ABSTRACT

One hundred and fourteen patients were studied before and after coronary bypass surgery using radionuclide techniques to assess myocardial perfusion and function. At baseline and at follow up visits each patient was assessed by a clinician. Regional and global myocardial perfusion was evaluated at rest and at peak exercise using a total of 60MBq of thallium 201. Rest and exercise thallium scintigraphy was repeated 9 months after CABG (late follow up). In order to assess myocardial hibernation redistribution of rest images were acquired at baseline before the exercise images.

Left and right ventricular ejection fractions (LVEF and RVEF) were measured by radionuclide ventriculography performed at baseline on a separate day from the thallium images. Regional ventricular wall motion was assessed on a continuous loop cine display of the 24 frames of the radionuclide ventriculogram with the aid of standard fourier amplitude and phase images. After the completion of the rest radionuclide ventriculogram dobutamine was administered at doses of 5-10μg/kg/min and the effect of the dobutamine on left ventricular regional wall motion was assessed. Radionuclide ventriculography was repeated 6 weeks (early follow up) and approximately 9 months (late follow up) after surgery.

Coronary bypass surgery produced a marked improvement in symptoms and exercise tolerance. Before the operation 98% of the patients described symptoms of angina. After bypass surgery 71% were completely angina free ($p<0.001$). Exercise time using a standardised protocol increased from 296.2 ± 87 seconds prior to surgery to 357 ± 98 seconds after surgery ($p<0.001$).

There was only minor variation in rest LVEF: LVEF at baseline was 32% (±10%). This rose to 34% (±11%) at the early follow up study ($p=0.02$). However by late follow up LVEF had returned to 33% (p=n.s.d. for change from

baseline). In contrast there was a sharp fall in RVEF: RVEF was 33% (±8%) at baseline; by early follow up RVEF had fallen to 27% (±7%), $p<0.001$. There was no recovery in RVEF at late follow up, 26% (± 7%), $p<0.001$ for change from baseline. This fall in RVEF was not related to the preoperative LVEF, total bypass time, total cross clamp time, or grafting of the right coronary artery.

The study confirmed major deterioration in septal function following coronary bypass surgery, previously detailed by other authors. There was also a minor deterioration in anterior and inferior regional function. However, posterolateral regional wall motion improved following CABG. Only 1 of the 25 (4%) septal territories that had impaired regional wall motion demonstrated improved function at early follow up. In comparison, 14 of the 20 (70%) posterolateral territories that had impaired regional wall motion at baseline demonstrated improved function at early follow up ($p<0.001$).

The total exercise myocardial perfusion score derived from the thallium scintigrams improved following CABG. The improved perfusion was most noted in the inferior and posteroseptal regions. There was no change in the mean perfusion score in the anterior, posterolateral and septal territories.

Rest redistribution imaging did identify patients that demonstrated an increased LVEF at early follow up. In the group of patients who demonstrated a reversible defect from rest to redistribution, LVEF rose from 32% (± 13%) to 36% (±13%) at early follow up, $p=0.004$. However at late follow up this was not sustained and LVEF fell back to (32%), $p<0.01$ for change from early follow up. In contrast amongst those who did not demonstrate reversibility from the rest to redistribution image there was no change in LVEF; at baseline LVEF was 33% (±10%), at early follow up 33% (±11%) and at late follow up 33% (±12%).

Similarly, those patients who demonstrated improvement in regional wall motion with dobutamine also demonstrated an initial rise in LVEF at early follow up with a subsequent return to baseline values. In this group LVEF was 27% (±8%)

at baseline and 30% (±10%) at early follow up ($p<0.01$). By late follow up LVEF had fallen back to 28% (±13%), $p<=0.04$).

Coronary bypass surgery has little effect on left ventricular ejection fraction. Right ventricular ejection fraction falls sharply, and the fall is sustained at least nine months after the operation. Septal regional function deteriorates after bypass surgery, while posterolateral function seems to improve. Global myocardial perfusion indices improve following CABG, particularly in the inferior and posteroseptal regions. Both rest redistribution thallium scintigraphy and low dose dobutamine radionuclide ventriculography can identify a group of patients whose LVEF improves 6 weeks after operation. However this improvement is not sustained, and by nine months after operation LVEF returns to baseline values.

	Description	Page
Figure 20	Plot of change in RVEF from baseline to late follow up against bypass time	96
Figure 21	Plot of change in RVEF from baseline to late follow up against LVEF before operation	97
Figure 22	Change in LVEF for those patients with poor pre-operative LV function	98
Figure 23	Change in LVEF for those patients showing an initial 5% or more improvement in ejection fraction	99
Figure 24	Change in LVEF for those patients showing a 5% or more improvement in ejection fraction at late follow up	100
CHAPTER 6		
Figure 25	Septal territory wall motion scores at baseline, early and late follow up	132
Figure 26	Posterolateral territory wall motion scores at baseline, early and late follow up	133
Figure 27	Radionuclide ventriculograms from a patient who demonstrated improved function in the posterolateral wall motion and impaired function in the septum after coronary surgery	134
CHAPTER 7		
Figure 28	Change in exercise myocardial perfusion scores from baseline to late follow up	160

	Description	Page
Figure 29	Example of a patient whose exercise thallium scan showed a large inferoposterior defect at baseline, but whose exercise thallium image was normal at late follow up	161
Figure 30	Change in rest perfusion scores from baseline to late follow up	162
Figure 31	Reversible territories at baseline: Exercise perfusion scores at baseline and late follow up	163
CHAPTER 8		
Figure 32	Example of a patient who shows an anterior perfusion defect on rest image, which improves on the redistribution of rest image	191
Figure 33	Change in LVEF in individuals demonstrating evidence of reversibility from rest to redistribution at baseline examination	192
Figure 34	Change in LVEF in individuals who did not demonstrate evidence of reversibility from rest to redistribution at baseline examination	193
APPENDIX 2		
Figure 35	Kappa values by segment for rest perfusion scans	238
Figure 36	Kappa values by segment for exercise perfusion scans	239
Figure 37	Kappa values by segment for blood pool images	240

Chapter 1

Introduction

The aim of this thesis is to investigate the effect of coronary bypass surgery on myocardial perfusion and function, primarily using radionuclide techniques. The study was conducted between August 1994 and July 1996 in the Department of Nuclear Cardiology, Glasgow Royal Infirmary.

In this study, I have concentrated on the clinically relevant effects of bypass surgery on myocardial perfusion and function i.e. the presence or absence of ischaemia following bypass surgery, the effect on ventricular function, and the prediction of improvement in ventricular function. I used non-invasive techniques to assess the effect of bypass surgery in order that the patients, who were largely asymptomatic after bypass surgery, were not subjected to potentially hazardous invasive investigations.

The layout of the thesis is as follows. Chapter 2 is an historical review of the development of coronary bypass surgery, and the effect of bypass surgery on symptoms and prognosis. Since coronary grafts must be patent to provide flow, the published literature on patency rates of coronary grafts will also be explored. A brief history of the assessment of myocardial perfusion and function by radionuclide techniques follows. This will be expanded in the subsequent, relevant, chapters. Finally, Chapter 2 also includes a brief description of the phenomenon of myocardial hibernation which is expanded upon in Chapters 8 and 9.

Chapter 3 describes the materials and methods used during the study. The patient population is described, and the study protocol outlined. The imaging methods used are described and the methods of image analysis delineated. The operations performed on the patients are enumerated, and the surgical technique described.

By five years the survival rate in the medically treated group (± 95% confidence interval) was 83.1% (± 3.9), significantly worse than the 92.4% (± 2.7) survival in the surgically treated group ($p=0.0001$). Despite a higher mortality between five and twelve years in the surgically treated group, the overall mortality figures still showed a slight benefit of surgical treatment over medical therapy at 12 years. The survival rate in the medically treated group was 66.7% (± 5.3) at 12 years versus 70.6% (± 5.8) in the surgical group ($p=0.04$). Thus, these results confirm that as time passes, the relative mortality benefit of surgical therapy diminishes.

However, when a lesion in the proximal segment of the LAD was found on angiography as a component of either two vessel or three vessel disease, it was the outstanding predictor of both a poor prognosis and improved outcome with early surgical treatment as compared with medical therapy.

Patients with three vessel disease had a significant improvement in survival with surgical therapy. At five years the survival rate in the medically treated group with three vessel disease was 82% (± 5.6) versus 94% (± 3.2) ($p=0.0002$); At ten years the survival rate was 68% (± 6.8) in the medically treated group compared to 78% (± 5.6) in the surgically treated group ($p=0.01$). The number of patients with left main coronary disease was small and the difference in mortality between the surgically and medically treated groups did not attain statistical significance.

The difference in favour of surgery was of borderline significance in patients with two vessel disease ($p=0.045$ at 5 years), unless the proximal segment of the LAD was involved in which case survival was significantly better with surgery $p=0.0055$ at 5 years, $p=0.013$ at eight years.

The Coronary Artery Surgery Study (CASS) (12) recruited patients between August 1975 and May 1979 from a registry of all patients undergoing coronary

Although 95% were angina free at 1 year, 83% were angina free at 5 years and just 63% at ten years. Angina was more likely to recur in women, patients with hyperlipidaemia or hypertension, and patients who had more severe symptoms prior to CABG. Recurrence of chest pain occurs because of progression of the disease within the native coronary vessels, and atheromatous changes within saphenous vein grafts as well as acute or chronic graft closure.

Coronary artery bypass grafting does offer long term freedom from symptoms in a proportion of patients. Lawrie et al (22) reported that in 1698 patients operated upon between 1968 and 1975, 63% were angina free 20 years after operation.

Finally, the use of the left internal mammary artery confers a long term symptomatic benefit to patients undergoing coronary bypass grafting. Acinapura et al (23) reported on 5125 patients operated upon between January 1978 and December 1990. Recurrent angina in this group occurred in only 15% of the patients at 13 years compared to 31% of the 2345 patients operated upon during the same time period in the same institution, but who only had saphenous vein grafts. This is almost certainly due to the much better patency rates of the left internal mammary artery, as discussed below.

Coronary bypass graft patency rates

There is a steep attrition rate of coronary artery saphenous vein grafts in the first year after operation (24-26) although the rate of graft closure slows down subsequently. Some of the first work in this field was published by Lawrie et al in 1976 (24). This was not a systematic study of vein grafts inserted, but was a report of the patency rates in patients who were restudied by coronary angiography at various times after CABG. Thus there may be some bias in the results toward patients with recurrent angina. The vein graft patency rate was: 92% at 1 month; 91% at 1-3 months; 84% at 4-6 months; and 77% at 7-12 months.

LIMA grafts are patent at 10 years (30,31). Indeed, Loop et al (32) showed that the actuarial 10 year survival rates of patients who received internal mammary artery grafts was significantly higher than that of patients who received only saphenous vein grafts. The data excluded hospital (perioperative) deaths. Surprisingly, the benefit was greatest amongst those with three vessel disease, in whom the 10 year survival rate for those with an IMA graft was 82.6%, compared to 71.0% for those who only had saphenous vein grafts ($p<0.0001$). Those with only saphenous vein grafts had a 1.61 times greater risk than those who had IMA grafts.

Nevertheless, there has been some concern that the small size of the internal mammary artery, when compared to the saphenous vein conduits, may restrict flow at peak exercise and lead to exercise induced wall motion abnormalities in a small proportion of patients. Kawasuji et al (33) studied 52 patients each of whom had at least one coronary artery with at least a 70% narrowing. Each patient was studied at baseline and one month after operation. Twenty-seven patients had an IMA graft to the left anterior descending (LAD) coronary artery, and twenty-five patients had a saphenous vein graft to the LAD. In seven of the patients who had an IMA graft, the LIMA was noted to have a smaller diameter than the LAD. Left ventricular ejection fraction was calculated from radionuclide ventriculography. Regional ejection fraction was calculated in three separate areas; one anteroseptal, one apical and one inferolateral. Although global exercise ejection fraction increased in both groups postoperatively, six of the patients who had LIMA grafts had exercise induced anteroseptal regional wall motion abnormalities, suggesting ischaemia in the LAD territory. In contrast, none of the patients who had saphenous vein grafts to the LAD had regional wall motion abnormalities on exercise ($p<0.05$).

The same group reported on a study of 100 patients in 1993 (34). Again, they used exercise radionuclide ventriculography as an index of myocardial velocity had dropped, the mean vessel diameter had increased, and flow reserve was comparable to that of the saphenous vein grafts.

While it should be noted that this is a very small study at each time period with poorly matched controls (the patients who had saphenous vein grafts were, on average, 10 years older than those who had LIMA grafts.), it does suggest that the LIMA tends to remodel in response to the increased flow requirements following CABG. Hence while the LIMA initially may be too small to allow adequate blood supply to the LAD at peak exercise, with time flow improves resulting in adequate perfusion even at peak exercise.

The assessment of ventricular function

1. Assessment of left ventricular function

A variety of methods have been developed which measure left ventricular function. Echocardiography, contrast ventriculography at the time of cardiac catheterisation, and equilibrium radionuclide ventriculography are all widely used for this purpose while first pass radionuclide ventriculography, and magnetic resonance imaging (MRI) are much less frequently employed in the UK. The design of this study required a technique that was accurate and reproducible, and also able to detect relatively small changes in left ventricular function. Additionally the technique had to allow left ventricular segmental function to be analysed. Furthermore, I wished to make a comparison between regional wall motion and myocardial perfusion. Therefore it was essential to employ techniques that would easily allow the identification of the same myocardial segments on the two studies.

Therefore radionuclide ventriculography, in 2 projections, was chosen as the most suitable technique to assess LV function. This technique has very good inter and intra observer variability (less than 2%) and the inter-study variability is less than 5% (36,37). This is far superior to echocardiography where the ejection fraction can vary by up to 15% in the same patient when measured by different observers, although the normal interobserver variability for this technique is of the order of 11% (38).

Ray et al (39) in a study of 99 patients, 40 of whom were studied in our hospital, found that the standard deviation of repeated measurements of LVEF by echocardiography was 3.4%. In contrast, the repeatability of LVEF measurements by radionuclide ventriculography in these patients was 1.9%.

2. Assessment of right ventricular function

Radionuclide ventriculography has the added advantage that it allows quantification of right ventricular function as well as left ventricular function. The crude geometric methods used in echocardiography to assess LV function cannot be applied to the right ventricle because of chamber size shape and position. A variety of other techniques have been attempted (40) but have suffered similar problems to the measurement of left ventricular function.

Nuclear techniques, however, offer highly reproducible measurements of RV function (41-44) without significant limitation by these factors. Of these techniques gated equilibrium radionuclide ventriculography (41,42) and first pass radionuclide ventriculography (43,44) have been applied. While there is a good correlation between both methods for the measurement of RV function (44), more importantly, both techniques are characterised by little interobserver variability and good reproducibility. These techniques are therefore ideally suited to serial assessment of both right and left ventricular function in individual patients.

The assessment of myocardial perfusion

Similar to the assessment of myocardial function, there are several ways to assess myocardial perfusion. The most widely practised are exercise testing, coronary angiography and radionuclide myocardial perfusion imaging.

The techniques used to identify hibernating myocardium have now evolved through various stages to the three techniques available today:

1) Thallium myocardial perfusion imaging;
2) PET myocardial perfusion imaging;
3) Low dose dobutamine echocardiography.

Thallium myocardial perfusion imaging to identify hibernating myocardium

A more detailed review of the literature on this subject is to be found in Chapter 8. In summary, there are three methods which are commonly used to identify hibernating myocardium with thallium imaging:

1) Rest-redistribution imaging (74);
2) Reinjection thallium imaging (75);
3) Late (24hr) redistribution imaging (76).

Rest redistribution imaging (74) involves an injection of thallium at rest with imaging at baseline and repeated 3-4 hours later. Segments that show improvement from rest to redistribution image are said to be viable, possibly representing hibernating myocardium.

Reinjection thallium imaging (75) requires three images to be acquired: Peak exercise; a redistribution image 3 – 4 hours after the first and finally an image after a further dose of thallium is given at the completion of the redistribution images. Finally late redistribution imaging (76) uses a third set of images taken 24 hours after the exercise images and therefore requires the patient to attend the nuclear cardiology department on a second day.

Positron emission tomography (PET) myocardial perfusion imaging to identify areas of hibernating myocardium.

