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Incidence of hibernating myocardium after acute myocardial infarction treated with thrombolysis

J N Adams, M Norton, R J Trent, P Mikecz, S Walton, N Evans

Abstract

***Objective*—To establish the incidence of hibernating myocardium after myocardial infarction treated with thrombolysis and to observe differences in the clinical outcome between patients with and without hibernating tissue.**

***Methods*—41 patients underwent gated positron emission tomography with 18–fluorodeoxyglucose and ^{13}N-ammonia at a median of eight days after first myocardial infarction.**

***Results*—All 41 subjects had a matched perfusion-metabolism deficit in the region of myocardium indicated as the site of infarction by an electrocardiograph; 32 patients (78%) had scans which also showed at least one area of reduced blood flow and contraction with a concomitant increase in glucose uptake, representing hibernating myocardium. Patients were followed up at a median of six months: all 41 were alive and none had sustained a further infarct or cardiac arrhythmia; 17 subjects with hibernating tissue (53·1%) and two without (25%) reported chest pain after myocardial infarction.**

***Conclusions*—Hibernating myocardium is relatively common shortly after myocardial infarction treated with thrombolysis. It does not influence mortality or the incidence of postinfarction chest pain.**

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Keywords: hibernating myocardium; positron emission tomography; myocardial infarction

Cardiac Department, Aberdeen Royal Infirmary, Foresterhill, Aberdeen
J N Adams
R J Trent
S Walton

Department of Medical Physics, University of Aberdeen, Foresterhill, Aberdeen
M Norton
P Mikecz
N Evans

Correspondence to:
Dr J N Adams, Department of Cardiology, Queen Elizabeth Building, Glasgow Royal Infirmary, Alexandra Parade, Glasgow G31 2ER.

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In patients with coronary artery disease, myocardial perfusion in some areas may be reduced to levels which are inadequate to maintain myocardial contraction, but are still sufficient to ensure cell viability. This non-contractile yet viable tissue has been called hibernating myocardium.[1 2] Following thrombolysis for acute myocardial infarction the patency of the infarct related vessel is generally less than 85%[3–5] and despite successful reperfusion significant residual stenosis is common. Patients who sustain an infarct often have multivessel disease. Therefore, areas of myocardium both adjacent to and distant from the infarct area may contain hibernating tissue.

The restoration of blood flow to hibernating tissue, either by coronary artery bypass surgery or by percutaneous coronary angioplasty, has been shown to result in the return of contractile function and thus improve overall left ventricular contraction.[6–8] In addition Eitzman *et al*[9] have shown that patients with hibernating myocardium have an increased risk of adverse cardiac event or death and those with impaired left ventricular function have most to benefit from revascularisation. It is therefore important to distinguish between non-contractile infarcted myocardium and hibernating tissue for several reasons. Positron emission tomography (PET) provides a method of assessing myocardial perfusion and metabolism and thus the identification of areas of hibernating tissue.[10 11]

Methods

Forty one patients, 35 men and six women, mean age 60 years (range 50–75 years), underwent PET scanning at a median of eight days after infarction (range 5–21 days). All patients had sustained a first myocardial infarction; all gave a history of chest pain consistent with myocardial infarction, and 40 (98%) developed both a twofold rise in cardiac enzymes (aspartate aminotransferase and lactate dehydrogenase) and pathological Q waves on the electrocardiogram after admission. The remaining patient had a rise in cardiac enzymes and developed T wave inversion. All patients who survived to the time of discharge were eligible for this study. The protocol for the study was approved by the local ethics committee and all patients gave informed written consent before they were scanned.

Tomographic imaging was performed using an ECAT II as described by Marshall *et al*.[11] To allow for photon attenuation six contiguous cross section transmission images were obtained 1·5 cm apart. An intravenous bolus of 15–20 mCi of ^{13}N-ammonia was then injected into a peripheral vein and images obtained in the same cross sectional planes. On the same day a 3–5 mCi bolus of ^{18}F-2-fluoro-2-deoxyglucose (FDG) was injected 1 h after patients had received 50 g glucose orally. Images were then acquired 45 min after injection. The second emission scan was gated using the R wave on the electrocardiogram. Images were generated at eight phases through the cardiac cycle.

