Prevalence of hibernating myocardium in patients with severely impaired ischaemic left ventricles

A Al-Mohammad, I R Mahy, M Y Norton, G Hillis, J C Patel, P Mikecz, S Walton

Abstract

Objective—Severe impairment of left ventricular (LV) contraction is associated with an adverse prognosis in patients with ischaemic heart disease. Revascularisation may improve the impaired LV contraction if hibernating myocardium is present. The proportion of patients likely to benefit from this intervention is unknown. Therefore, the prevalence of hibernating myocardium in patients with ischaemic heart disease and severe impairment of LV contraction was assessed.

Design—From a consecutive series of patients undergoing coronary angiography for the investigation of chest pain or LV impairment, all patients with ischaemic heart disease and an LV ejection fraction (LVEF) lower than 30% were identified. These patients underwent positron emission tomography (PET) to detect hibernating myocardium, identified by perfusion metabolism mismatch.

Setting—A teaching hospital directly serving 500 000 people.

Results—Of a total of 301 patients, 36 had ischaemic heart disease and an LVEF lower than 30%. Twenty-seven patients had PET images, while nine patients were not imaged because of emergency revascularisation (three), loss to follow up (one), inability to give consent (four), and age less than 50 years (one, ethics committee guidelines). Imaged and non-imaged groups were similar in LV impairment, demographic characteristics, and risk factor profile. Fourteen patients (52% of the imaged or 39% of all patients with ischaemic heart disease and LVEF lower than 30%) had significant areas of hibernating myocardium on PET.

Conclusion—It is possible that up to 50% of patients with ischaemic heart disease and severely impaired left ventricles have hibernating myocardium.

Keywords: hibernating myocardium; left ventricular impairment; positron emission tomography

The importance of heart failure lies not only in its high prevalence, but also in the adverse prognosis associated with the diagnosis. The most common aetiology of impaired left ventricular (LV) contraction is ischaemic heart disease in which the degree of impairment is closely associated with outcome. For patients with severe heart failure, mortality rates may be as high as 60% at one year, while in those with moderate heart failure optimal medical therapy may improve survival to no better than 70% at two years. The three main randomised surgical studies of revascularisation in ischaemic heart disease have suggested that it is the patients with impaired LV contraction who have most to gain in survival terms from surgery. However, intervention in patients with severe LV impairment carries increased risk, particularly in patients with an LV ejection fraction (LVEF) lower than 35% (a largely excluded subgroup from the main randomised surgical trials). Therefore, it is desirable to identify preoperatively those patients with poor LV contraction who are most likely to gain from surgery, thereby justifying their exposure to the increased perioperative risks.

Hibernating myocardium is the chronically ischaemic myocardium with impaired contraction, which improves with revascularisation. Preoperative identification of markers of hibernating myocardium has been shown to predict the recovery of regional and possibly global ventricular contraction after revascularisation. On the other hand, non-viable myocardium does not regain contraction with revascularisation. Identifying markers of hibernating myocardium in patients with severely impaired LV contraction preoperatively means, therefore, that only patients with most to gain need be exposed to the risks of surgery.

The proportion of patients with severe impairment of LV contraction who have hibernating myocardium remains unknown. However, Bonow estimates from several clinical series that between 25% and 40% of patients with chronic coronary artery disease and global LV impairment have the potential for significant improvement in LVEF after revascularisation. From that, the prevalence of hibernating myocardium in patients with ischaemic LV impairment was extrapolated. These series were affected by preselection bias, since they reported the incidence of hibernating myocardium in patients undergoing viability studies and revascularisation. There are, however, no preoperative studies of the true prevalence of hibernating myocardium in patients with poor LV contraction.

By definition the presence of hibernating myocardium can only be ascertained retrospectively, by demonstrating an improvement in LV contraction after revascularisation. Given the high risk of operating on patients with poor LV contraction, and the fact that only those with hibernating myocardium among the latter group would benefit from surgery, it is unethical to subject all patients with poor LV contraction to revascularisation to establish the
true prevalence of hibernating myocardium. Therefore, surrogate markers for hibernating myocardium could be studied preoperatively to assess indirectly the prevalence of the phenomenon in this high risk patient group. Of several techniques available to predict the presence of hibernating myocardium preoperatively, demonstrating areas of hyperperfused myocardium with increased glucose uptake, reduced perfusion at rest, and impaired contraction by positron emission tomography (PET), is widely accepted as the “gold standard”.