Positron Emission Tomography (PET) is a technique that utilises the high energy photons produced from the annihilation of an electron and a positron. The two photons produced have a high energy at 511keV, and their vector is exactly 180 degrees apart, allowing extremely good spatial resolution with coincidence detection. PET imaging using 18FDG glucose (77-79) is regarded by some as the optimal method of detecting hibernating myocardium. The technique depends on the ability to demonstrate metabolic activity within cardiac myocytes (detected by uptake of glucose into myocardial cells) where there is a severe impairment of coronary flow often detected by thallium myocardial perfusion imaging. However the technique is limited by:

1) The expense of the imaging equipment and tracers;
2) Proximity of the centre to a cyclotron. (The radioactive tracer used has to be delivered to the centre within 24 hours of production.)
3) The lack of PET imaging equipment in general use in the UK. At the time of writing there was only one clinically used PET scanner in Scotland.

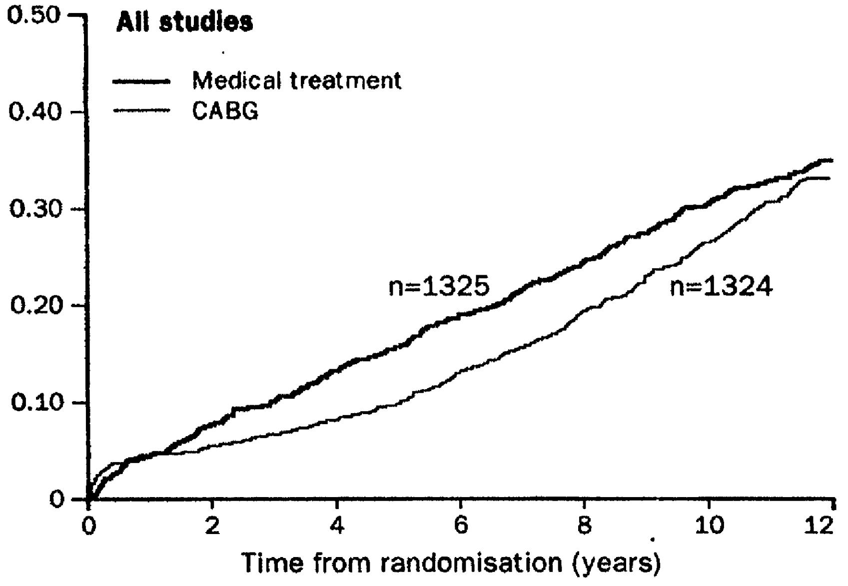
Low dose dobutamine echocardiography to detect myocardial hibernation.

A more detailed review of the literature on this subject is to be found in Chapter 9. This method has been developed from the observation that low dose catecholamine infusion during angiographic ventriculography (80) can cause segmental function to improve. A variety of studies using echocardiography as the imaging modality have been published (81-85). During the infusion of dobutamine, usually at a dose between 5μg/kg/min and 10μg/kg/min any segment that was previously akinetic that improves represents an area of hibernating myocardium. However echocardiography is a notoriously operator dependent technique (38), and up to 30% of patients may not be suitable for this method because of inadequate echocardiographic imaging.

SUMMARY

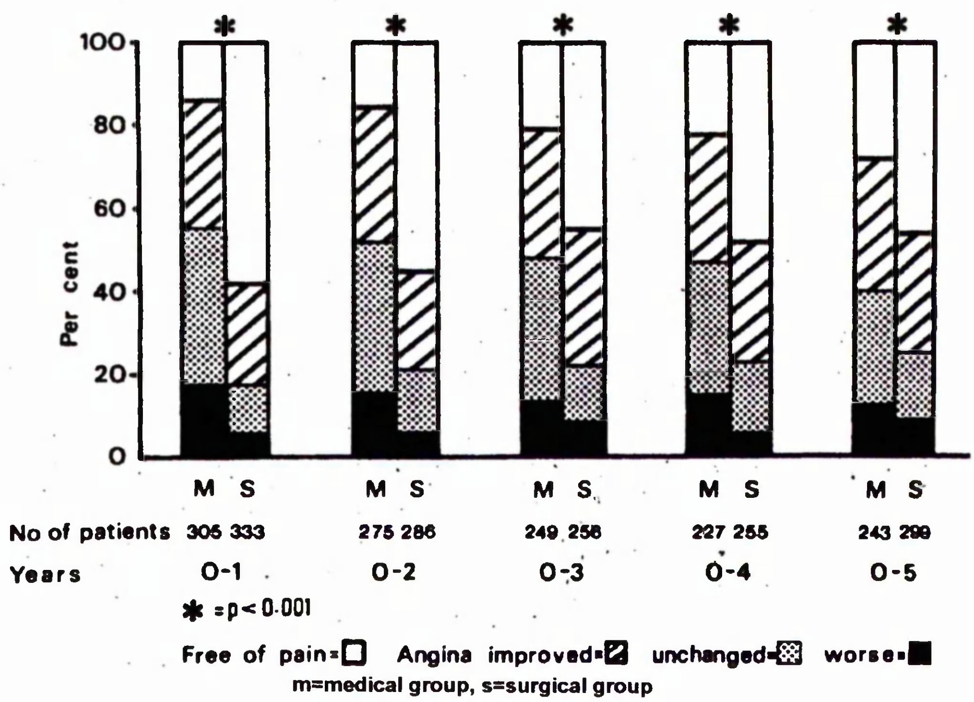
Coronary bypass surgery started in 1967. There has been a major increase in the number of cardiac surgical procedures since then. Coronary bypass surgery is extremely effective in relieving symptoms of ischaemic heart disease, and in some categories of patients in improving prognosis. There are many techniques used to measure left ventricular function in clinical practice, but the most reproducible and comprehensive in a research setting is radionuclide ventriculography. Myocardial perfusion scintigraphy can be used to assess the functional impact of coronary stenoses on blood supply to the myocardium. It may also be used to detect hibernating myocardium. Dobutamine echocardiography to detect improvements in regional wall motion is a technique also used to assess potential areas of myocardial hibernation.

Figure 1



Mortality curves for population in metanalysis by Yusuf et al (15)

Figure 3



Changes in angina pectoris from time of randomisation (in European Coronary Surgery Study (17))

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Chapter 3

Materials and Methods

INTRODUCTION

This chapter provides a detailed breakdown of the methods used during the entire study. In each succeeding chapter, the methods relevant to that chapter will be further described, but the whole study is delineated here for reference.

Section 1 will describe the study recruitment; Section 2 the study protocol; Section 3 the imaging techniques used; and Section 4 the surgical techniques used. The statistical methods used are described in each chapter.

SECTION 1

STUDY RECRUITMENT

The study population consisted of 114 patients who had coronary artery bypass grafting performed by one of three experienced consultant surgeons in Glasgow Royal Infirmary between 1st August 1994 and 5th January 1996. There were 98 men and 16 women in the group; The mean age was 60.0 years (range 40-75). Full details of the medical history and clinical status of the patients is given in Chapter 4.

As each patient was timetabled for surgery they were written to, and asked if they would consider taking part in the study. This was followed up by a telephone call and, if agreeable, the patients were invited up for the first of the baseline assessments. Less than 10% of the patients invited to take part in the study refused to do so.

At the first visit a full explanation of the study was given, and the patients were asked to complete the consent form approved by the Glasgow Royal Infirmary Research Ethics Committee. During this attendance, a full clinical history was taken, and the patient underwent a routine clinical examination. A form used to independent observers using a ten segment model for the LV and a three segment model for the RV (Figure 10, page 57).

Wall motion was reported on the following scale:

1) Normal;

2) Mildly hypokinetic;

3) Severely hypokinetic;

4) Akinetic;

5) Aneurysmal.

Any disagreements between the two observers were recorded and resolved by consensus. This scoring system is identical to that used in other studies (6,7). An analysis of the interobserver variability can be found in Appendix 2.

For assessment of regional wall motion the segments were grouped as per Figure 11 (page 58) into Septal, Anterior, Lateral and Inferior "territories" corresponding to the areas of supply of the major epicardial coronary arteries. The wall motion scores for each of these "territories" were compared at baseline, six to twelve weeks after the operation, and nine moths after operation. A territory was considered infarcted if the territorial wall motion score was greater than four for the septum and anterior walls and greater than six in the inferior and lateral walls. Significant improvement was said to occur if the wall motion score improved by two or more points after surgery. Significant deterioration was said to occur if the wall motion score increased by two points.

The territorial scores were produced for three reasons:

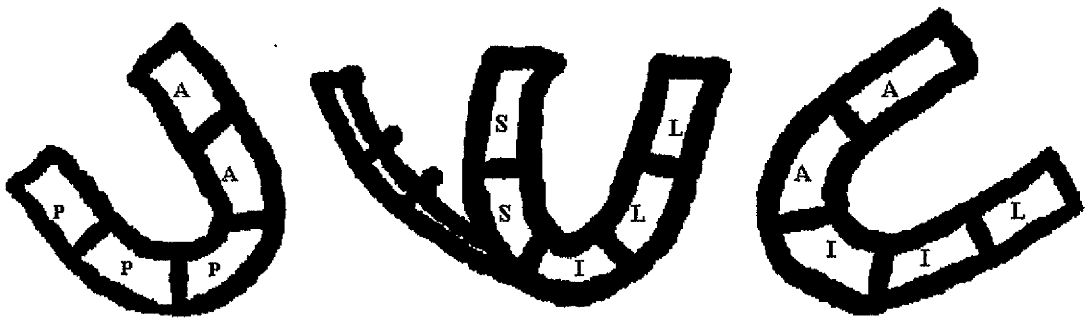
1. To minimise any error produced by minor misalignment of the camera at baseline, early and late follow up;
2. To make the segments broadly similar to those used in other studies eg Brundage et al (8)
3. To facilitate comparison with the perfusion studies.

Figure 5

Anterior 40° LAO 70° LAO

Fifteen segment model used for reporting thallium scans in anterior, 40 degree LAO and 70 degree LAO views

Figure 8



Anterior 40 LAO 70 LAO

P=Posteroseptal A=Anterior S=Septum I=Inferior L=Posterolateral

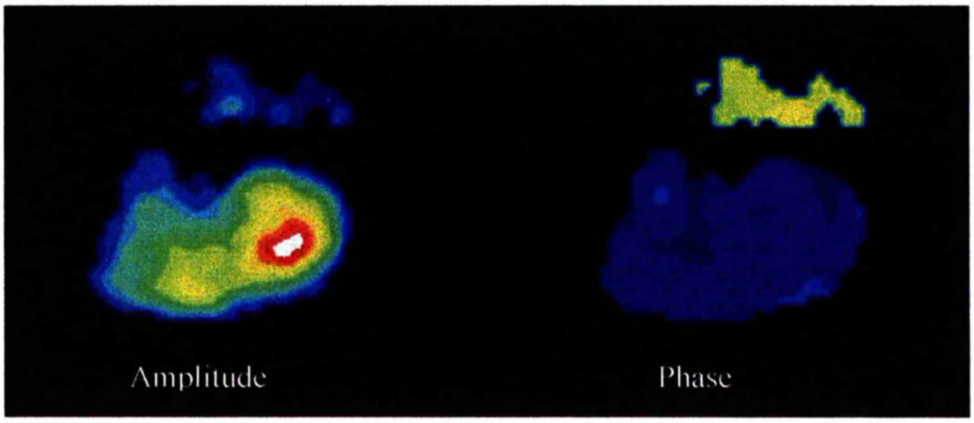
Schematic diagram showing segments used to produce "territorial" scores for thallium scans

Figure 10

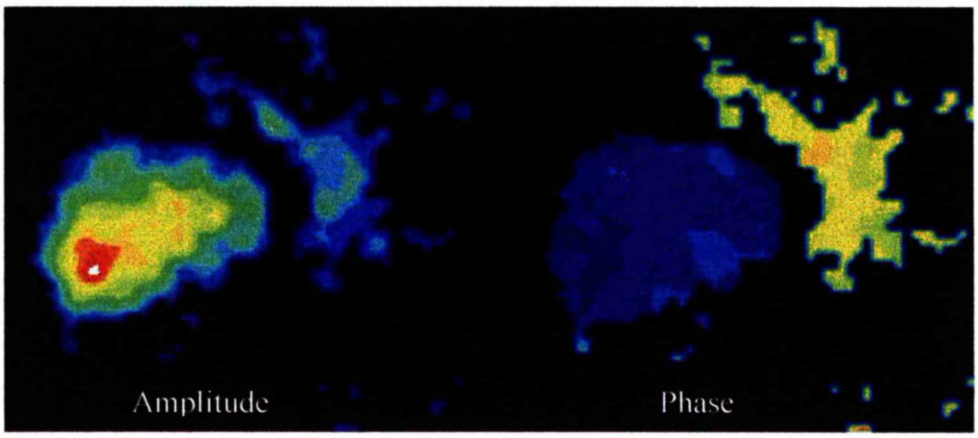
40° LAO 70° LAO

Segmental model used for the reporting of the blood pool ventriculograms

Figure 12



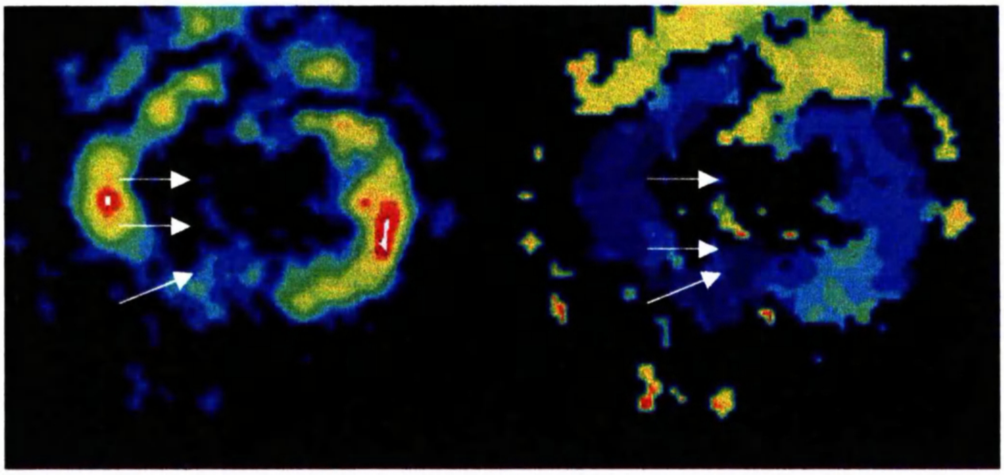
A



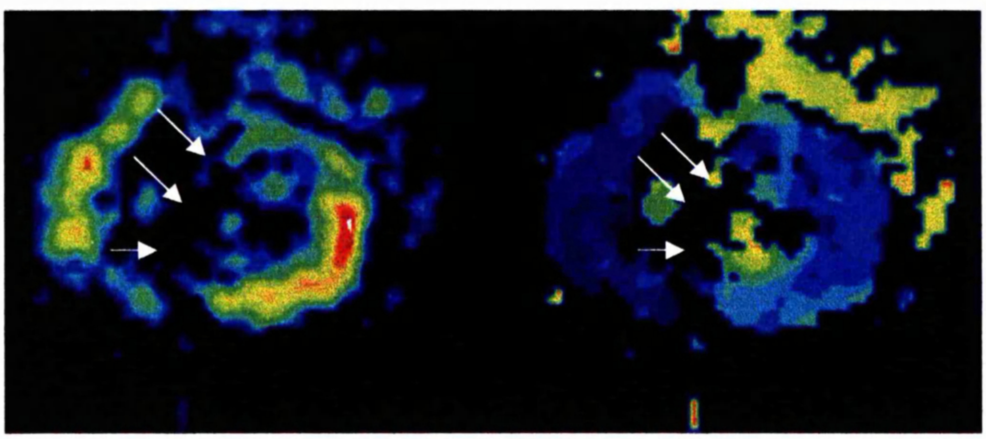
B

Amplitude and phase images showing normal regional wall motion in the 40° LAO projection (A) and 70° LAO (B) projections

Figure 13



A



B

Amplitude and phase images showing a very large anteroseptal wall motion abnormality (arrowed) in the 40° LAO projection (A) and 70° LAO (B) projections

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Chapter 4

Symptomatic Status of the Patients

INTRODUCTION

This chapter describes the effect of coronary bypass grafting on the symptomatic state of the study population. Although a considerable amount of data has already been published in this area, the importance of this chapter is to show that the operations performed during the period of the study were as successful in terms of symptomatic outcome as operations performed in other centres.

HISTORICAL REVIEW

The published data on the effect of coronary bypass grafting on symptoms have been extensively detailed in Chapter 2. In brief, symptomatic improvement in a large scale trial was first reported by Hultgren et al (1) reporting on behalf of the Veterans Administration Co-operative Study Group. In this study 78% of the patients who underwent coronary bypass surgery were angina free at one year, in contrast to the 38% of the medically treated group.