Analysis of tomographic images was performed on a Sun Spark Classic using PV wave software. Image reconstruction was performed using a maximum likelihood method.[12] After reconstruction, each patient dataset was

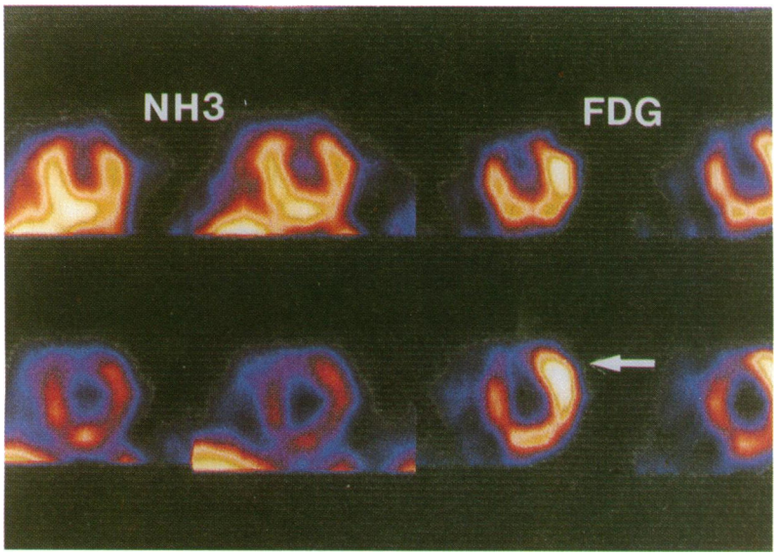
rotated and resliced to produce eight short axis sections covering the length of the ventricle. Regional myocardial uptake and wall motion was calculated using circumference profile analysis.[13]

Areas of hibernating myocardium were defined as regions with reduced uptake of ^{13}N-ammonia and increased uptake of FDG (a mismatched defect) associated with reduced contraction. Short axis images were divided equally into anterior, lateral, inferior, and septal regions. A large area of hibernating tissue was defined as a mismatched defect with reduced myocardial contraction involving the whole of one or more of these regions or part of two adjacent regions in two or more consecutive slices. Where mismatched defects involved only part of one region or were visualised at only one level, they were designated as small areas of hibernating tissue.

All patients were followed up at six months after infarction either at an outpatient appointment or at the time of further investigations. Patients who did not have a further hospital appointment were contacted by post and asked to complete a questionnaire assessing their progress, investigations, and treatment after discharge from hospital. An unpaired Student *t* test was used for normal distributions and non-parametric testing was performed using a Wilcoxon rank sum test.

Results

All 41 patients received streptokinase, the median time from onset of chest pain to administration of thrombolysis being 3·5 h (range 1–10·25 h). Three (7%) had a past history of chest pain consistent with angina, and seven (17%) were receiving β blockers, long acting nitrates, or calcium channel antagonists before admission. Fourteen patients (34%) had ECG changes in the anterior leads, and 27 (66%) in the inferior leads; 28 (68%) were cigarette smokers.



Positron emission tomography images of four short axis sections in a subject with an anterior myocardial infarction and an area of hibernating myocardium in the lateral wall (indicated by arrow). NH_3, ^{13}N-ammonia; FDG, ^{18}fluorodeoxyglucose.

INCIDENCE OF HIBERNATING MYOCARDIUM

Forty one subjects (100%) had a matched deficit in the ammonia and FDG scans associated with reduced or absent wall motion in the region identified by the admission ECG as the site of infarction. Nine subjects (22%) had scans which showed no areas of mismatch and therefore had no hibernating tissue. Thirty two patients (78%) had scans with at least one area of hibernating tissue. The figure shows a patient with an anterior wall infarct and an area of hibernating myocardium in the lateral wall. Of the subjects with hibernating myocardium, 13 (32%) had a single large area of mismatch and the remaining 19 (46%) had one or several small regions. There was no significant difference between the three groups for time to thrombolysis, past history of angina, and medication before or during admission.

Eight (61·5%) of the subjects with a large area of hibernating tissue had sustained an inferior infarct and five (38·5%) an anterior infarct. Of the patients with small areas of hibernation, 12 (63·2%) had inferior infarcts and seven (36·8%) anterior, while of the nine patients with no hibernating tissue seven (77·7%) had an inferior infarction. Therefore, of the patients with inferior infarction, eight (29·6%) had a large area, 12 (44·4%) a small area, and seven (26·0%) no region of hibernating myocardium, in contrast to those with anterior myocardial infarction, of whom five (35·7%) had a large area, seven (50%) a small area, and two (14·3%) no hibernating tissue.

