AN EVALUATION OF THE ROLE OF THALLIUM-201 MYOCARDIAL IMAGING IN THE INVESTIGATION OF ISCHAEMIC HEART DISEASE

by

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This thesis is dedicated to Caroline and Beth.

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DECLARATION

This thesis is a report of studies on thallium-201 myocardial imaging carried out by me between 1976 and 1978 whilst a Lecturer in the University Department of Medicine at Glasgow Royal Infirmary. The studies were conducted in the Department of Nuclear Medicine of that hospital.

I personally performed and analysed all the in vitro and in vivo radionuclide imaging described and was concerned with the detailed planning of all the work. The angiographic and electrocardiographic studies described were performed and analysed by members of the University Department of Medical Cardiology at Glasgow Royal Infirmary, notably Doctors A.R. Lorimer and R.G. Murray. Doctors Lorimer and Murray also collaborated in the planning of several of the studies.

Certain aspects of the work presented have already been published in The British Heart Journal (1978, 40, 870-873), The European Journal of Nuclear Medicine (1978, 3, 223-225) and in The Proceedings of the 13th International Bad Gastein Symposium on Radioactive Isotopes in Clinical Medicine and Research (Radioaktive Isotope in Klinik und Forschung, 1978, 13, 257-264). A copy of each of these papers is included in a pocket on the inside of the back cover of Volume II of the thesis.

I have personally delivered or (am due to deliver) papers based on this work to the following learned groups:

(1) The Scottish Society for Experimental Medicine (1977, Dundee and 1977, Aberdeen).

(2) International Symposium on "Radionuclides in the diagnosis of acute myocardial infarction" (1977, Lund).

(3) The Royal Medico-Chirurgical Society of Glasgow (1977, Glasgow).

(4) The 13th International Symposium on Radioactive Isotopes in Clinical Medicine and Research (1978, Bad Gastein).

(5) Joint meeting of The European and The British Nuclear Medicine Societies (1978, London).

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SUMMARY

Ischaemic heart disease due to coronary artery atherosclerosis is a major cause of death and morbidity in all Western countries with the West of Scotland having a particularly grim record in this respect. A definitive diagnosis of coronary artery disease during life can only be made on the basis of selective coronary arteriography. This technique, however, is difficult and associated with a small, but definite, mortality and morbidity. A noninvasive or minimally invasive investigation which could identify those patients in whom coronary arteriography is really indicated would, therefore, be of great value. The standard noninvasive methods presently available, such as electrocardiography or ultrasound, all have shortcomings.

Because of advances in instrumentation and the introduction of new radiopharmaceuticals, it has become possible in recent years to apply various radioisotope techniques to the study of cardiological problems. The potassium analogue thallium-201 became readily available for gamma camera imaging of the myocardium in 1975 and this thesis is concerned with an evaluation of its clinical role in the noninvasive diagnosis of coronary artery disease.

Chapter I is a review of the literature published on the application of nuclear medicine techniques (other than thallium-201 myocardial imaging) to the study of cardiac disease, especially coronary artery disease. The chapter is divided into several sections, which deal individually with different groups of investigation. Each method is discussed in terms of the history of its introduction, how it is performed, any associated technical or biological problems, and finally an assessment of its clinical and research role or potential.

Chapter II begins with a consideration of the whole body distribution and toxicology of thallium, then considers thallium-201 as a scintillation camera imaging agent. By means of measuring the intrinsic resolution of a gamma camera with thallium-201 and

by phantom studies using thallium-201, it is demonstrated that the physical properties of this radioisotope are less than ideal for gamma camera imaging, though acceptable.

The chapter then continues with a description of the methods used in the myocardial imaging studies described in the rest of the thesis.

Chapter II concludes with a consideration of the method of analysis of thallium-201 images. Visual interpretation is complicated by the fact that the distribution of the radiopharmaceutical is not entirely uniform in the normal myocardium. A "regions of interest" method for semiquantitatively analysing the images is presented, together with "normal ranges" derived from control studies on healthy young volunteers.

Chapter III describes a study comparing thallium-201 myocardial imaging, electrocardiography and selective coronary arteriography in a group of patients with chest pain. It is shown that, in this group, stress myocardial imaging had high sensitivity and specificity for detecting angiographically proven coronary artery disease, but that rest images were usually normal unless the patient showed left ventricular wall motion abnormalities during contrast ventriculography.

In addition to the presence of coronary artery disease, the extent of disease is prognostically and therapeutically important. Chapter III, therefore, also examines the accuracy with which the extent of coronary artery disease can be predicted from stress thallium-201 images. It is concluded that such predictions are often not accurate and some evidence is presented to show that the differing severity of individual stenoses in multiple vessel disease and a possible protective effect of collateral circulation may be among the factors implicated in this lack of accuracy.

Chapter III concludes with an assessment of the clinical value of thallium-201 imaging and electrocardiography in the noninvasive diagnosis of coronary artery disease.

Chapter IV is concerned with a comparison of visual analysis and semiquantitative analysis of the same group of myocardial images and presents some evidence that the accuracy of interpretation of myocardial images is increased when a semi-quantitative method is used.

Acute myocardial infarction can be diagnosed by standard methods in most patients, but in some the diagnosis remains uncertain. Myocardial imaging is a possible means of resolving this problem, but is not easy to perform in the early stages after the acute event. Chapter V, therefore, examines the clinical value of rest thallium-201 myocardial imaging performed 3 to 6 days after admission in 50 patients with suspected acute myocardial infarction. The results of this study indicate that whilst acute transmural infarction usually produces an abnormal myocardial image at this stage, the technique could not be relied upon to clarify the diagnosis in those patients in whom the standard investigations are equivocal or contradictory.

In patients with aortic valve disease it is well established that the presence of coronary artery disease is a major factor in the success or failure of surgical therapy for the valve lesion. As chest pain is not a reliable indication that the patient has coronary artery disease, coronary arteriography, with its attendant risk, is a routine part of the pre-operative assessment of most of these patients. Chapter VI describes a study to determine whether stress thallium-201 myocardial imaging can indicate which of these patients have coronary artery disease. It is concluded that the radionuclide technique does not aid the selection for coronary arteriography in this group of patients.

In Chapter VII, a comparison is made of post-operative stress thallium-201 myocardial imaging and selective coronary arteriography in a group of patients who had undergone coronary artery bypass graft surgery. Myocardial imaging successfully predicted the status of most bypass grafts and could also be used to detect disease of ungrafted vessels. It is concluded that myocardial imaging may be of value in the post-operative follow up of these patients, especially in those who continue to have chest pain.

The final Chapter in the thesis considers the clinical value of thallium-201 myocardial imaging for the noninvasive detection of ischaemic heart disease and discusses the problems associated with the technique. The conclusions drawn are based both on my own work and on that published in the literature by other groups.

ABBREVIATIONS

AI	aortic incompetence
AS	aortic stenosis
ATP	adenosine triphosphate
AVD	aortic valve disease
DTPA	diethylenetriamine pentaacetic acid
ECG	electrocardiogram
keV	kiloelectron volt
KPM	kilopond meter
LAD	left anterior descending coronary artery
LCx	left circumflex coronary artery
MAA	macroaggregates of albumin
Main L	main left coronary artery
mCi	millicurie
MeV	megaelectron volt
MS	mitral stenosis
PMPS	particulate myocardial perfusion scintigraphy
RCA	right coronary artery

CHAPTER I

AN HISTORICAL REVIEW OF THE APPLICATION OF RADIOISOTOPE MYOCARDIAL IMAGING TECHNIQUES IN PATIENTS WITH CORONARY ARTERY DISEASE

I. (1) Introduction

The first recorded use of a radioactive tracer in man was in the field of cardiovascular medicine. In 1927, five years before the discovery of artificial radioactivity by Irène Curie and Frédéric Joliot (Curie and Joliot, 1932), Hermann Blumgart and his colleagues measured the circulation time from one arm to the other using intravenous injections of aqueous solutions of radon and a cloud chamber (Blumgart and Yens, 1927) and demonstrated that a longer than normal circulation time was found in patients with auricular fibrillation or "myocardial degeneration" (Blumgart and Weiss, 1927). In the late 1940's the concept of using radioisotopes and an external detector to measure cardiovascular function was extended by the work of Prinzmetal and his group, when they described the technique of radiocardiography - "a method of graphically recording the passage of radioactive blood through the cardiac chambers" (Prinzmetal, Corday, Bergman et al., 1948; Prinzmetal, Corday, Spritzler and Flieg, 1949). Radioactive sodium was injected intravenously and activity recorded over the precordium using a carefully shielded Geiger-Muller tube. In most normal subjects two separate peaks of radioactivity were recorded, the "R wave" and the "L wave" corresponding respectively to the passage of the radioactive bolus through the right heart and the left heart (Prinzmetal et al., 1948).

The radiocardiogram was found to be normal in patients with breathlessness due to respiratory disease, but abnormal when breathlessness was due to cardiac dysfunction (Prinzmetal et al., 1949). Typical patterns of abnormality were also described for right to left and left to right intracardiac shunts (Prinzmetal et al., 1949). The technique of radiocardiography using an external probe has advanced considerably in the last thirty years. It has enabled accurate determination of such parameters as cardiac transit time, left ventricular ejection fraction and cardiac output and has been used in the quantification of intracardiac shunts. Further consideration of radiocardiography is outwith the scope of this thesis but there have been several recent extensive reviews (Donato, 1973; Parker, Weber, Van Dyke et al., 1974; Pierson and Van Dyke, 1974; Gottlieb, Sheps, Myerburg et al., 1975; Pierson, Alam, Kemp et al., 1977).

A new dimension to the potential value of radioisotopes in the assessment of the cardiac patient was opened up by the invention of the scintillation or gamma camera by Anger in the late 1950's (Anger, 1958). By 1965 the gamma camera had been used to produce images demonstrating the passage of a radioactive bolus through the central circulation (Anger, Van Dyke, Gottschalk et al., 1965). Gamma camera imaging using an intravascular tracer (radionuclide angiocardiography) has since been applied to the investigation of both cardiac structure and function. Detailed consideration of previous literature on radionuclide angiocardiography is not relevant to the main theme of this thesis but a brief summary follows. Recent large scale reviews of such studies have been provided by Freedman (1974); Pitt, Rigo and Strauss (1974); Strauss (1974); Kriss (1975); Parker and Treves (1977); Strauss and Pitt (1977a); Ashburn, Schelbert and Verba (1978).

The study of cardiac anatomy by using the gamma camera to record the first passage of a radioactive bolus through the central circulation has been principally developed by Kriss and the Stanford Group (Kriss, Yeh, Farrer et al., 1966; Kriss, 1975). The tracer usually used for such studies is technetium-99m either as free pertechnetate (Kriss, 1969) or bound to human serum albumin (Pitt et al., 1974) or to human red cells (Smith and Richards, 1976; Pavel, Zimmer and Patterson, 1977). The red cells can be satisfactorily labelled with technetium-99m either in vivo or in vitro (Hegge, Hamilton, Larson et al., 1978). In adults the usual dose of technetium-99m is 10-20 millicuries (Kriss, 1975). In children the recommended dose is 18.5 millicuries per square meter of body surface (Wesselhoft, Hurley, Wagner et al., 1972) or 0.1 millicuries per kilogram body weight (Kriss, Enwright, Hayden et al., 1971). Radionuclide angiocardiographic assessment of cardiac anatomy has been applied both to patients with congenital heart disease including young infants (Wesselhoft et al., 1972) and to those with acquired heart disease (Kriss et al., 1971). It may provide useful information with less risk and discomfort to the patient than cardiac catheterisation, and thus may be valuable as a screening test. Radionuclide angiocardiography, however, is handicapped by intrinsically poorer resolution than is possible with X-ray studies, even when the tracer is injected into the heart at cardiac catheterisation (Mason, Ashburn, Harbert et al., 1969), and by the lack of pressure measurements. It therefore seems likely that detailed assessment by cardiac catheterisation and X-ray angiography will remain necessary when surgical intervention is contemplated.

The study of cardiac function by radionuclide angiocardiography derives from the radiocardiographic approach using an external probe.

Like the studies of cardiac anatomy mentioned above it has benefited from improvements in the gamma camera allowing better resolution and acceptance of higher count rates, and from linkage of the gamma camera to computers which allow faster data storage and data processing (Wagner, 1977). Radionuclide angiography has been used particularly to assess regional left ventricular wall motion and to quantitate global ventricular function.

Assessment of cardiac function by X-ray angiography remains the standard against which all other techniques are judged. It should, however, be remembered that, in addition to morbidity associated with these studies, they may not always accurately reflect ventricular function. Thus, there is some evidence that the injection of contrast medium into the cardiac chambers during ventriculography may depress ventricular function (Gootman, Rudolph and Buckley, 1970; Karliner, Bouchard and Gault, 1972). Also the calculations of cardiac volumes from X-ray ventriculography usually use an area-length method, such as that introduced by Sandler and Dodge (1968). Such techniques assume a regular shape throughout the ventricle, and this may not always be justified, especially in ischaemic heart disease.

Cardiac function may be assessed from radionuclide angiography either during the first passage of the tracer through the central circulation (Kostuk, Ehsoni, Karliner et al., 1973; Weber, dos Remedios and Jasko, 1972) or by waiting until the equilibrium period when the tracer is uniformly mixed through the vascular compartment (Zaret, Strauss, Hurley et al., 1971; Strauss, Zaret, Hurley et al., 1971).

The first pass studies of cardiac function use a technique based on that for the anatomical studies described above, but with much greater temporal resolution of the time activity curve so that "high

frequency events" such as ejection fraction and rates of ventricular emptying and filling can be studied within individual cycles. The principal advantages of the first pass technique are (i) the rapidity with which data is collected, making it especially suitable for use in very ill patients (ii) the ability to study right and left ventricles separately as they are temporally isolated from one another with very little activity in background structures (iii) as the first pass only is being studied, tracers which do not remain intravascular may be used e.g. the study may be carried out during the injection of technetium-99m labelled pyrophosphate for "hot spot" infarct imaging (see Chapter I.(4)). The main disadvantages of the first pass study are (i) only one view per injection is obtained. Especially in ischaemic heart disease, where ventricular geometry is often irregular, it may be important to record more than one projection (Pitt et al., 1974). A second injection may be performed to allow another view in first pass studies but more than two views are not usually possible (Ashburn et al., 1978) (ii) the assumption that the 5 or 6 cycles recorded are truly representative of the patient's cardiac status (iii) the dependence on the arrival in the central circulation of a compact bolus of radioactivity.

Studies of cardiac function using data acquired in the equilibrium phase after injection of a tracer require a tracer which remains intravascular (usually human serum albumin or human red cells labelled with technetium-99m) and some form of physiological indicator to record the phase of the cardiac cycle. Usually the patient's electrocardiogram is used, though other markers, such as the phonocardiogram, can also be used (Berman, Salel, De Nardo, et al., 1975).

The early studies recorded only end systolic and end diastolic phases of the cycle. The R wave of the ECG started the delay timer in the "gating device" and the camera activated at the points of the cycle corresponding to end systole (the 40 milliseconds during the downslope of the T wave) and end diastole (the 60 milliseconds of the PR interval) (Pitt et al., 1974). Recording continued for several hundred cycles with superimposition of all end systolic images on one another and superimposition of all end diastolic images. The composite end systolic and end diastolic images so obtained can be used to detect abnormalities of left ventricular wall motion (Zaret et al., 1971). The ejection fraction can be calculated from the images using an area-length method similar to that used in contrast angiography (Strauss et al., 1971), but like contrast angiography this approach makes certain assumptions about left ventricular geometry. An alternative approach to the measurement of ejection fraction is to draw regions of interest round the left ventricle in end systole and end diastole and compute the total counts within the ventricle during each (Secker-Walker, Resnick, Kunz et al., 1973). This activity method does not assume regular geometry for the ventricle but correction for activity present in the (extracardiac) background is necessary.

End systolic and end diastolic gating of the gamma camera meant that data from the rest of the cycle was lost. A more recent technique (Green, Ostrow, Douglas et al., 1975) derives the count rate within the left ventricle throughout the entire cardiac cycle for each of many discrete segments of the cycle and sums the individual segments over several hundred cycles. In this way a time activity curve is generated for the entire composite cycle. At least 20-25 data points per cycle seem to be necessary for optimal recording (Ashburn et al., 1978).

The gating procedures mentioned so far require selection of the gating interval prior to study. This may lead to difficulties if the patient has a change in heart rate during the study or has an irregular cardiac rhythm (Strauss and Pitt, 1977a). This problem can be overcome by recording the raw scintigraphic data onto a computer disc, together with the patient's ECG. The R-R intervals can then be analysed retrospectively and irregular cycles excluded from further analysis.

The main advantages of the equilibrium phase study are (i) multiple views can be obtained following one injection (ii) following a single injection repeated studies, e.g. after therapy, may be carried out over a period of 4 hours, or perhaps longer. The main disadvantages of the technique are (i) some superimposition of the cardiac chambers is unavoidable. This can be reduced, but not abolished, by careful orientation of the gamma camera. (ii) 5 to 10 minutes may be necessary for each view. This may be too long a period of complete immobility for the seriously ill patient. Recent work, however, suggests that useful information may be obtained from shorter recording periods (Ashburn et al., 1978). (iii) Only tracers which remain intravascular over the period of study are suitable. Both first pass and equilibrium radioisotope angiocardiography have their proponents and each has been shown by various groups to correlate well with contrast angiography in the detection of abnormalities of left ventricular wall motion and determination of left ventricular ejection fraction (e.g. Secker-Walker et al., 1973; Schelbert, Verba, Johnson et al., 1975; Myers, 1976; Hannan, Hare, Hughes et al., 1977; Schad, 1977; Dymond, Jarritt, Britton et al., 1978; Hecht, Mirrell, Rollett et al., 1978, for first pass studies. Zaret et al., 1971; Strauss

et al., 1971; Rigo, Murray, Strauss et al., 1974, for end diastolic/ end systolic gating. Green, Brody, Douglas et al., 1976; Folland, Hamilton, Larson et al., 1977; Qureshi, Wagner, Alderson et al., 1978, for complete cycle time activity curves).

Further development of the technique will depend upon validation of wall motion assessment throughout the cardiac cycle and confirmation of the accuracy of ventricular volume curves derived for the complete cardiac cycle from time activity curves. A recent refinement which is of great potential value is the assessment of left ventricular function during or shortly after exercise. Borer, Bacharach, Green et al., (1977) and Ashburn et al., (1978), both using equilibrium radionuclide angiocardiography, have demonstrated exercise induced abnormalities of left ventricular wall motion and left ventricular ejection fraction in coronary artery disease patients who had normal left ventricular function at rest.

If the construction of time activity curves for the complete cycle and the ability to test ventricular function during stress can be perfected, it seems possible that radionuclide angiocardiography and not contrast radiology will become the method of choice in the future for assessing ventricular performance.

The techniques discussed so far have used tracers confined to blood passing through the heart. The other principal group of nuclear medicine procedures applied to cardiology use isotopes labelling of the myocardium itself:- myocardial imaging.

Gamma camera or rectilinear scanner imaging of the myocardium can be classified under three broad headings.

(i) Non invasive labelling of normal myocardium. These studies utilise tracers which are preferentially accumulated within the normal myocardial cell following intravenous injection. The principal, though not the only, factor determining the distribution of such tracers

is regional myocardial blood flow. Radioactive potassium and other monovalent cations which act as physiological analogues of potassium are the main radionuclides in this class of myocardial imaging agents. Other substances such as labelled fatty acids have also been used, though less widely.

(ii) Invasive assessment of regional myocardial blood flow in which the tracer is injected at the time of cardiac catheterisation, usually directly into the coronary arteries. The invasive studies use particulate indicators (aggregates, usually of albumin, or microspheres), labelled with a radioisotope or diffusible inert indicators such as the noble gases or iodoantipyrine.

(iii) Non invasive labelling of acute myocardial infarction, in which the radiopharmaceutical is injected intravenously and preferentially accumulated in acutely infarcted myocardium. A variety of apparently unrelated tracers have been employed for such studies, the bone scanning agent technetium-99m pyrophosphate being the principal one.

The remainder of this chapter will be a review of the previous literature on myocardial imaging, considered under the three main headings noted above.

I. (2) Non Invasive Labelling of Normal Myocardium

Following the development of the first cyclotron by Lawrence and Livingston in 1932 (Lawrence and Livingston, 1932) and its later improvement by Lawrence and Cooksey (Lawrence and Cooksey, 1936), Hamilton described the preparation of the artificial radioisotope potassium-42 which was suitable for biological use (Hamilton, 1938). Three years later work in rats demonstrated rapid accumulation of potassium-42 in the myocardium following intraperitoneal injection (Noonan, Fenn and Haege, 1941).

In the early 1950's work by Burch and his associates demonstrated that radioactive rubudium could be regarded for practical purposes as an analogue of potassium in tracer studies, though the behaviour of the two elements was not identical (Love and Burch, 1953; Love, Romney and Burch, 1954; Burch, Threefoot and Ray, 1955; Threefoot, Ray and Burch, 1955; Ray, Threefoot and Burch, 1955). Similar properties were also found for radioactive caesium (caesium-134), (Love and Burch, 1953).

The demonstration, by Burch and his colleagues, of rapid myocardial uptake of rubidium-86, suggested the possibility of "demonstrating the myocardium by photoscanning after administration of this radioisotope" to the Ann Arbor Group led by Carr (Carr, Beierwaltes, Patno et al., 1962). They confirmed the feasibility of imaging the myocardium of the beating heart of living dogs using rubidium-86 and a rectilinear scanner (Carr, Beierwaltes, Wegst et al., 1962) but found that "cold areas" due to experimental myocardial infarction could be identified reliably only after excision of the heart (Carr, Beierwaltes, Patno et al., 1962). They therefore considered this isotope unsuitable for in vivo imaging of the myocardium and turned their attention to caesium-131. Using this tracer, they reported the first successful imaging of the normal myocardium in man (Carr, Gleason, Shaw et al., 1964). In the same publication, they showed that the imaging technique could detect acute myocardial infarction in man.

In the 14 years since this work by Carr and his colleagues a variety of other diffusible monovalent cation extractable indicators have been used clinically for myocardial imaging. Those currently available are potassium-38, potassium-42 and potassium-43,

rubidium-81 and rubidium-82, caesium-129 and caesium-131, thallium-201 and nitrogen-13 labelled ammonia. Following an analysis of the relationship between myocardial blood flow and myocardial uptake of this group of tracers, the potassium, rubidium and caesium agents and nitrogen-13 ammonia will be considered individually. Thallium-201 will be considered as a myocardial imaging agent from the point of view of its biological and its radioisotope properties. Other aspects of thallium-201 will be considered in Chapter II.

I. (2)(a) The mechanism of myocardial uptake of radioactive potassium and its analogues

The use of radioactive potassium and its analogues as clinically acceptable myocardial imaging agents is based on three properties of myocardial cells:

(i) The intracellular concentration of potassium is much higher than that in blood (Walker and Brown, 1977) and is maintained by an active process requiring energy consumption; the so called "sodium-potassium pump" (summarised by Conway, 1960 and Davson, 1964).

(ii) The active process will allow radioactive potassium and analogues to be rapidly trapped by the myocardium after the tracer has been injected intravenously.

(iii) In pathological states of the myocardium, the active transport system becomes deranged causing alterations in myocardial potassium content and trapping. It has been recognised for some time that myocardial ischaemia causes loss of potassium from the myocardial cell (Iseri, Alexander, McCaughey et al., 1952; Cummings, 1960; Jennings, Sommers, Kaltenbach et al., 1964; Case, Nasser and Crampton, 1969; Parker, Chiong, West et al., 1970; Lie,

Pairolero, Holley et al., 1975) presumably due to abnormalities of the sodium-potassium pump. Because of the abnormal sodium-potassium pump reduced concentrations of the injected tracer are present in abnormal myocardium. Such decreased accumulation of the potassium analogues could be due to defective uptake of injected isotope by the myocardium or abnormal leakage of trapped isotope from the damaged myocardial cells. There is evidence from work with caesium-129 that defective trapping is the main abnormality (Levenson, Adolph, Romhilt et al., 1975), though experiments using potassium-43 suggest there may also be a contribution from radionuclide efflux (Haider, Oldewurtel, Moschos et al., 1976).

I. (2)(b) Does the myocardial uptake of potassium analogues reflect regional myocardial blood flow?

The use of potassium and its analogues to measure myocardial blood flow depends on the Sapirstein principle i. e. an indicator distributed in accordance with regional flow will maintain a distribution that reflects regional flow during an early period after injection (Sapirstein, 1956). This principle was first applied to the measurement of myocardial blood flow in the rat (Hershgold, Steiner and Sapirstein, 1959).

For the diffusible indicators like potassium, the rate of uptake of the isotope by the myocardium is dependent upon the rate of delivery of the isotope to the myocardial capillaries, the rate of extraction from blood by the myocardial cells and the rate of release of the isotope from the myocardial cell following trapping. With the diffusible cation indicators, which are not completely extracted by the myocardium on their first passage through the coronary circulation, there will be a critical time at which the regional uptake of radio-activity in the normal heart, is proportional to regional blood flow.

This time is at the point when the integrated regional venous efflux has equalled the integrated, recirculated arterial reflux (Adelstein and Maseri, 1977). In order for uptake in all regions to reflect regional blood flow at the same critical time all parts of the myocardium must have the same average integrated extraction efficiency. This is unlikely to apply in ischaemic heart disease.

Various experimental studies have investigated the relationship between myocardial uptake of radioactive potassium and its analogues and the regional myocardial blood flow. Love and Burch, working with dogs, found a non-linear relationship between rubidium-86 uptake by the myocardium and coronary plasma flow. Thus a 50% reduction in plasma flow from resting levels produced a 44% decrease in rubidium extraction whilst a 50% increase in plasma flow yielded a 38% increase in rubidium extraction (Love and Burch, 1959). Moir, also working with dogs and rubidium-86, found that although the isotope clearance changed in the same direction as blood flow metered by a rotameter, the tracer technique gave a systematic underestimate of the degree of change of flow, with more marked errors in the hyperaemic state (Moir, 1966). Subsequent work with other potassium analogues has confirmed that the relationship between isotope uptake and blood flow rate is more linear in conditions of reduced flow than in hyperaemia. Prokop, Strauss, Shaw et al., (1974) using dogs and potassium-43, noted close agreement between myocardial potassium-43 uptake and coronary blood flow as measured by a labelled microsphere technique under conditions of partial and complete occlusion of a coronary vessel. In post ischaemic hyperaemia, however, there was little change of potassium-43 extraction whilst blood flow increased by 1.5 times over the control. A very similar investigation in dogs by Strauss, Harrison, Langan et al., (1975) with thallium-201 showed that there was again a good correspondence

between decrease of thallium-201 uptake by the myocardium and decrease in regional blood flow during coronary occlusion, but less of an increase of thallium-201 uptake than myocardial blood flow during hyperaemia. The disparity between the increase in myocardial thallium-201 uptake and the increment in myocardial blood flow during coronary hyperaemia was confirmed by Hamilton, Narahara, Yee et al., (1978).

From the evidence summarised above it appears that, under conditions of artificially changed coronary blood flow, the uptake of potassium and its analogues by the myocardium gives a reasonable measure of coronary blood flow, especially in the situation of reduced flow which is likely to operate in ischaemic heart disease.

What other factors may influence the myocardial uptake of this group of tracers in clinical practice?

To reach the inside of the myocardial cell the tracer must traverse the capillary wall, the intercellular space and the cell membrane. It has been estimated that in skeletal muscle, about 70% of the resistance to intracellular potassium uptake is at the capillary wall and about 30% at the cell membrane (Sheehan and Renkin, 1972). The intercellular space does not appear to offer any significant resistance. For rubidium the capillary barrier and cell surface barrier appear to be equally strong (Sheehan and Renkin, 1972). Estimates of the relative magnitudes of the capillary and cell membrane barriers are not available for the other potassium analogues, nor are figures available for myocardial as opposed to skeletal muscle cells.

The capillary barrier appears to be passive and is flow dependent (Adelstein and Maseri, 1977) but the cell surface barrier involves the active transport system (the sodium-potassium pump)

and flow is only one of the controlling factors. Hypoxia is an important determinant of the rate of active trapping of potassium by the myocardium (Gerlings, Miller and Gilmore, 1969) and hypoxia without any change in flow has been shown to decrease caesium uptake, which is restored to normal by the return of oxygen tension to normal (Levenson et al., 1975). Recent work with thallium-201 in dogs suggested that regional myocardial uptake of this isotope is relatively insensitive to reduction in myocardial perfusion unless this is accompanied by ischaemia (McArthur, Selwyn, Pratt et al., 1978).

The myocardial uptake of the potassium analogues may be affected by changes in the acid-base status of the subject. Thus, Weich, Strauss and Pitt (1977), reported that thallium-201 extraction by the dog heart was decreased when the dog was metabolically acidotic by infusion of ammonium chloride, whilst both Weich et al., (1977) and Hetzel, Westerman, Quinn et al., (1977) found bicarbonate induced metabolic alkalosis increased myocardial thallium-201 extraction. The complexity of the situation was stressed by the finding of various workers such as Young, Sealy and Harris (1954) and Gonzalez, Hojo and Brown (1968) that myocardial uptake of potassium increases during respiratory acidosis. Spiker and Smith (1972) suggested that the effect of respiratory acidosis might be explained by the increased catecholamine activity which accompanies hypercapnia.

Another important influence on the uptake of potassium analogues by the myocardium is provided by various cardioactive drugs. Thus Schelbert, Ashburn, Chauncey et al., (1974) found that, in rats, infusion of insulin in 20% glucose caused substantial increases in potassium, rubidium and caesium uptake by the myocardium, whilst digoxin depressed myocardial uptake of these isotopes. Costin and

Zaret (1975) confirmed the depression of potassium-42 uptake in dog myocardium by intravenous digitalis and found a similar effect with intravenous propranolol. Thallium-201 myocardial uptake was also depressed by intravenous digitalis and propranolol. These findings for thallium-201 were recently confirmed by Hamilton, Narahara, Yee et al., (1978). By contrast Weich et al., (1977) found thallium-201 extraction by the myocardium to be unaffected by insulin infusion, propranolol or the cardiac glycoside stropanthin. The effects of diuretic drugs have not been extensively studied in relationship to uptake of the potassium analogues, but Seller, Banach, Namey et al., (1975) clearly demonstrated that the commonly used diuretic drugs cause a loss of myocardial cell potassium.

The non-blood flow influences on myocardial cell uptake of potassium analogues summarised above are all systemic and thus should affect the normal myocardium uniformly. The same assumption cannot be made of the abnormal myocardium as any pathology present may already have caused changes in the active transport system of the cell which the systemic influences may accentuate. For this reason imaging of the myocardium with the potassium analogues whilst dependent on flow should not be regarded as pure "myocardial perfusion imaging" but rather as an image which is the product of myocardial perfusion and myocardial cell function. To obtain the best estimate of myocardial flow from such images should be performed as soon after the administration of the radioindicator as the myocardial to background ratio allows. The longer the delay after administration the more likely the image is to represent regional myocardial potassium mass rather than regional myocardial flow (Adelstein and Maseri, 1977).

I. (2)(c) Rest and "stress" myocardial imaging

Early studies showed that acute myocardial infarction or myocardial fibrosis consequent on old infarction could be demonstrated by myocardial imaging performed after injection of the tracer with the patient at rest (Carr et al., 1964; McGeehan, Rodriguez-Antunez and Lewis, 1968; Hurley, Cooper, Reba et al., 1971; Bennett, Smith, Lehan et al., 1972; Gorten, Nishimura and Williams, 1973). Such rest studies, however, often did not show abnormalities due to significant coronary artery occlusions which had not caused myocardial infarction.

It is not surprising that rest myocardial imaging should fail to demonstrate coronary artery lesions not associated with infarcted myocardium. As discussed above, in ischaemic heart disease a principal determinant of the distribution of the potassium analogues within the myocardium is regional myocardial perfusion, with areas of decreased perfusion accumulating less tracer and so giving rise to a "cold spot". Various studies have shown that regional myocardial perfusion may not be significantly changed at rest in spite of coronary artery disease (Cannon, Dell and Dwyer, 1972b; Schwartz, Froggart, Corvey et al., 1973; Cannon, Weiss and Casarella, 1976). During exercise, increased myocardial oxygen consumption requires an increase in coronary blood flow. It has been presumed that during exercise in coronary artery disease there will be a relatively smaller increase in coronary blood flow distal to significant fixed coronary artery occlusions compared to the increased flow in normal vessels, resulting in inadequate oxygen supply to the myocardium supplied by the obstructed artery and thus angina pectoris (Epstein, Redwood, Goldstein et al., 1971).

The relationship between the severity of coronary artery stenosis and regional myocardial perfusion at rest and during stress

has been investigated by the Seattle Group in an elegant series of animal and clinical studies using dual isotope (indium-113m and technetium-99m) labelling of albumen macroaggregates (Gould, Lipscomb and Hamilton, 1974; Gould and Lipscomb, 1974; Gould, Hamilton, Lipscomb et al., 1974; Ritchie, Hamilton, Gould et al., 1975). They demonstrated that resting regional myocardial perfusion distal to a coronary artery stenosis remained normal until the occlusion exceeded 85 per cent of the luminal diameter. When, however, coronary artery hyperaemia was induced by intracoronary injection of the contrast agent "Hypaque-M, 75 per cent" the increment in coronary artery blood flow was less than normal distal to occlusions of 45 per cent or more of luminal diameter. The measurements of myocardial blood flow were paralleled by the appearance of "cold spots" on the gamma camera myocardial images obtained during hyperaemia in coronary artery disease patients whose images were normal at rest (Ritchie et al., 1975). The appearance of stress induced regional abnormalities in myocardial perfusion in coronary artery disease patients whose resting myocardial perfusion was normal was confirmed by Schmidt, Weiss, Casarella et al., (1976) using xenon-133 and right atrial pacing.

The isotopic detection of relatively decreased perfusion during exercise distal to significant coronary artery occlusions predated the investigations outlined above. In 1973 Strauss, Zaret, Martin et al. introduced the concept of stress myocardial imaging. They found that if potassium-43 was injected intravenously at the end point of a symptom limited exercise test, abnormal myocardial images could be obtained in coronary artery disease patients whose rest myocardial images were normal. This work demonstrated that the Sapirstein principle (Sapirstein, 1956) of the distribution of a

flow dependent tracer remaining constant for some time after injection held for long enough with potassium-43 to allow imaging of transient, stress induced regional underperfusion of the myocardium. As will be discussed in Chapter III, stress myocardial imaging with radiopotassium and its analogues has been extensively investigated and shown to significantly increase the sensitivity of the technique in detecting coronary artery disease. Recent work both in animals (Hamilton, Narahara, Yee et al., 1978) and in man (Bull, Strauer, Burger et al., 1978; Albro, Gould, Westcott et al., 1978; Duperrier, Devaux, Roucayrol et al., 1978) has indicated that pharmacologically mediated increases in coronary blood flow may be an alternative to exercise in stress imaging.

I. (2)(d) Potassium radioisotopes as myocardial imaging agents

Three radioisotopes of potassium have been used or proposed as myocardial imaging agents in man: potassium-42, potassium-43 and potassium-38.

Potassium-42, the first radioisotope of potassium to be used in man (Hamilton, 1938), was shown by Noonan et al., (1941) to accumulate in rat myocardium after intraperitoneal injection. Potassium-42 has a physical half-life of 12.4 hours and principally decays by electron emission, releasing a 1.51 MeV gamma ray (Love, Smith and Pulley, 1969). The radiation dose from this isotope to the heart and to the skeletal muscle has been estimated as 1 to 1.13 rads per millicurie (Marinelli, Quimby and Hine, 1948) (Table 1). The very high energy gamma ray of potassium-42 makes it unsuitable for imaging with the gamma camera though Bennett et al., (1972) demonstrated acute myocardial infarctions using potassium-42 and a rectilinear scanner.

Potassium-43 has been the radioisotope of potassium most widely used for myocardial imaging. Introduced as the chloride

by Hurley et al. in 1971, it has a physical half-life of 22 hrs. (Hurley et al., 1971) and principally emits two gamma rays, in roughly equal percentages, with energies of 373 and 615 keV (Budinger and Rollo, 1977). The whole body radiation dose for potassium-43 has been calculated as between 0.6 and 0.7 rads per millicurie (Table 1) (Hurley et al., 1971; Budinger and Rollo, 1977; Adelstein and Maseri, 1977). The lower energy (373 keV) gamma rays can be used for imaging the myocardium using either the rectilinear scanner or gamma camera (Hurley et al., 1977), but extra shielding of the gamma camera is necessary to minimise scatter, septal penetration and penetration of the collimator wall by the high energy photons (Zaret, Martin and Flamm, 1974). Even with such shielding resolution may be poor (Haider et al., 1976). In a dosage of 1 to 2 millicuries intravenously, potassium-43 has been used for imaging of acute myocardial infarction (Hurley et al., 1971; Gorten, 1972), and for demonstration of stress induced transient myocardial ischaemia (Strauss et al., 1973). Because of the collimation problems, potassium-43 has not been very extensively applied to clinical studies and consequently the cost per dose has remained in excess of 100 dollars (Poe, 1977).

Potassium-38 has a physical half-life of 7.7 minutes and decays by emission of positrons (each producing two annihilation photons of 511 keV at 180^{o} to one another) and 2.17 MeV gamma rays. Myers (1973) has argued that potassium-38 is superior to potassium-43 for myocardial imaging because the physical half-life of the former is similar to the time of maximal potassium uptake by the myocardium (see below) and the shorter half-life would allow higher doses to be administered to patients, with improved counting statistics. Potassium-38 however is difficult to separate from target materials and for clinical use requires an on site cyclotron

and a positron camera (Weiss, Siegel, Sobel et al., 1977). Consequently, it has not found any place in clinical nuclear medicine.

I. (2)(d)(i) The myocardial uptake of potassium tracers.

After injection potassium radioisotopes are rapidly taken up by the myocardium. Love, Ishihara, Lyon et al., (1968) calculated that during an intravenous infusion of potassium-42 an average of 71% of the isotope present in coronary arterial blood was removed by the myocardium during the first passage. Poe (1972) injected potassium-42 directly into the left anterior descending artery of a dog and also found 71% clearance by the myocardium on the first passage. Yudilevich and Martin de Julian (1965) had previously calculated a 69% first pass clearance for potassium-42 by the isolated dog heart. By contrast with these three studies Holman, Eldh, Adams et al., (1973) injected potassium-43 into the left anterior descending coronary artery of the intact dog and found only 30-42% first pass clearance. They attributed the low value to depression of the sodium-potassium pump by previously injected radiographic contrast material, which is known to have adverse effects on the myocardium (Snyder, Cramer and Amplatz, 1971).

The rapidity of myocardial uptake of potassium radioisotopes has been confirmed by several studies. Strauss et al., (1973) found in patient studies that maximal myocardial to background ratios occurred "immediately following tracer administration" whilst Poe (1972), in his animal work, showed that myocardial uptake of potassium-42 remained at the maximum level from 5 to 20 minutes after intrajugular injection. Nishiyama, Sodd, Adolph et al., (1976) broadly confirmed these findings and demonstrated that 10 to 20 minutes after intravenous injection was the optimal

time for imaging the dog heart using potassium-43 and a gamma camera.

The rapid uptake of potassium by the myocardium (and other organs such as liver and skeletal muscle) is paralleled by a rapid fall in peripheral blood levels. Poe (1972) found 2 minute post injection blood levels of potassium-42 to be 2.2% of the injected dose and the one hour blood level to be 1.6%. In the studies of Nishiyama et al., (1976) the blood potassium-43 level at 3 minutes after injection was only 10% that at 30 seconds after injection, whilst Haider et al., (1976) reported that the blood concentration of potassium-43 one hour after injection was 14% of that at one minute after injection and that one hour after injection the myocardium contained 44 times more activity per gram of tissue than blood.

As noted above there is substantial liver accumulation of radiopotassium and Hurley et al., (1971), Bennett et al., (1972) and Nishiyama et al., (1976) have all commented on the difficulty this may cause when imaging the inferior myocardium.

Following the rapid myocardial accumulation of potassium tracers there is a slow washout phase. Strauss et al., (1973) found that 2 hours after intravenous injection of potassium-43 into a resting human subject, there was minimal discrimination between heart and adjacent lung and that interpretable images could not be obtained more than 75 minutes after injection. Poe (1972) reported that after intravenous injection of potassium-42 the activity in the dog heart began to decline from the maximal uptake value at 20 minutes after injection, though the rate of loss became slower from 90 minutes after injection. He calculated the average half-life of potassium-42 in the dog myocardium to be 6.5 hours. Nishiyama et al., (1976) showed that the quality of dog myocardial

gamma camera images obtained with potassium-43 began to decline 30 minutes after injection and commented on the difficulties this might cause in obtaining good multiple views in clinical studies.

I. (2)(d)(ii) Are potassium radioisotopes useful myocardial imaging agents?

Potassium-43 has proved very valuable in the prototype studies of rest and stress myocardial imaging. However, the physical characteristics of the potassium radioisotopes presently available are far from ideal for gamma camera imaging. In addition, the rate of loss of this element from the myocardium may cause difficulties in obtaining complete studies. For those reasons it seems unlikely that potassium radioisotopes will have a major role to play in clinical myocardial imaging in the future.

I. (2)(e) Caesium radioisotopes as myocardial imaging agents

Caesium (atomic number 55) belongs to the same group of elements as potassium. Early studies on human erythrocytes *in vitro* (Love and Burch, 1953) established that it had some potassium like biological properties. Caesium-131, caesium-129 and caesium-134m have been used or proposed for use as myocardial imaging agents in man.

In 1964, Carr et al., using caesium-131 and a rectilinear scanner reported the first successful imaging of the human myocardium. Caesium-131 has a physical half-life of 9.7 days and has x-rays of about 30 keV energy as its principal emission (Budinger and Rollo, 1977). Two millicuries are usually administered for imaging purposes. The whole body radiation dose has been calculated as 0.3 rads per millicurie (Table 1) (Chandra, Braunstein, Streuli et al., 1973).

Caesium-129 was introduced as a radiopharmaceutical by Sodd, Blue and Scholz (1971) whilst Romhilt, Adolph, Sodd et al., (1973)

showed it could be used to obtain gamma camera images of the myocardium. Caesium-129 has a half-life of 33 hours and principally emits 372 and 412 keV gamma rays (Romhilt et al., 1973). The usual patient dose is two to three millicuries and the whole body radiation dose about 0.20 rads per millicurie (Table 1) (Chandra et al., 1973).

Caesium-134m was proposed as a myocardial imaging agent by Chandra et al., (1973). It has the advantage of a single gamma ray emission with an energy (128 keV) very suitable for use with the gamma camera. The short half-life (2.9 hours), however, causes difficulty in availability. This is compounded by the necessity to use the radioisotope shortly after production to avoid unacceptable build up of caesium-134 which is associated with a very high radiation dose (calculated as 62 rads per millicurie by Chandra et al., 1973) (Table 1). The radiation dose can be reduced by inhibiting reabsorption of excreted caesium from the gut by oral administration of Prussian blue (Stather, 1972) but it is recommended that caesium-134m must be used within three to four half-lives (i.e. 9-12 hours of production). For this reason caesium-134m is a feasible radiopharmaceutical only for hospitals close to a nuclear reactor and has not become established in nuclear medicine practice.

I.(2)(e)(i) The myocardial uptake of caesium tracers.

Although caesium belongs to the same elemental group as potassium, caesium has a much larger hydrated crystal radius (Poe, 1977) with resultant problems in transfer across cell membranes.

Love and Burch (1953) found that caesium-134 entered human erythrocytes in vitro only about one fifth as quickly as potassium-42 or rubidium-86. The imperfections of caesium as a potassium tracer has been confirmed by work on myocardial uptake.

Love et al., (1968) reported that during an intravenous infusion dog myocardium extracted 22% of caesium-134 on the first pass. Poe (1972) injected caesium-131 into the left anterior descending coronary artery of the dog and also found 22% extraction on the first pass. The time of peak myocardial uptake of caesium after intravenous injection was estimated as 120 to 180 minutes by Poe (1972) and as 60 to 120 minutes by Nishiyama et al., (1976). After the peak uptake there is a slow decline. No clear value for the biological half-life of caesium in the heart is available, but probably lies between 16 and 43 hours (Poe, 1972).

The relatively slow myocardial clearance is reflected by the blood levels, which fall more slowly than those of radiopotassium. Poe (1972) found the blood level 2 minutes after intravenous injection to be 42% of the administered dose and the 60 minute level to be 3.8%. In the dog experiments of Nishiyama et al., (1976) the blood level did not reach 10% of the immediate post-injection level until 35 minutes after injection.

As would be expected from the slow myocardial uptake of caesium, imaging must be delayed for some time after the injection of the tracer. Carr et al., (1964) found that 2 to 3 hours after injection of caesium-131 was the best time for imaging. Chandra et al., (1973) using caesium-134m recommended waiting about 30 minutes after injection as did Nishiyama et al., (1976) with caesium-129.

I. (2)(e)(ii) Are caesium radioisotopes useful myocardial imaging agents?

Carr et al., (1964) successfully demonstrated acute anterior myocardial infarcts in man using caesium-131. With the same isotope, McGeehan et al., (1968) claimed to have also demonstrated posterior infarcts, but as the criterion for the diagnosis was a

central "cold spot", this may merely have been due to a dilated ventricular cavity. Because of the low energy of its emission (circa 30 keV) caesium-131 must be imaged using the rectilinear scanner. The low energy of the x-rays also means that tissue absorption makes satisfactory examination of the posterior myocardium difficult. This was confirmed in phantom studies by Tieman, Gilchrist and Wellman (1969) and clinically by Burguet, Merchie and Kulbertus (1975).

Caesium-129 emits gamma rays which can be imaged by the scintillation camera and Romhilt et al., (1973) confirmed this isotope could be used to detect myocardial infarction in man. The myocardial images obtained with caesium-129 are superior to those obtained with potassium-42 and potassium-43 (Romhilt et al., 1973; Nishiyama et al., 1976) and the heart-to-liver activity ratios obtained with caesium-129 are higher than those with potassium-43 (Nishiyama et al., 1976). This last advantage, however, is somewhat offset by accumulation of caesium in the spleen and the fundus of the stomach (Nishiyama et al., 1976).

All of the radioisotopes of caesium have their clinical utility limited by the slow myocardial uptake as this makes them completely unsuited for stress imaging - the stress induced transient ischaemia has corrected before adequate myocardial uptake occurs. Thus although some centres have until recently continued to use caesium-129 for myocardial imaging (Sheyretova, Beleov and Kaloyanova, 1976; Walton, Rowlands, Shields et al., 1977) the inherent biological limitations and the availability of alternative myocardial imaging agents are likely to make caesium myocardial imaging of historical interest only.

I. (2)(f) Rubidium radioisotopes as myocardial imaging agents

Rubidium (atomic number 37) belongs to the same group of

elements as potassium and has some potassium-like physiological properties both in vitro (Love and Burch, 1953) and in vivo (Burch, Threefoot and Ray, 1955). The isotopes of rubidium which have been applied to studies of myocardial blood flow are rubidium-86, rubidium-84, rubidium-81 and rubidium-82m.

Rubidium-86 was the first radioisotope to be used for myocardial imaging. Carr, Beierwaltes, Wegst et al., (1962) showed decreased rubidium-86 uptake at the site of an experimental myocardial infarction in the excised dog heart. This isotope, with a physical half-life of 18.7 days, emits 1079 keV gamma rays (Budinger and Rollo, 1977). These photons are unsuitable for imaging with either the gamma camera or the rectilinear scanner. Therefore, although rubidium-86 has been used in methods of measuring coronary blood flow by external counting (Donato, Bartholomei and Giordani, 1964) it is unsuitable as a myocardial imaging agent.

Rubidium-84 has also been used in the measurement of coronary blood flow by external counting techniques (McHenry and Knoebel, 1967). Rubidium-84 has a 33 day half-life and decays by electron capture, emitting an 882 keV gamma ray, and also by positron emission with resultant 511 keV annihilation photons (Budinger and Rollo, 1977). The 882 keV gamma ray is unsuitable for use with the scintillation camera. The positron emission might be suitable for imaging with the positron camera but the clinical use of this isotope is likely to be prevented by the very high radiation dosage its use incurs (16 rads per millicurie according to Budinger and Rollo, 1977) (Table 1).

Rubidium-81 is the only rubidium radioisotope which has been used to any extent for human myocardial imaging, having been introduced in 1974 (Martin, Zaret, McGowan et al., 1974). This isotope has a physical half-life of 4.6 hours and decays with emission

of a 436 keV photon and 511 keV annihilation photons from positron emission. In addition, krypton-81m is formed during the decay and this 13 second half-life isotope decays to the stable krypton-81, yielding a 190 keV photon (Martin et al., 1974). Martin et al., (1974) and Berman, Salel, De Nardo and Mason (1975) have shown that rubidium-18 can be successfully employed, in a dose of 2-4 millicuries, for both rest and stress myocardial imaging.

The principal problem with rubidium-81 relates to contamination of the radiopharmaceutical by other rubidium radioisotopes. Martin et al., (1974) recommend using rubidium-81 as soon as possible after production to avoid degradation of the images by high energy photons emitted by the small amounts of rubidium-82m present. Nishiyama et al., (1976) found that the presence of contaminating rubidium-82m meant they could not obtain satisfactory scintillation camera images with rubidium-81. Rubidium-81 preparations are also contaminated by rubidium-83 and rubidium-84 (Rich, Lembares, Harper et al., 1975). In addition to degrading the rubidium-81 image, the contaminants also increase radiation dosage. Thus, although the radiation dose from pure rubidium-81 is calculated as 0.08 to 0.1 rads per millicurie (Feller and Sodd, 1975; Budinger and Rollo, 1977) the effective dose from available, contaminated preparations is 0.3 to 0.4 rads per millicurie (Martin et al., 1974; Budinger and Rollo, 1977) (Table 1).

Rubidium-82m has a physical half-life of 1.25 minutes and decays by positron emission, with 511 keV annihilation photons, and electron capture, emitting a 776 keV gamma ray (Budinger and Rollo, 1977). The positron emission has been shown to be suitable for myocardial imaging in the dog (Budinger, Yano and Hoop, 1975) and has been used to study changes in myocardial perfusion induced by nitroglycerin during experimental myocardial

ischaemia (Beller, Alton, Moore et al., 1976). This isotope, however, does not seem to have been used for myocardial imaging in man.

I. (2)(f)(i) The myocardial uptake of rubidium tracers.

Rubidium was introduced as a potassium tracer by Burch and his associates (Burch and Love, 1953; Burch, Threefoot and Ray, 1955; Threefoot, Burch and Ray, 1955). The whole body distribution and kinetics of rubidium differ somewhat from those of potassium both in the rabbit and in man (Kilpatrick, Renschler, Munro et al., 1956; Martin and Walker, 1958) but the myocardial uptake of the two elements is very similar.

Yudilevich and Martin de Julian (1965) estimated the first pass extraction of potassium-42 and rubidium-86 by the isolated dog heart to be identical at 69 per cent. Love et al., (1968) gave a constant infusion of rubidium-86 to intact dogs and calculated first pass myocardial clearance to be 65 per cent (compared to 71 per cent for potassium-42). Following the bolus injection of 100 microcuries of rubidium-81 into dogs, Nishiyama et al., (1976) showed a fast component in the myocardial uptake, with a half-life of 2.2 minutes (2.0 minutes for potassium-43). The blood activity of rubidium-81 reached 10 per cent of the immediate post injection level 7 to 8 minutes after injection, compared to 3 minutes for potassium (Nishiyama et al., 1976). Schelbert, Ashburn, Chauncey et al., (1974), working in rats, calculated that a maximal myocardial to blood ratio of 27 to 1 was obtained for both potassium-43 and rubidium-86 within 10 minutes of injection. Following the peak levels, the myocardial to blood activity ratios declined more slowly for rubidium than potassium with a calculated biological half-life in the heart of 3.35 hours for rubidium and 2.18

hours for potassium (Schelbert et al., 1974). This more prolonged retention of rubidium in the myocardium might be useful in myocardial imaging by making it easier to obtain multiple projections. The optimal time to begin myocardial imaging with rubidium is about 10 minutes after injection of the tracer into a resting subject (Nishiyama et al., 1976).

I. (2)(f)(ii) Are rubidium radioisotopes useful myocardial imaging agents?

The rubidium radioisotopes have not become established clinically as myocardial imaging agents. Only rubidium-81 is suitable for routine use with the scintillation camera. As noted above, because of contaminants, it is recommended that rubidium-81 be used shortly after production to avoid image degradation and to reduce radiation dosage. This effectively limits the use of the tracer to hospitals close to reactors and it thus seems unlikely it will become a widely used myocardial imaging agent.

Although not suitable for routine use, some research uses of rubidium radioisotopes may be possible.

Rubidium-82m is a positron emitter and thus can be used, with the positron camera, to perform tomography of the myocardium and thus, perhaps, increase accuracy of localisation of the abnormalities (Weiss et al., 1977). It also has a short half-life which allows sequential assessment of myocardial ischaemia and response to stress or intervention with drugs. Unlike most short lived positron emitting potassium analogues rubidium-82m can be obtained from a long lived (strontium-82) generator and is therefore available at will to hospitals situated some distance from reactors (Budinger et al., 1975).

Rubidium-81 generates krypton-81m (Jones and Matthews, 1971). Once the rubidium-81 is deposited in the myocardial cell

an equilibrium between the high energy rubidium-81 and the lower energy krypton-81m will be established. Whilst the active transport system will retain rubidium within the myocardial cell (though incompletely), krypton, as an inert gas, will be washed away according to regional blood flow. A ratio based on regional rubidium-81 to krypton-81m activities should give an index which could be related to regional myocardial blood flow (Martin et al., 1974). This technique has been used to measure splenic blood flow (Jones, Pettit, Rhodes et al., 1977) but has not yet been successfully applied in the myocardium.

I. (2)(g) Thallium radioisotopes as myocardial imaging agents

In 1861 the English chemist William Crookes noted a brilliant green line on the spectrum of some selenium residues. He confirmed that this was due to a new element which he named Thallium (symbol Tl) from the Greek θαλλος or Latin thallus (a budding twig) "a word which is frequently employed to express the beautiful green tint of young vegetation and which I chose on account of the green line which it communicated to the spectrum recalling with peculiar vividness the fresh colour of early spring" (Crookes, 1862).

Thallium (atomic number 81) is a heavy metal and belongs to a different elemental group from potassium, rubidium and caesium. Mullins and Moore (1960), however, noted that the crystal radius of the univalent thallous cation (1.44A) was between that of potassium (1.33A) and rubidium (1.49A) and thus felt that thallium might have physiological properties similar to those of potassium and rubidium. In an isolated preparation of frog sartorius muscle they found results which were "consistent with the view that the muscle fiber membrane cannot distinguish between the toxic heavy metal Tl^+ and K^+, provided that the concentrations of the former ion are kept low" (Mullins and

Moore, 1960). The biological similarities between potassium and thallium were confirmed by Gehring and Hammond in rabbit erythrocytes (Gehring and Hammond, 1964) and in rats and dogs (Gehring and Hammond, 1967). They concluded that "activation of the Na and K activated adenosine triphosphatase by the substitution of thallium for potassium supports the belief that the mechanism involved in the active transport of potassium cannot differentiate between potassium and thallium" (Gehring and Hammond, 1967). That thallium uptake by cells was due to activation of the sodium-potassium ATP-ase system was confirmed by Britten and Blank in the rabbit kidney, but their results suggested that the mechanism of uptake was not identical, with thallium binding on two sites in the enzyme system compared to one for potassium (Britten and Blank, 1968).

The first suggestion of the use of thallium as a potassium analogue for nuclear medicine purposes was by Kawana, Krizek, Porter et al., in 1970. Using thallium-199 they demonstrated the possibility of imaging the human myocardium, but the images were not optimal because of contaminating high energy gamma rays causing excitation of the lead in the collimator and they suggested that thallium-201 might be a more suitable radiopharmaceutical. This isotope (as thallous chloride) was eventually produced as a radiopharmaceutical by the Brookhaven National Laboratory in the U.S.A. (Belgrave and Lebowitz, 1972; Lebowitz, Greene, Fairchild et al., 1975). Using a cyclotron, they bombarded a natural thallium (203) target to produce lead-201 which decays to thallium-201. The thallium-201 is separated from the lead by a process involving dissolving the target in nitric acid and passing the solution through several resin exchange column stages.

Thallium-201 has a physical half-life of 73.5 hours and decays by electron capture to mercury-201 emitting gamma rays of 135 and 167

keV. The mercury-201 then decays with emission of 65-82 keV X-rays (Lebowitz et al., 1975; Duphar Laboratories, Thallium-201 product information sheet). The thallium-201 is contaminated with small amounts of thallium-200 (half-life 26.1 hours) and thallium-202 (half-life 288 hours) (Wackers and De Jong, 1976; Duphar Laboratories Thallium-201 product information sheet).

The gamma rays emitted by thallium-201 have suitable energies for scintillation camera imaging but they are present in very low incidence and use of the mercury X-rays is usually recommended. Atkins, Budinger, Lebowitz et al., (1977) found that they obtained a seven times greater counting rate with the X-rays compared to the gamma rays, in spite of some absorption of the X-rays by overlying chest wall. The newer gamma cameras can image the X-rays quite satisfactorily but with older cameras a pinhole collimator is necessary, with resultant loss of counting rate (Atkins et al., 1977).

The whole body radiation dose from Thallium-201 has been variously quoted as 0.07 to 0.24 rads per millicurie (see Table 1) (Feller and Sodd, 1975; Bradley-Moore, Lebowitz, Greene et al., 1975; Atkins et al., 1977; Budinger and Rollo, 1977; Adelstein and Maseri, 1977). The critical organ for radiation exposure is the kidney, as this contains the highest concentration of the radionuclide, particularly the renal medulla (Lebowitz et al., 1975). The kidney radiation dosage has been estimated to lie between 0.39 and 1.17 rads/millicurie (Table 1), with the renal medulla receiving approximately four times the dose of the renal cortex (Bradley-Moore et al., 1975).

I.(2)(g)(i) Myocardial uptake of injected thallium-201.

Like rubidium and potassium, thallium-201 is rapidly taken up by the myocardium. Abbate, Maseri, Biagini et al., (1977)

injected thallium-201 into the pulmonary artery of patients undergoing cardiac catheterisation and calculated first pass myocardial extraction to be 83%, whilst Pitt and Strauss (1976) quote a first pass extraction of 85% for the isotope.

The rate of blood clearance has been investigated in various species and broadly agree with one another. Bradley-Moore et al., (1975) working with goats found the half time of the disappearance from blood of intravenously injected thallium was less than one minute. Strauss and Pitt (1977b) similarly reported, in the dog, that the half time of disappearance of thallium from blood was less than 30 seconds with the blood activity 10 minutes after injection reaching 7 per cent of the level immediately after injection. Nishiyama et al., (1976), also working with dogs, found slightly slower clearance, which occurred in a biexponential fashion with the half time of the fast component being 2.9 minutes. The longer half time of clearance found by Nishiyama et al. was reflected in higher residual blood levels - 10 per cent of immediate post injection levels at 13 minutes after injection. The rate of blood clearance in humans was studied by Schelbert, Henning, Rigo et al., (1976) who found that at 15 minutes after injection the blood activity was about 1 per cent of the dose per litre of blood. Atkins et al., (1977) also investigated the rate of clearance in humans. They reported that thallium-201 was cleared from human blood in a bi-exponential fashion, with 91.5 per cent of the tracer having a disappearance half time of 5 minutes. The residual thallium in the blood had a much slower clearance (half time 40 hours) and was thought to be principally due to radioactivity in the red cells, though Strauss and Pitt (1977b) stated that the majority of the residual blood concentration was in plasma. Atkins et al., (1977) found that the 5 minute post injection blood activity was only 5 to 8 per cent of the injected dose.

