Regional myocardial perfusion: Experimental and clinical studies in patients with coronary artery disease.

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Abstract

Coronary artery disease has become a world wide medical problem. There is an overwhelming association between coronary atherosclerosis, angina pectoris, acute myocardial infarction and sudden death. The narrowing of coronary arteries is thought to damage the heart by limiting appropriate changes in coronary blood flow and by causing myocardial ischemia. This thesis attempts to examine the coronary circulation in patients who present with chest pain with and without coronary artery disease.

One of the aims of this thesis is to validate the use of a short-lived radionuclide to study changes in regional myocardial perfusion. This technique has been applied in clinical medicine in an attempt to describe the disturbances of regional myocardial perfusion that occur in patiehts with coronary artery disease. These disturbances of perfusion have been related to the patients symptoms, the electrocardiogram and the stenosed arteries seen in the arteriogram.

Krypton-81m in solution is an inert freely diffusible gas (half life 13 seconds) which emits a single 190 kev gamma ray. This tracer, a special catheter and a gamma camera have been developed in experiments to measure changes in regional myocardial perfusion. The systematic and random errors of the method have been defined in experiments. The results show that the mixing and delivered arterial concentration of krypton-81m are stable within a useful physiological range of changes in heart rate, blood pressure and coronary blood flow. Correlations with a reference technique have

shown that the method can measure changes in regional myocardial perfusion between 0 and 3 ml/ml/min.

The invasive method, the planar imaging and the need for calibration with washout at high levels of perfusion are investigated and described as limitations that must be considered.

Eighty patients presenting with chest pain have been investigated by routine clinical methods, precordial mapping of the electrocardiogram during exercise and coronary arteriography. Changes in regional myocardial perfusion at rest and during atrial pacing has been measured using krypton-81m. The results have shown that stable mixing and delivered arterial concentration of krypton-81m can be achieved in the patients. Fifteen patients with negative exercise tests all demonstrated uniform increases in regional myocardial perfusion with pacing. The remaining 65 patients with positive exercise tests and significant coronary artery disease all showed both regional increases and decreases in myocardial perfusion during atrial pacing. In 16 of the 65 patients the jeopardized segment of ventricular myocardium showed significant increases in perfusion during the first 4 to 7 minutes of pacing. The increase stopped and regional perfusion in the affected segment then decreased progressively until the pacing was stopped. In 23 of the 65 patients the affected segment showed no changes in perfusion for 5 to 7 minutes of atrial pacing and then showed progressive decreases in regional myocardial perfusion until the pacing was stopped. Finally, in 26 of the 65 patients the affected segment showed immediate and progressive decreases of regional myocardial perfusion starting with the commencement of atrial pacing.

In all the patients with disturbed perfusion ST segment depression in the electrocardiogram appeared after (140 ± 14 sec) the regional decrease of myocardial perfusion in the affected segment. Chest pain always appeared later at 220 ± 19 sec after the appearance of disturbed myocardial perfusion.

Regional myocardial perfusion returned to normal in all the patients after the atrial pacing was stopped. There was a spatial relationship between the region of the ventricles affected by disturbed perfusion and the region of the precordium showing abnormal electrocardiographic signs during the exercise test.

In conclusion, this clinical study has shown that patients with chest pain who have coronary artery disease suffer decreases of regional myocardial perfusion in affected segments of the ventricles during episodes of angina pectoris induced by atrial pacing. Regional perfusion may increase, remain stable or decrease in the affected segment following the onset of a stress test such as atrial pacing. This probably represents the amount of reserve function and adaptation left in the diseased coronary circulation and may be a useful physiological indicator of the severity of coronary disease and of patients at high risk. ST segment depression and pain have a close temporal relationship to the decreases of regional myocardial perfusion that occur in these patients. These studies suggest that there is a close relationship between myocardial perfusion and metabolism in health and disease. Both myocardial perfusion and metabolism will have to be affected by any rational therapy for angina pectoris and ischemic heart disease.

CHAPTER I

SECTION I

Historical notes on the coronary arteries

The recorded history of man's interest in his own coronary arteries starts with descriptions of sclerotic vessels left by the ancient Egyptians. There is evidence in excavated mummies that they noted sclerotic coronary arteries.[1] References to the heart in ancient Egyptian and other languages presented difficulties in interpretation as the word was frequently used to refer to the stomach as well. Nevertheless, there is archeological evidence that the ancient Egyptians were aware of a precordial pain "that threatens with death".[2]

Hippocrates described blockages and obstructions of viscera in his writings but did not clearly relate these to anginal pain or sudden death.[3] It was Galen who provided a clear anatomical description of the coronary arteries and he even mentioned their nutrient function.[4] Later, Leonardo di Vinci accurately depicted, but did not describe, the coronary vessels. He did, however, write about sclerotic changes in many other arteries of the body.[2]

During the sixteenth century, Benivieni described a case of, "heart pain" and Lustanus (1560) later described a, "case of sudden death due to obstruction in the heart". Unfortunately, this was not followed by pathological examination. In 1586 Salius Diversus gave an adequate description of cardiac syncope and sudden death, but again, did not clearly relate this to obstructed coronary arteries.[2]

The seventeenth century saw the monumental achievements of Harvey (1649) who described a "third and extremely short circulation". He described the coronary arteries and veins in a letter to Riolan and in a second letter, described a clinical state similar to acute myocardial infarction.[5] In 1683 Bellini described the nature of anginal chest pain, the coronary anatomy and occluded vessels. Thebesius (1708) provided another excellent description of the coronary vessels with brilliantly illustrated anatomy and pathology.

During the eighteenth century, the theory of blood coalescence developed earlier by Galen, Caelius and Malpighi, was re-examined. Harvey's discovery of the circulation of the blood revolutionised scientific thought in biology. There followed a great tradition of history taking and lengthy recording. Cases included descriptions of ossified coronary vessels, cartilagenous degeneration, aneurysms and pathology that resemble myocardial infarction. Anatomical descriptions became widespread. However, the examiners were interested mostly in cardiac rupture, dissection, pericardial effusion and calcific plaques. The coronary arteries received little systematic attention.

In 1761, Morgagni published his observations correlating clinical disturbances and underlying pathology. He noted and described rupture, aneurysms and scars of the myocardium. He is well-known for the following observation. "The force of the heart decreases so much more in proportion as the greater number of its parts become tendinous instead of fleshy."[2]

In 1768 Heberden read, "Some account of disorders of the breast", to the London College of Physicians. He expertly related precordial

symptoms to underlying heart disease, but did not use pathological correlations or historical references. He was followed by Fothergill, Black, Jenner and Parry who all produced original work correlating the symptoms described by Heberden and underlying pathological states. Parry (1799) observed that "angina pectoris arose from some morbid change in the structure of the heart which change was probably ossification or some similar disease of the coronary arteries."[6] Jenner and his surgeon, Paytheus, described coronary artery thrombosis. In 1799 Parry published a book, (An Inquiry into the symptoms and course of syncope anginosa, commonly called angina pectoris). This was illustrated by dissection and drew attention to the association between chest pain and diseased coronary arteries. Parry stated clearly his belief in a "direct connection between the mal-organisation of the coronary arteries and angina pectoris".[2]

In the latter part of the nineteenth century, the now international "coronary theory of angina pectoris" was criticised by Harren as too simple and not accounting for sclerosis by ossification . Scarfa and Lobstein (1804 and 1833), described atherosclerosis, the changes in the internal coat of the artery with ulceration and steatomatous disorganisation. They attributed this arterial disease to, "slow internal causes" and an, "abnormal state of nutrition of the tissues".[7] Virchow (1846), published his theories and findings on thrombosis, but he was not much concerned with the coronary arteries.[8]

In 1698 Chirac ligated the coronary artery of a dog and produced cardiac arrest. This experiment was followed by Ericksen (1842), Panum (1862), Bezold (1867), and Cohnheim (1881), who investigated the collateral circulation within the coronary tree.