The European Coronary Surgery Study (2) confirmed this finding of improvement in symptoms but also offered objective measurements with improvement in the rate pressure product on the exercise test, improvement in exercise time and peak heart rate achieved. In the CASS study (3) the mean exercise time increased by 1.5 minutes.

Patients do develop recurrent angina but 63% of the survivors are angina free 10-20 years after operation (4,5). Finally, the number of patients angina free at long term follow up can be increased by the use of the left internal mammary artery (6). In the study by Acinapura et al, twice as many patients who had LIMA grafting were painfree after 13 years.

METHODS

Each patient was assessed by questionnaire (see appendix 1) administered by a physician, at the time of the attendance for baseline investigations, and this was repeated during the attendance for the late follow up study. No assessment of symptomatic state was made at the early follow up study.

The questionnaire asked detailed questions regarding the presence of angina, exercise tolerance, breathlessness, ankle swelling, orthopnoea, medications taken, previous history, and cardiac risk factors (smoking, hypercholesterolaemia, family history, hypertension and diabetes). The questionnaire was followed by a simple cardiovascular examination.

Additionally an attempt was made to assess quality of life using the question "How would you grade the quality of your life on a scale of one to ten, where ten out of ten is the best you have ever felt, and one out of ten is the worst you could ever imagine yourself feeling?"

Total exercise time, peak HR, and peak blood pressure were recorded at time of exercise tests. The peak "double product" was calculated by multiplying the peak HR and peak systolic blood pressure. Finally, the exercise tests were reported in a standard manner and ST segment shift of 2mm or more, 80ms after the "J" point were said to be significant.

Study population

In total, 113 patients were assessed at baseline (the assessment of one patient was omitted at baseline) and 100 patients (5 patients died, 8 withdrew from the study, and one was omitted) were assessed at late follow up.

Of the 113 patients assessed at baseline, ninety-seven were males and sixteen females. The mean age of the patients at baseline investigation was 60.1 years (range 41-75).

STATISTICAL ANALYSES

Where two proportions were measured Chi squared, χ^2, was used for analysis. When comparing quality of life scores, total exercise time and peak double product, the Wilcoxon matched pairs signed rank sum test was used.

RESULTS

Symptoms

Of the 113 patients, 111 (98%) suffered from angina prior to the operation. Two (2%) were angina free prior to operation. Fifty-six patients (50%) had angina every day, twenty-two patients (19%) 3-6 times week, twenty-one patients (19%) angina 1-3 times per week, five patients (4%) 1-3 times per month and 6 patients (5%) less than once a month. One patient was unable to say how frequent her angina was.

In contrast after operation only twenty-nine patients (29%) had angina. Three patients (3%) had angina every day, four (4%) had angina 3-6 times per week, nine (9%) had angina 1-3 times per week, five (5%) had angina 1-3 times per month, and 7 patients (7%) had angina less than once a month. For one patient the frequency of anginal attacks was not recorded. Comparing the proportions of patients with angina before and after operation; $\chi^2 = 112.875$, $p<0.001$. These data are illustrated in Figure 15, page 69.

Prior to operation five of the patients (4%) could walk less than 20 yards without stopping with angina, thirteen patients (12%) could walk 20-50 yards before stopping with angina, eighteen patients (16%) between 50 and 100 yards, thirty-five patients (31%) between 100 yards and half a mile, eighteen patients (16%) between a half and one mile, nineteen patients (17%) 1-5 miles and three patients (3%) more than 5 miles. After the operation, all the patients with angina could walk more than fifty yards on a good day. One (1%) patient was still only able to walk a maximum of 100 yards before stopping with angina. A further fourteen patients (14%) could walk a maximum of half a mile before stopping with angina, four patients (4%)

Additionally there was significant improvement in the Canadian Heart Association's grading for angina. After the operation there was a marked reduction in the use of anti-anginal drugs. Those who remained on anti-anginal medication tended to be on far fewer medications than they were prior the operation.

However, this study was not designed to identify whether coronary bypass grafting improved symptoms following CABG. In particular, patients were not randomised to either medical therapy or coronary bypass grafting, but were all operated upon and each served as his / her own control. It is also important not to dismiss a significant placebo effect of coronary bypass surgery although it would be unlikely that this would be seen 9 months after operation.

The information above therefore supports the work previously published (1-6) and confirms that the patients enjoyed a similar symptomatic improvement seen in other studies.

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others have suggested that the type of cardioplegic solution (18), and method of its infusion (19) may have an influence on the postoperative RV function. Another study has suggested a relationship between the surface temperature of the RV during bypass and subsequent RV dysfunction (20).

Rabinovitch et al (15) investigated 15 consecutive patients by first pass radionuclide ventriculography. Three of the fifteen patients had a fall in RVEF of >10% (range 13-18%). There were no obvious variables that predicted postoperative RV dysfunction but the study was not really powered to identify the factors that led to RV dysfunction.

Part of the reason for the lack of data on RV function post bypass surgery is the inherent difficulty in measuring RVEF. The crude geometrical methods applied to measure LV function using echocardiography cannot be applied to RV function because of the chamber size, shape, and position (21).

Nuclear techniques, however, offer highly reproducible measurements of RV function (22-25) without significant limitation by these factors. Of these techniques gated equilibrium radionuclide ventriculography (21-22) and first pass radionuclide ventriculography (24-25) have been applied. While there is a good correlation between both methods for the measurement of RV function (25), more importantly, both techniques are characterised by little inter observer variability and good reproducibility. The techniques are therefore ideally suited to serial assessment of both right and left ventricular function in individual patients.

The first pass technique ideally requires the use of a multi-crystal camera, otherwise the photon count rate will exceed the camera's maximal count rate response. However the use of a multi-crystal camera reduces resolution, and would not have allowed us to simultaneously assess regional wall motion. Hence, in this study, equilibrium radionuclide ventriculography was used to assess right ventricular function.

A further reason for the poor description of RV function post bypass is the much lesser importance ascribed to the RV as a pumping chamber by many authors. This is despite the fact it has been shown that RV dysfunction following a myocardial infarction is a poor prognostic sign (26).

The aim of this part of the study was therefore to assess, in an unselected group of patients presenting for routine CABG:

1) The effect of surgery on global LV function with particular reference to the frequency of significant change in LV function in individual patients;

2) The effect of coronary bypass surgery on global RV function.

MATERIALS AND METHODS

Of the original 114 patients, one patient died between enrolment and operation, four patients died in the perioperative period, incomplete data were obtained in eight patients, six withdrew consent, and there were technical difficulties with three patients, leaving ninety-two patients in whom a complete set of imaging data was obtained.

The mean age was 60 years (range 41-75). There were 83 males and 9 females in the study population. Ninety patients were on conventional anti-anginal therapy prior to operation. Fifty patients were on beta-blockers, 71 on nitrates, and 77 on calcium channel blockers. Beta-blockers were stopped prior to the first scan in all but six patients. Fifty-eight patients gave a history of prior myocardial infarction, 25 a history of hypertension and 10 were diabetic. Two patients had previous coronary bypass surgery, and eleven patients had previous coronary angioplasty.

Eighty-five patients had standard bypass surgery using saphenous vein grafts and the left internal mammary artery (non-complex surgery). Seven patients had additional mitral valve annuloplasty, aneurysmectomy, or aneurysmal plication (complex surgery). Systemic cooling to a mean of 28 (range 24-35) degrees Celsius was performed. Ice applied around the heart was used to achieve topical hypothermia. Antegrade cardioplegia was used for all patients.

Further details of the surgical procedures can be found in Chapter 3. Details of the imaging techniques, and method of calculation of ejection fraction can also be found in Chapter 3.

An assessment of the New York Heart Association classification (NYHA) for patients with heart disease was made for each patient at baseline and at late follow up.

STATISTICAL ANALYSIS

The mean (± S.D.) LVEF and RVEF were calculated, and the non parametric Wilcoxon matched pairs signed rank sum test was used to test for any differences between the results obtained at baseline, early follow up and late follow up. A p value of less than 0.05 was considered significant. The non-parametric Spearman Rank test was used to test for a relationship between various variables (cross clamp time, bypass time, preoperative LVEF) and post operative LVEF. The chi squared (χ^2) test was used to compare two subgroups of the population: those exhibiting significant deterioration (>5% fall) in RVEF and those without a significant fall in RVEF.

RESULTS

All scans were of adequate quality to allow accurate measurement of LVEF and RVEF. The cross clamp time was unknown in two patients and the bypass time unknown in three patients. One patient who had a single saphenous vein graft to the LAD had an operation without the institution of bypass. Excluding this patient, the mean bypass time was 84 minutes (range 21 - 173 minutes) and the mean cross clamp time was 44 minutes (range 21-173).

NYHA grading

Thirty-four of the 113 patients (31%) were in NYHA class 1 prior to operation, fifteen (13%) were in NYHA class 2, fifty-nine (52%) in NYHA class 3, and five (4%) in NYHA class 4. At late follow up, thirty-nine patients (39%) were in NYHA class 1. Thirty-eight (38%) were in NYHA class 2, twenty-two (22%) in NYHA class 3 and one patient remained in NYHA class 4. Hence, prior to operation 44% of patients were in NYHA class 1 or 2, compared to 77% after operation; $\chi^2 = 24.483$, $p<0.001$. These data are illustrated in Figure 18, page 94.

Changes in global ventricular function

The LV ejection fraction changed little for the population undergoing bypass. Values were as follows: prior to operation the LVEF (mean (SD)) was 32% ± 10%; at early follow up the LVEF had risen slightly to 34% ± 11% ($p=0.02$); and at late follow up the LVEF was 33% ± 12%. There was no difference between the values obtained at baseline and late follow up. The change in LVEF from baseline to early follow up, although attaining statistical significance, is unlikely to be of any clinical relevance. RVEF fell significantly for the population from a mean of 33% ± 8% at baseline to 27% ± 7% at early follow up ($p<0.001$) and 26% ± 7% nine months after the procedure ($p<0.001$ for change from baseline). These data are summarised in Table 2, page 90. An example of a patient who demonstrated a marked deterioration in RV function is illustrated in Figure 19, page 95.

To try to explain this systematic decrease in RVEF, a variety of factors were investigated. There was no association between the change in RV ejection fraction from baseline to late follow up and bypass time (Figure 20, page 96) ($r_s=0.097$), $p>0.05$. Similarly, there was also no association between the change in RVEF at late follow up and cross clamp time ($r_s=0.124$, $p>0.05$) or between improvement or deterioration in LV function. Initial changes in LV function may not be sustained.

Table 3

	Baseline	Early Follow Up	Late Follow Up	n
LVEF	32% (10)	34% (11)**	33% (12)	82
RVEF	32% (8)	28% (7)*	26% (8)*	82

** = change from baseline p<0.001*

*** = change from baseline p=0.001*

Table 4

	Baseline	Early Follow Up	Late Follow Up	n
LVEF	36% (9)	29% (9)**	35% (10)•	10
RVEF	37% (6)	24% (6)*	28% (5)*	10

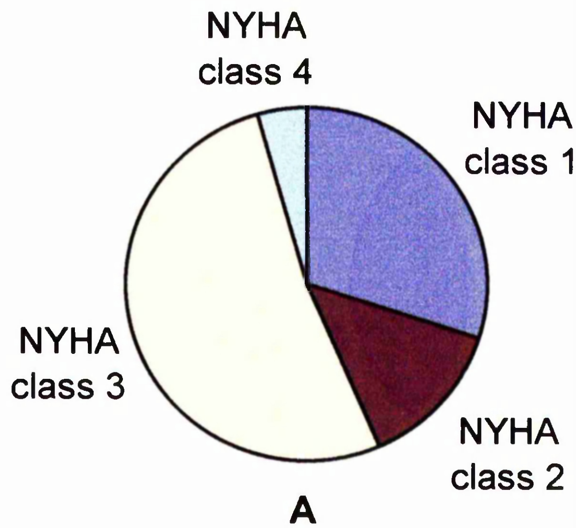
** = change from baseline p<0.01*

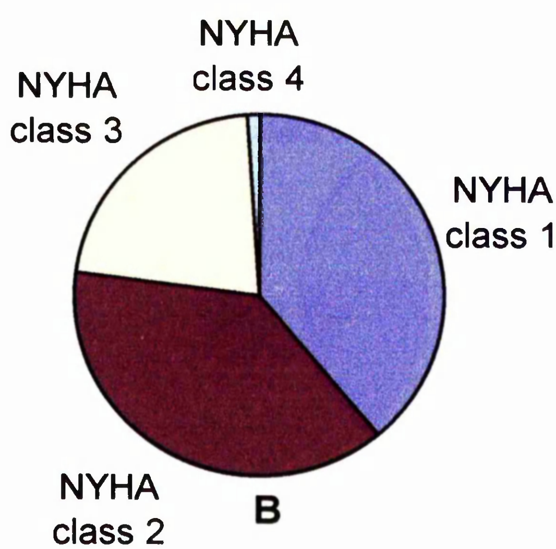
***= change from baseline p=0.01*

•= change from early follow up p<0.02

LVEF (mean (SD)) and RVEF (mean (SD)) at baseline, early follow up, and late follow up for those patients having a right coronary graft (Table 3) and those not having a right coronary graft (Table 4) at the time of operation

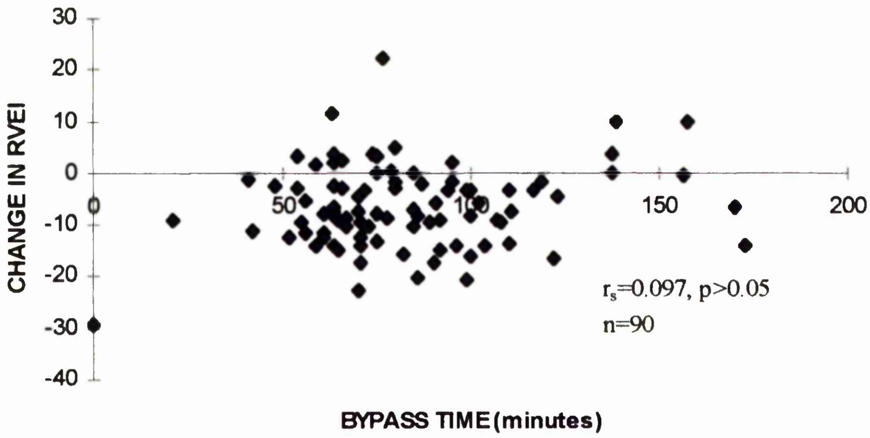
Figure 18





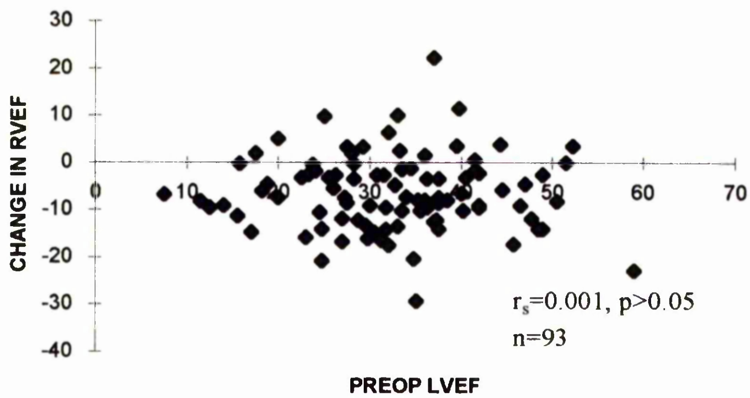
Pie charts showing proportion of patients in each NYHA class at baseline (A) and at late follow up (B)

Figure 20



Plot of change in RVEF from baseline to late follow up against bypass time

Figure 21



Plot of change in RVEF from baseline to late follow up against LVEF before operation

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This study was somewhat limited in its scope. Only 23 patients were studied and the follow up period varied from 2-6 months. The use of a single plane limits assessment, particularly of the anterior and inferior walls. Nevertheless, the study did give an indication of the complexity of changes in global and regional wall motion following CABG.

Jeppson et al (2) raised concerns over the methodology used at that time to measure regional ventricular function. This group studied 37 patients using quantitative contrast ventriculography before and (5-19 months, mean 7 months) after coronary bypass surgery. It is of note that these 37 patients were selected from a group of 216 patients, fulfilling the criteria of adequate preoperative and postoperative ventriculograms. Additionally, 11 patients who did not undergo surgery but who had repeated coronary and left ventricular angiography formed a control group. A further "normal" group of 32 patients who had coronary angiography for atypical chest pain was used to define abnormality on the ventriculograms. No patients in the control group had a significant change in clinical symptoms or sustained a myocardial infarction in the intervening period.

