Hibernating myocardium: clinical and functional response to revascularisation


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Abstract

Objective: We assessed the effects of coronary bypass grafting on left ventricular (LV) function, exercise capacity and symptom profile in patients with LV impairment and evaluated the role of identifying myocardial hibernation in a prospective non-randomised study. Methods: Of 120 patients screened, 47 patients with LV ejection fraction < 35% and three vessel coronary artery disease were studied. All underwent stress/redistribution and separate day rest/redistribution Tl-201 imaging together with cine MRI at enrolment, and cine MRI at follow-up. Group 1, 30 patients undergoing bypass surgery, underwent symptom limited treadmill exercise testing with peak VO₂ measurement, and symptom profile evaluation less than 3 months before, and 3–6 months after operation. Revascularisation was assessed by post-operative Tl-201 imaging and repeat coronary angiography. Group 2, 17 patients treated on medical therapy alone underwent symptom profile assessment at enrolment and follow-up for those who survived. Segmental hibernation was defined as the equivalent of greater than 50% of maximal Tl-201 uptake where wall motion was severely impaired on resting imaging. Patients were considered to be hibernating where two of nine LV segments fulfilled these criteria. Results: In group 1, five patients died (17%), peri-or post-operatively, two defaulted and 23 attended follow-up studies. In group 2, three patients died prior to follow-up (18%). In the surgical group there was an increase in mean LVEF from 24.0 ± 8% to 29.7 ± 11% (P < 0.05) while in the medical group there was a fall from 25.7 ± 10% to 20.6 ± 8% (P < 0.05). In group 1, the mean NYHA dyspnoea grade improved from 2.7 to 1.4 while in the medical group it was unchanged, 2.6 to 2.5. In patients with myocardial hibernation identified pre-operatively, 18/19 (95%) improved LVEF after CABG compared with 2/4 (50%) of patients without hibernation. 17/19 (86%) patients with hibernation improved NYHA dyspnoea class compared with 2/4 (50%) of patients without. 60/93 (65%) of hibernating segments improved function after revascularisation while 47/53 (89%) hibernating segments showed no improvement on medical therapy alone. Conclusion: In patients with severe LV impairment with myocardial hibernation, coronary artery bypass grafting improves both global and regional systolic LV function, and symptom profile. Medical treatment of patients with LV impairment and myocardial hibernation does not improve LV contractile function or symptoms. Both surgical and medical therapy carry a high mortality rate. © 1997 Elsevier Science B.V.

Keywords: Myocardial hibernation; Coronary bypass grafting; Left ventricular function; Thallium-201; Magnetic resonance imaging

1. Introduction

The importance of left ventricular function as a prognostic indicator in patients suffering from ischaemic heart disease has been illustrated in a number of studies [1,6]. The results of the CASS study indicated that mortality increased in a curvilinear fashion in...
relation to reduction in left ventricular ejection fraction (LVEF). Moreover the results showed that revascularisation was of benefit in patients with LVEF less than 25%, in whom 1 year mortality was 15% compared with 24% in patients treated on medical therapy alone. Notwithstanding this, there is a higher incidence of peri-operative mortality and morbidity in patients with marked LV dysfunction undergoing coronary bypass grafting (CABG) [1], so the selection of patients for intervention has to be rationalised.

Rahimtoola’s term ‘myocardial hibernation’ [13] refers to the potential for reversible dysfunction following revascularisation in regions of hypocontractile myocardium. The identification of hibernating myocardium is therefore a valuable step in the selection of patients with LV impairment for coronary bypass surgery, although this approach is yet to achieve widespread implementation. The primary means of identifying myocardial hibernation is by cardiac imaging. Techniques include positron emission tomography [11], myocardial scintigraphy with Tl-201[12] or Tc-99m labelled tracers [7], and dobutamine echocardiography [9], or magnetic resonance imaging (MRI) [2]. Comparative studies of the merits and shortcomings of these imaging modalities have been widely reported. However there is less data available on the effects of revascularising patients with myocardial hibernation on clinical parameters such as symptoms, exercise performance and LV dimensions. There is little comparative data between medical and surgical management of hibernation.