A clinical description of acute myocardial infarction was given by Dubin in 1859, Weigart in 1880, and Huber in 1882.[2] They all associated the illness with diseased coronary arteries and Hammer (1878) made a very important reportof a case of coronary artery thrombosis. Leydan (1884), published pathological reports drawing together diseased coronary arteries, acute softening and haemorrhage of the myocardium, chronic fibrosis with degeneration of the myocardium and a combination of these findings.[2]

Between 1850 and 1900 many scholarly works on coronary disease in patients were published. Osler's, "lectures on angina pectoris and allied states" (1897), with the descriptions by Obrastzow and Straschesko (1910), further clarified the clinical condition. In 1912 Herrick gave a famous clinical account of the condition, but it was Osler in 1910, (in the Lumleian Lecture) who began to systematically separate angina pectoris, coronary thrombosis and acute myocardial infarction.[9,10]

After 1900 it was accepted that angina pectoris and coronary thrombosis were not only pathological conditions but were compatible with life and demanded the attention of the clinicians. With the discovery of the electrocardiograph, the ECG changes of myocardial infarction were published by Herrick in 1919, changes in angina were published in 1918, and Smith demonstrated ECG changes following the ligation of a coronary artery in dogs in 1919. In 1920 Pardee described the typical elevation of the ST segment associated with myocardial infarction. The widespread application of the ECG greatly encouraged the clinical interest in angina pectoris, coronary disease and acute myocardial infarction. Libman and Levin, (1916 and 1918),

described the raised white cell count in acute infarction. Scherk, in 1933, described the raised erythrocyte sedimentation rate and the blood transaminase activity was first measured by Le Due and Wroblewski in 1954. These more specific tests served to encourage further enquiry into the coronary anatomy, physiology, atherosclerosis, angina and infarction.[2]

During the twentieth century there has been a great increase in research into the physiology of the coronary circulation. Morawvitz and Zabrin described the contribution of the coronary arteries and veins to inflow and outflow of blood in the heart. Maldi and Starling extended these studies, and Gregg described in experiments a more precise estimate of the roles played by the coronary sinus, Thebesian veins and coronary arteries. Techniques, such as arterial and coronary sinus sampling of metabolites and pressure measurements allowed investigations into the mechanical effects of systole, coronary vasomotor tone and the physiological control of coronary blood flow.[11] Fick, Zierler and Saperstein, amongst others, have described the theoretical application of tracers and particles for the measurement of coronary blood flow. The electromechanical flow probe, the left atrial injection of labelled particles and coronary venous sampling have all provided measures for the experimental investigation of coronary blood flow.[12]

In patients, catheterization of the coronary sinus, inert gases, radionuclides, thermodilution and other methods have all played an important role in the investigation of the coronary circulation in man.[11,12] These latter aspects of the subject are discussed further in the thesis.

CHAPTER I

Section I

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CHAPTER I

SECTION II

The physiology of coronary blood flow

Knowledge of the control of coronary blood flow or myocardial perfusion has developed together with the discovery of new methods that measure pulsatile flow in large arteries, tissue perfusion, tissue oxygen tension and finally histochemistry, spectrophotometry and enzyme assays.[1,2]

There is a close and interdependent relationship between cardiac muscle work, myocardial oxygen requirements and coronary blood flow. In health, the resistance to flow in large coronary arteries is small and the arterioles are minimally dilated with a large reserve capacity. The arterioles are responsive to metabolic demands and control flow mainly by varying vasomotor tone.[3]

Coronary blood flow will depend on the vascular resistance and driving pressure. The former is determined by vasomotor tone and the changing pressure exerted by surrounding myocardium throughout systole and diastole.[3] The intramyocardial pressures are determined by intraventricular pressure that is developed and they cause cyclical variations in coronary blood flow described by Gregg and Fisher in 1963.[4] The intramyocardial pressure is thought to be greatest at the endocardium and to decline linearly towards zero at the epicardium. There is experimental evidence to show that this greater pressure in the subendocardium is compensated by a lower vasomotor tone resulting in the same vascular resistance to blood flow in health.[5,6] A variety of experiemnts have shown that the subendocardial blood flow and tissue

oxygen tension cannot be regulated to the same extent as subepicardial flow. Decreases in systolic or diastolic perfusion pressures, increases in intracavity pressure or coronary stenosis will therefore affect the subendocardium of the left ventricle more quickly than the rest of the heart.[7,8,9,10]

Autoregulation

The coronary circulation can be affected by changes in perfusion pressure (transient alterations) but will immediately tend to readjust back to a steady state related to the myocardial oxygen requirements. Tissue pressure and myogenic reflexes are less likely explanations for this adaptive phenomenon. The most widely held view at present is that the coronary vasomotor tone alters, so changing vascular resistance in order to meet the requirements of the heart for oxygen. This response is probably mediated by metabolites arising from the parenchymal cells and circulating in the intercellular and intravascular spaces.[11,12]

The link between blood flow and metabolism

There is evidence that the level of coronary blood flow is carefully regulated according to the needs of the myocardial tissues for oxygen.[13] Oxygen consumption is in itself determined by the frequency and force of contraction, aortic blood pressure and cardiac output.[14,15] When tissue oxygen tension increases above the physiological range (above normal coronary venous PO_2, i.e., $\leq$25mmHg) the relationship between oxygen supply, MVO_2 and coronary blood flow is lost and the level of flow then becomes dependent on perfusion pressure.[16] A decrease in the delivery of oxygen to the myocardium (either as diminished blood flow or diminished PaO_2) results in tissue ischemia or hypoxia which remains the most potent stimulus to increasing coronary blood flow.

The balance between oxygen supply and demand in the heart seems to be the most consistent parameter controlling coronary blood flow. However, there is still debate as to whether this affects resistance vessels directly or via active metabolites.[3]

Potassium, lactate, phosphate, CO_2 and hydrogen ions are certainly involved in myocardial metabolism and changes in coronary blood flow. They do not seem to be primary regulators and are thought to modulate the responsiveness of the coronary vasculature to the factors controlling flow.[17,18,19]

Metabolites and coronary blood flow

During the normal metabolism of 5' adenylic acid in the heart hydrolysis releases adenosine. This is released into the intercellular and intravascular spaces and is a powerful vasodilator.[20] The concentration of this substance is increased in a variety of circumstances that are associated with increases in coronary blood flow. Although this substance is rapidly metabolized to inosine and hyoxanthine or re-phosphorylated to AMP, there is mounting evidence to show that it is an important intermediary substance in the regulation of coronary blood flow.[21,22,23] Support for this theory arises from the fact that adenosine is released from AMP by 5-nucleotidase on the cell membrane and then released into the extracellular spaces. The intracellular concentrations are very low.[21,23,24]

The links between substrate metabolism, myocardial oxygen requirements, the concentrations of ATP, ADP and AMP, adenosine release and coronary flow are not yet clearly understood.

The nervous system and coronary blood flow

It is now well known that sympathetic nerve stimulation produces coronary vasoconstriction and parasympathetic stimulation produces dilitation.[25] Feigl has shown that these mechanisms can alter coronary vascular resistance by 30-40% which is small in relation to the influence of metabolic demands. Noreprinephrine produces first vasoconstriction (mediated via α adreno-receptors) and then a marked increase in myocardial oxygen requirements giving rise to coronary vasodilitation mediated via beta adreno-receptors.[26,27,28] Hackett and Vatner have shown that the sympathetic nervous system exerts a moderate degree of vasoconstriction which can be modulated.[29,30] There is also some evidence for coronary beta-receptor mediated dilitation via the direct effects of epinephrine. There are a large number of questions concerning the separate effects of myocardial and coronary beta-receptors, the separate properties of beta receptors in different sites of the vascular tree and the relative physiological importance of this system in the intact conscious subject.[3]

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Section II

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CHAPTER I

SECTION III

Measurement of Coronary Blood Flow

A variety of methods are available that will measure different aspects of coronary blood flow.[1] Zierler has stressed the importance of avoiding ambiguities when using the term (i.e., blood flow). The unit measure used in clinical work must be understood. Secondly, he suggests that it is essential to decide which aspects of the physiology of coronary blood flow are under investigation and to select a method that is appropriate.[2]

Destructive methods of experimental practice

The right heart bypass preparation with coronary venous drainage and the electromagnetic flow probe are quantitative and widely accepted methods to measure coronary blood flow. There are, however, technical and ethical reasons why they have very limited applications in patients.