Using the midpoint of the long axis of the ventricle as a reference, radii were drawn to the epicardial surface. From this a "regional percentage shortening value" (RPS) was calculated for 11 segments. Any segment whose RPS was more than two standard deviations above or below the figures obtained from the normal patients were designated as hyperkinetic or hypokinetic respectively. All other segments were classified as normal.

In the control group, 14 out of 22 regions that were classified as hypokinetic in the first angiogram were classified as normal in the second angiogram. Additionally, 18 of the 92 regions classified as normal on the first angiogram were classified as abnormal on the second. However, overall analysis of the regional wall motion scores showed no change from the first to the second angiogram.

In contrast there was much greater variability in the regional wall motion scores in those who underwent coronary bypass surgery, and the change in regional wall motion scores was statistically significant. Of 107 hypokinetic segments, 50 remained unchanged, 57 became normal. Of 276 normal segments at baseline, 30 became hypokinetic, 234 remained normal, and 12 became hyperkinetic. Finally of 24 hyperkinetic segments 19 became normal and 5 remained hyperkinetic. Interestingly, most of the improvement in regional wall motion scores came in the anterior and inferior walls.

The authors concluded that there was limited but significant improvement in regional ventricular function in those undergoing coronary bypass surgery. However, they also concluded that the variability in the measurement of regional ventricular function limited its use in individual patients, and they suggested that such measurements are only applied to groups.

The methods used in this study involved the tracing of the ventricular cavity on a ventriculogram. The identification of the exact long axis of the ventricle is difficult and thus the technique is likely to be associated with a significant interobserver variability, contrasting greatly with radionuclide ventriculography.

Rubenson et al (3) used echocardiography to study 20 patients who underwent CABG. Each patient had a baseline echocardiogram on the day before operation and a repeat echocardiogram 5-14 days after operation. Sixteen patients returned for a further echocardiogram 21-86 days after the operation. Each echocardiogram was divided into 9 standard segments (4). A four point scale was used to assess wall motion: normal (Score =2), hypokinesis (Score=1), akinesis (Score=0), dyskinesis (Score=-1).

cardiopulmonary bypass; abnormal septal wall motion may occur as a consequence of or, conversely, may be the cause of right ventricular dysfunction.

Lindsay et al (12) examined 25 consecutive patients by radionuclide ventriculography before and 2-13 months after coronary bypass surgery. An inclusion criterion for the study was normal septal wall motion prior to surgery, although two patients had ECG evidence of previous anterior myocardial infarction. Two patients had evidence of a peri-operative myocardial infarction. A five segment model was used in the 40° LAO view which included two septal segments: one basal and the other apical. The other three segments consisted of one apical and two lateral segments. A five point scoring system was used to determine regional wall motion. Although septal wall motion was normal in all 25 patients pre-operatively, only three had normal wall motion postoperatively. Both apical and basal segments were said to be severely hypokinetic in 13 patients and akinetic or dyskinetic in 7 patients. Both septal segments were mildly hypokinetic in one patient and only the apical segment was hypokinetic in one patient. In 6 patients with a new septal wall motion abnormality who underwent exercise thallium imaging, all had normal septal perfusion. Thus, this study showed the ability of radionuclide ventriculography to detect new areas of regional wall motion abnormality after coronary bypass surgery.

Schoolman et al (13) examined 43 consecutive male patients who had coronary bypass surgery by first pass radionuclide ventriculography using a multi-crystal camera. In this study 38 of the 43 patients had normal or unchanged septal motion at follow up. In five patients there was a new wall motion abnormality and in four of these there was a significant change in the resting ECG. This result, suggesting a much lower rate of change in septal function, may be explained by the poor spatial resolution inherent in the imaging technique used. Multi-crystal cameras are optimised for high count rates, and are ideal for first pass imaging. However the spatial resolution is much poorer compared to conventional single crystal cameras.

Jacobson et al (14) examined 106 patients by first pass radionuclide ventriculography, although five were excluded because of perioperative myocardial infarction. Thus 101 patients were followed up 5-20 days after surgery. Using a regions of interest method, regional ejection fractions were calculated. The mean septal regional ejection fraction was unchanged, although 32% of the patients exhibited a fall in the proximal septal segment's regional ejection fraction. The apex and posterolateral wall segments all showed evidence of significant improvement in regional ejection fraction. The improvement was most commonly seen in the proximal posterolateral segment, then the distal posterolateral segment, and finally in the apical segment. Again this study suffers from the criticism that the poor spatial resolution of the technique used will limit the ability to detect relatively small changes in regional ejection fraction. In particular, in this study a change in regional ejection fraction of 6.25% was taken to be significant. Since the regions of interest have to be drawn twice, and the regions of interest made to correspond from one study to the next, it is highly doubtful that this change would lie outside the reproducibility error of the technique, a fact not addressed within the paper itself.

Okada et al (15) investigated a small group of men (n=16) 2-5 days before surgery and 1-2 days after surgery. Equilibrium radionuclide ventriculograms were obtained in all patients along with rest redistribution planar thallium images. In the pre-operative scans septal wall motion was normal in 14 and abnormal in 2 patients. In the post operative scans septal wall motion was abnormal in all 16 patients. A further radionuclide ventriculogram was performed in 12 patients imaged 2-26 months after surgery. In all of these patients septal wall motion was abnormal. Post-operative septal perfusion was normal in 11 of the 16 patients. This small study suggests that abnormal septal wall motion is not caused exclusively by septal ischaemia, and could even occur in patients who demonstrated improved thallium uptake in the septum postoperatively.

More recently, Metcalfe et al (16) examined 20 patients before and after bypass surgery using tomographic radionuclide ventriculography. For each patient, six transaxial slices were produced 16mm apart and reconstructed into a three dimensional matrix. Short axis images were produced from the 3 dimensional matrix. Images were acquired in frame mode, and normalised in 8 frames per cardiac cycle. A polar map of normal contraction was obtained by pooling the data obtained from 25 normal volunteers. This was compared to a polar map obtained from the patients and abnormality defined as being outwith 2 standard deviations of the mean pooled data. Ejection fraction was calculated by calculating the change in stroke count density within a left ventricular region of interest.

There was no change in overall LVEF. Of the 20 patients, 10 had normal phase pattern (i.e. normal contraction) prior to surgery, and only 1 of these patients developed a new phase abnormality after surgery. Amongst the 10 with abnormal phase at baseline, 5 showed significant improvement, 2 showed no change, and 3 deteriorated. Regional ejection fraction measurements showed 24 of the 80 segments to improve, 31 to deteriorate and 25 remained unchanged. Interestingly, there was marked improvement in the phase analysis suggesting retained septal function during systole, perhaps because imaging of the septum is less dependent on its position utilising this method. The authors conclude that septal dysfunction following CABG is probably artefactual and caused by the movement of the heart anteriorly and medially.

However, using the authors' own data it is clear that the septal ejection fraction fell by more than 5% in 12 patients, stayed the same in 5 patients and improved in 3 patients. Additionally, only 8 frames per cardiac cycle were used, the data were not acquired using listmode and this may significantly blunt the ability of the technique to detect wall motion abnormalities. Finally, the optimal technique for reconstruction of tomographic ventriculograms has not yet been identified in any centre, although it remains a promising technique for the future.

One of the most recent studies of septal function after coronary bypass surgery was reported by Chouraqui et al in 1997 (17). This group investigated a study population of 21 patients by equilibrium radionuclide ventriculography 1 week before and 1 week after cardiac surgery. During coronary bypass 9 patients had antegrade cardioplegia alone and 12 patients had combined antegrade and retrograde cardioplegia. However there was no significant difference in the frequency of abnormal septal wall motion between the two groups, suggesting that combined antegrade/retrograde cardioplegia does not protect the interventricular septum.

Myocardial hibernation

The subject of myocardial hibernation is dealt with in detail in Chapters 8 and 9. However, in brief, myocardial hibernation is said to occur when areas of myocardial tissue are so ischaemic, that although viability is preserved, function is not. Revascularisation, in the form of coronary artery bypass grafting or coronary angioplasty may restore flow and function and lead to improved LVEF, either globally or regionally. Myocardial segments containing significant quantities of hibernating myocardium should therefore be akinetic or severely hypokinetic at rest, but following successful revascularisation should show improved or even normal wall motion. Therefore identification of such segments is vital if we are to understand fully the effect of coronary bypass surgery on myocardial function.

Myocardial infarction complicating coronary bypass surgery

This subject has been dealt with in detail in Chapter 5. Coronary bypass surgery does not have exclusively beneficial effects on myocardial function. Myocardial infarction is said to occur as a complication of the operative procedure in about 10-14% of patients (18,19). New wall motion abnormalities may occur following CABG because of an increase in the ischaemic burden of any particular myocardial segment. This may occur because of competitive coronary flow, or because of worsening disease in the arteries subtending the myocardial segment.

Imaging modalities to identify regional left ventricular function

The relative merits of echocardiography and radionuclide ventriculography are discussed in detail in Chapter 2. Radionuclide ventriculography can be used to assess regional wall motion. Although the spatial resolution of radionuclide techniques is inferior to that of echocardiography, there are advantages to using this technique to assess regional wall motion. Echocardiography is a highly operator dependent technique, which is also seriously limited in a relatively high proportion of patients in whom it is not possible to gain adequate images. Additionally the precise alignment of the probe can have an effect on the assessment of regional ventricular function. It is however possible to gain adequate images from most patients using radionuclide ventriculography and the positioning of the gamma camera head does not require to be as precise as the positioning of the probe in echocardiography.

Radionuclide ventriculography has several other advantages. The most important of these is the ability to produce functional images from the raw data. The most commonly used of these images are:

1) the stroke volume image;

2) the paradox image;

3) the fourier amplitude image;

4) the fourier phase image.

The stroke volume image is produced by subtracting the end systolic image from the end diastolic image and the resultant image shows the total change in counts between end diastole and end systole. Thus, this image is a map of regional myocardial function. The paradox image is produced by subtracting the end diastolic image from the end systolic image, and therefore demonstrates areas that fill (e.g. the atria, aneurysms) during ventricular systole.

The raw data from the activity curves of the radionuclide ventriculograms can also be subjected to a fourier transformation to produce amplitude and phase images. The amplitude image is similar to the more crude stroke volume image. It produces a map of the changes counts over the cardiac cycle, and as such is a guide to the wall motion in any particular myocardial segment. The fourier phase image is a fourier transformation of the time data of each individual pixel. It therefore produces a map of the timing of contraction in each myocardial segment.

Electrical activity is conducted relatively slowly in a myocardial segment with large numbers of infarcted myocardial cells. Thus subsequent myocardial contraction is late. Depending on the number of viable myocardial cells left in an area of myocardial infarction, the fourier images may show 3 different patterns. If there are a large number of viable contracting cells present, then the fourier phase image will show a segment contracting late but wall motion may be partially preserved. If there are fewer contractile cells there may no motion in a segment and the phase and amplitude images will show a defect in that region. Finally if there are very few contractile cells within the segment the segment may become aneurysmal. This will cause the phase image to show the segment at or around 180 degrees out of phase with the rest of the ventricle, as peak activity within that area will occur during systole rather than diastole.

Hence septal territories, whether infarcted or not on the baseline evaluation, tend to show deterioration in function. In contrast postero-lateral territories tend to show improved function following bypass surgery.

Changes in patients with significantly depressed LV function

There were 34 patients whose LV ejection fraction was less than or equal to 30% in whom there was a complete set of data at baseline, early follow up and late follow up. The mean LVEF was 23% at baseline, 26% at early follow up, and 24% at late follow up.

The mean wall motion scores for each of the territories at baseline, early and late follow up are detailed in Table 10, page 130. A similar pattern is again observed as for whole patient population. Septal function deteriorates, with mean territory score rising from 5.1 (2-9) at baseline to 6.9 (3-10) at early follow up ($p<0.01$ for change from baseline) and 6.7 (3-10) at late follow up ($p<0.01$ for change from baseline). Similarly, there was a deterioration in anterior territory function: mean score at baseline 3.6 (2-7); at early follow up 4.5 (2-8) ($p<0.05$); and at late follow up 4.6 (2-8) ($p<0.01$). Again, there was an improvement in posterolateral function at early follow up: Mean posterolateral wall score fell from 6.0 (3-12) to 5.0 (3-10) at early follow up ($p<0.01$). However this was not sustained at late follow up: Mean posterolateral wall motion score was 5.6 (3-11), n.s.d. for change from baseline.

In the 34 patients with impaired preoperative LVEF, and in whom there was complete data, there were 68 territories (24 septal, 13 anterior, 19 inferior and 12 posterolateral) with impaired function at baseline. At late follow up only 13 (0 septal (0%), 1 anterior (8%), 5 inferior (26%), and 7 posterolateral (58%)) territories demonstrated significant improvement. Hence only 19% of all the infarcted territories demonstrated improved function following bypass surgery. These data are summarised in Table 5, page 131.

DISCUSSION

The significant change in mean total wall motion score from baseline to early and late follow up is quite surprising, and requires explanation. The most likely reason is the fact that we chose not to acquire an anterior view. While the anterior view can be very difficult to interpret for wall motion analysis because of the overlying right ventricle, omitting it does result in poorer visualisation of the most infero-posterior part of the interventricular septum and posterior wall of the LV. As we have shown the postero-lateral wall does tend to improve following coronary bypass surgery, and it is possible that had this view been included, there would have been no overall change in total wall motion scores.

A second possible reason is that there was no scope in the scoring system to allow for segments that became hyperdynamic after operation. It is certainly possible that some postero-lateral segments, classified as normal on the baseline studies showed even better function after operation, perhaps to compensate for other, hypokinetic areas. The result would be a higher total wall motion score than would be calculated if hyperdynamic areas were taken into account.

The present study confirms the reduction in septal wall motion previously reported both in echocardiographic (10,11) and radionuclide studies (12-17). However, there is considerable controversy in the literature regarding the importance of this finding. As has already been shown in chapter 5 there is no change in overall left ventricular function, which may lend credence to the view put forward by Metcalfe et al (16) that the reduction in septal wall motion is a product of a change in the motion of the heart in the post operative setting. However, even in Metcalfe's study using tomographic radionuclide ventriculography there was a reduction in septal ejection fraction in the majority of the patients. Other authors (9) have contended that septal function is preserved because there is preserved thickening of the septum visible on echocardiography, that rely on the identification of improvement in regional wall motion as an index of hibernating myocardium will be dominated by patients with improvement in posterolateral LV function. Despite this improvement in posterolateral function I have demonstrated that there is no change in global left ventricular function, as measured by the ejection fraction. This calls into question the clinical importance of changes in posterolateral regional function following CABG.

As stated above, these findings in this regard are no different from those in other studies. With this background it is clear that it is indefensible to use improvement in regional wall motion as being indicative of improvement in global myocardial function. Any recovery of function seen, particularly in the postero-lateral wall, may be a normal response to coronary bypass surgery, and not a reflection of, for instance, improved perfusion to a segment of hibernating myocardium. Thus in chapters 8 and 9, where hibernating myocardium is considered, improvement in LV function will be defined as improvement in left ventricular ejection fraction, not regional wall motion. This will set this study apart from many others in this field.

CONCLUSIONS

This study confirms that septal function deteriorates following coronary bypass surgery. The posterolateral wall tends to improve following coronary bypass grafting. These findings have major implications for the identification of hibernating myocardium, and studies that rely on assessment of regional ventricular function alone will be dominated by patients who manifest improvement in posterolateral regional function.

