%). The remaining 33 patients were discharged and maintained on medical treatment for heart failure, including ACE inhibitors and diuretics. The ACE inhibitor dose was maintained unchanged, while the dose of diuretics was reduced in eight patients. Antianginal treatment was discontinued following CABG. Patients were followed up by regular visits to an outpatient department ($n = 28$) or by telephone survey ($n = 5$). During follow up (mean 33 (14) months) six patients died (18%). Death was sudden in four patients and caused by progressive heart failure deterioration in two patients. One patient with progressive heart failure died two days following cardiac transplantation (table 1). Comparison of age, NYHA class, LVEF, and peak VO$_2$ between survivors and patients who died is shown in table 2.

**SURVIVAL ANALYSIS**

To analyse the impact of viable myocardium on cardiac event free survival, patients were stratified in two groups according to the number of viable dysfunctional segments revascularised: group 1, 21 patients with $\geq$ 8 segments (mean 12 (2), range 8–15); and group 2, 14 patients with $<$ 8 segments (mean 3.5 (3), range 0–7). We chose this cut off on the basis of our previous study which showed that the presence of $\geq$ 8 (out of 16) viable dysfunctional segments revascularised is associated with a significant improvement in survival and $p = 0.01$ log rank test (fig 1). The two groups were not significantly different for any clinical variable or known prognostic indicator (table 3). Analysis by Cox proportional hazard model revealed three independent factors for cardiac event free survival: presence of $\geq$ 8 viable dysfunctional segments revascularised ($p = 0.006$); preoperative LVEF ($p = 0.002$); and patient age at time of CABG ($p = 0.01$). The hazard ratios for this analysis are shown in table 4. The preoperative NYHA class and peak VO$_2$ did not provide additional significance when added to the analysis. In an attempt to define the minimum number of viable left ventricular segments required to detect a survival advantage, we found that the presence of at least six viable segments revascularised was also associated with a significant estimated five year survival advantage ($84\% \times 50\%, p = 0.01$ log rank test) (fig 2).

**Table 2** Prognostic indicators in survivors and non-survivors before CABG

<table>
<thead>
<tr>
<th></th>
<th>Survivors</th>
<th>Non-survivors</th>
<th>$p$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>57 (7)</td>
<td>59 (8)</td>
<td>0.5</td>
</tr>
<tr>
<td>NYHA class IV</td>
<td>3/26</td>
<td>4/9</td>
<td>0.05</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>25 (7)</td>
<td>19 (7)</td>
<td>0.02</td>
</tr>
<tr>
<td>Peak VO$_2$ (ml/kg/min)</td>
<td>15 (5)</td>
<td>14 (2)</td>
<td>0.1</td>
</tr>
<tr>
<td>Number of viable segments</td>
<td>10 (5)</td>
<td>6 (5)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

**Table 3** Comparison of prognostic indicators between the two groups

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>$p$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>58 (7)</td>
<td>57 (8)</td>
<td>0.8</td>
</tr>
<tr>
<td>NYHA class IV</td>
<td>6/21</td>
<td>1/14</td>
<td>0.5</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>23 (6)</td>
<td>23 (8)</td>
<td>0.6</td>
</tr>
<tr>
<td>Peak VO$_2$ (ml/kg/min)</td>
<td>14 (5)</td>
<td>15 (3)</td>
<td>0.9</td>
</tr>
</tbody>
</table>

Group 1, $\geq$ 8 viable segments; Group 2, $<$ 8 viable segments.

**Table 4** Hazard ratios for independent predictors of survival

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>$p$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\geq$ 8 viable segments</td>
<td>17.2</td>
<td>2.2 to 134</td>
<td>0.006</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>0.78</td>
<td>0.7 to 0.9</td>
<td>0.002</td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.83</td>
<td>0.7 to 0.9</td>
<td>0.02</td>
</tr>
</tbody>
</table>

$\geq$ 8 viable segments indicates the number of viable left ventricular segments revascularised.
Coronary revascularisation in heart failure

Figure 1 Kaplan-Meier curves showing estimated cardiac event free survival for patients in group 1 (≥ 8 viable segments) and group 2 (< 8 viable segments).

Figure 2 Kaplan-Meier curves showing estimated cardiac event free survival for patients with ≥ 6 viable segments and patients with < 6 viable segments.

Discussion
In patients with heart failure caused by coronary artery disease undergoing surgical revascularisation, the amount of viable myocardium is a determinant of survival. The prognostic importance of this factor is equivalent to the LVEF. This corroborates our previous observation that the amount of viable myocardium is related to the improvement in left ventricular function after revascularisation. Viability assessment may allow the identification of a group of patients with postischaemic heart failure who may benefit both symptomatically and prognostically from surgical revascularisation.

The prognostic value of myocardial viability has also been shown in retrospective studies of patients with less severe left ventricular dysfunction and less severe heart failure. In addition to the amount of viable myocardium, our study confirmed the prognostic value of LVEF and to a lesser extent the age of the patients. Peak aerobic capacity, a known powerful prognostic indicator in patients with heart failure, did not add significant information. The latter finding needs further explanation. A relatively high proportion (38%) of patients did not attain anaerobic threshold during the exercise test and therefore maximal aerobic capacity may have been underesti-
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