The injection of microspheres started with Pohlman in 1909 and Prinzmetal in 1947.[3,4] They studied the distribution of ceramic and glass microspheres in the foetal pig circulation and anastamotic vessels of the heart. There followed the application of Sapirsteins principle (1958) which determines cardiac output and regional tissue flow by studying the fractional distribution of spheres injected during the first transit through the circulation.[5]

These principles have been refined into a delicate but quantitative method of injecting radioactively labelled microspheres into the left atrium and studying the proportions distributed to weighed segments of the myocardium. If one assumes that the label stays bound, the spheres are

perfectly mixed in the afferent circulation, that they are distributed according to blood flow and no recirculation occurs then this destructive method provides quantitative values of flow in ml/gm/min.[6]

Non-destructive methods used in patients

Labelled microspheres

Radioactively labelled microspheres can be injected directly into the right or left coronary artery at the time of coronary arteriography. The most common technique employed is the two isotope method using 1 to 2 mCi of technetium-99m-labelled microspheres (size range 10-40 μ) containing approximately 10000 particles for the left circulation and indium-113m-microspheres for the right circulation. By imaging the isotopes separately in multiple views an evaluation of the area perfused by each artery can be obtained.

The method requires that the coronary ostia are engaged and assumes that the spheres can mix in the left and right main stem coronary arteries. The results do not easily show changes in response to physiological interventions and cannot be expressed quantitatively.

This approach has been used in patients to image the distribution of blood flow at rest, during stress and coronary vasodilitation.[7,8,9]

Inert gases and thermodilution in the coronary sinus

Inert gases

The introduction of coronary sinus catheterization has made it possible to measure the arterio-venous differences of various indicators across the heart. The patient can breath nitrous oxide, krypton, xenon, hydrogen, helium or argon until an equilibrium is reached in the circulation and the myocardium. The wash-in and wash-out of these tracers can be studied by repeatedly measuring the arterial and venous

concentrations. The theoretical and methodological features of these techniques have been explained in detail by Zierler, Klocke and Wittenberg.[2,10,11]

These methods provide a measure of flow per unit volume which represents the whole myocardium. Some important considerations are listed below.

1. Myocardial perfusion is heterogenous and this technique preferentially represents areas of high flow.
2. The measurement of the tracer must be very sensitive and accurate in order to detect small differences between arterial and venous concentrations.
3. Coronary sinus sampling must exclude right atrial blood.
4. The assumption that the tissue to blood partition is determined only by perfusion may not be true with tracers that have a high affinity for fat (e.g., xenon).
5. Mass transport of the tracer through the myocardium may have to consider diffusional shunting and counter current exchange.
6. The technique cannot easily resolve regional changes in myocardial perfusion. This facility is particularly desirable when looking at the segmental effects of coronary artery disease.

Thermodilution

The infusion of cold solutions into the coronary sinus and detection of temperature changes can be used to calculate flow in ml/min. The systematic and random errors when used experimentally and in man seem to be adequate. The method detects rapid changes in flow, allows repeatable estimates and uses relatively inexpensive equipment. Again,

the segmental or regional effects of coronary artery disease cannot easily be assessed by this method.[12]

Wash-out of inert tracers - external detection

The wash-out or tracer clearance technique is a relatively easy and invasive method for quantitating regional myocardial flow per unit volume. An inert, long-lived and freely diffusing tracer is drawn-up in saline and injected as a bolus into the coronary circulation at the time of angiography. Using a gamma camera linked to a digital computer regional myocardial data can be obtained. Kety, Zierler and Chinard formulated the theoretical basis and experimental evidence to show that if a diffusible tracer is mixed in a compartment, the flow through the compartment will determine the clearance of the tracer.[13,14,15,16] Renkins concepts explained that at low flow rates, capillary flow dominated clearance whereas at high flow rates extra-vascular diffusion and capillary membrane permeability were limiting factors.[17] Bassingthwaite has reviewed the relationships between delivery of tracer, capillary physiology, transport in the myocardium and clearance of the tracer. He has shown that the limitations for calculating flow per unit volume from the wash-out of tracers, involves the heterogeneity of tissue blood flow and volumes also the limitations of diffusion and permeability. He also discusses the possible effects of diffusional shunting and counter-current exchange on mass transport of the tracer within the heart.[18]

The technique in clinical practice has now developed using krypton-85 or xenon-133 with a gamma camera and a high speed digital computer. Recent reviews have described the properties of the isotopes, energy detection, cameras, collimaters and computing that are suitable.[19]

The most recent and recommended technique involves multiple injections of xenon-133 in different views and analysis of regional wash-out curves. These methods have been used to study ischemic heart disease,[19] cardiomyopathy,[20] and aortic stenosis.[21]

There is a long list of practical features that limit the application of this method.[18]

1. There are uncertainties about mixing of the bolus during the initial distribution.
2. There are variations in the partitioning between blood, myocardium and fat in health and disease.
3. Variations exist in myocardial volume.
4. The method cannot easily measure regions of reduced flow per unit volume.
5. There is relatively poor spatial resolution of low energy emissions.
6. Hetergeneous flow, diffusional shunting and counter current exchange must be considered.
7. Separation of epicardial and endocardial events is not possible.
8. There are difficulties in observing changes resulting from interventions.

Myocardial imaging with extracted cations

In 1954 Lowe studied the distribution of radioactive potassium and rubidium-86 in the organs of the dog and noted the tracers concentrated in the myocardium in relation to surrounding tissues.[22] Later, these agents were used specifically to image the myocardium in health and disease.[23,24] Since that time a variety of nuclides (potassium-43, casium-129, rubidium-81 and thallium-201) have been shown to concentrate

in the myocardium.[25;26,27] These cyclotron or accelerator produced cations all have high energy spectra and long half-lives. The high energy diminishes the quality of images and the resolution of the events while the long life increases the dose to the patient.

Thallium-201 has emerged as the potassium analogue of choice.[28] This is because it concentrates well in the myocardium (±70% extraction on single passage). The 80 kev emissions result in attenuation and absorption of photons with impaired resolution in images while the long half-life (72 hours) results in a considerable dose to the patient.[28]

High intracellular concentrations of potassium are an essential part of the membrane function and metabolism of myocardial cells. Maintenance of this concentration gradient between intra- and extracellular spaces requires energy, oxygen and membrane sodium-potassium ATPase (Na/K ATPase) activity.[29] The uptake of potassium analogues will depend on myocardial blood flow, delivered arterial concentration, capillary permeability, diffusion and energy dependent extraction at the cell membrane. If a peripheral intravenous dose of thallium-201 is administered the myocardium receives approximately 5% delivered by the coronary circulation.[5] More than 70% will be extracted by the heart on first passage and peak myocardial concentrations occur at between 5 and 10 minutes. The concentration at any given moment will also have to consider the volume of tissue, the efflux of tracer, fractional escape rates, recirculation and redistribution of thallium-201.[30] It is important to consider in practice that the extraction is inversely related to the level of blood flow and the energy dependent extraction of these indicators is affected by hypoxia, ischemia, infarction, drugs, hormones and acidosis.[31-37]

Myocardial imaging using thallium-201 in patients is performed between 5 and 15 minutes after injecting the tracer when the activity in blood has decreased sufficiently. Zaret has reviewed the technique and applications for this investigation in patients with exercise induced angina pectoris, acute myocardial infarction, transient ischemia at rest and for the diagnosis of coronary artery disease.[28] These methods are non-invasive and provide spatial resolution of events in regions of the myocardium. There are, however, problems such as the quality and sensitivity of the myocardial images, strict quantitation of perfusion or infarct size, the two dimensional representation of a three dimensional heart and finally the long half-life which makes dynamic studies difficult.

Computerized tomography and positron emitting nuclides

The previous sections have all dealt with some common problems in the application of myocardial imaging. The gamma camera represents the 3 dimensions of the heart in two dimensions. Areas of interest are obscured by the superimposition of structures, background and the introduction of artefacts. The collimation, scatter and attenuation of photons prevent the accurate quantitation of tissue radioactivity.[38]

If a series of radiation profiles are recorded from different angles around the chest these can be superimposed and the multilpe projections subjected to deblurring. An algorithm is used to sharpen definition and attenuation correction applied. In this way a transverse section of the distribution of radioactivity in the tissues can be reconstructed which accurately reflects the distribution of activity in the tissues.[38,39] If positron emitting nuclides are used with

multiple coincidence detection, electronic collimation and computed tomographic reconstruction the activity in tissues can be accurately quantified.