Table 8

Territory	Early follow up		Late follow up		Number of infarcted territories at baseline
	n (%)	χ^2	n (%)	χ^2	
Septal	1 (4%)	11.8*	0 (0%)	13.0*	25
Anterior	2 (17%)	1.18	1 (8%)	2.3	12
Inferior	6 (30%)	0.00	5 (25%)	0.01	20
Posterolateral	14 (70%)	21.0*	14 (70%)	27.2*	20

**=p<0.001 compared with other territories*

Territories with significant wall motion impairment at baseline showing significant improvement at early and late follow up

Table 9

Territory	Early follow up		Late follow up		Number of normal territories at baseline
	n (%)	χ^2	n (%)	χ^2	
Septal	45 (75%)	41.0*	40 (66%)	27.1*	60
Anterior	32 (44%)	0.800	32 (44%)	1.65	73
Inferior	20 (31%)	2.78	19 (29%)	2.60	65
Posterolateral	7 (11%)	29.9*	8 (12%)	23.6*	65

**=p<0.001 compared with other territories*

Territories with normal wall motion at baseline showing significant deterioration at early and late follow up

Table 10

	Baseline	Early follow up	Late follow up	n
Septum	5.1 (2-9)	6.9 (3-10)*	6.7 (3-10)*	34
Anterior	3.6 (2-7)	4.5 (2-8)**	4.6 (2-8)*	34
Inferior	7.3 (3-14)	7.5 (3-14)	8.5 (3-14)**•	34
Posterolateral	6.0 (3-12)	5.0 (3-10)*	5.6 (3-11)•	34

**= Change from baseline $p<0.01$*

***= Change from baseline $p<0.05$*

•= Change from early follow up $p<0.05$

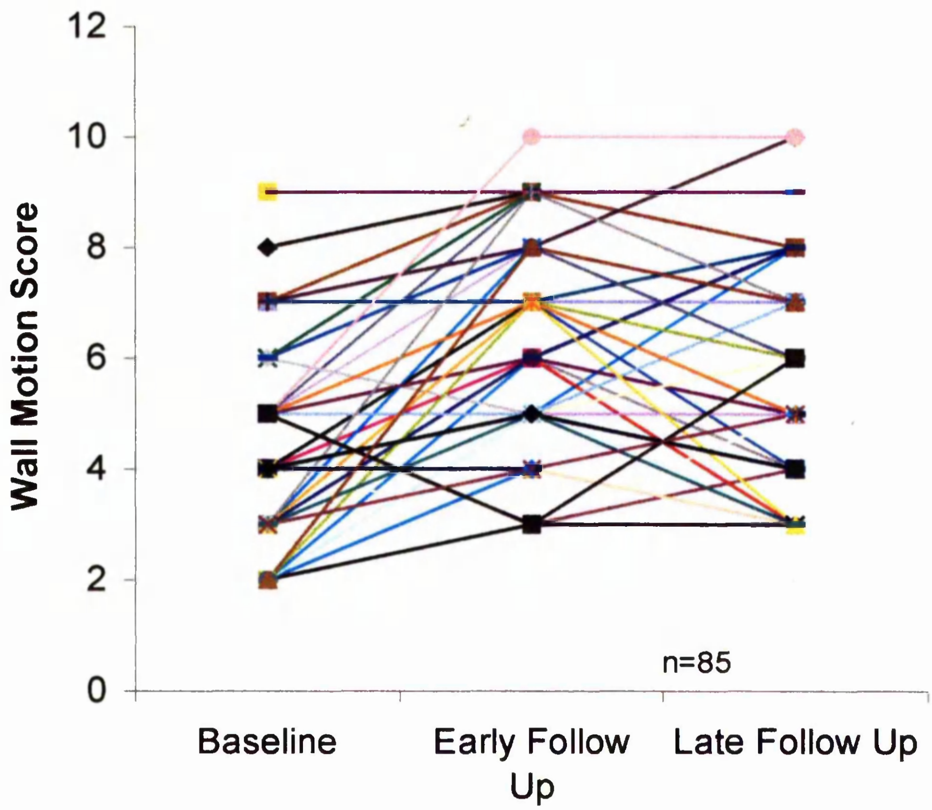
Mean territorial scores at baseline early and late follow up for the 34 patients with impaired LV function at baseline (i.e. LVEF<=30%)

Table 11

Territory	Late follow up	Number of infarcted territories at baseline
Septal	0 (0%)	24
Anterior	1 (8%)	13
Inferior	5 (26%)	19
Posterolateral	7 (58%)	12

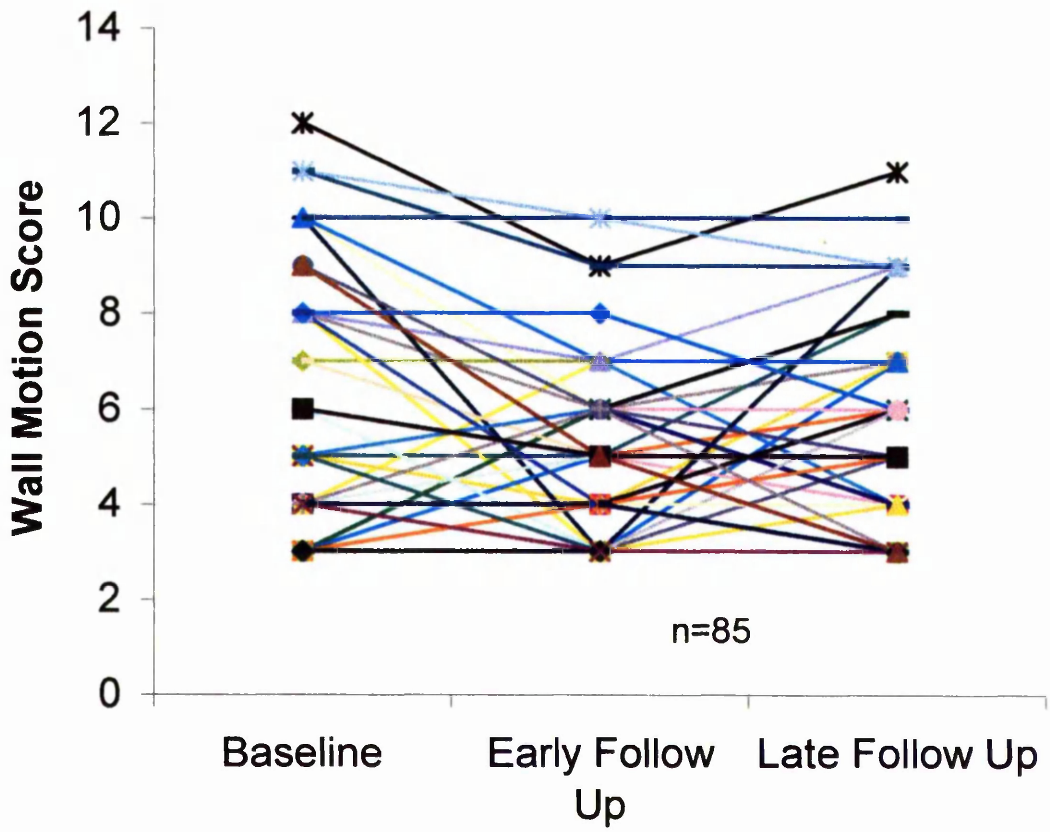
Territories that improved at late follow up in the 34 patients with significantly impaired LV function at baseline

Figure 25



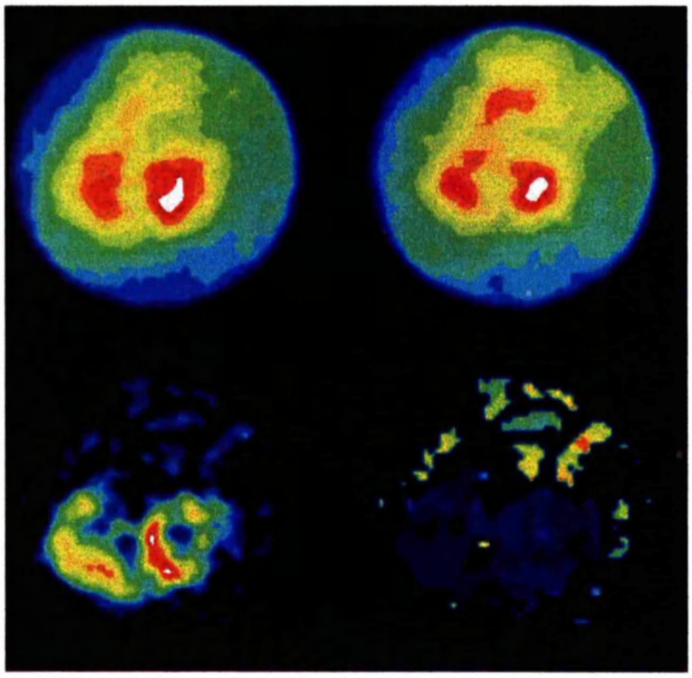
Septal territory wall motion scores at baseline, early and late follow up

Figure 26

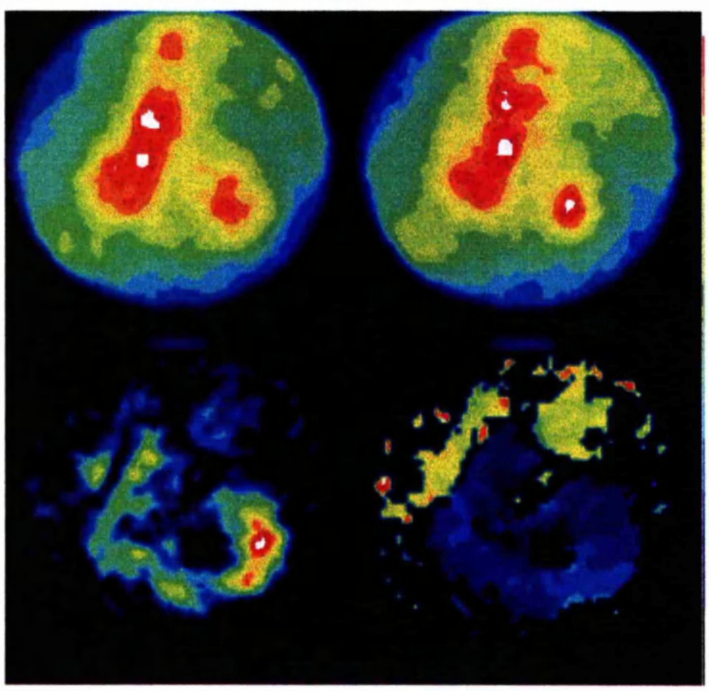


Posterolateral territory wall motion scores at baseline, early and late follow up

Figure 27



Baseline



Late Follow Up

Radionuclide ventriculograms from a patient who demonstrated improved function in the posterolateral wall motion and impaired function in the septum after coronary surgery

Chapter 7

Myocardial Perfusion Following CABG

INTRODUCTION

Several previous studies have examined the effect of coronary bypass grafting on myocardial perfusion following bypass surgery. While most have shown some improvement in perfusion, the extent of this improvement is more controversial. Additionally, some studies have suggested that myocardial perfusion imaging may be used to detect stenosed or occluded grafts, without the need for invasive imaging.

It would be reasonable to expect that myocardial perfusion images would improve following coronary bypass surgery. As detailed in Chapter 4, 98% of the patients in this study complained of angina prior to their operation. However, after bypass surgery only 29% complained of angina. Even amongst those with residual angina, most noted a significant improvement in their symptoms after coronary bypass surgery.

The nature of the patients operated upon has changed significantly in the thirty years that coronary bypass surgery has been widely practised. Patients who were previously thought to be inoperable because of widespread and diffuse coronary disease are now commonly accepted for surgery. As a result of improved anaesthetic and surgical techniques, patients who previously would not have been operated upon because of chest disease, poor left ventricular function or lack of venous conduits are now commonly having coronary bypass procedures. Finally, in the early days of coronary bypass surgery many patients were operated upon who had single vessel coronary disease. In current practice this is unusual, since most patients with single vessel disease and significant symptoms would be offered coronary angioplasty rather than elective surgery.

In the present study only 3 (3%) patients out of 112 whose operation was completed, had single vessel coronary grafts. Thus in this study single vessel coronary bypass grafting is a comparatively rare operation, and this would be expected to have an effect on the perfusion images. It is much less likely that complete revascularisation is achievable in patients with widespread, diffuse coronary disease because there may be stenoses proximal and distal to the graft insertion site, or there may be disease in coronary arteries too small to have bypass grafts attached.

HISTORICAL REVIEW

Studies of myocardial perfusion before and after surgery

The earliest work using myocardial perfusion scintigraphy for the evaluation of patients following bypass surgery was performed in the early 1970's using potassium–43 (1) and rubidium-81 (2). However it was only with the advent of thallium for myocardial perfusion imaging that use of this technique following bypass surgery became more widespread.

Ritchie et al (3) studied twenty patients before and after coronary bypass surgery. At that time it was their routine to perform pre and post operative coronary angiography and thallium imaging. However of the 20 patients who were recruited into this study 9 had only resting pre-operative thallium scans presumably because they had unstable symptoms; the other 11 patients had rest and exercise scans. Although all of the patients had a significant symptomatic improvement, four (20%) had remaining angina.

Ten of the eleven pre-operative exercise scans were abnormal. In five of these patients (50%) the defects returned to normal in the post operative scans. Amongst the remaining five, three (30%) showed improved perfusion (i.e. increased thallium uptake) in a defect area but did not return to normal, one (10%) showed no change and one (10%) showed a major deterioration in exercise myocardial perfusion. The patient with a normal exercise thallium scan before operation, had a normal scan after operation.

Amongst the nine patients with only pre-operative rest scans, four (44%) had normal rest thallium images. Two patients whose scans were normal remained normal. Three patients (33%), including the other two patients with normal pre-operative scans showed deterioration in scan appearances; two patients (22%) showed improved resting scans; and two patients (22%) with defects on resting scans showed no change. The conclusion from this early study (published in 1977) was that exercise perfusion images tend to improve but many patients do not show normalisation of thallium images. The effect on rest images is less predictable and a substantial proportion of these patients demonstrated deterioration in rest thallium images.

Verani et al (4) also published one of the early studies using thallium to examine the effect of coronary bypass grafting on myocardial perfusion. There were 23 patients in the study group of whom 14 (61%) had triple vessel disease, and nine (39%) had double vessel disease. Only exercise thallium scintigraphy was performed and there was no attempt to perform either resting or redistribution thallium imaging. Although there was an improvement in the perfusion in 19 patients (83%), only in nine (39%) patients did postoperative perfusion return to normal. There was a significant improvement in exercise tolerance and functional ability as measured by the New York Heart Association classification. The mean NYHA grade fell from 3.2 ± 0.1 to 1.2 ± 0.2, $p<0.005$. The authors concluded that failure of regional myocardial perfusion to improve does not preclude marked alleviation of angina and improved exercise tolerance.

Robinson et al (5) studied 36 patients by planar exercise thallium scintigraphy, using separate rest and exercise injections pre-operatively, and repeated four to six months post-operatively. Four patients (11%) had single vessel disease, eight

(22%) had double vessel disease and 24 (67%) had triple vessel disease. New resting thallium defects were found in eight patients after the bypass operation. Fifteen patients (42%) still had abnormal exercise thallium scans, although the majority of scans were improved after operation.

Eichstadt et al (6) reported on 34 patients studied before and 4 weeks – 8 months after bypass surgery. This study is somewhat biased by a very high recurrence rate of angina pectoris; ten of the thirty-four patients (29%) had recurrent angina at follow up. Therefore, it is not surprising that in only three patients (9%) did the thallium scan return to normal.

Hirzel et al (7) examined 54 consecutive patients undergoing coronary bypass surgery. Pre and post-operative exercise thallium scans were performed in each patient, of whom seven (13%) had single vessel disease, seventeen (31%) had two vessel coronary disease, and thirty (56%) had triple vessel disease. The mean follow up time was 24 (±10) weeks. Observers were not blinded to results of the pre-operative thallium images. In 31 patients (57%) the thallium scans returned to normal in the preoperative ischaemic regions; in 16 patients (30%) the images were unchanged and in 7 (13%) patients the images deteriorated. Amongst those patients whose thallium scans returned to normal the bypass graft patency rate at angiography was 81%, whilst in those whose scans remained unchanged the patency rate was 38% and in the group whose scans deteriorated the patency rate was 15%. The authors pointed out that "the interpretation of the postoperative scintigram is more difficult than that of the preoperative one because of the improvement of flow to previously ischaemic regions may result in complex changes in the thallium distribution especially if more than one bypass graft has been implanted".

Pfisterer at al (8) studied fifty-five consecutive patients undergoing bypass surgery. They were studied at baseline, 2 weeks post bypass surgery and then 1 between one and ninety-four months after coronary bypass surgery. The sensitivity for the detection of an occluded graft was 65%. However the positive predictive accuracy was 100%.

Zimmermann et al (15) applied analysis of thallium washout rates to try and improve the determination of graft occlusion in thirty-four patients. They compared standard thallium assessment with analysis of washout rates as a test for graft patency. It is of note that the sensitivity for the detection of coronary disease using visual interpretation of the images in this study was very low (71%). This improved to 84% when analysis of thallium washout rates was used. It is therefore not surprising that the sensitivity for the detection of graft patency was only 64% rising to 82% with washout rate analysis. The authors do admit to a "conservative bias" in conventional visual image interpretation. Finally, despite all vein grafts being patent in 23 patients, nine (39%) still had abnormal post-operative thallium scans.