Within the group of subjects with a single large area of hibernating myocardium, four (31%) had a region in the anterior/anterolateral wall, four (31%) in the inferior/inferolateral wall, three (23%) in the septal/inferoseptal wall, one in the lateral wall, and one in the anterior/anteroseptal wall. Ten (77%) of these 13 areas of hibernating tissue involved myocardium directly adjacent to the infarcted area. Of the three patients with hibernating tissue distant from the site of infarction, two had inferior and one an anterior infarct.

SIX MONTH FOLLOW UP

Forty patients (97·6%) were followed up at a median time of 6·5 months after myocardial infarction (range 5·5–11 months). The remaining patient was sent a questionnaire at six months, which he did not return. His general practitioner confirmed that the patient was alive, was free of angina and heart failure, and gave details of his current medication. Therefore all 41 patients were alive at six month follow up. No patient had sustained a further myocardial infarction or been noted to have a cardiac arrhythmia. There was no significant difference in the incidence of angina, with six (46·2%) of those with large areas, 11 (57·9%) of those with small areas, and two (25%) subjects with no hibernating tissue reporting chest pain. Similarly there was no difference in the incidence of breathlessness or readmission to hospital. The subjects in each group were taking similar antianginal drugs and there was no difference in the numbers

who had returned to work after infarction.

Twenty patients performed a Bruce protocol exercise test during the six month follow up period: eight with a large areas of hibernating myocardium, nine with only a small area, and three with no hibernating tissue. The mean times completed on the treadmill were 8·0 minutes, 8·0 minutes, and 8·9 minutes respectively. Among the 17 patients who had some evidence of hibernation and had performed an exercise test, six showed no evidence of ST segment depression. Of the three patients with no hibernating myocardium who performed exercise tests, all three showed ST depression.

Eight subjects (19·5%) had undergone cardiac catheterisation following infarction; all had a stenosis or occlusion in the infarct associated artery. In addition two subjects had hibernating tissue distant from the site of infarction and in both, disease was detected in the appropriate artery. Of the subjects undergoing angiography, four had occluded infarct related vessels and four had severe (> 50%) stenoses. Six subjects had triple vessel disease, one double vessel disease, and one single vessel disease. The proportion of patients undergoing angiography was similar between the three groups. At the time of follow up, one patient had undergone an unsuccessful percutaneous coronary angioplasty, two were awaiting coronary artery bypass grafting, and one was in hospital recovering from coronary surgery.

Discussion

Conventional methods of imaging radioisotopes provide a somewhat distorted image since the field of view varies as a function of the depth and there is difficulty in distinguishing between the organ of interest and the tissue in front and behind. In effect, three dimensions are compressed into two. The development of techniques similar to those used in computerised axial tomography has made it possible to localise a source of radiation more accurately within the human body. PET measures the concentrations of positron emitting radioisotopes within a three dimensional object by the use of external measurements of the radiation from these isotopes. The localisation is sufficiently accurate to allow the data to be presented as grey scale images in cross section, with the intensity of each pixel proportional to the isotope concentration at that position in the object being scanned. Carbon, nitrogen, fluorine, and oxygen are among the positron emitting radionucleides available. All these elements are found in compounds that constitute or are consumed by the human body. PET combines the ability to assess biochemical pathology with the ability to localise the point of interest accurately. Therefore PET readily lends itself to the in vivo study of the fates of isotopes and is considered to be the gold standard in the detection of hibernating myocardium.[14]

Hibernating tissue was originally defined as arising from a chronic reduction in coronary flow.[1,2] However, more recent studies have provided evidence that hibernation can also occur after acute occlusion.[15-17] This differs from stunned myocardium, which is defined as postischaemic left ventricular dysfunction in the presence of restored coronary blood flow.[2,18] This current series shows that in the acute phase after myocardial infarction over one third of patients have large areas of hibernating myocardium as detected by PET. Schwaiger *et al* found that in patients imaged at a mean of 72 hours after infarction 69·2% had evidence of hibernating tissue; however, none had received thrombolysis.[16] Czernin *et al* found the incidence of hibernating myocardium in patients imaged at 21–170 hours after infarction to be 45·6%; reperfusion was attempted in 45·5% of these subjects.[17] Pierard *et al* scanned patients at a mean of nine days after infarction; all received thrombolysis and 35·3% were found to have hibernating myocardium.[19] The variation in the incidence between studies may partly be due to the differences in the rate of thrombolysis or the timing of scans. When perfusion and metabolism scans are compared, particularly using computer based subtraction techniques, there is often at least a small area of mismatch. There is at present no generally accepted figure for the size of mismatch which should be considered to represent a clinically significant region of hibernating tissue. This may also explain the variation in incidence of hibernating myocardium. In the current study it was decided to differentiate between large and small areas of mismatch using a definition based on the number of regions and sections involved. This was easy to use and required only comparative rather than quantitative analysis of the data.