Positron emitting nuclides such as oxygen-15, nitrogen-13 and carbon-11 are involved in every aspect of metabolism. The nuclides can be manipulated by the radiochemists either as diffusible tracers to measure blood flow (i.e., oxygen-15 labelled water, carbon-15 labelled carbon dioxide, nitrogen-13 labelled nitrous oxide, krypton-77), extracted tracers (i.e., potassium-38, rubidium-81, rubidium-82) or metabolic substrates (i.e., ^{11}C-palmitate, ^{11}C-glucose or lactate and nitrogen-13 labelled ammonia). Weiss has reviewed the applications for these tracers for imaging myocardial blood flow, structure and metabolism.[39,40]

There seems little doubt that computed tomography can overcome the spatial problems and quantitation of activity in tissues. The use of nitrogen-13 labelled ammonia and other cations for quantification of regional myocardial perfusion will be limited by the same systematic errors discussed in the section covering extracted cations. They may, however, be very sensitive markers of myocardial hypoxia, ischemia or infarction.

Carbon-11, nitrogen-13 and oxygen-15 labelled substrates can be used to study metabolism in-vivo and hopefully the more fundamental disturbances that occur in ischemia, infarction and cardiomyopathy.[41]

The radiochemistry is complex and not fully developed. The instrumentation is prohibitively expensive and many of these methods require a cyclotron on-site. These requirements will severely limit the application in clinical practice.

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CHAPTER I

SECTION IV

Myocardial Metabolism

This section does not attempt to discuss every aspect of myocardial metabolism but tries to briefly review the links between coronary flow, cell integrity and contractile function. The coronary circulation serves the integrity and function of the cell membrane, organelles and the contractile apparatus (i.e., sarcomeres arranged in fibrils). This is achieved by the supply of oxygen and substrates and by removing the products of aerobic metabolism.[1]

The relative importance of aerobic and anaerobic metabolism has been reviewed. Myocardial metabolic requirements for oxygen are provided by flow, dissociation of oxygen from haemoglobin, transport by diffusion and myoglobin followed by involvement in the electron chain, cytochrome enzymes and redistribution to the water of metabolism in the mitochondria.[1] Myocardial oxygen requirements are largely determined by the wall tension developed, frequency of contraction, intraventricular pressure, and afterload. Cardiac output, external contractile element work, fibre shortening, depolarization and electro-mechanical coupling all play a less important role.[2]

The major sources of energy in the normally oxygenated heart are free fatty acids, glucose and lactate. Opie has reviewed the processes involved in substrate utilization, energy production and expenditure.[1,3] These substrates are delivered and taken-up by the myocardium according to the level of coronary flow, delivered arterial concentrations and the needs of the heart for energy supply. Diffusion, permeability, surface

area and energy dependent extraction and transport all govern the movement of these substrates into the parenchymal myocardial cells. These essential substrates are then oxidised to release energy that is held in the phosphate bonds of adenosine triphosphate and creatine phosphate. The compartmentalization within the cell, membrane function, enzyme reactions and supply of co-factors all depend on the presence of ATP, oxygen and those cofactors that accept protons (i.e., hydrogen ions).[4,5,6,7,8]

Many of the metabolic consequences of myocardial ischemia have been investigated experimentally. They include the depletion of ATP and other high energy phosphates, reduced glycogen, loss of potassium with increases in sodium and chloride ions. There is an accumulation of lactate, reduced intracellular pH, increased intracellular fluid and swelling of mitochondria.[9,10,11,12,13] Plasma membranes become more permeable, and cytosolic enzymes and other metabolic products leak out of cells. Histochemical and morphological studies in animals have shown that 20 to 40 minutes after the onset of myocardial ischemia a number of irreversible functional and structural changes occur in mitochondria and lysozomes. Isolated mitochondria become incapable of reproducing aerobic metabolism and lysozomal membranes become unstable and allow passage of acid hydrolaze enzymes.[14,15,16]

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CHAPTER I

SECTION V

Coronary artery disease and regional perfusion

The prevalence of coronary atheroma and ischemic heart disease has been extensively studied and in Epstein's research coronary heart disease accounted for approximately 40% of all deaths among middle aged American men aged 40 to 59 years.[1,2] The community aspects of this disease can be appreciated by a summary of existing studies.[3,4] If 1000 middle-aged American men are followed for 10 years, 25 will die suddenly, 75 will suffer acute myocardial infarction and 20 of these will die within one month. Figure 1 provides a clear picture of the importance of atherosclerotic heart disease in the United Kingdom.[5]

The important manifestations of coronary artery disease (CAD) and ischemic heart disease (IHD) are sudden death, myocardial infarction, angina pectoris, cardiac arrhythmias and heart failure. A number of studies have shown that approximately 200,000 individuals die each year in the U.S.A. from cardiac failure as a consequence of IHD. At least half of these are under 65 years of age, and must be considered premature deaths.[6,7,8]

A number of studies have shown that patients with angiographic evidence of significant stenosis in one coronary artery will suffer a mortality of approximately 8% in 5 years. In two vessel disease the mortality is 35% and in 3 vessel disease 45% in 5 years.[9,10,11]

The worldwide interest in the aetiology and pathogenesis of atherosclerosis has not yet established a treatment plan of clearly

proven efficacy.[12] The epidemiological research referred to earlier has singled out raised blood pressure and plasma lipids also cigarette smoking and diabetes as "risk factors" which are associated with a relatively early onset of clinically apparent coronary atherosclerosis. Although it may seem reasonable to eliminate or reduce these factors, convincing evidence for controlling this disease is lacking. The appropriate treatment of individuals without known risk factors is even less clear. The role of anticoagulants in preventing or arresting coronary atherosclerosis and myocardial infarction is not established.[13,14,15,16,17]

The following hypothesis is widely held to explain the relationship between coronary artery disease and myocardial ischemia. Significant rigid stenosis of a large coronary artery imposes an added resistance to flow and restricts the regional increases in myocardial perfusion normally produced by dilitation of the arterioles in response to metabolic demand. The severity of the stenosis, the ability of collaterals to reduce total resistance at arterial level and the demands of myocardial metabolism will determine how quickly increases in myocardial oxygen required will outstrip the available regional perfusion resulting in myocardial ischemia.[18-23]

The experimental animal model used to study coronary flow has proved invaluable for investigating techniques of measurement and basic physiology. This approach does not, however, easily provide an accurate model of coronary artery disease which develops in patients over decades. There are only a few techniques for studying regional perfusion in patients and these do not easily describe the regional

myocardial abnormalities that are thought to characterize ischemic heart disease.[24]

Coronary artery disease is segmental and when proven angiographically is associated with increased morbidity and mortality.[10] Acute myocardial infarction affects 1.3 million people annually in the U.S.A. The extent of left ventricular damage and degree of dysfunction are considered important determinants of morbidity and mortality. There seems to be a strong relationship between advanced coronary artery disease, premature or sudden death, acute infarction and angina pectoris.[25-30]

Patients with angina pectoris and coronary artery disease are at increased risk and are thought to have transient regional disturbances of myocardial perfusion during stress. This is thought to result in an inhomogeneous distribution of flow. The methods available for investigating the regional myocardial disturbances of perfusion during rest and stress are limited.[18,19,20,21,23]

If these disturbances in regional myocardial perfusion are caused by coronary artery disease, it is important to try and answer the following research questions.

1. What is the nature and distribution of any disturbance of regional myocardial perfusion during stress in patients with coronary artery disease?
2. What relationship exists between regional disturbances of perfusion, symptoms such as pain and non-invasive and familiar ECG evidence of myocardial ischemia?
3. What is the relationship between disturbed perfusion and stenosed coronary arteries as seen in the coronary arteriogram?