Prognosis following CABG

Lauer et al (16) studied 873 symptom free patients following CABG. Over 58% of these patients (508 patients) had thallium defects. The authors found that perfusion defects following CABG were a predictor of a bad prognosis in a 3 year follow up. Patients who had any thallium defect had a mortality of 9% at 3 years, compared to those with homogeneous perfusion who had a mortality of 3%, $p=0.0004$. In those with reversible thallium defects the mortality rate was 12% compared to 5% in those without reversible defects ($p=0.002$). The authors suggested that asymptomatic patients should be assessed by exercise thallium imaging after CABG. However it is well recognised by others (17) that there is little therapeutic option for these patients, who in any event will already be on almost all secondary prevention measures.

In summary, post operative myocardial perfusion scans are frequently abnormal. This may arise because of graft stenosis, occlusion or diffuse coronary disease. Despite the relatively high frequency of abnormal thallium scans, patients frequently report a marked symptomatic benefit. Myocardial perfusion imaging may have a role in detecting graft stenosis and occlusion. Reversible thallium defects after bypass surgery may indicate a poorer prognosis.

Studies of the left internal mammary artery after coronary bypass surgery

As discussed in Chapter 2, previous authors (18-20) had suggested that flow down the left internal mammary artery (LIMA) is less than flow down an equivalent saphenous vein graft, and hence may not be sufficient at peak exercise. These studies relied on the use of intra-operative techniques, and therefore the data makes no allowance for adaptive changes in LIMA flow following CABG.

Johnson et al (21) investigated twenty-four patients who had CABG using the left internal mammary artery by postoperative stress thallium scintigraphy. Most of these patients had additional saphenous vein grafts to the right coronary and circumflex coronary arteries. There were three control groups: the first a group of twenty-five patients with normal coronary arteries (Group1); the second a group of twenty-five patients who had saphenous vein grafts to the LAD (Group 3); the third a group of thirty-four patients who underwent PTCA to the LAD (Group 4). Group 2 consisted of patients who had LIMA grafts to the LAD. In Groups 2 and 3 thallium scintigraphy was performed within 8 weeks of the procedure. In Group 4 thallium scintigraphy was performed within 6 weeks of the procedure. Each patient was studied by quantitative planar exercise thallium scintigraphy, and the ratio of thallium uptake in the anteroseptal wall to the posterolateral wall calculated. In Group 1 (normal coronary arteries) the anteroseptal: posterolateral thallium uptake ratio was 1.0 ± 0.15; In group 2 (those who had LIMA grafts) the

Rest perfusion became significantly less uniform after bypass surgery, in parallel with the higher number of rest defects following bypass surgery. Total rest perfusion score rose from 34.6 ± 6.2 to 37.0 ± 7.1 after operation, $p=0.002$. In particular anterior and septal territorial scores deteriorated. Anterior perfusion scores rose from a mean of 7.5 ± 2.9 to 8.3 ± 2.8, $p=0.001$. Septal perfusion scores rose from 3.6 ± 1.5 to 4.3 ± 1.8, $p<0.0001$. There was no change in inferior, posterolateral and posteroseptal territories. These data are summarised in Table 13 (page 159), and illustrated in Figure 30 (page 162).

Although there is only a small improvement in exercise perfusion scores, territories that were reversible from exercise to rest, showed improved perfusion at peak exercise following bypass surgery. The mean total perfusion score in these 67 territories was 9.9 ± 2.6 in the pre-operative scans, and 7.4 ± 2.8 in the post-operative scans ($p<0.001$). The data from the individual patients is illustrated in Figure 31, page 163.

Of the 67 territories that were reversible from exercise to rest in the pre-operative scans, thirty-five showed improved exercise perfusion post bypass surgery. The sensitivity of a reversible defect for detecting improvement in perfusion post bypass surgery is therefore 52%. Of the 401 defects that did not show improvement in perfusion post bypass surgery, 368 were not reversible preoperatively. Hence the specificity of reversibility from exercise to rest at baseline was 92% for detecting improvement in perfusion at late follow up.

DISCUSSION

This study has confirmed that coronary bypass surgery reduces the number of defects seen on exercise thallium imaging. However the improvement in the myocardial perfusion images is perhaps not as great as might be expected, and certainly not as great as in some previously published studies.

For example, Pfisterer et al (8) reported that 34 of the 37 patients with reversible defects no longer had reversible defects early after coronary surgery. An important distinction here is the counting of "reversible defects". In the present study a defect was counted before or after surgery regardless of whether it was reversible. At the time Pfisterer reported on his patients, it was assumed that fixed defects represented areas of myocardial infarction. We now know this not to be the case. As will be discussed in Chapter 8, segments that fail to redistribute on early (2-3 hour) post injection imaging may redistribute after 24 hours (25) or after a further resting injection of thallium (26). Indeed Pfisterer himself reported that two of the four patients with fixed defects had normal two week post operative thallium scans.

As stated above, Gibson's study (10) differs from the present one because of the much higher rate of poor ventricular function in the present study cohort. In the present study the mean ejection fraction was 33% ± 10% compared to 60% ± 15% in Gibson's study. This would suggest a much higher rate of previous myocardial infarction amongst the patients included in the present study, and since scarred myocardium is not able to concentrate thallium it would be expected that a far higher number of defects would persist.

This study does confirm the work of other studies (3-7) which show that thallium imaging after coronary bypass grafting produces complex images and as Verani et al stated (4) failure of myocardial perfusion to improve does not preclude marked alleviation of angina and improved exercise tolerance. Additionally the present study confirms that exercise defects do show improved perfusion following coronary bypass surgery.

The complexity of the changes in thallium images following coronary bypass grafting is not surprising and there are several possible explanations for the relatively small reduction in exercise defects:

1. The repeat studies were performed approximately 9 months after coronary bypass surgery, and it is already known that 10-20% of saphenous vein grafts occlude within the first year (9,27-28). The graft attrition rate in this study is not known but may be assumed to be of this order. Assuming only vessels with stenoses or occlusions are grafted 10-20% of defects would still be present following surgery.
2. The patients had diffuse disease prior to surgery. Out of 1425 segments on the exercise perfusion scans, 641 (45%) had a perfusion score at baseline sufficiently high to be called a defect. Scotland has the second highest rate of ischaemic heart disease in the world (29). As a result patients tend to have more severe, diffuse, disease than anywhere else in the world. The more diffuse the disease the less likely coronary artery bypass grafting is to produce "normal" perfusion.
3. It is perhaps simplistic to believe that following coronary bypass surgery there will be uniform perfusion in all regions of the heart. At one extreme, areas of myocardium subtended by stenosed vessels and by a graft will have a dual blood supply while those distal to a native vessel occlusion, but supplied by a graft, will have a single blood supply. The grafts are, with the exception of the LIMA, denervated and therefore autoregulation of blood supply may be less than optimal. As a myocardial perfusion image represents relative rather than absolute perfusion in the myocardium the areas of least thallium uptake i.e. defects may represent zones supplied by a single blood supply.

The latter comment is not inconsistent with the studies that suggest that myocardial perfusion imaging following coronary bypass surgery is useful in detecting graft stenoses or occlusion, particularly in patients with recurrent angina. In these patients the recurrent angina is likely to be caused by the area with least myocardial perfusion and this will be the area that takes up the least thallium after exercise.

However in a patient without recurrent angina pectoris it is possible that myocardial perfusion, although vastly increased following coronary bypass surgery, is still relatively lower in some zones even in the absence of graft occlusion. In these patients total exercise time would be expected to have increased. Other modalities such as exercise RNVG may be useful in this context. If there was no new wall motion abnormality on exercise RNVG in these territories, it is likely that clinically relevant myocardial ischaemia is not present.

Although I have not measured absolute myocardial thallium uptake as a proportion of the injected dose (there are no published studies that do so), a future study might investigate whether more thallium is taken up by the heart following coronary bypass surgery. If the above theory were true the total amount of thallium taken up by the myocardium (as opposed to skeletal muscle) would rise following coronary bypass surgery. Furthermore, although defects would still be seen after coronary surgery, the absolute thallium uptake in the defect zones would be far higher in those supplied by patent grafts compared to those with occluded grafts.

Some weight to this theory may be lent by the work of Zimmerman et al (15). As stated above this group used a semi-quantitative method of thallium washout analysis. They found a marked improvement in the rates of detection of graft occlusion using this technique.

Finally, the work of Wilson and White (30) using coronary doppler flow wires has suggested that coronary vein grafts attached to an artery with a proximal occlusion only restore normal maximal coronary flow in the absence of left ventricular hypertrophy, myocardial infarction, diffuse coronary atherosclerosis and obstructive lesions in the graft or native artery. All these criteria are unlikely to be met by all the patients in a routine clinical population undergoing CABG.

The improvement in exercise perfusion in the inferior territories after coronary bypass surgery is intriguing, particularly since, as has been shown in Chapter 6, it is the postero-lateral territory, not the inferior territory that is the one most likely to show improvement in regional wall motion. The reason behind this finding is unclear.

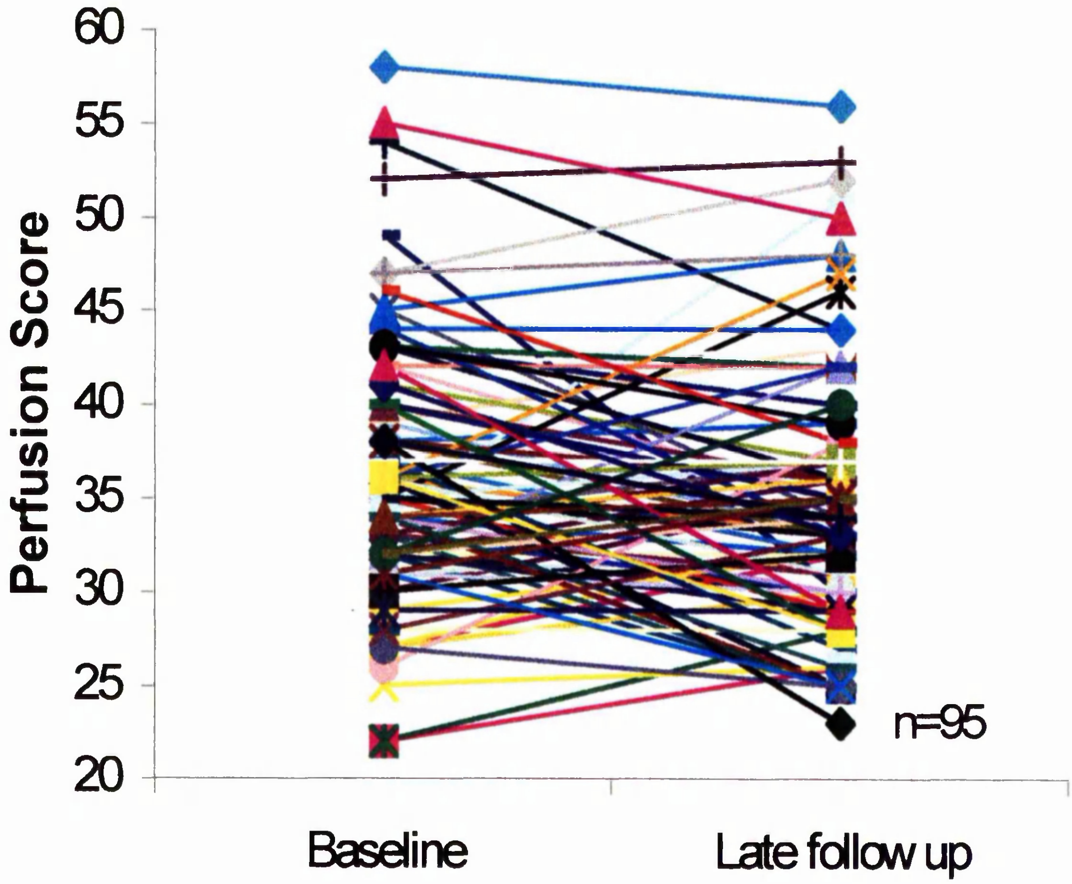
The failure of the anterior territory to demonstrate improved exercise perfusion may lend some credence to the theory that the LIMA is incapable of providing satisfactory flow at peak exercise. However, many authors have suggested that the LIMA increases in size in the months following CABG, and this change in calibre may go on past the nine month post bypass follow up in this study.

This study has shown that rest perfusion becomes less uniform following coronary bypass surgery. There have been no large scale studies that have examined rest perfusion before and after coronary bypass surgery and this finding underlines the complexity of the changes in thallium images following CABG.

Perhaps this finding can also be explained by the theory above. In a patient with normal coronary arteries and no bypass grafts, it would be expected that thallium uptake would be uniform at rest. However, the introduction of coronary grafts may again introduce areas of myocardium subtended by a dual blood supply leading to non-uniformity of thallium perfusion images. This area requires further investigation.

This study has confirmed that myocardial segments which show evidence of "reversibility" are likely to show improvement in perfusion following coronary bypass surgery. However, while the specificity of this finding is quite high, the sensitivity is quite low in contrast with some other studies. There are several explanations:

Figure 28



Change in exercise myocardial perfusion scores from baseline to late follow up

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Chapter 8

The Identification of Hibernating Myocardium by Thallium Scintigraphy

INTRODUCTION

This study has demonstrated that approximately 28% of patients have a significant improvement in left ventricular function early after a coronary bypass procedure, although this is not always sustained. Nevertheless, 21% of the population undergoing CABG showed improved LVEF 9 months after bypass surgery. Predicting those patients that show improved left ventricular function has become of great topical interest.

Hibernating myocardium is said to occur when myocardial oxygen demand exceeds supply to the extent that contraction is no longer possible. However supply is said to be adequate to maintain cell integrity. The phenomenon has been described by Rahimtoola (1).

A technique that is capable of detecting large amounts of hibernating myocardium is potentially very interesting, particularly for patients suffering from heart failure. The most likely use of such a technique is in patients who have poor left ventricular function secondary to ischaemic heart disease, who would in other situations be considered for cardiac transplantation (2,3).

However, the definition of improvement in cardiac function is not an easy one. As already described in this thesis, it is particularly difficult to identify true changes in regional wall motion, whatever the technique used. This is because the cardiac orientation changes considerably with coronary bypass operations, the right ventricle becoming even more anterior, perhaps due to the RV dilatation and impaired function seen in many patients following bypass. Additionally there is a recognisable pattern of change in regional wall motion following CABG: the septum appearing hypokinetic and the posterolateral region improving in function.

Therefore in this thesis I have defined an improvement, or deterioration, in myocardial function to have occurred if there is a change in global myocardial function as defined by the ejection fraction. Hibernating myocardium will be defined retrospectively to have been present if there has been a measurable improvement in left ventricular ejection fraction following coronary bypass surgery.

HISTORICAL REVIEW

Use of thallium to identify viable myocardium

The use of thallium as an agent to discern irreversibly damaged myocardium from ischaemic tissue is dependent on the fact that thallium uptake requires sarcolemmal integrity of the myocytes concerned. Goldhaber et al (4) showed that in a cultured foetal mouse heart preparation subjected to ischaemic like injury, the amount of thallium uptake was inversely related to the amount of lactate dehydrogenase released. Loss of this enzyme is characteristically associated with cell death. In a study by Granato et al (5) thallium uptake did not occur in necrotic areas of the hearts of anaesthetised open chested dogs.

The initial extraction fraction of thallium (that proportion of the tracer that is taken up by the myocytes in the first pass through the heart) is 88% ± 2.1% in a canine model (6). The extraction fraction is not altered by heart rates as high as 195 beats per minute (6). However over a wide range of physiological blood flows the uptake of thallium is proportional to blood flow (7). As a result low thallium uptake occurs in areas of relative hypoperfusion caused by ischaemia, especially at peak exercise or where coronary vasodilators have been used. However thallium does not remain fixed within myocardial cells after the initial extraction. Rather, it is continuously exchanged with new thallium from systemic recirculation (8). This is redistribution.

The first attempts to distinguish ischaemic from infarcted myocardium used separate rest and exercise injections of thallium. However it soon became apparent that a large amount of information could be obtained from a single injection of thallium (9) with the redistribution image being used in place of the rest image.

Rozanski et al (10) published a seminal paper for nuclear cardiology in 1981. This study used radionuclide ventriculography to assess regional wall motion before and after surgery. In this group of twenty five patients thallium-201 redistribution imaging was highly predictive of post-operative improvement in function in segments which are akinetic at rest. The redistribution pattern was normal in 90% of segments with reversible akinesis and abnormal in 76% of segments with irreversible akinesis.

It has subsequently become clear that the rest image and the redistribution image are substantially different, and that the redistribution image identifies more segments that concentrate thallium, when compared to the rest image (11). In this study by Woldman et al, 30 patients were given a small dose (10-15MBq) of thallium and imaging in the three standard planar views performed. At the end of rest imaging, patients were exercised and a further 45-60 MBq of thallium administered. The three exercise views were acquired, and after a further 2-3 hours redistribution images were obtained. Finally, radionuclide ventriculography using 600MBq of technetium pertechnetate was performed.