As would be expected from the short blood disappearance half times, the times reported for attainment of maximal myocardial uptake are short ranging from 5 minutes in humans (Atkins et al., 1977) through 10 minutes in goats (Bradley-Moore et al., 1975) to 5 to 15 minutes in dogs (Nishiyama et al., 1976).

Thallium-201 has been shown to have greater myocardial concentration and lower liver concentration than rubidium or caesium in mice (Strauss et al., 1975) and in rats (Schelbert et al., 1975), though this finding was not confirmed in dogs, where caesium produced a better heart to liver activity ratio than thallium, though thallium was superior in this respect to potassium-43 (Nishiyama et al., 1976).

Following attainment of maximal myocardial uptake, the thallium-201 is retained within myocardium longer than potassium (Nishiyama et al., 1976; Pitt and Strauss, 1976). Thus Atkins et al., (1977) found that the myocardial uptake of thallium-201 did not significantly change from 5 to 60 minutes after injection in human subjects. Bradley-Moore et al., (1975) reported that clearance from the goat heart occurred in a two compartmental form which had half times of 4.4 hours and 40 hours.

The best time to begin myocardial imaging is 5 to 10 minutes after injection of thallium-201. Atkins et al., (1977) obtained good myocardial images in humans from 5 to 60 minutes after injection. Strauss et al., (1975) found the heart to blood activity ratio was maximal 10 minutes after injection in mice, whilst Bradley-Moore et al., (1975) demonstrated maximal heart to background activity 10 to 25 minutes after injection in goats.

I. (2)(g)(ii) Is thallium-201 a useful myocardial imaging agent?

The answer to this question in the clinical context is the basis of the rest of this thesis and will be discussed in detail in the following

chapters. From physical and biological considerations thallium-201 is the potassium analogue of choice at present. The physical half-life is sufficiently long to give a convenient shelf life, but not so long as to prevent repeat studies within a reasonably short period. The X-rays emitted are suitable for imaging with the conventional gamma camera without the need for special shielding. The rapid myocardial uptake makes it suitable for both stress and rest imaging whilst the myocardial retention is sufficiently long to allow multiple views to be easily obtained.

Although thallium-201 is the current potassium analogue of choice, it is not the perfect myocardial imaging agent. The X-rays are of such an energy that some tissue absorption occurs in overlying chest wall and have an energy somewhat lower than the optimal one for use with the standard scintillation camera. The high concentration of thallium-201 in the renal medulla and the physical half life mean that the dose which can be administered for any one study is limited to about 2 millicuries (though 5 millicuries was proposed for "high risk" patients by Nishiyama et al., (1976)). The final problem relating to thallium-201 is one of the method of production. This is a complicated procedure, involving a cyclotron and purification measures. As a result thallium-201 is relatively expensive (about £45 per 2 millicurie dose in the U.K. in 1978) and is unlikely to drop significantly in price.

I.(2)(h) Other tracers for non invasively imaging normal myocardium

During metabolic studies in dogs undertaken at the Sloan Kettering Institute it was noticed that nitrogen-13 labelled ammonia accumulated within the myocardium (Hunter and Monahan, 1971; Monahan, Tilbury and Laughlin, 1972). The Chicago group confirmed that this radiopharmaceutical could be used for myocardial imaging in man (Harper, Schwartz, Beck et al., 1973) and that it was

possible to detect acute and old myocardial infarction in man using nitrogen-13 ammonia and a portable scintillation camera (Walsh, Harper, Resnekov et al., 1976).

Nitrogen-13 has a 10 minute physical half-life and decays by positron emission with production of two annihilation photons at 180^{o} to one another. These photons can be imaged using the standard scintillation camera (Walsh et al., 1976). Because of the high energy of the photons, however, heavy collimation is necessary. If a lead collimator is used a coarse grid pattern is produced. It is, therefore, recommended that a specially constructed tungsten collimator (which has thinner septa) is used and that this is rotated twice through 120^{o} during imaging (Walsh, Fill and Harper, 1977). Optimal images from nitrogen-13 ammonia, however, can be obtained only when a positron camera is used. The use of the positron camera enables very high quality tomographic images of the myocardium to be produced (Weiss et al., 1977).

The mechanism of cellular uptake of nitrogen-13 ammonia has not been fully elucidated. Studies in human red cells have shown that ammonium ion may substitute for potassium in the sodium-potassium ATP-ase dependent pump (Post and Jolly, 1957) but this property has not yet been shown to be present in myocardial tissue. The alternative mechanism, which is considered more likely, is that uptake occurs by diffusion of free ammonia (Walsh, Fill and Harper, 1977). Once intracellular it is thought that the ammonia is principally removed by incorporation into glutamine via the glutamine synthetase pathway. The labelled glutamine then becomes dispersed throughout the body amino acid pool (Walsh, Fill and Harper, 1977). An alternative method of removal of intracellular ammonia may be conversion to carbomyl phosphate, the first step in the synthesis of urea. There is some evidence

this pathway may be more important in the pathological than in the normal heart (Chazov, Smirnov, Mazaev et al., 1973).

The nitrogen-13 ammonia is administered as an intravenous bolus of 20 to 25 millicuries of carrier free tracer. Maximal uptake of the isotope occurs in the liver, which accumulates about 15% of the administered dose, but 2 to 4 per cent is taken up by myocardium (Harper, Lathrop, Krizek et al., 1972). Myocardial uptake of nitrogen-13 ammonia is rapid, with a first pass extraction of 85 to 90 per cent (Harper et al., 1972; Smith, Beller, Gold et al., 1974). The mean biological half-life of the tracer in the dog myocardium is about 70 minutes (Smith et al., 1972) and the cardiac levels remain constant in man for 30 minutes (Harper et al., 1972). Myocardial imaging with nitrogen-13 ammonia may be complicated by substantial pulmonary uptake, especially in smokers (Walsh, Fill and Harper, 1977). Because of the short half-life a low radiation dose is received by the patient during myocardial imaging with this radionuclide (Table 1), the whole body dose being of the order of 0.005 rads per millicurie and the liver dose 0.025 rads per millicurie (Harper et al., 1972).

Is nitrogen-13 labelled ammonia a useful myocardial imaging agent? Animal studies have shown a good correlation between the distribution of nitrogen-13 ammonia and technetium microspheres in the myocardium (Walsh, Fill and Harper, 1977). Clinical studies have demonstrated that the technique can be used to detect acute or old myocardial infarction in man and that increases or decreases in the size of the defect due to acute infarcts on sequential studies correlated well with the patient's clinical course (Walsh, Fill and Harper, 1977). Stress imaging with nitrogen-13 ammonia is feasible, in view of the rapid myocardial uptake and initial studies in patients were promising (Al-Sadir, Harper, Goldbarg et al., 1973). Later results, however, have been more difficult to

interpret as, in some patients, defects present on rest images decreased in size or disappeared during stress (Walsh, Fill and Harper, 1977).

The principal problem in the clinical use of nitrogen-13 ammonia is the need for a cyclotron close to the hospital, preferably a medical cyclotron actually in the hospital (Walsh, Fill and Harper, 1977). Because of this severe limitation on ease of availability it seems likely that, though nitrogen-13 ammonia may be an interesting research tool for some centres, it will not become widely used. Even if more nuclear medicine departments eventually have positron cameras, other positron emitting radionuclides (such as generator produced rubidium-82m) are perhaps more likely to be used for myocardial scintigraphic tomography.

Labelled fatty acids have also been used for myocardial imaging. Evans, Gunton, Baker et al., (1965) demonstrated that oleic acid iodinated across its double bond could be used to obtain rectilinear scanner images of the myocardium. This substance, however, never became clinically useful because only a low specific activity iodine-131 product was available. Various other fatty acids have been tried for myocardial images with varying success, but recently terminally radioiodinated 16-hexadecenoic acid has been prepared (Robinson and Lee, 1975) and shown to be efficiently extracted by the myocardium. The labelling process is rapid enough to allow use of the short lived iodine-123 and preliminary results suggest that this may be a clinically useful radiopharmaceutical (Poe, Robinson and Zielinski, 1976). Using a pinhole collimator, which magnifies the heart image by two, images can be obtained at the rate of 100,000 counts per minute for a 5 millicurie dose (Poe et al., 1976).

Studies using a positron camera have also been carried out with fatty acids labelled with carbon-11 (Weiss, Hoffman, Phelps et al., 1976). Recently, 17 iodo-heptadecenoic acid has been suggested as a myocardial imaging agent (Machulla, Stocklin, Kupfernagel et al., 1978).

The ultimate role of labelled fatty acids as myocardial imaging agents is not yet clear. Should iodine-123 become readily available for labelling, they might prove very interesting as gamma emitting tracers which are distributed in proportion to regional blood flow but also give information on the intermediary metabolism of the myocardium.

Radioiodine labelled toluidine blue was used for myocardial imaging in dog studies (Carr, Carroll, Di Guilio et al., 1973) but has never been developed any further.

I. (3) Assessment of Myocardial Blood Flow by Intracoronary Injection of Radioactive Tracers

Three main types of radioactive tracers have been injected directly into the coronary arteries to assess myocardial blood flow:

- potassium analogues are partially distributed in proportion to regional blood flow. However, as has already been discussed (Chapter I. (2)(b)) other factors may affect myocardial uptake of these substances. For this reason, though they may be useful for qualitative studies they cannot be used to quantitate accurately regional myocardial perfusion and they will not be considered further.
- diffusible inert indicators such as the inert gases krypton and xenon and extractable particulate indicators have both been used extensively in quantitative studies and will be considered in turn.

I. (3)(a) Diffusible inert indicators

The use of diffusible inert substances to measure myocardial blood flow is based on the technique initially devised by Kety and Schmidt using nitrous oxide to measure cerebral blood flow (Kety and Schmidt, 1945). The general principle was later extended to measurement of blood flow through other organs (Kety, 1951; Kety, 1960). The principle of such studies is, that if a substance is freely diffusible into an organ, is neither trapped nor retained in the organ by any active process and is neither metabolised or synthesised by the organ, then the rate of disappearance of the substance after injection into the organ is proportional to the blood flow per unit mass of tissue.

Early applications of the Kety-Schmidt technique to measurement of myocardial blood flow used non-radioactive substances such as nitrous oxide (Bing, Hammond, Handelsman et al., 1949; Rowe, 1959) or hydrogen (Klocke, Koberstein, Pittman et al., 1968). The substances were inhaled or infused into the coronary artery until the myocardium was saturated. The coronary sinus and arterial concentrations of the indicator during desaturation were measured and the blood flow per unit mass calculated from the formula

$$\frac{F}{W} = \frac{\lambda C_v(t_s) / \rho}{\int_0^\infty \{C_v(t') - C_a(t')\}\, dt'}$$

where F/W = flow per unit mass of tissue, λ is the partition coefficient for the indicator between blood and the myocardium, $C_v t_s$ is venous concentration at the time of saturation, ρ = specific gravity of the tissue and $C_v(t')$ and $C_a(t')$ are arterial and venous concentrations of the indicator at time t (Cannon, Weiss and Sciacca, 1977).

The desaturation method of measuring myocardial blood can also be applied to radioactive tracers. The method, however, has some important practical disadvantages (Cannon et al., 1977). The measurements require that all tissue be loaded to the same concentration. This is often difficult to achieve in practice, especially in ischaemic regions. The concentration of the indicator must be accurately measured at the tail of the washout curve. This is often difficult. Perhaps most important of all, the measurements of blood flow obtained relate to the whole field of drainage of the venous circulation sampled and it is impossible to measure regional myocardial blood flow.

For these reasons the measurement of myocardial blood flow by radioactive inert gas techniques usually use the "residue method" (Cannon et al., 1977). In this technique the tracer is injected as a bolus into the coronary artery and an external detector (a probe or scintillation camera) measures the radioactivity remaining in the heart as a function of time. Blood flow is then given by the formula

$$\frac{F}{W} = \frac{\lambda\, q_o / \rho}{\int_o^\infty q_t(t')dt'}$$

where q_o is the response of the detector at time zero corresponding to the injected dose and $\int_o^\infty q_t(t')dt'$ is the area under the curve recorded by the external detector (Cannon et al., 1977). If it is assumed there is no exchange of tracer between regions, the function can be extended to measure regional myocardial blood flow. The residue function method is complicated by the need to measure the concentration of the tracer until time infinity. As will be explained below various manoeuvres have been devised to overcome this problem.

I. (3)(a)(i) Radioactive inert gases used for measuring myocardial blood flow.

The radioactive tracers used for inert diffusible indicator measurement of myocardial blood flow are mainly the inert gases krypton and xenon. Radiolabelled water, a positron emitter, and radioiodine labelled antipyrine have also been used (Adelstein and Maseri, 1977). These indicators have the advantage over the inert gases of not accumulating in lipid tissue (see below). However, they are unsuitable for imaging with standard scintillation cameras and, because they recirculate to a significant extent, an additional correction factor must be introduced into the calculations, adding further uncertainty to the measurements (Maseri, Pesola, L'Abbate et al., 1974).

Xenon-133 is the indicator most widely used for human studies. This 5.3 day half-life radioisotope decays to cerium-133 emitting 347 keV β particles, 81 keV gamma rays and 31 keV X-rays. The 81 keV gamma ray can be used for imaging with the scintillation camera, but the image is somewhat degraded by the production of Compton scatter radiation of energy sufficiently similar to the 81 keV photopeak that is in the primary energy window (Cannon et al., 1977). The use of xenon is also complicated by the accumulation of the tracer in epicardial and pericardial fat (Shaw, Pitt and Friesinger, 1971). The myocardium may act as a tonometer for the inert gas, with xenon initially flowing from myocardial to epicardial fat stores and then vice versa when, during myocardial washout, the xenon gradient is reversed. This effect, more significant at the end than the beginning of the washout curve, reduces the slope (Maseri et al., 1974). The inert gases, however, are almost free from problems induced by recirculation as more than 95% of the intra-arterial dose is excreted in one passage through the lungs (Chidsey, Fritts, Hardewig et al., 1959). An intravenous dose of 40 millicuries of

xenon-133 yields a gonadal radiation dose of approximately 10 millirads (Cannon et al., 1977).

Xenon-127 has a half-life of 36.4 days and decays by electron capture emitting 172 keV and 204 keV photons which are suitable for imaging. It also emits 375 keV photons. The isotope, however, has limited availability (Adelstein and Maseri, 1977) and this, together with interference from multiple photopeaks, has restricted its use.

Krypton-85 was the first radioisotope of an inert gas to be used to measure myocardial blood flow in animals (Herd, Hollenberg, Thorburn et al., 1962). However, this isotope has not been widely used in man because its decay emits a high percentage of beta radiation and gamma rays with high energy, thus increasing the radiation exposure to the patient (Cannon et al., 1977).

Krypton-81m is a daughter of rubidium-81. It has a photopeak of 190 keV and a very short physical half-life of 13 seconds (Polcyn and Nickles, 1977). Though the invasive nature of the technique and the physical half-life of the isotope probably preclude widespread use, the ability to obtain krypton-81m from a rubidium-81 generator means that this very short lived isotope is available to centres not situated close to a cyclotron. By infusing constant elutions of krypton-81m from a rubidium-81 generator into a special ring catheter placed in the aortic root, the Hammersmith group have been able to study myocardial blood flow responses in patients during pharmacological interventions (Selwyn, 1976).

Carbon-11 labelled carbon dioxide, oxygen-15 labelled carbon dioxide and nitrogen-13 are all short lived positron emitters which could also be used to study myocardial blood flow at centres equipped with a cyclotron and a positron camera (Budinger and Rollo, 1977).

I. (3)(a)(ii) Analysis of myocardial activity curves obtained from radioactive inert gas washout.

As noted above, the determination of myocardial blood flow following the bolus injection of an inert tracer into the coronary artery requires, in theory, the measurement of the area under the disappearance curve until the activity has disappeared. In practice, when this stochastic or lumped approach is employed, the long tail on the washout curve and the effect of lipid dissolved xenon-133 on the tail of the curve require that some form of empirical truncation be employed (Bassingthwaighte, Strandell and Donald, 1968). Since the stochastic approach was introduced to avoid empirical assumptions (Zierler, 1965) its use for measuring myocardial blood flow is not recommended (Adelstein and Maseri, 1977).

An alternative approach is to measure the initial distribution of the tracer. This is linearly related to the proportion of abnormal flow in each region (Adelstein and Maseri, 1977). However, it reflects the distribution of flow only from the afferent vessels into which the indicator is introduced and thus will underestimate total regional flow if there is significant collateral circulation (Adelstein and Maseri, 1977). Also, because it measures fractional flow, the amount of radioactivity deposited initially depends both upon flow in the region and the mass of tissue.

The third group of approaches utilises analyses of the washout slopes. The simplest method assumes homogeneous tracer distribution and analyses the washout monoexponentially. There is some experimental evidence that tracer distribution, even in conditions of normal perfusion, is not uniform. Thus, Yipintsoi and Bassingthwaighte (1970) measuring myocardial transit times of various tracers in the isolated perfused dog heart, found some evidence of shunting by diffusion across arteriolar or capillary

vascular loops in the left ventricular subendocardial region. Such shunting would lead to uneven tracer distribution, but the effect is thought to be too small to be quantitatively significant (Cannon et al., 1977). Cannon, Dell and Dwyer (1972a) devised a method for monoemponential analysis of the first forty seconds of the washout in the human heart. By calculating the "initial washout" slope, k, they calculated myocardial blood flow from the formula

$$F = k\lambda/\rho$$

where F = myocardial blood flow in millilitres per 100 grams of tissue per minute, λ is the partition coefficient of xenon between blood and myocardium and ρ is the tissue specific gravity. The initial 40 seconds of the curve was chosen for analysis because it is the part of the curve least affected by arrival of isotope in chest wall or lung behind the heart (Cannon et al., 1972a) and because the washout curve is then least affected by isotope in non muscular structures (fibrous and adipose tissue) around the heart (Shaw et al., 1971). Myocardial blood flows derived from the "initial slope" of washout of inert gases have been shown to correlate well with direct flowmeter measurements of coronary blood flow in dogs (Herd et al., 1962; Ross, Ueda, Lichtlen et al., 1964; Shaw et al., 1971).

The derivation of myocardial blood flow from monoexponential analyses of the initial slope, has been criticised by the Pisa group (Maseri et al., 1974) who noted that the approach reasonably fitted the observed curves, at best, down to 10-30% of the peak. The deviation from the monoexponential course could be explained on the basis of recirculation of the tracer, indicator diffusion hold up in fat and non-uniform perfusion of the myocardium (Maseri et al., 1974). Maseri also claims (Adelstein and Maseri, 1977) that when the initial slope of the washout is used as an index of regional perfusion its value is not linearly related to the percentage of

abnormal flow in each region but instead overestimates the perfusion because of the greater weighting by the normally perfused myocardium that has received a greater initial share of the indicator. For this reason he advocates that the washout curve should be followed beyond the initial slope and that various methods of analyses should be employed - initial distribution, residual distribution, analyses of initial and secondary slopes - to derive the most complete picture of regional perfusion (Adelstein and Maseri, 1977). The importance of this point is stressed by a recent publication from Maseri's group, in which it was shown that the initial washout of xenon-133 from post stenotic areas of the myocardium of coronary artery disease patients was normal at rest, but that at the time that 90% of the total injectate had been washed out, the residual activity was greater in post stenotic than in areas supplied by normal coronary arteries (Maseri, L'Abbate, Pesola, Michelassi et al., 1977).

I. (3)(a)(iii) Applications of inert gas washout estimation of myocardial blood flow.

The inert gas washout techniques have been used to establish normal values for myocardial blood flow. Such studies have yielded values for left ventricular blood flow at rest of 60 to 75 mls per minute per 100 grams of tissue (Cannon, Dell and Dwyer, 1972a; Holman, Adams, Jewitt et al., 1974; Cannon, Schmidt, Weiss et al., 1975). The mean perfusion in the right ventricle at rest was found by Cannon, Dell and Dwyer (1972a) to be significantly lower at 47 ml/100 g/min. A similar difference in myocardial blood flow per unit mass for left and right ventricles in man was reported by Ross et al., (1964) and by Pitt, Friesinger and Ross (1969), using inert gases and a single probe, but Klein, Cohen and Gorlin (1965) failed to demonstrate any difference between the ventricles using krypton-85 washout and

precordial counting.

The distribution of blood flow in the normal left ventricle has been shown to have some nonhomogeneity. Thus Cannon, Dell and Dwyer (1972b) found the average coefficient of variation of left ventricular local myocardial blood flow rates was 15.8% in patients with normal arteriograms, whilst in normal dogs, Brandi, Fam and McGregor (1968) showed an 18% variation in xenon-133 clearance rate after local injection into the myocardium. There is some evidence from microsphere studies in dogs, that the myocardial blood flow per unit mass is not uniform transmurally with slightly greater values found in the endocardium (Domenech, Hoffman, Noble et al., 1969). Such transmural flow differences are slight under normal conditions, but are increased during coronary occlusion (Becker, Fortuin and Pitt, 1971). Transmural flow gradients, however, cannot be demonstrated with inert gas washout techniques (nor are they likely to be appreciated on ungated potassium analogue images).

The main clinical application of inert gas washout has been in the study of the effect of coronary artery occlusions on myocardial blood flow. Mean left ventricular perfusion at rest, calculated by "initial slope" methods, is usually normal in single vessel disease (Cannon et al., 1976) but usually decreased in multiple vessel disease (Cannon et al., 1977).

Smith, Gorlin, Herman et al., (1972) injected xenon-133 distal to coronary artery occlusions via bypass grafts during coronary artery bypass surgery. The graft was temporarily occluded and the clearance of the xenon-133 studied. The myocardial blood flow was reduced distal to the native circulation occlusion only if the stenosis was greater than 80% of the luminal diameter. As discussed earlier, Gould et al., (1974) found resting myocardial blood flow, estimated by labelled microsphere techniques, to be

reduced during by coronary artery occlusions only if the occlusion was 85% or more of the luminal diameter. Cannon et al., (1976) reported that in coronary artery disease, resting regional perfusion, measured by xenon-133 washout, was reduced distal to complete obstruction of the left anterior descending artery, but that in patients with less than 100% occlusion, the regional resting perfusion was not significantly reduced from the average perfusion rate in the rest of the ventricle.

Regional resting myocardial perfusion has been shown to be reduced at the sites of previous transmural myocardial infarctions (Dwyer, Dell and Cannon, 1973). Patients with cardiac aneurysms were found to have a much lower than normal peak of initial activity in the region of the scar and either no washout or low activity with excessive scatter of the individual points (Cannon, Sciacca, Fowler et al., 1975).

The study of myocardial blood flow during atrial pacing has shown that regional perfusion abnormalities appear during stress in patients with normal rest studies (Schmidt, Weiss, Casarella et al., 1976) - patients with coronary artery disease showed less increase of mean myocardial flow during stress than normal subjects and the regional perfusion distal to the occlusion increased less than that in the remainder of the ventricle. Maseri et al., (1977) found similar results during atrial pacing, though as already mentioned this group also noted greater residual activity than normal at rest distal to coronary stenoses.

The xenon washout technique has also been applied to assessment of collateral circulation in coronary artery disease. There is considerable, as yet unresolved, debate as to whether the collaterals visualised at coronary arteriography in patients with ischaemic heart disease are able to preserve perfusion distal to a coronary stenosis (McGregor, 1975). Schmidt et al., (1976)

documented that, in three patients with radiographically "adequate" collaterals, resting regional myocardial flow rates were normal or near normal in the areas supplied by the collaterals and that such areas showed a normal regional increase in perfusion during atrial pacing. The complexity of the situation was stressed by Frick, Valle, Korhola et al., (1976) who found that, though some radiographically evident collaterals could mediate normal increases in regional flow during stress, this was not always the case and they concluded "collaterals observed by routine coronary angiography are not functionally equipotent". The significance of collateral vessels in relationship to thallium-201 imaging will be considered further in Chapter III.

Finally xenon-133 washout has been used to assess the efficacy of coronary artery bypass grafting. Korbuly, Formanek, Gypser et al., (1975) studied xenon-133 washout with a scintillation camera in 14 patients before and after surgery. Myocardial perfusion increased in 11 patients and decreased in 3 post operatively. The improvement in myocardial blood flow correlated with improved exercise tolerance.

I. (3)(a)(iv) The role of inert gas washout measurements of myocardial blood flow.

Measurement of myocardial blood flow from xenon-133 washout requires direct introduction of the tracer into the coronary artery at coronary arteriography, a scintillation camera in the catheterisation room and the performance of complicated calculations, usually done by computers. Because of the complexity of the technique and the fact that the measurement of coronary blood flow has not yet been shown to be directly relevant to the clinical management of patients with coronary artery disease, it seems likely that it will not become established as a routine clinical investigation.

However, since it allows quantitation of total and regional myocardial blood flow, it can be used to assess the functional effect of individual coronary artery lesions and collateral vessels. It may, therefore, continue to prove a useful experimental technique in the study of the pathophysiological mechanisms involved in angina pectoris and in the assessment of the cardio-active drugs and other therapies designed to improve myocardial blood flow.

I. (3)(b) Particulate extractable indicators

The use of particulate indicators to measure blood flow in an organ is based on the premise that if the particles are uniformly mixed in the afferent blood supply to the organ, the indicators will impact in the organ's microcirculation in proportion to regional blood flow. As such, the technique is a derivation of the Sapirstein principle (Sapirstein, 1956).

Pohlmann (1909) was the first to use particles for investigation of the circulation, when he injected starch granules into foetal pigs to trace the flow patterns in the foetal heart. The technique was first applied to the human heart by Prinzmetal, Simkin, Bergman et al., (1947), when they studied the coronary collateral circulation by injecting glass microspheres into the coronary arteries of hearts post mortem. McLean, Hedenstrom and Kim (1961), bombarded the glass microspheres with neutrons and thus converted some of the sodium-23 content of the glass to radioactive sodium-24. Using the radioactive glass microspheres they were able to show uniform distribution of blood flow in the normal dog heart and a decrease in blood flow in the territory of a ligated left anterior descending coronary artery (McLean et al., 1961).

The use of radioactive particle distribution techniques for regional blood flow measurement became a clinical reality in 1964.

In that year two groups (Taplin, Johnston, Dore et al., 1964; Wagner, Sabiston, Iio et al., 1964) reported the use of macro-aggregates of albumin (MAA) labelled with iodine-131 for assessment of regional pulmonary blood flow and the diagnosis of pulmonary embolism. Two years later Quinn, Serratto and Kezdi (1966) employed iodine-131 labelled MAA for myocardial scanning in dogs, injecting the tracer into the aortic root proximal to an occlusive aortic balloon catheter. With this technique they were able to demonstrate decreased regional perfusion consequent upon experimental myocardial infarction. Because of the micro-embolisation produced there was considerable caution about injecting particles into the coronary circulation of living patients and the first clinical studies on the coronary circulation were not reported until 1970. Ashburn, Braunwald, Simon et al., (1970) injected technetium-99m labelled macroaggregates (MAA) into the coronary arteries of patients undergoing coronary arteriography and observed no ill-effects. Scintillation camera images of the myocardium showed areas of decreased radioactivity distal to coronary stenoses. The next year they introduced the concept of dual isotope imaging by injecting technetium-99m labelled MAA into the left coronary artery and iodine-131 labelled MAA into the right coronary artery (Ashburn, Braunwald, Simon et al., 1971). Because of the different energies of the emissions of the two isotopes the circulation of each coronary artery could be visualised separately.

Since 1971 the technique of injecting labelled particles into the coronary circulation (particulate myocardial perfusion scintigraphy or PMPS) has been used clinically by various investigators, most notably by the Loma Linda University group led by Judkins.

Although macroaggregates of albumin were the first particles used for these studies clinically, they had the disadvantage of a wide

variation in particle size (Adelstein and Maseri, 1977). For this reason microspheres of albumin, whose size can be carefully controlled, are preferred to macroaggregates for quantitative studies (Adelstein and Maseri, 1977). Recently microspheres of dextran and plastic microspheres have also become available for clinical use (Heymann, Payne, Hoffman et al., 1977).

For scintillation camera imaging, technetium-99m is the radionuclide of choice for labelling the microspheres. If two studies are performed, either to separate right and left coronary artery circulations or to measure the response to some manoeuvre, indium-113m is the best choice as the second label (Adelstein and Maseri, 1977). The 391 keV photopeak of indium-113m is sufficiently different from that of technetium-99m (140 keV) to allow good discrimination between the two. Iodine-131 is less satisfactory for gamma camera imaging as it can be administered only in small doses.

I. (3)(b)(i) Technical requirements for successful particulate myocardial perfusion scintigraphy.

The first requirement for the safe use of intracoronary particle injections is that they must not cause any circulatory disturbance. In addition to the safety aspects, this is necessary to ensure the study accurately reflects myocardial perfusion. The possible hazards of inducing myocardial capillary block are self evident but do not appear to arise in practice. Schelbert, Ashburn, Covell et al., (1971) studied the effects of intracoronary injection of iodine-131 and technetium-99m labelled macroaggregates in 17 dogs. Good quality scintigrams could be obtained in all without any adverse haemodynamic effects. Sequential intracoronary injections of MAA to a total cumulative dose ten times that necessary for an adequate image did not significantly impair left ventricular function (Schelbert et al.,

1971). Poe (1971), also working with dogs, found that myocardial contractile force diminished after intracoronary injection of MAA only if more than 0.05 mg were injected (approximately 0.5×10^6 particles of 60-70 micron size) and concluded the method could be safely used in humans if the number and size of particles were carefully controlled. Grames, Jansen, Gander et al., (1974) reviewed the effects of labelled MAA or microsphere studies in 800 patients undergoing coronary arteriography and found no evidence of any morbidity which could be attributed to the macro-aggregates or microspheres as opposed to the coronary angiography itself.

It is important that the particles are of uniform size. Variation in size will cause impaction to occur in vessels of varying calibre and will not allow accurate assessment of regional perfusion. The precautions necessary to ensure against excessive variation in particle size and clumping of particles are well summarised by Heymann et al., (1977). The average particle size is also important. Large particles (50-60 microns) are completely extracted, but it has been shown in animals that microspheres any larger than 15 microns pass preferentially to regions of high flow velocity and thus exaggerate the normal subepicardial to subendocardial flow gradient (Yipintsoi, Dubbs and Scanlon et al., 1973; Utley, Carlson, Hoffman et al., 1974). For this reason microspheres of 8-15 micron diameter are recommended for myocardial blood flow studies (Heymann et al., 1977).

For the distribution of the microspheres to reflect the distribution of blood flow accurately, there must be good mixing of the particles at the site of injection before the first branch of the coronary vessel. In order to avoid background activity in non-cardiac structures and microembolisation of vital organs not under study, particle studies of myocardial blood flow have been conducted by intracoronary

injection of the indicator rather than injection into the cardiac chambers, though the latter should allow satisfactory myocardial visualisation (Adelstein and Maseri, 1977). Inadequate mixing of the particles is usually due to a short left main stem coronary artery or to shifting of the catheter tip directing the particles more towards one coronary branch than the other (Kirk, Adams, Jansen et al., 1977). Preferential injection into one coronary branch can be detected if contrast material is injected simultaneously with the particles (Kirk et al., 1977). It should also be remembered that if the particles are injected separately into the right coronary and left coronary arteries, it is not possible to measure their relative blood flows (Adelstein and Maseri, 1977).

I. (3)(b)(ii) The clinical value of particulate myocardial perfusion scintigraphy.

The clinical use of particulate myocardial perfusion scintigraphy in coronary artery disease is based on the assumption that, in the case of the heart, perfused tissue can be presumed to be viable (Kirk et al., 1977). Is this, in practice, a justified assumption?

Kirk et al., (1977) have reviewed 194 patients who had the study performed before and after coronary artery bypass surgery. If the assumption is justified then improved regional ventricular function would be expected at areas of myocardium which were distal to coronary stenosis but showed perfusion preoperatively, whilst non perfused areas should not improve after revascularisation. They found that this was indeed the case. If patients with peri-operative infarction or occluded grafts were excluded, then the presence or absence of improvement in regional ventricular function correlated well with the normality or otherwise of preoperative perfusion as judged by perfusion scintigraphy. The scintigraphic technique was a much more reliable predictor of myocardial viability than contrast ventriculography or electrocardiography (Kirk et al., 1977).

Hamilton, Ritchie, Allen et al., (1975) correlated the appearance of MAA perfusion images with surgical or autopsy examination of the ventricle in 77 patients and found that the defects seen on the perfusion image correlated with myocardial scars, except in three patients in whom the defect was due to preinfarction angina. They concluded that particulate perfusion imaging was more sensitive in the detection of myocardial scar than standard ECG, clinical evaluation or biplane left ventriculography (Hamilton et al., 1975). From these two studies it appears that the assumption that perfused myocardium is viable is justified and particulate myocardial perfusion scintigraphy may therefore have a useful role to play in the more rational selection of patients who are likely to benefit from coronary artery bypass surgery.

A further clinical role for the technique has been described by the Seattle group. They studied myocardial perfusion by particulate scintigraphy both under resting conditions and when hyperaemia had been induced by intracoronary injection of contrast medium (Ritchie, Hamilton, Gould et al., 1975). By doing so they could demonstrate abnormalities in perfusion in patients who had normal resting images. By comparing the rest and stress images the regional coronary vascular reserve during stress could be evaluated and the functional significance of arteriographically observed coronary stenosis could be assessed (Ritchie, Hamilton, Gould et al., 1975).

I. (4) Non Invasive Labelling of Acute Myocardial Infarction

A clinical diagnosis of acute myocardial infarction is usually confirmed or refuted by several electrocardiograms and serial estimations of serum enzyme levels. These investigations are usually very satisfactory in detecting infarction but they do have limitations, such as the inability to use the electrocardiogram for

diagnosis of acute infarction when left bundle branch block is present. In the last 5 years or so considerable interest has been shown in therapies designed to minimise the degree of myocardial cell death in patients with established acute infarction (Maroko and Braunwald, 1973). Attempts have been made to quantify the size of the acute infarct using precordial mapping of ST segment elevation on the electrocardiogram (Maroko, Libby, Covell et al., 1972) or by summing serial serum enzyme estimations, especially creatinine phosphokinase (Shell, Kjekshus and Sobel, 1971; Sobel, 1974).

In order to allow diagnosis of acute infarction when standard electrocardiographic and enzyme techniques are unhelpful or are equivocal a search has been made for radiopharmaceuticals which would label acutely infarcted myocardium but not normal or viable, though ischaemic, myocardium (Holman, 1974). It is also hoped that such scintigraphic techniques ("positive infarct imaging") will allow more direct measurement of the size of the acute infarction.

The use of radioisotope imaging in the diagnosis of acute myocardial infarction got off to a false start in 1960 when Dreyfuss, Ben-Porath and Menczel demonstrated increased activity over the precordium after injection of iodine-131 in patients with acute myocardial infarction. This increased activity could be demonstrated from several days to several weeks after the acute infarction. However, the concentration of iodine-131 in the infarcted tissue from a patient who died 7 days after acute infarction was only 1.5 times that in normal myocardium, a difference which was not likely to be sufficient for infarct detection by external imaging (Dreyfuss et al., 1960). This apparent contradiction was explained by Mason and colleagues (Mason, Frye and Wagner, 1961) who found that the increased activity over the left side of the chest in patients with recent myocardial infarction was due to iodine

accumulation in the cardia of the stomach, presumably due to gastric stasis from enforced bed rest.

Since 1961 many radiopharmaceuticals have been shown to accumulate in experimentally infarcted myocardium including mercury-203 chloromerodrin (Carr, Beierwaltes, Patno et al., 1962; Carr, Carfuny and Bartlett, 1963), mercury-203 mercurifluorescein (Malek, Ratusky, Varrejn et al., 1967; Ramanathan, Ganatra, Daulatram et al. 1971), gallium-67 (Kramer, Goldstein, Hirshfeld et al., 1974), technetium-99m tetracycline (Holman, Dewanjee, Idoine et al., 1973), technetium-99m labelled glucoheptonate (Rossman, Strauss, Siegel et al., 1975), technetium-99m phosphate bone scanning agents (Parkey, Bonte, Buja et al., 1977), technetium-99m heparin (Kulkarni, Parkey, Buja et al., 1977), carbon-14 oleic acid (Bilheimer, Buja, Parkey et al., 1978) and iodine-131 labelled antibody to cardiac myosin (Khaw, Beller and Haber, 1978). Only the phosphate, glucoheptonate and tetracycline compounds have been used to any extent clinically and only they will be considered further.

I. (4)(a) Technetium-99m labelled compounds for imaging acute myocardial infarction

Technetium-99m pyrophosphate, a bone scanning agent, was first shown to localise in acutely infarcted myocardium by Bonte and colleagues (Bonte, Parkey, Graham et al., 1974). Uptake by myocardial infarction has also been shown for other bone scanning agents such as hydroxyethylidene diphosphonate (Zweiman, Holman, O'Keefe et al., 1975), polyphosphate (McLaughlin, Coates, Wood et al., 1975), methylene diphosphonate (Grossman, Foster, McAfee et al., 1977) and imidodiphosphonate (Ell, Langford, Pearce et al., 1978; Joseph, Ell, Ross et al., 1978). Most clinical experience has been obtained with pyrophosphate and none of the other agents

has been shown to be clinically superior to it, though in animal experiments the highest ratios of uptake of tracer between infarcted and normal myocardium was obtained with imido-diphosphonate (Grossman et al., 1977; Ell et al., 1978).

Acute infarct labelling with technetium-99m pyrophosphate has been intensively studied by many investigators, notably by the Dallas group led by Parkey and Bonte. Certain technical factors are crucial if the technique is to be reliable. Poor labelling of the pyrophosphate with technetium-99m or rapid breakdown of the labelling in the vial or syringe leads to free technetium in the blood, and a blood pool image is obtained in the region of the heart (Parkey et al., 1977). If this is recognised repeat examination is necessary; if it is not recognised the study may be falsely interpreted as positive. For this reason each batch of radio-pharmaceutical has to be tested for labelling efficiency and the tracer should be injected with one hour of preparation (Parkey et al., 1977). The usual dosage for acute infarct imaging is 15 millicuries (Perez, 1976; Parkey et al., 1977).

Imaging should be performed with the gamma camera, rather than the rectilinear scanner, as the scanner causes positioning difficulties, increased imaging times and incomplete myocardial studies because of the tomographic effect of the focused collimators (Parkey et al., 1977). Good field uniformity in the gamma camera is essential, and the utility of the technique can be greatly enhanced by the use of a mobile gamma camera (Parkey et al., 1977). Images are performed in several projections, usually anterior, left anterior oblique and left lateral, as this allows better interpretation of the site of abnormality within the myocardium (Parkey et al., 1977). Computer processing is not necessary for visualising infarcts but may be used for removing rib activity if the infarct is being sized. Simple background subtraction and contrast enhancement

are usually sufficient, but more complicated procedures utilising nine point smoothing have also been used (Lancaster and Stokely, 1976).

Myocardial scintigrams are usually obtained 60 to 90 minutes after injection of technetium-99m pyrophosphate (Parkey et al., 1977). Earlier imaging than this is complicated by high background activity in blood whilst late imaging (after 2 hours) has the problem of marked bone uptake.

In experimental infarction, positive infarct imaging with technetium-99m pyrophosphate becomes possible from 10 to 12 hours after coronary ligation. In patients with acute myocardial infarction, technetium-99m pyrophosphate images usually become positive within 12 hours of myocardial infarction (Willerson, Parkey, Bonte et al., 1975), but maximal myocardial uptake of the tracer does not occur until 2 days (Willerson et al., 1975) to 5 days (Ennis and Walsh, 1975) after the acute infarct. Serial imaging from 24 hours to 72 hours after the suspected infarction is recommended to improve the sensitivity of the technique (Parkey et al., 1977).

Technetium-99m labelled tetracycline was introduced as an agent for imaging acute experimental infarcts in dogs by Holman, Dewanjee, Idoine et al., (1973). This group subsequently showed that the radiopharmaceutical could be used for positive infarct labelling in man and that the site and size of the infarct by scintigraphy correlated well with electrocardiographic and enzyme studies (Holman, Lesch, Zweiman et al., 1974). The optimal time for imaging was in the first three days after the onset of symptoms (Holman et al., 1974).

Although technetium-99m tetracycline can be used clinically to detect acute myocardial infarction, the tracer is cleared slowly from blood (Holman et al., 1973) so that a 24 hour delay between

injection of the tracer and imaging is recommended. Because of this delay and the poorer infarct to normal myocardium ratios obtained with tetracycline (Zweiman et al., 1975), technetium-99m tetracycline has been abandoned as an acute infarct positive imaging agent in favour of the technetium-99m phosphates.

Technetium-99m labelled glucoheptonate, a renal scanning agent, was shown to localise in experimentally infarcted myocardium by two independent groups (Fink/Bennett, Dworkin and Lee, 1974; Rossman, Strauss, Siegel et al., 1975). Initial studies with glucoheptonate suggested that good ratios of uptake between infarcted and normal tissue could be obtained, with ratios of 21 to 1 reported 6 hours after experimental coronary artery occlusion (Rossman, Strauss, Siegel and Pitt, 1975). Later studies, however, failed to confirm such good differential uptake with Zweiman et al., (1975) reporting infarcted to normal myocardial uptakes of 11 to 1 and Grossman et al., (1977) ratios of only 2 to 1. Initial clinical studies were also promising with demonstration of moderate to large infarcts in patients as little as 5 hours after the onset of symptoms (Rossman, Rouleau, Strauss et al., 1975). Subsequent clinical evaluation of technetium-99m glucoheptonate has been less encouraging. In the series of Holman, Davis and Hanson (1977) only 3 of 13 patients with acute myocardial infarction had abnormal studies with this radionuclide. These poor results, and the low count rates obtained with technetium-99m glucoheptonate, have caused it to be largely abandoned as a positive infarct imaging agent.

I. (4)(b) Mechanism of uptake of technetium-99m labelled compounds by acutely infarcted myocardium.

The uptake of technetium-99m bone scanning agents, technetium-99m tetracycline and technetium-99m glucoheptonate at the site of acute myocardial infarction is not clearly understood but is generally thought to be related to their properties as chelating agents (Parkey et al., 1977).

For uptake to occur, perfusion must be maintained to some extent, and significant perfusion in the outer, peripheral zones of transmural myocardial infarctions has been explained on the basis of collateral flow to these regions (Gregg, 1974; Cox, Pass, Wechsler et al., 1975). Experimental studies have demonstrated that in such areas with necrosis but only temporarily interrupted perfusion, intracellular accumulation of calcium occurs (Kloner, Ganote and Jennings, 1974) and that such accumulations of calcium are localised to the mitochondria (Shen and Jennings, 1972; Buja, Parkey, Dees et al., 1975). Central areas of infarcts with no blood or very severely reduced blood flow do not show calcium accumulation (Shen and Jennings, 1972; Buja, Parkey, Dees et al., 1975; Buja, Parkey, Stokely et al., 1976).

The uptake of technetium-99m pyrophosphate in acute myocardial infarction predominantly occurs in areas with myocardial necrosis but some residual perfusion i.e. in the outer zones of transmural infarcts, giving rise to a "doughnut" pattern on the scintigraphic images, both in experimental animals (Buja et al., 1975) and in some patients with large anterior myocardial infarcts (Willerson et al., 1975).

The uptake of pyrophosphate and the other chelating agents has generally been assumed to be due to binding to the intramitochondrial calcium (Parkey et al., 1977) and there is some experimental evidence to support this. Tofe, Buja, Parkey et al., (1976) found that the uptake of technetium-99m pyrophosphate and diphosphonate in experimentally infarcted dog myocardium paralleled the increase in calcium content. These results were not confirmed by Dewanjee and Kahn (1976), working in the rabbit, who reported that pyrophosphate and tetracycline uptake by experimentally infarcted myocardium was due to binding to denatured protein macromolecules rather than to calcium in the mitochondria. Schelbert, Ingwall, Sybers et al., (1976) also found that pyrophosphate uptake by necrotic myocardial

cells was independent of cellular calcium uptake, though their findings are more difficult to relate to acute myocardial infarction as they used foetal mouse hearts in tissue culture, damaged by insulin and glucose deprivation, as their model. It has also been generally thought that the whole chelate molecule is taken up by the damaged myocardium, and this was supported by the finding of Tofe et al., (1976) that the uptake of tritiated diphosphonate by necrotic myocardium paralleled that of the technetium-99m labelled radiopharmaceutical. Recently, however, Poe (1977) has suggested that the uptake might be due to transchelation of the technetium at the injury site. He cites as evidence the finding that whereas the uptake of technetium at the site of necrosis is low with technetium-99m DTPA, a strong chelating agent, it is high with technetium-99m tetracycline, a much weaker chelating agent.

I. (4)(c) Is myocardial uptake of technetium-99m pyrophosphate specific for acute myocardial infarction?

Initial studies of patients admitted with acute chest pain showed that myocardial imaging with technetium-99m phosphate agents was a sensitive technique for the diagnosis of acute myocardial infarction (Willerson et al., 1975; Perez, 1976) with a low incidence of false positives. Subsequent studies have largely confirmed this and have shown that the sensitivity may be further increased by combining such images with blood pool studies of ventricular wall motion (Pitt and Strauss, 1977; Van Hove, Heck and Kight, 1977).

A number of recognised causes of false positive myocardial scintigrams have emerged i.e. positive pyrophosphate images in the absence of acute myocardial infarction. Perhaps the commonest cause for such a false positive study is unstable angina pectoris, with positive scintigrams in this condition being reported by various groups including Willerson et al., (1975), Abdulla, Canedo, Cortez et al., (1976), and Walsh, Karunaratne, Resnekov et al., (1977),

though the uptake in such cases was usually less intense than that seen with acute transmural infarction. It has been suggested that such positive studies may reflect foci of microscopic necrosis in patients with unstable angina pectoris (Parkey et al., 1977). This interpretation is partially supported by the observation of Miller, Gilmour, Grossman et al., (1977) that diffuse microscopic foci of myocardial injury induced in the rat heart by subcutaneous catecholamine injection and stress were associated with uptake of technetium-99m phosphate bone scanning agents. A few patients with stable angina pectoris have also been reported to have positive myocardial pyrophosphate scintigrams (Willerson et al., 1975; Walsh, Karunaratne, Resnekov et al., 1977).

"False positive" pyrophosphate scintigrams have also been reported in patients with left ventricular aneurysms but no acute myocardial infarction (Ahmad, Dubiel, Verdon et al., 1976; Kelly, Cowan, Maynard et al., 1977), in dogs subjected to electrical cardioversion (Pugh, Buja, Parkey et al., 1976), in patients with cytotoxic drug induced cardiomyopathy (Chacko, Gordon, Bennett et al., 1977; Sty and Garrett, 1978), following radiotherapy to the chest for cancer (Soin, Cox, Youker et al., 1977), in patients with calcified heart valves (Epstein, 1977; O'Rourke, Righetti, Schelbert et al., 1976) and in cardiomyopathies (Perez, 1976). Diffusely positive scans have also been reported in a few asymptomatic subjects (Prasquier, Tarasash, Botvinick et al., 1977) but, in at least some, persisting blood pool activity may have been the cause. In groups of patients admitted with chest pain the overall false positive rate is of the order of 8-20% (Parkey et al., 1977).

I. (4)(d) Clinical value of positive infarct imaging

The principal clinical use for positive myocardial infarct imaging has been in screening patients admitted with chest pain for acute myocardial infarction. The Dallas group reported only a four per cent false negative rate in such patients (Willerson et al., 1975) and found that even subendocardial myocardial infarcts could be reliably detected (Parkey, Poliner, Bonte et al., 1976). The site of abnormality on the scintigram correlated well with localisation by ECG. The high sensitivity was confirmed by Perez (1976) and by Berger, Gottschalk and Zaret (1978) but not by Walsh, Karunaratne, Resnekov et al., (1977) or Tetalman, Foley, Spencer et al., (1977) who respectively found sensitivities of 59% and 69%.

Positive infarct imaging has been applied to the sizing of experimental infarction in dogs (Stokely, Buja, Lewis et al., 1975) and shown to correlate well with the histological size of an infarct induced by ligating the left anterior descending artery of a dog. Initial studies in humans by Henning, Schelbert, O'Rourke et al., (1976) suggested that pyrophosphate imaging is of value in sizing acute anterior myocardial infarction but frequently underestimates the size of inferior infarcts. This aspect of pyrophosphate infarct imaging clearly merits further investigation, but in view of reports of pyrophosphate uptake in patients with unstable, or occasionally even stable, angina caution is necessary.

Recently technetium-99m pyrophosphate myocardial imaging has been related to prognosis. Ahmad, Logan and Martin (1978) have shown that the mortality for patients with acute myocardial infarction was higher with the doughnut pattern of uptake compared to those who showed either localised uptake or diffuse uptake, whilst Olson, Lyons, Aronow et al., (1978) found that a persistently positive pyrophosphate scintigram more than 6 weeks after the

acute infarct was associated with an increased morbidity and mortality.

The other principal area in which positive infarct imaging has been applied is in the detection of acute infarction under conditions in which standard techniques are unhelpful, notably following cardiac surgery. Both Howe, Goodrich, Bruno et al., (1976) and Lowenthal, Parisi, Tow et al., (1977) reported that technetium-99m pyrophosphate imaging was of value in determining whether patients who had undergone cardiac surgery had sustained perioperative myocardial infarctions. Sharpe, Botvinick, Shames et al., (1978) found that pyrophosphate imaging combined with blood pool imaging could be used in the diagnosis of right ventricular myocardial infarction.

In summary, it appears that pyrophosphate myocardial imaging may have value in diagnosing myocardial infarction in situations where more standard techniques are unhelpful or equivocal. It may also prove to be of value in assessing the size of acute myocardial infarction. Whether it has value in the routine investigation of most patients with acute myocardial infarction is highly debatable. In most of these patients the diagnosis can be made within 24 hours of admission using electrocardiography and serum enzymes and in many cases optimal myocardial images cannot be obtained until at least 24-48 hours after the acute event. On balance, therefore, I believe the routine use of positive infarct imaging cannot be justified.

CHAPTER II

THALLIUM-201 FOR MYOCARDIAL IMAGING

II. (1) Whole Body Distribution of Thallium-201

As discussed in Chapter I, thallium does not belong to the same group in the periodic table as potassium but does behave in vivo as a potassium analogue (Gehring and Hammond, 1964; Gehring and Hammond, 1967). Following intravenous injection it is widely distributed in the body (Figure 1).

Atkins et al., (1977) measured whole body retention of thallium-201 in three volunteers using a whole body counter and found a mean whole body disappearance half time of 9.8 days, but an effective whole body half-life of 57 hours. Excretion of thallium is thought to be principally by the urinary tract, with 3 to 8 per cent of the injected dose being excreted in the urine in the first 24 hours in man (Schelbert, Henning, Rigo et al., 1976; Atkins et al., 1977). Faecal excretion of thallium appears to be insignificant (Atkins et al., 1977).

The kidney is the critical organ in terms of radiation dosage with thallium-201 with a reported radiation dose of 0.39 to 1.17 rads per millicurie (Table 1). This dose is unlikely to cause renal damage as no significant long term functional or anatomical effects were observed in dog kidneys irradiated with 400 rads (Maier and Casarett, 1963). Renal uptake occurs rapidly, being maximal 10 minutes after injection in goats (Bradley-Moore et al., 1975) and between 10 and 20 minutes after injection in mice (Strauss et al., 1975). The renal medulla accumulates considerably more thallium-201 than the cortex, both in goats (Bradley-Moore et al., 1975) and in dogs (Hamilton et al., 1978). Four hours after injection of the tracer the ratio of renal to background activity is reduced from that

shortly after injection but some accentuation of renal uptake can still be seen on images performed 5 days after injection (Atkins et al., 1977).

The colon shows considerable uptake of thallium-201 and, as in the kidneys, there is prolonged retention of activity (Atkins et al., 1977). Liver uptake is marked when the tracer is injected into animals at rest (Bradley-Moore et al., 1975; Schelbert, Henning, Rigo et al., 1976), but in clinical studies liver uptake can be considerably reduced by injecting the radionuclide with the patient standing and fasting (Atkins et al., 1977). Colonic, hepatic and splenic uptake are reduced by injecting the tracer during exercise, which also produces a better myocardial to lung activity ratio (Cook et al., 1976; Wackers and de Jong, 1976). Testicular tissue was found to accumulate 0.15 per cent of the injected dose in man with a calculated testicular radiation dose of 0.59 rads per millicurie (Atkins et al., 1977). The thyroid also has marked thallium-201 uptake (Atkins et al., 1977). This appears to be related to the cationic side of the iodide pump, or possibly to thyroidal blood flow, and parallels iodide uptake in rats treated with TSH or triiodothyronine, though it is not blocked by perchlorate administration (Oster, Strauss, Harrison et al., 1978). If thallium-201 is injected during exercise there is considerable uptake by the exercising muscles (Wackers and de Jong, 1976) (Figure 1), and leg muscle uptake during walking on a treadmill has been applied to the assessment of patients with arterial disease (Christenson, Larsson, Svensson et al., 1977). It seems unlikely, however, that this will prove to be of major clinical value in the assessment of peripheral vascular disease.

In addition to uptake in metabolically active normal tissues, thallium-201 has also been found to accumulate in certain pathological

tissues. Cox, Belfer and van der Pompe (1976) reported abnormal concentration of thallium-201 in the primary tumour of a man with bronchial carcinoma and also showed that the nuclide was taken up by rhabdomyosarcoma implants in rats. Tonami, Michigishi, Bunko et al., (1977) investigated thallium-201 as a tumour imaging agent in man. They found that accumulation of this isotope occurred in 14 out of 15 patients with hepatomas but in none of 8 patients with hepatic metastases. In patients with thyroid nodules, 14 of 15 with thyroid cancer had a "hot spot" with thallium-201 but only 6 of 19 benign adenomas, which were cold on technetium-99m imaging, showed thallium-201 uptake. On the basis of these findings Tonami et al., (1977) suggested that thallium-201 imaging might be useful in differentiating hepatoma and secondary tumour in the liver. They also concluded that if a non functional thyroid nodule does not accumulate thallium-201 then the probability of malignancy is low.

II. (2) Toxicology of Thallium

The toxic properties of thallium were first demonstrated soon after the discovery of the metal by Crookes in 1861. Lamy, a contemporary of Crookes, noted the onset of lassitude and weakness whilst working with the element and fed thallous sulphate to dogs, ducks and hens, all of which died within a few days (cited in Reed, Crawley, Faro et al., 1963).

Thallium has found application in many industrial processes including the manufacture of optical lenses, fireworks and dyes and is an effective insecticide and rodenticide (Browning, 1961). In the second half of the nineteenth century, the metal was used as a therapy for a miscellany of conditions such as syphilis, gonorrhoea, gout, dysentery and night sweats in tuberculosis, but was abandoned because of side effects, notably alopecia (Reed et al., 1963). The depilatory effect of thallous sulphate was utilised in the treatment of ringworm of the scalp, but because of central nervous system and gastro-intestinal effects, not infrequently fatal (Munch, 1934), this use had

been largely abandoned by the 1940's (Reed et al., 1963).

The toxicity of thallium at the electrophysiological level was observed by Mullins and Moore (1960) in their work with the isolated frog sartorius muscle, when they found that increasing concentrations of thallous ion in the bathing solution produced progressive depolarisation of the muscle cell and that high concentrations (e.g. 1 millimole per litre) could produce irreversible damage.

The main early effects of acute poisoning with large amounts of thallium administered orally are gastro-intestinal haemorrhage, abdominal colic with either constipation or diarrhoea, headache and tachycardia (Reed et al., 1963). Neurological symptoms, such as delirium, convulsions, or coma appear 2 to 5 days after ingestion of large amounts and death may follow in 5 to 7 days from respiratory paralysis (Reed et al., 1963). Subacute or chronic poisoning may develop from the ingestion of a single smaller dose or, because of the slow excretion, from the cumulative effect of several sub-toxic doses. In subacute or chronic poisoning the most prominent symptoms and signs are neurological with ataxia, paraesthesiae, autonomic dysfunction (producing gastro-intestinal effects particularly) and cranial nerve involvement, especially retrobulbar neuritis (Reed et al., 1963; Bank, Pleasure, Suzuki et al., 1972). Alopecia is common in subacute or chronic poisoning, the skin becomes dry and scaly, white transverse bands (Mee's Strips) may develop in the nails and a blue line may appear in the gums (Reed et al., 1963). Diagnosis of thallium poisoning is made by demonstrating the presence of the metal in the patient's urine (Bank et al., 1972). Histology of the nervous system in fatal cases of thallium poisoning has shown degeneration of peripheral nerve fibres and chromatolysis of affected motor neurone cells in the central nervous system (Cavanagh, Fuller, Johnson et al., 1974). Therapy in thallium poisoning is essentially supportive, though it may be possible to

promote excretion by administering potassium salts (Reed et al., 1963) whilst the rate of absorption from the gut can be slowed by giving Prussian blue (Kamerbeek, Rauws, ten Ham et al., 1971).

Criminal poisoning with thallium is rare, though it was the method of murder in Agatha Christie's novel "The White Horse". Thallium also featured in the bizarre case of Graham Frederick Young (The Times, 1972). This man had been committed to a psychiatric hospital at the age of 14 because of attempting to murder various relatives by poisoning, but was released 8 years later. He had a considerable interest in toxicology and experimented by administering thallium rat poison to eight work mates, carefully recording the doses and times of administration. Two of his victims (who are the subjects of the report by Cavanagh et al., 1974) died and Young was convicted of their murder.

The minimum lethal dose of thallium for man is thought to be 8 to 12 milligrams per kilogram body weight (Browning, 1961) but non fatal side effects have been reported with doses as low as 0.1 milligrams per kilogram (Bradley-Moore et al., 1975). Thallium-201 supplied for myocardial imaging is almost carrier free and Schelbert, Henning, Rigo et al., (1976) calculated the dose administered in diagnostic studies using 2 millicuries to be of the order of 0.07 to 0.15 nanograms per kilogram body weight. There is, therefore, a very large margin of safety when using Thallium-201 for myocardial imaging, even when repeat studies are carried out. As yet, there have been no reports of ill effects following administration of the radiopharmaceutical, and none were observed in any of the subjects of the studies described in this thesis.

II. (3) Materials and Equipment for Thallium-201 Myocardial Imaging

II. (3)(a) Radionuclide

All studies described in this thesis were performed using

Thallous Chloride (Tl201) injection (product number DRN 8103) supplied by Duphar Laboratories Limited (Duphar House, Gaters Hill, West End, Southampton). The isotope is supplied as a sterile isotonic solution in sodium chloride at a pH of 5 to 7. At the calibration time the solution contains 1 millicurie of activity per millilitre and is virtually carrier free with a specific activity of more than 500 millicuries of thallium-201 per milligram of thallium. Radionuclidic purity is also high with less than one per cent thallium-200 and less than 0.5 per cent thallium-202 at the calibration time.

Thallous Chloride (Tl201) injection does not yet have a product licence in the United Kingdom and permission for all studies was therefore obtained from the Isotope Advisory Panel of the Department of Health and Social Security and from the local Ethical Committee.

II. (3)(b) Imaging equipment

The myocardial images were obtained using an Ohio Nuclear Series 100 (standard field of view) gamma camera. The camera was fitted with a 17,000 parallel hole, low sensitivity, high resolution, low energy collimator. As noted in Chapter I. (2)(g), although thallium-201 emits 135 and 167 keV gamma rays, these are present in very low incidence and Atkins et al., (1977) found a seven times greater counting rate when detecting the 65-82 keV X-rays also emitted. Accordingly, in the studies described in this thesis the energy window of the gamma camera was centred over the 65-82 keV X-rays to include the full photopeak.