4. If collateral vessels are seen in the arteriogram what aibility do they have for maintaining perfusion to segments supplied by sterosed vessels?
5. How can rational therapy be introduced that will prevent or improve any disturbances of regional myocardial perfusion that may come between the coronary artery disease and ischaemic damage to the myocardium?
6. What is the relative importance of increased myocardial oxygen requirements, vasospasm, platelet aggregation and superimposed thrombosis in complicating the course of ischaemic heart disease?[31]

CHAPTER I

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CHAPTER I

SECTION VI

Aims of the thesis

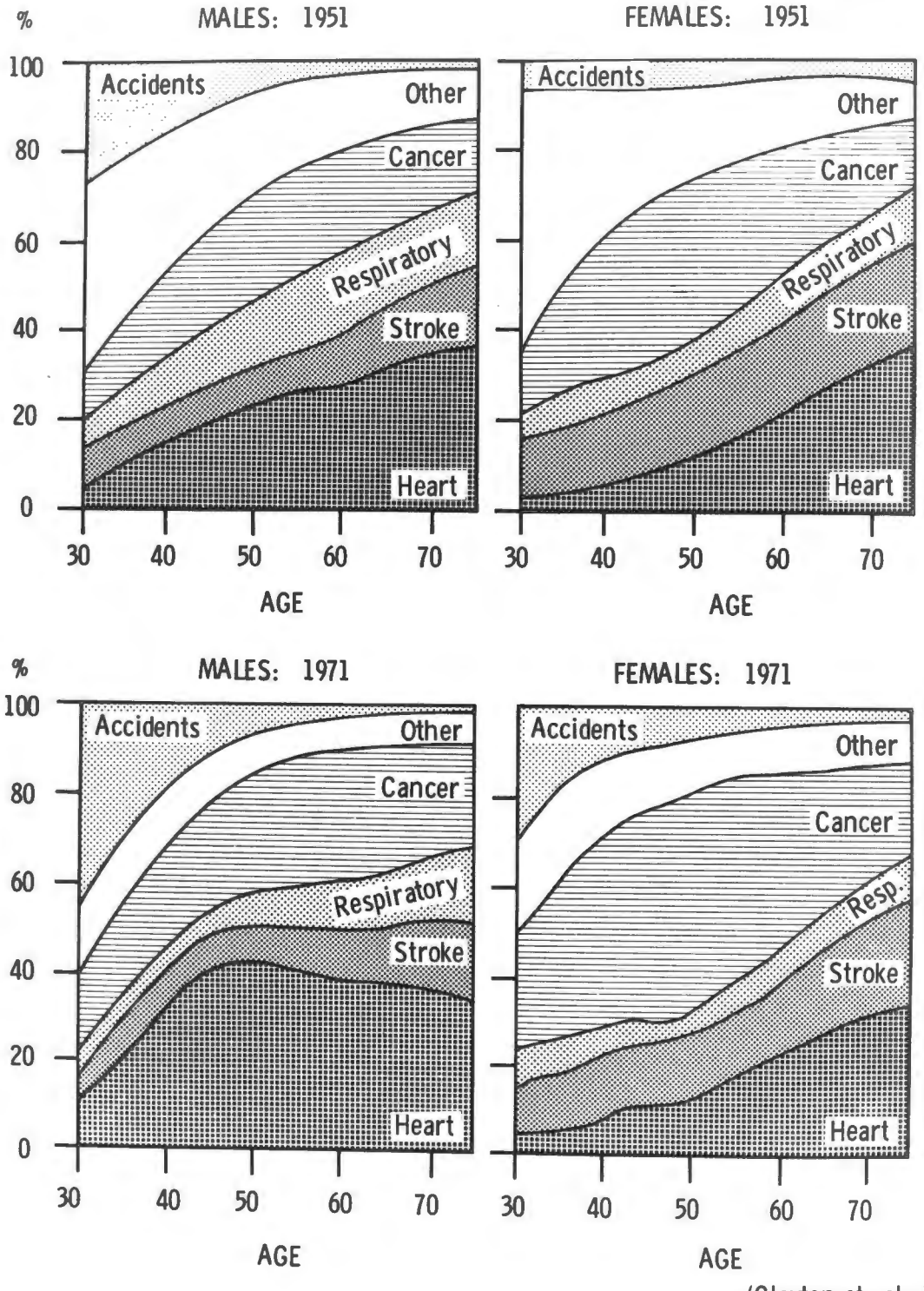
The first part of this thesis attempts to introduce a new technique for measuring changes in tissue flow in the heart. The purpose being to understand the limitations and then apply the method in patients in an attempt to examine the disturbances of myocardial perfusion that occur in coronary artery disease. Any disturbances of perfusion in patients will be related to the coronary artery anatomy in order to test the interpretation of stenotic lesions seen in the coronary arteriogram in clinical practice. The distribution and time course of any disturbances of perfusion will also be related to parameters such as reported chest pain, electrocardiographic signs of ischemia and exercise capacity. By this means a specific and invasive method will be used to improve our understanding of more simple and widely available parameters when investigating the mechanisms and treatment of ischemic heart disease.

Summary of aims

1. The production and properties of rubidium-81-krypton-81m generators are described and discussed.
2. The theoretical basis for using an ultra short-lived radionuclide (krypton-81m) to continuously infuse and image changes in regional myocardial perfusion is given.
3. The systematic and random errors of this approach are tested in experiments in order to understand the limitations of the technique.

4. A catheter and technique have been developed from the experimental work and used in patients in order to measure changes in regional myocardial perfusion using krypton-81m.
5. The method will be used to describe the distribution and time course of any changes in regional myocardial perfusion in patients with and without coronary atherosclerosis. This will be done at rest and during stress.
6. These changes in perfusion at rest and during stress will be used to check on the physiological significance of stenosed arteries seen in the arteriogram.
7. This investigation of myocardial blood flow will try to link coronary atherosclerosis and ischemic myocardial disturbances. The data on perfusion obtained using an invasive and specific method will be used to try and improve our understanding of chest pain, electrocardiographic evidence of ischemia and exercise testing.

RELATIVE CONTRIBUTION OF THE MAJOR CAUSES OF DEATH TO TOTAL MORTALITY BY AGE (30 - 75 years) IN MALES AND FEMALES FOR 1951 AND 1971.



(Clayton et. al. 1977).

Figure 1: This population study performed in the United Kingdom shows the major contribution of heart disease to mortality at different ages.

CHAPTER II

SECTION I

Experimental studies - continuous assessment of regional myocardial perfusion using krypton-81m.

Introduction

The introduction to this thesis has outlined the considerable medical problem of coronary artery disease. This condition is thought to cause disturbances of regional myocardial blood flow which becomes incapable of meeting the metabolic requirements of the myocardium. Working heart muscle is thus jeopardized and an assessment of these disturbances may help to reationalize the treatment of ischemic heart disease.

Any new method for measuring regional myocardial perfusion must consider the theory, assumptions and violations related to the tracer, the circulation under study and the method of detection. In addition, the investigator must decide which units of flow are required for the specific clinical situation.[1,2]

In 1968, Yano and Anger first suggested that ultra-short lived radionuclides such as krypton-81m could be used to visualise blood vessels and organs.[3] Krypton-81m generators were designed to allow the intermittent elution of this gas indicator from its parent compound, rubidium-81.[4,5] This was initially used for ventilation and perfusion studies of the lungs, and later for cerebral blood flow.[6,7]

Krypton-81m (half-life 13 seconds) has allowed the introduction of a technique for continuous observation and assessment of regional myocardial perfusion in dogs. Although the theoretical considerations

and initial experiments are of interest, a practical validation of the results by an independent method has not been done.[8,9,10]

The purpose of this chapter is to briefly describe how rubidium-81 and the rubidium-81 - krypton-81m generators are made. The theoretical background for using krypton-81m to image the heart and measure changes in regional myocardial perfusion in the dog is discussed. Experiments were performed to demonstrate the physical properties of the tracer and the signal obtained when scintigrams of the heart are recorded. The limitations of using krypton-81m to measure changes in tissue perfusion have been identified. Factors such as the stability of the delivered arterial concentration and the degree of mixing of krypton-81m in the afferent circulation have been tested. Lastly, the systematic and random errors of the method have been measured by using a reference technique and by testing the reproducibility of the signals.