We have, therefore, used PET to study the prevalence of hibernating myocardium in a consecutive series of patients undergoing coronary angiography, who have coronary artery disease and severely impaired left ventricles.

Methods

SUBJECTS

A consecutive series of patients with ischaemic heart disease and severely impaired LV contraction were prospectively identified as follows.

All patients undergoing coronary angiography for the investigation of chest pain or LV impairment under the care of one senior investigator between March and October 1995 were considered for inclusion in the study (n = 301, 204 male). This was carried out in a teaching hospital directly serving a population base of 500 000. Therefore, the patients’ population base is representative of the general population and is not affected by the preselection bias that normally affects series from tertiary referral centres. From this cohort of 301 patients, all subjects fulfilling the following angiographic entry criteria were prospectively identified: (a) presence of severe stenosis in at least one major epicardial coronary artery; (b) LVEF ≤ 30% as measured by the modified Sandler and Dodge Area-Length method; (c) for regional wall motion analysis by gated LV angiography because of the presence of intra-ventricular thrombosis; her LVEF was measured on transthoracic echocardiography.

ETHICS COMMITTEE APPROVAL

All patients gave written informed consent before they had PET imaging. The protocol for this research study was approved by the local research ethics committee. It was a condition of approval that only subjects over the age of 50 years should be studied. One 47 year old male patient, however, underwent PET imaging for clinical reasons, and his data were included as he was part of the total cohort of patients with poor LV contraction.

ASSESSMENT OF HIBERNATION

The presence of hibernation was detected by PET, based on the assessment of metabolism and flow using two different tracers. [15N]-ammonia ([15N-NH3]) was used to study the regional myocardial perfusion16–22 18F-2-fluoro-2-deoxyglucose ([18F-FDG]) was used to differentiate between viable myocardium and scar tissue.15 23

Tomographic imaging was performed using a Siemens Exact 31 PET scanner (CTI PET Systems Inc, Knoxville, Tennessee, USA). This system produces 31 slices, with a slice separation of 3 mm resulting in a volume image 10.6 cm deep. Reconstructed image resolution is 10 mm. Attenuation correction was achieved by performing a transmission scan using three revolving rod sources before the emission scan.

For each subject, a mean (SD) of 11.2 (5.2) mCi of [15N-NH3] was given intravenously and volume images of myocardial uptake gathered up to 20 minutes after injection. On the same day, a mean (SD) of 4.8 (0.5) mCi of [18F-FDG] was injected intravenously one hour after the patient had received 50 g of oral glucose.24 Diabetic patients received intravenous soluble insulin at a dose of 4–10 units, according to their serum glucose concentration. The images were acquired 60 minutes postinjection. The [18F-FDG] emission scan was gathered in ECG gated mode using the R wave on the ECG in all patients who were in sinus rhythm.25

For regional wall motion analysis by gated FDG, we assessed wall thickening in the following fashion.

Myocardial uptake was measured by reforming the ventricle into four short axis sections covering the base to mid-ventricle. The apex to mid-ventricle was reformatted as eight long axis sections at 22.5° intervals round the ventricle’s long axis. Axial profiles were formed at 22.5° intervals round each short axis section producing 16 profiles for each short axis section. Five radial profiles were formed at 30° intervals from each of the long axis sections. This three dimensional sampling profile set more closely reflects the most likely wall thickening direction than simple short axis sampling. A complete set of wall profiles was obtained at each of eight phases using a fixed laboratory frame of reference.

Each profile is analysed to obtain a hybrid wall thickness parameter given by the product of maximum wall uptake in the profile and the “thickness” of the wall as given by the second moment of the radial profile. Use of the second moment of radial profile allows for partial volume effects.26 The product of uptake and...
Table 1  A comparison between the imaged and non-imaged patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Imaged patients (n = 27)</th>
<th>Non-imaged patients (n = 9)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD) age (years)</td>
<td>63.4 (9.3)</td>
<td>64.4 (11.4)</td>
<td>NS</td>
</tr>
<tr>
<td>Male sex</td>
<td>22/27 (81.5%)</td>
<td>7/9 (77.8%)</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking§</td>
<td>23/27 (85.2%)</td>
<td>7/9 (77.8%)</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes**</td>
<td>3/27 (11.1%)</td>
<td>1/9 (11.1%)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension††</td>
<td>4/27 (14.8%)</td>
<td>3/9 (33.3%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS, not significant (significance is when p < 0.05); *Number of epicardial coronary arteries with the time of catheterisation or in the past, whether on treatment. Irrespective of the treatment modality; ††Hypertension, either blood pressure > 140/90 mm Hg at non-insulin dependent diabetes mellitus according to World Health Organisation criteria; **Diabetes, both insulin dependent and diabetic patients; §Smoking, patients who are current smokers or exsmokers; ¶Hypercholesterolaemia was defined as total serum cholesterol > 5.2 mmol/l; 