Therefore we prospectively assessed the effects of coronary artery bypass grafting on exercise tolerance, peak oxygen consumption, LV parameters and symptom profile in patients with markedly impaired left ventricular function. In addition we evaluated the effect of medical treatment alone on LV parameters and symptom profile in patients with impaired left ventricular function who had undergone hibernation imaging assessment.

2. Methods

2.1. Patient population

Of 120 patients referred for hibernation assessment for clinical purposes, over a period of 28 months, 96 were found to have a resting left ventricular ejection fraction (LVEF) of <35% on magnetic resonance imaging. Of these patients, 38 subsequently underwent coronary bypass surgery (CABG), 8 (21%) of whom died in the peri-operative period or within 6 months of surgery. One patient underwent percutaneous transluminal angioplasty. Patients, 58, remained on medical therapy. Seven (12%) died within a year of the hibernation assessment. Two of the 96 patients were found to have normal coronary arteries on subsequent angiography.

From this group, 30 patients (26 male, four female: median age 61 years, range 40–70 years) scheduled for CABG within 3 months, were recruited into the study (group 1-surgical). All had an LVEF of less than 35% and three vessel coronary artery disease (defined as greater than 70% luminal stenosis) demonstrated on angiography. All 30 had previously suffered myocardial infarction and presented with exertional dyspnoea as a major symptom. Patients in group 1 were studied less than 3 months prior to surgery, and follow-up assessment was performed between 3 and 6 months post-operatively. All were studied on identical medication before and after revascularisation.

A further 17 patients (15 male, two female, median age 63 years) who remained on medical therapy alone were studied (group 2-medical). Patients with significant valve disease, uncontrolled atrial fibrillation, permanent pacemaker in situ or previous coronary bypass surgery were not included in the study.

2.2. Imaging

2.2.1. Tl-201 scintigraphy

All 47 patients underwent stress/redistribution and separate day rest/redistribution Tl-201 SPECT at enrolment, and patients in group 1 underwent a repeat stress/redistribution study 3–6 months following bypass grafting in order to assess post-operative perfusion. Myocardial stress was performed by infusion of 140 ug/kg per min of adenosine coupled with ergometer cycling for a period of 6 min. Blood pressure, pulse and ECG were monitored throughout the stress procedure. At 4 minutes stress, 80 MBq of Tl-201 was injected intravenously. Images were acquired within 5 min of completion of stress, on a dual-headed Optima gamma camera (IGE). Redistribution images were acquired after a delay of 4 h. For the resting study a separate day resting injection of 80 MBq of Tl-201 was administered and images acquired after 15 min delay, and after 4 h redistribution.

Acquisition was conducted over 180° from right anterior oblique to left posterior oblique involving 64 projections of 20 s per stop. Two low energy, high resolution collimators were used with energy peaks set at 72 and 169 keV with 20% windows and no offset. Data were processed using a Hanning pre-filter with a cut-off frequency of 0.8 cycles/cm and a Ramp filter during the back-projection algorithm. The reconstructed transaxial slices were reorientated into the vertical and horizontal long, and short axes.
2.2.2. SPECT image analysis

A 9 segment model of the left ventricle was used—the basal and apical parts of the septum, anterior, lateral, and inferior walls, with the apex as the ninth segment. These segments were viewed using the central vertical and horizontal long axis slices, together with a basal and an apical short axis slice. The SPECT images were visually scored for tracer uptake, by two independent observers, using a five point scale (normal, mildly reduced, moderately reduced, severely reduced, absent), where the divide between moderate and severe reduction corresponded to 50% of maximal uptake.