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CHAPTER 2

SECTION II

Production of rubidium-81/krypton-81m generators

Rubidium-81 ($t_{\frac{1}{2}}$ = 4.58 hrs) is a cyclotron produced radionuclide which decays by B+ emission and electron captive through the metastable state of krypton-81m. Krypton-81m decays with a half-life ($t_{\frac{1}{2}}$) of 13 seconds and emits 190 keV photons in 65% of its transitions (the remaining 35% being internally converted) to the ground state of krypton-81 ($t_{\frac{1}{2}}$ = 2.1 x 10^5yrs).

By binding the rubidium-81 to an ion exchange column it is possible to elute the krypton-81m activity either as a gas or in a solution. This is the basis of the rubidium-81/krypton-81m generator system.[1,2,3]

There are two main types of ion exchange columns for solution generators, these are:-

1) an inorganic ion exchange column,

and 2) an organic ion exchange column.

The choice of column depends largely on the methods used for the production of rubidium-81 and the associated chemical separation and processing techniques employed.

The main differences in the columns are in their physical designs and in their loading criteria.

The inorganic type uses a small column, approximately 6 mm x 30mm in size, filled with zirconium phosphate (either 50-100 mesh or 100-200 mesh, Bio Rad Z.P.1). The zirconium phosphate material shows a high affinity for rubidium and therefore allows its rapid loading onto the column, especially at high sodium bromide concentrations. The elution

efficiency of this type of column is approximately 70% (maximum 78% of elution rate at 26 mls.min^{-1}). This is the type of column in use at the M.R.C. Cyclotron Unit at Hammersmith Hospital.

The organic ion exchange process uses a column of larger dimensions, approximately 11mm x 60mm in size, filled with the strongly organic material, Bio Rad AG50 X 4 (200-400 mesh). This type of column creates problems due to the inherent slow speed of loading the rubidium-81 but even so elution efficiencies vary from 10% to approximately 65%. (NB. Mediphysics Corp. have reported elution efficiencies, with this type of column, of up to 90%.)

There are a number of important parameters to be considered in the design of the generator. The main ones being the dimensions of the column and the type and size of the output connections.

The packing of the material in the ion exchange column is a compromise, such that efficient elutions of rubidium-81 can be obtained from the target solution and yet the leakage of rubidium-81 is within the accepted range of values. If the volume of the material is very large, i.e., the column is tightly packed, the elution efficiency will decrease. This has the effect of producing longer elution times and lowering the radioactive concentrations of the eluent. The size of the dead space caused by the output connections is another important parameter and should be kept to a minimum. An increase in dead space volume will also produce a lower concentration of radioactivity.

The column must be adequately shielded with lead to cut down the external radiation dose for safe transportation and clinical use. For an average rubidium-81/krypton-81m solution generator, of between 15 and 25 mCi of rubidium-81 produced by the M.R.C. Cyclotron Unit, a

transport index is calculated. This is the external surface dose rate at 1 m from the generator and is found to be in the order of 1.5 - 2 mR/hr. A surface dose rate of less than 0.5 mR/hr is found at a distance of 2.5 - 3m, this is the normal range of values for the distance between the generator and the staff and patients using it in a clinical environment. For a further reduction in the dose rate the generator is normally positioned behind a wall of lead bricks.

Figure 2 shows a krypton-81m solution generator set up for constant infusion with a solution of 5% dextrose in water. A second ion exchange column may be placed in series, in the output circuit, to trap any rubidium-81 breakthrough from the generator. Although this stops any problem of contamination, it also has the undesirable effect of diminishing the specific activity.

Medical Research Council Cyclotron production of rubidium-81

The Cyclotron of the M.R.C. Unit at Hammersmith Hospital is one of the 'classical cyclotron design' utilizing a fixed field and fixed frequency. It is able to accelerate three different particle beams, these are:-

a) Alpha-particle beam - 32 MeV energy

b) Deutron beam - 16 MeV energy

and c) Proton beam - 8 MeV energy

There are a number of possible reactions which are in use for the production of rubidium-81, a few of the more common reactions are shown in Table 1. The widely differeing nuclear reactions used are dependent on the particle beam energies available at the different centres.

The M.R.C. Cyclotron Unit produces rubidium-81 by bombarding bromine, in the form of sodium bromide with 30 MeV alpha particles. The reaction involved is:-

$$^{78}_{35}Br\left(\alpha,\ 2n\right)\quad ^{81}_{37}Rb \qquad \text{Q value} = -14.38 \text{ MeV}$$

Due to the high energy of the alpha beam, other rubidium radionuclides are produced as contaminants, the most important being rubidium-82 ($t\frac{1}{2}$ = 6.3 hrs, γ = 777 keV). This activity is formed by the reaction:

$$^{78}Br\ (\alpha,n)\qquad \text{rubidium-82}\qquad \text{Q value} = 6.0 \text{ MeV}$$

and can contribute up to 20% of the rubidium activity. In addition, small quantities of other rubidium contaminants are also present, these are rubidium-83 ($t\frac{1}{2}$ = 83 days, γ = 553 keV) and rubidium-84 ($t\frac{1}{2}$ = 33 days, γ = 888 keV). Their contribution to the overall rubidium activity is less than 1%.

The target material is G.P.R. grade sodium bromide and can be either the powder or melted type of target. The melted type of target is used at Hammersmith because it is more reliable at high intensity irradiations. The target is prepared by melting approximately 2.5 to 3.5 g of sodium bromide onto a grooved copper target plate by eddy current heating in 'ARATON' (a reducing atmosphere) to avoid the oxidation of the copper. The target is then covered by a loose foil of 0.0005" thick copper. The target is then loaded and can be irradiated using a beam current of between 30 and 50 micro-amperes for a period of 1.5 to 2 hrs without any serious damage to the target structure.

After irradiation the target is automatically removed from the cyclotron target position and transported to a lead shielded, 'Hot-Cell'

in the radiochemistry section. The rubidium-81 is recovered by washing the target with approximately 10 ml of water, to dissolve the sodium bromide target material. The sodium bromide solution is pumped onto the ion exchange column and the rubidium-81 activity adheres to the zirconium phosphate. The column is then treated with serial washings with water for injection until all the waste products (i.e., sodium-27 and sodium-24) and the unwanted sodium bromine is removed. Test elutions must now be obtained before the generator can be released for clinical use. This is covered in the next section.

The practical yield of rubidium-81 during a routine production run at the M.R.C. Cyclotron Unit is in the region of 1.5 - 2.0 mCi.μA, hr^{-1}. Therefore, for a beam current of 50 μA, an irradiation time of between 1.5 - 2.0 hrs would produce enough rubidium-81 (60-80 mCi) to load 2 to 4 generators. The actual yield is dependent on many operating factors. One of the main factors is the beam distribution on the target. A uniform distribution produces a uniform concentration of rubidium-81 in the target material without damaging the target structure itself. Whereas if the beam has a non-uniform distribution the copper foil that retains the target material can be damaged resulting in localized contamination as well as uneven distribution (or concentration) of the rubidium-81.

Rubidium-81/krypton-81m generators - infusions for experimental cardiac studies

Before the generator and its delivery system can be released for clinical or experiment use, a number of test elutions are collected and

a variety of procedures are carried out to check:

a) The krypton-81m elution activity.

b) The amount of rubidium-81 breakthrough present.

c) The chemical and biological purity of the system.

The krypton-81m elution activity is, as its name suggests, the measurement of a known volume of eluent in a calibrated counter system such that the specific activity of krypton-81m can be calculated.

The test elutions are then assayed in a calibrated gamma spectrometer to measure the percentage content of rubidium-81. A typical rubidium-81 log plot gamma ray spectrum obtained from a routine test elution of a clinical rubidium-81/krypton-81m generator is shown in figure 3. It is very important not to elute the generator with saline solution as this produces an increase in the leakage of the parent isotope (i.e., the rubidium-81 breakthrough). It is advised that the generators should always be eluted with water for injection or a physiologic solution such as 5% dextrose in water.[1,2,3]

The samples are also analysed by standard procedures to check if any contaminants are present due to generator malfunction or breakdown. Biological tests are performed to check that the eluate is sterile and pyrogen free.