The images were recorded in two ways. Black and white Polaroid prints were obtained from the gamma camera oscilloscope. In addition, the camera was interfaced to a Varian 620/L computer and the images stored on magnetic tape. The digital images were displayed on a colour television screen using

a fourteen point scale (Figure 2) which ranges from blue for the lowest activity level through green, orange and finally red for maximum activity. Using the computer nine point smoothing of the images could be carried out, to compensate for statistical fluctuations in activity. Uniformity correction (to compensate for variation in the gamma camera's performance at different points of its field of view) was not carried out. Also, by using the computer, the digital images could be subjected to background subtraction (deletion of all activity levels below X per cent of maximum) and contrast enhancement (all activities above Y per cent of maximum displayed as white) and the fourteen colours then displayed over the activity range of X per cent to Y per cent. The levels of X and Y could be varied at will by the operator. The value of such processing of the image will be discussed later.

II. (4) In Vitro Studies with Thallium-201

As noted in Chapter I. (2)(g)(ii) the 65-82 keV X-rays emitted by the mercury daughter of thallium-201 are not ideal for scintillation camera imaging. Phantom studies were thus performed with the Ohio Nuclear Series 100 gamma camera to measure its intrinsic resolution using thallium-201 and to assess the ability to detect "lesions" in simple organ phantoms.

II. (4)(a) Measurement of intrinsic resolution of Ohio Nuclear Series 100 gamma camera using thallium-201

These studies were performed, using thallium-201, with no collimator fitted to the camera and with its energy window centred over 65-82 keV X-rays. For comparison, they were repeated using technetium-99m after adjusting the camera's energy window appropriately.

Experiment 1. Method: A standard Anger phantom (a lead sheet with holes of different sizes) was placed on the face of the

camera crystal. The arrangement of the holes in the phantom is shown schematically in Figure 3A. A 2 millicurie "point source" of thallium-201 was sited 6 feet away in the field of view of the gamma camera and images containing 500,000 counts obtained. The procedure was repeated with a technetium-99m point source, after adjusting the camera energy window to the 140 keV gamma rays of this radioisotope.

Results: Polaroid images of the Anger phantom using thallium-201 and technetium-99m are shown in Figure 3B and Figure 3C respectively. The holes of all sizes are more sharply visualised with technetium-99m. In particular the 2.5 mm holes, which are well resolved with technetium-99m, are poorly seen with thallium-201 whilst the 2 mm holes, which are partially resolved with technetium-99m, are not seen at all with thallium-201.

Experiment 2. Method: The full width half maximum resolution of a line source using thallium-201 was also measured. The tubing of the line source was filled with 0.5 millicuries thallium-201 and the gain of the gamma camera altered so that the width of the line was increased by a factor of 16. A profile of activity through the line was then obtained.

Results: The measured full width half maximum resolution of the line phantom using thallium-201 and the Ohio Nuclear Series 100 gamma camera was 6.7 mm. Using the same camera and technetium-99m the full width half maximum resolution of the line phantom has previously been found to be 4.7 mm (R.G. Bessent, personal communication).

Discussion

The results confirm that the intrinsic resolution of the gamma camera with thallium-201 is considerably poorer than that obtained with technetium-99m.

II. (4)(b) Measurement of "lesion" resolution with thallium-201

Having established the poor intrinsic resolution of the gamma camera with thallium-201 the ability of the camera to detect "lesions" in organ phantoms was assessed. A standard "liver phantom" and a simple "heart phantom" were studied. For these studies the gamma camera was fitted with the low sensitivity, high resolution collimator.

Experiment 1. Method: The standard liver phantom is made of perspex and has five rows of wells ranging in size from 0.5 to 3.0 cm. The depth of the wells is varied in such a way that the 3 columns of wells have "lesion to background" activity ratios of 2 to 1, 3 to 1 and 4 to 1 (Figure 4A).

The phantom was filled with water containing 0.5 mCi (thallium-201. Images, containing 500,000 counts, were obtained both with the phantom touching the collimator ("0 cm") and placed 10 cm from the camera. The procedure was repeated after substituting technetium-99m for thallium-201.

Results: Polaroid prints of the images obtained with thallium-201 and the phantom at 0 cm and at 10 cm are shown respectively in Figures 4B and 4D. The technetium-99m images at 0 and 10 cm are shown in Figures 4C and 4E. With thallium-201 and the phantom at 0 cm (Figure 4B) the 0.5 cm 4 to 1 activity ratio and 1 cm 2 to 1 activity ratio wells are only just seen. With technetium-99m at 0 cm (Figure 4C) only the 0.5 cm 2 to 1 activity ratio well is not seen. The poorer resolution with thallium-201 compared to technetium-99m is confirmed with the phantom at 10 cm (Figures 4D and 4E).

Experiment 2. In myocardial imaging with a potassium analogue abnormalities commonly appear as an area of decreased tracer uptake (i.e. a "cold spot"), rather than a "hot spot" as seen with the liver phantom. The ability to detect "cold spots" with thallium-201 was investigated using a simple heart phantom.

Method: The heart phantom used consisted of two concentric glass beakers with the smaller of the two (50 ml capacity) supported on a hollow plastic cylinder inside the larger (250 ml). The arrangement is shown diagrammatically in Figure 5. The 50 ml beaker contained saline to simulate tracer free blood in the ventricular cavity and to prevent the beaker from floating. The space between the two beakers was filled with saline containing 1 millicurie of thallium-201. Images, each containing 300,000 counts, were obtained.

Myocardial lesions were simulated by placing pieces of modelling wax in the space between the two beakers (Figure 5). The "lesions" were all full thickness i.e. they completely bridged the gap between the outer wall of the 50 ml beaker and the inner wall of the 250 ml beaker. Each lesion was constructed to have heights and depths which were equal and were either 1 centimetre or 2 centimetres. One lesion at a time was studied and the phantom was rotated so that the lesion was imaged in positions ranging at 45 degree intervals from full anterior as seen by the gamma camera (position 1 in Figure 5B) to full posterior (position 5 in Figure 5B). Control studies with no lesions present were also performed.

Results: When the phantom was imaged with the 2 cm lesion in place, it could be detected whilst it was anterior i.e. in positions 1 to 3, but could not be identified in positions 4 and 5 (Figure 6). The 1 cm lesion could not be seen in any position (Figure 7).

Discussion

The phantom studies confirm that thallium-201 is a far from ideal radionuclide for gamma camera imaging. From the heart phantom studies it seems likely that full thickness lesions smaller than 2 cm in diameter will not be detected. These studies probably

overestimate the resolution which will be possible in vivo, for several reasons. Firstly, the lesions used for the phantom studies were modelling wax which is likely to be denser than ischaemic or fibrotic myocardium. Secondly, in the phantom studies background activity and scatter and absorption of the X-rays by overlying structures were not simulated, although some scatter and absorption will be produced by the glass of the outer beaker. In relation to this point it is of interest that Strauss and Pitt (1977b) reported that when a similar phantom was imaged with 3 centimetres of lucite scatter between the phantom and the gamma camera, "full thickness lesions" less than 2.5 cm in size could not be identified.

II. (5) Technique of Myocardial Imaging with Thallium-201

The myocardial imaging studies described in this thesis are of two types (a) those performed after injection of the tracer with the patient at rest ("rest imaging") (b) those performed after injection of the tracer at the end of a symptom limited maximal exercise test ("stress imaging").

II. (5)(a) Rest myocardial imaging

2 millicuries thallium-201 (Thallous Chloride) in 2 millilitres of normal saline were injected as a bolus into an antecubital vein. The tracer was administered in the erect position to minimise hepatic blood flow and hepatic uptake of thallium-201 (Cook et al., 1976). Whenever possible, rest studies were performed at least 3 hours after the patient's previous meal, as fasting has also been reported to reduce hepatic uptake (Wackers and de Jong, 1976; Atkins et al., 1977).

Following injection the patient lay supine on a trolley and the gamma camera face placed over the left anterior chest (Figure 8A). After a delay of at least 5 minutes after injection, if the operator judged that adequate lung clearance of activity had occurred, imaging commenced.

In almost all studies, each image contained at least 300,000 counts. Occasionally, with low count rates and an ill patient a lower count total was accepted. The average time taken for each view in rest studies was 5 to 7 minutes. The images were displayed on black and white Polaroid film and on the colour television interfaced to the computer.

The anterior projection (Figure 8A) was performed first, and then, by rotating the camera head, a 30 degree left anterior oblique (LAO) view was obtained (Figure 8B). 60 degree LAO and left lateral views were carried out with the patient lying supine and with the left arm abducted above the patient's head (Figures 8C and 8D). The time elapsing from injection of the tracer to completion of the four rest views was, on average, 30 to 40 minutes.

II.(5)(b) Stress myocardial imaging

All exercise tests were performed in the gamma camera room and were supervised by both a cardiologist (Dr. R.G. Murray) and myself. Full resuscitation facilities (oxygen, cardioactive drugs, a defibrillator and an intravenous infusion set) were available in the room during all exercise tests though, with the exception of the administration of atropine to one patient who had a vasovagal attack before exercise could begin, they were not required for any subject.

On arrival the patient was questioned regarding recent symptoms and exercise was not carried out if chest pain suggestive of acute myocardial infarction or unstable angina had occurred recently. In the absence of such symptoms ECG electrodes were attached to the patient's chest to allow recording of a modified V5 signal and the electrodes connected to the transmitter of a telemetry system. The telemetry receiver fed the ECG signal both to an oscilloscope and to a standard ECG machine. A sample of the patient's ECG at rest was recorded to exclude serious cardiac arrythmias or changes of recent acute myocardial infarction.

A cannula with a 3 way tap attached was inserted into an antecubital vein and flushed with 100 units of heparin in 1 millilitre of saline.

The symptomatic end points of the exercise test (see below) were then explained to the patient and the patient asked to provide, if possible, 45 to 60 seconds warning of when they felt they would have to stop exercise.

Exercise was performed on a Tunturi bicycle ergometer (Figure 9A) with an initial work load of 300 KPM per minute, increasing by steps of 300 KPM per minute at three minute intervals. The ECG was monitored continuously on the oscilloscope throughout exercise and printed samples obtained from the ECG machine at three minute intervals and at the end of exercise. ECG monitoring and sampling continued for up to 12 minutes after exercise.

The symptomatic end points for the exercise test were onset of chest pain, severe dyspnoea, fatigue or intermittent claudication. The ECG criteria for ending exercise were attainment of 90 per cent of the predicted maximal heart rate for the patient, defined as 200 beats per minute minus the patient's age in years (Faris, McHenry and Morris, 1978), development of any cardiac arrythmia or horizontal or downsloping ST segment depression of at least 1.0 millimetres persisting for at least 0.08 seconds (Demany, Tambe and Zimmerman, 1967; McConahay, McCallister and Smith, 1971; Martin and McConahay, 1972; Friesinger and Smith, 1972).

When an exercise end point was reached, 2 millicuries of thallium-201 were injected via the cannula (Figure 9B) and the patient encouraged to continue exercise at the same level for a further 30 to 60 seconds. On completion of exercise the patient was transferred to a trolley and imaging begun 5 minutes after injection of the tracer. Anterior, 30 and 60 degree LAO and left lateral views were obtained in the same manner as for rest studies.

II. (6) Analysis of Myocardial Images

The scintigraphic images obtained with a scintillation camera are two dimensional projections of different areas of the myocardium. On rest studies, only the left ventricular myocardium is usually seen, though the right ventricle may become visible when there is right ventricular hypertrophy (Wackers and de Jong, 1976; Cohen, Baird, Rouleau et al., 1976). On stress images both right and left ventricular myocardium are seen in most normal subjects (Wackers and de Jong, 1976; Cook et al., 1976).

The main contribution to the left ventricular image is made by those areas of the myocardium perpendicular to, or almost perpendicular to, the front of the gamma camera (Wackers and de Jong, 1976). The precise areas seen in any projection will vary somewhat depending on the orientation of the left ventricle in the chest. The nomenclature used in this thesis for the different areas of left ventricular myocardium seen on the four chosen projections is shown in Figure 10. This nomenclature was compiled from the data presented by Wackers and de Jong (1976), Cook et al., (1976), Parkey, Bonte, Stokely et al., (1976) and Lenaers, Block, van Thiel et al., (1977).

Myocardial images are usually analysed by visual inspection for areas of decreased tracer accumulation. This was performed in all studies for both the Polaroid images and for the colour television images. The colour television images were subjected to nine point smoothing and to background subtraction and contrast enhancement (Figures 11A, 11B and 11C).

Visual analysis of thallium-201 myocardial images for areas of decreased tracer uptake is complicated by some non-homogeneity of tracer uptake in the normal myocardium. This has been demonstrated both in experimental animals (Bradley-Moore et al., 1976; Schelbert, Henning, Rigo et al., 1976) and in clinical studies

in man (Cook et al., 1976; Strauss and Pitt, 1977b). To attempt to overcome this problem of non-homogeneity it was decided to analyse the myocardial image by a regions of interest technique.

Using the computer, regions of interest were drawn on the colour television image (Figure 11D) to correspond to each of the anatomical areas shown in Figure 10. The computer was then used to calculate the counts in each region of interest and its area and thus a count density (counts per unit area) was calculated for each region. In each image the maximum calculated regional count density was scored as 100% and the count densities from the other regions of interest in the same image expressed as a percentage of this. To obtain a "normal range" for this regions of interest technique a group of control subjects were studied.

II. (7) Thallium-201 Myocardial Imaging in Control Subjects

Subjects. The subjects chosen for control studies were all young men aged 20 to 30 years, either members of the staff of the Royal Infirmary or patients admitted with non cardiac and non respiratory complaints (principally minor alcohol induced haematemesis, drug overdosage and haemophilia). None of the subjects had any symptoms, signs or past history of cardio-respiratory disease and all were normotensive. The experimental nature of the procedure was explained and informed consent obtained. Approval for the study was obtained from the Isotope Advisory Panel of the Department of Health and Social Security and from the local Ethical Committee, but because of the radiation dose only a limited number of studies were approved and the rest and stress studies were performed on different groups of subjects.

Method. Using the techniques already described rest imaging was performed in 14 subjects. In a separate group of 10 control subjects stress imaging was performed. In the stress imaging group,

stress ECG's were obtained and the maximal oxygen consumption calculated indirectly from the heart rate and blood pressure at the end of exercise (Varnauskas, 1977).

Results. Examples of colour television and Polaroid images from the control subjects are shown in Figures 12 to 15.

The results of the regions of interest method of analysis of the rest images are summarised in Figure 16. The reference value of 100% obtained for each image has not been charted, but if a second value of 100% was obtained in the same image, this has been included. Most of the values (90/126) were in excess of 90% but values as low as 80% were obtained.

Figure 17 summarises the comparable results of the stress control studies. Again most values (75/90) were in excess of 90%. No values below 85% were found. During the stress tests all subjects had normal ECG's and attained a maximal oxygen consumption in excess of 75% of the predicted maximum for that subject (Astrand and Rodahl, 1970) i. e. were able to attain a "normal" maximal exercise level.

Discussion

The count density results confirm that the distribution of thallium-201 in the normal myocardium is not entirely uniform. It has been suggested, from visual assessment, that the distribution is more uniform in stress as compared to rest studies (Cook et al., 1976). Initial examination of the results presented above seems to confirm this impression. The range of count densities in the rest studies extended down to 80% compared to 85% for the stress studies and the proportion of areas with values of 90% or less in the rest studies (36/126 or 28.6%) was almost double that in the stress studies (15/90 or 16.7%). When, however, all the minimum values for the rest group in each view were compared to the minimum values in the same view for the stress group, (using the unpaired Wilcoxon

rank test) no significant differences were found ($p>0.05$ in each case). When the different views within the rest studies were compared for significantly lower minimum values, (using the paired Wilcoxon rank test) a borderline significance was obtained for the 30 LAO view compared to the 60 LAO ($p<0.05$). No other significant differences were found in the rest studies. None of the intercomparisons of views for the stress studies showed significant differences ($p>0.05$ in each case). The myocardial area showing maximal count density in any view was not constant in the different subjects.

The regions of interest technique is less subjective than visual assessment but is not wholly objective as it requires the selection of the regions of interest by the observer. It is also only semi-quantitative in that the count densities calculated for given areas in the left ventricular myocardium will be influenced by the bulk of muscle present, to some extent by background (non cardiac) activity and by activity in adjacent, partially overlapping myocardium. It also does not take account of absorption of photons by overlying structures.

It seemed worthwhile, however, to examine the utility of the semiquantitative approach to analysing Thallium-201 images. In the clinical studies presented in the following chapters areas of myocardium with count densities of less than 80% of maximal myocardial uptake during rest studies were considered abnormal. For stress studies the "lower limit" of normal was considered to be 85%.

A direct comparison of this semiquantitative method and visual analysis will be made in Chapter IV.

II. (8) Statistical Methods

All statistical tests were performed using a Hewlett Packard HP-65 programmeable calculator or the Varian 620/L computer. Probability levels were determined from Documenta Geigy, Scientific Tables, 6th edition (1962).

CHAPTER III

THALLIUM-201 MYOCARDIAL IMAGING IN PATIENTS WITH ANGINA PECTORIS OR ATYPICAL CHEST PAIN. A COMPARISON WITH ELECTROCARDIOGRAPHY AND CONTRAST RADIOLOGY

III. (1) Introduction - The Diagnosis of Coronary Artery Disease

Angina pectoris was first described by Heberden in 1768 and recognised to be associated with disease of the coronary arteries in the late eighteenth century (Matthews, 1977a). Obstructive disease of the coronary arteries is usually present in patients with typical angina pectoris (Proudfit, Shirey and Jones, 1966), but in clinical practice the decision whether or not the patient has angina may be difficult. Thus, when 3 cardiologists independently interviewed 57 men presenting with chest pain to decide whether or not the patients had angina, if one physician diagnosed angina there was only a 55% chance that his two colleagues would agree (cited in Banks and Shugoll, 1967). The situation is further complicated by the finding that some patients with chest pain not typical of angina have coronary artery disease (Proudfit et al., 1966; Matthews, 1977b) and that some patients with typical angina pectoris have normal coronary arteries both angiographically (Gorlin, 1965; Hermann, Cohn and Gorlin, 1973) and pathologically (Hermann et al., 1973).

There is no physical sign which is pathognomonic of coronary artery disease and the main aim of physical examination of the patient with chest pain is to look for complications of coronary artery disease (such as congestive cardiac failure or cardiomegaly), to exclude factors (such as anaemia, thyrotoxicosis or valvular disease) which may cause angina in the absence of coronary artery disease, or to

look for clinical evidence of other conditions (such as hyperlipidaemia) known to predispose to coronary artery disease (Matthews, 1977b; Kenmure, 1977).

Coronary arteriography is the most reliable investigation currently available for the detection of coronary artery disease in the living subject. From 1945 to 1960 attempts were made to define the anatomy of the coronary arteries using forms of aortography (Griffith and Achuff, 1977), but these were overtaken by the introduction of selective coronary arteriography (Sones, Shirey, Proudfit et al., 1959; Ricketts and Abrams, 1962). The two principal methods of selective catheterisation of the coronary arteries are the Sones' technique of introducing a catheter into a brachial artery cut down and the Judkins' technique of percutaneous introduction of a specially formed catheter into the femoral artery (Judkins, 1968). Selective coronary arteriography allows visualisation of vessels down to 100 microns in size (Gensini and da Costa, 1969).

Coronary arteriography is an invasive technique with an associated mortality and morbidity. Adams, Fraser and Abrams (1973) conducted a questionnaire survey of 46,904 coronary arteriograms performed at 173 centres in the U.S.A. in 1970 to 1971. The overall mortality rate was 0.45% and was higher in institutions performing less than 200 examinations in the two years compared to those performing more than 800 arteriograms in the same period. Serious non fatal complications were also more common in less experienced centres (Adams et al., 1973). Bourassa and Noble (1976) reported a mortality rate of 0.23% in 5250 percutaneous transfemoral coronary arteriograms carried out in Montreal from 1970-1974, whilst from this country Pridie, Booth, Fawzey et al., (1976) experienced 7 fatalities in 1500 coronary arteriograms since 1970. The risk of death or serious non fatal complications from

coronary arteriography is proportional to the severity of the coronary artery disease and the degree of left ventricular dysfunction (Griffith and Achuff, 1977). Bourassa and Noble (1976) found no serious complications in patients with normal arteriograms but, of the 12 who died in their series, 11 had lesions of the main stem left coronary artery. The increased risk associated with arteriography in patients with lesions of the left main stem coronary artery was also noted by Abrams and Adams (1975).

The coronary arteriogram is usually performed in several projections and is then analysed for the presence of obstructing lesions in the main coronary arteries and their branches. The method of reporting varies in different laboratories but the usual technique is to measure the reduction in luminal diameter caused by a lesion as judged by the most severe appearance in the various projections (Griffith and Achuff, 1977). The abnormality is usually expressed as a percentage obstruction and lesions causing 50% or more reduction in luminal diameter are generally considered haemodynamically significant, though some institutions use a figure of 70% reduction in diameter (Griffith and Achuff, 1977). Several studies have correlated the severity of coronary artery occlusions at autopsy with the angiographic estimation of severity and have found that the arteriogram will tend to underestimate the severity of the disease, especially in the distal vessels (Vlodaver, Frech, Van Tassel et al., 1973; Schwartz, Dong, Hackel et al., 1975). It has also been shown that different observers will disagree to some extent in their interpretation of the same angiogram (De Rouen, Murray and Owen, 1977). In spite of these difficulties coronary arteriography has been generally accepted as a reliable tool in the identification of clinically significant coronary artery lesions (Schwartz et al., 1975; Griffith and Achuff, 1977) and it

has been shown that the severity and extent of coronary artery disease as judged by findings at coronary arteriography are closely related to the patient's prognosis (Bruschke, Proudfit and Sones, 1973a; Humphries, Kuller, Ross et al., 1974).

Additional prognostic information can be obtained at the time of catheterisation by performing left ventriculography. Bruschke, Proudfit and Sones (1973b) have demonstrated that mortality from coronary artery disease is related to the degree of impairment of left ventricular function demonstrated at ventriculography. It is now usual to combine coronary arteriography with left ventriculography.

Coronary arteriography with left ventriculography is principally indicated in patients in whom coronary artery surgery is being considered. It is also often performed in patients with disabling chest pain of uncertain aetiology. The investigation is not indicated in stable post infarction or angina pectoris patients (Griffith and Achuff, 1977) and it is completely unsuitable as a screening test of asymptomatic subjects.

The standard non invasive technique for the detection of coronary artery disease has been electrocardiography. The first descriptions of the electrocardiographic changes during attacks of angina pectoris appeared some 50 to 60 years ago, initially in a patient with syphilitic aortitis (Bousfield, 1918) and later in patients with coronary artery disease (Parkinson and Bedford, 1931). The characteristic abnormalities were well established by 1950 (Wood, McGregor, Magidson et al., 1950). The most typical ECG finding in angina pectoris is horizontal, downsloping or sagging depression of the ST segment (Varnauskas, 1977). Junctional (J) depression with an upward sloping distal part of the ST segment which merges into the T wave is usually a normal phenomenon (Wood et al., 1950),

often associated with sinus tachycardia (Sjostrand, 1950). Although ST segment depression is characteristic of myocardial ischaemia, it is not specific and may also be seen in other circumstances such as digoxin or quinidine therapy, sympathetic nervous system dysfunction, hypokalaemia, left ventricular hypertrophy and strain, myocarditis and the Wolff Parkinson White syndrome (Varnauskas, 1977).

Less frequently the ST segment may be elevated during an attack of angina pectoris. This type of abnormality may be associated with attacks of angina at rest and was named variant angina by Prinzmetal and his colleagues (Prinzmetal, Kennamer, Merliss et al., 1959). The significance of variant angina remains somewhat controversial. It has been described both in patients with coronary artery disease, often affecting one vessel (Prinzmetal, Ekmekci, Kennamer et al., 1960; Endo, Kanda, Hosada et al., 1975; Selzer, Langston, Ruggeroli et al., 1976), and in those with normal or near normal coronary arteriograms (Endo et al., 1975; Selzer et al., 1976). The role of coronary artery spasm in producing variant angina was first suggested by Prinzmetal's group (Prinzmetal et al., 1959) and though not completely proven, was supported by recent work demonstrating coronary spasm at arteriography during attacks of variant angina in patients both with and without atherosclerotic coronary artery disease (Maseri, L'Abbate, Pesola, Ballestra et al., 1977).

In classical angina pectoris the ECG may show abnormalities of the Q wave, the T wave, the U wave, the QT interval, the QRS complex or the cardiac rhythm, but in the absence of ST segment changes these are not diagnostic of coronary artery disease (Varnauskas, 1977).

The rest electrocardiogram is an insensitive means of detecting coronary artery disease and is normal in approximately 50% of patients with coronary disease (Wood et al., 1950; Bruschke et al., 1973b; Humphries et al., 1974). Normal rest ECG's may be found in patients with multiple vessel disease (Swartz, Pichard, Meller et al., 1977), but patients with a normal rest ECG and coronary artery disease have a lower mortality rate than those with an abnormal rest ECG and coronary disease (Bruschke et al., 1973b; Humphries et al., 1974).

Because of the low sensitivity of resting electrocardiography, exercise testing with electrocardiographic monitoring as an aid to the diagnosis of ischaemic heart disease was proposed in 1932 (Goldhammer and Scherf, 1932) and in 1941 Master introduced the two step test (summarised in Master, 1968). However, this test demanded a relatively low level of effort and was found to have insufficient sensitivity in the diagnosis of coronary artery disease (Demany, Tambe and Zimmerman, 1967) and has largely been replaced by graded exercise testing in which the work load is increased at intervals using a treadmill or bicycle ergometer (Faris, McHenry and Morris, 1978). The ECG is usually obtained using a single precordial lead and monitored throughout the test on an oscilloscope, with intermittent written samples being obtained (Faris et al., 1978). Exercise tests may be classified as maximal (in which the subject exercises to the point of exhaustion) or sub-maximal (in which a target heart rate or work load is defined) but in either, the test may be ended because of onset of symptoms such as chest pain, dyspnoea or lightheadedness, or because of the development of ECG abnormalities (Varnauskas et al., 1977; Faris et al., 1978).

Exercising patients with coronary artery disease is potentially hazardous, but, in practice, when supervised by experienced personnel,

is remarkably safe. Rochmis and Blackburn (1971), in a multi-centre questionnaire survey, discovered only 16 exercise deaths in 170,000 tests and 40 patients requiring admission to hospital for non fatal complications. Death, however, has been reported after a test with a normal result (Lintgen, 1976). The test is contra-indicated in patients with recent infarction or unstable angina, in those with overt congestive cardiac failure and in those with severe ventricular arrythmias at rest (Faris et al., 1978). The generally accepted ECG criteria for ending the test are excessive and progressive ST depression, frequent or multi-focal ventricular ectopic beats and supraventricular arrythmias with a rapid ventricular response rate (Faris et al., 1978).

A "positive" exercise ECG is generally defined as one showing significant ST segment depression. To be clinically useful a degree of ST segment depression must be chosen which has high sensitivity (i. e. few negative tests in patients with coronary artery disease) and high specificity (few positive results in subjects free of coronary artery disease). Masters considered ST segment depression of 0.5 mm or more to be abnormal (Masters, 1968). This, however, produces an unacceptably high number of false positive tests and 1 mm ST segment depression is now the generally accepted criterion for a "positive" exercise ECG (Varnauskas, 1977; Faris et al., 1978).

The overall sensitivity of exercise electrocardiography in detecting arteriographically proven coronary artery disease ranges from 54 to 85 per cent in various series (Faris et al., 1978) with most series showing a sensitivity of around 70 per cent (Varnauskas, 1977). The incidence of positive exercise ECG's is higher in patients with multivessel disease, compared to single vessel disease (Faris et al., 1978; Varnauskas, 1977) but the number of abnormal vessels cannot be predicted from the exercise ECG.

The specificity of exercise electrocardiography is more difficult to assess. ST segment changes during exercise, similar to those produced by ischaemia, may be caused by various other factors such as hyperventilation, and electrolyte disturbances and may produce "false positive" exercise ECG tests in subjects with normal coronary arteriograms (Varnauskas, 1977). The prevalence of abnormal exercise ECG's in apparently normal populations has been reported as 12 to 14 per cent in male subjects and as 16 to 24 per cent in females (Varnauskas, 1977). In some of these subjects, the positive ECG reflects occult coronary artery disease, and a positive exercise test in an asymptomatic subject is associated with an increased risk of later angina pectoris or myocardial infarction (Robb and Marks, 1967). In others, however, the results are false positives. Because of the finding of false positive results, the role of exercise ECG tests in the assessment of asymptomatic subjects or those with atypical chest pain remains controversial (Varnauskas, 1977; Faris et al., 1978; British Medical Journal, 1978a; Borer, Brensike, Redwood et al., 1975).

A further difficulty encountered in using the exercise ECG for the detection of coronary artery disease is that certain other electrocardiographic abnormalities (e.g. left bundle branch block, left ventricular hypertrophy or changes induced by digoxin therapy) invalidate the use of the ST segment depression as an indication of myocardial ischaemia (Varnauskas, 1977).

For a variety of reasons, therefore, electrocardiography is not an entirely satisfactory technique for the non invasive diagnosis of coronary artery disease. Indeed, it has been suggested (Borer et al., 1975) that whilst "exercise testing is of value as an epidemiological tool when large groups are studied", it is "of very limited value in the diagnosis of haemodynamically important large vessel coronary artery stenosis in the individual patient". This,

however, is an extreme point of view, not held by most cardiologists.

Radioisotope myocardial imaging offers an alternative, and possibly more direct, approach to the non invasive assessment of patients with suspected ischaemic heart disease. As discussed in Chapter I, the potassium isotopes and potassium analogues available until 1975 had biological or physical properties which made them unsuitable for widespread use. The position changed, however, with the introduction of thallium-201. The study to be presented and discussed in the rest of this chapter was designed to evaluate myocardial imaging with this isotope as a tool in the diagnosis of coronary artery disease.

III. (2) Aims of the Study

This study has compared thallium-201 myocardial imaging to electrocardiography and to selective coronary arteriography with left ventriculography in a group of patients with disabling chest pain.

The questions posed were:

(i) What is the sensitivity and specificity of stress thallium-201 myocardial imaging in diagnosing arteriographically proven coronary artery disease in a group of patients presenting with chest pain?

(ii) What role, if any, does rest myocardial imaging have in these patients?

(iii) Can thallium-201 imaging be used to predict the extent of coronary artery disease?

(iv) How does thallium-201 imaging relate to electrocardiography in the non invasive diagnosis of coronary artery disease?

III. (3) Subjects

A total of 85 patients were studied. All were undergoing selective coronary arteriography with left ventriculography either for assessment of suitability for coronary artery bypass surgery or for diagnosis of disabling chest pain of uncertain aetiology.

71 of the patients were male and 14 female and they ranged in age from 27 to 59 years (Mean = 45.3 years).

III. (4) Methods

III. (4)(a) Myocardial imaging

Rest and exercise thallium-201 myocardial imaging were performed in the manner already described in Chapter II. In the early part of the study (the first 50 patients approximately) both rest and stress imaging were carried out in all subjects, with a minimum of seven days between the two tests. Later, stress images were obtained first and if these were normal, rest imaging was not performed. The stress myocardial imaging was usually carried out in the week preceding or the week following coronary arteriography, and in no case was the interval between the two studies more than two months.

The myocardial images were analysed by the regions of interest technique, described in Chapter II. All analyses were performed by me, independent of any knowledge of the result of the coronary arteriogram.

III. (4)(b) Electrocardiograms

12 lead rest electrocardiograms were performed before the thallium imaging. Stress ECG's were obtained during the exercise for the stress thallium-201 imaging. All ECG's were interpreted by Dr. R.G. Murray. The ST segment was considered abnormal if it showed horizontal or downsloping depression of 1 mm or more of at least 0.08 seconds duration. Lesser ST segment changes were classified as equivocal. If the ECG showed pathological Q waves it was considered positive. Other changes e.g. ventricular arrythmias, bundle branch block and T wave abnormalities without ST segment changes were classified as equivocal.

III. (4)(c) Radiological studies

The cardiac catheterisation studies were performed via the percutaneous transfemoral route. Biplane left ventriculography was performed first, in the left lateral and 30 degree right anterior oblique projections.

Following completion of the ventriculogram, a separate catheter was introduced and selective coronary arteriography performed (Judkins' technique), with views obtained in multiple projections.

The radiological studies were interpreted by a group of cardiologists, including the one carrying out the catheterisation. The ventriculogram was assessed for both global left ventricular function and for regional wall motion. On the coronary arteriograms the right coronary artery (RCA), the main left coronary artery (main left), the left anterior descending coronary artery (LAD) and the left circumflex coronary artery (LCx) and their major branches were analysed. Lesions which reduced the luminal diameter of any of these vessels by 50% or more in any projection were considered significant, and the patients were thus classified as having single, double or triple vessel disease, with main left lesions being considered as double vessel disease.

III. (5) Results

In the comparison of the different techniques the results of coronary arteriography and left ventriculography were considered as the standards against which other results were compared.

III. (5)(a) Results of coronary arteriography and left ventriculography

At coronary arteriography 34 patients were considered to have no significant abnormality i. e. none of the vessels had any lesion of 50% or greater of the luminal diameter. In the remaining 51 patients the arteriography revealed abnormal coronary arteries - 13 patients

had single vessel disease, 26 double vessel disease and 12 triple vessel disease (Table 2). In the single vessel disease patients 10 had lesions of the left anterior descending coronary (LAD) and 3 lesions of the right coronary artery (RCA). No case of isolated left circumflex (LCx) disease was encountered (Table 3). The arteriographic abnormalities in the patients with double vessel disease are summarised in Table 4. The commonest combination was LAD and RCA disease, present in 14 patients. LAD and LCx disease was present in 6 patients and LCx and RCA disease in 5. One patient had an abnormal main left coronary artery.

The results of left ventriculography are summarised in Table 5. All 34 patients with normal coronary angiograms had normal ventriculograms. Of the 51 patients with abnormal arteriograms, the left ventriculogram was normal in 30 and abnormal in 21.

III. (5)(b) Sensitivity of thallium-201 myocardial imaging in the detection of coronary artery disease

Stress thallium-201 myocardial imaging could not be performed in 2 patients with LAD disease and in 2 with LAD and RCA disease who had chest pain and breathlessness at rest. The results of stress imaging in the remaining 47 patients with abnormal coronary arteriograms are summarised in Table 6. Of 11 patients with single vessel disease, 10 had abnormal stress images, whilst 22 of 24 patients with double vessel disease and 11 of 12 with triple vessel disease had abnormal images. If sensitivity is defined as $\frac{\text{True Positives}}{\text{True Positives + False Negatives}}$ (Reba and Charkes, 1975), then the overall sensitivity of stress thallium-201 myocardial imaging in this study for the detection of significant coronary artery disease was 43/47 i.e. 91.5%.

In some patients the abnormalities seen on stress imaging were extensive. An example of markedly abnormal stress thallium-201 images is shown in Figure 18. Examples of more subtle abnormalities are demonstrated in Figures 19 and 20 whilst Figure 21 shows a false negative study in a patient with triple vessel disease.

Areas of marked abnormality often corresponded to sites of previous myocardial infarction. The inclusion of a large number of patients with previous infarcts might give rise to a falsely high incidence of positive studies. Sensitivity was therefore also calculated in those patients who had no evidence of previous infarction. "No evidence of previous infarction" was defined, for this purpose as no history suggestive of previous infarction plus no ECG (Q wave) evidence of previous infarction plus a normal left ventriculogram. Twenty-nine of the patients in whom stress images had been obtained fulfilled these criteria. The images were abnormal in 26. Thus the sensitivity of stress imaging in the patients with no evidence of previous myocardial infarction was 26/29 or 89.7%. This does not differ significantly from the sensitivity in the whole series (Chi squared test, $p > 0.05$).

Rest imaging was performed in 42 patients with abnormal arteriograms, including the 4 in whom stress imaging was not possible. The results are summarised in Table 7. A total of 21 patients had abnormal rest images, an overall sensitivity of 50%. The frequency of abnormal rest images was 3/11 in single vessel disease, 11/21 in double vessel disease and 7/10 in triple vessel disease. No statistically significant differences for the frequency of a positive rest study were found in the three groups (Chi squared tests, $p > 0.05$ in each case).

In 15 patients with abnormal rest images the site of abnormality correlated well with the site of previous infarction as judged by the presence of Q waves on the ECG. The remaining 6 with abnormal rest images had no history or ECG evidence of previous infarction. The significance of these findings will be considered further in the discussion.

The sensitivity of stress imaging in this series (43/47 or 91.5%) was significantly higher than that of rest imaging (21/42) (Chi squared test, $p<0.002$). Examples are given in Figures 20, 22 and 23 of abnormalities appearing on the stress study which were not present at rest. In addition to new defects appearing on stress studies, defects present on rest studies often enlarged on stress studies (Figure 24).

III. (5)(c) Specificity of thallium-201 myocardial imaging for the detection of coronary artery disease

The results of myocardial imaging in the 34 patients with chest pain and normal coronary arteriograms are summarised in Tables 8 and 9.

Thirty one of these patients had normal stress images (Table 8). An example is given in Figure 25 of such a normal study. Three patients with normal arteriograms had abnormal stress images. Two, both women, had typical anginal pain and strongly "positive" stress ECG studies but normal arteriograms. Figure 26 is from one of these women. The third patient had atypical chest pain, a normal stress ECG and a normal arteriogram.

If specificity is defined as $\frac{\text{True Negatives}}{\text{True Negatives + False Positives}}$ (Reba and Charkes, 1975), the specificity of thallium-201 stress imaging for coronary artery disease in this study was 31/34 (91.2%).

Rest imaging was performed in only 16 patients with chest pain and normal coronary arteriograms (Table 9) because, in the later stages of the study, rest images were obtained only when the stress images were abnormal. 14 patients, including two with abnormal stress studies, had normal rest images. Two patients had abnormal rest images. The woman whose stress study is illustrated in Figure 26, showed a similar abnormality on rest imaging. The second rest image abnormality (Figure 27) was in a 27 year old man admitted with pain suggestive of acute myocardial infarction. An acute infarction was excluded by ECG and enzyme studies. Full cardiological investigation (including coronary arteriography) was performed 6 weeks later and a final diagnosis of myocarditis (possibly viral) was made. Stress myocardial imaging was also performed at this time and was normal (Figure 27).

The specificity of rest imaging for coronary artery disease was 14/16 (87.5%). This is possibly an underestimate of the specificity as many patients with a normal stress study were not imaged at rest.

III.(5)(d) Myocardial scan abnormalities associated with occlusions of particular coronary arteries

By analysis of the stress images of patients with single vessel or double vessel disease, information was obtained on the distribution of abnormalities associated with occlusions of each of the three major coronary arteries. The results are summarised in Table 10.

Stress images were obtained in 3 patients with isolated RCA lesions. In the anterior view, 2 showed decreased tracer uptake posteroseptally and all had apico-inferior abnormalities. All showed decreased uptake apico-inferiorly in the 30 LAO view and in all of them the 60 LAO view was normal. In all 3 the left lateral

view demonstrated posterior and inferior abnormalities. These abnormalities are demonstrated in Figure 28.

Seven patients with isolated LAD lesions had stress imaging performed. Abnormalities in the following areas were found (though not all areas were abnormal in all patients): in the anterior view, posteroseptal, apical and anterolateral; in the 30 LAO view, anteroseptal, apical and lateral and in the 60 LAO and left lateral views, anterior and apical areas. The stress myocardial images of a patient with isolated LAD disease are shown in Figure 29.

The association of the above abnormalities with RCA and LAD disease was further confirmed by analysis of the images of patients with double vessel disease.

No patients with isolated left circumflex disease were studied. However, from the images of patients with double vessel disease, it was found that decreased uptake posterolaterally in the 60 LAO view and posteriorly in the left lateral view were associated with lesions of the left circumflex coronary artery. This association was confirmed by the scan appearances of patients with disease of ungrafted left circumflex coronary arteries and patent bypass grafts to their other diseased vessels (Figure 30).

III. (5)(e) Correlation of extent of stress myocardial image abnormalities with radiographic findings

In the 47 patients with abnormal arteriograms who had stress imaging performed, the image abnormalities were compared to the coronary arteriogram findings to assess how completely the scan reflected the extent of the arteriographic lesions. Using the correlations of regional abnormalities on the scan with particular arteriographic lesions described in section III. (5)(d) the myocardial image was considered to reflect the coronary artery lesion if any appropriate area was abnormal e.g. in a patient with RCA and LAD

if the scan showed posteroseptal, apical and anteroseptal abnormalities this was considered to reflect both arterial lesions.

In the eleven patients with single vessel disease, one with LAD disease had normal myocardial images. In the other 10 image abnormalities developed in the appropriate areas. Of the 24 patients with double vessel disease, 14 showed myocardial image abnormalities corresponding to both stenosed vessels. Two patients (both with LAD and RCA disease) had normal myocardial images and a further 8 patients had image abnormalities corresponding to only one of the abnormal vessels. In the 12 triple vessel disease patients one had a normal stress thallium-201 study (i.e. all 3 vessels "missed"). 7 had myocardial images reflecting single vessel disease and 3 double vessel disease. In only 1 patient did the abnormalities reflect triple vessel disease.

The distribution of coronary artery occlusions not reflected on the stress images is summarised in Table 11. Appropriate myocardial image abnormalities failed to develop in a total of 33/95 (35%) lesions. Analysis of the results for the individual vessels shows that 6/39 (15.4%) LAD lesions, 12/32 (37.5%) RCA lesions and 15/24 (62.5%) LCx lesions were "missed". The frequency with which abnormalities appropriate to LCx disease failed to develop was significantly higher (Chi squared test, $p<0.002$) than that for LAD lesions. No other statistically significant differences were found (Chi squared tests, $p>0.05$ in each case).

To attempt to explain why abnormalities appropriate to particular occlusions failed to develop on stress imaging, Dr. R.G. Murray has undertaken further analysis of the coronary arteriograms of 30 patients with double or triple vessel disease and has assessed firstly, whether coronary collateral vessels were present and

secondly, the relative severity of the individual occlusions in each patient.

In these 30 patients there were 70 significantly (>50% occluded) coronary vessels, with failure to develop appropriate myocardial image abnormalities in the vascular territories of 25 abnormal vessels.

Collateral circulation was present to 24 abnormal vessels. The relationship between the image appearance and the presence of collaterals is summarised in Table 12. Eight of the areas subtended by abnormal vessels with collaterals present were the site of previous myocardial infarction on electrocardiographic or ventriculographic criteria. All 8 were abnormal on the stress myocardial image. Of the remaining 16 vascular territories of abnormal vessels with collaterals, 9 appeared normal on stress myocardial imaging whilst 7 were abnormal. These results suggest that in some cases the failure of abnormalities to develop on myocardial imaging is due to a "protective" effect of collateral circulation. The collaterals, however, are not invariably protective and abnormalities will appear at the sites of previous infarction in spite of the presence of collateral vessels. In the 46 territories supplied by abnormal major epicardial vessels and with no collateral circulation, 16 remained normal on stress imaging. In 7 cases the failure to develop an abnormality in the territory of a vessel with a 50-75% stenosis was accompanied by the presence, in the same patient, of a myocardial image abnormality in the territory of a vessel with a more severe (i. e. 75-99% or a 100%) stenosis. In 3 patients failure to develop an abnormality in the territory of a 75-99% stenosed vessel was accompanied by an image abnormality in the area supplied by a 100% stenosed vessel. A further 6 areas, supplied by abnormal vessels with no collateral circulation were normal on stress imaging,

and were not associated with abnormalities in the territory of more severely stenosed vessels. It is not clear why these areas were normal.

III. (5)(f) Correlation of the extent of rest myocardial image abnormalities with radiographic findings

As described in Chapter III. (5)(b) the rest myocardial images were performed in 42 patients with significant coronary artery stenoses and were abnormal in 21. The abnormalities reflected the extent of coronary artery disease in a total of 6 patients, 3 with single vessel disease and 3 with double vessel disease.

A much better correlation was found between the appearance of the rest thallium-201 image and left ventricular wall motion as judged from the left ventriculogram. This is summarised in Table 13. In 37 of the 42 patients (88.1%) there was correlation between the presence or absence of abnormalities on the two studies, with good agreement as to the anatomical sites of the abnormalities. In two patients with inferior dyskinesia on the ventriculogram the rest thallium-201 image was normal, whilst 3 patients with normal ventriculograms showed lesions on the nuclide study.

III. (5)(g) Prediction of the extent of coronary artery disease from stress thallium-201 images

As shown in Chapter III. (5)(d) and Table 10, certain areas on the myocardial image may be supplied by more than one coronary artery. In predicting the extent of coronary artery disease from the myocardial scan, therefore, two strategies are possible i.e. predicting the minimum or the maximum number of vessels which could account for the image abnormalities. Because of the difficulty of associating apical abnormalities with any vessel, they were excluded from consideration except in one patient who had an isolated apical abnormality. This patient was considered to have single vessel disease.

The results of the prediction of the number of abnormal vessels using the "minimum vessel approach" are compared to the arteriographic findings in the 81 patients who had stress imaging (34 with normal arteriograms and 47 with abnormal arteriograms) in Table 14. In the 3 patients with normal arteriograms but abnormal stress images, the myocardial image appearances suggested single vessel disease. In the patients with abnormal arteriograms the extent of vessel disease was correctly predicted from the radionuclide study in 9 patients with single vessel disease, in 9 with double vessel disease and in 1 with triple vessel disease - a total of 19/47 patients (40.4%). If the patients with abnormal arteriograms were classified as single or multiple (double or triple) vessel disease, the presence of single vessel disease was correctly predicted in 9/11 patients (81.8%) and multivessel disease in 13/36 (36.1%). In all the division into single or multiple vessel disease was correctly predicted in 22/47 (46.8%) of the patients.

To assess whether the accuracy of prediction of the extent of vessel disease was affected by the presence of abnormalities due to previous myocardial infarction, the "minimum vessel prediction" was carried out separately for the 29 patients with abnormal arteriograms and no ventriculographic or electrocardiographic evidence of previous infarction. The results are summarised in Table 15. The number of abnormal vessels was predicted correctly in 7/9 patients with single vessel disease, 5/14 with double vessel disease and 1/6 with triple vessel disease. The presence of single or multiple vessel disease was accurately predicted in 13/29 patients (44.8%) with no previous myocardial infarction. This does not differ significantly from the accuracy of prediction in the whole group with abnormal arteriograms (Chi squared test, $p>0.05$).

The results of the prediction of the maximum number of abnormal vessels from the stress thallium-201 image appearances are summarised in Table 16. The number of abnormal vessels was correctly predicted in 5/11 patients with single vessel disease, 9/24 with double vessel disease and 1/12 with triple vessel disease. The prediction of the number of abnormal vessels was accurate in a total of 15/47 patients (31.9%) with abnormal arteriograms. The division of patients into single or multiple vessel disease from the stress myocardial image appearances was accurate in 5/11 patients with single vessel disease and 18/36 with multivessel disease i.e. an overall accuracy of 23/47 (48.9%). This is not significantly different from the accuracy achieved for this prediction using the "minimum vessel strategy" (Chi squared test, $p>0.05$).

Table 17 shows the accuracy of the "maximum vessel prediction" for the 29 patients with abnormal arteriograms and no previous myocardial infarction. In this group the number of abnormal vessels was correctly predicted in 3/9 single vessel disease, 6/14 double vessel disease and 1/6 triple vessel disease patients. The presence of multiple vessel disease was correctly predicted in 10/20 patients and the division into single or multiple vessel disease correctly made in 13/29 patients (44.8%).

III. (5)(h) Comparative sensitivity and specificity of thallium-201 myocardial imaging and electrocardiography in the diagnosis of coronary artery disease

The results of the electrocardiographic studies are summarised in Tables 18 and 19.

In the patients with abnormal coronary arteriograms, the rest ECG was abnormal in 26 of the 48 patients for whom results were obtainable. 17 of these patients showed pathological Q waves, with or without abnormal ST-T changes, 7 had "ischaemic" ST segments at rest, 1 had first degree heart block and 1 left bundle branch block.

Two patients had 1 mm ST segment depression at rest but were receiving digoxin therapy - these were considered equivocal. 20 patients had a normal rest ECG. The sensitivity of rest electrocardiography for the detection of coronary artery disease was 26/48 (54.2%) or 28/48 (58.3%) if the equivocal ECG's are considered abnormal. These sensitivities are not significantly different from those of rest thallium-201 myocardial imaging (Chi squared tests, $p>0.05$).

The exercise ECG was definitely abnormal (pathological Q waves or "significant" ST segment depression) in 29 of 44 patients (65.9%). Equivocal changes (ventricular arrythmias or ST segment changes not meeting the criteria defined in section II.(4)(b)) were found in a further 6 patients. The stress ECG was "normal" in 9/44 patients (20.5%) with abnormal coronary arteriograms. The sensitivity of stress imaging in the diagnosis of coronary artery disease (43/47) is significantly higher than that of exercise electrocardiography if the equivocal tests are considered negative (Chi squared test, $p<0.01$) but not if they are considered positive (Chi square $p>0.05$).

Of the 47 patients with abnormal arteriograms who had stress studies performed only 1 (with a distal lesion of the right coronary artery) had both a normal stress image and a normal exercise ECG. The combined sensitivity of the two techniques was thus 97.9%.

Rest electrocardiography was abnormal in 3/34 patients with normal coronary arteriograms and equivocal in a further 2 (Table 19). The specificity of an abnormal rest ECG for coronary artery disease was thus 91.2% if the equivocal tests are considered negative or 85.3% if they are taken as positive. These specificities are not significantly different from those of rest thallium-201 imaging (Chi squared tests, $p>0.05$).

Stress ECG's were definitely abnormal in 8/34 patients with normal coronary arteriograms and equivocal in a further 5. The specificity of an abnormal stress ECG for coronary artery disease was thus 76.5% if equivocal tests are considered negative and 61.8% if they are considered positive. The specificity of stress thallium-201 imaging is greater than that of exercise electrocardiography if the equivocal ECG's are considered positive (Chi squared, $p<0.02$) but not when they are considered negative (Chi squared test, $p>0.05$).

The predictive value of a positive test for a diagnosis can be defined as $\frac{\text{True Positives}}{\text{True Positives} + \text{False Positives}}$ whilst the predictive value of a negative test in excluding the diagnosis is $\frac{\text{True Negatives}}{\text{True Negatives} + \text{False Negatives}}$ (Reba and Charkes, 1975). Using these definitions the predictive value of a positive (i.e. abnormal) stress thallium-201 myocardial image for the diagnosis of coronary artery disease in the present series of patients with chest pain was $\frac{43}{43 + 3}$ or 93.5%. If the patients with equivocal ECG results are excluded, the predictive value of a positive stress ECG was $\frac{29}{29 + 8}$ or 78.4%. The predictive value of a positive stress thallium-201 image is statistically significantly greater than that of a positive stress ECG (Chi squared, $p<0.05$).

The predictive value of a negative stress thallium-201 test in excluding coronary artery disease was $\frac{31}{31 + 4}$ or 88.6% and the predictive value of a negative stress ECG (excluding equivocal studies) was $\frac{21}{21 + 9}$ or 70%. The differences between stress thallium-201 imaging and stress electrocardiography are not significant (Chi squared test, $p>0.05$).

III. (6) Discussion

The discussion of this study is arranged in four sections, each corresponding to one of the questions posed at the outset of the study (Chapter III. (2)).

III. (6)(a) What is the sensitivity and specificity of stress thallium-201 myocardial imaging in the detection of coronary artery disease?

The present series suggests that stress thallium-201 myocardial imaging is a very sensitive technique for the non invasive detection of coronary artery disease in patients with chest pain, with an overall sensitivity of 91.5%. How does this sensitivity compare with that found in other centres?

Thallium-201 myocardial imaging has been the subject of intensive investigation in the last three years. Because the technique is relatively new there are, as yet, not many full scientific papers published on the subject, but a larger number of abstracts of papers delivered to learned societies have recently appeared. A summary of a selection of these papers and abstracts is given in Table 20.

The reported sensitivites range from 68% to 100%. The differences may be partly explained by differing criteria for the severity of coronary artery stenosis considered "significant" and by the small numbers included in some of the series.

If only the larger series are considered (i.e. those with 70 or more patients) they appear to be divided into two groups: those with a sensitivity of around 90% or more (Lenaers, Block, Van Thiel et al., 1977; Lenaers, Van Thiel, Block et al., 1978; Rehn, Griffith, Achuff et al., 1978; Wainwright, Maisey and Sowton, 1978) and those with a sensitivity of around 70 to 75% (Bailey, Griffith, Rouleau et al., 1977; Ritchie, Trobaugh, Hamilton et al., 1977;

Ritchie, Zaret, Strauss et al., 1977; Turner, Battle, Deshmukh et al., 1978). There are no obvious major differences between the two groups in terms of the patient populations and, in particular, each includes a series of patients with chest pain but no previous myocardial infarction (Lenaers et al., 1978; Turner et al., 1978). An interesting point emerges, however, if the method of analysis of the images is considered.

The method of analysis is not specified in the studies by Rehn et al., (1978) and by Ritchie, Zaret, Strauss et al., (1977) but is in the six remaining series. Lenaers et al., (1977), Lenaers et al., (1978) and Wainwright et al., (1978) all used a form of quantitative assessment - in the case of Lenaers et al., any myocardial areas showing activity below the 75% iso count level were considered abnormal, whilst Wainwright et al., utilised a "regions of interest" technique, details of which are given in Wainwright (1977). These three series all report a sensitivity in excess of 90%, similar to that found in my own study, which is based on a "regions of interest" approach. By comparison Bailey, Griffith, Rouleau et al., (1977), Ritchie, Trobaugh, Hamilton et al., (1977) and Turner et al., (1978) all relied on visual assessment of the images and found sensitivities ranging from 68 to 76%. From these results it appears possible that the sensitivity of stress thallium-201 myocardial imaging may be improved from 70-75% to 90-95% by the use of a quantitative or semiquantitative approach rather than visual analyses. This point will be considered further in Chapter IV.

The specificity of an abnormal stress thallium-201 myocardial image for coronary artery disease in the present series was 91.2%. The stress images were abnormal in 3 patients with chest pain but a normal coronary arteriogram. The first such patient, a man aged 42,

had chest pain which usually developed on exertion but was not anginal in quality. His rest and stress ECG's were normal as was his coronary arteriogram, but the stress thallium-201 image was abnormal on two occasions separated by two weeks. No final diagnosis was obtained in this patient, but it seems possible that he does not have cardiac disease and his nuclide study must at present be regarded as a "false positive".

The two other patients with abnormal myocardial images and normal arteriograms present an interesting problem. Both were women in their forties who had classical angina pectoris, normal rest but strongly positive stress electrocardiograms and no significant stenosis of the coronary vessels at arteriography. It is possible that the arteriogram has missed a significant lesion but it is perhaps more likely that they fall into the category of "angina with normal coronary arteries" (Kemp, Vokonas, Cohn et al., 1973; Hermann et al., 1973). This syndrome appears to be associated with a relatively benign prognosis (Kemp et al., 1973) though myocardial infarction may occur (Rosenblatt and Selzer, 1977). These two patients had no evidence of any systemic metabolic cause of angina, nor of any of the syndromes reported to cause abnormalities of the small arteries of the heart (James, 1977). Coronary artery spasm may cause angina in the absence of fixed stenosis of the coronary arteries (Maseri, L'Abbate, Pesola, Ballestra et al., 1977) and has been reported to produce abnormalities on thallium-201 images obtained during the attack of pain (Maseri, Parodi, Severi et al., 1976). Pharmacologically induced coronary spasm has also been reported to produce focal abnormalities on thallium-201 myocardial images of patients with angina and normal coronary arteries (Rothman, Bergman, Atkinson et al., 1978). Neither of our patients showed the ECG

changes usually seen in variant angina nor was there any arteriographic evidence of coronary spasm. Mitral valve prolapse may also cause anginal type pain in patients with normal coronary arteriograms (Popp and Winkle, 1976) and has been reported to be associated with an abnormal thallium-201 image in the absence of coronary artery disease (Tresch, Soin, Siegel et al., 1978) though this finding was not confirmed by Massie, Botvinick, Shames et al., (1978). Neither of the patients being presently considered had clinical or ventriculographic evidence of mitral valve prolapse. Oral contraceptive therapy has been reported as a cause of myocardial infarction in women with normal coronary vessels and shown to cause reduction in regional coronary blood flow as measured by the xenon-133 technique (Engel, Hundeshagen and Lichtlen, 1977), but neither of the women was taking or had taken contraceptive therapy. Focal abnormalities on myocardial images have also been seen in patients with noncoronary cardiomyopathies (Bull et al., 1976; Poe, Eber, Norman et al., 1977; Pitcher, Wainwright, Maisey et al., 1978).

As is shown in Table 20, the specificity of stress imaging in this series is very similar to most of the results reported in the literature, with most series reporting a small number of chest pain patients with normal coronary angiograms but abnormal thallium-201 images. Three of the series merit special consideration. Berman, Amsterdam, Jove et al., (1978) studied 21 patients who were asymptomatic but had abnormal stress electrocardiograms. Stress thallium-201 images were abnormal in 6 of 7 patients with abnormal coronary arteriograms and normal in all 14 patients with normal arteriograms. Pond, Rehn, Bailey et al., (1978) found normal myocardial images in 48 of 53 patients with chest pain but no significant (>50%) coronary stenoses. The abnormal studies could not be related to abnormal ventricular

function, mitral valve prolapse or suspected coronary artery spasm. Wainwright, Maisey and Sowton (1978) report the lowest specificity of the studies cited. In an interesting study they found that 18 of 21 patients with angiographically normal coronary arteries and angina pectoris had abnormal areas on their stress thallium-201 images. By contrast, Raphael, Cowley, Logic et al., (1976) found normal stress thallium-201 images in all 9 of a group of patients with "angina and normal coronary arteriograms".

In summary, therefore, from my own results and from others in the literature it appears that an abnormal stress thallium-201 myocardial image in a patient with chest pain is most likely to be due to coronary artery disease. The exact specificity of such an abnormality for coronary artery disease, however, will depend on the population studied, and in particular on the prevalence of other myocardial pathologies which cause "false positive" results.

III. (6)(b) The rest thallium-201 image in the patient with chest pain

Rest thallium-201 myocardial images were abnormal in 21 of 42 patients with abnormal arteriograms. No ischaemic heart disease patient was seen who had abnormal rest but normal stress myocardial images. The sensitivity of rest myocardial imaging in the detection of coronary artery disease in this series is very similar to that found by Bailey, Strauss and Pitt (1977) but somewhat higher than that of Ritchie, Trobaugh, Hamilton et al., (1977). The specificity of an abnormal rest thallium-201 myocardial image for coronary artery disease in patients with chest pain was 87.5 per cent, but the accuracy of this figure is questionable in view of the small number of patients with normal coronary arteriograms who had rest imaging performed. Abnormalities on rest thallium-201 imaging have been described in a variety of cardiac pathologies other than coronary artery disease including sarcoid heart disease (Bulkley, Rouleau,

Whitaker et al., 1977) other cardiomyopathies (Bull et al., 1976; Bulkley, Rouleau, Strauss et al., 1975; Feiglin, Huckell, Staniloff et al., 1978) and pulmonary hypertension (Cohen, Baird, Rouleau et al., 1976).

The rest thallium-201 images in the ischaemic heart disease patients in the present series showed good overall agreement with the results of left ventriculography (Table 13) a finding confirmed by other series such as these of Bull et al., (1976) and Pitt and Strauss (1976).

It is generally held that abnormalities on the rest thallium-201 image in the patient with coronary artery disease represent myocardial scarring consequent upon previous myocardial infarction (Pabst, Hor, Lichte et al., 1976; Bull et al., 1976; Ritchie, Trobaugh, Hamilton et al., 1977; Berger, Gottschalk and Zaret, 1978). This view is supported by the good correlation between the rest myocardial image abnormalities and wall motion abnormalities at ventriculography, though it should be noted that Hutchins, Bulkley, Ridolfi et al., (1977), in a comparison of ventriculographic and post mortem findings, have shown that abnormal left ventricular wall motion may occur in coronary artery disease patients at sites showing no pathological evidence of acute or old myocardial infarction.

