

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

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## 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  $\geq$  III), mean left ventricular ejection fraction (LVEF) 24 (7)% (range 10–35%), and limited exercise capacity (peak oxygen consumption ( $\text{VO}_2$ ) 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  $^{18}\text{F}$ -fluorodeoxyglucose (FDG) (viable segment = FDG uptake  $\geq$  0.25  $\mu\text{mol}/\text{min}/\text{g}$ ) in all patients before coronary artery bypass grafting. Patients were divided into two groups: group 1,  $\geq$  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  $\text{VO}_2$ .

**Results**—Two patients died perioperatively and seven patients died during follow up (mean 33 (14) months). All deaths were from cardiac causes. Kaplan-Meier 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  $\geq$  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,<sup>1</sup> 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.<sup>2</sup> 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”.<sup>3</sup> As left ventricular function is an important determinant of prognosis,<sup>4,5</sup> 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).<sup>6</sup> 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 ( $\geq$  6 months) heart failure (NYHA class  $\geq$  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

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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  $^{18}\text{F}$ -

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 ( $\text{VO}_2$ ) was calculated as the mean of the values recorded during 30 seconds before peak exercise.<sup>5</sup> Attainment of the anaerobic threshold was assessed as the point at which carbon dioxide ( $\text{VCO}_2$ ) increases disproportionately to  $\text{VO}_2$  (v-slope method).<sup>7</sup> 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.<sup>8</sup> 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.<sup>8</sup> 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  $\kappa$  agreement coefficient: interobserver  $\kappa = 0.82$  (95% confidence interval (CI) 0.69 to 0.95); intraobserver  $\kappa = 0.90$  (95% CI 0.80 to 1.00).

#### PET

The study for the measurement of myocardial glucose utilisation was carried out during hyperinsulinaemic euglycaemic clamp with the glucose analogue FDG as described previously.<sup>9</sup> 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.<sup>8</sup> A dysfunctional segment was considered viable if FDG uptake was  $\geq 0.25 \mu\text{mol}/\text{min}/\text{g}$ .<sup>10</sup>

#### MUGA

All patients underwent radionuclide ventriculography for the assessment of LVEF.<sup>9</sup> 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.<sup>11</sup> 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

Table 1 Patient characteristics

Patient	Age	Sex	NYHA	Peak $\text{VO}_2$ (ml/kg/min)	LVEF (%)	WMSI	Viable segments	Follow up (months)
1	45	M	III	19	32	1.8	9	48
2	49	M	IV	13	17	2.3	14	36*
3	70	M	IV	12	15	2.3	13	0.2†
4	50	M	IV	21	30	2.2	13	46
5	68	M	III	12	15	2.2	7	45
6	59	M	III	17	26	2.4	15	45
7	57	M	III	13	25	2.3	4	28†
8	66	M	III	20	21	2.0	7	44
9	59	M	III	18	21	1.8	4	2†
10	72	F	III	13	19	2.6	15	44
11	57	M	III	21	23	2.3	13	43
12	62	M	III	11	14	2.1	6	2†
13	57	M	III	7	22	2.6	13	42
14	65	F	III	7	37	1.6	8	42
15	62	M	IV	17	14	2.2	0	3†
16	54	M	III	15	30	1.8	9	42
17	63	M	III	17	20	2.2	15	42
18	41	F	III	15	37	1.8	5	41
19	66	M	IV	–	21	2.5	11	41
20	59	M	III	12	15	2.3	0	0.2†
21	68	M	III	10	25	2.6	4	40
22	50	M	III	12	21	2.1	13	39
23	62	M	IV	6	10	2.5	13	39
24	66	M	III	22	22	2.7	16	38
25	48	M	IV	12	19	2.1	9	21†
26	60	M	III	10	18	2.4	12	38
27	55	F	III	22	27	1.7	10	37
28	59	M	III	15	26	2.5	14	37
29	59	M	III	13	25	2.0	9	37
30	49	M	III	14	35	1.7	3	20†
31	53	M	III	19	35	1.7	0	35
32	50	M	III	16	37	2.3	6	34
33	63	M	III	17	20	2.1	13	34
34	48	M	III	14	32	1.9	4	31
35	65	M	III	18	23	2.2	0	20

Viable segments, the number of viable segments revascularised.  
Follow up, the latest follow up time.

\*This patient died following heart transplantation.

†Cardiac death.

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

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

Table 3 Comparison of prognostic indicators between the two groups

	Group 1	Group 2	p Value
Age (years)	58 (7)	57 (8)	0.8
NYHA class IV	6/21	1/14	0.5
LVEF (%)	23 (6)	25 (8)	0.6
Peak VO <sub>2</sub> (ml/kg/min)	14 (5)	15 (3)	0.9

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

Table 4 Hazard ratios for independent predictors of survival

Variable	Hazard ratio	95% CI	p Value
$\geq 8$ viable segments	17.2	2.2 to 134	0.006
LVEF (%)	0.78	0.7 to 0.9	0.002
Age (years)	0.83	0.7 to 0.9	0.02

$\geq 8$  viable segments indicates the number of viable left ventricular segments revascularised.

occurring 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-Wilks 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<sub>2</sub> was 15 (4) ml/kg/min (range 7–22 ml/kg/min) (table 1).