Results of 36 patients fulfilling the entry criteria, 27 (23 men) underwent successful PET imaging. Nine patients were not imaged because of emergency revascularisation (three), loss to follow up (one), refusal or inability to give consent (four), and age < 50 years (one, ethics committee guidelines).

Imaged and non-imaged patients were similar for demographic characteristics, risk factor profile, the number of significantly stenosed or occluded coronary arteries, and LV wall motion score (table 1). However, one third of the non-imaged patients had Canadian Cardiovascular Society (CCS) class IV angina, whereas the CCS class of all imaged patients was less than class IV.

The significance of coronary artery stenosis was assessed by eyeballing, and the stenosis was significant if it was ≥ 70%. Smokers were defined as current or exsmokers, whereas nonsmokers were the patients who were never actively exposed to smoking. Hypercholesterolaemia was defined as a total serum cholesterol concentration ≥ 5.2 mmol/l. Patients were considered hypertensive if they had a systolic blood pressure > 140 mm Hg and/or a diastolic blood pressure > 90 mm Hg.
pressure > 90 mm Hg, or if they were on treatment for hypertension. Diabetics were considered together irrespective of their diabetes type or their treatment's modality. The detailed characteristics of the imaged patients are presented in table 2.

Of the 27 patients with images suitable for analysis, 14 had at least one region on the polar map fulfilling the PET criteria for hibernation. Thus, 14 of 27 (52%) of the imaged patients and at least 14 of 36 (39%) of the total cohort demonstrated evidence of hibernating myocardium. There were no statistically significant differences between patients with and without hibernating myocardium, except for hypertension, which affected four of the 14 patients with hibernating myocardium and none of the patients with no hibernating myocardium (p < 0.05) (table 3).

### Discussion

These data provide an estimate of the prevalence of hibernating myocardium in a consecutive series of patients with poor LV contraction using the best surrogate marker for the preoperative detection of hibernating myocardium. It appears that 50% of patients 50 years and older, with an LVEF < 50%, have the potential for improvement in LV contraction following revascularisation.

Although hibernating myocardium is defined by its recovery following revascularisation, a true estimate of prevalence cannot be defined in this way because not all patients have an indication for coronary artery bypass surgery on conventional grounds. Indeed, many patients are denied coronary artery bypass surgery because the risks of the operation are perceived to be excessive owing to their poor LV contraction. Of the currently available preoperative predictors of hibernation, PET has the best predictive accuracy and provides the best surrogate marker for hibernating myocardium to be predicted. Therefore, the mismatch pattern on PET was used in this report as a surrogate for hibernating myocardium.

The principles of the diagnosis of hibernating myocardium by PET lie in the biochemical behaviour of the ischaemic myocardium. The myocardium is unable to metabolise anaerobically due to the long chain free fatty acids, which are its main source (approximately 70%) of energy under normal conditions. Therefore, under ischaemic conditions, the myocardium will rely increasingly on the anaerobic metabolism of glucose as its main energy source, although the hibernating myocardium's metabolism is not exclusively anaerobic.26 Given these changes, the PET marker for hibernating myocardium is the mismatch between hypoperfusion of the region of interest and normal or increased uptake of the extrinsic glucose analogue 18F-FDG in that region. This pattern is labelled as perfusion metabolism mismatch.27 The mismatch pattern has a high positive and negative predictive accuracy of functional improvement with myocardial revascularisation.24 25 26 27 28 29 30 31 32 The predictive value of PET is highest in the myocardial regions with severely impaired contractile function, and at least 14 of 36 (39%) of the total cohort demonstrated evidence of hibernating myocardium. There were no statistically significant differences between patients with and without hibernating myocardium, except for hypertension, which affected four of the 14 patients with hibernating myocardium and none of the patients with no hibernating myocardium (p < 0.05) (table 3).