Of the 21 patients with abnormal rest images and abnormal arteriograms, 15 had Q waves on their resting ECG and abnormal left ventriculograms. It seems likely that the abnormal rest study in these patients represents myocardial scarring from previous myocardial infarction. In 4 other patients, there was no history to suggest acute infarction and the rest ECG was normal, but the rest thallium-201 image abnormality corresponded to areas of hypokinesia at ventriculography. Previous myocardial infarction is possible in these patients as the condition may be clinically silent (Margolis, Kannel, Feinleib et al., 1973) and there may be complete resolution of the ECG evidence of acute myocardial

infarction following recovery (Cox, 1967; Kalbfleisch, Shadaksharappa, Conrad et al., 1968). It is also possible, however, that the rest image abnormalities in these patients was due to myocardial ischaemia. The case for myocardial ischaemia as the cause of these abnormalities would have been further supported by the demonstration of improvement in wall motion after the administration of nitroglycerin (Helfant, Pine, Meister et al., 1974) or in the beat following an induced extra-systole (Dyke, Cohn, Gorlin et al., 1974). This information, however, is not available. The possibility of myocardial ischaemia as the cause of an abnormal rest thallium-201 myocardial image is even stronger in the two remaining patients, both of whom had no history of previous infarction, normal electrocardiograms and normal left ventriculograms.

It has recently been suggested that a separate rest study is unnecessary as the same information may be obtainable from myocardial images performed some hours (usually about 4) after the injection of the tracer during stress (Pohost, Zir, Moore et al., 1977; Hor, Sebening, Sauer et al., 1977). It is not yet resolved whether the appearances some hours after stress injection are produced primarily by loss of thallium-201 by the normal myocardium (Schelbert, Schuler, Ashburn et al., 1977) or late uptake of the tracer by the transiently ischaemic myocardium (Beller and Pohost, 1978), but the delayed images are thought to reflect the myocardial potassium pool and thus indicate viable myocardial tissue rather than blood flow (Adelstein and Maseri, 1977).

The main reason for performing rest myocardial imaging is to allow differentiation between transiently ischaemic and fibrosed or necrosed myocardium. Our results and those found in most other series (Ritchie, Trobaugh, Hamilton et al., 1977; Bailey,

Griffith, Rouleau et al., 1977) indicate that in patients with coronary artery disease an abnormal rest image usually is due to previous infarction. However, my results also suggest that in some patients ischaemia rather than fibrosis may produce rest image abnormalities. This belief is strengthened by the observations made by Gewirtz, Beller, Strauss et al., (1978) that if serial imaging is carried out after injection of a single dose of thallium-201 at rest, abnormalities seen initially may either disappear or become less marked. Such resolving abnormalities were usually associated with a normal left ventriculogram or only slightly disordered left ventricular wall motion (Gewirtz et al., 1978). Analogous results have been reported by Pond, Rehn, Burow et al., (1977), who found that, in patients with suspected acute myocardial infarction, abnormalities produced on the immediate post-injection thallium-201 rest image by myocardial ischaemia rather than infarction showed resolution when imaging was repeated 3 hours later (without injecting a second dose of radioisotope).

My findings regarding rest image abnormalities and those of Gewirtz et al., (1978) and Pond et al., (1977) have possible therapeutic implications as they indicate that such abnormalities, especially when associated with normal or only slightly abnormal left ventricular wall motion, do not always imply irreversibly damaged myocardium and thus do not necessarily preclude successful revascularisation of that area by coronary artery surgery.

In summary, the role of the rest thallium-201 image in the patient with suspected ischaemic heart disease is a limited one. If an initial screening test is wished in the angina or atypical chest pain patient then stress imaging is indicated and if this is normal a rest image is not required. If the stress image is abnormal a

rest image may have some value in demonstrating the reversibility of some defects seen at stress and this may strengthen the case for the abnormalities being due to coronary artery disease rather than other pathologies. An abnormal rest image in the coronary artery disease patient indicates that there will probably be corresponding areas of disordered wall motion, but it cannot be presumed that it indicates previous myocardial infarction. The value of rest thallium-201 myocardial imaging in the patient with a suspected acute myocardial infarction will be considered separately in Chapter V.

III. (6)(c) Can the extent of coronary artery disease be predicted from thallium-201 myocardial images?

The results presented in sections III. (5)(e)(f) and (g) indicate that our technique of thallium-201 myocardial imaging cannot reliably predict the number of abnormal vessels. If a pattern suggesting multiple vessel disease is present when the minimum number of abnormal vessels are being predicted, then it is probable that the patient does have more than one abnormal coronary vessel. A pattern suggestive of single vessel disease does not exclude multiple vessel disease, and a single vessel disease pattern was present on stress images of 20/36 (56%) multiple vessel disease patients studied.

A low accuracy of prediction of the number of abnormal vessels from stress thallium-201 myocardial images has also been found by Lenaers et al., (1977) and by Rigo, Bailey, Rehn et al., (1978), whilst Rosenblatt et al., (1977) reported that the correlation between scan defects and the sites of coronary stenosis was poorer in multiple vessel disease than single vessel disease patients. By contrast, however, other groups have felt that a higher accuracy of prediction is possible. Thus, Massie, Dash,

Botvinick et al., (1978) found that there were certain scintigraphic patterns suggestive of left main stem disease or three vessel disease and that stress thallium-201 imaging could reliably identify such "high risk" patients. Similarly Weisberger (1977) suggested that the finding of a normal rest thallium-201 image but minimal anteroseptal and anterolateral uptake at stress was specific for left main stem disease. Rehn et al., (1978), however, reported that whilst stress myocardial imaging was sensitive in left main coronary disease, the appearances were not specific for it. Wainwright et al., (1978) have found a high degree of predictive accuracy of the number of abnormal vessels from stress thallium-201 images, with correct identification of 70% of 13 single vessel disease patients and 94% of 53 multivessel disease patients.

Even if possible inaccuracies inherent in the interpretation of the coronary arteriogram (Vlodaver et al., 1973; Schwartz et al., 1975; DeRouen et al., 1977) are excluded, there are a number of theoretical considerations which might account for the failure of myocardial imaging to identify the number of abnormal coronary arteries.

The first point to be considered is the variability of the vascular territory supplied by the individual main coronary arteries in different patients and in particular the reciprocal relationship that exists between the right and left circumflex coronary arteries (Fulton, 1965; Kalbfleisch and Hort, 1977). Because of this variation, as shown in Table 10 and in the paper by Lenaers et al., (1977), abnormalities in certain "watershed" myocardial segments may be associated with lesions in more than one coronary artery.

A further possible reason for the discrepancy between arteriographic and scintigraphic findings is the fact that they are demonstrating

different aspects of the problem in coronary artery disease. Thus coronary arteriography shows stenosis of major coronary vessels whilst abnormal thallium-201 uptake indicates the impact of these anatomical abnormalities on myocardial perfusion (Strauss et al., 1975) and cellular function (Gehring and Hammond, 1967). Recent experimental work has indicated that thallium-201 uptake in dog myocardium is relatively insensitive to reduction in myocardial perfusion unless it is also accompanied by myocardial ischaemia (McArthur, Selwyn, Pratt et al., 1978). It is probable, however, that under conditions of stress in coronary heart disease patients, the reduced perfusion which is known to occur distal to stenosis of more than 50% of the luminal diameter (Gould et al., 1974) will be accompanied by myocardial ischaemia and thus reduced thallium-201 uptake by the myocardium.

It is likely that some of the discrepancy between the two techniques is due to thallium-201 myocardial images (like all potassium analogue tracers) reflecting relative (regional) myocardial perfusion (Strauss et al., 1975) rather than absolute flow. Attempts have been made to quantitate overall myocardial uptake of thallium-201 (Pitt and Strauss, 1976; Bull et al., 1976) but these have not met with general acceptance and almost all studies of myocardial imaging with thallium-201 concentrate, either visually or by some semiquantiative approach similar to my own, on relative uptake of the nuclide in one area of myocardium compared to another myocardial area in the same view. Granted this comparative approach it is easy to understand how myocardial imaging might underestimate the number of abnormal vessels. In the patient with multiple vessel disease, if one vessel is more diseased than another, then during stress the patient may develop myocardial ischaemia in the territory of that severely abnormal vessel (and thus develop symptoms which bring a symptom limited test to an end) before the

territory of the less abnormal vessel becomes ischaemic. In my own series the fact that most patients who developed myocardial ischaemia could not carry on exercise for more than 30 to 60 seconds after the onset of pain may have made this particular factor an important one.

Even if the flow in the less abnormal vessel is reduced in absolute terms during such a test, it is likely to be less so than that in the more diseased vessel and thus the territory of the former vessel will show relatively greater thallium-201 uptake. Evidence has been presented in Chapter III. (5)(e) which supports this point of view - in an analysis of the coronary arteriograms of 30 patients with multiple vessel coronary artery disease there were 46 myocardial areas subtended by diseased vessels and not supplied by collateral circulation. Sixteen such areas failed to develop abnormalities on stress myocardial imaging and in 10 this could be "explained" by the development of image defects in the territories of other more severely occluded vessels. Very similar evidence to this has recently been presented to the American College of Cardiology by Rigo, Becker, Griffith et al., (1978).

A further factor to be considered in the comparison of the findings of coronary arteriography and myocardial imaging is the possible role of coronary collateral vessels.

In 1959, Blumgart, in an Editorial article in Circulation, stated that "there is no question about the development of inter-coronary anastomoses in response to obstructive coronary disease and their importance in lessening the consequences of coronary artery occlusion". Whilst it is generally accepted that collaterals do develop in patients with coronary artery disease, their functional significance is less clear (McGregor, 1975; Gorlin, 1976) as will be evident from three selected studies cited below.

Frick, Korhola, Valle et al., (1976), using the intra-coronary xenon-133 clearance method, studied regional increases in myocardial perfusion during pacing induced ischaemia in 38 patients with coronary artery disease and related the results to the response, on coronary arteriography, of collateral vessels. 24 patients were seen to have collateral vessels present and 10 of them showed angiographically increased collaterals during pacing. The remaining 14 showed no change or a decrease in angiographically visible collaterals during pacing. Under basal conditions the regional myocardial blood flow rates were similar in areas supplied by collaterals and in those devoid of them. During pacing the greatest regional flow increment occurred in patients who showed increased collaterals angiographically during pacing and there was reasonable agreement between the visual assessment (at angiography) of collateral response to ischaemia and the change in regional perfusion. They concluded that "similar collateral patterns observed by routine coronary angiography are not functionally equipotent" though in some cases the collaterals did appear to enhance myocardial perfusion during stress. They also found, however, (Frick, Valle, Korhola et al., 1976) that the collaterals did not seem to protect against the development of angina.

By contrast Gould et al., (1974) studying myocardial blood flow responses to contrast agent induced hyperaemia by a double isotope technique were unable to demonstrate any "protective" effect from collateral vessels in patients with coronary artery disease.

Bodenheimer, Banka, Herman et al., (1977) adopted the approach of analysing the histopathological and electrophysiological characteristics of the myocardium of patients undergoing open heart surgery. From these studies they concluded that they were unable to demonstrate any beneficial effect resulting from the presence of

collaterals.

As I have indicated in Chapter III. (5)(e), Dr. R. G. Murray and I have analysed the effect of angiographically documented collateral vessels on the appearance of stress thallium-201 images in 30 patients with coronary artery disease. A total of 24 abnormal vessels in these patients were associated with collateral circulation. Eight of these abnormal vessels supplied areas of myocardium which had been the site of previous myocardial infarction and all 8 areas were abnormal on stress imaging. Of the remaining 16 areas supplied by abnormal vessels with collateral circulation, 9 appeared normal on stress imaging whilst 7 were abnormal. From these results we concluded that, as the results of Frick et al., (1976) indicated, some collateral vessels appear to be able to offer at least relative protection of myocardial perfusion distal to significant coronary stenoses, but this is not invariably so. In the presence of previous myocardial infarction, collateral vessels are unable to exert any beneficial effect on myocardial perfusion.

Rigo, Becker, Griffith et al., (1978) have undertaken a very similar analysis relating stress myocardial imaging and the presence of collaterals. In their study 17 vascular areas were perfused by angiographically visualised collaterals in the absence of any evidence of myocardial infarction, and 10 of these areas failed to become abnormal on stress imaging. Thirteen previously infarcted vascular areas were supplied by collaterals, but in each case they were abnormal on stress imaging, "indicating lack of protection".

Robinson, Crowther, Croft et al., (1978) also examined stress thallium-201 images with knowledge of the cross filling present at coronary arteriography in 48 patients. They were unable to demonstrate any protective effect from cross filling.

In summary, therefore, there are a variety of explanations why, from a theoretical point of view, stress thallium-201 imaging might not give an accurate prediction of the number of abnormal vessels in the patient with coronary artery disease. From our own results it would appear that if the minimum number of abnormal vessels which would produce the observed myocardial image abnormalities is predicted, the finding of a scintigraphic pattern suggestive of multiple vessel disease will usually mean that the patient does indeed have multiple vessel disease. Appearances of single vessel disease, however, are seen both in single vessel disease patients and in a considerable proportion of multiple vessel disease patients. For this reason, stress thallium-201 myocardial imaging will not accurately separate patients into those with single and multivessel disease in a large number of cases.

III. (6)(d) What is the relationship between thallium-201 myocardial imaging and electrocardiography in the non invasive diagnosis of coronary artery disease?

As the results presented in Chapter III. (5)(h) indicate, in this series of patients with chest pain, rest thallium-201 myocardial imaging and rest electrocardiography did not differ significantly either in sensitivity or specificity for the detection of coronary artery disease. The position in regard to stress imaging and stress electrocardiography is more difficult to summarise because of "equivocal" stress ECG results. Considering sensitivity, if only definitely abnormal ECG's are classed as "positive" (i.e. equivocal results treated as "negative"), stress thallium-201 imaging was significantly more sensitive than stress ECG's in detecting coronary artery disease. If equivocal ECG's are considered as positive, the difference in sensitivity is no longer significant. The specificity of stress thallium-201 imaging in detecting coronary artery disease is

greater than that of stress electrocardiography if only definitely normal ECG's are considered as normal (i.e. "equivocal" = "positive"). If equivocal ECG's are considered as negative the difference in specificity is no longer significant.

The results of the stress studies can also be considered from the point of view of accuracy with which patients were categorised as having or not having coronary artery disease. Stress thallium-201 imaging allowed this distinction to be made accurately in 74 patients but was inaccurate in 7 (4 false negative, 3 false positive). Stress ECG results were available in 78 patients. Fifty patients were accurately categorised by this study, but the categorisation was either inaccurate or could not be made in 28 patients (9 false negative, 8 false positive, 11 equivocal). The accuracy of categorisation was significantly greater with stress thallium-201 imaging than with stress electrocardiography (Chi squared test, $p<0.0025$).

A number of studies are now available in the literature comparing the sensitivity and specificity of stress myocardial imaging and stress electrocardiography in the non invasive diagnosis of coronary artery disease. Several have shown stress thallium-201 imaging to have a significantly higher sensitivity than stress electrocardiography (Bailey, Strauss and Pitt, 1976; Shames, Taradashi, Botvinick et al., 1976; Ritchie, Trobaugh, Hamilton et al., 1977). Turner et al., (1978) were unable to show any significant difference in sensitivity. Ritchie, Zaret, Strauss et al., (1978), reporting the results of a 5 centre study, found new exercise image defects occurred in 78/132 patients with coronary artery disease and ST depression in 62/132. These differences, however, just failed to reach statistical significance ($p = 0.06$). If both rest and exercise image defects were considered, the sensitivity of myocardial imaging was 115/148 (78%).

Some conflict in results is also found when series comparing the specificity of stress thallium-201 imaging and stress electrocardiography are examined. Ritchie, Hamilton, Trobaugh et al., (1977) and Ritchie, Zaret, Strauss et al., (1977) in studies of patients undergoing coronary arteriography for chest pain from one and five centres respectively, failed to find any difference in specificity between stress imaging and stress electrocardiography. However, both Raphael et al., (1976) and Pond et al., (1978) reported that stress thallium-201 imaging was more specific than stress electrocardiography in patients with chest pain and normal coronary arteriograms, whilst Turner et al., (1978) found similarly increased specificity in patients with chest pain and no previous myocardial infarction. Berman et al., (1978) carried out myocardial imaging in asymptomatic subjects with a positive stress ECG. The stress thallium-201 images were abnormal in 6 of 7 patients with coronary artery disease, but normal in all 14 with normal coronary arteriograms.

The balance of evidence from results in the literature and from my own study suggests that a patient with chest pain is more likely to be correctly classified as having or not having coronary artery disease by stress myocardial imaging than by stress electrocardiography. Neither technique, however, is completely accurate.

What roles, then, do stress myocardial imaging and stress electrocardiography have to play in the non invasive diagnosis of coronary artery disease? The answer to this question depends upon the group of patients being considered.

Firstly there are patients with classical angina pectoris. If the patient has symptoms of sufficient severity to merit consideration of coronary artery surgery then coronary arteriography is indicated and the results of stress electrocardiography and myocardial imaging are irrelevant, though a pre-operative stress thallium-201 study may

be useful for comparison in the post-operative assessment of the success of myocardial revascularisation (see Chapter VII).

The patient with classical angina pectoris which is not sufficiently severe to warrant coronary artery surgery presents a more difficult problem. The demonstration of ischaemic ST segment changes does not really further the assessment of such patients and stress electrocardiography, therefore, is not strictly indicated. Similarly the demonstration of an abnormal myocardial image, does not alter management. It is possible, however, that a normal myocardial image increases the probability of the patient having "angina with normal coronary arteries" and thus may be associated with a better prognosis. This, however, remains to be proven.

It is, perhaps, in the patients with atypical chest pain that non invasive methods are likely to prove more useful. The finding of an abnormal stress myocardial image and an abnormal stress ECG argue strongly in favour of myocardial pathology, and in a population such as that found in the West of Scotland, coronary artery disease is the most likely diagnosis. If both studies are negative the likelihood of myocardial pathology is low. If there is disagreement between the myocardial images and stress electrocardiography, then further investigations are indicated. In the patient with atypical chest pain it is likely that thallium-201 imaging will be the more accurate technique in detecting or excluding coronary artery disease, and myocardial imaging may be useful in clarifying equivocal ECG responses. Patients whose ECG shows left bundle branch block (LBBB) merit special mention here. McGowan, Welch, Zaret et al., (1977) performed myocardial imaging at rest with potassium-43 and rubidium-81 in patients with LBBB and demonstrated abnormalities in the septal area,

irrespective of the presence or absence of coronary artery disease. These abnormalities did not correlate with abnormal flow, as judged by labelled microsphere studies, and either disappeared or became less marked on stress imaging. They were uncertain as to the cause of these abnormalities. Wackers, Lie, Sokole et al., (1975), using thallium-201 imaging in patients with suspected acute myocardial infarction, did not find rest image defects in patients with LBBB in the absence of myocardial infarction.

The screening of asymptomatic subjects is a setting in which stress electrocardiography has been widely applied, though its usefulness here is by no means universally accepted (Borer et al., 1975; British Medical Journal, 1978). Because of the cost of myocardial imaging, the complexity of carrying out the test and the low yield of return, screening asymptomatic populations with thallium-201 imaging is probably unwarranted (Trobaugh, Hamilton, Ritchie et al., 1978). Myocardial imaging, however, may be useful in differentiating true and false positive stress ECG results in asymptomatic subjects (Berman et al., 1978).

CHAPTER IV

A COMPARISON OF VISUAL AND SEMIQUANTITATIVE ANALYSIS OF STRESS THALLIUM-201 MYOCARDIAL IMAGES

IV. (1) Introduction

In Chapter II. (6) it was noted that the distribution of thallium-201 in the normal heart shows some nonhomogeneity in different areas of the left ventricular myocardium, both in animals (Bradley-Moore et al., 1976; Schelbert, Henning, Rigo et al., 1976) and in man (Cook et al., 1976; Strauss and Pitt, 1977b). This non-homogeneity, which is probably less marked on stress images, was confirmed by my own studies on normal control subjects (Chapter II. (7)).

This normal variation of thallium-201 uptake by the myocardium complicates visual assessment of the images as the observer must bear the "normal range" in mind. Many centres read myocardial images from unprocessed Polaroid photos. Other authors (e.g. Berger, Gottschalk and Zaret, 1978) believe that colour coded images with background subtraction and contrast enhancement are essential for maximum sensitivity. In background subtraction the operator chooses a lower limit for the range of counts to be displayed whilst in contrast enhancement an upper limit is set. All colour levels are then used to display the range of activities between these two limits. Such processing has the potential disadvantage of accentuating normal variations and thus might lead to false positive studies (Fletcher, Walter, Witzum et al., 1978; Narahara, Hamilton, Williams et al., 1977).

In this chapter visual interpretation of stress thallium-201 myocardial images from Polaroid photographs and from computer

processed colour television images has been compared to a regions of interest method of semiquantitative assessment.

IV. (2) Subjects

The subjects for this study were 79 patients with chest pain who had undergone both stress myocardial imaging and selective coronary arteriography. They are the same patients as were the subjects for the study described in Chapter III, with the exception of two patients with normal coronary arteriograms in whom the stress Polaroid images had been lost.

IV. (3) Methods

The black and white Polaroid images were independently interpreted by three observers who were unaware of the identity of the patient whose study they were examining. Each set of images was classified as "normal" or "abnormal" by each observer. Their decision was based on all four images but they were not required to specify the site or extent of abnormalities. No "equivocal" group was allowed.

The same 3 observers also independently assessed the colour television images of the same 79 studies. The colour pictures were displayed using a fourteen colour activity scale (Figure 2). Nine point smoothing was performed if the observer wished it, but no uniformity correction was made. The extent to which background subtraction and contrast enhancement were carried out was at the discretion of each observer. Again each set of images was classified as "normal" or "abnormal" by each observer.

Semiquantitative analysis of the images was performed by the "regions of interest" technique described in Chapter II. (7). The images were considered abnormal if any myocardial area had a count density of less than 85% of the maximum count density in the same image.

The sensitivity and specificity of each method of analysis for the detection of coronary artery disease was determined by comparing the results to those of selective coronary arteriography. In addition the overall accuracy of classification of patients as to the presence or absence of significant coronary artery disease was calculated for each method of analysis.

IV. (4) Results

The results of visual interpretation of the Polaroid images are summarised in Table 21. This lists the sensitivity, specificity and accuracy for each individual observer and also for the consensus opinion i. e. the majority verdict obtained from the three independent individual decisions on each set of images.

No significant differences were found in the sensitivity, specificity and accuracy of the individual observers, nor between any individual and the consensus opinion. Agreement between the 3 possible pairs of observers was obtained in 75%, 75% and 67% of cases respectively. Complete interobserver agreement was attained in 54/79 patients (68%).

Table 22 summarises the results of visual analysis of the computer processed colour images. No significant differences in interpretation were found between the individual observers or between the individuals and the majority decision. Interobserver agreement for the 3 pairs of observers was 80%, 81% and 78%. Complete agreement between the 3 observers was obtained in 51/79 patients (64. 5%).

Comparison of the consensus interpretation of the Polaroid and the colour images reveals a similar overall accuracy (59/79 versus 61/79). Interpretation from Polaroids showed a lower sensitivity but higher specificity than that from colour images, but these differences fail to reach statistical significance (Chi squared test, $p > 0.05$).

The regions of interest method of assessment was carried out by one observer only (myself) because of the time consuming nature of the procedure - whereas visual assessment of the Polaroids and colour images required an average time of 2-3 minutes per patient the semiquantitative interpretation (including calculation of results) required about 20 minutes per study. On this single assessment the regions of interest method had a sensitivity of 43/47 (91%), a specificity of 29/32 (90%) and an overall accuracy of 72/79 (91%).

The regions of interest technique produced a significantly higher sensitivity than the consensus interpretation from Polaroid pictures (Chi squared test, $p<0.025$) but did not differ significantly from the sensitivity of visual assessment of the colour images ($p>0.05$). There were no significant differences in specificity between the three methods. The overall accuracy of classification by the regions of interest technique was significantly higher than that obtained from either method of visual analysis (Chi squared tests, $p<0.05$ for "colour assessment" versus "regions of interest", $p<0.025$ for "Polaroid assessment" versus "regions of interest").

Discussion

The results presented above suggest that the sensitivity, specificity and accuracy of interpretation of stress thallium-201 images are affected by the method of analysis, and that "quantitative" analysis may increase accuracy.

Visual assessment of black and white Polaroid pictures of the stress myocardial images produced a sensitivity of 68% and a specificity of 84%. These figures are similar to those recorded by Ritchie, Trobaugh, Hamilton et al., (1977) for interpretation of Polaroid photos. Complete interobserver agreement was obtained in 68% of our patients. Ritchie, Trobaugh, Hamilton et al., (1977) found complete agreement between three observers in 79% of Polaroid

images. Trobaugh, Wackers, Sokole et al., (1978) investigated interobserver agreement between 4 observers from 2 centres reading 100 rest thallium-201 myocardial images recorded on black and white Polaroid film. Complete agreement was obtained between the 4 observers in only 44% but essential agreement (i.e. 3 observers agreeing as to normal/abnormal and the fourth saying "borderline") was present in 79%. Our figures for agreement between pairs of observers are similar to those found by Trobaugh, Wackers, Sokole et al., (1978).

Visual analysis of the processed colour images in the present study showed a higher sensitivity and lower specificity than Polaroid interpretation, though the differences failed to attain statistical significance. Overall accuracy was similar for the two methods as was the degree of interobserver agreement. The results of visual analysis of the colour images support the contention of Fletcher et al., (1978) and Narahara et al., (1977) that, whilst computer processed myocardial images are visually more pleasing, they result in an increased rate of false positive studies.

When the coronary arteriographic findings were taken as the basis upon which patients were classified as either normal or abnormal, the regions of interest method produced a higher accuracy of classification than did either method of visual analysis. When compared to looking at Polaroid images the increased accuracy of the semiquantitative method was principally due to increased sensitivity, whilst when compared to visual analysis of the colour images, the superiority of the semiquantitative method was mainly a result of increased specificity.

As discussed in Chapter III. (6)(a) consideration of the series of stress thallium-201 imaging in the literature suggest that the sensitivity of the technique in detecting coronary artery disease may be greater in those which use some form of quantitation compared to

those which rely on purely visual interpretation. However, because of possible differences in techniques and patient populations, comparisons between different centres are not reliable. Relatively few studies are available which compare "quantitation" and visual analysis in the same patients. Recently, however, Fletcher et al., (1978) derived an index of "perfusion homogeneity" by computer analysis of the activity in each matrix element occupied by the myocardial image. By this method of analysis, thallium-201 images were abnormal in 19/24 patients with coronary artery disease compared to 14/24 from visual assessment of unprocessed images. In 8 patients with normal arteriograms, thallium-201 images were adjudged normal in 7 by "quantitative" analysis and in all 8 on visual inspection. When these images were again interpreted visually after background subtraction the sensitivity for the detection of coronary artery disease rose to 75%, but specificity was then unacceptably low at 50% (Fletcher et al., 1978).

Methods of quantitation of thallium-201 images such as the one used in the present study and those of other groups such as Wainwright (1977), Lenaers et al., (1977), Bull et al., (1978) and Fletcher et al., (1978) are, at best, only semiquantitative as the two dimensional compression present on standard gamma camera studies means that the derived values will be affected, at least in part, by contributions from background or overlying noncardiac structures and from overlapping areas of myocardium. This problem could be overcome by the use of isotopic tomographic techniques. However, until tomographic methods are more generally available my data, and those of Fletcher et al., (1978) suggest that, whilst the use of semiquantitative methods of analysing thallium-201 myocardial images lengthen the time required for interpretation, they may significantly increase the overall accuracy of classification and thus merit further study.

CHAPTER V

THE ROLE OF THALLIUM-201 MYOCARDIAL IMAGING IN SUSPECTED ACUTE MYOCARDIAL INFARCTION

V. (1) Introduction

When a patient presents with severe acute chest pain which is possibly cardiac in origin, the main questions to be answered are whether or not he or she has sustained an acute myocardial infarction and, if so, how extensive has it been? The answers to these questions are important in deciding the immediate management of the patient and have implications regarding immediate and long term survival (Peel, Semple, Wang et al., 1962; Norris, Caughey, Deeming et al., 1970; Helmers, 1974; Braunwald, 1976) and physical (Wood, 1968a) and psychosocial (Stern, Pascale and McLoone, 1976) wellbeing after recovery from the acute infarct.

The diagnosis of acute myocardial infarction can often be strongly suspected on clinical grounds but because of the large number of other causes of anterior chest pain (Lancet, 1977) the diagnosis should be supported by laboratory investigations. The standard methods of confirming acute myocardial infarction are electrocardiography and serum enzyme studies.

Certain electrocardiographic features are strongly suggestive of acute myocardial infarction. The ECG, however, should not be interpreted in isolation as many of the ECG changes can occur in the absence of acute myocardial infarction, e.g. Horan, Flowers and Johnson (1971) found that in patients with normal conduction patterns on their ECG, Q waves limited to the anteroseptal or inferior leads were often not indicative of myocardial infarction. The diagnostic specificity of the ECG for acute myocardial infarction can be improved by obtaining serial tracings in the days following the

acute event (Reid, 1978). It is also possible for the ECG to remain normal during an acute myocardial infarction (Todd, 1976; Reid, 1978), though this is relatively uncommon if serial tracings are obtained (McGuinness, Begg and Semple, 1976). A further problem which may be encountered is the presence of other changes, such as left bundle branch block, which may make the ECG diagnosis of acute infarction more difficult or even impossible (Reid, 1978).

Sequential estimation of serum levels of enzymes released from dying myocardial cells is the second major method routinely used for confirming the diagnosis of acute myocardial infarction (Coodley, 1969). Interpretation of enzyme studies may be made more difficult by the fact that the serum levels may be elevated due to release from sites other than myocardium, though this problem can be partially overcome by isoenzyme studies (Coodley, 1969). False negative enzyme studies are less frequently a problem if samples are obtained early enough in the course of the acute infarct, but they may occur, usually due to technical problems (Coodley, 1969; Nierenberg, 1977).

The site of an acute myocardial infarction cannot be determined from enzyme studies but can often be deduced from the ECG (Reid, 1978).

Methods for the estimation of the size of an acute myocardial infarction remain somewhat controversial. Various clinical indices have been derived which give indirect evidence of the severity of acute infarction and these are of some prognostic value (Peel et al., 1962; Norris et al., 1970; Braunwald, 1976).

Attempts have also been made to quantify the degree of myocardial damage by mapping ST-T segment changes on the ECG (Maroko, Libby, Covell et al., 1972; Reid, Taylor, Kelly et al., 1974) or from serial serum enzyme levels (Shell, Kjekshus and Sobel, 1971; Sobel, Bresnahan, Shell et al., 1972). These methods have been used in experimental studies, but each has limitations

(Maroko, 1974) and they have therefore found only a very limited place in clinical practice.

Radioisotope methods of diagnosing acute myocardial infarction have been introduced with the aims of (1) enabling earlier diagnosis than is possible from ECG and enzyme studies (2) clarifying the diagnosis in patients with equivocal or contradictory ECG and enzyme results (3) quantifying the size of acute myocardial infarction (4) studying whether the extent of myocardial infarction can be modified by various therapeutic manoeuvres.

Recently various compounds, notably the bone scanning agent pyrophosphate, which appear to accumulate in acutely infarcted myocardium have been the subject of extensive research. Such "hot spot" infarct imaging has already been discussed in Chapter I. (4).

The alternative approach is to inject a tracer taken up by normal myocardium and thus demonstrate the infarct as a "cold spot". Early studies with caesium-131 (Carr et al., 1964; McGeehan et al., 1968) and with potassium-43 (Hurley et al., 1971) showed that myocardial infarcts could be detected in this way.

Following the introduction of thallium-201, the Amsterdam group led by Frans Wackers have been particularly active in the use of this radioisotope for the diagnosis of acute myocardial infarction. Initial studies with thallium-201 showed that it could be used to localise acute transmural myocardial infarction (Wackers, van der Schoot, Sokole et al., 1975; Schelbert, Rigo, Henning et al., 1975; Pabst, Hor, Lichte et al., 1976). Wackers' group have subsequently reported that a normal thallium-201 myocardial image obtained within 6 hours of the onset of symptoms virtually excludes an acute myocardial infarction (Wackers, Sokole, Samson et al., 1976) and that the technique may be useful in confirming the diagnosis and siting the infarcts in patients with left bundle branch block (Wackers, Lie, Sokole et al., 1975).

Wackers' study, however, also indicates that the frequency of abnormal scans is less in patients with acute myocardial infarction studied more than 24 hours after the onset of symptoms (Wackers et al., 1976). To study patients in the first 6 hours after the onset of symptoms requires a constant availability of thallium-201, and Wackers and his colleagues are almost uniquely privileged in this respect by their proximity to the Petten cyclotron. Early imaging also requires either a mobile gamma camera or one situated in the coronary care unit or its environs, conditions not fulfilled by most hospitals in the United Kingdom (British Medical Journal, 1978b).

The purpose of the study described in this chapter, therefore, was to assess the clinical value of thallium-201 myocardial imaging performed some days after the admission of a patient with acute chest pain, at a time when the patient was considered fit enough to be moved to the nuclear medicine department.

V.(2) Patients and Methods

Fifty patients were studied. They ranged in age from 27 to 76 years (mean = 56.2 years) and all had been admitted with severe acute chest pain suggestive of possible acute myocardial infarction.

Standard 12 lead ECG's were performed on all patients on each of the first 3 days following admission, and serum levels of glutamic oxaloacetic transaminase (SGOT), glutamic pyruvate transaminase (SGPT), lactic dehydrogenase (LDH) and creatine phosphokinase (CPK) were also estimated on each of the first three days.

An acute transmural myocardial infarction was diagnosed on the basis of ECG evidence of pathological Q waves and sequential ST segment changes. A nontransmural myocardial infarction was diagnosed if the ECG was either normal or showed only ST segment changes but the serum enzyme levels were pathologically high. No patients with left bundle branch block were studied. The site of the

acute myocardial infarction was decided from standard electrocardiographic criteria (Reid, 1978).

In patients with no evidence of acute or old myocardial infarction or other cardiac pathology the final clinical diagnosis was established by other appropriate investigations such as gastrointestinal radiology, lung scanning, pulmonary angiography and viral studies.

Rest thallium-201 images were obtained in the manner already described in Chapter II. (5)(a) and analysed by the regions of interest method described in Chapter II. (6). Imaging was performed 3 to 6 days after admission, the time of study being determined by when the clinician in charge of the patient considered them fit to be moved and by the availability of the radionuclide.

V. (3) Results

The final clinical diagnoses and the results of the myocardial imaging are summarised in Table 23.

Twenty-two patients had acute transmural myocardial infarction: 6 inferior, 6 anteroseptal, 5 anterolateral and 5 widespread anterior. Focal myocardial image abnormalities were present in 20. Examples of images from patients with widespread anterior, anteroseptal, anterolateral and inferior infarcts are given in Figures 31 to 33.

Myocardial images were normal in two patients with acute transmural infarcts. One patient with an acute inferior infarct had a completely normal image whilst a second patient with a widespread anterior infarct showed a dilated cavity but no focal myocardial defect.

Five patients had evidence of an acute nontransmural myocardial infarction. Only one showed a focal defect on thallium-201 imaging.

Focal abnormalities were present on the thallium-201 images of 7 of the 9 patients who had a history and ECG (Q wave) evidence of previous myocardial infarction. The defects due to old infarcts could

not be differentiated visually from those produced by acute infarcts, nor did the two groups differ significantly in the calculated count densities at the sites of the infarcts (Figure 34).

Of 5 patients with ECG evidence of myocardial ischaemia but no ECG or enzyme evidence of myocardial infarction, 1 showed a focal scan defect.

Nine patients had final diagnoses of a "non coronary" nature. Eight had no focal defect on imaging but the ninth, a man with multiple pulmonary emboli and acute cor pulmonale showed decreased tracer uptake in the region of the interventricular septum (Figure 35). This patient had no clinical or laboratory evidence of acute or previous myocardial infarction, though these cannot be entirely discounted as the cause of the scan defect. A possible alternative explanation is that the scan abnormality reflects the massive load placed on the septum by the acute pulmonary hypertension.

In the series as a whole the sensitivity of rest thallium-201 myocardial imaging in detecting acute myocardial infarction was 78% whilst the specificity of a rest image abnormality for diagnosing acute myocardial infarction was 61%. The predictive value of a focally abnormal image for the presence of acute infarction can be calculated as $\frac{\text{True Positives}}{\text{True Positives + False Positives}}$ (Reba and Charkes, 1975) and was 70%. The predictive value of a normal myocardial image in excluding acute infarction $\left(\frac{\text{True Negatives}}{\text{True Negatives + False Negatives}}\right)$ was also 70%.

V. (4) Discussion

The results presented above suggest that a single rest thallium-201 study obtained some days after admission is of little clinical value in the patient with a suspected acute myocardial infarction. When the images are abnormal it is not possible to say whether this represents acute infarction, old infarction or severe myocardial ischaemia. The question of myocardial ischaemia as a cause of abnormal rest images in this setting can perhaps be resolved by

repeating the imaging some hours after injection of the tracer. Pond, Rehn, Burow et al., (1977) performed rest thallium-201 myocardial imaging in a group of patients admitted with suspected acute myocardial infarction and found that 3 hours after injection redistribution of the tracer into areas of abnormality present on the immediate post injection images was characteristic of myocardial ischaemia. In patients with infarction no such redistribution occurred. There appears to be no means of differentiating acute and old myocardial infarction on thallium-201 imaging, and this is not surprising in view of the nature of the technique.

As discussed in the introduction to this chapter Wackers et al., (1976) found that a normal rest thallium-201 image obtained less than 6 hours after the onset of symptoms virtually excluded an acute infarction. Such early imaging may not be possible as many patients are not admitted to hospital until more than 6 hours after the onset of symptoms (McNeilly and Pemberton, 1968). If the study was not performed until more than 24 hours after the onset of symptoms, then false negative (i.e. normal) studies were found in some patients with acute infarcts (Wackers et al., 1976). My own results confirm this and indicate that normal images, obtained some days after the patient's admission to hospital, do not exclude an acute infarct, especially a nontransmural one. Delayed thallium-201 imaging thus cannot be relied on to clarify the diagnosis in the patient with equivocal or unhelpful ECG and enzyme studies.

Does "hot spot" imaging have any advantages over thallium-201 imaging in this context? In the very early post-infarct period (i.e. the first 6-12 hours), if the logistical difficulties can be overcome, thallium-201 imaging is superior as it is highly sensitive in this period (Wackers et al., 1976) whilst the pyrophosphate "hot spot" image does not usually become positive until at least 12 hours post-infarction (Willerson, Parkey, Bonte et al., 1975).

If imaging is delayed until some days after the onset of chest pain, "hot spot" imaging has advantages over thallium-201 studies. Most series of pyrophosphate imaging performed at this time report a high sensitivity in diagnosing acute infarction (Willerson et al., 1975; Perez, 1976; Berger, Gottshalk and Zaret, 1977; Walton, Kefetzakis, Shields et al., 1978) though not all authors agree with this finding (Walsh, Karunaratne, Resnekov et al., 1977; Tetalman, Foley, Spencer et al., 1977). Hot spot imaging also has higher specificity than thallium-201 imaging for acute infarction as opposed to old infarction or ischaemia, though some false positive occur due to conditions such as unstable angina (Willerson et al., 1975; Abdulla, Canedo, Cortez et al., 1976; Walsh, Karunaratne, Resnekov et al., 1977), left ventricular aneurysms (Ahmad, Dubiel, Verdon et al., 1976; Kelly, Cowan, Maynard et al., 1977) stable angina pectoris (Willerson et al., 1975; Walsh, Karunaratne, Resnekov et al., 1977) and other miscellaneous myocardial disorders. This question has been fully discussed in Chapter I. (4)(c).

The techniques of hot and cold spot imaging have been applied to estimating the size of myocardial infarction. Wackers, Becker, Samson et al., (1977) have compared the results of early thallium-201 imaging and post mortem pathology in 23 patients who died of acute myocardial infarction shortly after admission and have found good correlation between the two studies both in terms of the site and the extent of infarction. Fletcher, Rao, Herbig et al., (1978) performed thallium-201 imaging within the first 12 hours after the onset of symptoms in patients with acute transmural infarction and reported good correlation between infarct size estimation from the scintigraphic images and from serial estimations of serum creatine phosphokinase. It is of interest, however, that Wackers et al., (1976) have noted that the size of defect on thallium-201 images produced by acute myocardial infarction decreases on serial

imaging of the same patient in the days following the acute incident. Similar results have been reported with serial imaging in patients with nitrogen-13 labelled ammonia (Karunaratne, Cantez, Harper et al., 1978) and in dogs with experimental myocardial infarction images with thallium-201 (Misbach, Botvinick, Shames et al., 1978). In the longer term, Schelbert, Henning, Rigo et al., (1977) performed serial imaging in patients with rubidium-81 up to one year after acute infarction, and were able to demonstrate that in most patients there was a decrease in the size of the myocardial image defect with time. The mechanism of decreasing size of such defects is uncertain, but may be related either to perfusion of organising scar tissue or of superimposed myocardium or to reperfusion of ischaemic myocardium around the infarct (Misbach et al., 1978). Whatever the explanation, these findings are likely to limit the value of thallium-201 imaging in sizing acute infarction, and, in particular, may make it unsuitable for assessing the effect of therapeutic interventions.

Early studies on experimental myocardial infarction in dogs suggested that pyrophosphate imaging could be used to size accurately anterior transmural infarcts (Botvinick, Shames, Lappin et al., 1975; Stokely, Buja, Lewis et al., 1976). This, however, has not been entirely borne out in clinical practice. Henning, Schelbert, O'Rourke et al., (1976) reported accurate estimation of the size of anterior acute myocardial infarction from pyrophosphate imaging but found that the size of inferior infarcts was frequently underestimated. Coleman, Klein, Roberts et al., (1976) found that, in clinical studies, there was a poor correlation between the infarct size estimated from pyrophosphate images and that estimated from serial serum CPK values. There is, at present, no definite consensus on the accuracy of estimating infarct size from "hot spot" images but caution is necessary (Parkey, Bonte, Buja et al., 1977; Wynne, Holman and

Lesch, 1978; British Medical Journal, 1978b; The Lancet, 1978).

Combined "cold spot" imaging with a potassium analogue and "hot spot" imaging with pyrophosphate may increase the sensitivity of diagnosis of acute myocardial infarction (Berger et al., 1978; Kim, Gorten, Williams et al., 1978; Walton et al., 1978) and the specificity of diagnosis may be increased when both studies are abnormal in patients with no previous myocardial infarction (Kim et al., 1978). Most studies comparing the size of abnormalities on the two methods have found the "cold spot" defect to be usually either equal to or greater than the "hot spot" abnormality (Parkey, Bonte, Stokely et al., 1976; Walton et al., 1978) though not all groups agree with this finding (Berger et al., 1978).

It has also been claimed that the combination of gated blood pool imaging and either hot or cold spot infarct imaging can increase the sensitivity of detection and the accuracy of localisation of acute infarction (Pitt and Strauss, 1977; Van Hove, Heck and Kight, 1977). The use of blood pool imaging may be especially useful in the rather unusual setting of right ventricular infarction (Pitt and Strauss, 1977; Sharpe, Botvinick, Shames et al., 1978).

The prognostic implications of radionuclide infarct imaging are not yet clear. Thallium-201 imaging may be of some value in indicating the extent of functional myocardial tissue remaining (Parkey, Bonte, Stokely et al., 1976) and in a group of patients with acute myocardial infarction the incidence of congestive cardiac failure was highest in patients in whom the thallium-201 image defect was greater than the pyrophosphate image abnormality (Parkey, Bonte, Stokely et al., 1976). In studies of pyrophosphate imaging it has been shown that the complication rate in hospital and after leaving hospital was less for patients with acute myocardial infarction and normal pyrophosphate images compared to those with acute infarction

and a pattern of focal or intense myocardial uptake of pyrophosphate (Holman, Chisholm and Braunwald, 1978). It has also been reported that a persistently positive pyrophosphate scintigram more than 6 weeks after the acute infarct was associated with an increased complication and mortality rate (Olson, Lyons, Aronow et al., 1978).

Is radionuclide imaging valuable in acute myocardial infarction? Sufficient information is not yet available to answer this question with certainty. The studies may sometimes be helpful in assessing patients in whom the conventional investigations are unhelpful or equivocal, but this is a relatively small number of patients, and as the imaging will usually be performed some days after the acute event, the results must be interpreted with great caution. In the routine assessment of myocardial infarction, scintigraphic techniques do not provide any information which is essential for the management of patients (The Lancet, 1978). It therefore seems reasonable to regard them as research techniques which may give insight into the pathophysiology of acute infarction but, in the clinical context, as "the icing on the diagnosis of an infarct" (British Medical Journal, 1978b).

CHAPTER VI

THALLIUM-201 MYOCARDIAL IMAGING IN AORTIC VALVE DISEASE

VI. (1) Introduction

The presence of coexisting coronary artery disease in the patient with aortic valve disease appears to be an important determinant in operative mortality during aortic valve replacement (Linhart, de la Torre, Ramsey et al., 1968; Peterson, Herr, Crisera et al., 1967) and a major factor in post-operative left ventricular function (Peterson et al., 1967; Linhart and Wheat, 1967). In addition to its prognostic value, the knowledge that a patient with aortic valve disease also has coronary artery disease may be therapeutically important as saphenous vein bypass grafting is now possible at the time of aortic valve replacement (Loop, Favarolo, Shirey et al., 1972; Merin, Danielson, Wallace et al., 1973) though the initial reports give conflicting results on whether this improves or increases operative mortality (Berndt, Hancock, Shumway et al., 1974; Moraski, Russell, Mantle et al., 1976).

Angina pectoris is a common presenting symptom in aortic stenosis and frequently occurs in patients with normal coronary arteries (Basta, Raines, Najjar et al., 1975; Harris, Kaplan, Parker et al., 1975; Mandal and Gray, 1976; Swanton, Brooksby, Jenkins et al., 1977; Baxter, Reid, McGuinness et al., 1978). Angina in this situation is indistinguishable from that in occlusive coronary artery disease (Wood, 1968b). Patients with predominant aortic incompetence may also develop angina in the absence of coronary artery disease, but the angina is rarely the presenting symptom, may be severe at rest or during the night and is usually preceded by features of cardiac failure (Basta et al., 1975).

Coleman and Soloff (1970) stated that "clinical evidence of significant coronary artery disease in individuals with valvular heart disease may be difficult to recognise. Suggestive symptoms may be few or absent". There is, however, considerable debate as to whether coronary artery disease can occur in aortic valve disease patients in the absence of angina pectoris. Bonchek, Anderson and Rosch (1973) and Basta et al., (1975) found that all aortic valve disease patients with coronary artery disease had angina but other workers (Harris et al., 1975; Swanton et al., 1977; Baxter et al., 1978) report that a small number of such patients are angina free.

Electrocardiography cannot be used to determine whether this group of patients have coronary artery disease. At rest, the ECG frequently shows left ventricular hypertrophy and strain in aortic stenosis without coronary artery disease (Oram, 1971). In the absence of coronary artery disease, deep Q waves, simulating myocardial infarction, may develop (Oram, 1971) as may left bundle branch block (Burch and Winsor, 1972). Increased ST segment depression during exercise in aortic stenosis patients is equally common in those with and those without occlusive coronary disease (Bailey, Come, Kelly et al., 1977).

Because of the impossibility of diagnosing coexisting coronary artery disease on clinical or electrocardiographic grounds, it is generally recommended that selective coronary arteriography should be performed pre-operatively in all candidates for aortic valve replacement who have angina (Swanton et al., 1977; Baxter et al., 1978), though there is less agreement on whether routine coronary arteriography is (Linhart et al., 1968; Coleman and Soloff, 1970; Swanton et al., 1977) or is not (Bonchek et al., 1973; Basta et al., 1975; Baxter et al., 1978) necessary in patients who do not have angina.

As discussed in Chapter III. (1), coronary arteriography is associated with a small, but definite, hazard. It would be useful, therefore, if aortic valve disease patients who do not require coronary arteriography could be identified by a non invasive method. We have, for this reason, examined stress thallium-201 imaging in a group of aortic valve disease patients undergoing cardiac catheterisation and coronary arteriography.

VI. (2) Patients

Eighteen patients have been studied, ranging in age from 30 to 64 years. Three were female and 15 male. All patients had angina pectoris, though this was the dominant symptom in only 10.

VI. (3) Methods

Left heart catheterisation and selective coronary arteriography were performed by the transfemoral route. The catheter studies were interpreted by the consultant cardiologist performing the catheterisation or in charge of the patient. The patient was considered to have coronary artery disease if any of the major vessels showed any stenosis of 50% luminal diameter or greater.

The exercise tests were performed on a bicycle ergometer, the severity of exercise being progressively increased at 3 minute intervals in the manner described in Chapter II. (5)(b). The ECG was continuously monitored on an oscilloscope and written samples obtained every minute. The patient's blood pressure was recorded each minute, using a standard sphygomanometer.

The end points of the exercise test were chest pain, light-headedness, dyspnoea, failure to develop an adequate blood pressure response to exercise or ECG evidence of cardiac arrythmias. At the end point 2 mCi thallium-201 were injected intravenously through a previously inserted cannula and the load immediately removed from the patient, though he was asked to keep his legs turning over slowly to prevent postural hypotension.

Myocardial imaging was begun 5 minutes later and the 4 standard scintigraphic views obtained. Images were analysed by the regions of interest technique described in Chapter II. (6).

VI. (4) Results

Table 24 summarises the findings at cardiac catheterisation and coronary arteriography.

Ten patients had no significant coronary artery disease. Five had pure aortic stenosis and five had combined aortic stenosis and incompetence, though the stenosis was judged to be the dominant lesion in all but one. One patient with combined aortic stenosis and incompetence and one with aortic stenosis also had mitral stenosis.

Eight patients had significant coronary artery disease, 4 single vessel disease and 4 double vessel disease. Two patients with single vessel disease had aortic stenosis without incompetence, but the six other coronary artery disease patients had combined aortic stenosis and incompetence, with the stenosis being the dominant lesion in each. Two patients, one with aortic stenosis and one with aortic stenosis and incompetence, also had mitral stenosis.

The results of stress myocardial imaging are summarised in Table 25. Six of the 10 patients with no coronary artery disease had normal stress thallium-201 images, apart from evidence of left ventricular hypertrophy in all. The remaining 4 patients free of coronary artery disease showed focal myocardial image abnormalities. In 1 the defect was confined to the apex (Figure 36), and another had an abnormality which was principally apical but showed some extension to the anterior myocardial wall (Figure 37). The other two patients with no coronary artery disease who had abnormal myocardial images had infero-posterior abnormalities (Figure 38).

The myocardial images were normal, apart from left ventricular hypertrophy, in 3 of the 8 patients with coronary artery disease. The other 5 coronary artery disease patients showed focal abnormalities,

anterior in patients T. B. and A. C. with LAD disease and in J. R. with LAD and LCx disease, and infero-posterior in both patient A. B. with RCA disease and P. C. with combined LAD and LCx disease (Figure 38).

VI. (5) Discussion

Conclusions drawn from the data presented above must be tentative in view of the relatively small number of patients studied. The results, however, suggest that stress thallium-201 myocardial imaging is unlikely to be of major clinical value in the assessment of aortic valve disease patients with chest pain. In this study a normal stress thallium-201 did not exclude significant coronary artery disease, nor did the presence of focal abnormalities always correspond to coronary artery disease.

The failure of development of focal abnormalities in coronary artery disease patients might be explained by the exercise test being terminated by other symptoms before myocardial ischaemia occurred. Indeed, in two patients with coronary artery disease and normal stress images, exercise was stopped because of breathlessness and light-headedness respectively before angina developed. In the third patient with coronary artery disease and normal stress images, however, the exercise test ended because of the onset of typical angina accompanied by marked depression of the ST segments on ECG. It is possible that this patient's chest pain was due to diffuse subendocardial ischaemia, which is known to occur in aortic stenosis (Vincent, Buckberg and Hoffman, 1974). Such diffuse ischaemia would not produce a focal abnormality on the myocardial image and thus would not be detected on an isolated stress study.

Bailey, Come, Kelly et al., (1977) have recently reported a similar study of thallium-201 myocardial imaging in aortic stenosis. They, however, also performed rest imaging and were able to demonstrate widespread left ventricular wall "thinning" in the post exercise image of 14 patients and suggested this was a scintigraphic

manifestation of diffuse subendocardial ischaemia. The wall thinning was seen both in patients with and in those without coronary artery disease. Bailey, Come, Kelly et al., (1977) found that focal defects were present on the stress images of 7 of 11 patients with aortic valve disease plus coronary artery disease.

To turn to the focal defects in the myocardial images of patients with no significant coronary artery disease, it is conceivable that the apical abnormalities present in two may be an accentuation, produced by left ventricular hypertrophy, of the apical thinning present on many normal stress thallium-201 images (Cook et al., 1976), though in one patient at least (Figure 37), the abnormality showed more anterior extension than one would have expected on this basis.

The infero-posterior abnormalities present in two patients with normal coronary arteriograms cannot be explained as normal variants. Bailey, Come, Kelly et al., (1977) noted that focal defects were seen on the stress images of patients who had minor coronary artery lesions (30% or less narrowing) which would normally be regarded as functionally insignificant. They have suggested that such minor occlusions may become functionally critical during stress in the presence of aortic stenosis. The infero-posterior abnormalities in the two patients with normal coronary arteriograms in my study, however, did not appear to be related to minor coronary disease. Whether they represent some local abnormality of small vessel perfusion induced by the high intramyocardial pressures these patients will have or are due to some focal cardiomyopathic process induced by the high pressure and left ventricular hypertrophy must remain speculative.

My results, and those of Bailey, Come, Kelly et al., (1977) suggest that stress thallium-201 myocardial imaging cannot be used in patients with aortic valve disease and chest pain to decide whether or not they also have coronary artery disease. The radionuclide technique, therefore, does not help to identify which patients require coronary arteriography.

CHAPTER VII

A COMPARISON OF CORONARY ARTERIOGRAPHY AND STRESS THALLIUM-201 MYOCARDIAL IMAGING FOLLOWING CORONARY ARTERY BYPASS SURGERY

VII. (1) Introduction

The concept of surgical therapy for the relief of the symptoms of coronary artery disease was introduced by Francois-Franck in 1899 when he proposed sympathectomy for angina pectoris. In 1916 Jonnesco performed such an operation and reported (Jonnesco, 1920) relief of the patient's chest pain. The rationale behind such operations was to cut the nerves containing the afferent fibres from the source of pain and a variety of dennervation operations were performed from that time until the 1950's. However, the pain relief produced by such operations although "at times dramatic" was "not consistent" and the "late mortality of 50% in a $2\frac{1}{2}$ year period after operation suggests that the progress of the primary disease has not been significantly altered" (Harken, Black, Dickson et al., 1955). Thus from the 1930's onwards attempts were made to introduce surgical procedures which had the more physiological aim of revascularising ischaemic myocardium.

Beck (1935) described the technique of opening the pericardium, abrading the epicardium, installing bone dust as an irritant to produce further irritation of the epicardium and then swinging a pectoralis major graft into place, the muscle acting as a source of new blood supply to the inflamed epicardium. This and similar techniques did produce improvement in some patients but also caused deterioration in others because of the development of chronic pericarditis resulting in the pain of pericarditis and the sequelae of chronic constrictive pericarditis (Preston, 1977).

In the early 1930's anastomotic channels were demonstrated between the coronary arteries and the internal mammary arterial system (Hudson, Moritz and Wearn, 1932). This led to the introduction of internal mammary artery ligation as a surgical therapy for angina in the years just before and just after the Second World War (see Preston, 1977). The value of such operations was a source of considerable controversy until Cobb, Thomas, Dillard et al., (1959) and Dimond, Kittle and Crockett (1960) demonstrated that the degree of symptom relief obtained was no better than the placebo response from a "sham" operation in which a skin incision was made but no arterial ligation performed.

The ligation of internal mammary arteries was replaced as a surgical therapy for angina by the so called "Vineberg procedure". In 1950 Vineberg and Niloff, reporting an animal study, described an operation in which a tunnel was made in the myocardium and into this a bleeding internal mammary artery was placed (Vineberg and Niloff, 1950). The initial reports of the clinical results of this procedure were encouraging (Vineberg and Walker, 1957) and whilst it remained controversial, it enjoyed considerable vogue, though it has now been largely replaced by techniques of more direct coronary revascularisation.

Endarterectomy of the coronary arteries was introduced, but when this alone was done the mortality was excessive (Dunkman, Perloff, Kastor et al., 1974) and thus the procedure is now only carried out in conjunction with other coronary artery operations.

The standard surgical procedure now carried out for the treatment of occlusive coronary disease is some type of bypass from the aorta or its branches to the diseased coronary artery distal to the occlusion, either in the form of a saphenous vein graft from the aorta to the coronary vessel (Favorolo, 1969) or direct internal mammary to coronary bypass (Green, 1972).

Such "direct myocardial revascularisation procedures" have been very extensively performed both in the U. S. A. and in Europe in the last 10 years and it is accepted by most authorities that in patients with severe angina which is unresponsive or poorly responsive to adequate medical therapy coronary artery bypass surgery may achieve symptomatic relief (Mundth and Austen, 1975; Braunwald, 1977). It is less clear whether coronary artery surgery prolongs survival more than adequate medical therapy (Preston, 1977; Braunwald, 1977) and in view of the great cost of such operations there is considerable debate on whether they should be generally available (Neuhauser, 1977; Hiatt, 1977; Preston, 1977; McIntosh and Garcia, 1978).

The symptomatic improvement following coronary bypass surgery has been postulated to be due to a number of possible factors including (1) improved flow via patent grafts to the ischaemic areas (2) the psychogenic impact of surgery (i. e. purely a placebo effect) (3) peri-operative myocardial infarction causing necrosis of pain triggering ischaemic areas and thus rendering them painless (4) the destruction of the pericoronary nerve plexus during surgery (i. e. essentially the same mechanism as sympathectomy) (5) reduced myocardial oxygen demand due to a reduction in wall stress as a result of better left ventricular function.

Whilst any of the above mechanisms may be important in pain relief in individual patients (Mnayer, Chahine and Raizner, 1977) the balance of evidence suggests that the completeness of revascularisation of the myocardium plays the dominant role (Frick, 1976). Such completeness of revascularisation is dependent upon the patency of the bypass grafts and the freedom from disease of the ungrafted vessels.

Coronary arteriography has been the standard method of assessing the completeness of revascularisation after coronary bypass surgery. In addition to the invasive nature of this technique it has the disadvantage

of not allowing visualisation of vessels smaller than 100 microns in diameter (Gensini and da Costa, 1969). Thallium-201 imaging offers a possible means of overcoming these problems, and we have therefore examined the value of stress thallium-201 myocardial imaging in assessing the patency of bypass grafts and the state of the ungrafted native circulation. Previous studies using potassium-43 (Zaret, Martin, McGowan et al., 1974) and rubidium-81 (Lurie, Salel, Berman et al., 1976) yielded promising results.

VII. (2) Design of Study

The ideal design for this study would have been to perform myocardial imaging in a group of patients both before and after coronary artery bypass surgery and to compare this to pre- and post-operative coronary arteriography. However, because of the discomfort and hazard involved, post-operative coronary arteriography is not now routinely performed in Glasgow Royal Infirmary and is carried out only if the patient has persistent, disabling chest pain and further surgery is being contemplated. Such patients are relatively rare.

It was, therefore, decided to study not patients currently undergoing coronary surgery, but rather a group operated on between 1973 and 1976. These patients were included in a multicentre European Coronary Artery Surgery Trial and all had repeat coronary arteriograms 12 to 18 months post-operatively for the purposes of the trial.