The column can be dismantled and all the tubing and connections are washed in a cleansing solution and then left in a solution of 'Cedox' for 24 hrs before being put together again on the day of use.

CHAPTER II

Section II

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CHAPTER II

SECTION III

Theoretical considerations:

Rubidium-81 can be produced in a cyclotron and this nuclide devays with a half-life of 4.58 hours. The first decay product of this cation is krypton-81m. This inert and freely diffusing nuclide emits a single 190 keV gamma ray and decays with a half-life of 13 seconds (constant = 3.2/min). If a constant amount of krypton-81m can be eluted from the rubidium-81 and dissolved in 5% dextrose this could be delivered as a continuous infusion into the right and left aortic sinuses. The constant infusion of krypton-81m would then mix with the pulsatile vortex pattern of blood flow in the aortic sinuses. If equal quantities of tracer are delivered to each sinus and then adequately mixed and if the mean arterial concentration during 30 second periods is constant then krypton-81m will be delivered to the myocardium according to coronary perfusion.[1] The tracer is delivered into the aortic sinuses which act as afferent mixing chambers. The tracer partitions and mixes at this site before reaching the coronary circulation.

The delivery of krypton-81m to the heart would depend on coronary blood flow (F) and delivered arterial concentration (Ca). The tracer will diffuse into the volume of the myocardium (V). The partition co-efficient for krypton-81m is considered to be 1 and therefore blood flow is the main factor determining diffusion of the tracer in the tissues. Removal of the tracer will be governed by washout ($\frac{F}{V}$) and radiocative decay (turnover rate = 3.2/min).[2] The equation

below shows how these factors influence the myocardial or regional myocardial signal detected when krypton-81m is used as described.

$$[Kr] = g \cdot \frac{F \times Ca}{P\left(\frac{F}{V} + \lambda\right)} \quad \text{.....1.}$$

[Kr] is the myocardial signal of krypton-81m detected and g are the geometrical factors relating the heart to the gamma camera which affect the counting efficiency during each experiment.[3]

If the delivered arterial concentration (Ca) remains stable and the counting geometry (g) does not change then the myocardial signal will vary according to changes in coronary flow (F), decay (λ) and washout ($\frac{F}{V}$). The decay constant of krypton-81m (3.2/min) is much greater than the time constant for the turnover of myocardial perfusion (0.5 to 1.5 ml/ml/min). This means that during a constant infusion of krypton-81m with an equilibrium of activity in the myocardium the majority of this tracer will decay to extinction within the water space of the heart. The tracer will not equilibrate in the volume of the myocardium. The dynamic equilibrium of activity will depend mostly on arrival of tracer (coronary perfusion) and decay. Washout ($\frac{F}{V}$) will therefore not be an important determinant with perfusion below or within the physiological range.

In contrast, when a long-lived tracer is infused it will distribute in the volume of the myocardium.[2]

If the myocardial equilibrium of krypton-81m depends mostly on perfusion and constant radioactive decay then this signal should respond to alterations in myocardial blood flow. However, a number of

considerations will need to be investigated in experiments. Firstly, what are the physiological limits within which the delivered arterial concentration of krypton-81m remains stable? Is mixing of the tracer in the aortic sinuses adequate? When myocardial perfusion increases above the physiological range and approaches the decay constant of the nuclide washout of krypton-81m will become increasingly important. The theoretical relations between the myocardial signal and perfusion are shown in figure 4. This demonstrates the increasing importance of washout as perfusion approaches 3.2 ml/ml/min. Radiochemical purity, heart to background ratio of activity also spatial and temporal resolution of events are factors that must also be investigated.[3]

CHAPTER II

Section III

REFERENCES

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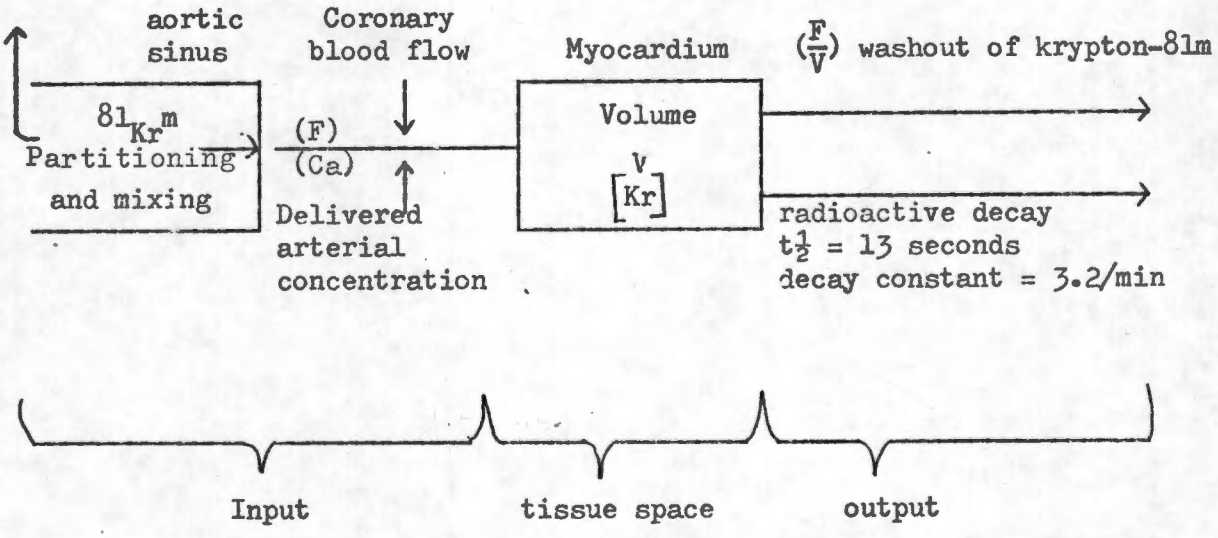
This diagram outlines the compartments involved when a continuous infusion of krytpon-81m is delivered to the aortic sinuses.



CHAPTER II

SECTION IV

Methods:

The production of rubidium-81 in a cyclotron has been described in detail. This nuclide is contained in a safe portable generator which has inlet and outlet luer ports.

Radiochemical purity:

Ten ml/min of 5% dextrose was pumped through 10 generators in separate experiments lasting 5 hours each. The total output of each generator was tested using a lithium drifted gamma ray spectrometer and <0.1 μCi of rubidium-81, rubidium-82m, rubidium-83 and rubidium-84 were detected. Atomic absorption spectrometry was used and no zirconium phosphate could be detected in the eluate. The generators contained 20 to 40 mCi of rubidium-81 and between 10 and 20 mCi of krypton-81m were eluted in 10 ml/min of 5% dextrose.

Elution of krypton-81m from rubidium-81:

A Watson-Marlow roller pump (HRE 888) was calibrated using timed collections and then set to deliver 10 ml/min of 5% dextrose. During 5 hours the output varied by $< \pm$ 4%. There were no consistent or significant deviation from the 10 ml/min (using Wilcoxon tests for paired differences). This flow was delivered to 10 rubidium-81 generators for 5 hours in separate experiments. The output tubing (Portex PE60) was taped to the detector of a gamm camera (Toshiba GCA 202). This was linked to a digital computer (Deltron-Nova 1220) which was

programmed to record the 190 Kev ± 15% gamma ray emissions of krypton-81m as quantitative 30 second frames. This could be replayed on a visual display unit. The activity in the output from each generator was calculated as a time-activity graph. The activity at 60 sec. intervals throughout the 5 hour experiments was corrected for the decay of the parent (rubidium-81).

$$\text{Corrected activity} = \text{measured activity} \times e^{-\lambda t}$$

where e = natural log

$\lambda = \frac{0.693}{4.58}$ hours

t = time of measurement.

The delivery of krypton-81m in dogs

Five mongrel dogs weighing 25 to 45 kg were sacrificed using intravenous potassium chloride. The aortic sinuses, valve and thoracic aorta were dissected free and fixed in a formalin solution. These were used to produce casts and glass models of the aortic root. Six french Kifa polyethylene tubing was heat-moulded to fit the right and left aortic sinuses (figure 5). The range for the dimensions was determined and 3 holes were positioned on the lateral surface of each loop in order to deliver equal volumes of 5% dextrose into the base of the right and left sinuses. This was tested by delivering between 5 and 15 ml/min of 5% dextrose and measuring timed collections from each loop. The proximal holes were smaller than the distal 3 so that equal volumes were delivered per unit time.