2.2.3. Cine magnetic resonance imaging

Resting cine magnetic resonance imaging was performed in order to assess left ventricular contractile function. Patients in group 1 were studied less than 3 months prior to surgery and again 3–6 months following CABG. Patients in group 2 were studied at baseline and again after 9 months–1 year. Imaging was conducted using a 1.5 Tesla (Picker International, HPQ) system. Images were acquired in the anatomical short axis (basal and apical) and long axis (vertical and horizontal) of the left ventricle, using an ECG-triggered gradient echo sequence (TE 4.6 ms, flip angle 25°, two averages of 128 phase encoding steps, slice thickness 10 mm, field of view 400 mm, 12 frames per cardiac cycle). A 5 mm presaturation band was placed on either side of the slice in order to suppress signal from blood and to provide a ‘black-blood’ cine.

2.2.4. MRI image analysis

The images were visually analysed by two independent observers without knowledge of the findings of the other imaging techniques. The same 9 segment model of the left ventricle was used. For the cine images, endocardial motion in each segment was scored using a 5 point scale (normal, mildly hypokinetic, severely hypokinetic, akinetic, dyskinetic). Systolic myocardial thickening was scored using a 4 point scale (normal, mildly reduced, markedly reduced, absent), and diastolic myocardial thickness was scored using a 3 point scale (normal, mildly reduced, markedly reduced).

Left ventricular parameters (end diastolic and end systolic volume) were calculated from endocardial trackerball area values using the biplanar area-length method. Values for left ventricular stroke volume and ejection fraction were generated.

2.3. Segmental hibernation

Pre-operatively myocardial segments were assigned as hibernating where a tracer uptake score of ‘moderately reduced’ or greater on late-rest Ti-201 imaging (corresponding to approximately 50% or more of maximal counts) was recorded, together with a wall motion score of ‘severely hypokinetic’ or worse on cine MRI. Segmental revascularisation was considered to be unsuccessful where the post-operative Ti-201 redistribution score was greater than 1 grade less than the pre-operative redistribution score, or where repeat coronary angiography showed occlusion of the graft supplying that segment. Such segments were excluded from analysis.

2.4. Patient hibernation

A patient was considered to have hibernating myocardium where two or more of the nine segments were assigned as hibernating according to the criteria detailed above. Where less than two segments were assigned as hibernating, the patient was considered not to have myocardial hibernation.

2.5. Symptom profile assessment

Symptom profile questionnaires were completed at enrolment and at follow-up. Angina was graded according to the Canadian Cardiovascular Society (CCS) anginal classification, while the degree of dyspnoea was graded according to the New York Heart Association (NYHA) classification.

2.6. Exercise capacity and oxygen consumption

Patients in group 1 underwent treadmill exercise testing at enrolment and following CABG, carried out on the modified Bruce protocol to symptom limitation. Pulse, blood pressure, and 12 lead electrocardiogram (ECG) were recorded at baseline, every 3 min during stress and for up to 10 min into recovery. Respiratory gas exchange analysis was carried out by means of a respiratory mass spectrometer (Amis 2000, Innovision). Patients were encouraged to exercise to exhaustion. Peak oxygen consumption (peak VO₂), V̇E/V̇CO₂ slope and V̇CO₂/VO₂ respiratory exchange ratio at peak exercise were calculated. Treadmill exercise testing was not carried out in those patients who were limited by claudication (n = 3).

2.7. Statistical analysis

Continuous data was analysed using the paired Student’s t-test. Comparison of categoric data was conducted using the X² test or the Fisher’s exact test as appropriate. A level of probability P < 0.05 was considered significant. Data are as mean value ± S.D.
3. Results

Of the 30 patients recruited in group 1, five died (16%), two peri-operatively and three in the post-operative period prior to follow-up (45, 64 and 150 days after CABG). Two patients defaulted on follow-up. Therefore 23 patients underwent imaging assessments both pre-and post CABG. The results of mean values for LV parameters, peak VO₂ and exercise duration, for this group are illustrated in Table 1. Three patients complained of claudication as a limiting symptom and were unable to undergo treadmill exercise testing.

Of the 17 patients in Group 2, three died (17%) from cardiac causes (30, 41 and 56 days after enrolment), leaving 14 patients at follow-up. Table 2 displays the results of LV parameters at enrolment and follow-up for the 14 patients in group 2. Mean LVEF in patients undergoing surgery (group 1) increased significantly, but fell significantly in patients on medical treatment alone (group 2). The marginal improvements in mean exercise time and peak VO₂ values after surgery did not achieve statistical significance.