Pre-operative imaging was, of course, not obtainable in these subjects and the post-operative myocardial imaging was carried out 1 to 3 years after the patient's post-operative angiogram. This may obviously lead to some difficulty in correlating the results of the two investigations, but there is a general feeling amongst cardiologists that graft occlusion is most likely to occur in the period shortly after surgery. This impression has been supported by data recently

published from The National Institutes of Health in Bethesda (Seides, Borer, Kent et al., 1978). In this study repeat coronary arteriography was carried out 53 to 84 months after operation in 22 patients who had been shown angiographically to have at least one patent graft in the early (3 to 9 months) post-operative period. They found that most grafts patent in the early study were still patent on the late arteriogram and that symptomatic deterioration was most commonly due to progression of disease in ungrafted vessels. Similar findings have been reported in two other series (Campeau, Lesperance, Corbara et al., 1978; Robert, Guthaner, Wexler et al., 1978).

VII. (3) Patients and Methods

A total of 30 patients, all male, were studied. All had at least 2 vessel disease before operation. At the time of myocardial imaging they ranged in age from 39 to 60 years. The time of operations was as follows: 1973, 3 patients; 1974, 6 patients; 1975, 13 patients; 1976, 8 patients. A total of 45 coronary artery bypass grafts were performed in the 30 patients. The distribution of grafts is summarised in Table 26.

In 9 patients only the left anterior descending coronary artery was grafted whilst in 6 the right coronary artery alone was grafted. In 15 patients both of these vessels were grafted. Thus a total of 24 grafts were placed to the left anterior descending coronary artery and 21 grafts to the right coronary artery. No left circumflex coronary artery grafts were performed.

Selective coronary arteriography (Judkin's technique) was performed in all patients 12 to 18 months after operation.

Stress thallium-201 myocardial imaging was performed in all patients in the manner described in Chapter II. (5)(b) and the images analysed by the regions of interest technique described in Chapter II. (6). The prediction of graft patency or occlusion and the presence

of disease in ungrafted native vessels was made on the basis of the association between individual coronary arteries and particular myocardial areas described in Table 10. In the areas which are associated with more than one coronary artery the presence of an abnormality was attributed to the vessel whose other areas showed abnormalities e.g. a posteroseptal abnormality associated with an anterior defect was attributed to LAD disease or graft occlusion whilst in the presence of an inferior abnormality the posteroseptal defect was attributed to right coronary artery problems. As previously noted, the apex is a difficult area to interpret and may be associated with occlusions of any of the three major vessels. Following coronary bypass surgery, this area is even more difficult to interpret, because many patients show apical abnormalities post-operatively, probably due to the vent placed in the apex of the left ventricle during surgery (Figure 39). The apex, therefore, was not analysed in this study.

The myocardial images were interpreted with the knowledge of which vessels had been grafted but not the results of the post-operative arteriogram. An image defect in the territory of a graft was taken to imply graft occlusion whilst a normal uptake of radionuclide in its territory implied graft patency. Image abnormalities in the territories of ungrafted vessels were interpreted as evidence of native vessel disease.

VII. (4) Results

Only the correlation between post-operative coronary arteriography and stress myocardial imaging will be considered here. The relationship between image appearances and symptomatic improvement, exercise capacity and the results of stress electrocardiography will be reported separately by Dr. R.G. Murray.

VII. (4)(a) Results of coronary arteriography

The findings at post-operative coronary arteriography are

summarised in Tables 27 to 29.

In the patients with LAD grafts alone, 6 were patent and 3 occluded (Table 27). In the 6 patients with RCA grafts alone, 5 were patent and 1 occluded (Table 28). In the 15 patients who had both RCA and LAD grafts placed, both grafts were patent in 4 patients, both occluded in 1 patient, the RCA graft patent and the LAD occluded in 4 and the RCA occluded and LAD patent in 6 (Table 29). In total, therefore, 29 grafts (16 LAD plus 13 RCA) were patent and 16 (8 LAD and 8 RCA) occluded. There was a total of 31 diseased ungrafted vessels (5 LAD, 7 RCA and 19 LCx) (Tables 27 to 29).

VII. (4)(b) Results of stress thallium-201 imaging

The findings at post-operative stress thallium-201 imaging are summarised in Tables 30 to 34. Figure 39 demonstrates images associated with patent and occluded LAD grafts and Figure 40 patent and occluded RCA grafts. Figure 30 shows the image appearances in a patient with patent LAD and RCA grafts but disease of the ungrafted LCx vessel.

In the patients with LAD grafts only, all 6 patent grafts were correctly identified as such. Two occluded LAD grafts were identified but 1 was "missed" (Table 30).

In the patients with RCA grafts only, 4 patent grafts and one occluded graft were correctly identified (Table 31). In the sixth patient in this group, however, a patent RCA graft was associated with a posteroseptal and postero-inferior abnormality. This was attributed to occlusion of the graft but may reflect the disease of (ungrafted) LAD and LCx vessels present in this patient.

In the 15 patients with both LAD and RCA grafts, graft status was accurately predicted in 3 patients with both grafts patent, 1 patient with both occluded, 3 with a patent RCA graft and occluded LAD graft and in 3 patients with an occluded RCA graft and patent LAD graft (Table 32). In 1 patient with both grafts patent, the LAD

graft was predicted to be occluded and RCA graft patent, whilst in 1 patient with a patent RCA graft and occluded LAD graft, the stress myocardial image suggested both grafts were patent and in 3 patients with occluded RCA grafts and patent LAD grafts the images suggested both grafts were patent.

In summary, 27 out of 29 patent grafts and 11 out of 16 occluded grafts were correctly identified from stress myocardial images (Table 33). From these figures, the predictive value of an abnormality in the territory of a graft on stress thallium-201 imaging for graft occlusion was 11/13 (84.6%) and the predictive value of a regionally normal image for graft patency was 27/32 (84.3%).

Considering grafts to individual vessels, patency was correctly predicted from the stress images in 11/13 RCA grafts and 16/16 LAD grafts and occlusion in 5/8 RCA grafts and 6/8 LAD grafts. The accuracy of prediction of graft status did not differ significantly for the two vessels (Chi squared test, $p>0.05$).

Post-operative angiography revealed disease in 31 ungrafted vessels in 25 patients (Tables 27 to 29). The stress myocardial images identified disease of ungrafted vessels in 3 of 5 LAD lesions, 4 of 7 RCA lesions and 8 of 19 LCx lesions (Table 34). In total, the stress images identified 15 of 31 abnormal ungrafted vessels.

Of the 30 patients, 3 had completely patent grafts and no significant disease of the ungrafted vessels. 27 patients, therefore, had at least one vascular territory which had impaired blood supply, either because of disease of ungrafted vessels or occlusion of a graft. The stress thallium-201 images were abnormal in 20 - an overall sensitivity for the detection of coronary artery disease of 20/27 (74%). A further patient had a gross apical abnormality. If this is considered as indicating coronary artery disease, the sensitivity becomes 21/27 (78%).

VII. (5) Discussion

In the series described above, stress thallium-201 myocardial imaging allowed accurate prediction of the patency or occlusion of 38/45 (84%) coronary artery bypass grafts. The figure obtained, however, may not be an entirely accurate representation of the value of thallium-201 imaging as the frequency with which occluded grafts were detected (11/16 or 69%) was less than the frequency of correct prediction of graft patency (27/29 or 93%). Thus, in a population with a higher frequency of graft occlusion, the overall accuracy of prediction of graft status might be lower. The accuracy of prediction might also be lower if left circumflex grafts were being studied, as results from patients with native left circumflex disease, show this is the most difficult vessel abnormality to detect on myocardial imaging (Chapter III. (5)(e)). The accuracy of prediction of graft status (i.e. "extent of disease") might also be lower in patients with three bypass grafts (Chapter III. (5)(g)).

In two patients occlusion of RCA grafts were predicted from the thallium-201 images, but the grafts were patent at arteriography. In the first of these patients, who had a patent RCA graft but disease of the ungrafted LAD and LCx vessels, posteroseptal and postero-inferior abnormalities on the myocardial image were interpreted as indicating occlusion of the graft. It is possible that they, in fact, are manifestations of the disease in the ungrafted vessels. In the second patient falsely predicted to have an occluded RCA graft, the inferior abnormality upon which this prediction was based may reflect the disease present in the ungrafted LCx vessel. Another possible explanation for the scan findings in these patients is occlusion of the graft or progression of disease in the native vessel distal to the graft in the period between the post-operative angiogram and the myocardial imaging study (4 years and 2 years respectively).

The occlusion of grafts was not predicted from the stress thallium-201 images in 5 cases. In the first, occlusion of an LAD graft was missed on imaging. This patient also had a 50% stenosis of his left circumflex artery but a normal right coronary artery. His post-operative exercise test was characterised by an increase of his work capacity by a factor of more than 2 from the pre-operative level, a normal exercise ECG and a complete absence of chest pain, both during the test and in the 3 years since the operation. It is difficult to assess the results in this patient. The thallium-201 imaging results are in keeping with the symptomatic relief, the increased work capacity and the normal exercise ECG, but they conflict with the arteriographic findings. For the purposes of this study, the myocardial image findings in this patient must be regarded as a false negative, though it is possible that the arteriographic "occlusion" of the graft was due to failure to enter the graft orifice at catheterisation.

A second false negative occurred in a patient with a patent RCA graft and occluded LAD graft. The stress images in this patient showed a gross apical abnormality in all projections but were otherwise normal. This abnormality may be a reflection of the occluded LAD graft but, because the apex was not included for the analysis of graft patency, this patient was predicted to have two patent grafts.

In three patients with occluded RCA grafts and patent LAD grafts, it was predicted from the thallium-201 images that both grafts were patent. In two of these patients, who had chest pain during the exercise test and a positive stress ECG, the myocardial images showed posterolateral and posterior abnormalities compatible with the disease present in their (ungrafted) LCx vessels. The third patient did not develop chest pain during the exercise test but did have an abnormal stress ECG. In this patient the myocardial images were entirely normal in spite of occlusion of the RCA graft and the ungrafted LCx vessel.

The myocardial images detected the presence of disease in 15 of 31 (48%) ungrafted vessels. This detection rate for the presence of abnormal vessels is somewhat lower than that found in patients with multivessel coronary artery disease who had not undergone coronary artery bypass surgery (Chapter III. (5)(e)). One possible reason for this is the predominance of left circumflex lesions, which have previously been shown to be the vessel abnormalities most often "missed" on stress myocardial imaging (Chapter III. (5)(e)). Disease in ungrafted LAD or RCA vessels was detected in 7/12 (58%) cases and overall (ungrafted or grafted) LAD and RCA disease was detected in 18/28 (64%) of cases. When LCx lesions are included the overall detection rate for diseased (grafted or ungrafted) vessels was 26/47 (55%).

Another possible explanation for the failure to detect graft occlusion or disease in ungrafted vessels is the development of collateral circulation between a non diseased vessel or a patent bypass graft and the diseased vessel. Such collaterals have been demonstrated at post-operative angiography (Di Luzio, Roy, Sowton et al., 1975) but unfortunately I do not have information on collateral circulation in our bypass patients.

A further factor to be considered in the development of myocardial image abnormalities after bypass surgery is peri-operative myocardial infarction. Only one patient was known to have sustained this operative complication and an appropriate inferior abnormality was seen on his radionuclide study. The diagnosis of perioperative myocardial infarction may be difficult (Frick, 1976; Lowenthal et al., 1977) and it is therefore possible that some other scintigraphic abnormalities were due to this process. As, however, there are no rest or redistribution images available in these patients, this point cannot be further elucidated. The occurrence of unsuspected perioperative myocardial infarction might be implicated in the false

prediction of graft occlusion, as areas of myocardial necrosis may be associated with an angiographically patent graft (Bulkley and Hutchins, 1977).

Several studies have recently appeared in the literature regarding the clinical utility of thallium-201 myocardial imaging in patients who have undergone coronary artery bypass surgery.

Ormand, Platt, Mills et al., (1978) concluded that, in patients with an abnormal pre-operative study, post-operative thallium-201 imaging may be useful as a non invasive screen of graft patency. Wainwright, Maisey and Sowton (1977) found that pre- and post-operative stress imaging was a sensitive indicator of altered myocardial perfusion following coronary artery bypass grafting but that the "sensitivity to detect graft closure was directly related to the importance of the graft with respect to the severity of native coronary disease".

Ritchie, Narahara, Trobaugh et al., (1977) reported that, in 11 patients who had stress myocardial imaging performed pre- and post-operatively, 7 showed improvement post-operatively and in these patients the bypass grafts were patent. They also observed that in 12 patients who underwent both rest and stress imaging post-operatively, 7 had new defects on the stress compared to the rest study and in each case this was associated with either an occluded graft or residual unoperated disease. They concluded that pre- and post-operative imaging may be useful in non invasively predicting graft closure and/or improved regional perfusion due to patent grafts.

Rosenblatt et al., (1977) were able to compare post-operative stress thallium-201 imaging and coronary arteriography in 8 patients who remained symptomatic following coronary bypass surgery. Two had normal stress myocardial images and in both all grafts were patent, although one patient also had disease in two ungrafted vessels.

Six patients had abnormal images due to "aortocoronary bypass occlusion, patent grafts with additional unbypassed native coronary lesions or a combination of unbypassed lesions and at least one graft occlusion".

Verani, Marcus, Spoto et al., (1978) derived an index of myocardial perfusion from visual inspection of thallium-201 images and applied this to the analysis of stress studies obtained 72 hours pre-operatively and 8 to 12 weeks post-operatively in a group of patients undergoing coronary bypass surgery. No post-operative coronary arteriograms were performed. Nine patients showed return of their images to normal post-operatively and in another 10 the post-operative images were improved compared to the pre-operative findings. This improvement did not correlate with changes in stress ECG studies but did agree well with symptomatic improvement. Three patients had deterioration of regional myocardial perfusion post-operatively, as judged by myocardial imaging. None had evidence of perioperative myocardial infarction and two had improvement of their anginal symptoms post-operatively. In the absence of knowledge of the post-operative coronary anatomy these findings are impossible to interpret. The third patient whose myocardial images worsened post-operatively also had deterioration in his functional classification after surgery. From this study Verani et al., (1978) concluded that thallium-201 imaging can demonstrate that "regional myocardial perfusion improves in most patients following coronary bypass grafting". They also note, however, that "failure of regional myocardial perfusion to improve post-operatively does not preclude marked alleviation of angina and improved exercise tolerance".

Greenberg, Hart, Botvinick et al., (1978) have recently compared myocardial imaging to coronary arteriographic findings in 25 patients who were 2 to 70 months post coronary bypass surgery. The maximum

time between the two studies in any patient was 4 months. Thirteen patients had either normal post-operative images or abnormalities which did not change between rest and stress studies. Ten of these patients had angiographically complete revascularisation. The three "false negative" studies comprised 2 patients with no patent grafts or native vessels (i.e. effective triple vessel disease) and a third who had a fixed defect during rest and exercise in a region supplied by an occluded graft. Ten patients had abnormal post-operative stress images. Eight of them had at least one occluded bypass graft and the other 2 had significant disease in ungrafted vessels. By regional analysis of the myocardial images 19 of 28 (68%) vessels with significant (more than 75% luminal diameter) stenoses were detected non invasively. This "pick up" rate for abnormal vessels is somewhat higher than that in my own series (26 of 47 vessels or 55%). This may be due to the fact that in my study stenoses of 50% luminal diameter rather than 75% were considered abnormal. With knowledge of which vessels had been grafted, Greenberg et al., (1978) could determine whether myocardial image abnormalities reflected graft occlusion or disease of ungrafted vessels. In 7 of the patients, pre-operative images were also obtained, but although comparison of the pre- and post-operative images demonstrated improved myocardial perfusion after surgery, the use of pre-operative scintigraphy did not contribute to the predictive accuracy of the technique.

What role does my own and the other studies suggest for thallium-201 myocardial imaging in the assessment of the patient who has undergone coronary artery bypass surgery? A comparison of pre-operative and post-operative images may demonstrate the degree of improvement of myocardial perfusion produced by the surgery. Whilst this may be of research interest, in itself it has very limited clinical value. The comparison of post-operative rest

and exercise images may be useful in determining whether the patient has had a perioperative myocardial infarction, especially when the pre-operative rest image appearances are known. This information may have some prognostic significance but again is likely to be of limited clinical value. It is perhaps in the patient who continues to have chest pain post-operatively that the technique is most valuable. This may apply to 20% to 30% of patients undergoing coronary artery bypass surgery (Caves and Stinson, 1977) and may be related to continuing myocardial ischaemia or to other factors e.g. bone trauma at the time of operation.

From several studies it appears that an abnormal post-operative myocardial image reflects incomplete myocardial revascularisation due either to occlusion of grafts, disease of grafted vessels distal to the site of insertion of the graft or disease in ungrafted vessels. An abnormal image, therefore, suggests the pain is due to myocardial ischaemia and this may have therapeutic implications as it has now been demonstrated that some patients in this category can obtain symptomatic relief from further coronary artery surgery (Caves and Stinson, 1977; Brooks, Catell, Balcon et al., 1978; Bennett, Canepa-Anson, Bourdillon et al., 1978).

The value of a negative test in the patient with continuing chest pain is more difficult to assess. In my own series some of the patients with a normal stress myocardial image but an abnormal post-operative angiogram were asymptomatic. The normal stress images in these patients are probably false negative studies but another possible explanation is that some of these patients had normal small vessel perfusion in spite of the major vessel abnormalities demonstrated at arteriography. The same comments apply to the group studied by Greenberg et al., (1978). It seems likely that a normal stress myocardial image in a patient with chest pain after coronary artery surgery goes a considerable way in suggesting that the symptom is not due to impaired myocardial blood flow.

CHAPTER VIII

CONCLUSIONS: THE VALUE AND THE LIMITATIONS OF THALLIUM-201 MYOCARDIAL IMAGING FOR THE DETECTION OF CORONARY ARTERY DISEASE

Thallium-201 became generally available for myocardial imaging in humans some three years ago. As a method of non invasively visualising the myocardium and its blood flow, it had great potential both in clinical practice and as a research tool. This chapter will be concerned with an assessment of how far this promise has been realised and will consist of an examination of both my own work and that published by other workers in terms of the problems associated with thallium-201 imaging and the value of the technique, particularly when used clinically for the detection of ischaemic heart disease.

VIII. (1) Problems associated with Thallium-201 Myocardial Imaging

The problems associated with thallium-201 imaging can be divided into those which apply to any potassium analogue used for myocardial imaging and those which are due to the nature of thallium-201 itself. These points have already been considered at length in Chapters I, II and III but will be restated briefly here.

For the production of myocardial images, all potassium analogues depend both upon the delivery of the isotope to the myocardial cell (principally determined by myocardial blood flow) and the integrity of the myocardial sodium-potassium pump. This means that whilst abnormal images will be produced by coronary artery disease, focal abnormalities may also result from cardiomyopathies not due to ischaemic heart disease (Chapters I. (2)(b), I. (2)(c), III. (5)(c), III. (6)(a), V. (3), V. (4), VI. (4) and VI. (5)).

When potassium tracers are used in ischaemic heart disease, a further problem arises because of the fact that the image gives an indication of regional relative blood flow rather than absolute blood flow. Measurement of overall uptake of the tracer by the myocardium might allow assessment of absolute myocardial blood flow. Possible approaches to this would be to compare uptake by the myocardium to that by other organs or to an external source. Methods using comparison to lung uptake or to mediastinal uptake have been proposed (Chapter III. (6)(c)) but are complicated by the dependency of myocardial cation uptake on the level of exercise (McLaughlin et al., 1977) and the many factors influencing the degree of uptake of the nuclide by other organs e.g. lung uptake of thallium-201 is more marked in smokers compared to non-smokers (Strauss and Pitt, 1977b). Comparison with an external source is not feasible with thallium-201 - the relatively low energy (65-82 keV) of the rays imaged means that the degree of absorption by overlying tissues will vary greatly between individuals of different build. For these reasons overall quantitation of myocardial thallium-201 uptake is not carried out by most workers.

The demonstration of an abnormality on potassium analogue myocardial imaging in coronary artery disease depends upon a reduction in blood flow distal to the coronary stenosis. When the tracer is injected at rest abnormalities due to myocardial infarction will be demonstrated, but in the absence of infarction flow will not be reduced distal to any stenosis of less than 85% of the luminal diameter (Chapter I. (2)(c)). In practice lesions of 50% or more of the luminal diameter are considered haemodynamically significant by many cardiologists. Rest imaging will thus fail to detect many clinically important coronary occlusions and, for a high sensitivity, the tracer must be injected during stress (Chapter I. (2)(c)). Such stress imaging characteristically takes the form of injecting the

tracer at the end of a symptom limited exercise test. These tests, however, may be handicapped by the inability of the patient to exercise adequately because of symptoms not due to ischaemic heart disease e. g. arthritis or dyspnoea from respiratory disease. This limitation may be overcome if further studies validate the usefulness of either pharmacological dilatation of the coronary vessels by substances such as dipyridamole or "pharmacological stress tests" such as infusion of isoprenaline intravenously (Chapter I. (2)(c)). In addition to the difficulty some patients experience in achieving adequate levels of exercise, stress tests on patients with possible coronary artery disease require careful monitoring of the ECG throughout the test and the immediate availability of full resuscitation equipment and drugs. Such tests must be conducted by a physician fully trained in conducting exercise tests preferably accompanied by another individual fully trained in cardiopulmonary resuscitation. Because of the redistribution of the radionuclide into transiently ischaemic areas of myocardium which begins soon after the termination of the exercise test, the studies should be performed close to the gamma camera, preferably in the same room. These constraints on personnel, equipment and site of testing, make the studies more difficult logistically and more expensive.

The problems discussed so far relate to all potassium analogues. There are also some difficulties associated with thallium-201 specifically. The 65-82 keV X-rays are not ideal for scintillation camera imaging and reduce the resolution obtained when compared to technetium-99m (Chapter II. (4)). The high radiation dose administered to the kidneys with thallium-201, limits the acceptable dose in clinical studies to around 2 mCi (Chapter I. (2)(g)). At this dosage, each myocardial image will take 4 to 10

minutes to acquire, if no gating is employed (Chapter II. (5)). The resolution obtained could theoretically be improved by the use of cardiac and/or respiratory gating. Such manoeuvres, however, would prolong the imaging time unacceptably.

A further problem encountered with thallium-201 imaging of the myocardium is the nonhomogeneity of tracer uptake seen in normal hearts (Chapter II. (7)). As discussed in Chapter II. (6) and in Chapter IV, this complicates the interpretation of the images, especially when contrast enhancement and background subtraction are employed. To some extent this problem may possibly be overcome by methods of trying to quantitate regional myocardial uptake of the radioisotope (Chapter IV).

The final problem relating to the use of thallium-201 for myocardial imaging is one of expense. As the production from the cyclotron of the isotope and its subsequent purification are relatively difficult, few producers exist and, with a half-life of 72 hours, most users have the substance transported to them by air. It is unlikely that thallium-201 will become significantly less expensive in the future.

VIII. (2) The Value of Thallium-201 Myocardial Imaging

In this section I propose to discuss what I believe to be the clinical value of thallium-201 myocardial imaging by discussing the role of the technique in certain clinical settings.

VIII. (2)(a) Acute myocardial infarction

As discussed in Chapter I. (2)(c) and Chapter V the potassium analogues can be used to demonstrate myocardial infarcts and normal rest thallium-201 myocardial images obtained within 6 hours of the onset of chest pain appear to effectively exclude an acute myocardial infarct. However, such early imaging is often not possible and studies obtained later than this have a considerably lower sensitivity,

especially in detecting acute subendocardial infarction (Chapter V). When an abnormality is demonstrated in the patient with suspected acute infarction it is not possible, from the appearance of the image, to say whether this represents acute myocardial infarction, myocardial fibrosis from previous infarction, myocardial ischaemia or other myocardial pathology. The differentiation of acute infarction from old infarction or myocardial ischaemia can be aided by the concomitant use of "hot spot imaging" whilst it may be possible to separate infarction from ischaemia by re-imaging the myocardium some hours after the injection of the tracer at rest. Overall, however, I feel that thallium-201 imaging has a very limited role, if any, in the routine diagnosis of acute myocardial infarction.

From a research point of view, myocardial imaging might be useful in acute myocardial infarction if it could be used to estimate accurately the extent of tissue damage and if serial imaging could demonstrate the response or lack of it to therapies aimed at limiting the size of the infarct. As I have indicated in Chapter V. (4) there is some doubt as to the reliability of potassium analogue imaging in this context. If, however, the extent of infarction could be reliably estimated in this manner, thallium-201 imaging might also have some prognostic value both in patients presenting with acute infarction and in those convalescent from it, by demonstrating the amount of viable myocardial tissue remaining.

VIII. (2)(b) Angina pectoris

The role of thallium-201 imaging in the patient with angina pectoris is controversial at present. If the patient has angina of sufficient severity to merit consideration of possible coronary artery surgery, whether myocardial imaging has a place or not depends upon its ability to predict reliably the extent of coronary artery disease. If the extent of disease can be established from thallium-201 imaging,

then the technique may be a useful prelude to coronary arteriography by indicating high risk patients who require urgent investigation. If, however, as my own and some other workers' results indicate (Chapter III. (5)(g), III. (6)(c)), the extent of coronary artery disease cannot be reliably judged from stress myocardial images, coronary arteriography is the investigation indicated and the results of thallium-201 imaging are not really clinically relevant. Pre-operative images, however, may be useful for comparing to post-operative studies carried out to assess graft patency. A pre-operative rest or redistribution study to indicate probably fibrosed areas of myocardium would also have some value in this context.

In the patient with less severe angina, the results of thallium-201 imaging are unlikely to cause any major change in management. The technique, therefore, is probably again of limited value here, though normal stress images may increase the likelihood of "angina with normal coronary arteries" and thus indicate a better prognosis. This, however, remains to be proven.

VIII. (2)(c) Atypical chest pain and the asymptomatic subject

The patient with atypical chest pain probably represents the best indication for thallium-201 imaging at present. If such a patient is able to perform an adequate level of exercise, the demonstration of normal stress myocardial images and a normal stress electrocardiogram gives a high probability that the pain is not due to cardiac disease. Thallium-201 imaging may also be useful in helping to clarify an equivocal ECG in the patient with atypical chest pain (Chapter III).

The demonstration of normal stress thallium-201 images may also be useful in the asymptomatic subject with an abnormal or equivocal ECG, and may suggest that coronary arteriography is not required.

It is important that subclinical or atypical ischaemic heart disease is detected in certain groups of people e. g. airline pilots,

train drivers, steeple jacks. Because of the expense, myocardial imaging probably cannot be justified in the routine, regular screening of these subjects but may be useful when there is some indication of possible heart disease, such as an equivocal or abnormal ECG or atypical chest pain.

VIII. (2)(d) Follow up of coronary bypass surgery

As discussed in Chapter VII, stress myocardial imaging may be a useful non invasive means of following up patients after coronary bypass surgery. The comparison of pre-operative and post-operative images can be used to demonstrate improvement in myocardial perfusion following operation, whilst rest or redistribution post-operative images may indicate areas of myocardial necrosis. This may be of some value in determining the mechanism of symptomatic improvement after coronary artery surgery.

From a clinical point of view, perhaps more important will be the use of stress imaging in the patient who continues to have chest pain, especially atypical chest pain, after surgery. The demonstration of abnormalities on the myocardial images would support continuing myocardial ischaemia as the cause of the patient's symptoms whilst normal images at the end of an adequate stress test (or possibly a pharmacological vasodilatation test) would provide some evidence of complete revascularisation and thus suggest some other mechanism for the continuing chest pain.

VIII. (2)(e) Miscellaneous situations

Recent work by the Pisa group has shown that coronary artery spasm producing variant angina is associated with the development of abnormalities on the myocardial image (Chapter III. (6)(a)). In the patient with angiographically normal vessels who is suspected of having variant angina, the demonstration of myocardial image abnormalities during an attack would provide useful indirect

confirmation of the pathology. During arteriography, coronary artery spasm may be provoked in susceptible subjects by certain pharmacological manoeuvres. Whilst regarded by some authorities as useful, these tests are associated with definite risk and, therefore, the acceptability of such drug administration prior to myocardial imaging performed independent of coronary arteriography is questionable as, in the absence of arteriography, there is no direct evidence of the severity of spasm induced and whether it has been successfully reversed at the end of the test.

As discussed in Chapter VI, myocardial imaging was a potential means of clarifying which patients with aortic valve disease should undergo selective coronary arteriography. However, in practice, as indicated by my own and by the Johns Hopkins group's study, thallium-201 imaging cannot be used to determine whether patients with aortic valve disease also have coronary artery disease. Thus, whilst the development of focal abnormalities in aortic valve disease patients with no coronary disease is pathogenetically interesting, the technique is not clinically useful in this setting.

Several groups have examined thallium-201 imaging in patients with chest pain and mitral valve prolapse. The evidence here is somewhat conflicting (Chapter III. (6)(a)), but the balance suggests that myocardial image abnormalities in these patients indicate associated coronary artery disease and do not develop from mitral valve prolapse per se. Thallium-201 images in these patients, therefore, may help to clarify whether coronary arteriography is indicated.

Finally myocardial imaging has been applied in a variety of situations such as sarcoid heart disease, asymmetric septal hypertrophy and other cardiomyopathies. In these settings the myocardial images may provide useful objective evidence of cardiac pathology, though as the abnormalities may be focal in nature it may not be possible to exclude ischaemic heart disease.

VIII. (3) Final Remarks

In summary, therefore, it appears that whilst the clinical utility of thallium-201 myocardial imaging is perhaps less than was hoped at the time of its introduction, it does have a definite place in certain circumstances. As discussed in Chapter I, thallium-201 imaging is only one of several nuclear medicine techniques at present being assessed in cardiology. The precise clinical and research roles of each have still to be established, but, as I have stressed at several points in the thesis, much useful information can now be obtained non invasively, especially when a combination of the procedures is used.

The word Thallium comes from the Greek for a "budding twig". The techniques of "nuclear cardiology" could perhaps more accurately be compared to a developing tree. The final size of the tree and even the exact nature of its individual branches are not yet clear, but the potential for continued growth in the future seems bright.

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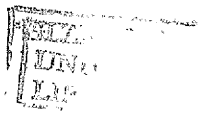

AN EVALUATION OF THE ROLE OF THALLIUM-201 MYOCARDIAL IMAGING IN THE INVESTIGATION OF ISCHAEMIC HEART DISEASE

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VOLUME II

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Table 1

Comparative absorbed radiation doses (rads) per millicurie of intravenously administered potassium analogue myocardial imaging agents

Isotope	Whole body	Heart	Kidney	Liver	Lungs	Testes	References
Potassium-43	0.60-0.70	0.52	0.52	0.53	0.43	0.58	1, 4, 5, 7
Potassium-42	1-1.13						6
Caesium-129	0.17-0.24	0.25	0.23	0.22	0.16	0.21	1, 4, 5, 8
Caesium-131	0.3						8
Caesium-134m	0.24-0.48						8
Caesium-134	62						8
Rubidium-81	0.08-0.22	0.16	0.22	0.14	0.10	0.09	1, 4, 5, 9
Rubidium-81 + contaminants	0.22-0.4					0.28	4, 9
Rubidium-84	16						4
Thallium-201	0.07-0.24	0.17-0.32	0.39-1.17	0.15	0.12	0.25-0.59	1, 2, 3, 4, 5
Nitrogen-13 ammonia	0.005			0.025			10

References:
1. Feller & Sodd, 1975
2. Bradley-Moore et al., 1975
3. Atkins et al., 1977
4. Budinger & Rollo, 1977
5. Adelstein & Maseri, 1977
6. Marinelli et al., 1948
7. Hurley et al., 1971
8. Chandra et al., 1973
9. Martin et al., 1974
10. Harper et al., 1972

Table 2

Summary of results of selective coronary arteriography

Number of abnormal vessels	Number of patients
None	34
One	13
Two	26
Three	12

Table 3

Summary of abnormal vessels in single vessel disease patients

Vessel abnormal*	Number of patients
LAD	10
RCA	3
LCx	0

*LAD = Left anterior descending coronary artery
RCA = Right coronary artery
LCx = Left circumflex coronary artery

Table 4

Distribution of vessel abnormalities in patients with double vessel disease

Vessels abnormal*	Number of patients
LAD + RCA	14
LAD + LCx	6
LCx + RCA	5
Main left	1

*LAD = Left anterior descending coronary artery
RCA = Right coronary artery
LCx = Left circumflex coronary artery
Main left = Main left coronary artery

Table 5

Summary of results of left ventriculography

(Figures refer to numbers of patients)

	Normal left ventriculogram	Abnormal left ventriculogram
Normal coronary angiogram	34	0
Abnormal coronary angiogram	30	21

Table 6

Results of stress thallium-201 myocardial imaging in patients with abnormal coronary arteriograms

(Figures refer to numbers of patients)

Extent of coronary artery disease at arteriography	Stress thallium-201 images	
	Normal	Abnormal
Single vessel disease	1	10
Double vessel disease	2	22
Triple vessel disease	1	11
Totals	4	43

Table 7

Results of rest thallium-201 myocardial imaging in patients with abnormal coronary arteriograms

Extent of coronary artery disease at arteriography	Rest thallium-201 images	
	Normal	Abnormal
Single vessel disease	8	3
Double vessel disease	10	11
Triple vessel disease	3	7
Totals	21	21

Table 8

Summary of results of stress myocardial imaging in patients with chest pain and normal coronary arteriograms

	Number of patients
Stress thallium-201 images normal	31
Stress thallium-201 images abnormal	3

Table 9

Summary of results of rest myocardial imaging in patients with chest pain and normal coronary arteriograms

	Number of patients
Rest thallium-201 images normal	14
Rest thallium-201 images abnormal	2*

*Includes 1 patient with a normal stress study

Table 10

Coronary artery lesions associated with abnormalities of particular regions on myocardial image

Myocardial region abnormal*	Associated abnormal coronary artery**
Posteroseptal	LAD or RCA
Anteroseptal	LAD
Anterolateral	LAD
Anterior	LAD
Lateral	LAD or LCx
Posterolateral	LCx
Inferior	RCA
Posterior	LCx or RCA
Apical	Any vessel

* Nomenclature as defined in Figure 10.

**LAD = Left anterior descending coronary artery

RCA = Right coronary artery

LCx = Left circumflex coronary artery

Table 11

Number of occasions on which significant stenoses of each coronary artery failed to cause appropriate abnormalities on stress thallium-201 images

Severity of vessel disease at coronary arteriography	Number of occasions lesions of each coronary artery was "missed" on stress thallium-201 imaging		
	RCA	LAD	LCx
Single	0	1	-
Double	5	2	5
Triple	7	3	10

RCA = Right coronary artery

LAD = Left anterior descending coronary artery

LCx = Left circumflex coronary artery

Table 12

Analysis of stress thallium-201 image appearance of myocardial areas supplied by diseased coronary arteries but with collateral circulation present

(Figures refer to numbers of myocardial areas)

	Myocardial areas subtended by stenosed coronary arteries with collateral circulation present	
	Previous infarct present	No previous infarct
Area normal on stress thallium-201 image	0	9
Area abnormal on stress thallium-201 image	8	7

Table 13

Comparison of results of rest thallium-201 imaging and left ventriculography

(Figures refer to numbers of patients)

	Left ventriculogram findings	
	Wall motion abnormalities present	Wall motion abnormalities absent
Rest thallium-201 image abnormal	18	3
Rest thallium-201 image normal	2	19

Table 14

Comparison of prediction of minimum extent of coronary artery disease (CAD) from stress thallium-201 image appearances and coronary arteriographic findings

(Figures refer to numbers of patients)

Extent of CAD predicted from stress thallium-201 images	Extent of CAD at coronary arteriography			
	None	Single vessel	Double vessel	Triple vessel
None	31	1	2	1
Single vessel	3	9	13	7
Double vessel	0	1	9	3
Triple vessel	0	0	0	1

Table 15

Comparison of prediction of minimum extent of coronary artery disease (CAD) from stress thallium-201 image appearances and coronary arteriographic findings in patients with abnormal arteriograms and no previous myocardial infarction

(Figures refer to numbers of patients)

Extent of CAD predicted from stress thallium-201 images	Extent of CAD at coronary arteriography		
	Single vessel	Double vessel	Triple vessel
None	1	1	1
Single vessel	7	8	4
Double vessel	1	5	0
Triple vessel	0	0	1

Table 16

Comparison of prediction of maximum extent of coronary artery disease (CAD) from stress thallium-201 image appearances and coronary arteriographic findings

(Figures refer to numbers of patients)

Extent of CAD predicted from stress thallium-201 images	Extent of CAD at coronary arteriography			
	None	Single vessel	Double vessel	Triple vessel
None	31	1	2	1
Single vessel	3	5	8	7
Double vessel	0	5	9	3
Triple vessel	0	0	5	1

Table 17

Comparison of prediction of maximum extent of coronary artery disease (CAD) from stress thallium-201 image appearances and coronary arteriographic findings in patients with abnormal arteriograms and no previous myocardial infarction

(Figures refer to numbers of patients)

Extent of CAD predicted from stress thallium-201 images	Extent of CAD at coronary arteriography		
	Single vessel	Double vessel	Triple vessel
None	1	1	1
Single vessel	3	4	4
Double vessel	5	6	0
Triple vessel	0	3	1

Table 18

Results of electrocardiography in patients with abnormal coronary arteriograms

(Figures refer to numbers of patients)

	Rest ECG	Exercise ECG
Abnormal	26	29
Equivocal	2	6
Normal	20	9

Table 19

Results of electrocardiography in patients with normal coronary arteriograms

	Rest ECG	Exercise ECG
Abnormal	3	8
Equivocal	2	5
Normal	29	21

Table 20

Sensitivity and specificity of thallium-201 myocardial imaging in diagnosis of coronary artery disease - summary of results in literature

Authors	No. of pts.	Coronary stenosis considered significant	Method of analysis of Tl201 images	Sensitivity	Specificity	Comments
Bailey, Griffith, Rouleau et al., 1977	83	>70%	Unprocessed images	75%	100%	
Berman et al., 1978	21	>75%	Not specified	86%	100%	All asymptomat patients with abnormal stres ECG
Botvinick et al., 1978	65	>75%	Not specified	85%	89%	
Lenaers et al., 1977	70	>50%	Processed analogue images. Areas <75% myocardial isocount line abnormal	95%	93%	
Lenaers et al., 1978	100	>50%	As above	92%	86%	No patient with previous myocardial infa

Massie et al., 1978	32	Not specified	Not specified	96.9%		All patients with 2 or 3 vessel disease
Pond et al., 1978	53	>50%	Not specified		91%	Patients with chest pain and normal corona angiograms
Raphael et al., 1976	9	Not specified	Not specified		100%	Patients with chest pain and normal corona angiograms
Rehn et al., 1978	161	>50%	Not specified	88%		
Ritchie, Trobaugh, Hamilton et al., 1977	101	>50%	Unprocessed Polaroid	76%	96%	
Ritchie, Zaret, Strauss et al., 1977	190	>50%	Not specified	78%	88%	Multicentre study
Rosenblatt et al., 1977	22	>75%	Not specified	93%	86%	
Shames et al., 1978	23	>75%	Not specified	95%	100%	
Taradash et al., 1976	34	Not specified	Not specified	87.5%	100%	
Turner et al., 1978	75	>75%	Unprocessed Polaroid	68%	97%	Patients with no previous myocardial infarction
Wainwright et al., 1978	111	>50%	Regions of interest technique	99%	56%	

Table 21

Results of visual interpretation of Polaroid stress thallium-201 images in 79 patients with chest pain undergoing coronary arteriography

	Observer 1	Observer 2	Observer 3	Consensus
Sensitivity	33/47	30/47	33/47	32/47 (68%)
Specificity	27/32	25/32	24/32	27/32 (84%)
Accuracy	60/79	55/79	57/79	59/79 (75%)

Table 22

Results of visual assessment of computer processed colour stress thallium-201 images in 79 patients with chest pain undergoing coronary arteriography

	Observer 1	Observer 2	Observer 3	Consensus
Sensitivity	38/47	39/47	38/47	39/47 (83%)
Specificity	23/32	25/32	26/32	23/32 (72%)
Accuracy	61/79	64/79	64/79	61/79 (77%)

Table 23

Comparison of results of rest thallium-201 myocardial images (performed 3 to 6 days after admission) and final clinical diagnosis in 50 patients with suspected acute myocardial infarction

Diagnosis	Number of patients	Number showing focal scan defects
Acute transmural myocardial infarction	22	20
Acute nontransmural myocardial infarction	5	1
Old transmural myocardial infarction	9	7
Myocardial ischaemia	5	1
Miscellaneous		
Pulmonary embolism	4	1
Myocarditis	1	0
Pericarditis	1	0
Intercostal myalgia	1	0
Hiatus hernia	2	0

Table 24

Summary of results of left heart catheterisation and selective coronary arteriography in aortic valve disease patients

Patient	Valvular lesions*	Coronary arteries abnormal at arteriography**
MA	AS/AI/MS	None
JC	AS/AI	None
JF	AS	None
IG	AS	None
EK	AS	None
WM	AS/MS	None
AN	AS/AI	None
GP	AS/AI	None
PS	AS	None
JW	AS/AI	None
TB	AS/AI	LAD
AB	AS/AI	RCA
AC	AS/MS	LAD
PC	AS/AI	LAD/LCx
AG	AS/AI	LAD/RCA
AM	AS	RCA
JM	AS/AI	LAD/RCA
JR	AS/AI/MS	LAD/LCx

*AS = aortic stenosis
AI = aortic incompetence
MS = mitral stenosis
Dominant lesion underlined e.g. AS/AI/MS

**RCA = right coronary artery
LAD = left anterior descending coronary artery
LCx = left circumflex coronary artery

Table 25

Results of stress thallium-201 myocardial imaging in patients with aortic valve disease

	Focal defects present on stress thallium-201 images	Focal defects absent on stress thallium-201 images
Patients with aortic valve disease and no coronary artery disease	4	6
Patients with aortic valve disease plus coronary artery disease	5	3

Table 26

Distribution of coronary artery bypass grafts in patients undergoing post-operative stress thallium-201 myocardial imaging

Aortocoronary bypass grafts placed to	Number of patients
Left anterior descending coronary artery alone	9
Right coronary artery alone	6
Left anterior descending and right coronary arteries	15

Table 27

Results of post-operative coronary arteriography in patients who had received left anterior descending coronary artery bypass grafts only (N = 9)

LAD graft status*		Ungrafted vessel disease present*		
Patent	Occluded	RCA	LCx	RCA + LCx
6	3	3	1	4

*LAD = Left anterior descending coronary artery
RCA = Right coronary artery
LCx = Left circumflex coronary artery

Table 28

Results of post-operative coronary arteriography in patients who had received right coronary artery bypass grafts only (N = 6)

Status of RCA graft*		Ungrafted vessel disease present*		
Patent	Occluded	LAD	LCx	LAD + LCx
5	1	1	1	4

*LAD = Left anterior descending coronary artery
RCA = Right coronary artery
LCx = Left circumflex coronary artery

Table 29

Results of post-operative coronary arteriography in patients who had received bypass grafts to both the left anterior descending and right coronary arteries (N = 15)

Graft Status*				Ungrafted vessel* (LCx)
Both Patent	Both Occluded	RCA patent LAD occluded	RCA occluded LAD patent	Disease present
4	1	4	6	9

*LAD = Left anterior descending coronary artery

RCA = Right coronary artery

LCx = Left circumflex coronary artery

Table 30

Comparison of post-operative angiographic graft status and prediction of graft status from stress myocardial images in patients with left anterior descending coronary artery (LAD) bypass grafts only

LAD graft status at angiography	Graft status predicted from stress thallium-201 images	
	Patent	Occluded
Patent	6	0
Occluded	1	2

Table 31

Comparison of post-operative angiographic graft status and prediction of graft status from stress myocardial images in patients with right coronary artery (RCA) bypass grafts only

RCA graft status at angiography	Graft status predicted from stress thallium-201 images	
	Patent	Occluded
Patent	4	1
Occluded	0	1

Table 32

Comparison of post-operative angiographic graft status and prediction of graft status from stress myocardial images in patients with left anterior descending (LAD) plus right coronary artery (RCA) bypass grafts

	Graft status predicted from stress thallium-201 images			
Angiographic graft status	Both patent	Both occluded	RCA patent LAD occluded	RCA occluded LAD patent
Both patent	3	0	0	1
Both occluded	0	1		
RCA patent LAD occluded	1	0	3	0
RCA occluded LAD patent	3	0	0	3

Table 33

Summary of comparison of post-operative angiographic graft status and prediction of graft status from stress thallium-201 images

Angiographic graft status	Status predicted from stress thallium-201 images	
	Patent	Occluded
Patent	27	2
Occluded	5	11

Table 34

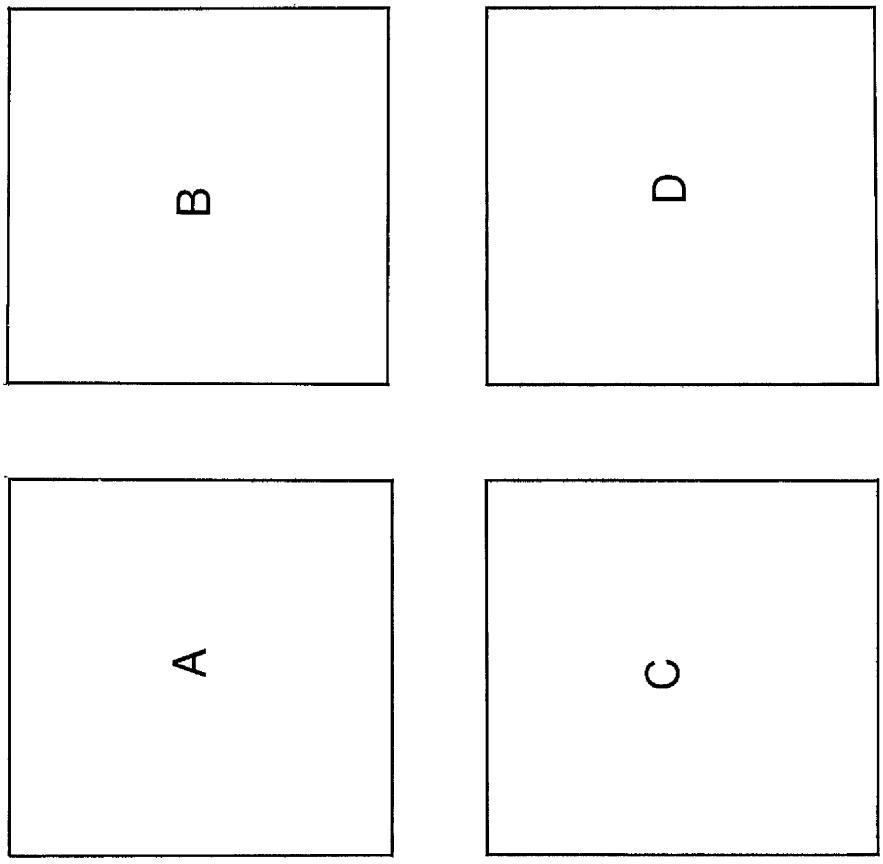
Detection by stress thallium-201 myocardial imaging of disease of ungrafted vessels in patients who had undergone aortocoronary bypass surgery

Ungrafted vessel*	Frequency of abnormality at angiography	Number of times detected from myocardial images
LAD	5	3
RCA	7	4
LCx	19	8
Total	31	15

*LAD = Left anterior descending coronary artery
RCA = Right coronary artery
LCx = Left circumflex coronary artery

FIGURES 1 to 40

The legend to each figure is on the page preceding the figure. In the figures containing four colour prints the individual prints are arranged as shown below.



In the other figures the individual parts are labelled A, B etc.

Figure 1. Whole body distribution of thallium-201 after intravenous injection during exercise.

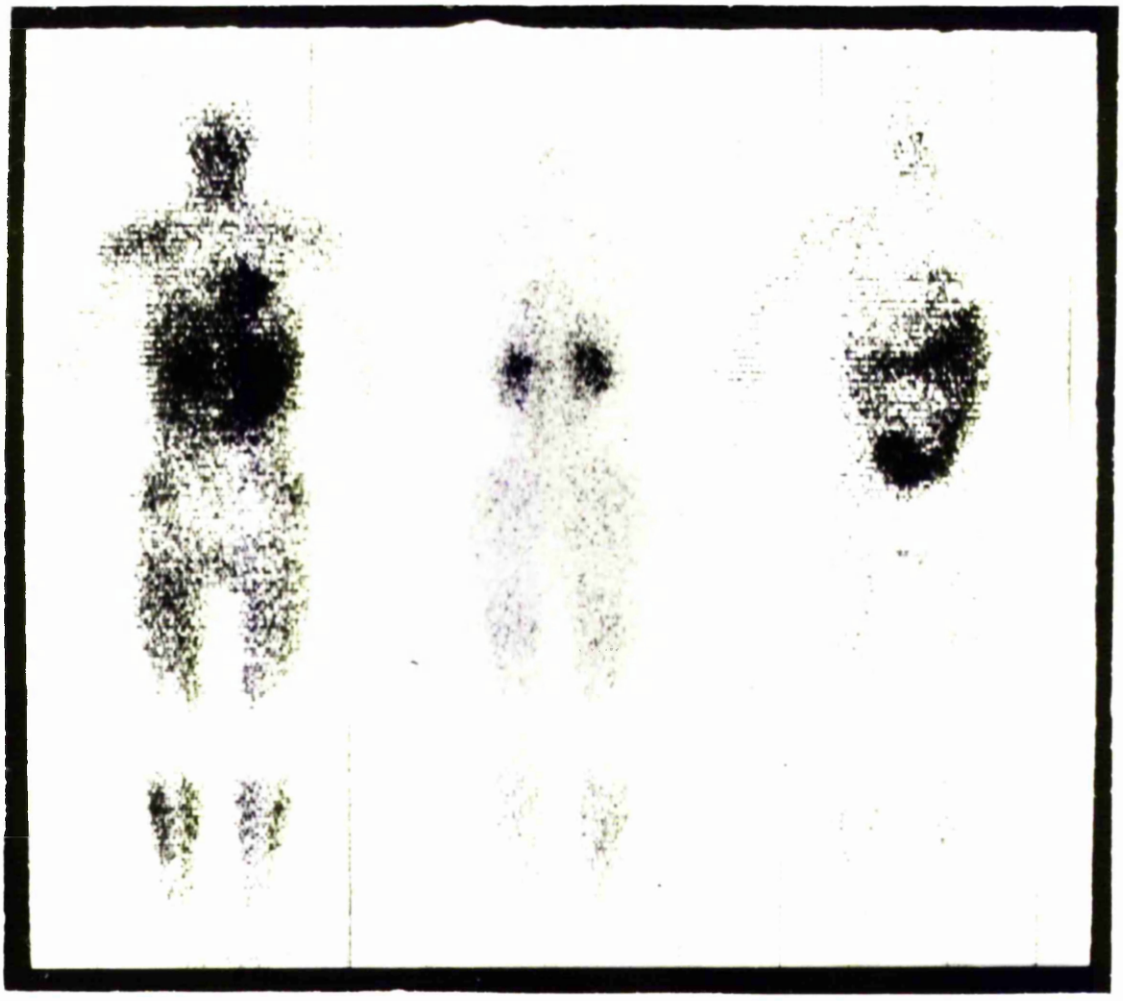
Gamma camera images of whole body thallium-201 distribution following intravenous injection of the tracer into a normal subject during maximal exercise on bicycle ergometer.

(A) Anterior image obtained shortly after cessation of exercise. Marked uptake seen in left ventricular myocardium, liver, spleen, kidneys and exercising skeletal muscle.

(B) Posterior image obtained one hour after cessation of exercise. Marked renal uptake.

(C) Anterior image obtained 72 hours after injection of tracer. Very marked colonic activity. Some residual activity can still be seen in myocardium and skeletal muscle.

(This figure is reproduced by the kind permission of Dr. H. W. Gray).



A B C

Figure 2. Fourteen point scale used in the colour television display of scintillation camera images.

Each colour change represents a range of activities on a linear scale. Areas of activity in the top 1/14th of the range being displayed are red, whilst those in the lowest 1/14th are dark blue. Areas above the range of activity being displayed appear white, whilst those below this range are black.

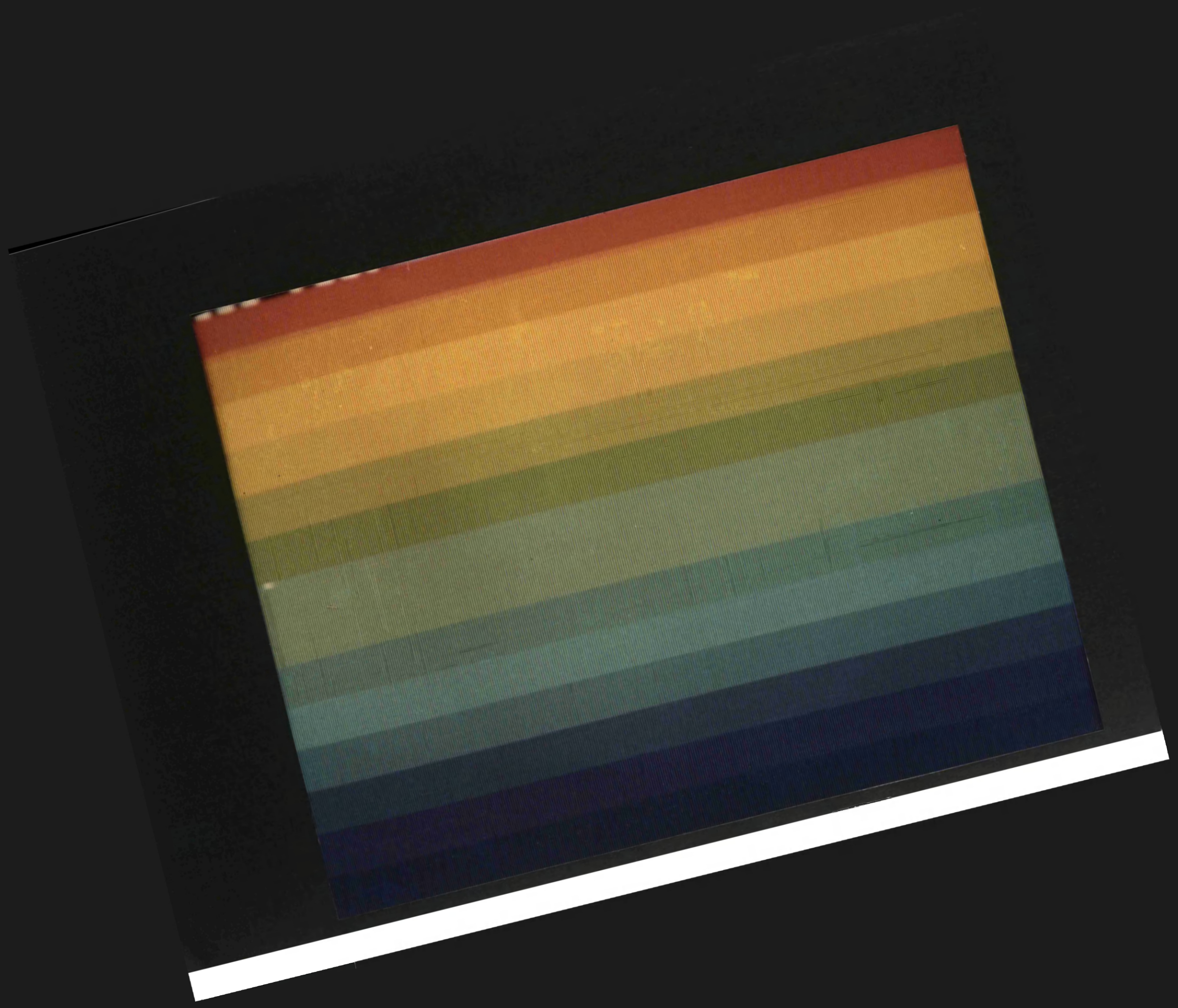
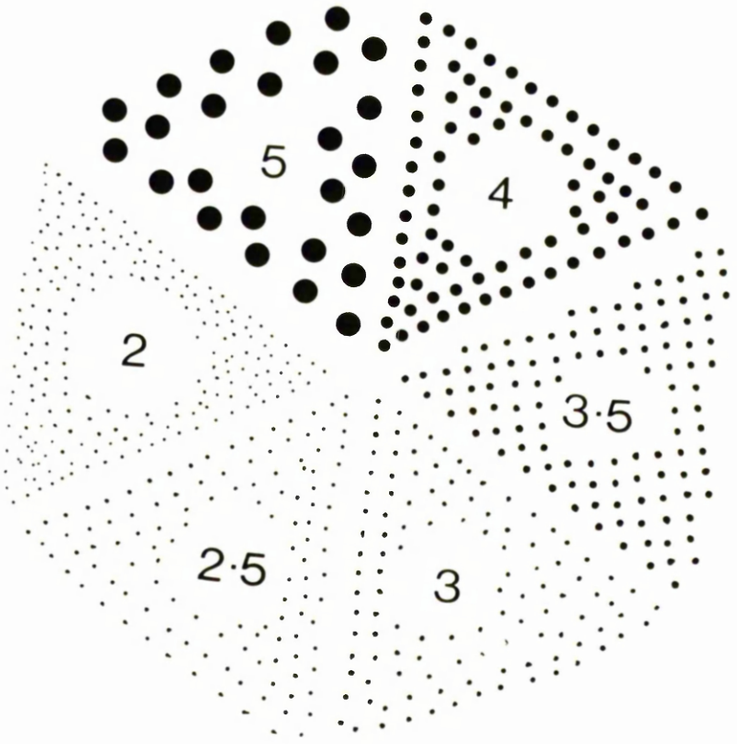


Figure 3. Anger phantom studies with thallium-201 and technetium-99m.

(A) Diagram of the phantom. The figures represent the diameters (in millimetres) of the individual holes.

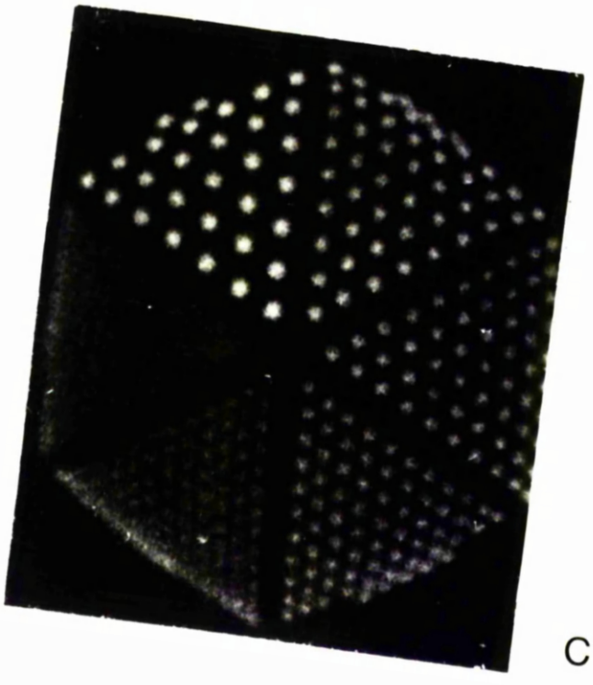
(B) and (C)

Polaroid prints of images of the Anger phantom obtained with the Ohio Nuclear Series 100 gamma camera using a point source of thallium-201 (B) and technetium-99m (C). The resolution obtained with thallium-201 is considerably poorer than that with technetium-99m.