There were 150 abnormal segments on the exercise thallium scans. Of these 74 (49%), were identified as being reversible on the redistribution images, and significantly fewer, 58 (39%) on the rest images, χ^2=17.392, $p<0.001$. Furthermore, only 39 (53%) of the defects identified as being reversible on the redistribution scans were also identified as being reversible on the rest scans. However, 84% of the reversible defects on the rest scans, and 92% of the reversible defects on the redistribution scans had normal wall motion, substantiating the theory that uptake of thallium by myocytes confirms viability.

Therefore, although it is certainly true to say that when myocardial necrosis is present no redistribution of thallium is seen in the delayed images, the converse is not true: i.e. the absence of redistribution does not necessarily imply a myocardial infarction. This had first come to light in the work of Gibson et al in 1983 (12). In this study some persistent thallium-201 defects which showed no redistribution showed improved thallium uptake after revascularisation. Additionally it has been shown that some persistent defects have preserved wall motion making myocardial infarction extremely unlikely (11).

As a result, various techniques have emerged to attempt to improve the identification of viable myocardial segments. One approach is to identify regional wall motion in the area of the defect, as in our study mentioned above (11). In this case an area of myocardial infarction would only be identified if there were lack of redistribution, and a significant regional wall motion abnormality detected on radionuclide ventriculography. However, this may be an incomplete estimation of myocardial viability if the phenomenon of hibernating myocardium does truly exist. In this scenario, a myocardial segment which demonstrates a persistent defect and an associated regional wall motion abnormality, may show improved regional function after revascularisation. In order to make significant clinical impact, one would hope to observe an improvement in global myocardial function as measured by the left ventricular ejection fraction.

Thus, various other approaches have been made toward identifying hibernating myocardium. Yamamoto et al (13) reported that improvement in regional wall

Other methods of identifying myocardial hibernation

A variety of other methods have been described to identify area of hibernating myocardium. While low dose dobutamine stress will be dealt with in chapter 9, positron emission tomography (PET), usually with 18FDG glucose, has been used by many to detect hibernation (27-29). A detailed discussion of PET imaging lies outwith the scope of this thesis. However while some do regard this technique as the "gold standard" for the detection of hibernating myocardium, its use is severely limited by the expense involved, and by the lack of equipment available to perform the imaging. (At the time of writing, there was only one clinically available PET scanner in Scotland).

Influence on prognosis of the identification of myocardial hibernation

Gioia et al (30) followed up 81 patients over a period of 31 ± 24 months. The patients were divided into two groups; 43 who had evidence of viability on rest redistribution SPECT thallium imaging and 38 who did not. Both groups of patients had impaired LV (27% ± 8% in patients with no redistribution, and 26% ± 7% in patients with redistribution, n.s.d.) There were 22 cardiovascular deaths (51%) in patients with rest/redistribution, compared to just 11 (29%) in the group without ($p<0.05$). Multivariate Cox analysis demonstrated that the thallium images were an independent predictor of death, $\chi^2=5$, $p=0.03$. This is a retrospective case-control study and, while the results are interesting, it is not a randomised trial. Furthermore, no intervention was performed, and there is no evidence on the basis of this trial that intervention would influence prognosis in any way.

Cuocolo et al (31) followed up 76 patients over 1 year, 39 of whom underwent revascularisation (23 CABG, 16 PTCA). The remainder either were unsuitable for angioplasty and refused surgery, or were suitable for angioplasty and refused to consider emergency bypass surgery and were treated with medical therapy. All the patients had evidence of redistribution of thallium following rest imaging. Ejection fraction improved by 5% or more in just 16 of these patients, 14 of whom had a revascularisation procedure. Survival rates were 66% for the medically treated group, and 97% for the revascularised group. From multivariate regression analysis, the thallium scintigraphy added prognostic data over that obtained from clinical data and assessment of LV function, when the endpoint of death was considered. However equivalent prognostic data was available from coronary angiography. As this is not a randomised controlled trial, it is difficult to believe that the medically and surgically treated groups were well matched, although there were no measurable differences between the two groups.

Of further note is a study published by Zafrir et al (32). This group retrospectively analysed 366 patients who had exercise thallium redistribution and reinjection thallium scintigraphy. Mean follow-up was 33 ± 12 months. Cardiac events occurred in 48 patients (40 deaths, 8 myocardial infarctions). Using stepwise Cox regression analysis, reinjection thallium imaging was shown to have no predictive accuracy for cardiac events.

While these studies are certainly interesting, they are not randomised controlled trials, but retrospective analyses and a large randomised controlled trial would be of great benefit in this area.

In summary, there are at least six available methods (exercise-redistribution thallium imaging, late (24 hour post exercise) thallium imaging, reinjection thallium imaging, rest-redistribution thallium imaging, dobutamine stress testing and 18FDG PET imaging) to detect hibernating myocardium. Each of the published studies and techniques have their drawbacks, but there may be prognostic and clinical importance in the identification of hibernating myocardium. As demonstrated in chapter 5, few studies have looked at the long term effect of coronary bypass surgery on LV function, and almost all of the published studies on hibernating myocardium have terminated follow up at 2-3 months after surgery. Even fewer studies have defined myocardial hibernation as improvement in global myocardial function. However, I have demonstrated in earlier chapters the major limitations of using changes in regional wall motion analysis as a reliable indicator of hibernating myocardium.

The aim of this part of the study was therefore:

1. To investigate whether a same day rest/redistribution/exercise study could prospectively identify patients who would have an improvement in LVEF;
2. To follow up patients for at least nine months to delineate changes in LV function over this time period.

MATERIALS AND METHODS

In this study two of the above methods were used to attempt to identify hibernating myocardium. In this chapter the use of rest-redistribution thallium imaging as a technique will be described, and in the following chapter the use of low dose dobutamine as a stressor agent will be investigated.

As already described in Chapter 7, each view on the thallium images was split into five segments, giving a total of fifteen segments per patient for each acquisition at rest, redistribution of rest, and finally exercise. Territorial scores were then produced from the segments as described in Chapter 3.

The redistribution territorial scores were then subtracted from the rest scores for each patient. Each territory that showed a result of three or greater was said to show significant redistribution. For each patient with at least one reversible territory, the ejection fractions measured by radionuclide ventriculography at baseline, six weeks after operation, and nine months post operation were compared. The thallium studies were graded by the observers on a five point scale (excellent, good, poor, very poor, unreadable) for overall quality of image.

Table 15

	Baseline	Early Follow Up	Late Follow Up	n
LVEF	33% (10)	33% (11)	33% (12)	70
RVEF	33% (8)	27% (8)*	26% (8)*	70

**= change from baseline $p<0.001$*

Left and right ventricular ejection fractions at baseline, early follow up and late follow up (mean (SD)) in patients who did not demonstrate reversibility of rest image to redistribution image

Table 16

	Baseline	Early Follow Up	Late Follow Up	n
LVEF	31% (10)	34% (12)**	32% (13)	40
RVEF	33% (8)	29% (7)*	28% (8)**	40

**=change from baseline p=0.04*

***= change from baseline p=0.001*

Left and right ventricular ejection fractions at baseline, early follow up and late follow up (mean (SD)) in patients who demonstrated reversibility from exercise image to rest image

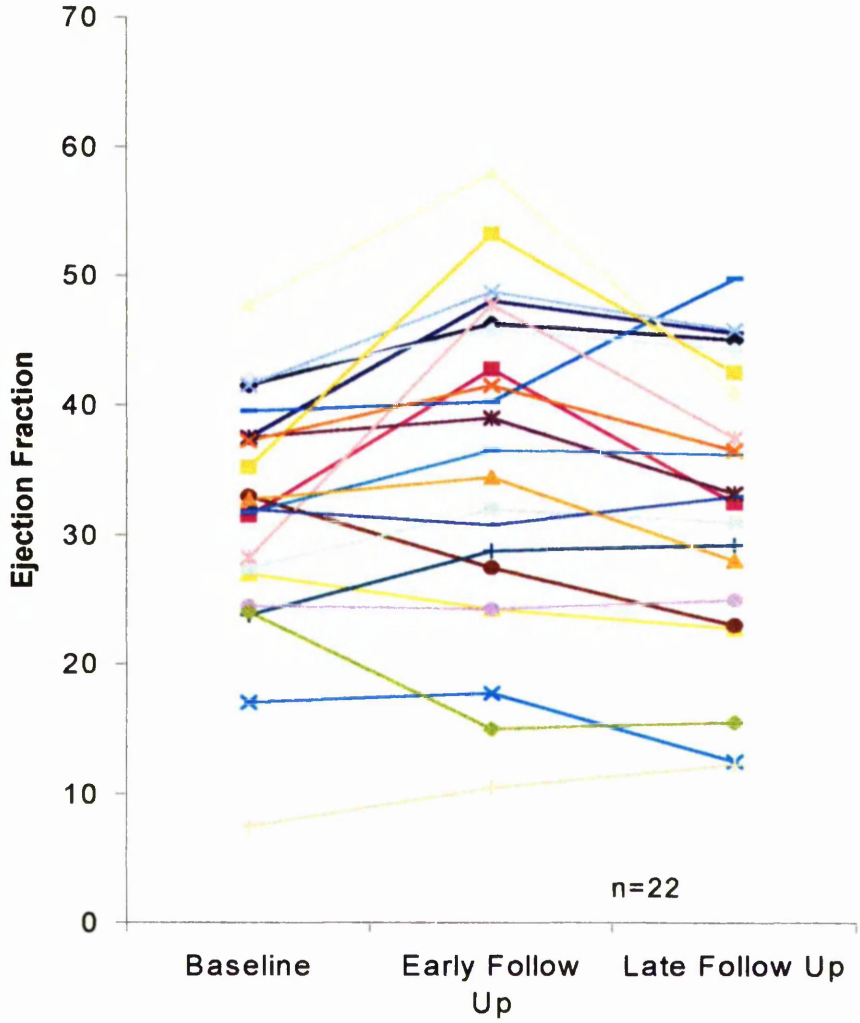
Table 17

	Baseline	Early Follow Up	Late Follow Up	n
LVEF	33% (10)	33% (10)	33% (11)	51
RVEF	32% (8)	26% (7)**	24% (6)**	51

**= *change from baseline p<0.001*

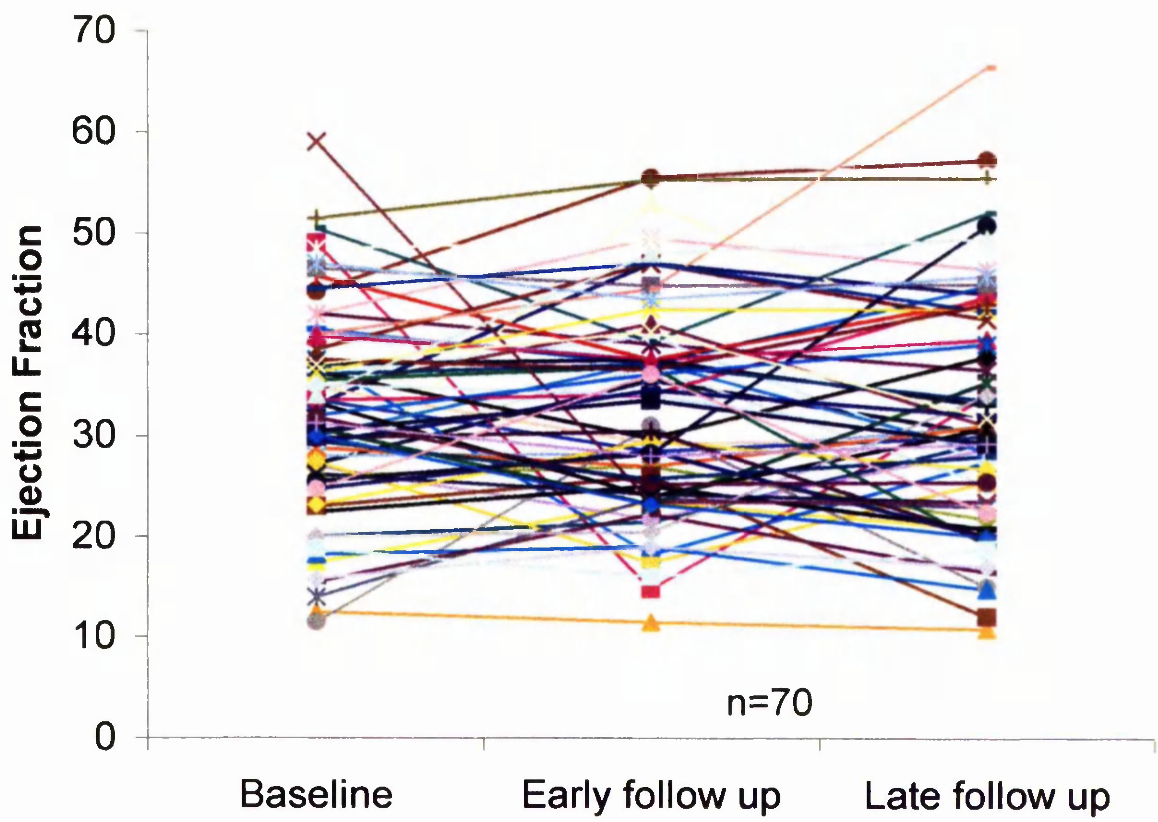
Left and right ventricular ejection fractions at baseline, early follow up and late follow up (mean (SD)) in patients who did not demonstrate reversibility from exercise image to rest image

Figure 33



Change in LVEF in individuals demonstrating evidence of reversibility from rest to redistribution at baseline examination

Figure 34



Change in LVEF in individuals who did not demonstrate evidence of reversibility from rest to redistribution at baseline examination

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routine patients may be such poor echo subjects that any examination by echocardiography is limited.

The resolution of an echocardiographic probe can be as good as 2 mm, while the resolution of a gamma camera at this depth is about 1cm. However it is unlikely that areas of myocardium that are in the range of 2mm to 1cm in diameter are clinically significant. Thickening of the LV wall can be seen by echocardiography; this cannot be determined at all by radionuclide ventriculography. Myocardial thickening is said to be a cardinal sign of myocardial hibernation on low dose dobutamine echocardiography.

Only two other study groups have used radionuclide ventriculography to assess LV function and its response to dobutamine stress (8,9). Matsuo et al (8) investigated 38 patients using low dose dobutamine (5μg/kg/min) and a continuous infusion of isosorbide dinitrate. Hibernating myocardium was said to be present if there was improvement in regional wall motion in contrast ventriculography performed 3 months after the revascularisation procedure. However in only 22 of the 38 patients was revascularisation successfully achieved at 3 months, most of the others having had an unsuccessful PTCA or evidence of restenosis at this stage. Only four of these patients underwent (successful) CABG, the rest having PTCA. This study group is therefore demonstrably different form that of my study population, all of whom had CABG.

Forty-seven of 110 (59%) segments demonstrated severe wall motion abnormalities at baseline. With infusion of dobutamine and isosorbide dinitrate wall motion improved in 28 (60%), remained unchanged in 17 (36%) and deteriorated in 2 (4%). Post-operative wall motion improvement occurred in 23 of the 28 segments (82%), that responded to dobutamine and isosorbide dinitrate.

remainder underwent PTCA. Myocardial hibernation was said to be present if regional function improved after intervention.

In this study a biphasic response to dobutamine (initial improvement followed by deterioration in function, as dobutamine dose was increased), was found to be the best predictor of myocardial hibernation. This has been found in at least one other study (5). The sensitivity of the dobutamine protocol for the detection of hibernation was 74% with a specificity of 89%. The sensitivity of the thallium protocol using the quantitative analysis was 90% with a specificity of 56%.

Kostopoulos et al (15) examined 31 patients, 12 of whom went on to PTCA and 19 to CABG. Infusion of dobutamine at 5 and 10μg/kg/min was performed, and a rest redistribution SPECT thallium protocol was used for thallium imaging. Regional wall motion on the baseline echocardiogram and follow up, post revascularisation, echocardiogram were used to define segments said to have had hibernating myocardium present. Follow up echocardiography was performed a mean of 97 ± 12 days after revascularisation. A four point regional wall motion scoring system was used ranging from normal (1) to dyskinesia (4). Significant improvement was said to occur if an akinetic or dyskinetic segment became normal or mildly hypokinetic.

The sensitivity for the dobutamine protocol was 86.5%, specificity 94.4%, while the thallium imaging was 90.5% sensitive and 69% specific.