Based on the criteria described above (two of nine segments hibernating) 19 of the 23 patients in group 1 were considered to have hibernating myocardium (subgroup 1H), while four patients were not. Fig. 1(a–f) illustrate the comparative results for NYHA dyspnoea class, CCS angina classification, peak VO₂ measurement, exercise duration, LVEF and LVEDV based on these findings. The results indicate that patients classified as hibernating show a statistically significant improvement in LVEF and NYHA dyspnoea class when compared with patients without myocardial hibernation. In group 2, 13 of the 14 patients were classified as hibernating (subgroup 2H).

Fig. 2a and b illustrate the comparative results for improvement in segmental function for the surgical and medical hibernation sub-groups, 1H and 2H. Fig. 2a indicates the findings for all segments with severely impaired contractile function (graded ‘markedly hypokinetic’ or worse) while 2b indicates the findings for segments which were assigned a hibernating on initial imaging. In group 1H, 77 of 131 (58%) severely impaired segments improved function after surgery. This compares with 67 of 76 (88%) severely impaired segments which failed to improve function on medical therapy alone in the interval between the initial and the follow-up study, while 47 of 93 (50%) of the hibernating segments showed no improvement, and 11 (21%) showed deterioration in function. These results were statistically significant. Fig. 3a shows that 18 of 19 patients in group 1H showed an improvement in ejection fraction whereas only three of 13 patients in group 2H improved (P < 0.05). As shown in Fig. 3b only five patients in group 1H showed an increase in LVEDV and two in 2H (P = ns). There is a significant difference between the number of hibernating patients showing improvement in angina and with surgery compared with medical therapy (Fig. 3c and d).
### Table 2
Left ventricular parameters and symptom response at enrolment and on follow-up in group 2 (n = 14) and hibernating subgroup 2H (n = 13)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Medical group 2 (n = 14)</th>
<th>Medical hibernation subgroup 2H (n = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initial assessment</td>
<td>Follow-up</td>
</tr>
<tr>
<td>LV ejection fraction</td>
<td>25.7 ± 10.7%</td>
<td>20.6 ± 8.6%</td>
</tr>
<tr>
<td>LV end diastolic volume</td>
<td>235 ± 99 mls</td>
<td>269 ± 92</td>
</tr>
<tr>
<td>LV stroke volume</td>
<td>53 ± 18 mls</td>
<td>50 ± 15</td>
</tr>
<tr>
<td>NYHA dyspnoea grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>0 (patients)</td>
<td>9</td>
</tr>
<tr>
<td>III</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>II</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>I</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Mean</td>
<td>2.6 ± 0.6</td>
<td>2.5 ± 0.8</td>
</tr>
<tr>
<td>CCS angina class</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>III</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>II</td>
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<td>3</td>
</tr>
<tr>
<td>I</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Nil</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Mean</td>
<td>1.1 ± 0.7</td>
<td>1.2 ± 0.8</td>
</tr>
</tbody>
</table>

Time between initial assessment and follow-up. Median 11 months.

In patients in group 1 there was good correlation between change in ejection fraction and change in exercise duration between the pre-operative and post-operative assessments ($r = 0.68$, $P < 0.01$). Correlation between change in peak VO$_2$ values and change in ejection fraction was however poor ($r = 0.42$, $P = ns$), as was the correlation between change in peak VO$_2$ and exercise duration ($r = 0.35$, $P = ns$).

### 4. Discussion

#### 4.1. Imaging criteria for hibernation

In a previous study, we compared the value of dobutamine cine MRI, Tc-99m tetrofosmin SPECT and Tl-201 SPECT in predicting functional improvement in regional LV asynergy following coronary artery bypass surgery [5]. We found that tracer uptake of at least 50% detected in severely hypofunctional segments on late-rest Tl-201 imaging was the most sensitive technique (78%) in identifying myocardial hibernation, and hence these criteria have been applied to the pre-operative labelling of hibernating segments in the current study. A small isolated region of hibernating myocardium detected pre-operatively is unlikely to significantly alter global LV performance after revascularisation, and for this reason, patients in this study were categorised as ‘hibernating’ where two or more segments in the nine segment model displayed the predetermined imaging characteristics described above.