A

B



C

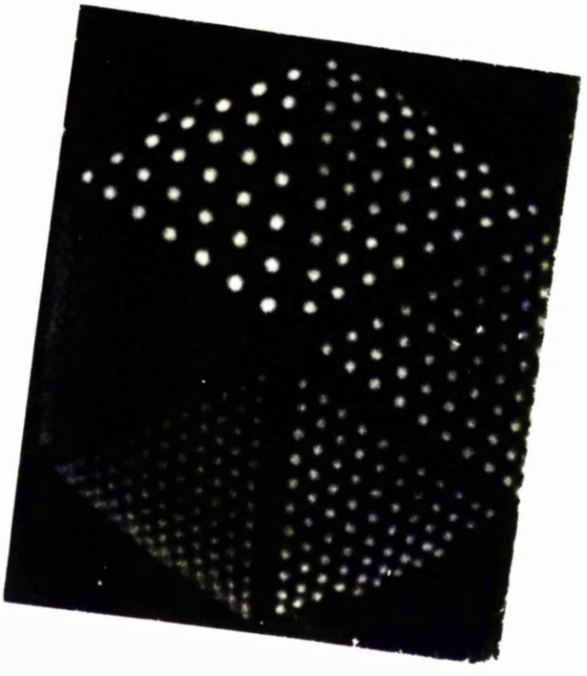


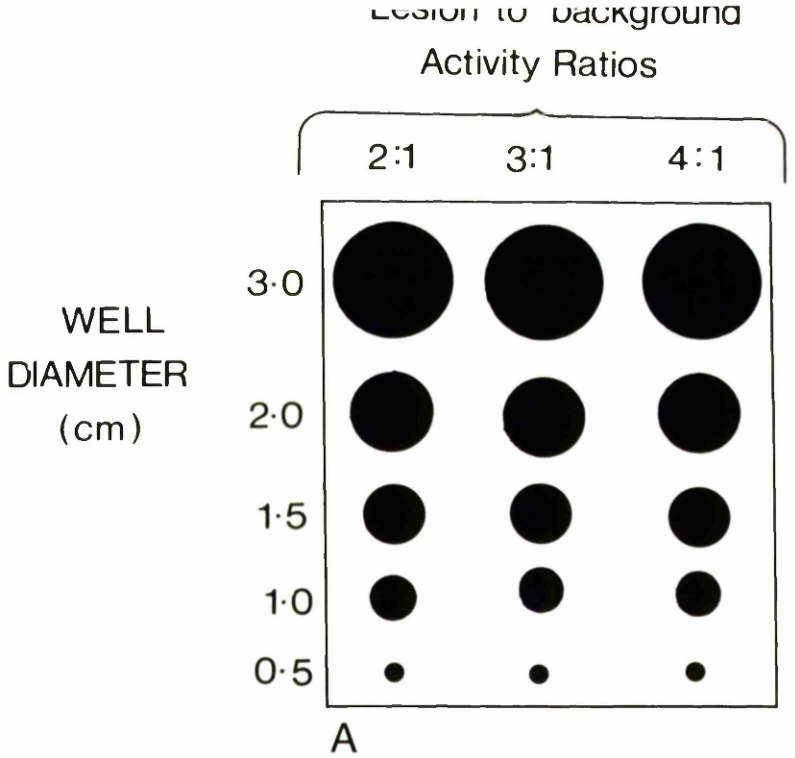
Figure 4. Liver phantom studies with thallium-201 and technetium 99m.

(A) Diagram of liver phantom. The diameters of the individual rows of wells are as shown. The columns have varying depths, such that the "well to background" activity ratios are 2 to 1, 3 to 1 and 4 to 1.

(B) - (E)

Polaroid prints of Ohio Nuclear Series 100 gamma camera images of the liver phantom. With the phantom touching the collimator face images were obtained with the phantom containing thallium-201 (B) and technetium-99m (C) solutions. With the phantom 10 cms. from the camera face images were obtained using thallium-201 (D) and technetium-99m (E).

In both pairs of studies the resolution obtained with thallium-201 is poorer than that with technetium-99m.


Lesion to background
Activity Ratios
2:1
3:1
4:1
WELL
DIAMETER
(cm)
3·0
2·0
1·5
1·0
0·5
A

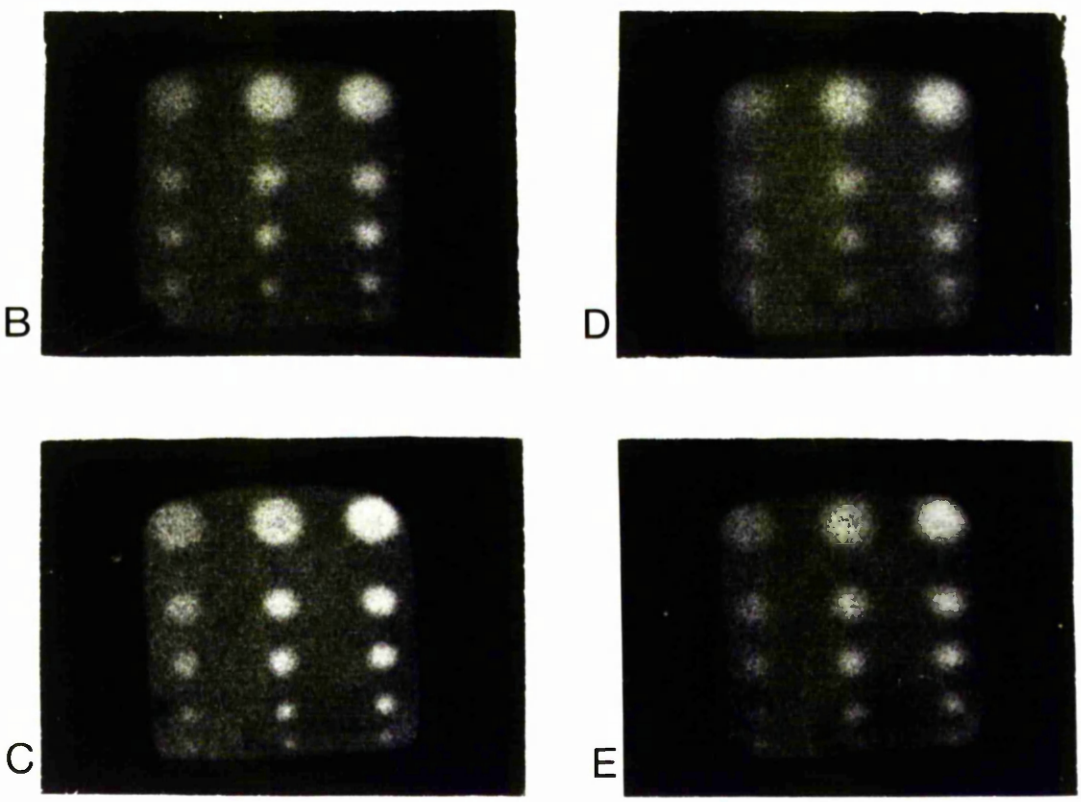
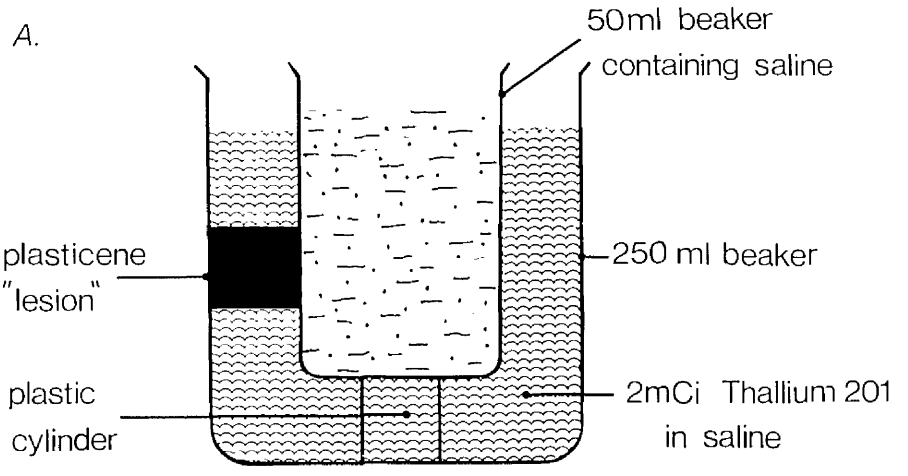

B
D
C
E

Figure 5. Heart phantom.

(A) Diagram of simple heart phantom seen from the side.

(B) Diagram of simple heart phantom seen from above. The figures 1 to 5 represent the positions in which the plasticine "lesion" was placed relative to the gamma camera head.

A.


50ml beaker
containing saline
plasticene
"lesion"
250 ml beaker
plastic
cylinder
2mCi Thallium 201
in saline

B.

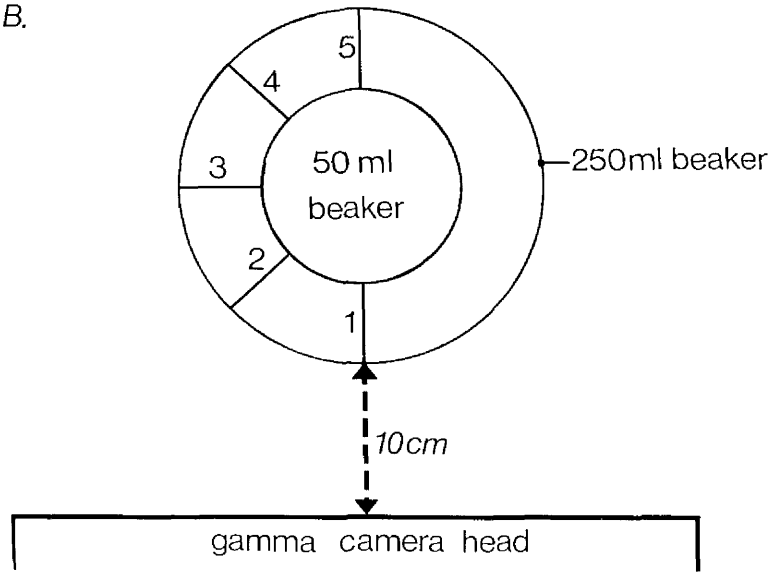

5
4
3
50 ml
beaker
250ml beaker
2
1
10cm
gamma camera head

Figure 6. Heart phantom studies (1).

Polaroid prints of gamma camera images of heart phantom using thallium-201 and a 2 cm. plasticine lesion. Using the nomenclature in Figure 5(B) the lesion was seen as a "cold spot" in positions 1, 2 and 3 (Figures 6(A) to 6(C) respectively), but not in positions 4 and 5 (Figures 6(D) and 6(E)). Figure 6(F) shows an image obtained with no lesion present.

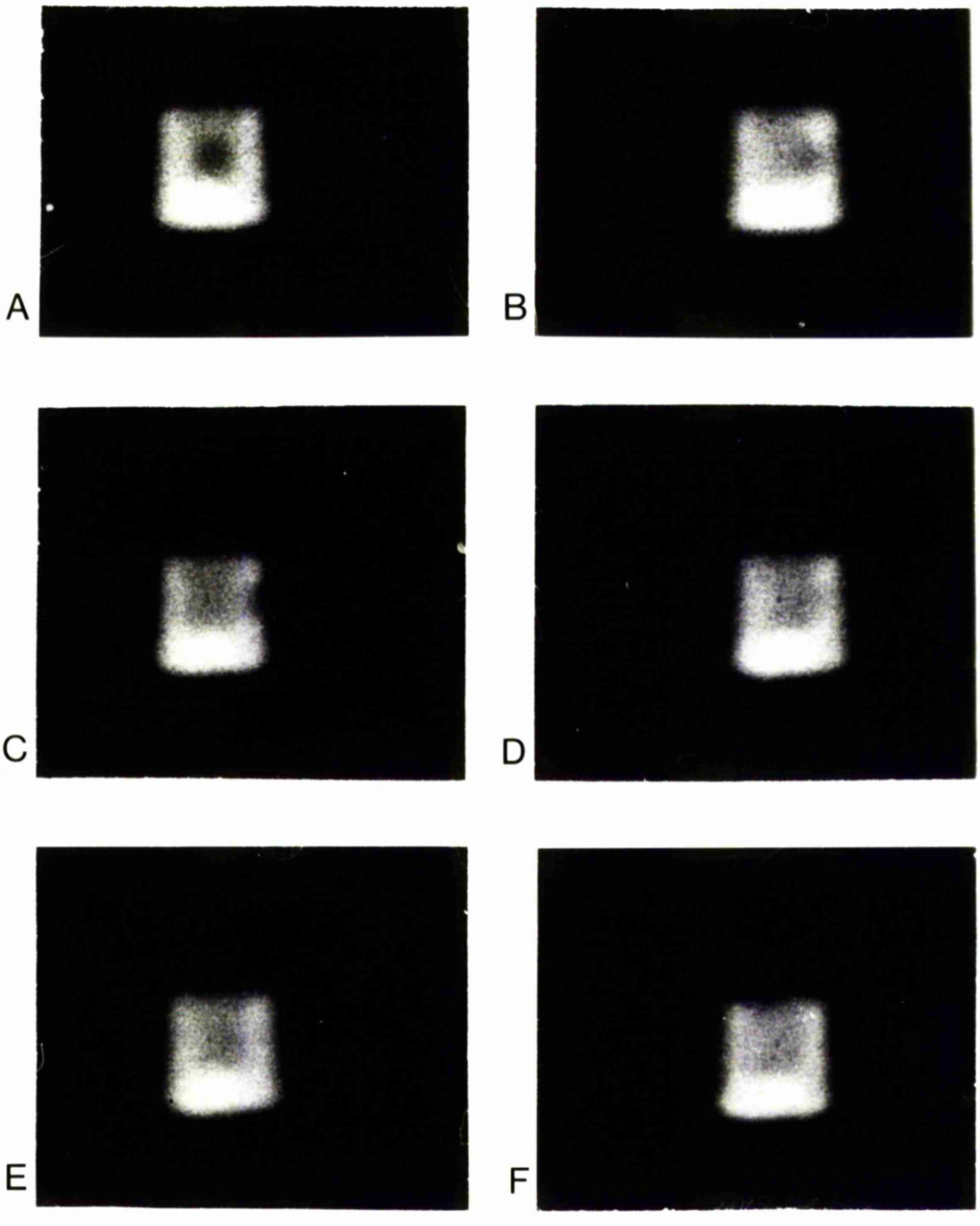
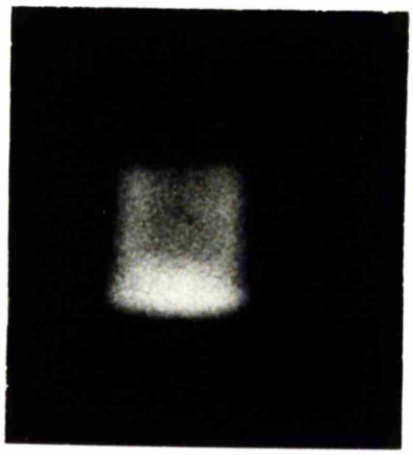
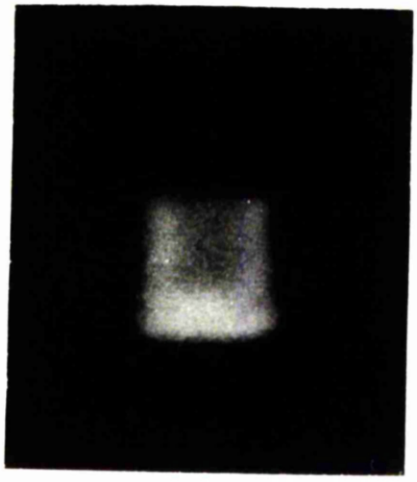

A
B
C
D
E
F

Figure 7. Heart phantom studies (2).

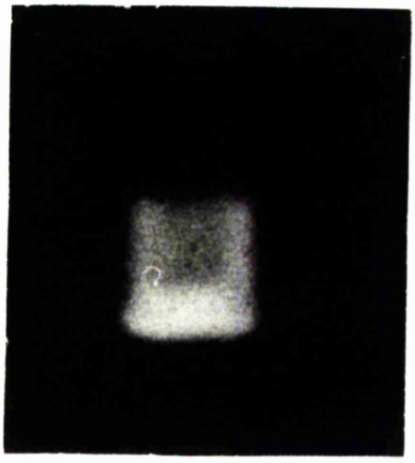
Polaroid prints of gamma camera images of heart phantom using thallium-201 and 1 cm. plasticine lesion in positions 1 to 3. The lesion is not seen in any position (Figures 7(A) to 7(C)).



A



B



C

Figure 8. Methods used for obtaining the myocardial images in the four standard projections.

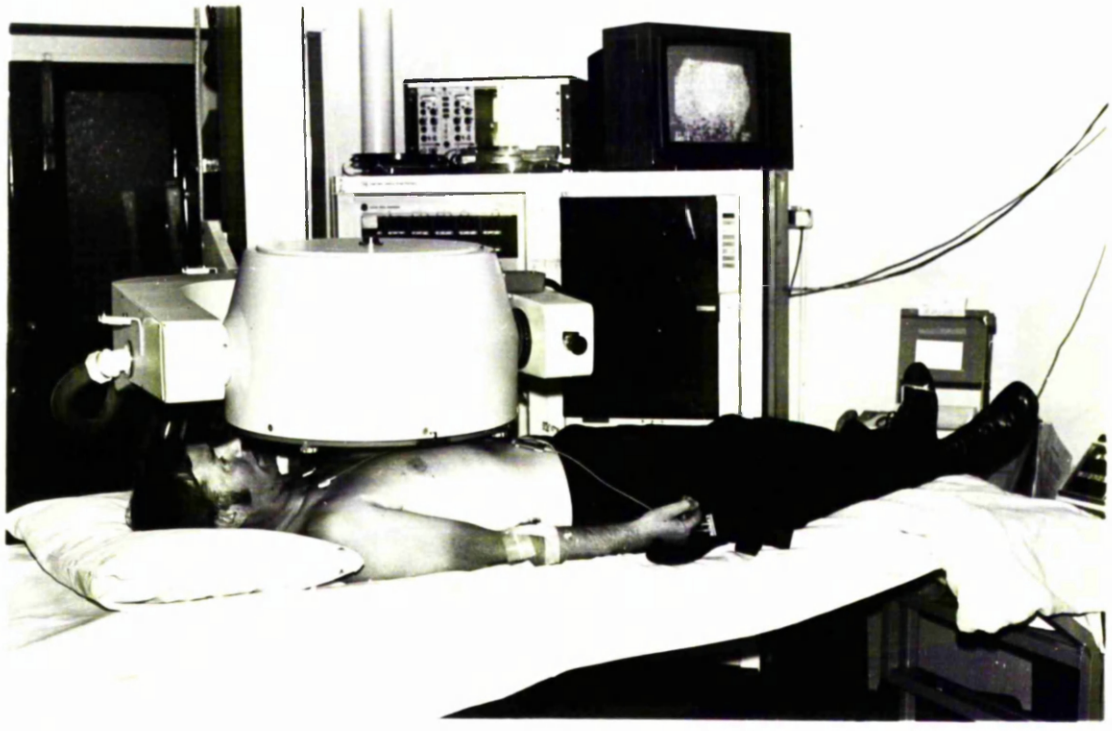
(A) Anterior projection.

(B) 30 degree left anterior oblique (30^{o} LAO) projection.

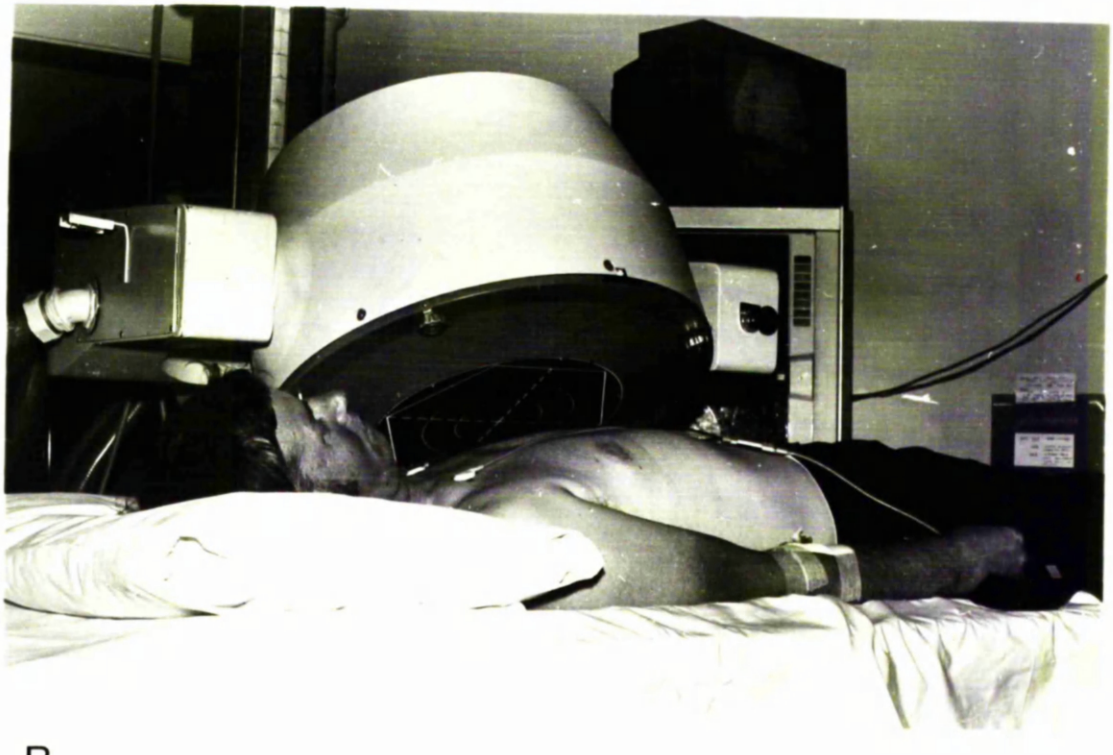
(C) 60 degree left anterior oblique (60^{o} LAO) projection.

(D) Left lateral projection.

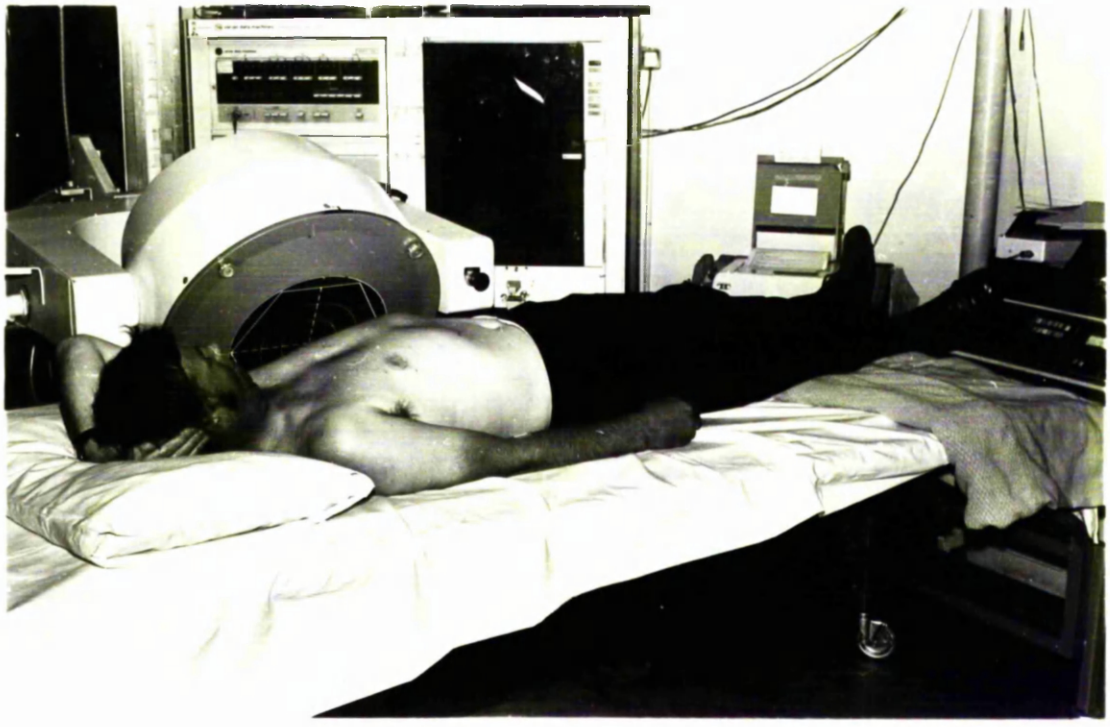
(This figure is displayed on the next two pages).



A



B



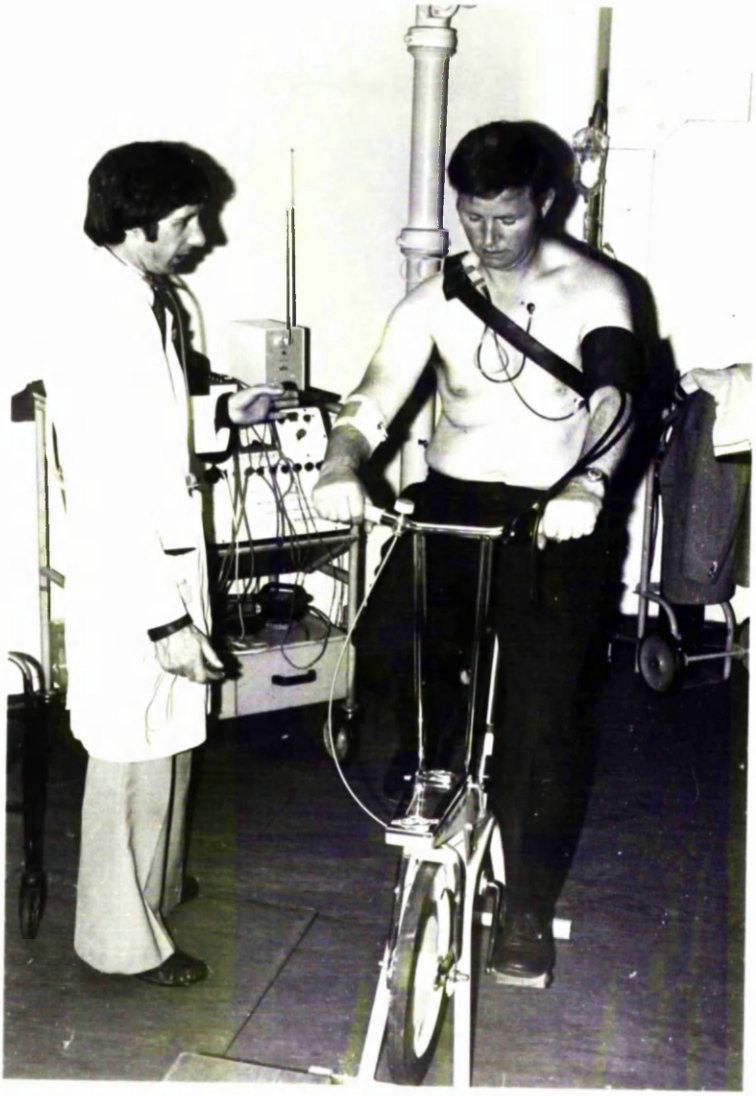
C

D

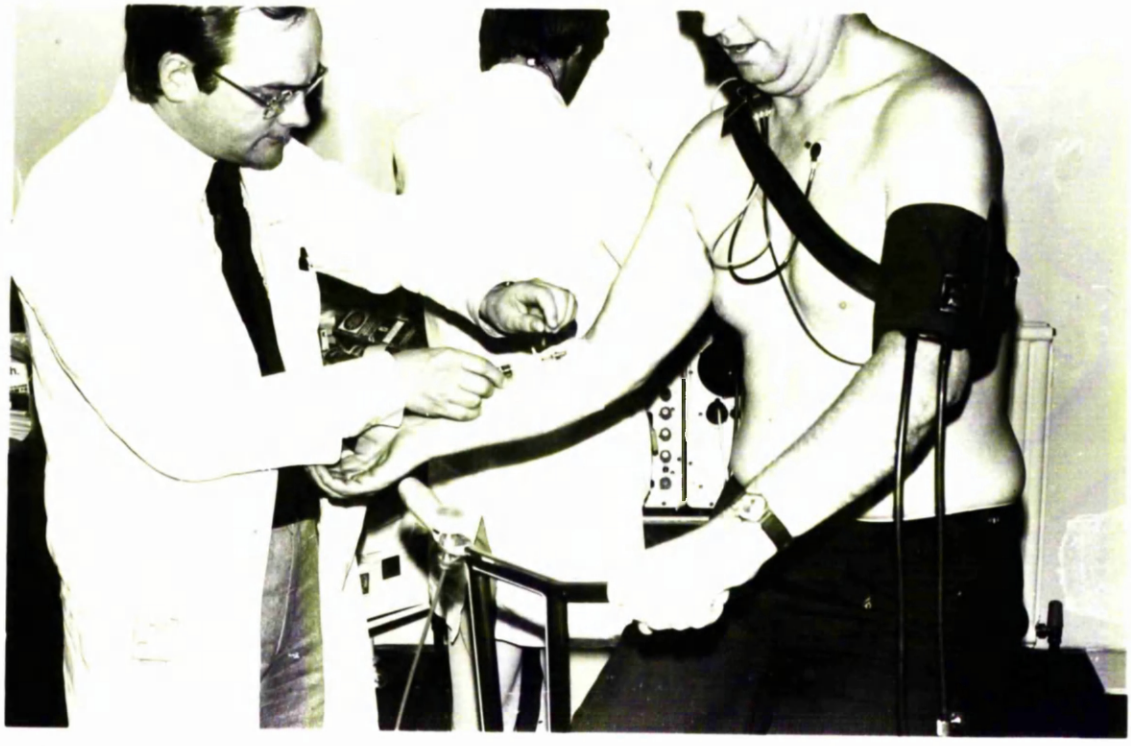
Figure 9. Performance of stress test.

(A) Patient exercising on Tunturi bicycle ergometer. The ECG is monitored by a telemetry apparatus with continuous oscilloscope display and intermittent written sampling. The blood pressure is checked at intervals using a standard sphygomanometer.

(B) Injection at exercise endpoint of 2 millicuries thallium-201 solution through previously inserted intravenous cannula.



A



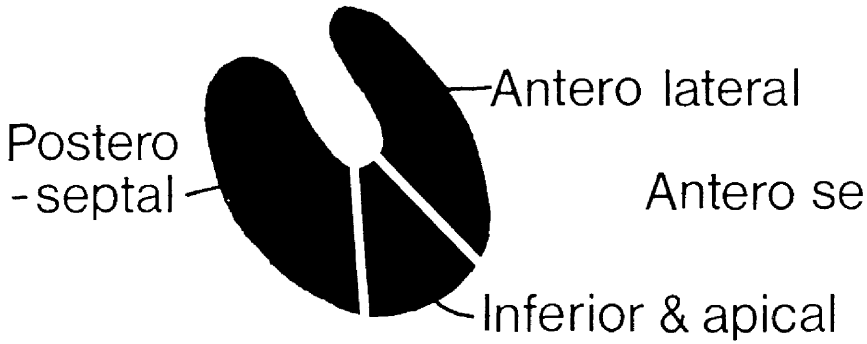
B

Figure 10. Nomenclature of myocardial areas.

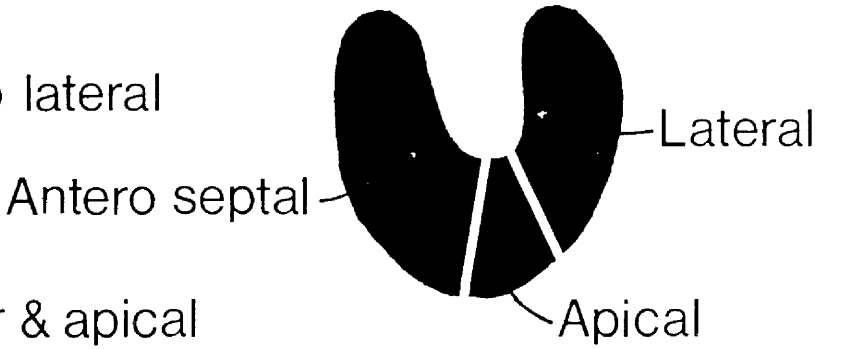
Nomenclature used for the different areas of left ventricular myocardium seen in each projection.

For ease of comparison with the figures illustrating myocardial image studies a separate loose leaf copy of this figure is enclosed in the pocket in the back inside cover of Volume II of the thesis.

(This figure is reproduced from The European Journal of Nuclear Medicine by kind permission of the editor).

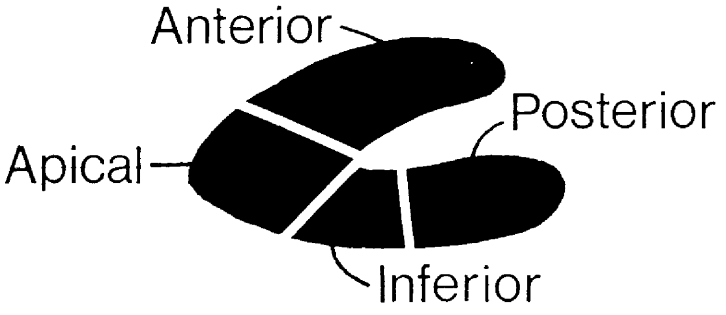


ANTERIOR



30° LAO

60° LAO



L. LATERAL

Figure 11. Computer processing of myocardial images.

This figure illustrates the different possible steps in the computer processing of colour television displayed myocardial images.

(A) Unprocessed image. In the top left hand corner the projection (60 degree left anterior oblique in this case) is displayed. At the bottom of the picture, the time taken to acquire the image, in seconds, is displayed, along with the number of counts in the whole field and the frame number. (For the purposes of photography the images were stored on a computer disc and the frame numbers are taken from the disc).

(B) The same image after nine point smoothing. All colour images shown hereafter have undergone nine point smoothing.

(C) The same image after background subtraction (of 25%) and contrast enhancement (no activity levels above 65% displayed). The degree of background subtraction and contrast enhancement are displayed at the top of the image.

(D) The same image after drawing three regions of interest for derivation of count densities.

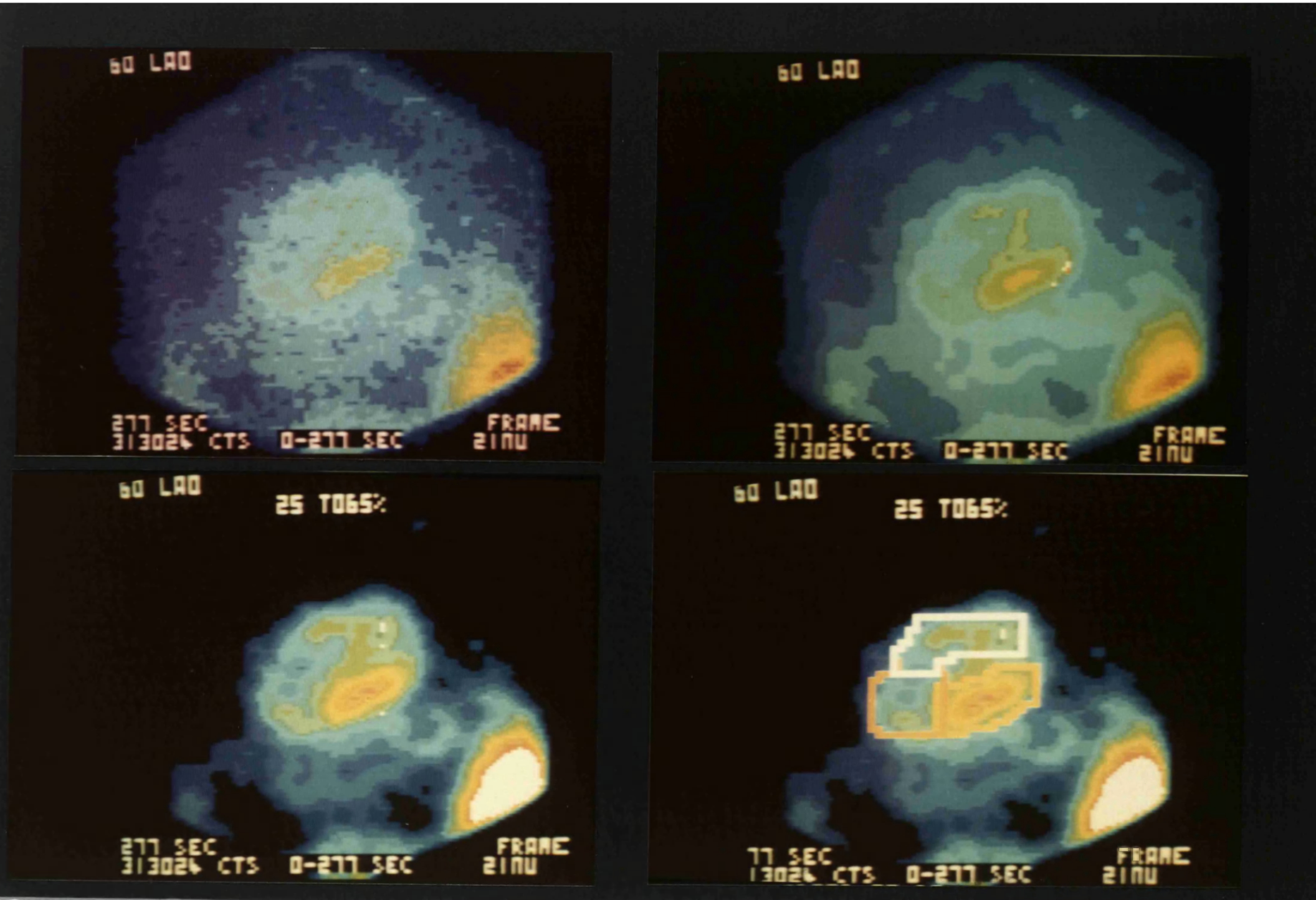

60 LAO
277 SEC
313026 CTS
0-277 SEC
FRAME
21NU
60 LAO
277 SEC
313026 CTS
0-277 SEC
FRAME
21NU
60 LAO
25 T065%
277 SEC
313026 CTS
0-277 SEC
FRAME
21NU
60 LAO
25 T065%
77 SEC
13026 CTS
0-277 SEC
FRAME
21NU

Figure 12. Normal rest myocardial images (Polaroid display).

Normal subject J. M.

Polaroid prints of myocardial images obtained after intravenous injection of 2 millicuries thallium-201 at rest.

The four projections are illustrated:

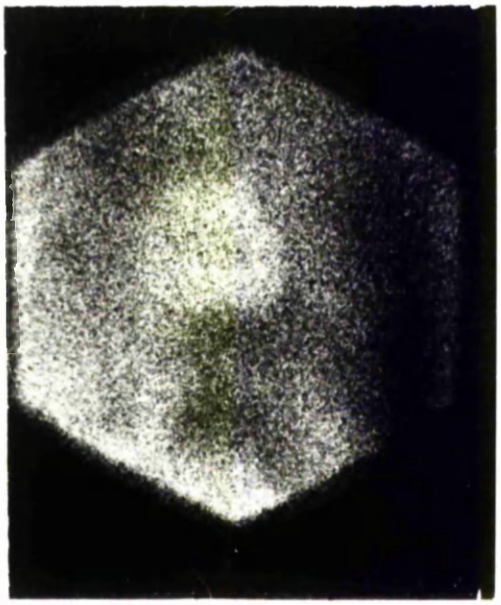
(A) Anterior

(B) 30^{O} LAO

(C) 60^{O} LAO

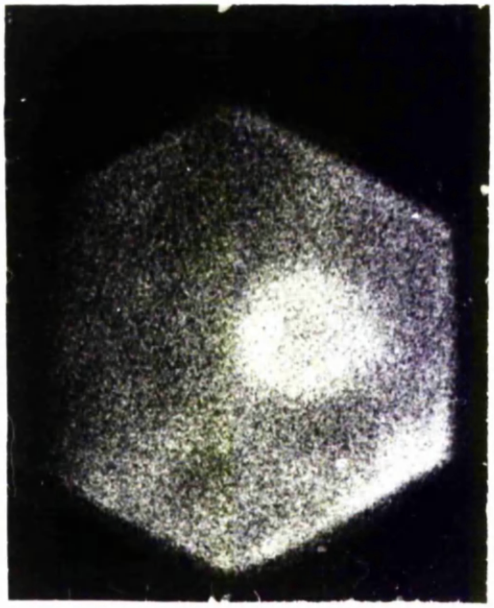
(D) Left lateral

The right ventricular myocardium is not seen and there is considerable extracardiac activity, especially in abdominal organs.

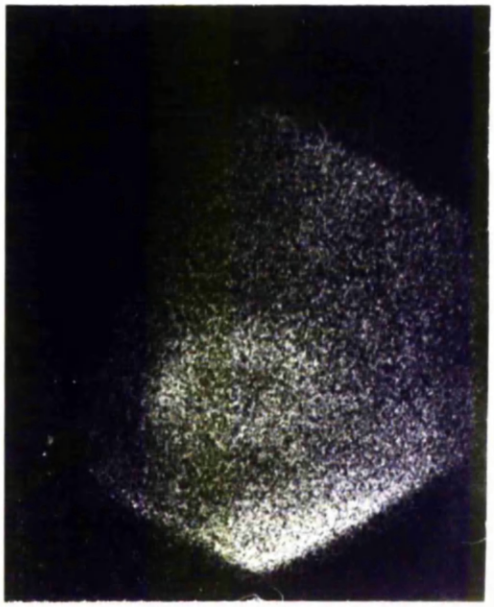


A

B



C



D

Figure 13. Normal rest myocardial images (colour television display).

Same study as illustrated in Figure 12.

(A) Anterior projection

(B) 30^{O} LAO projection

(C) 60^{O} LAO projection

(D) Left lateral projection

By background subtraction and contrast enhancement the myocardium can be made more prominent than it is on the Polaroid image. This is particularly evident in the left lateral.

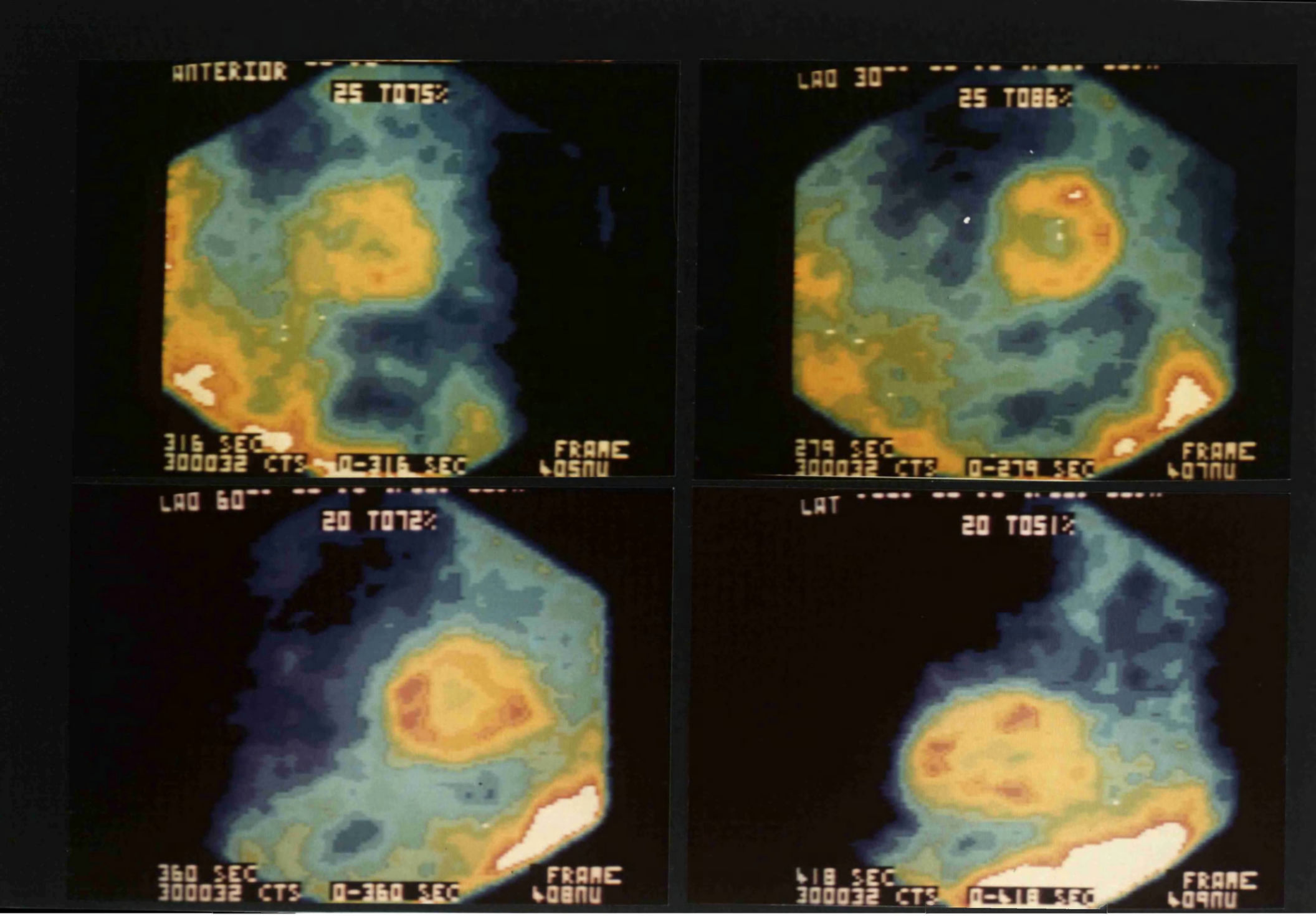

ANTERIOR
25 TO75%
316 SEC
300032 CTS
0-316 SEC
FRAME
LAO 30
25 TO86%
279 SEC
300032 CTS
0-279 SEC
FRAME
LAO 60
20 TO72%
360 SEC
300032 CTS
0-360 SEC
FRAME
LAT
20 TO51%
FRAME

Figure 14. Normal stress myocardial images (Polaroid display).

Normal subject J. T.

Polaroid prints of myocardial images obtained after intravenous injection of 2 millicuries thallium-201 at the end of a maximal exercise test.

The four projections are illustrated:

(A) Anterior

(B) 30^{O} LAO

(C) 60^{O} LAO

(D) Left lateral

The right ventricular myocardium can be visualised, especially in the 30 and 60 degree LAO images. The myocardial to background activity ratios are higher than on the rest study shown in Figure 12.

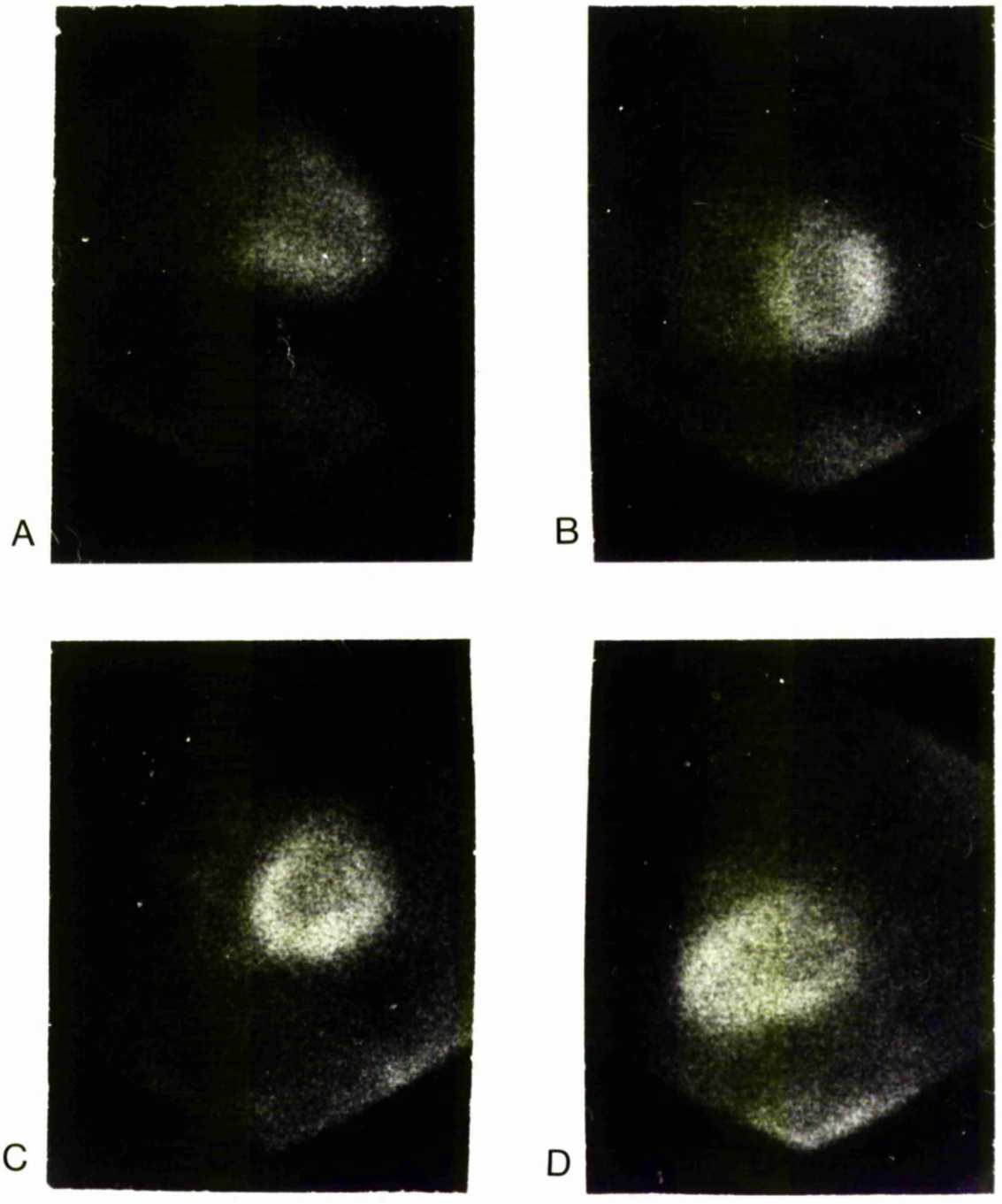

A
B
C
D

Figure 15. Normal stress myocardial images (colour television display).

Same study as illustrated in Figure 14.

(A) Anterior projection

(B) 30^{O} LAO projection

(C) 60^{O} LAO projection

(D) Left lateral projection

Because of the background subtraction the right ventricular myocardium is poorly visualised.

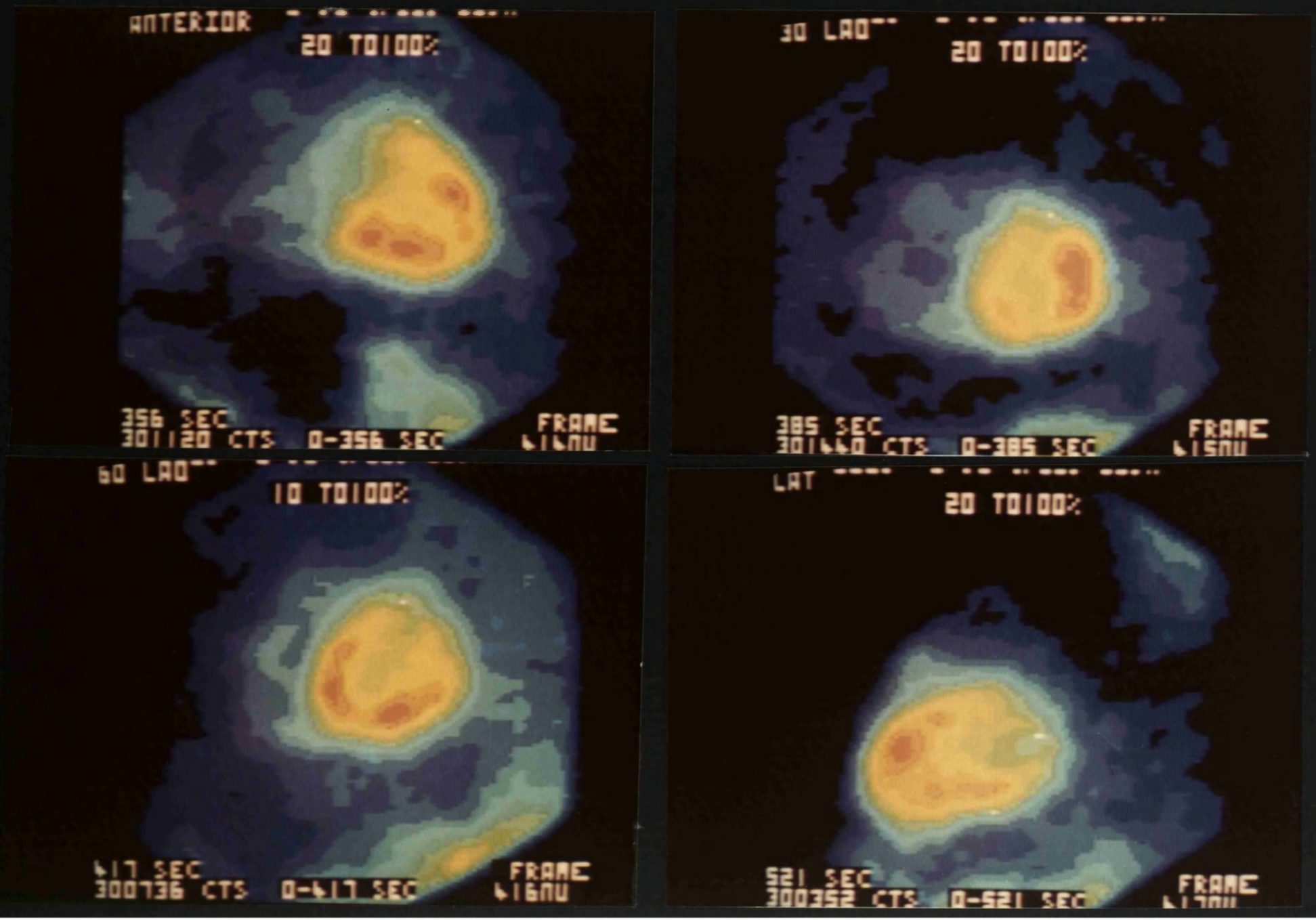

ANTERIOR
20 TO100%
356 SEC
301120 CTS
0-356 SEC
FRAME
30 LAO
20 TO100%
385 SEC
FRAME
60 LAO
10 TO100%
617 SEC
300736 CTS
0-617 SEC
FRAME
LAT
20 TO100%
521 SEC
300352 CTS
0-521 SEC
FRAME

Figure 16. Count densities in normal rest studies.

The distribution of regional myocardial densities calculated from rest studies in 14 normal subjects. Most values were in excess of 90%, but some as low as 80% were found.
(Reproduced from The European Journal of Nuclear Medicine by kind permission of the editor).

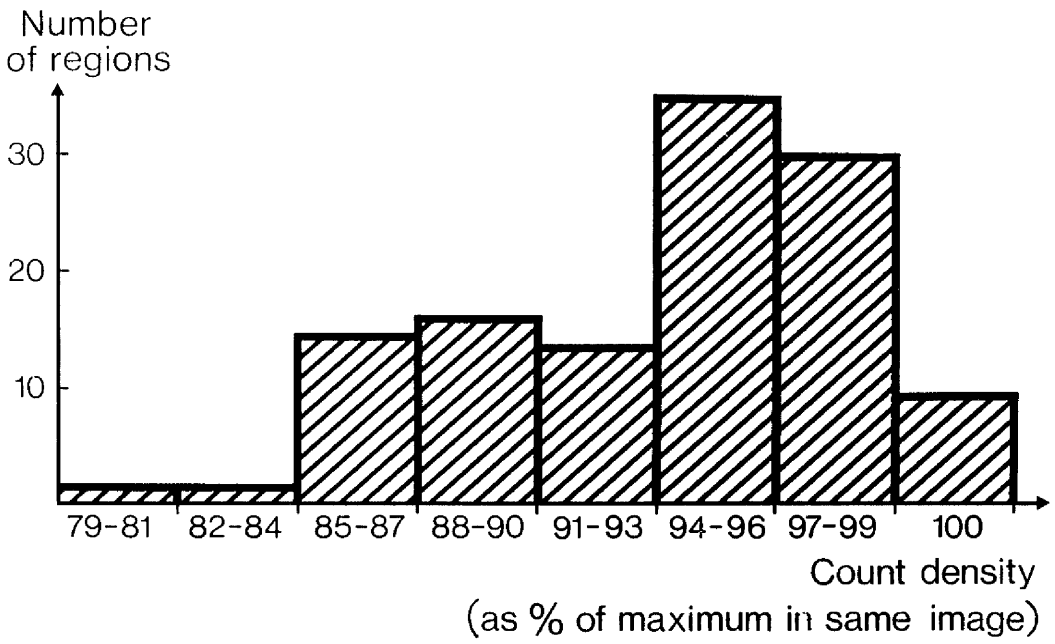

Number
of regions
30
20
10
79-81
82-84
85-87
88-90
91-93
94-96
97-99
100
Count density
(as % of maximum in same image)

Figure 17. Count densities in normal stress studies.

The distribution of regional myocardial count densities calculated from stress studies in 10 normal subjects. Most values are in excess of 90% and none below 85% were found. (Reproduced from The European Journal of Nuclear Medicine by kind permission of the editor).

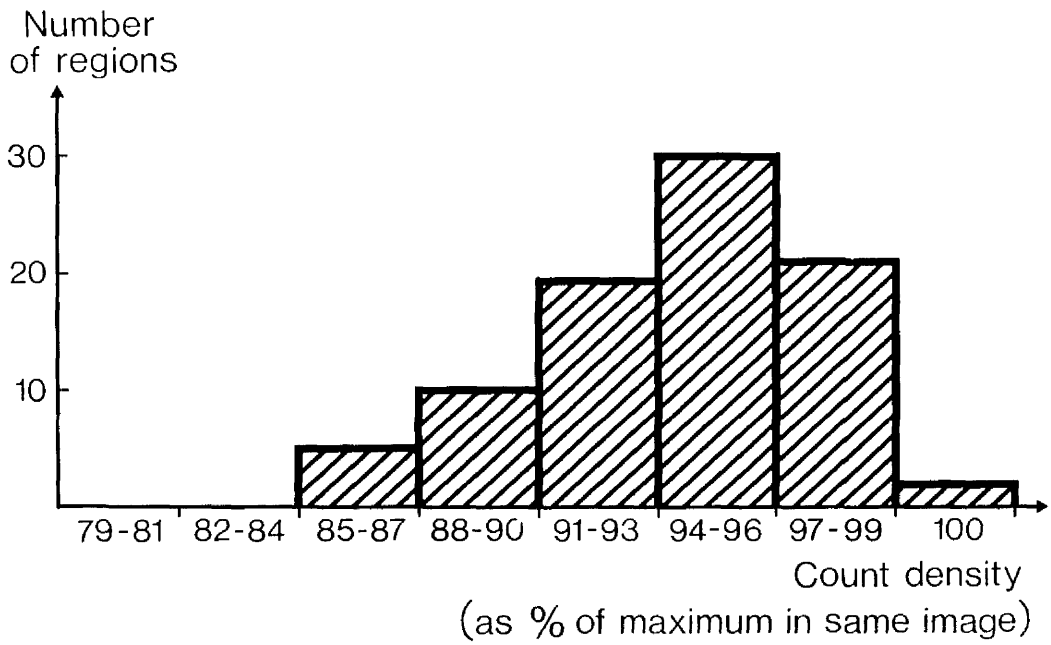

Number
of regions
30
20
10
79-81
82-84
85-87
88-90
91-93
94-96
97-99
100
Count density
(as % of maximum in same image)

Figure 18. Markedly abnormal stress myocardial images.

Patient A. H. Right and left circumflex coronary artery stenoses. Normal left anterior descending coronary artery. Normal left ventriculogram. No evidence of previous myocardial infarction.

Stress images: Chest pain during exercise test and positive stress E. C. G.

(A) Anterior projection: abnormal apical and anterolateral uptake. Posteroseptal and inferior areas normal.

(B) 30^{O} LAO projection: apical and lateral abnormality. Good anteroseptal tracer uptake.

(C) 60^{O} LAO projection: posterolateral abnormality. Good anterior and apical uptake.

(D) Left lateral projection: apical, inferior and posterior abnormalities. Good anterior uptake. Probably dilated left ventricular cavity.