Vanoverschelde et al (16) investigated 73 patients who had severe regional dysfunction secondary to a stenosis in an epicardial coronary artery. They used a quantitative exercise-redistribution-reinjection protocol for the thallium, and doses as high as 40μg/kg/min for the dobutamine stress echo. CABG was performed in 51 patients and PTCA in 22 patients. Follow-up was performed a mean of 5.5 ± 2.5 months after operation. Regional myocardial function was interpreted using a three point scale (normal, hypokinetic, and akinetic).

Improvement by one grade was taken to be significant during dobutamine infusion, or at follow up echocardiography.

There were 167 akinetic segments with improved function after revascularisation. Of these 127 (76%) showed a response to dobutamine in the pre-operative scans. In the thallium studies, 129 of these 167 segments (77%) had thallium uptake on reinjection of more than 50% of peak. Overall, the thallium images had a sensitivity of 88% and a specificity of 73% for the detection of improvement in regional function post bypass surgery. The dobutamine stress echocardiography had a sensitivity of 88% and a specificity of 77%.

Finally, Nagueh et al (17) compared an echo contrast method, rest-redistribution SPECT imaging and dobutamine echocardiography with doses of up to 40µg/kg/min in 18 patients, 16 of whom went on to PTCA, and 2 who went on to CABG. A biphasic response to dobutamine stress (i.e. initial improvement followed by subsequent decrease) had a sensitivity of 68%, and a specificity of 83%. Any improvement in a segment during dobutamine infusion (but not necessarily with biphasic response) had a sensitivity of 91%, but a specificity of 67% The thallium images had a sensitivity of 91%, and a specificity of 43%, while contrast echo had a sensitivity of 89% and a specificity of 57%.

Most of the comparative studies to date have therefore suggested that thallium imaging for hibernation has better sensitivity but poorer specificity than low dose dobutamine echocardiography. However it is important to remember that a wide variety of protocols were used in the above studies, both for thallium and for dobutamine, and hence it is difficult to make a true comparison.

The aim of this part of the study was to examine the clinical utility of low dose dobutamine stress blood pool ventriculography in the assessment of myocardial hibernation in a group of clinical patients undergoing CABG.

DISCUSSION

This study has confirmed that low dose dobutamine when used in conjunction with radionuclide ventriculography can identify patients who will demonstrate improvement in left ventricular ejection fraction following CABG. However the mean change in LVEF is small, and unlikely to be of major clinical significance. In patients with poor LVEF the study protocol did identify patients that as a group, manifested a significant improvement in ejection fraction at early follow up.

Disappointingly, as with the thallium data, the improved LVEF did not persist and the reason for this is unclear. However the present study is one of few that investigated patients as long as nine months after CABG, and further long term follow up studies of such patients are now required.

Low dose dobutamine echocardiography has been reported to be less sensitive, but more specific for the detection of myocardial hibernation than rest redistribution thallium imaging. It is therefore possible that a combined approach of dobutamine echocardiography and rest redistribution thallium imaging would have better sensitivity and specificity. Indeed, at least one group of investigators has reported on such a study (18).

Echocardiography has been reported to be superior to radionuclide ventriculography as an imaging technique in this situation. Echocardiography has much improved spatial resolution over radionuclide ventriculography. Additionally since radionuclide ventriculography does not allow visualisation of ventricular walls, it is impossible to identify thickening of left ventricle during dobutamine infusion. This is said, by some authors, to be the first sign of viability.

Finally, the biplane collimator used can only acquire the 45° LAO view and 75° LAO view simultaneously. We were therefore unable to acquire an anterior view at the same time as the other images. In order to acquire an anterior view, we would have had to prolong the time for the infusion of dobutamine considerably, and this is more likely to be associated with significant side effects for the patients.

Some of the new multi-headed gamma cameras may be able to get round this problem by acquiring three views simultaneously. However, this will still leave the difficulty of the overlying right ventricle in the anterior view making the images difficult to interpret.

Perhaps the most exciting developments at present is the increasing possibility of SPECT acquisition of radionuclide ventriculograms. This would certainly allow much more accurate delineation of regional left ventricular function than is possible with planar imaging. There has already been one published study following CABG (19). However the technique is in its infancy, the computer processing power required is vast, and the optimal method of reconstruction has yet to be identified.

Finally, the possibility of dobutamine magnetic resonance imaging is currently being investigated by some groups (20). However, the technique may be limited by the expense involved in running the machine. Secondly many patients find the long magnet a claustrophobic experience, an effect likely to be worsened by the anxiety precipitated by infusion of dobutamine.

CONCLUSIONS

Low dose dobutamine radionuclide ventriculography identifies a group of patients who manifest significant improvements in LVEF 6 weeks after operation. This improved LVEF is not maintained. Further studies with longer follow up times are required to define whether low dose dobutamine echo is capable of detecting those patients who will manifest long term improvements in LVEF. A combined approach of low dose dobutamine echocardiography, and rest-redistribution thallium imaging may improve the accuracy of identification of patients with hibernating myocardium. The newer techniques of SPECT radionuclide ventriculography, and magnetic resonance imaging may refine the technique further.

Table 18

	Baseline	Early Follow Up	Late Follow Up	n
LVEF	27% (8)	30% (10)*	28% (13) •	46
RVEF	32% (9)	27% (7)*	25% (6)**	46

**=Change from baseline $p<0.01$*

***=Change from baseline $p<0.001$*

•=Change from early follow up $p=0.04$

Left and right ventricular ejection fractions at baseline, early follow up and late follow up (mean (SD)) in patients who demonstrated improvement in at least 1 segment's function with dobutamine

Table 19

	Baseline	Early Follow Up	Late Follow Up	n
LVEF	40% (8)	39% (10)	40% (10)	29
RVEF	34% (7)	26% (8)*	27% (9)*	29

**=Change from baseline p<0.001*

Left and right ventricular ejection fractions at baseline, early follow up and late follow up (mean (SD)) in patients who did not demonstrate improvement in at least 1 segment's function with dobutamine

Table 20

	Baseline	Early Follow Up	Late Follow Up	n
LVEF	22% (6)	26% (9)*	23% (7) •	28
RVEF	29% (8)	25% (7)**	23% (6)*	28

**=Change from baseline $p<0.01$*

***=Change from baseline $p=0.05$*

•=Change from early follow up $p<0.05$

Left and right ventricular ejection fractions at baseline, early follow up and late follow up (mean (SD)) in patients with poor preoperative LV function who demonstrated improvement in at least 1 segment's function with dobutamine

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Chapter 10

Conclusions

The Impact of Coronary Bypass Surgery on Myocardial Perfusion and Function

INTRODUCTION

The aim of this chapter is briefly to review the subject of the impact of coronary bypass surgery on myocardial perfusion and function, with particular reference to the work presented in this thesis. The main findings from previous chapters are combined and reviewed in the context of previous work. Recommendations for future investigation are included.

The impact of coronary bypass surgery on myocardial function

a) Left ventricular function

Coronary bypass surgery has only a marginal effect on the mean left ventricular ejection fraction for the population undergoing routine coronary bypass grafting. There was a slight improvement in the mean LVEF 6 weeks after operation, but this did not persist, and there was no difference between baseline LVEF and LVEF measured 9 months after operation. This is broadly in line with other published work (1,2).

However, the clinical importance of improved LVEF applies most to those whose LV function is seriously impaired prior to operation. Amongst this group of patients there was also a marginal improvement in LV ejection fraction 6 weeks after operation. At late follow up, nine months after operation, LVEF had fallen back to preoperative levels. This has only been reported in one previous study, that by Jacobson et al (3). However few studies with the exception of Cuocolo et al (4) have followed up patients so long after coronary bypass grafting. Cuocolo's paper disagrees with my findings, although many of Cuocolo's patients underwent PTCA rather than CABG.

The patients in my study with poor LV function probably had worse pre-operative LV function than most patient groups in the literature. A further study to look at the long term effects of coronary bypass grafting on LV function is required. Follow up should go on for a considerable period of time, at least one year after bypass surgery.

While there is little effect on left ventricular function for the population undergoing bypass surgery, individuals do demonstrate striking changes in LVEF. Approximately 28% of patients undergoing CABG have a 5% or more improvement in LVEF with surgery 6 weeks after the operation. This proportion is broadly in line with that reported by Dilsizian who has written that approximately one third of patients undergoing CABG in their centre manifest a significant improvement in LVEF following surgery (5).

This importance of a 5% improvement in LVEF should not be underestimated. If the starting LVEF for a patient is 30% (about average in the present study) a 5% improvement in LVEF represents a 17% relative improvement in LV function. However, if the starting LVEF is 15%, as it is commonly in those referred for cardiac transplantation, a 5% improvement in LVEF represents a 33% relative improvement in function. This certainly may obviate the need for cardiac transplant and provide hope to those not suitable for transplant (6).

Although the degree of improvement in LV function was not maintained in those patients who manifested a significant rise in LVEF at early follow up, there was still a significant improvement in the late follow up LVEF amongst the patients who manifested a 5% or more improvement in LVEF 6 weeks after operation.

Most studies that have investigated techniques to identify "hibernating myocardium" have concentrated on the effect of bypass surgery on regional ventricular function. The results presented in Chapter 6 clearly demonstrate the fallacy of this concept and the method cannot be justified in practice.

For many years it has been known that septal regional wall motion apparently deteriorates with coronary bypass surgery. Debate has raged as to whether this is a real phenomenon or a by-product of the change in cardiac orientation that accompanies cardiac surgery (7,8). My study has confirmed that there is significant septal dysfunction following CABG, although the cause of this remains obscure. However, since there is no change in global left ventricular function there must be some other change that compensates for the deterioration in septal function. Close analysis of my data suggests that posterolateral wall motion tends to improve with bypass surgery. While this may also be a product of the change in orientation of the left ventricle, it is equally possible that the improvement in posterolateral function is a compensation for the impaired septal function.

Of particular note in the data presented in Chapter 6, was the fact that of 25 "infarcted" septal territories none improved at 9 months after surgery. In the anterior wall, just one "infarcted" territory improved 9 months after surgery. In contrast, in the postero-lateral wall 70% of "infarcted" territories improved after surgery. Therefore in this study, if we were to have defined hibernating myocardium as improvement in regional left ventricular function following surgery, then our patients would have had no hibernation in the septum and little in the anterior wall. It seems unlikely that the phenomenon of myocardial hibernation is restricted to the posterolateral wall of the left ventricle. Future studies should concentrate on finding techniques that reliably predict improvement in global left ventricular function with bypass surgery. Of course, improvement in global LV function is likely to be the most clinically relevant to patients with poor LV function.

rather than absolute blood supply, the use of the rest image post coronary bypass can be misleading. Further studies could investigate the amount of thallium taken up by the myocardium, as a proportion of the injected dose. It would be expected that the myocardium would take up significantly more thallium on resting studies after coronary bypass grafting.

d) Detecting hibernating myocardium

Various techniques have been suggested to identify hibernating myocardium. Each has its drawbacks. 18FDG PET (18-19) is expensive, and not widely available to clinicians. Late (24hr) redistribution of thallium imaging (20-21) is inconvenient for the patient who has to return to the nuclear cardiology lab the next day, and inconvenient for the department. Poor thallium photon count statistics limit its use. Re-injection thallium imaging (22) is also expensive, and requires a further dose of radiation to be given to the patient. Rest-redistribution imaging (23) is probably the most widely used technique in current clinical practice. Certainly the weight of published evidence suggests that this is probably the best technique of identifying patients that will demonstrate improved LV function following bypass surgery. However this technique does not allow same day acquisition of the exercise thallium images that contain within them such important prognostic information. Low dose dobutamine echocardiography (24-25) suffers from a poorer sensitivity, but perhaps a better specificity for the detection of hibernating myocardium than thallium imaging.

Since all these other techniques have drawbacks two new techniques were evaluated to identify myocardial hibernation. The first was low dose rest-redistribution thallium imaging, followed by exercise thallium imaging. This technique allowed exercise perfusion imaging to be performed in addition to the rest redistribution images. Thus, ideally, the prognostic information from exercise thallium scintigraphy would be gained as well as information on myocardial hibernation. While this method certainly identified a proportion of patients whose LVEF improved 6 weeks after operation, by late follow up the relative benefit had disappeared, and the technique had no ability to identify patients whose LVEF was improved 9 months after surgery.

Similarly, the dobutamine technique identified some patients, particularly those with poor pre-operative LV function whose LVEF improved immediately after surgery, but again this improvement was not sustained. Perhaps a combined approach of low dose dobutamine echocardiography and rest redistribution thallium may improve the diagnostic ability to prospectively detect myocardial hibernation (26).

Future studies of hibernating myocardium should concentrate on the prospective identification of improved LVEF nine months or more after surgery. A long term prospective prognostic study of asymptomatic patients with myocardial hibernation, randomised to CABG or medical therapy is urgently required.

SUMMARY

Coronary bypass surgery has little effect on LV function for the population undergoing the procedure. Individuals do show significant variation. Prospectively identifying those that will manifest a significant improvement in LVEF may be important for some patients. However the improvement must be sustained to be clinically relevant. RV function deteriorates after bypass surgery and the causes and significance of this require further research. Exercise myocardial perfusion images improve after bypass surgery, but do not normalise in the majority of patients. Change in rest perfusion images are extremely complex and require further study. There is still no ideal method to identify myocardial hibernation prior to bypass surgery.

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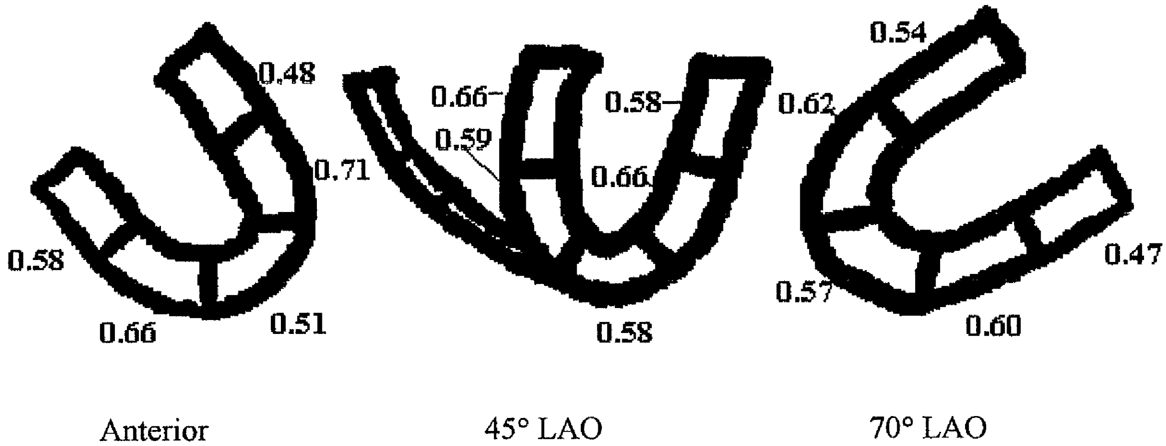
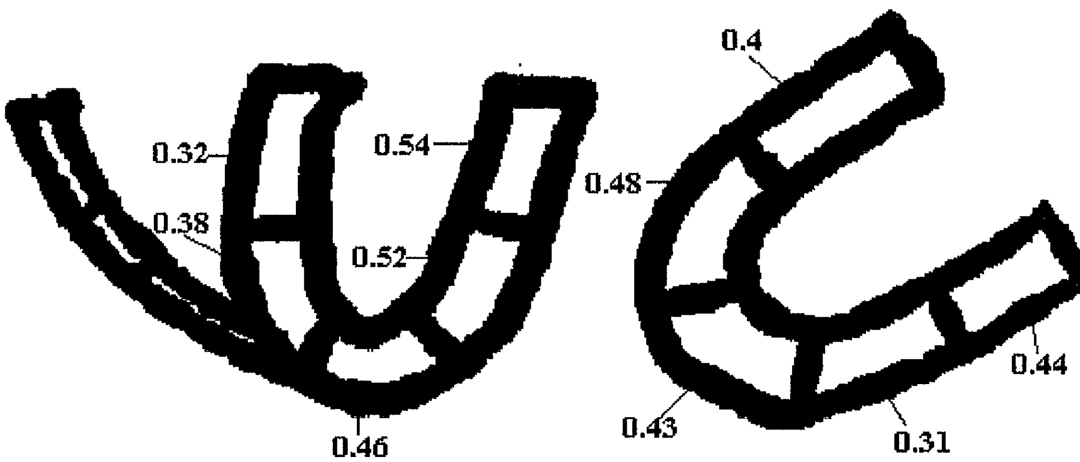
Figure 35



Kappa values by segment for rest perfusion scans

Figure 37



45° LAO

70° LAO

Kappa values by segment for blood pool images

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