The gold standard in confirming hibernation is the observation of functional recovery following revascularisation. Several authors including Rahimtoola have emphasised that improvement in contractility is unlikely to be observed immediately post-operatively but may take 3–12 months to achieve full recovery potential [14]. The postulated reason is that time is required in order to reverse ultrastructural changes which have been observed in hibernating tissue such as loss of contractile protein and glycogen accumulation. For this reason our post-operative assessment was carried out after 3–6 months (median 5 months). In order to prevent confounding the data as a result of graft occlusion, or unsuccessful revascularisation, we only analysed segments which did not show deterioration at follow-up Tl-201 imaging.

#### 4.2. Symptom response

Previous studies have assessed the outcome of coronary bypass grafting in similar patient groups where LV function is impaired. Mickleborough and colleagues [10] studied a heterogenous group of 79 patients (mean LVEF 18%) and reported improvement in CCS angina class from 3.2 ± 1.0 to 1.5 ± 0.8 for the surviving patients, but found no overall improvement in mean NYHA dyspnoea class (1.9 ± 1.1) although improvement by one class was detected in 26% of patients. No imaging characteristics were reported in this study so hibernation assessment did not play a role in the pre-selection of patients for surgery. These results differ from those of our study, where for the surgical group (group 1), the mean NYHA functional class pre-operatively 2.7 ± 0.5 improved to 1.4 ± 0.8, where this improvement seen in 19 of the 23 patients. The results of
other investigators bear out these findings. Paolini and colleagues [11] reported improvement in NYHA class in eight of nine patients undergoing CABG, pre-selected for surgery based on PET imaging characteristics. Di Carli and colleagues [4] assessed the predictive value of PET metabolism/perfusion mismatch in predicting functional improvement, and found that both the presence and degree of mismatch, and by inference, myocardial hibernation, predicted improvement in NYHA symptom class following revascularisation (mean LVEF 25%). There was no significant change in symptoms of heart failure in the 17 patients without PET mismatch who underwent revascularisation.

Moreover, Di Carli studied 50 patients who were treated medically (17 who had mismatch and 33 who had no mismatch) and reported ten deaths in this group over 13.6 months. No significant change in either angina or heart failure symptoms was reported in the surviving patients over this period. These findings are in agreement with our own, where the mean NYHA dyspnoea class and CCS angina class at enrolment and at follow-up shows little change in the medical group (2.64 versus 2.57 and 1.14 versus 1.21, respectively). Furthermore the comparison of numbers of patients displaying improvement, no change, or deterioration in symptom is significantly different when the medical and surgical groups are compared (Fig. 3c and d).

The results in Fig. 1a indicate that while only 50% of patients without hibernation undergoing CABG show an improvement in NYHA class, 89% of those with hibernation improve these symptoms ($P < 0.05$). There is however no difference between these two subgroups in terms of improvement in angina class where 78% of the hibernation group show improvement as do 75% of the non-hibernation group ($P = \text{ns}$).

4.3. Left ventricular parameters

The results of symptom response are reflected in the change in LVEF for the groups of patients in this study. In the surgical group overall the LVEF increased (24.0–29.7%, $P < 0.05$) while in the medical group the LVEF falls over the follow-up period (25.7–20.6%). Moreover in the surgical group 95% of the patients with myocardial hibernation showed an improvement in LVEF, compared with only 50% of the
non-hibernators. There are several studies which show an appreciable increment in LVEF in patients with ischaemic cardiomyopathy and the various imaging techniques for the identification of myocardial hibernation, with PET [8], radionuclide scintigraphy [12] and functional response to dobutamine [9], have all being predictive. Ragosta and colleagues [12] showed that ten patients with hibernation identified on pre-operative Tl-201 imaging improved LVEF from 29 to 41%, while the group without hibernation showed little improvement (27–30%). Lucignani showed that patients with an FDG PET/perfusion mismatch improved LVEF from 38 to 48% 6 months after revascularisation [8].