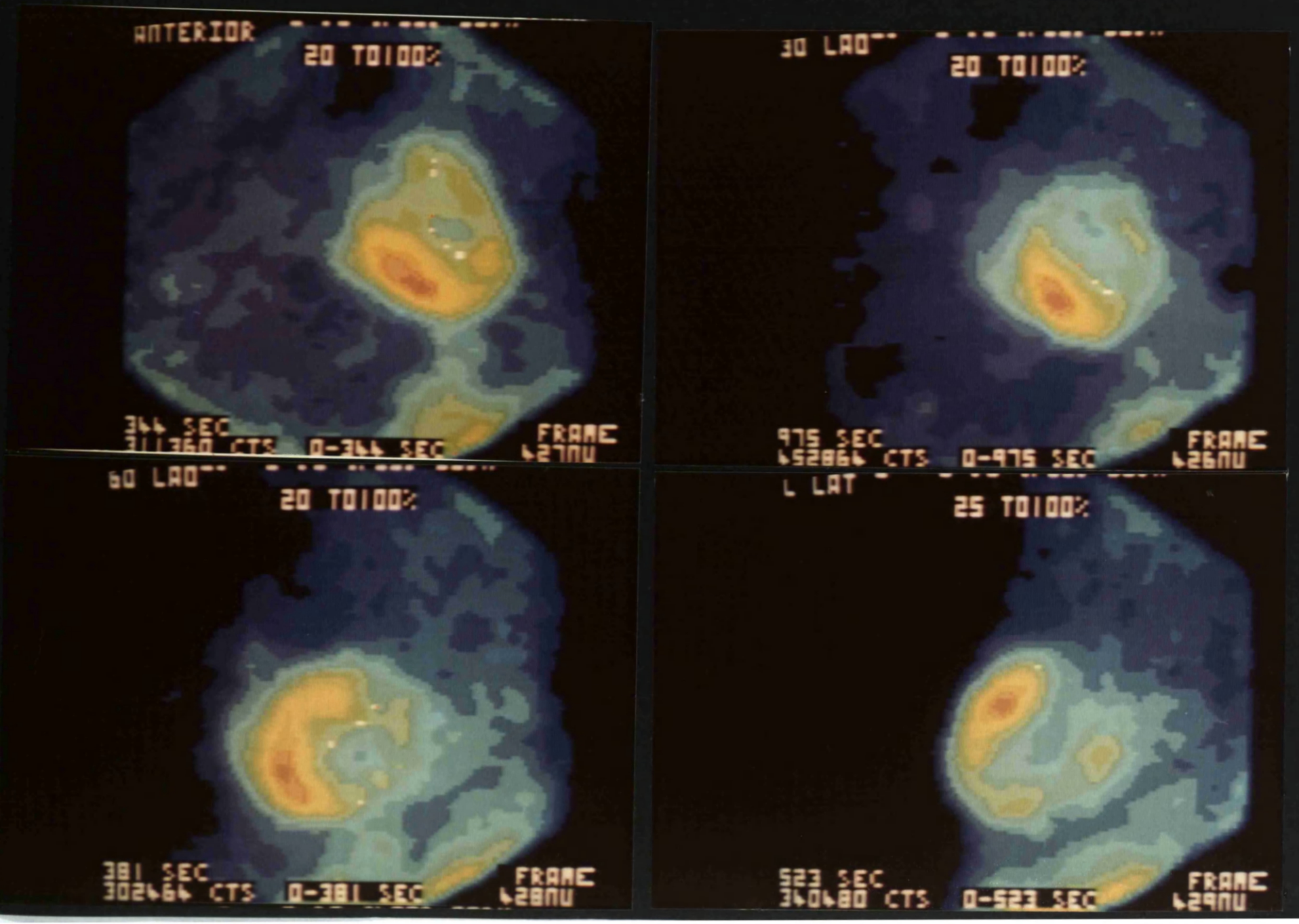

ANTERIOR
20 TO100%
344 SEC
311360 CTS
0-344 SEC
FRAME
▶27NU
30 LAO
20 TO100%
975 SEC
▶52866 CTS
0-975 SEC
FRAME
▶26NU
60 LAO
20 TO100%
381 SEC
302666 CTS
0-381 SEC
FRAME
▶28NU
L LAT
25 TO100%
523 SEC
340680 CTS
0-523 SEC
FRAME
▶29NU

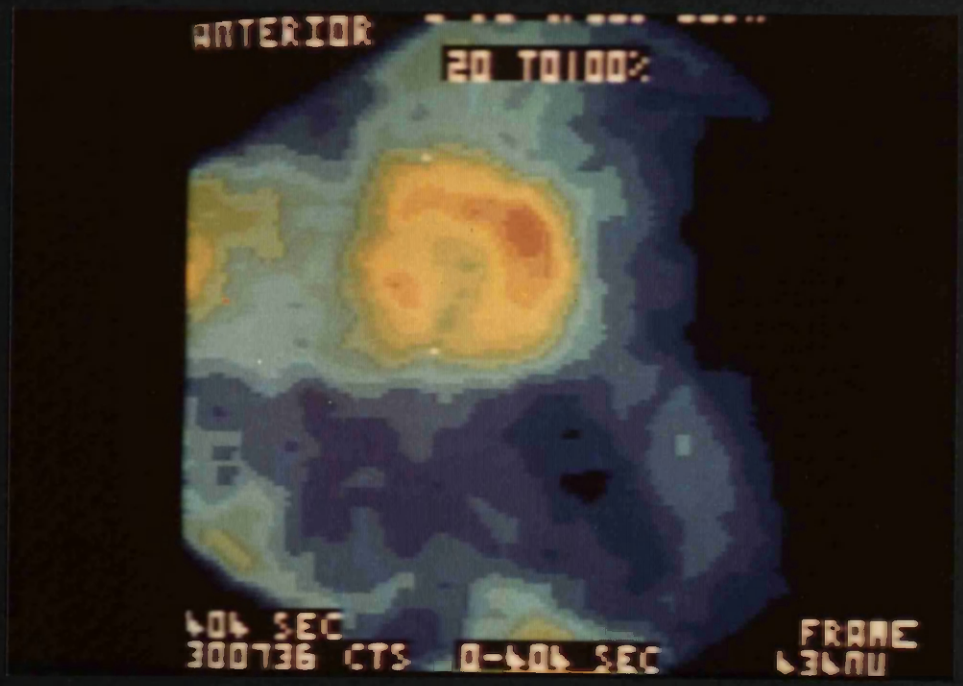
Figure 19. Subtle stress myocardial image abnormality.

Patient R. T. Isolated right coronary artery stenosis. Normal left ventriculogram. No evidence of previous myocardial infarction.

Stress images: Chest pain during exercise test. Normal stress E. C. G.

(A) Anterior projection: localised inferior defect.

(B) 30^{O} LAO projection: localised apico-inferior defect.


ANTERIOR
20 TO100%
606 SEC
300736 CTS
0-606 SEC
FRAME

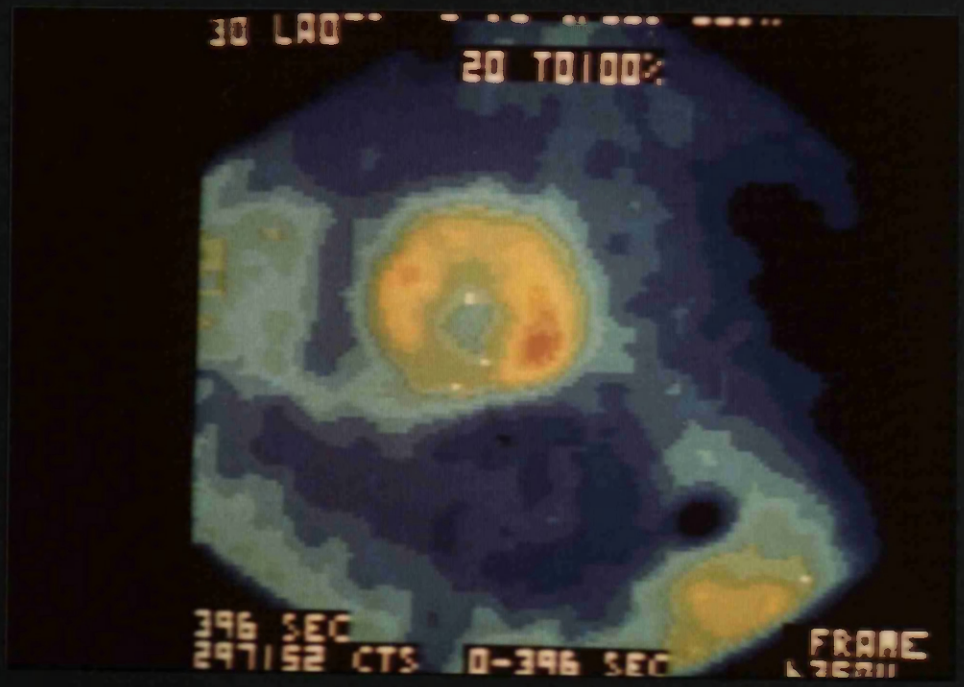

30 LAO
20 TO100%
396 SEC
297152 CTS
0-396 SEC
FRAME

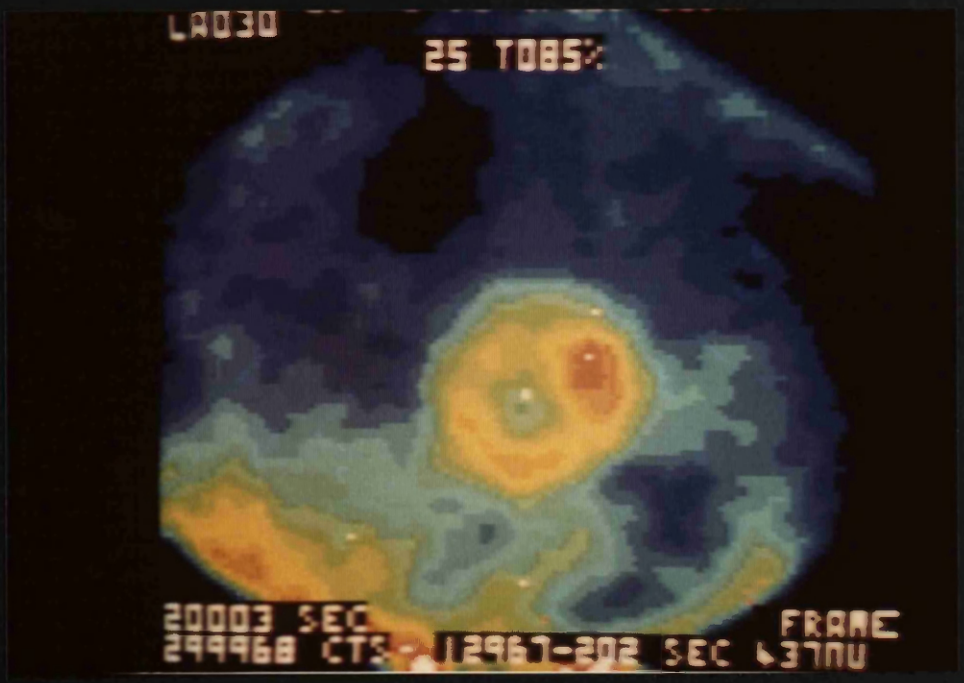
Figure 20. Subtle stress myocardial image abnormality.

Patient J. W. Triple vessel disease.
Normal left ventriculogram.
No evidence of previous myocardial infarction.

(A) 30^{O} LAO projection, rest study: normal.

(B) 30^{O} LAO projection, stress study: localised apical abnormality. The other 3 stress images were normal. During stress test patient developed chest pain and had a positive stress E. C. G.

Comment: the myocardial images grossly underestimated the extent of coronary artery disease in this patient.


LA030
25 T085%
20003 SEC
249968 CTS
FRAME

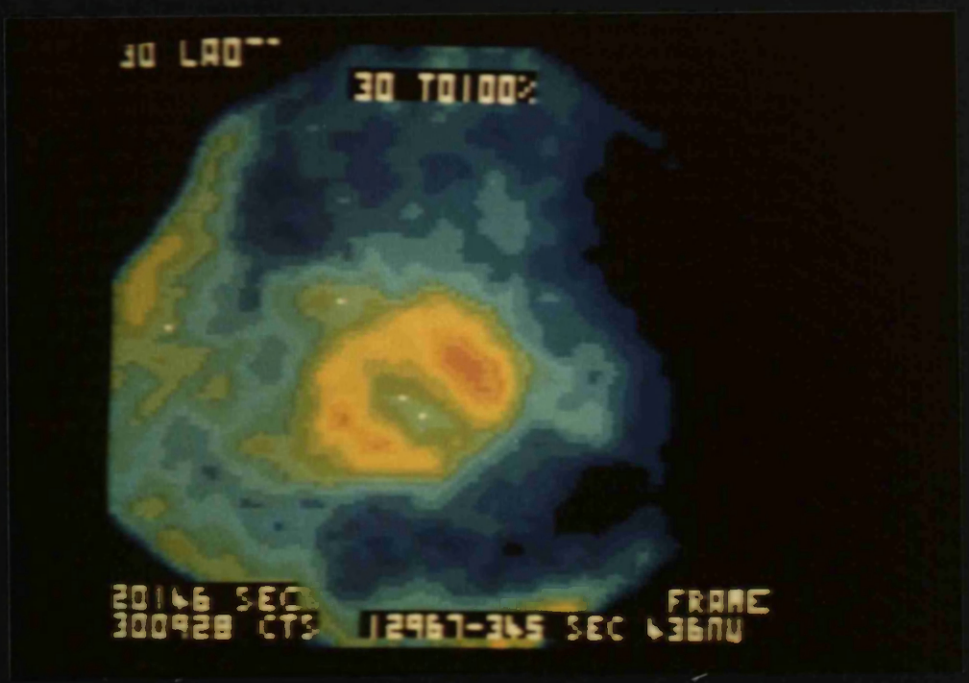

30 LA0
30 T0100%
20166 SEC
300928 CTS
FRAME

Figure 21. False normal stress myocardial images.

Patient F. C. Triple vessel disease.
Normal left ventriculogram.
No evidence of previous myocardial infarction.

Stress images: Chest pain during exercise test and positive exercise E. C. G.

(A) Anterior projection

(B) 30^{O} LAO projection

(C) 60^{O} LAO projection

(D) Left lateral projection

The myocardial images are all normal.

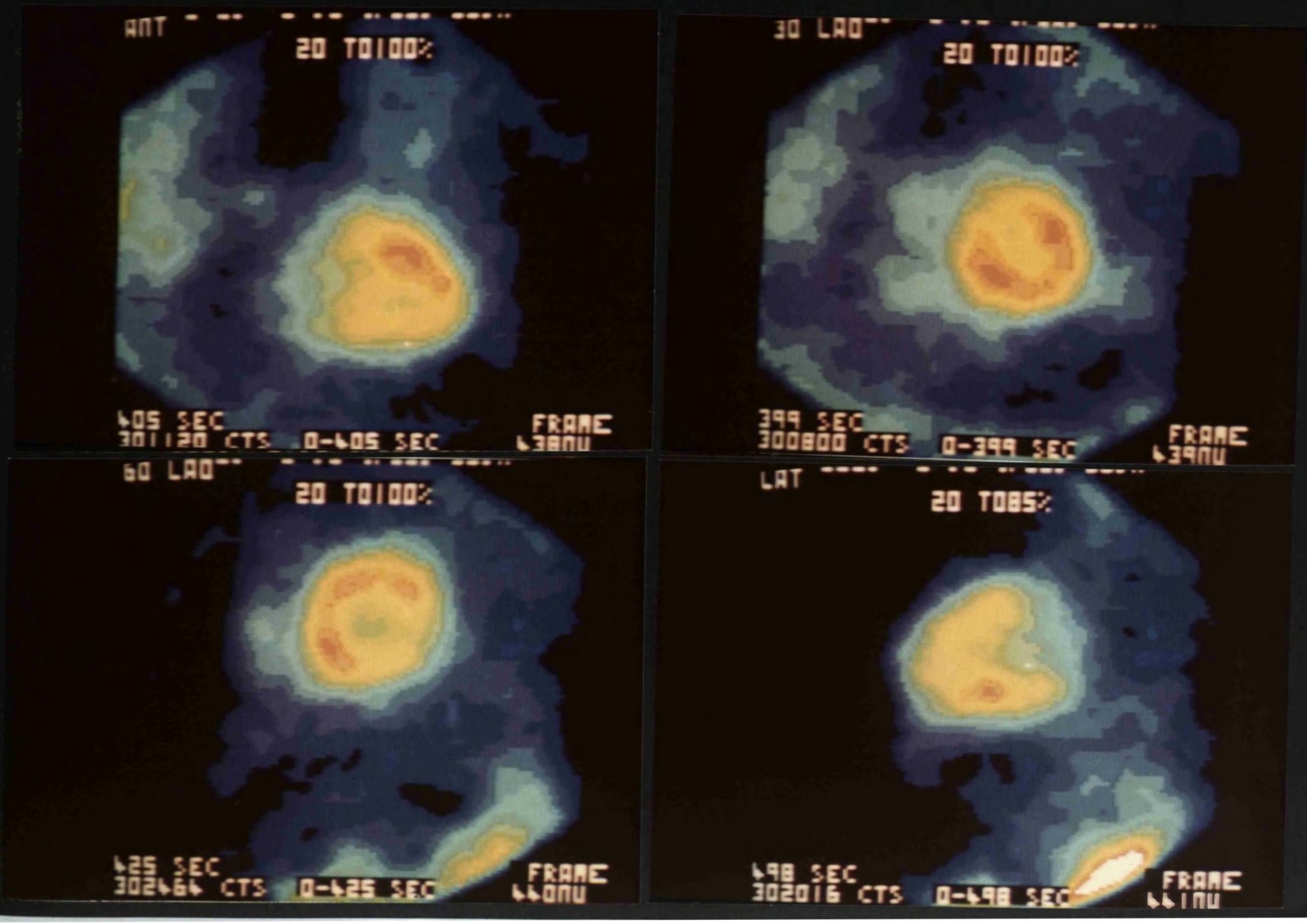

ANT
20 TO100%
605 SEC
301120 CTS
0-605 SEC
FRAME
30 LAO
20 TO100%
399 SEC
300800 CTS
0-399 SEC
FRAME
60 LAO
20 TO100%
625 SEC
302666 CTS
0-625 SEC
FRAME
LAT
20 TO85%
698 SEC
302016 CTS
0-698 SEC
FRAME

Figure 22. Comparison of rest and stress myocardial imaging.

Patient C. G. Right and left anterior descending coronary artery stenoses.
Normal left circumflex coronary artery.
Minor inferior dyskinesia on left ventriculogram.
Previous inferior myocardial infarction.

Rest images:

(A) Anterior projection: normal

(B) 30^{O} LAO projection: normal

Stress images: Chest pain and positive E. C. G. during exercise.

(C) Anterior projection: posteroseptal and apico-inferior abnormality

(D) 30^{O} LAO projection: marked anteroseptal and apical abnormality

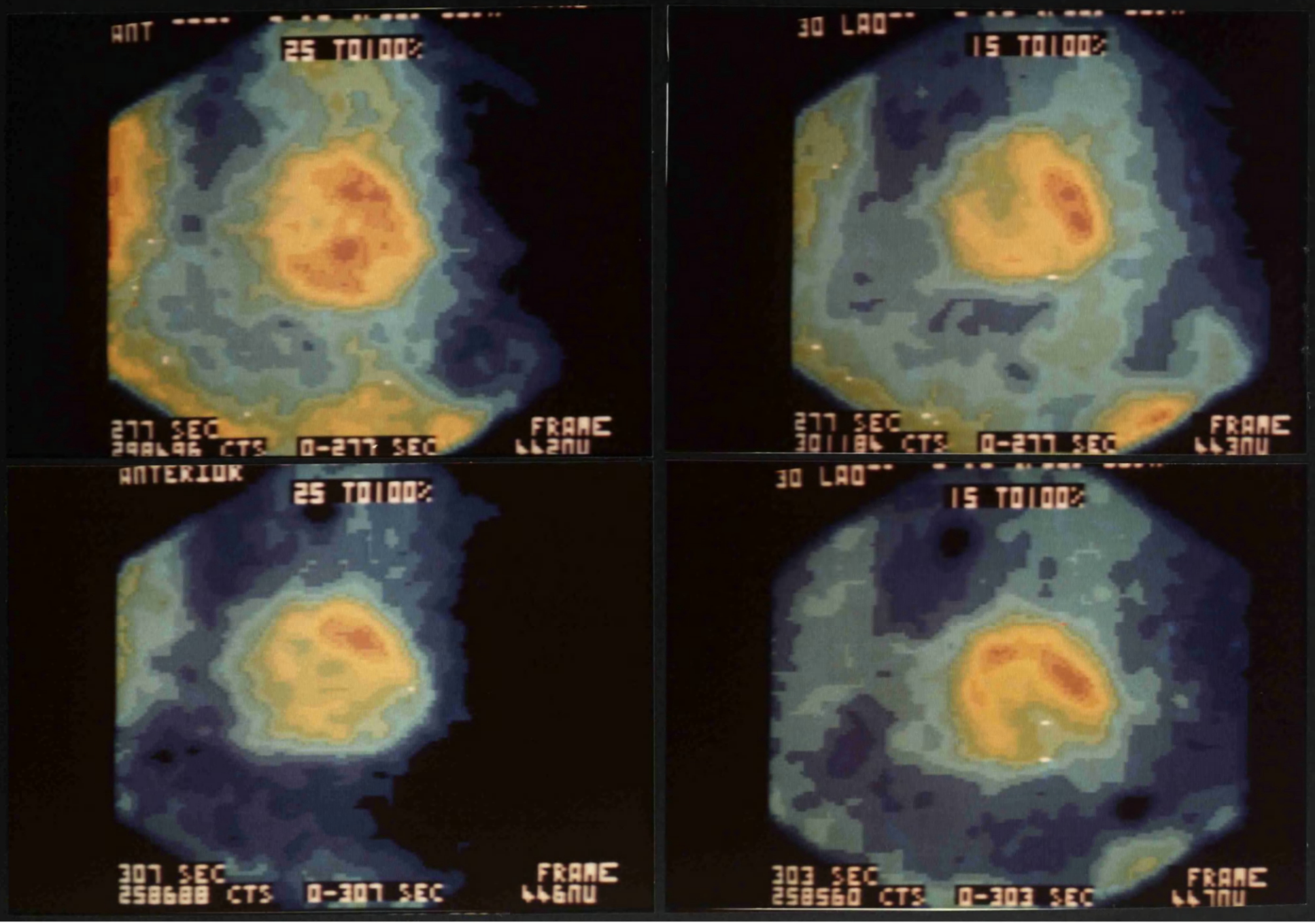
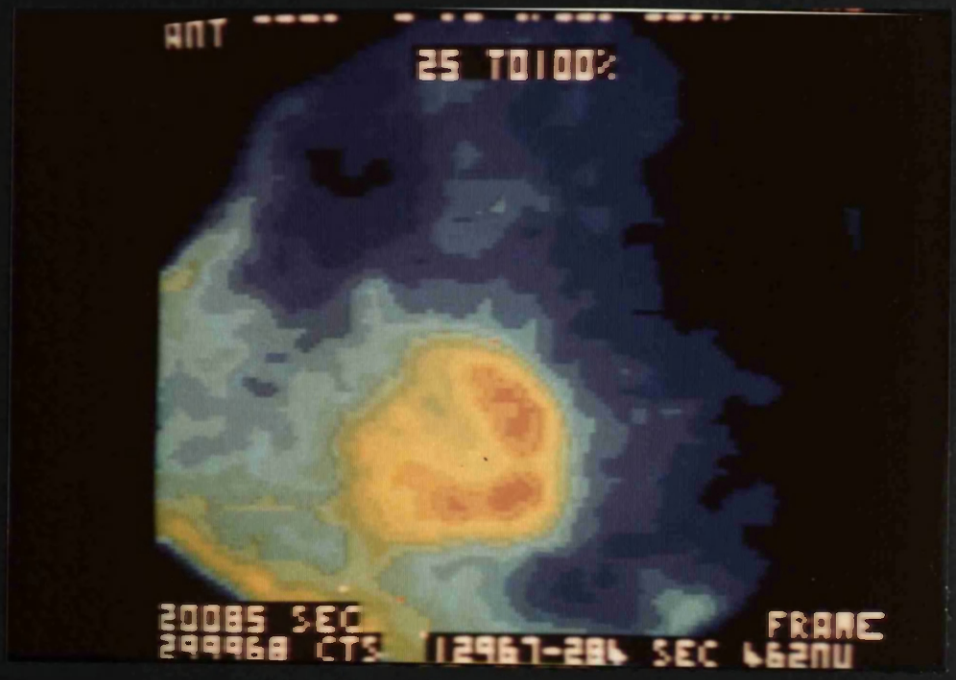

ANT
25 TO100%
277 SEC
FRAME
0-277 SEC
30 LAO
15 TO100%
277 SEC
0-277 SEC
FRAME
ANTERIOR
25 TO100%
307 SEC
258688 CTS
0-307 SEC
FRAME
30 LAO
15 TO100%
303 SEC
258560 CTS
0-303 SEC
FRAME

Figure 23. Comparison of rest and stress myocardial imaging.

Patient Jos. C. Isolated left anterior descending coronary artery stenosis.
Normal left ventriculogram.
No previous myocardial infarction.

(A) Anterior projection, rest study: normal

(B) Anterior projection, stress study: marked posteroseptal abnormality. During exercise the patient had chest pain and a positive stress E. C. G.


ANT
25 TO100%
20085 SEC
299968 CTS
12967-284 SEC
FRAME

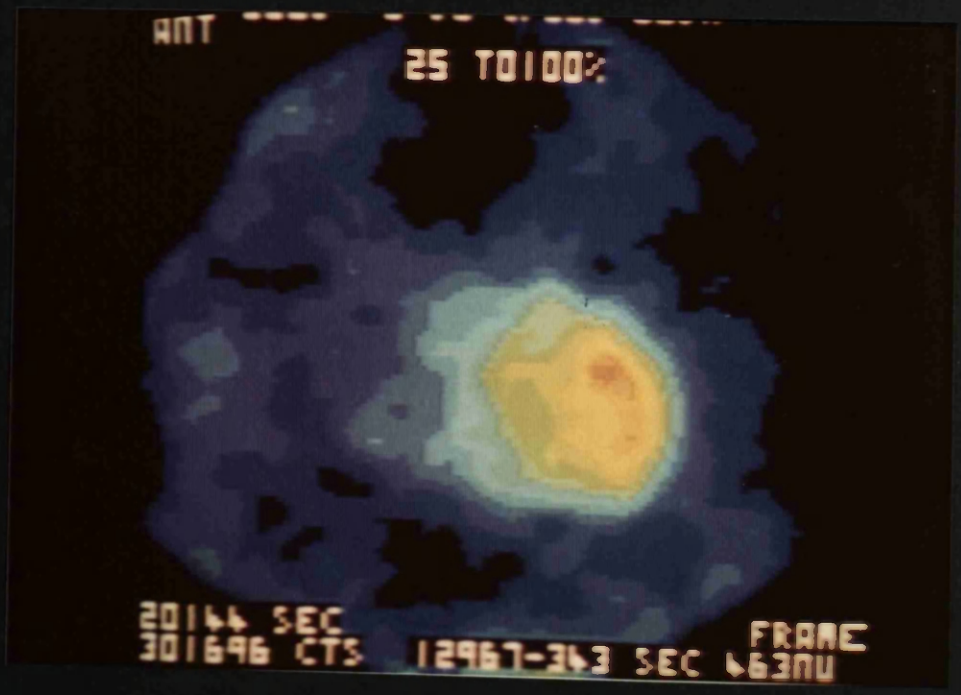

ANT
25 TO100%
20144 SEC
301696 CTS
12967-343 SEC
FRAME

Figure 24. Extension of rest image abnormality during stress.

Patient Jas. C. (1)

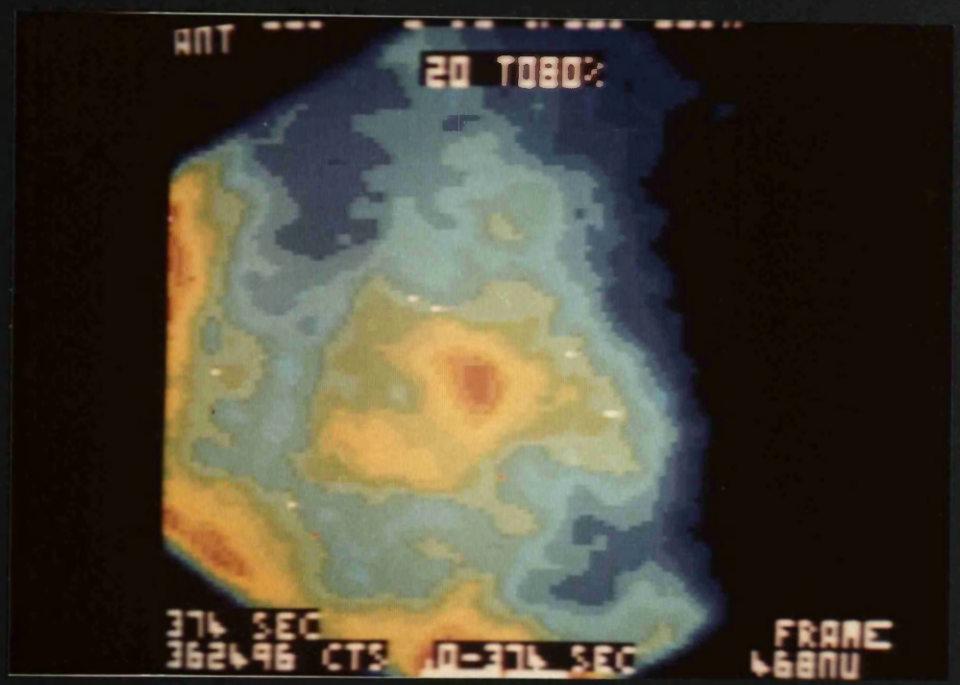
Triple vessel disease.

Septal akinesia at left ventriculography.

No known previous infarction.

(A) Anterior projection, rest study: decreased uptake in upper part of posteroseptal area.

(B) Anterior projection, stress study: markedly abnormal posteroseptally and apico-inferiorly. Patient had chest pain during exercise but E. C. G. was normal at rest and during exercise.


ANT
20 TO80%
376 SEC
362696 CTS
0-376 SEC
FRAME
668NU

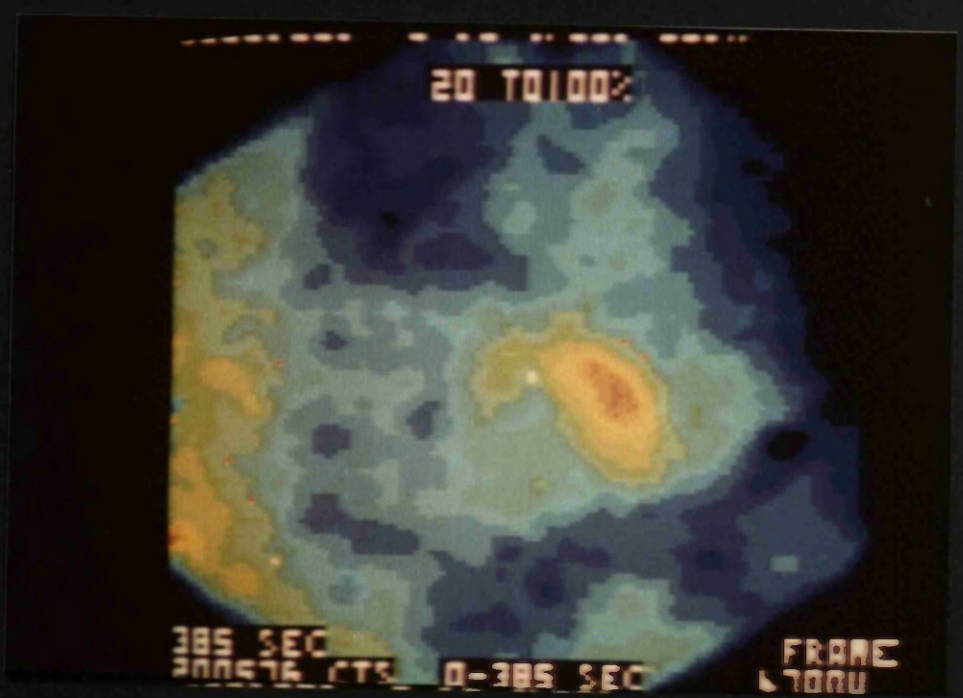

20 TO100%
385 SEC
0-385 SEC
FRAME
670NU

Figure 25. Normal stress myocardial images in patient with chest pain and normal coronary arteriogram.

Patient P. McA. Chest pain, possibly anginal. Equivocal stress E. C. G.
Normal coronary arteriogram and left ventriculogram.

Stress images: No chest pain during exercise.

(A) Anterior projection

(B) 30^{O} LAO projection

(C) 60^{O} LAO projection

(D) Left lateral projection

Normal myocardial images. The right ventricle is well seen on the 30^{O} LAO image.

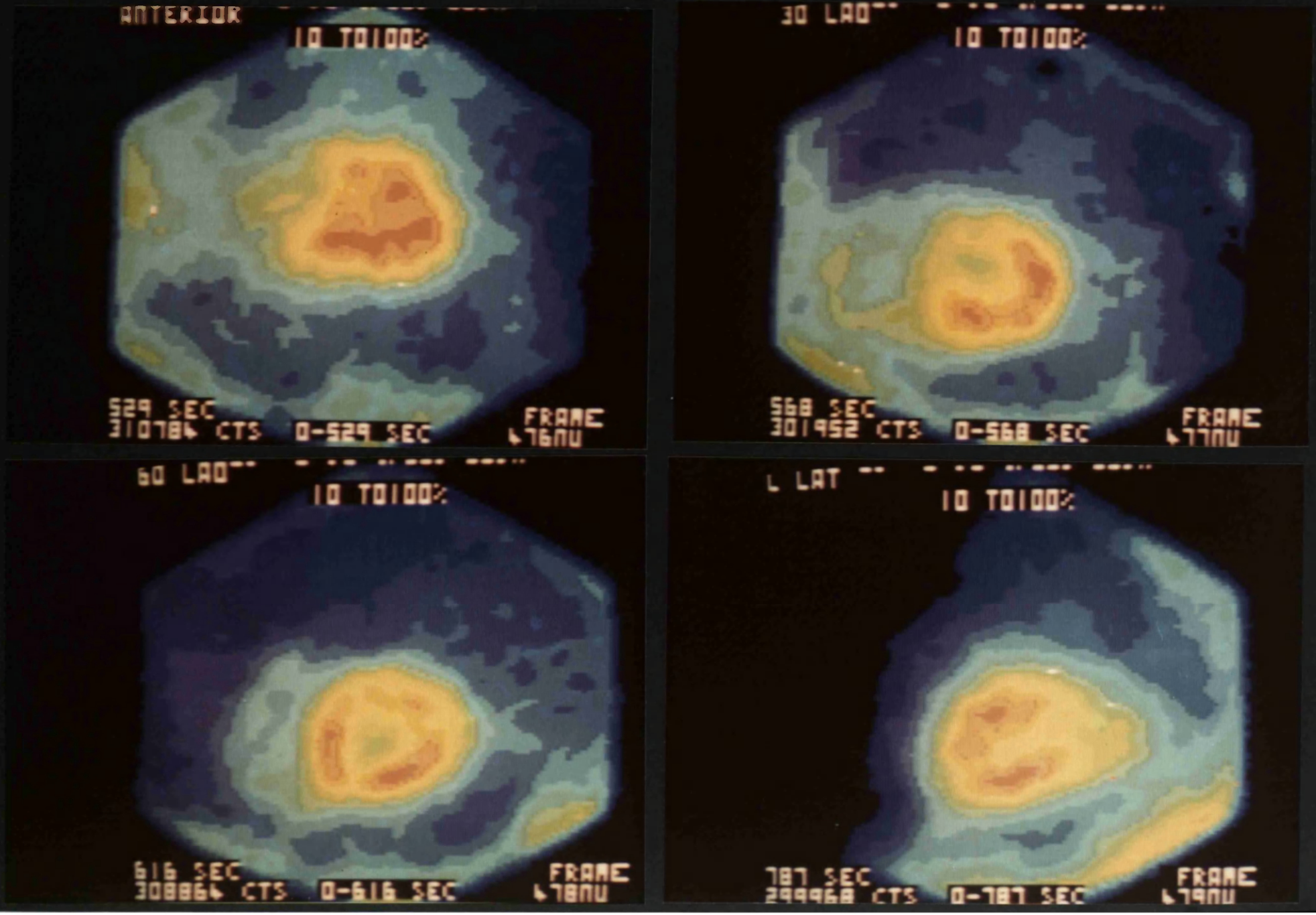

ANTERIOR
10 TO100%
529 SEC
310786 CTS
0-529 SEC
FRAME
76NU
30 LAO
10 TO100%
568 SEC
301952 CTS
0-568 SEC
FRAME
77NU
60 LAO
10 TO100%
616 SEC
308866 CTS
0-616 SEC
FRAME
78NU
L LAT
10 TO100%
787 SEC
299468 CTS
0-787 SEC
FRAME
79NU

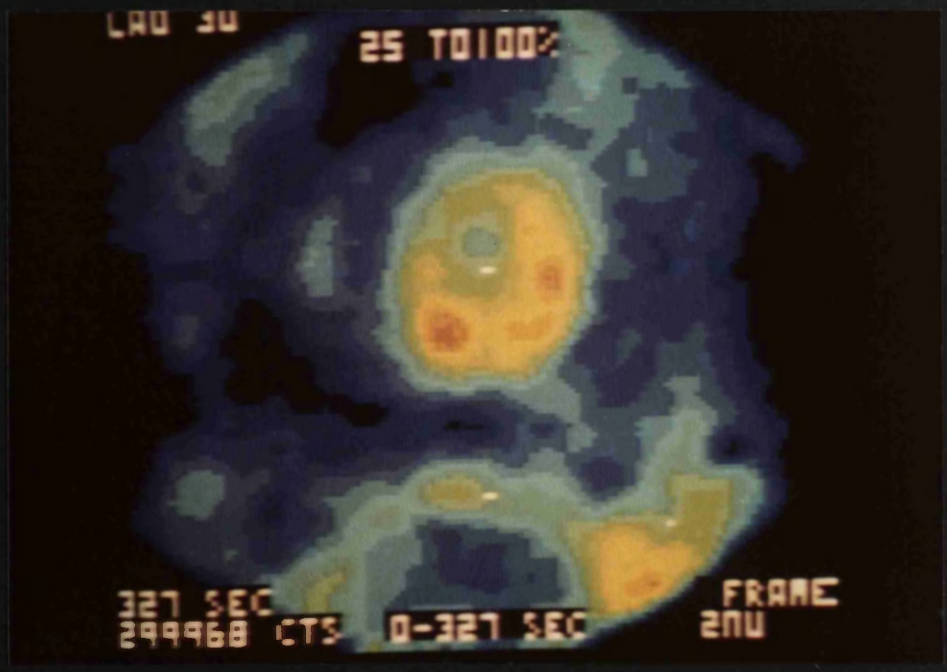
Figure 26. Abnormal stress myocardial images in patients with chest pain and normal coronary arteriogram.

Patient M. B. Classical anginal pain. Positive exercise E. C. G. Normal coronary arteriogram and left ventriculogram.

Stress images: Chest pain during exercise.

(A) 30^{O} LAO projection: anteroseptal abnormality

(B) 60^{O} LAO projection: anterior abnormality


25 TO100%
327 SEC
299968 CTS
0-327 SEC
FRAME
2NU

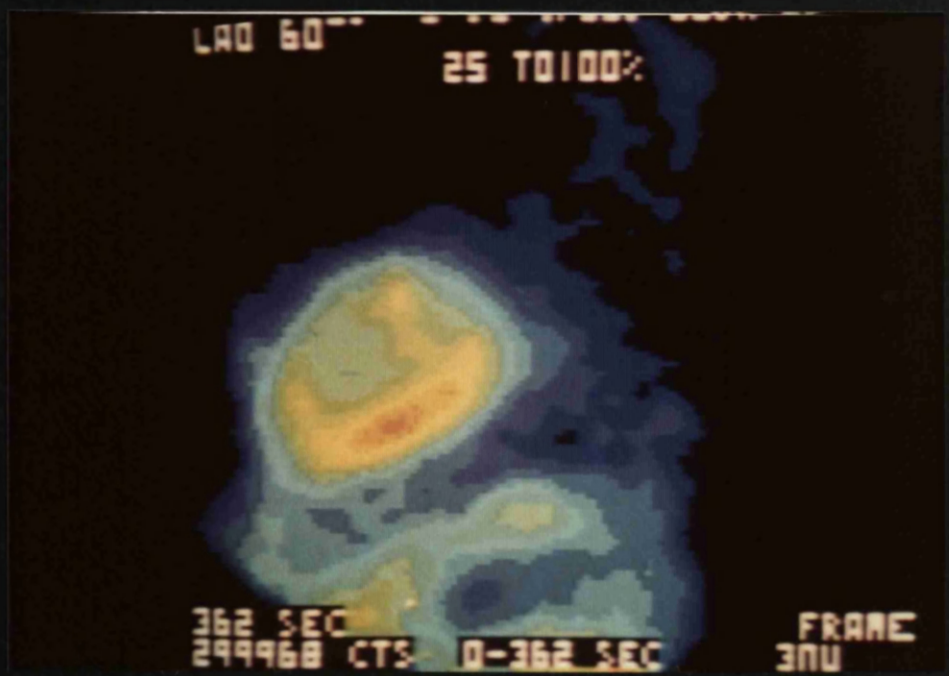

25 TO100%
362 SEC
299968 CTS
0-362 SEC
FRAME
3NU

Figure 27. Abnormal rest image in patient with chest pain and normal coronary arteriogram.

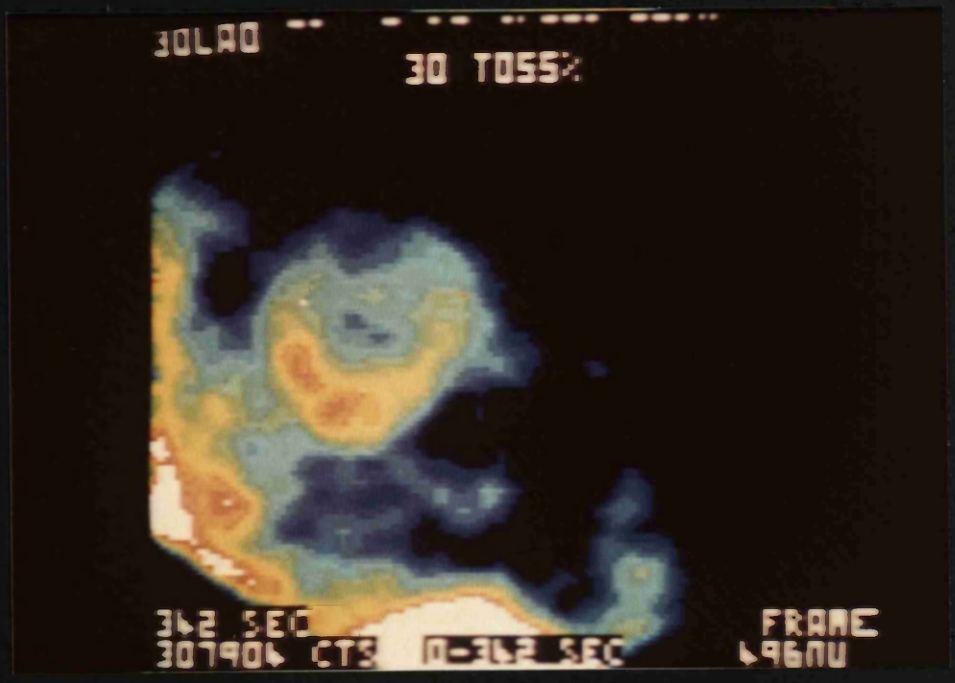
Patient J. G. Admitted with acute chest pain - no evidence of acute myocardial infarction on investigation.

(A) 30^{O} LAO projection, rest image, obtained at that time: dilated myocardial cavity. Abnormal lateral uptake.

Readmitted 6 weeks later - pain free. Coronary arteriogram and left ventriculogram normal.

(B) 30^{O} LAO projection, stress image, obtained then: normal image.

Final diagnosis: probable myocarditis.


30LAD
30 T055%
362 SEC
307906 CTS
0-362 SEC
FRAME
1960U

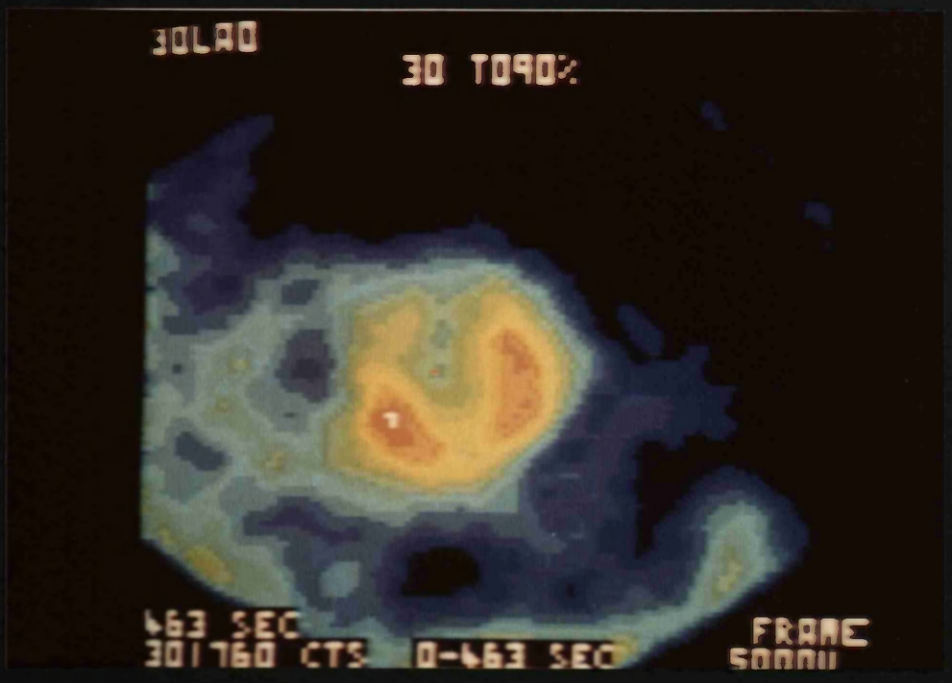

30LAD
30 T090%
663 SEC
301760 CTS
0-663 SEC
FRAME
5000U

Figure 28. Stress myocardial images in patient with right coronary artery disease.

Patient H. S. Isolated right coronary artery lesion.
Normal left ventriculogram.
No evidence of previous infarction.

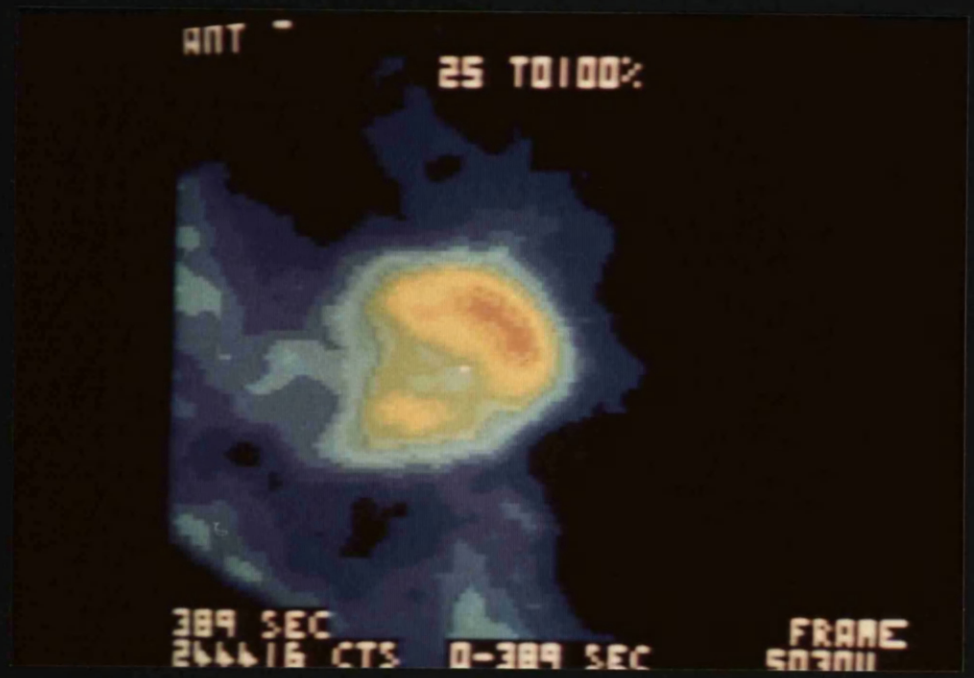
Stress images: Chest pain during exercise. Normal stress E. C. G.

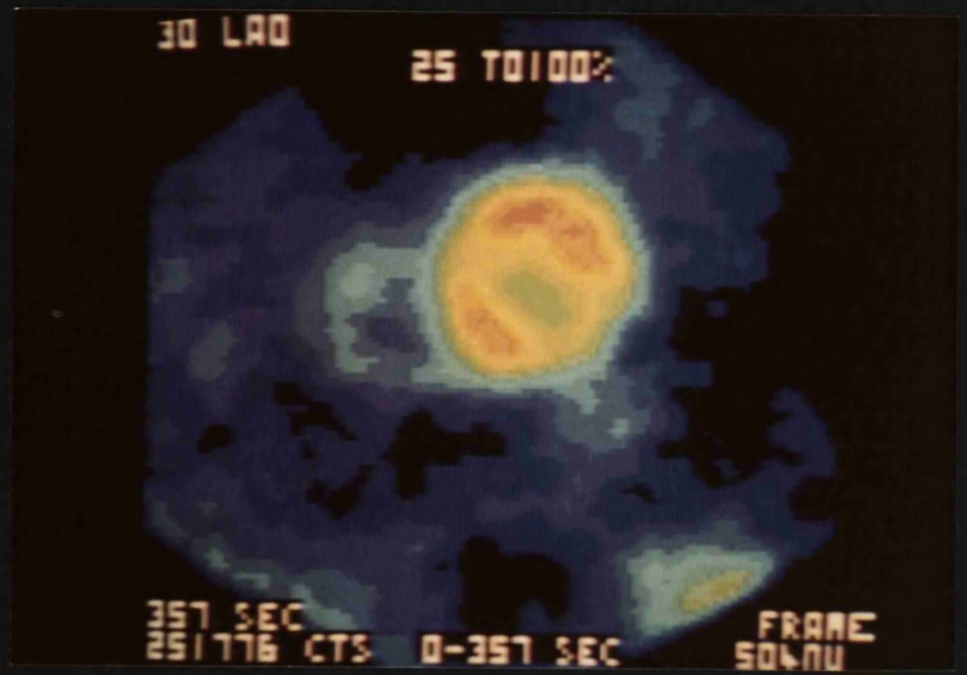
(A) Anterior projection: posteroseptal and infero-apical abnormality.

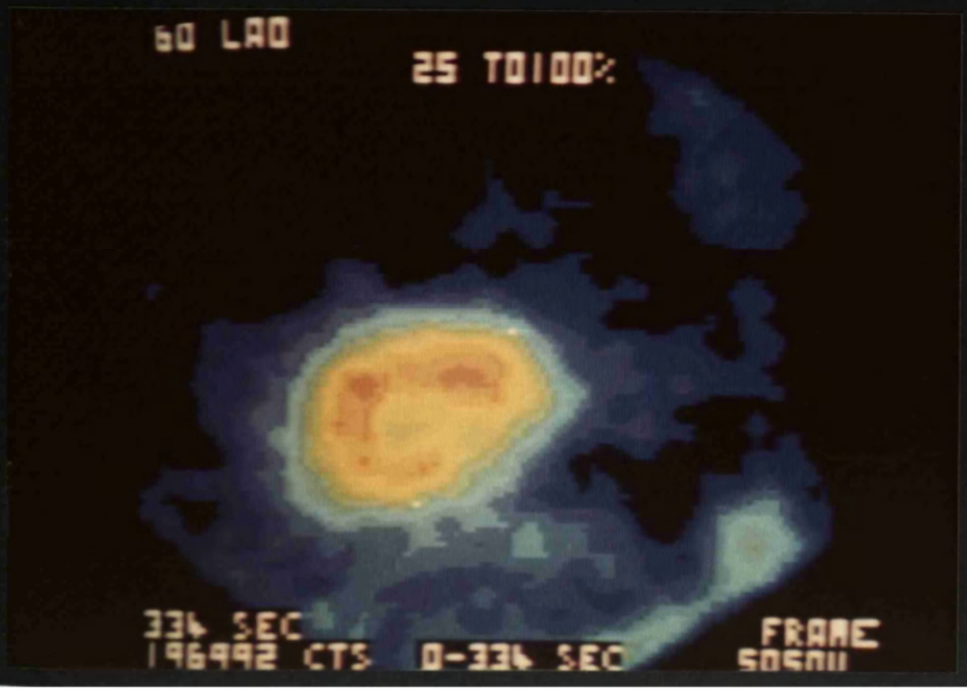
(B) 30^{O} LAO projection: minor infero-apical abnormality (much less marked than that in Figure 19(B)).

(C) 60^{O} LAO projection: normal image.

(D) Left lateral projection: infero-posterior abnormality.


ANT -
25 TO100%
389 SEC
266616 CTS
0-389 SEC
FRAME


30 LAO
25 TO100%
357 SEC
251776 CTS
0-357 SEC
FRAME


60 LAO
25 TO100%
336 SEC
196992 CTS
0-336 SEC
FRAME

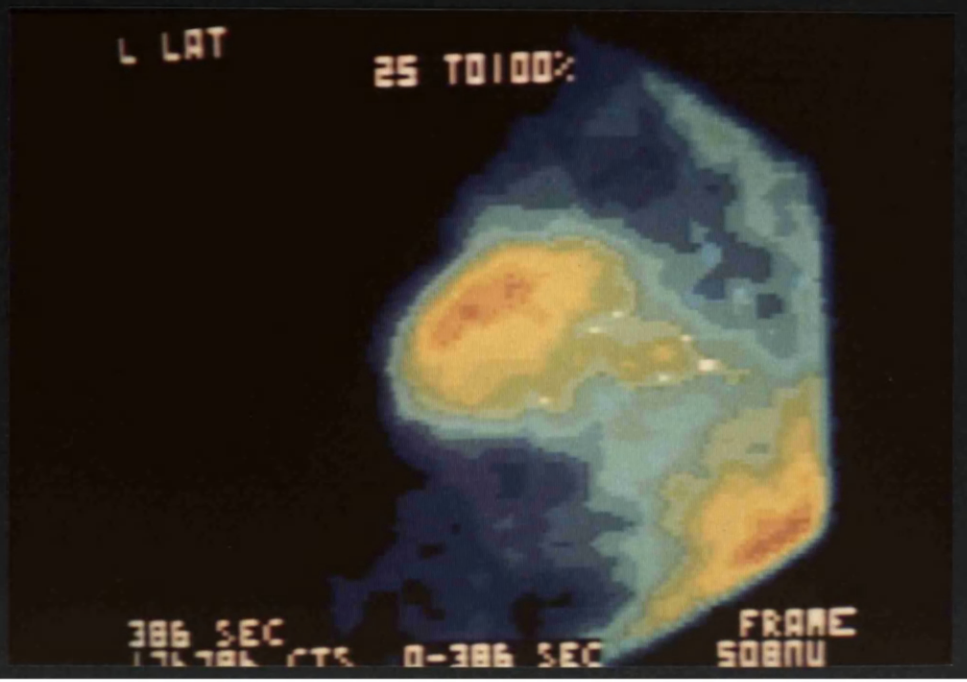

L LAT
25 TO100%
386 SEC
0-386 SEC
FRAME

Figure 29. Stress myocardial images in patient with left anterior descending coronary artery disease.

Patient Jas. C. (2)

Isolated left anterior descending coronary artery disease.

Normal left ventriculogram.

No evidence of previous myocardial infarction.

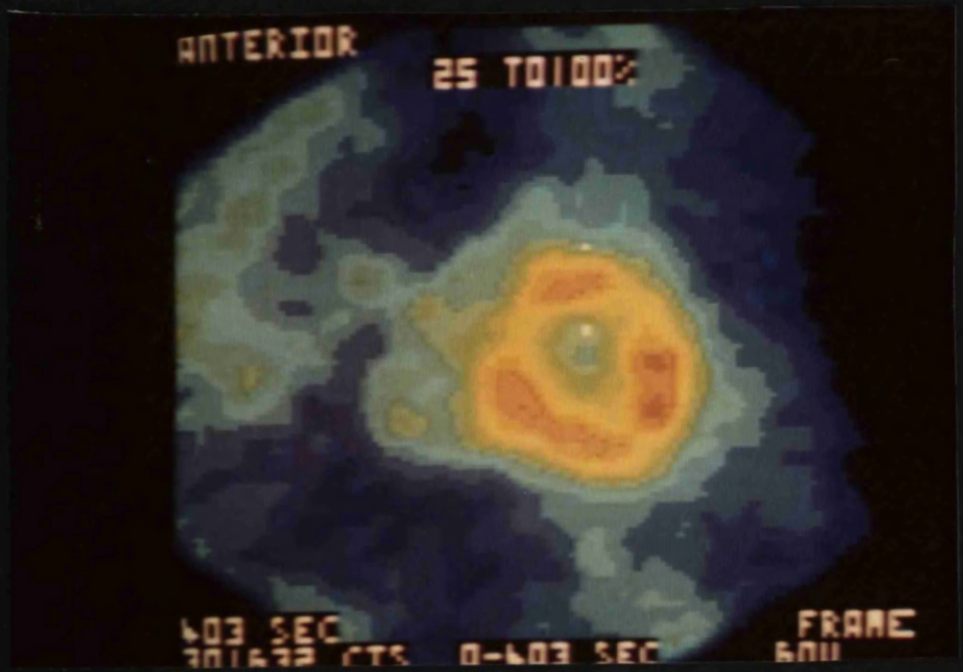
Stress images: Chest pain and positive E. C. G. during exercise.

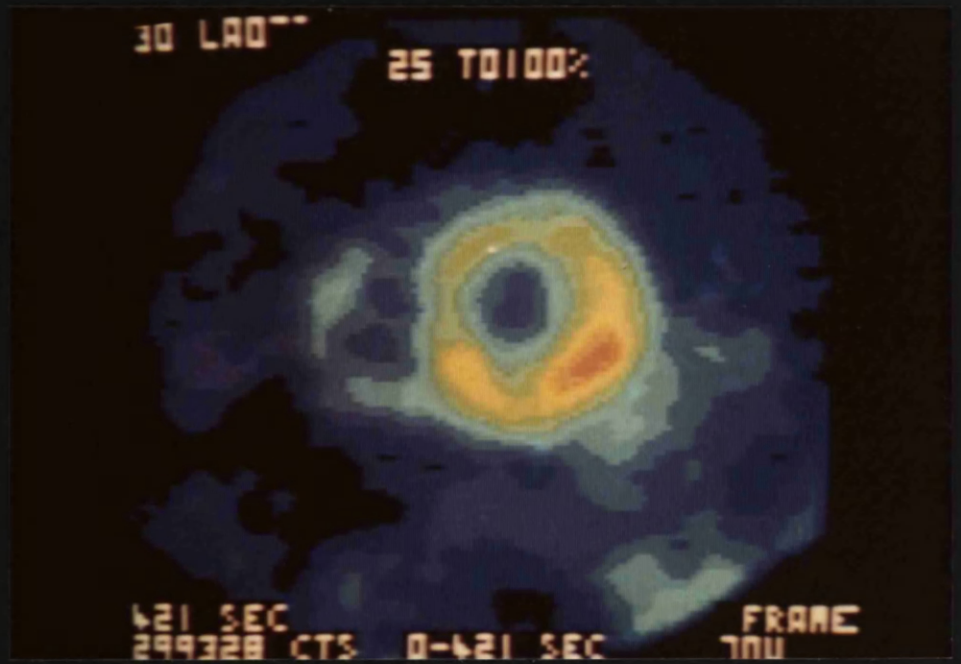
(A) Anterior projection: normal. Note patients with LAD disease may develop posteroseptal abnormalities (see Figure 23(B)).