#### CORONARY ARTERY REVASCUARISATION

CABG was performed by one surgeon using intermittent aortic cross clamping and induced ventricular fibrillation technique. The quality of the coronary vessels subtending 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<sub>2</sub> 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 LVEF in these patients.<sup>6</sup> Kaplan-Meier analysis showed a better estimated five year survival for group 1 versus group 2 (86% *v* 57%,  $p = 0.03$ ) (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<sub>2</sub> 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% *v* 50%,  $p = 0.01$  log rank test) (fig 2).

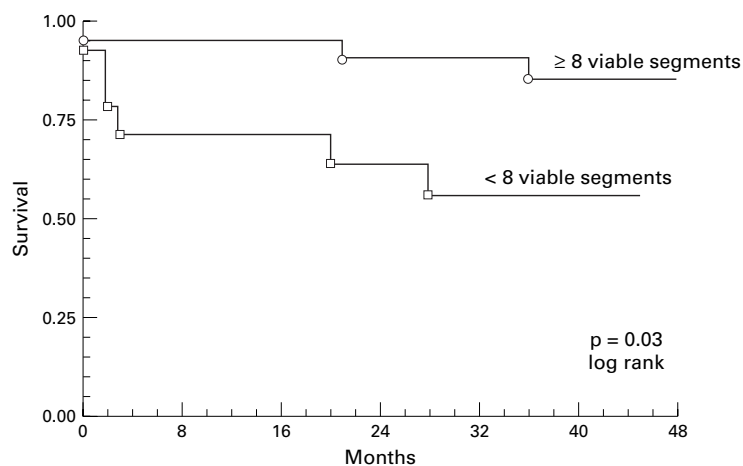


Figure 1 Kaplan-Meier curves showing estimated cardiac event free survival for patients in group 1 ( $\geq 8$  viable segments) and group 2 ( $< 8$  viable segments).

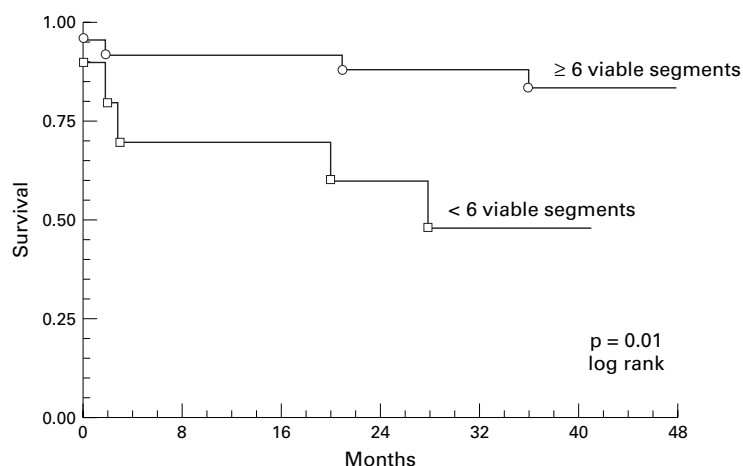


Figure 2 Kaplan-Meier curves showing estimated cardiac event free survival for patients with  $\geq 6$  viable segments and patients with  $< 6$  viable segments.

### 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.<sup>6-12</sup> 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.<sup>13, 14</sup> 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,<sup>5</sup> 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-

mated. This was usually the case in patients with angina, in whom development of chest pain preceded the threshold of maximal exercise, thus limiting the prognostic value of peak  $\text{VO}_2$ . In addition, peak  $\text{VO}_2$  values were similar in the survivors and in the mortality patients indicating that patient groups were homogenous for this variable.

There are a number of potential mechanisms to explain the improved survival detected in patients with large amounts of viable myocardium. Firstly, as we have previously shown,<sup>6</sup> the presence of significant amounts of viable myocardium before CABG is the best discriminator to predict convincing improvements in LVEF, which is a strong prognostic indicator in patients with coronary artery disease and heart failure.<sup>5</sup> In addition, revascularisation of viable myocardium leads to improvements in myocardial contractile reserve,<sup>15</sup> may reduce the risk of fatal arrhythmias, and may have a beneficial effect on left ventricular remodelling.<sup>16</sup>

Although we did not aim to compare CABG to medical treatment, it is noticeable that the survival detected in patients with at least six viable dysfunctional segments revascularised was significantly better than that usually reported for patients with class III or IV heart failure treated medically.<sup>17-19</sup> This finding acquires more significance in view of the fact that most of the patients in our study had no symptoms of angina or evidence of exercise inducible ischaemia, thus constituting a group of patients who, in the past, were not recommended for CABG.<sup>2</sup>

### STUDY LIMITATIONS

We have not compared the effects of CABG with those of continued medical treatment, and although the survival detected in our patients is encouraging, we believe that a prospective randomised study to address this issue is both necessary and justified.

In our study viability was assessed using the most sophisticated technique, PET, which is not widely available, at least in the UK. Although the value of thallium 201 scintigraphy<sup>14</sup> and dobutamine echocardiography<sup>13</sup> in the identification of patients with long term benefit has been described, the potential limitations of dobutamine echocardiography in assessing viability in patients with severe postischaemic heart failure have been underlined previously.<sup>12, 20</sup>

We did not measure LVEF after six months and this could have provided further insight into the potential mechanisms of prolonged survival in patients with more viability.

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