^{13}N-ammonia has been established as a useful marker of myocardial blood flow.[20,21] It is rapidly extracted by myocardial tissue, but its retention within the cell depends on conversion to glutamine and thus on intracellular metabolism.[21,22] Although the retention of ammonia is affected by low pH or reduced levels of intracellular adenosine triphosphate, it has been shown that metabolic trapping of NH_3 is relatively constant over a wide range of haemodynamic and metabolic conditions and it is therefore still a useful imaging agent for blood flow.[21] The use of ^{15}O-water or ^{11}C-acetate in addition to NH_3 and fluorodeoxyglucose would provide additional information on perfusion and oxidative metabolism, but would have increased both the technical complexity of the study and the scanning time. Vanoverschelde *et al* found that regional oxidative metabolism is intimately coupled to myocardial blood flow and therefore the assessment of myocardial oxidative metabolism does not provide additional independent information on myocardial viability.[23]

The clinical outcome at six month follow up was similar in terms of both mortality and morbidity, irrespective of the presence or absence of hibernating myocardium. This is in contrast to work by other investigators which has shown that patients with hibernating myocardium have an increased risk of adverse

cardiac event or death.[9] In the current study there was some bias in the selection of subjects in that only patients who were fit for scanning at the time of discharge were included. Patients who had significant persistent pulmonary oedema or other life threatening complications after infarction were excluded. The preponderance of inferior infarcts in the study group probably arises as a result of this selection process. Patients in the study performed by Eitzman[9] all had impaired left ventricular function and therefore represent a different patient population. In addition patients in this series were only followed up for a median of six months, while in the previous study follow up was complete for up to one year.

The significance of the hibernating tissue depends on the ability to regain contractile function. If in this series we had found only a very small proportion of patients with large areas of hibernation then there would be little point in attempting to detect hibernating myocardium in most patients after infarction. The best test of the clinical significance of hibernating myocardium would be for those with hibernating tissue to undergo revascularisation followed by further PET scanning and evaluation of left ventricular function. However, it was decided that it would be unethical to submit asymptomatic patients to coronary bypass surgery. A number of subjects including several with hibernating tissue are awaiting coronary surgery, the results of which will be assessed at a later date.

PET imaging is not widely available in the United Kingdom, although in some parts of the world it is becoming increasingly common. Radioisotope studies of coronary blood flow using thallium-201 have, however, been used extensively in clinical practice to assess myocardial perfusion. Lui *et al* found that 75% of myocardial segments with a fixed thallium-201 defect after stress scintigraphy recovered normal function after angioplasty to the culprit lesion.[24] Reinjection of thallium immediately after redistribution improves the detection of hibernating myocardium.[25] Several publications have shown the superiority of PET imaging over stress-redistribution thallium imaging,[26 27] but when reinjection of thallium is compared with PET scanning the results compare more favourably, with concordance rates between the two techniques of 88%.[28] This could provide a more widely available method of detecting hibernating myocardium in the clinical setting, although PET imaging remains the method of choice.

CONCLUSIONS

In the acute phase after infarction a significant proportion of patients have regions of hibernating myocardium, both adjacent to and distant from the area of infarction. The incidence of hibernating tissue in our series is consistent with the findings of other workers who have studied comparable subjects. It was not influenced by the time to thrombolysis or the site of infarction. In our study the presence of hibernating tissue did not affect the mortality or morbidity rates at six month follow up.