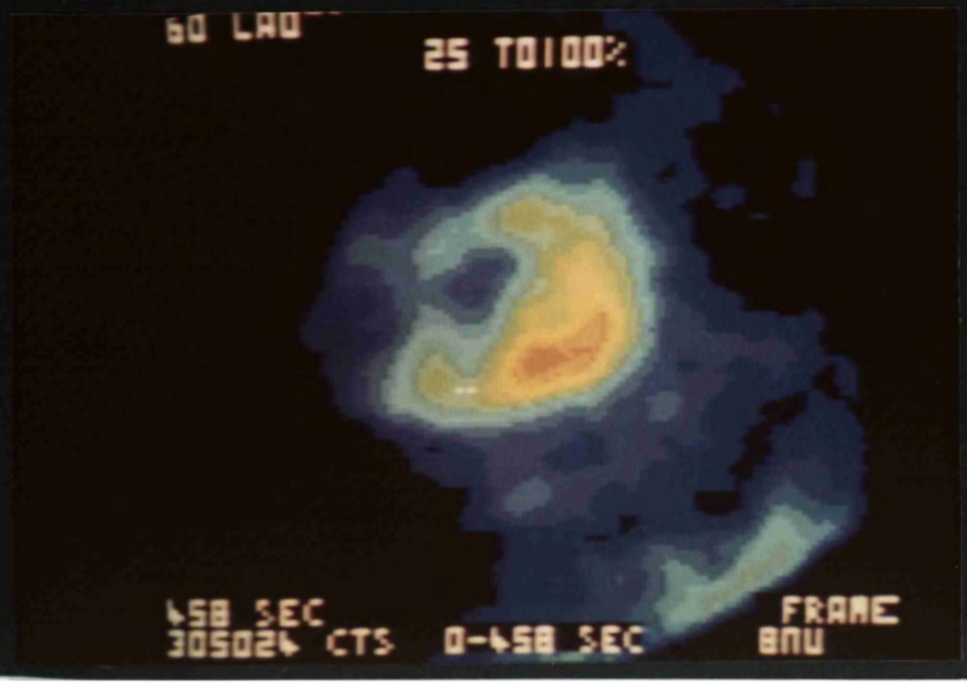
(B) 30^{O} LAO projection: anteroseptal abnormality. Dilated cavity.

(C) 60^{O} LAO projection: marked antero-apical abnormality.

(D) Left lateral projection: antero-apical abnormality.


ANTERIOR
25 TO100%
603 SEC
FRAME
0-603 SEC
600


30 LAO
25 TO100%
621 SEC
299328 CTS
0-621 SEC
FRAME
700


60 LAO
25 TO100%
658 SEC
305026 CTS
0-658 SEC
FRAME
800

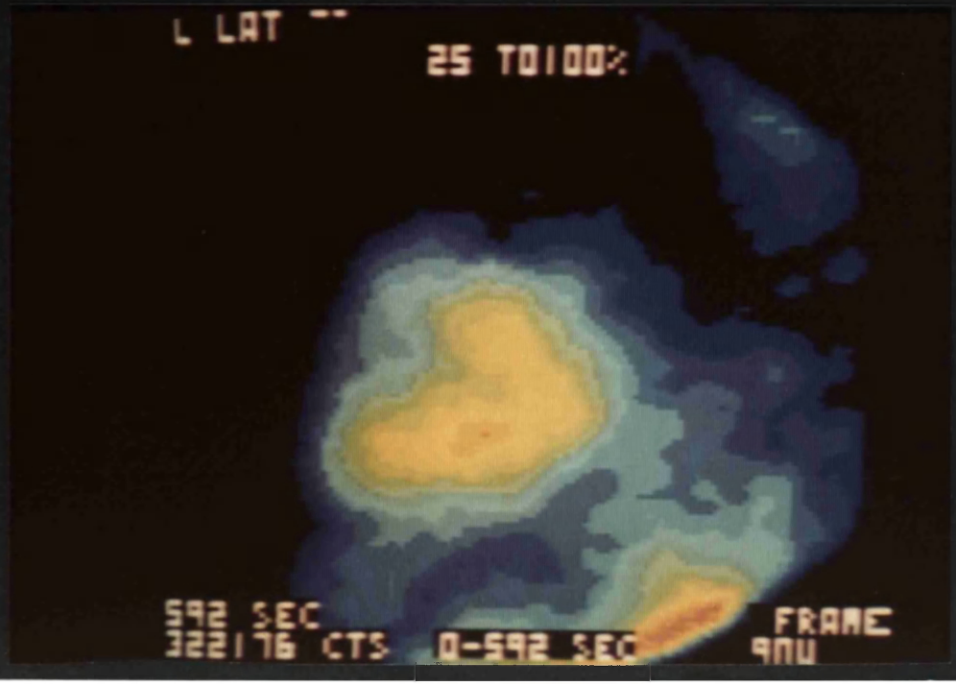

L LAT
25 TO100%
592 SEC
322176 CTS
0-592 SEC
FRAME
900

Figure 30. Stress myocardial images in patient with left circumflex coronary artery disease.

Patient H. K. Triple vessel disease. Coronary artery bypass surgery in 1976 - grafts placed to right and left anterior descending coronary arteries. Continuing chest pain post-operatively. Post-operative coronary arteriogram: both grafts patent but extensive left circumflex disease. Normal left ventriculogram.

Post-operative stress images: Chest pain during exercise and positive exercise E. C. G.

(A) Anterior projection: normal image.

(B) 30^{O} LAO projection: normal.

(C) 60^{O} LAO projection: posterolateral abnormality.

(D) Left lateral projection: posterior abnormality.

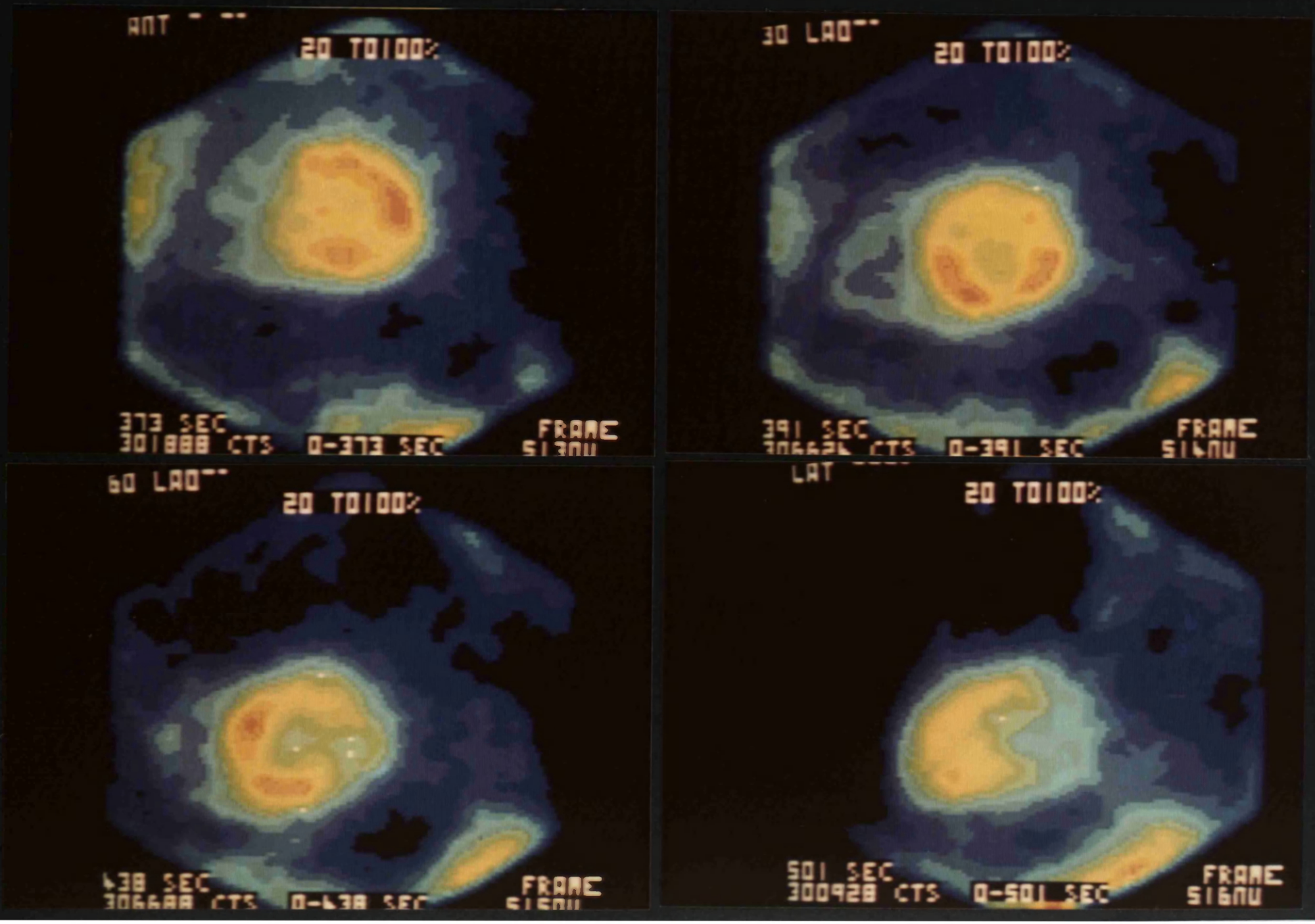

ANT - --
20 TO100%
373 SEC
301888 CTS
0-373 SEC
FRAME
30 LAO--
20 TO100%
391 SEC
0-391 SEC
FRAME
60 LAO--
20 TO100%
638 SEC
0-638 SEC
FRAME
LAT
20 TO100%
501 SEC
300928 CTS
0-501 SEC
FRAME

Figure 31. Acute widespread anterior myocardial infarction.

Patient J. B. 36 year old man with acute myocardial infarction. E. C. G. showed widespread anterior changes.

Rest images obtained 6 days after admission:

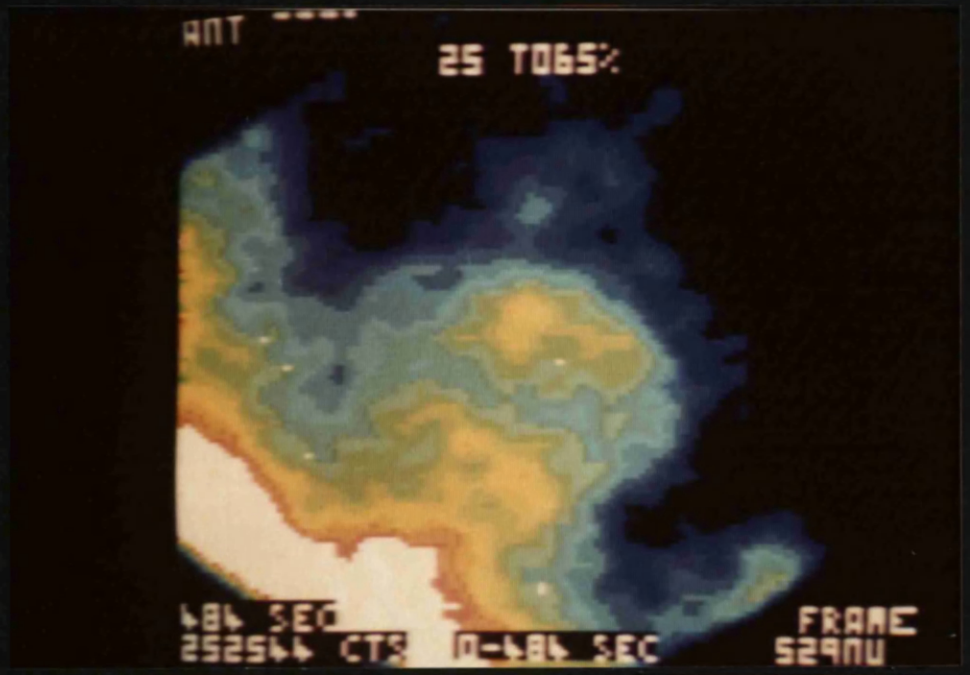
(A) Anterior projection: cardiac activity difficult to identify but some tracer uptake in the lower posteroseptal and upper anterolateral area. Very dilated left ventricular cavity.

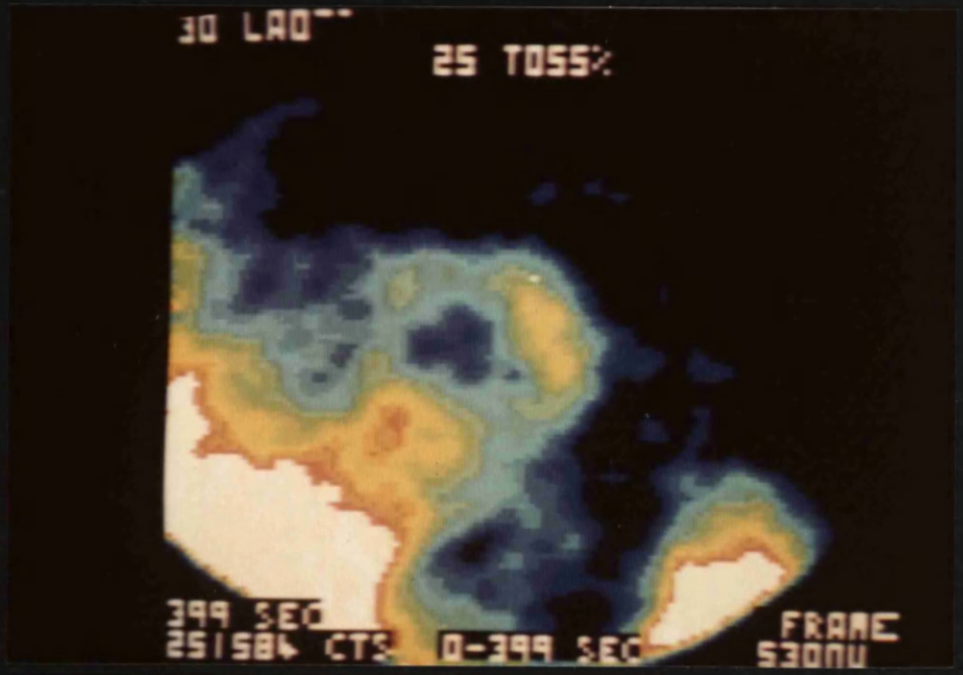
(B) 30^{O} LAO projection: again patchy uptake in anteroseptal and lateral walls. Cavity very dilated.

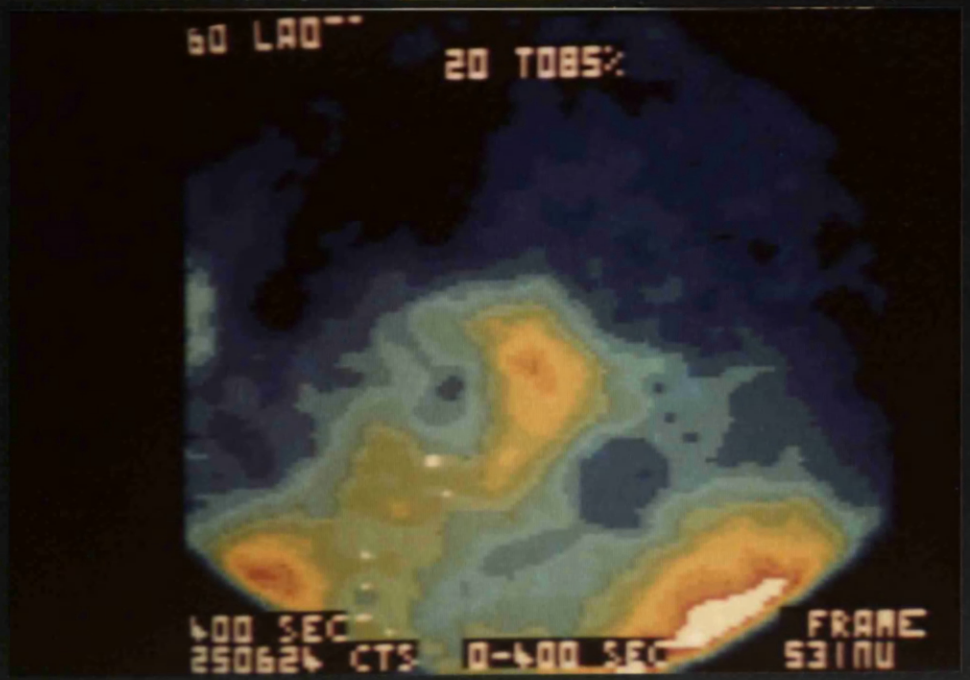
(C) 60^{O} LAO projection: reasonable tracer uptake postero-laterally. Little or no antero-apical uptake.

(D) Left lateral: again antero-apical abnormality.

Comment: The 60^{O} LAO and left lateral images confirm the anterior location of the infarct. The anterior and 30^{O} LAO projections demonstrate how extensive it is - there is very little normal cardiac activity in these views.


ANT
25 T065%
484 SEC
252544 CTS
0-484 SEC
FRAME
529NU


30 LAO
25 T055%
399 SEC
251584 CTS
0-399 SEC
FRAME
530NU


60 LAO
20 T085%
600 SEC
250624 CTS
0-600 SEC
FRAME
531NU

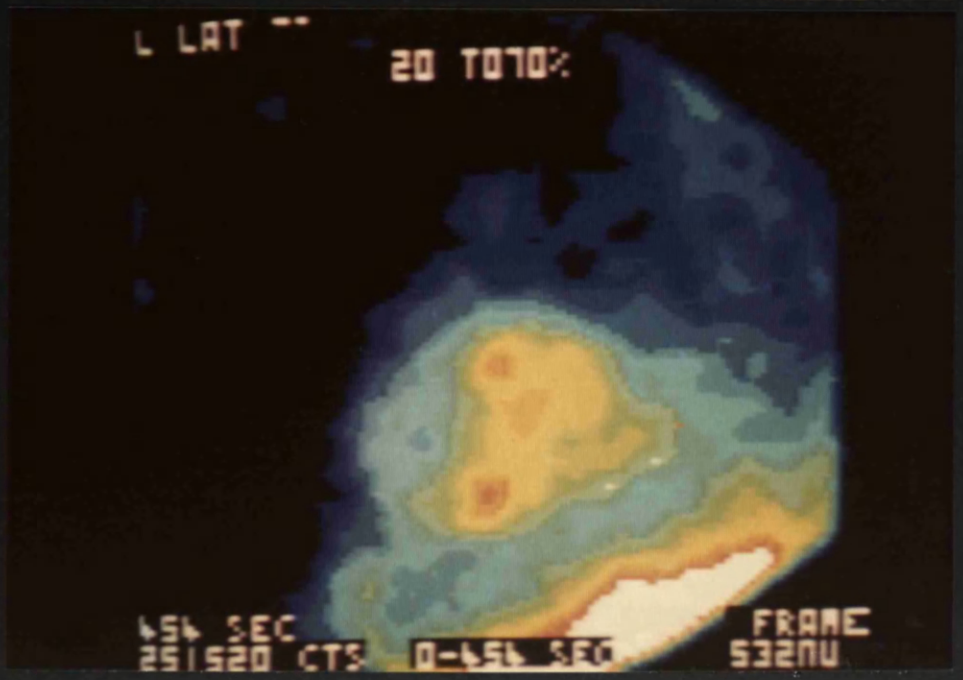

L LAT
20 T070%
654 SEC
251520 CTS
0-654 SEC
FRAME
532NU

Figure 32. Acute anteroseptal and acute anterolateral myocardial infarction.

(i) Patient J. P.

65 year old man with acute myocardial infarction.

E. C. G. showed anteroseptal localisation.

Rest images obtained 4 days after admission:

(A) Anterior projection: decreased septal and apical uptake. Very dilated left ventricular cavity.

(B) 30^{O} LAO projection: greatly decreased anteroseptal and apical uptake.

Comment: There is good anterolateral and lateral uptake compared to Figure 31.

(ii) Patient S. W.

62 year old woman with acute myocardial infarction.

E. C. G. showed anterolateral changes.

Rest images obtained 3 days after admission:

(C) Anterior projection: decreased apical and anterolateral uptake. Dilated cavity.

(D) 30^{O} LAO projection: decreased apical and lateral uptake. Dilated cavity.

Comment: Better septal and anteroseptal uptake than in Figure 31.

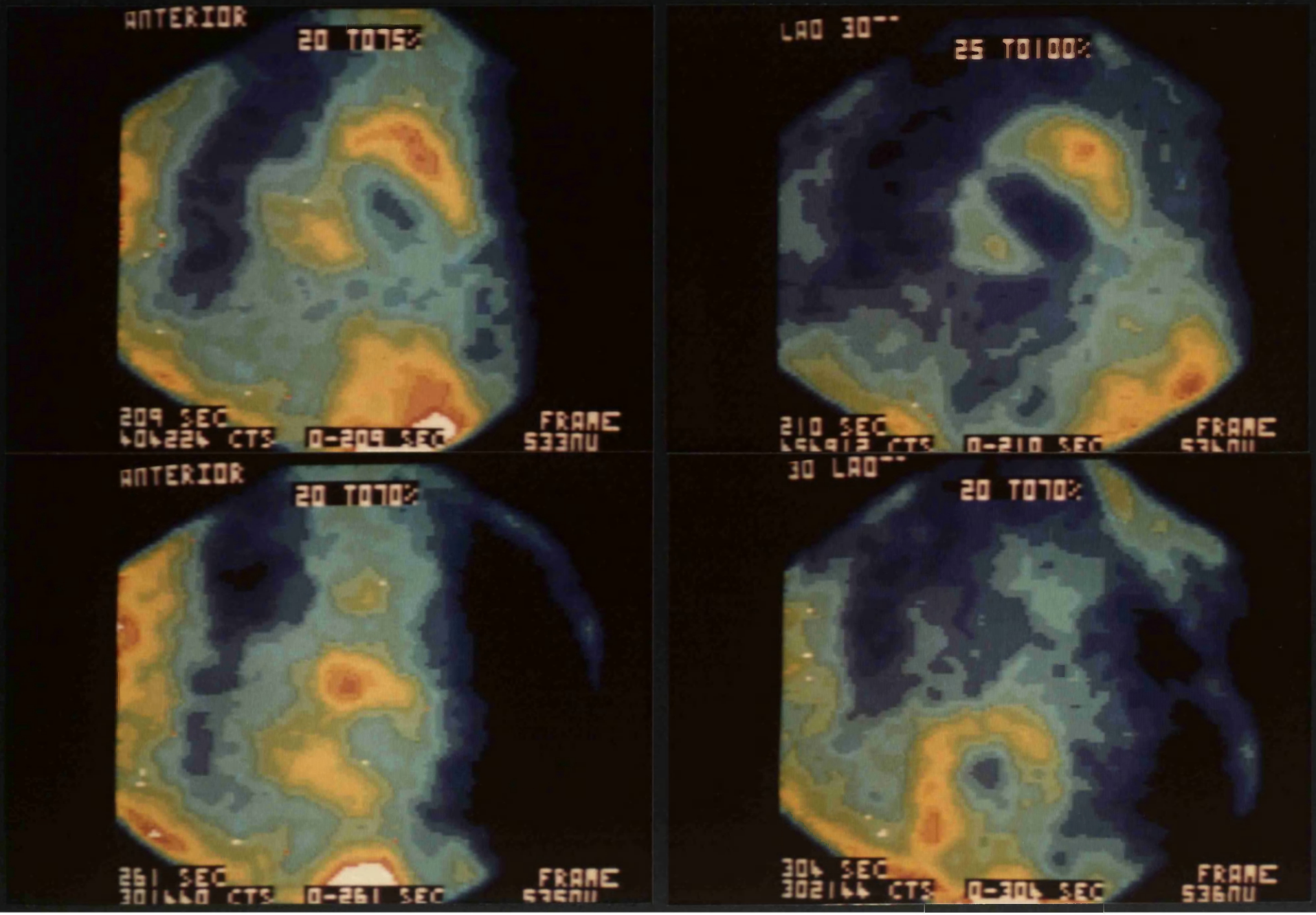

ANTERIOR
20 TO75%
209 SEC
606226 CTS
0-209 SEC
FRAME
533NU
LAO 30°
25 TO100%
210 SEC
0-210 SEC
ANTERIOR
20 TO70%
261 SEC
0-261 SEC
30 LAO
20 TO70%
304 SEC
0-304 SEC
FRAME
536NU

Figure 33. Acute inferior myocardial infarction.

Patient W. C. 55 year old man with acute myocardial infarction. E. C. G. showed acute changes limited to the inferior leads.

Rest images obtained 4 days after admission:

(A) Anterior projection: decreased posteroseptal and apico-inferior uptake.

(B) 30^{O} LAO projection: decreased apico-inferior uptake. Dilated cavity.

(C) 60^{O} LAO projection: normal image.

(D) Left lateral: decreased inferior and posterior tracer uptake.

Comment: Posterior and posteroseptal abnormalities were seen in addition to inferior abnormalities in several patients with E. C. G. evidence of acute inferior myocardial infarction.

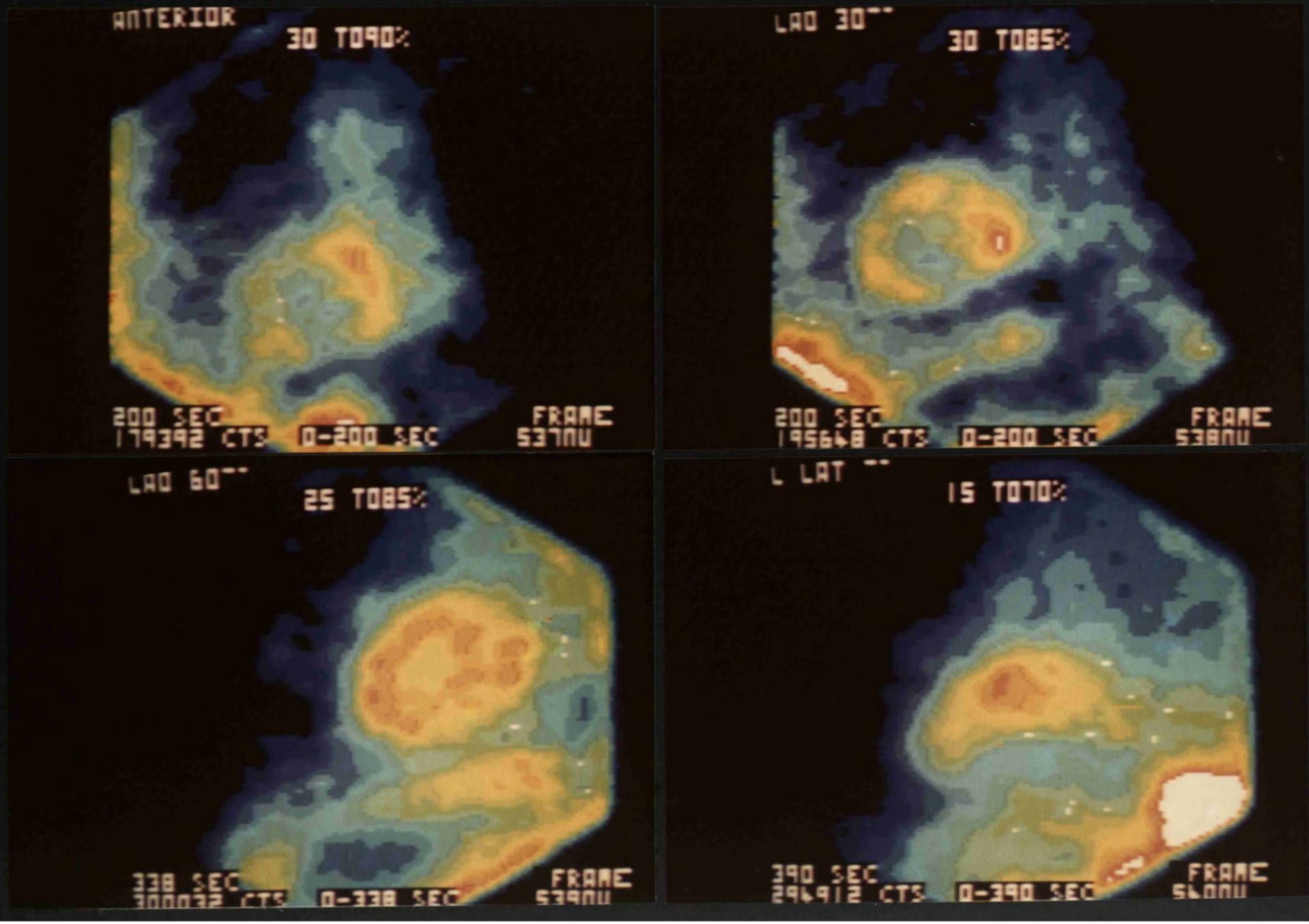

ANTERIOR
30 TO90%
200 SEC
179392 CTS
0-200 SEC
FRAME
537NU
LAO 30°°
30 TO85%
200 SEC
195648 CTS
0-200 SEC
FRAME
538NU
LAO 60°°
25 TO85%
338 SEC
300032 CTS
0-338 SEC
FRAME
539NU
L LAT °°
15 TO70%
390 SEC
296912 CTS
0-390 SEC
FRAME
540NU

Figure 34. Count densities in acute and old transmural myocardial infarctions.

Comparison of count densities at the site of acute and old transmural myocardial infarctions. The count densities in the infarcts are expressed as a percentage of the maximum regional count density in the same image. For infarcts seen in several images, the lowest percentage count density is charted.

The two groups cannot be separated.

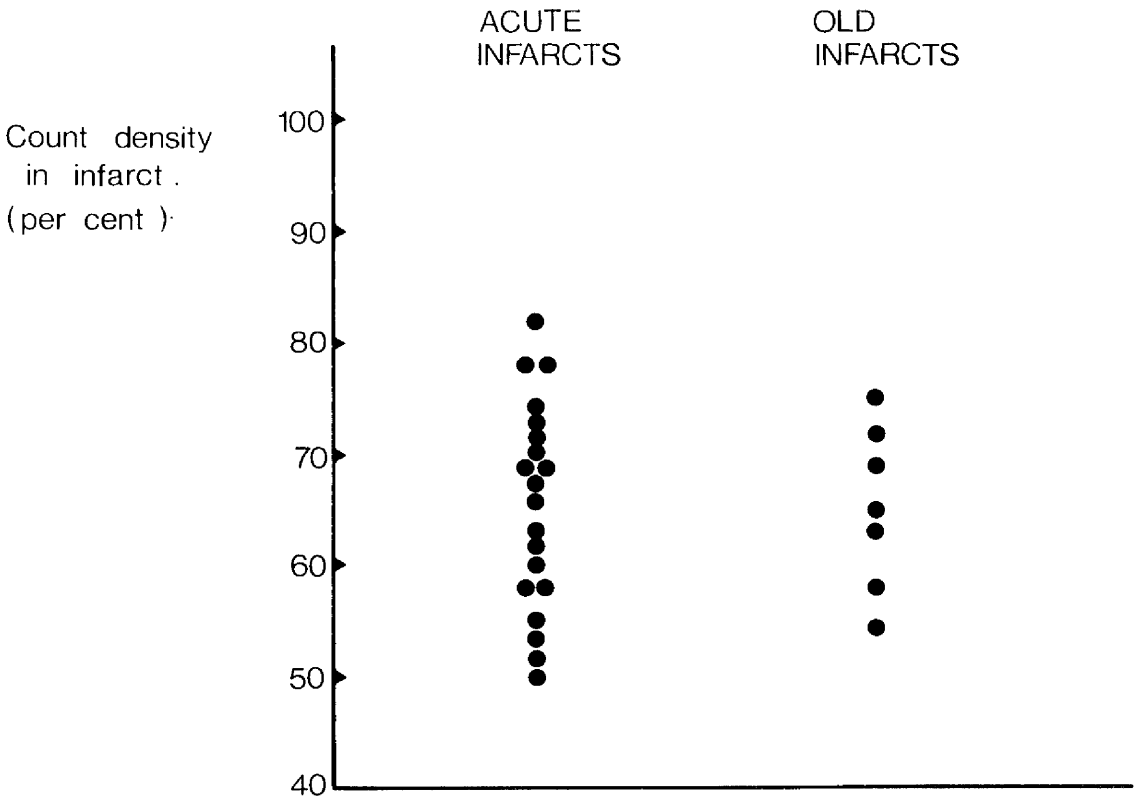

ACUTE
INFARCTS
OLD
INFARCTS
Count density
in infarct.
(per cent)
100
90
80
70
60
50
40

Figure 35. Abnormal myocardial image in acute pulmonary embolism.

Patient G. T. 65 year old man admitted with acute chest pain and marked right ventricular failure. No E. C. G. or enzyme evidence of acute myocardial infarction. Perfusion lung scan changes compatible with multiple pulmonary emboli and venographic evidence of ilio-femoral deep venous thrombosis.

Rest images obtained 5 days after admission:

(A) 30^{O} LAO projection: decreased anteroseptal and apical tracer uptake. Very dilated left ventricular cavity.

Comment: The myocardial image abnormalities may reflect unsuspected old myocardial infarction or occult recent infarction. There was no other evidence, however, to suggest either of these. An alternative possibility is septal dysfunction due to acute cor pulmonale.

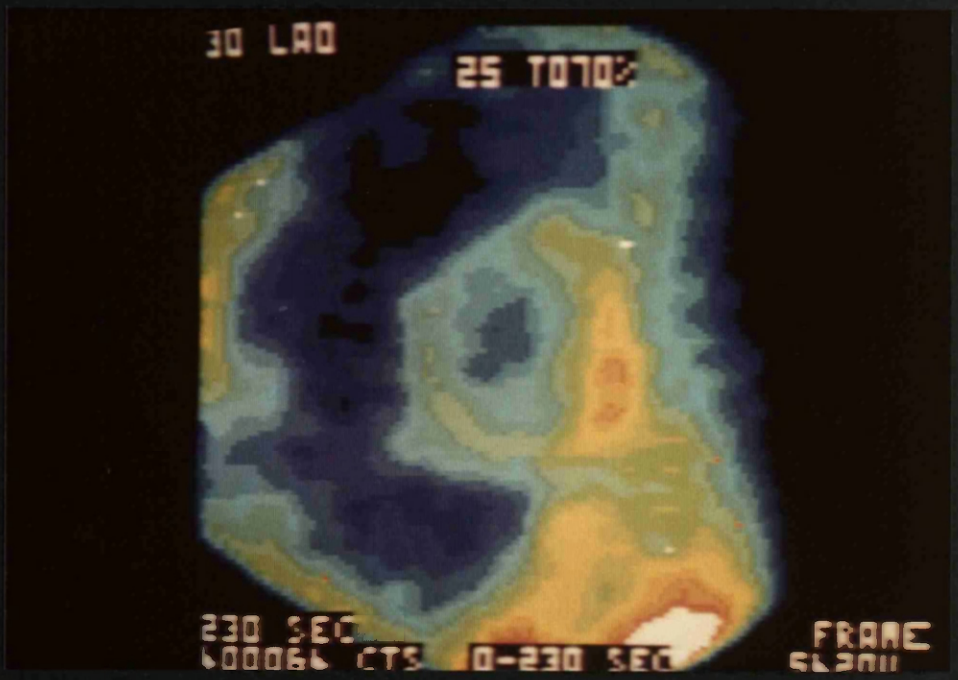

30 LAO
25 TO70%
230 SEC
0-230 SEC
FRAME

Figure 36. Focal myocardial image abnormality in aortic valve disease.

Patient P. S. 52 year old with calcific aortic stenosis and angina.

Normal coronary arteriogram.

Stress image: Angina during exercise:

(A) 60^{O} LAO projection: marked apical abnormality. Thick left ventricular wall.

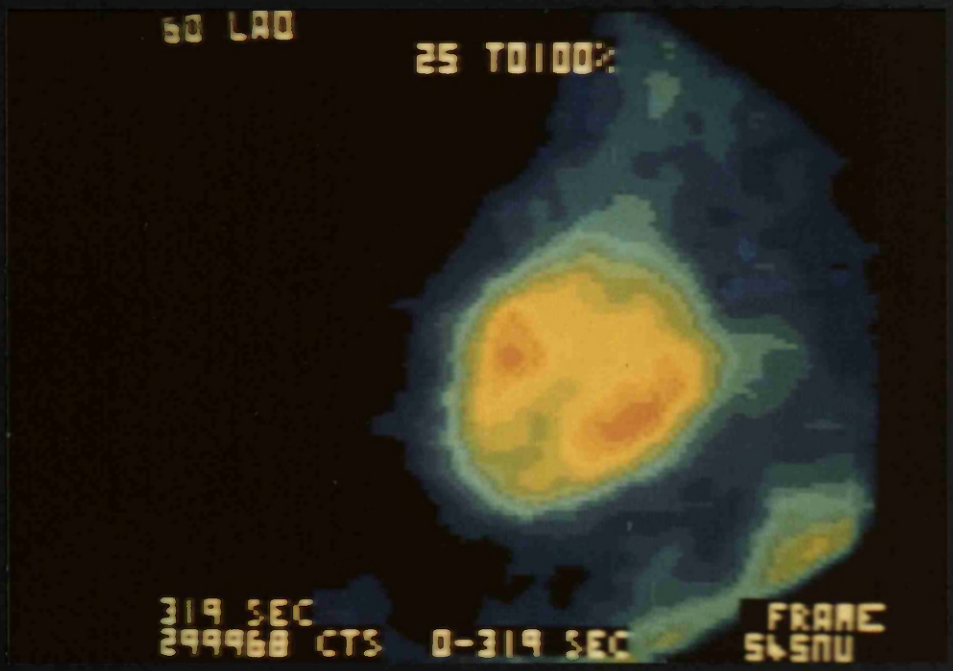

60 LAO
25 TO100%
319 SEC
299968 CTS
0-319 SEC
FRAME
5459NU

Figure 37. Focal myocardial image abnormality in aortic valve disease.

Patient E.K. 48 year old with calcific aortic stenosis and mild angina.

Normal coronary arteriogram.

Stress image: Exercise ended because of lightheadedness and failure to develop adequate blood pressure response to exercise.

(A) 60^{O} LAO projection: antero-apical abnormality.

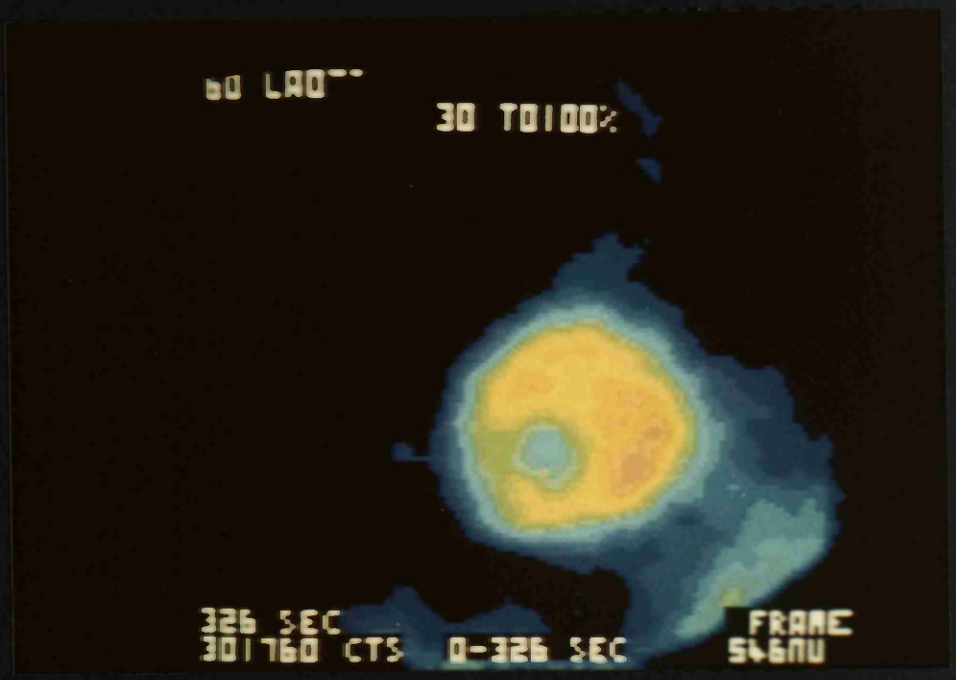

60 LAO
30 TO100%
326 SEC
301760 CTS
0-326 SEC
FRAME
546MU

Figure 38. Focal myocardial image abnormality in aortic valve disease.

(i) Patient J. W.

49 year old with aortic stenosis and incompetence.

Mild angina only.

Normal coronary arteriogram.

Stress image: Exercise ended because of breathlessness:

(A) Left lateral image: infero-posterior abnormality.

(ii) Patient A. B.

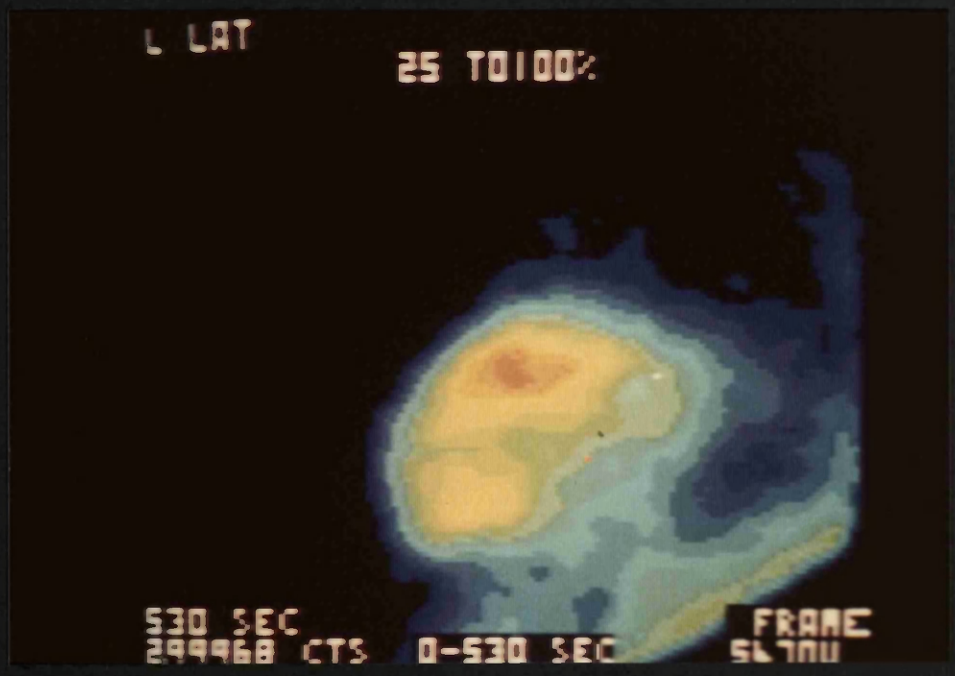
56 year old with calcific aortic stenosis and angina.

Right coronary artery stenosis at arteriography.

Stress image: Exercise ended because of angina:

(B) Left lateral image: infero-posterior abnormality.

Comment: These images could not be used to distinguish the patient without coronary artery disease from the one with coronary artery disease.


L LAT
25 TO100%
530 SEC
299968 CTS
0-530 SEC
FRAME
5L7NU

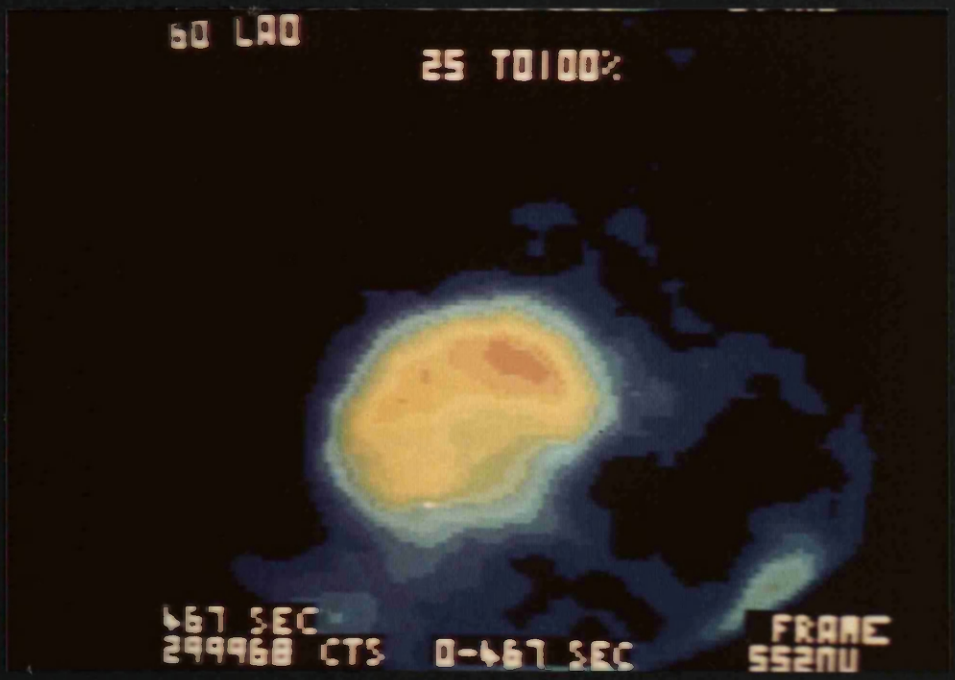

60 LAO
25 TO100%
667 SEC
299968 CTS
0-667 SEC
FRAME
552NU

Figure 39. Determination of left anterior descending coronary artery graft patency from myocardial images.

(i) Patient J. B.

3 years post coronary artery bypass surgery. Left anterior descending coronary artery bypass graft patent at arteriography 18 months post-operatively.

Stress images: Exercise ended because of tiredness:

(A) 30^{O} LAO image: slight decrease of tracer uptake in high anteroseptal area and small apical abnormality ("vent sign"). Otherwise normal.

(B) 60^{O} LAO image: apical vent sign. Otherwise normal image.

(ii) Patient A. H.

2 years post left anterior descending coronary artery bypass grafting. Graft occluded at angiography 1 year after operation.

Stress images: Exercise ended because of breathlessness:

(C) 30^{O} LAO image: probable anteroseptal abnormality. Dilated left ventricular cavity.

(D) 60^{O} LAO image: marked antero-apical abnormality.

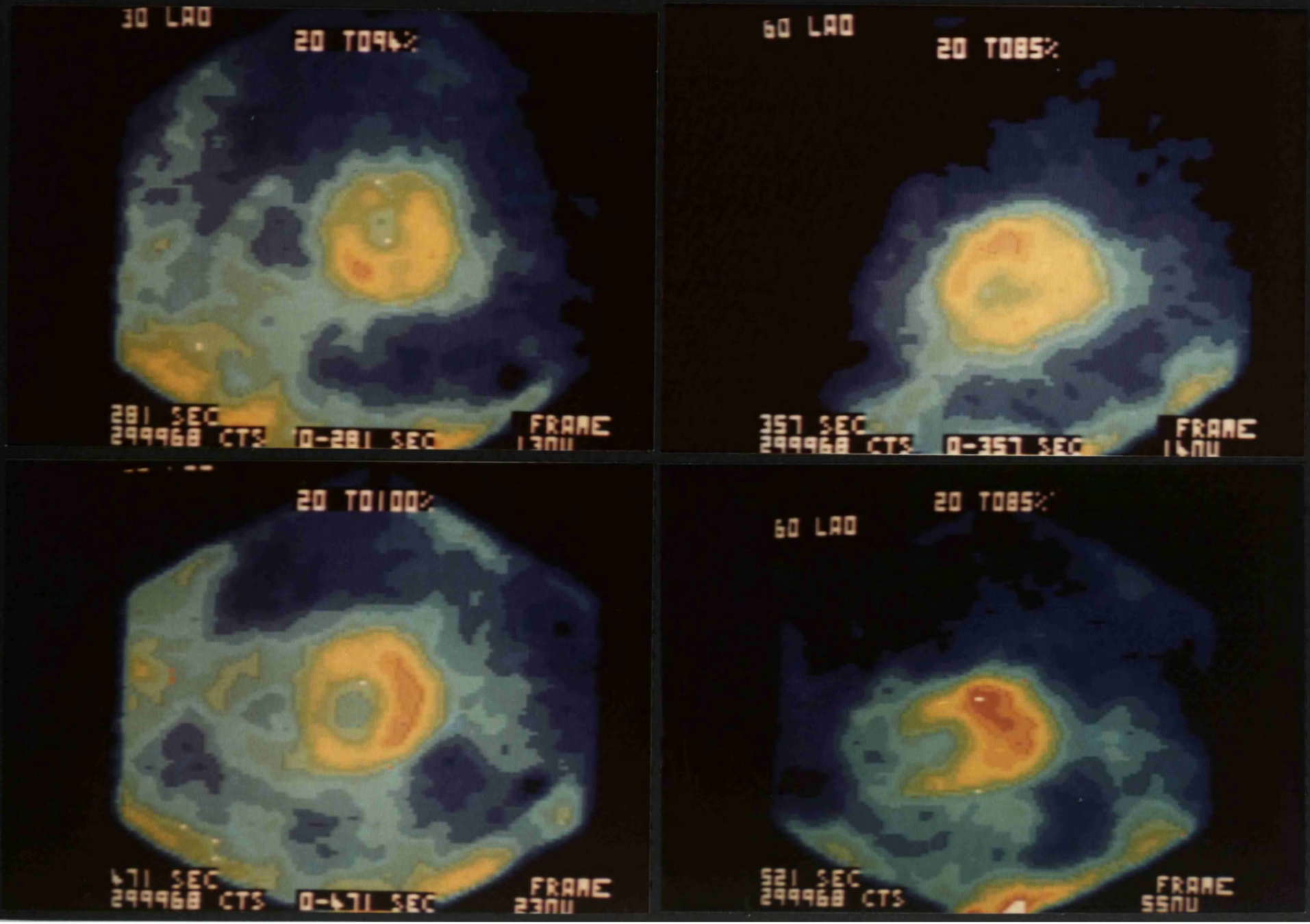

30 LAO
20 TO96%
281 SEC
299968 CTS
0-281 SEC
FRAME
60 LAO
20 TO85%
357 SEC
299968 CTS
0-357 SEC
FRAME
20 TO100%
671 SEC
299968 CTS
0-671 SEC
FRAME
23OU
20 TO85%
60 LAO
521 SEC
299968 CTS
FRAME
55OU

Figure 40. Determination of right coronary artery graft patency from myocardial images.

(i) Patient J. O'D.

4 years post coronary artery bypass surgery.
Right coronary artery graft patent at arteriography 1 year post-operatively.

Stress images: Exercise ended because of breathlessness:

(A) Anterior image: minor apical defect, otherwise normal.

(B) Left lateral image: normal.

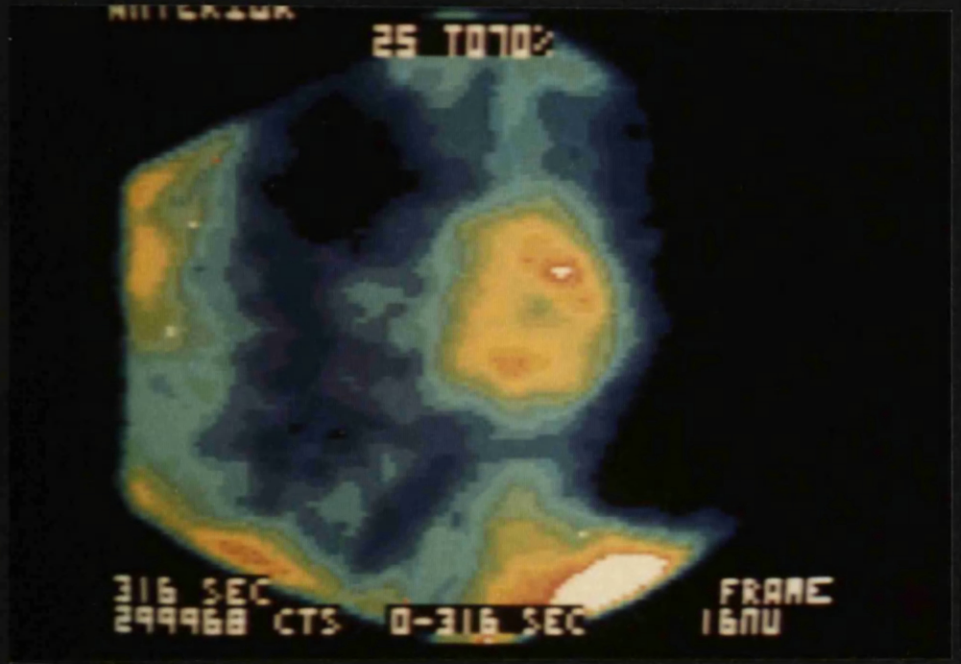
(ii) Patient T. McD.

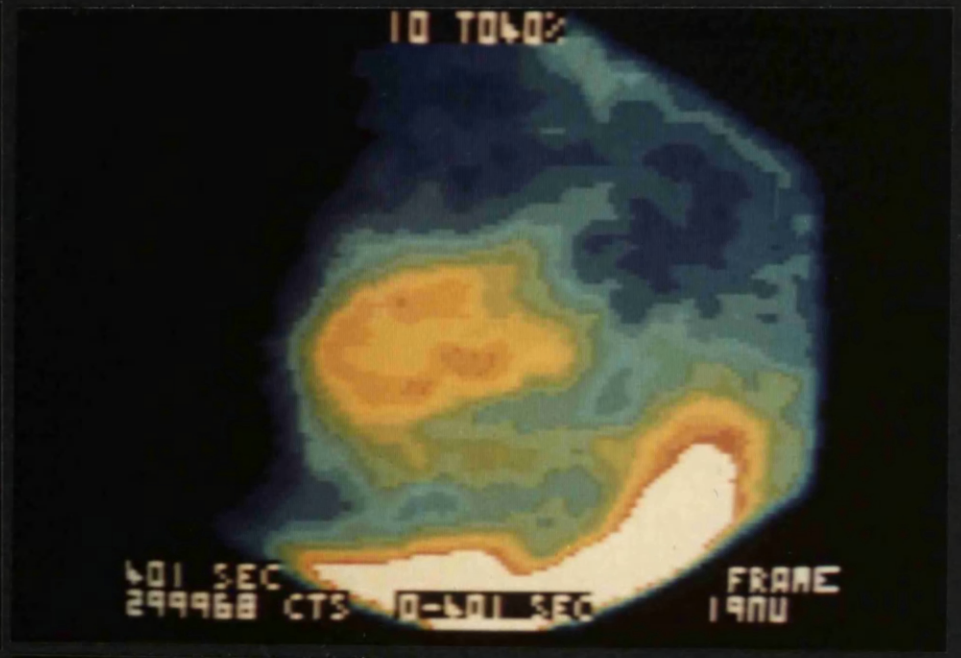
2 years post coronary artery bypass surgery.
Right coronary artery graft occluded at angiography 15 months post-operatively.

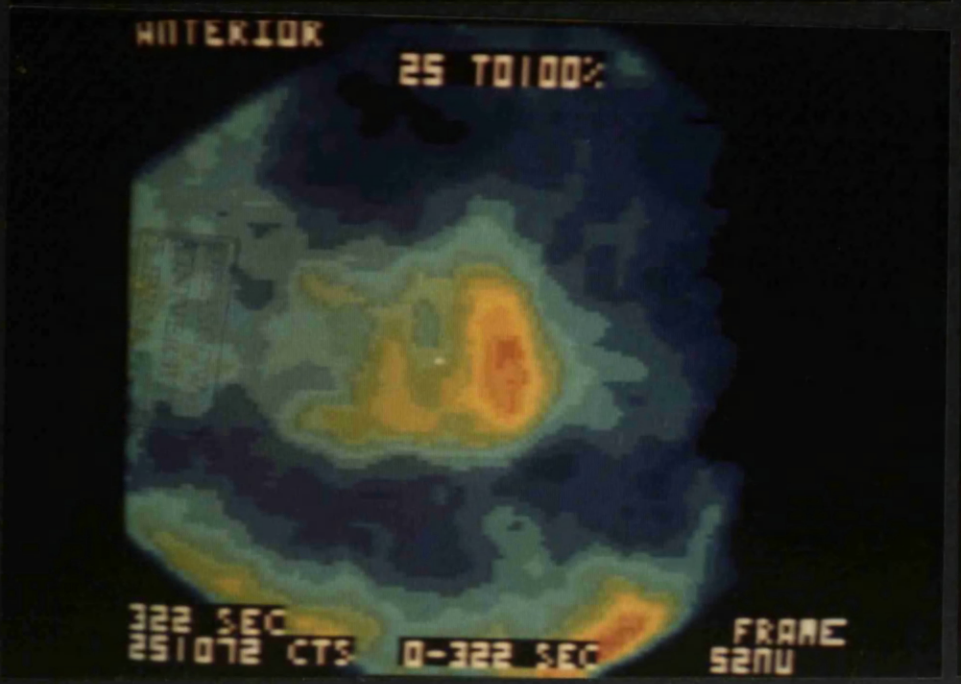
Stress images: Exercise ended because of chest pain:

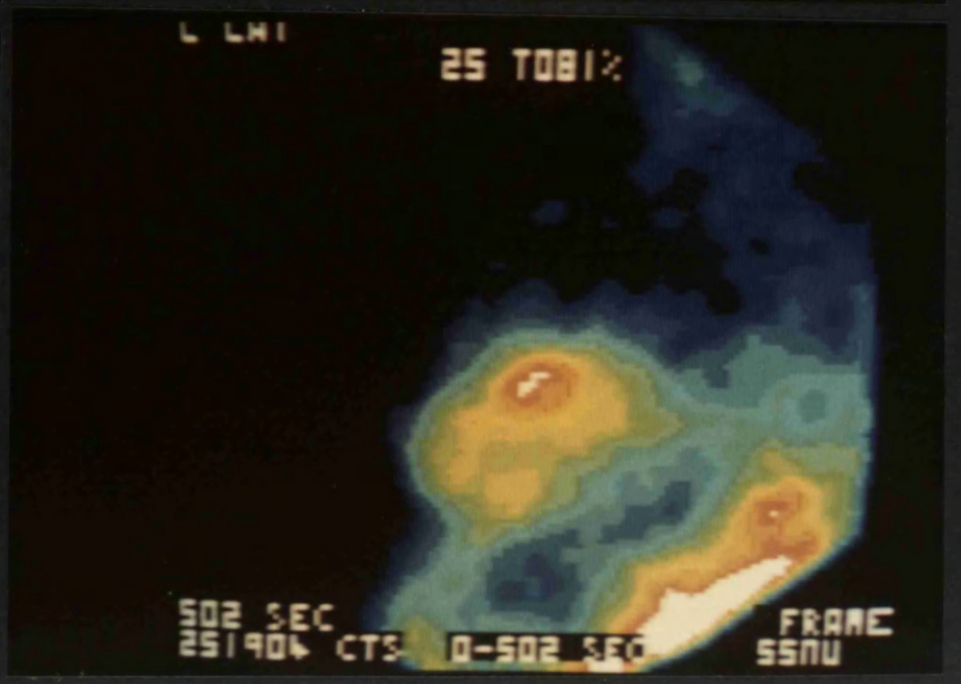
(C) Anterior image: posteroseptal and apico-inferior abnormality.

(D) Left lateral image: postero-inferior abnormality.


25 TO70%
316 SEC
299968 CTS
0-316 SEC
FRAME
16NU


10 TO60%
601 SEC
299968 CTS
0-601 SEC
FRAME
19NU


INTERIOR
25 TO100%
322 SEC
251072 CTS
0-322 SEC
FRAME
52NU


L LMI
25 TO81%
502 SEC
251904 CTS
0-502 SEC
FRAME
55NU