In both the surgical and medical therapy groups in our study there was an increase in mean end-diastolic volume (LVEDV) between enrolment and follow-up, which achieved statistical significance in the medical group but not in those undergoing CABG. There is a paucity of data on the effects of revascularisation on LVEDV, as LVEF is the more commonly quoted index of LV function. Meluzin and colleagues [9] defining hibernating and non-hibernating groups on dobutamine echo showed little change in LVEDV in either group following surgery. However the mean LVEF in each group (38% in both) was considerably higher than patients in our study (26% medical, 24% surgical) and the baseline LVEDV was lower. The increase in LVEF in the surgical group results from an increase in LV stroke volume (Table 1), but the stroke volume remains constant in group 2 and mean LVEF falls as the LVEDV increases. The changes in global left ventricular function are reflected in the results for segmental analysis (Fig. 2a and b).

4.4. Exercise capacity

While left ventricular parameters improve overall in the surgical group, we observed only a small but non-significant increment in both treadmill exercise time and peak VO2 measurement in this group, and the comparison of proportions did not suggest that identification of myocardial hibernation was discriminatory in predicting improvement in exercise duration or peak VO2 (see Fig. 1c and d). There was however a good correlation between the change in ejection fraction and the change in exercise time \( r = 0.68 \) with poorer correlation with change in peak VO2 consumption \( r = 0.42 \). In conducting the treadmill stress tests, exercise was carried out to exhaustion to attain values for VO2 as close to the maximum as possible. Nevertheless the improvement in symptom profile and left ventricular parameters following surgery does not appear to translate proportionately into an increment in this index of exercise capacity.

4.5. Limitations

The selection of treatment for patients was made on clinical grounds alone and not on a randomised basis. The number of patients without myocardial hibernation undergoing CABG was small as the information from the hibernation imaging assessment was incorporated into the selection process for surgery. The median follow-up period for the medical group, 11 months, was 3 months longer than that of the surgical group. While the results of this study provide insight into the clinical outcome of both medical management of patients with ischaemic cardiomyopathy and myocardial...
dial hibernation, a randomised study would need to fully compare these therapeutic options.

5. Conclusion

In patients with significantly impaired left ventricular function due to ischaemic heart disease, coronary bypass grafting may improve global and regional left ventricular performance as well as symptom profile. Patients with myocardial hibernation identified on pre-operative imaging assessment are more likely to improve left ventricular contractility and functional capacity than patients without evidence of hibernation. Medical management of myocardial hibernation does not result in improvement in symptoms and left ventricular performance deteriorates over time without revascularisation. Both medical and surgical management of patients with left ventricular impairment, including those in whom myocardial hibernation is identified, carry a high mortality rate.

References


Appendix A. Conference discussion

Dr R. Replogue (Illinois): Dr Gunning, what was the time interval between the onset of damage to the ventricle and the date of your study and revascularisation? Is the state of hibernation described one of chronicity or is it an acute process?

Mr M. Gunning: That question is not possible to answer really in the sense that these patients get referred having had a fairly long history of left ventricular impairment on a clinical basis, but they are not serially studied in an objective manner prior to arriving for a clinical hibernation assessment. The question of how long hibernation has to take place before there is significant impairment has not yet been answered by any study that I am aware of, and I am afraid we did not arrive at that answer either.

Dr R. Repilogue: Would you recommend, on the basis of your study, that the possibility of improved left ventricular function in most patients is a distinct possibility and would you give them a guideline of what they might expect from revascularisation?

Mr M. Gunning: Certainly from what we have picked up it appears that patients in this group, in other words, those with significant impaired left ventricular function, benefit rather more from revascularisation than being left on medical therapy alone. If we conduct a hibernation assessment and detect hibernating myocardium, these are the patients who should indeed undergo revascularisation based on these results.