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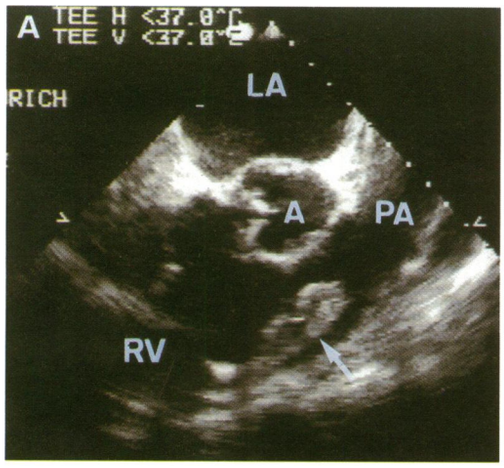
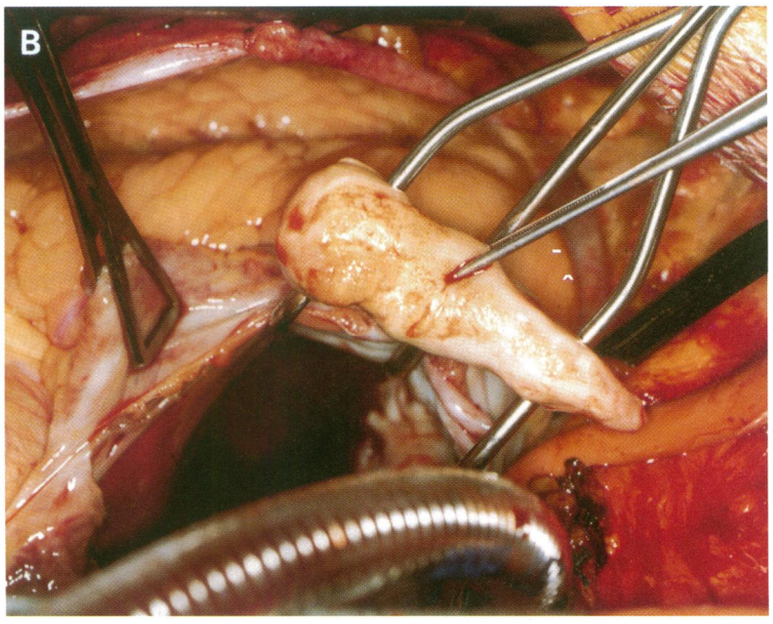
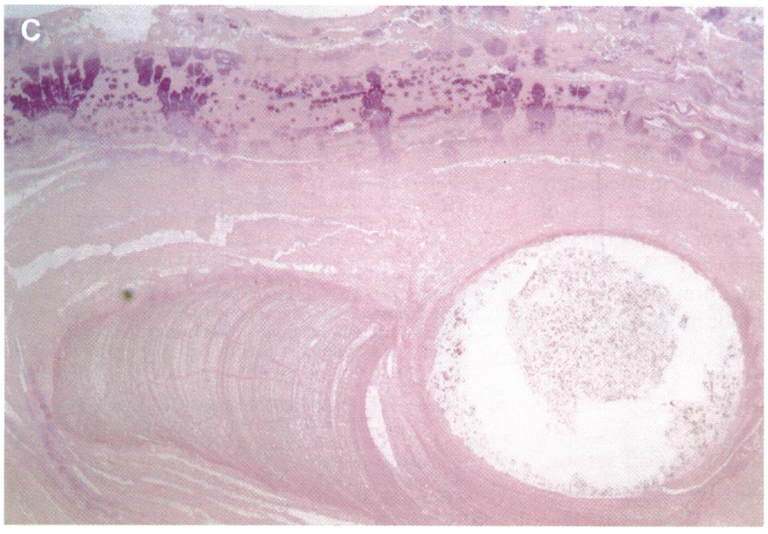
IMAGES IN CARDIOLOGY

Pacemaker endocarditis







Blood cultures in a 70 year old patient who presented with intermittent fever were positive for *Staphylococcus epidermidis* and *Corynebacterium jeikeium*. A year before a VDD pacemaker with a tripolar transvenous right ventricular electrode had been implanted in the right subclavicular area because of a complete heart block. The pacemaker was removed seven months later because of pouch infection and the lead was cut proximally. A new pacemaker with another right ventricular electrode was inserted contralaterally.

Transoesophageal echocardiography (A) revealed prolapse of the proximal parts of the first electrode into the right ventricular outflow tract and the main pulmonary artery with a large (2 × 5 cm) club-shaped vegetation (arrow; LA, left atrium; A, aorta; RV, right ventricle; PA, pulmonary artery). The electrodes and the vegetation were removed through a right atriotomy (B). A new pacemaker with a right ventricular lead was inserted a day later. Gram staining of the vegetation (× 16) (C) showed dense colonies of Gram positive bacteria (dark purple) in the superficial parts of an anuclear thrombus (pink). The space in the lower right portion of this panel shows the position of the lead. With antibiotic treatment the patient recovered and was doing well five months postoperatively without signs of recurrent infection.

MARTIN FEDERMANN
OLAF R DIRSCH
ROLF JENNI

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J. N. Adams, M. Norton, R. J. Trent, et al.

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