Several investigators suggested the use of the hyperinsulinaemic euglycaemic glucose clamp technique while studying myocardial glucose metabolism, particularly in patients with coronary artery disease, who are known to have a high incidence of insulin resistance. However, the great majority of PET groups use our technique while studying myocardial glucose metabolism, particularly in patients with coronary artery disease, who are known to have a high incidence of insulin resistance. However, the great majority of PET groups use our technique while studying myocardial glucose metabolism, particularly in patients with coronary artery disease, who are known to have a high incidence of insulin resistance. However, the great majority of PET groups use our technique while studying myocardial glucose metabolism, particularly in patients with coronary artery disease, who are known to have a high incidence of insulin resistance. However, the great majority of PET groups use our technique while studying myocardial glucose metabolism, particularly in patients with coronary artery disease, who are known to have a high incidence of insulin resistance. However, the great majority of PET groups use our technique while studying myocardial glucose metabolism, particularly in patients with coronary artery disease, who are known to have a high incidence of insulin resistance. However, the great majority of PET groups use our technique while studying myocardial glucose metabolism, particularly in patients with coronary artery disease, who are known to have a high incidence of insulin resistance.
have suggested might be the case. Although it is possible that the group of patients not imaged may have skewed the results, even if none of these patients had evidence of hibernating myocardium the prevalence would be 39% (14 of 36). Such a bias is unlikely, given the similarity of the imaged and non-imaged groups. The two groups were comparable in all aspects except for the presence of angina at rest would affect the CCS angina class.

We are unaware of any data to suggest that the presence of angina at rest would affect the presence of hibernating myocardium in a patient with severely impaired LV contraction. It would be reasonable, therefore, to suggest that the findings in the imaged group are applicable to the total cohort of patients with severe impairment of LV contraction.

As for the comparison of the risk factors profile and demographic data between the patients with hibernating myocardium and those with no hibernating myocardium, significantly more hypertensive patients were present in the group with hibernating myocardium compared to those without. However, clinically important conclusions cannot be drawn from this observation, as we did not set out to investigate the differences between patients with and without hibernating myocardium. This is an observational study to investigate the prevalence of a phenomenon rather than to detect its contributing factors.

There is no consensus as to how much of the LV myocardium should be hibernating for a significant improvement to be expected with revascularisation. However, the figure of 20% has been quoted.\textsuperscript{33} We have used this level as a cut off point in deciding the threshold at which the patient is said to have hibernating myocardium. This, however, is an arbitrary point. We recognise that setting a different threshold could result in a different prevalence level.

The institution where this study was carried out is unique in that it is the only hospital in the country which has access to a PET facility, while directly serving the community, rather than relying on other institutions for referral. Therefore, this series is less likely to have been affected by the preselection bias that affects the series from tertiary referral centres.

The mortality of patients with coronary artery disease and severely impaired LV contraction is high, even on optimal medical therapy.\textsuperscript{2} However, revascularisation can lead to improved symptoms and prognosis in patients with impaired LV contract as demonstrated in the surgical studies.\textsuperscript{21,29,34}

Given the risks of revascularisation in these patients, the preoperative identification of viable myocardium in patients with poor LV contraction would define the group of patients who stand to benefit most from revascularisation, justifying the risk of the operation.\textsuperscript{2} Furthermore, in addition to predicting improvement after revascularisation, there is evidence that the PET pattern of mismatch identifies a group of patients who are at very high risk for cardiac death if they were assigned to medical therapy alone.\textsuperscript{2} Our data from a consecutive series suggest that as many as 50% of patients with severely impaired LV contraction could benefit from revascularisation. This finding has important implications for the investigation and management strategies in this group of patients with poor prognosis.

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Heart foundations on stamps (1)

New Zealand has issued health stamps each year since 1929. These stamps always bear a charity surcharge and were originally used to support health camps for children. A set of two health stamps was issued on 2 August 1978. The first commemorates the 50th anniversary of health stamp issues, and the original stamp from 1929 has been reproduced in the design. There were two versions of the 1929 stamp, which are identical apart from the inscription. The original stamp was inscribed “Help stamp out tuberculosis” and the later issue “Help promote health”. The second 1978 health stamp, depicting cardiac surgery, commemorates the 10th anniversary of the formation of the National Heart Foundation of New Zealand, which was incorporated under the provisions of the Charitable Trusts Act on 26 April 1968. The emblem of the National Heart Foundation of New Zealand is incorporated in the lower left corner of the main stamp design. These stamps were on sale for nearly a year until 30 June 1979.
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