Myocardial scintigraphy using krypton-81m in dogs

Mongrel dogs were anaesthetized with intravenous (IV) thiophentone sodium (7 to 12 mg/kg). An endotracheal tube and mechanical ventilator were used to maintain respiration. Pentabarbitone sodium was used intermittently (2mg/kg) to maintain anesthesia. The ventilator and intravenous route were used to maintain the partial pressure of oxygen in arterial blood between 36 and 42 mmHg and the pH between 7.41 and 7.48. The parameters were measured at intervals using standardized and calibrated equipment.

Eight french cardiac catheters and 3 way taps were filled with heparinized saline (1000 iu/ml). The catheters were positioned in the thoracic aorta via a left femoral arteriotomy and in the inferior vena cava via a right femoral venotomy. Phasic arterial pressure was measured by connecting the aortic catheter to a P23dB Statham transducer, an amplifier and a multichannel recorder (Hewlett-Packard 7788A).

A left thoracotomy was performed and the heart supported in a pericardial cradle. Pacing wires were stitched to the left atrium. A 4 french catheter and 3 way tap were filled with heparinized saline and inserted through a purse-string suture into the left atrium. A reversible remote control snare was positioned on a major branch or the mid-portion of the left anterior descending coronary artery (LAD). This allowed graded narrowing, occlusion and release of the vessel without moving the dog under the gamma camera.

The aortic sinus catheter was straightened using a guide wire, inserted via a right femoral arteriotomy and advanced to the ascending

thoracic aorta. The guide wire was removed and the catheter was seated in the right and left aortic sinuses. Krypton-81m was continuously eluted in 5% dextrose from a rubidium-81 generator (containing 20 to 45 mCi of the cation) and delivered (at 10 ml/min) into the right and left aortic sinuses using a constant infusion pump (Watson-Marlow HRE 88).

The dog's chest was positioned within the field of a gamma camera (Toshiba GCA 202 or General Electric Maxicamera 400T). This was linked to a digital computer which was programmed to record the counts of krypton-81m as quantitative images every 28 seconds. These counts were corrected for the decay of rubidium-81 in the next 2 seconds. These 30 second periods (frames) were recorded on magnetic disc for up to 5 hours. A visual display unit, a 64 x 64 matrix of squares, an electronic light pen and up to 7 areas of interest were available to construct time-activity graphs. Images were also recorded by collecting 250,000 counts on polaroid or 35 mm film.

Groups of dogs were used for different experiments.

Group 1

Myocardial counts and images of the heart were recorded in 30 second frames during a continuous infusion of krypton-81m in 10 dogs. Images of the myocardium, aortic root and thoracic aorta were recorded. This was continued for 1 hour while heart rate, blood pressure, blood gases and pH varied by $\leq \pm$ 5%. The left anterior descending coronary artery was then occluded for 30 seconds and a region on the heart showing diminished krypton-81m activity was identified. The camera was rotated in relation to the heart so that the area of interest was

positioned on the edge of the image. This diminished the effects of counts from the opposite side of the heart when investigating the regional counts per minute in an area of interest. Quantitative images were then recorded every 30 seconds before, during and after the following interventions.

1. Atrial pacing was used to increase the heart rate by 10 beats per minute every 6 minutes up to 200 per minute (n = 10 dogs).
2. Intravenous isoprenaline (0.15 to 0.40 μg/kg/min) was used to increase the heart rate by at least 30% and/or decrease mean aortic pressure by at least 30% (n = 10).
3. The left anterior descending coronary artery was occluded for 5 minutes and then released. (n = 10).
4. Intravenous methoxamine (0.14 to 0.30mg/kg) was used to increase mean aortic pressure by at least 15% (n = 10).
5. Pentabarbitone was used intravenously (2 to 10 mg/kg) to produce a decrease in heart rate, blood pressure and cardiac output at the end of half of the experiments (n = 5).
6. Intravenous propranolol was used (0.2 to 0.5 mg/kg) to decrease the heart rate by 20 to 40% (n = 5).

In these epxeriments total and regional myocardial counts per minute of krypton-81m were recorded with images before, during and after each intervention when heart rate and blood pressure were stable.

Spatial resolution: Following the interventions the outlet tubing from the rubidium-81 generator was connected to Portex PE 60 tubing (outer diameter = 2 mm). This carried the infusion of krypton-81m in 5% dextrose and was used as a line source. The full width half maximum was calculated with the tubing positioned on the back of the heart, then on the surface of the heart nearest the camera. This was repeated with the chest closed and again when the heart was asystolic and the ventilator turned off.

At the end of each experiment the images were recalled on the visual display unit. This displayed the distribution of activity using a 16 point grey scale. An electronic light pen was used to enclose areas of interest including the total myocardium, the aortic root, a length of the catheter, an area in the lung fields outside of and equal to the total myocardial area, the area of diminished activity on occlusion of the left anterior descending coronary artery and the rest of the myocardium.

Group 2.

Thirty mongrel dogs were prepared as described in group one. In addition, portex tubing (outer diameter 0.60 mm) was filled with heparin and saline and introduced into the left anterior descending coronary artery using a puncture technique. Care was taken to select a coronary artery that was large enough to insert this catheter without detecting changes in an epicardial electrocardiogram,[1,2] aortic pressure, appearance of the epicardium or the regional myocardial distribution of krypton-81m. This catheter and a catheter in the right aortic sinus were connected to roller pumps (Watson-Marlow MREE 88)

and shielded scintillation detectors (Bicron, 1.5M2/2P). Blood was continuously removed from the right sinus and the left anterior descending coronary artery catheter at 5 ml/min, passed over the detector and then infused into the femoral venous catheter. The scintillation detectors were connected to a multichannel analyser (Nuclear Data ND100). This recording equipment was set to detect the 190 kev of krypton-81m ($\pm$ 8%) and to record the counts per minute in the 5 ml/min. of blood continuously drawn from the two sites. The tubing connecting these two sites to the sodium iodide crystal had a constant volume of 6 ml in each dog, (Figure 6a).

The dog's chest was positioned within the field of the gamma camera and quantitative images of the heart were recorded at 30 second intervals using the computer. The camera was set to detect 190 kev $\pm$ 15% for krypton-81m and later 140 kev $\pm$ 15% for technicium-99m - labelled microspheres.

The above 30 dogs were divided into 3 groups.

Group 2a.

Krypton-81m scintigrams, heart rate, blood pressure and the activity of krypton-81m in the left anterior descending coronary artery and right sinus were continuously recorded for two hours in 10 dogs. Microspheres (Duphar, mean diameter 8 to 10 μ, approximately 2000000 per injection) were labelled with technicium-99m, suspended in normal saline, agitated and injected into the left atrium as recommended by Bartrum et al.[3] The camera's detection setting was changed from 190 to 140 kev and the krypton-81m infusion was turned off. After one minute a quantitative image was recorded by collecting 250,000 counts

within the field of view of the gamma camera. Krypton-81m and technicium-99m - microsphere images were recorded in the left lateral position only, in order to separate the myocardial distribution of the technicium-99m microspheres from surrounding structures.

The gamma camera detection was reset to 190 kev and the krypton-81m infusion restarted. Krypton-81m images, heart rate, blood pressure and the activities of krypton-81m in the left anterior descending coronary artery and the right aortic sinus were continuously measured before, during and after the same interventions listed in group one.

Groups 2b and 2c.

The same experiment was performed as described for group 2a except that in group 2b the technicium-99m microspheres were given during left atrial pacing (at the maximum heart rate attained) and in group 2c they were given while the left anterior descending coronary artery was occluded. A schematic diagram of the experiment is shown in figure 6b.

At the end of each experiment the krypton-81m scintigrams on the visual display unit were divided into seven areas of interest using an electronic light pen. The counts in each area were divided by the total myocardial counts in the image. The technicium-99m microsphere image from the same experiment was displayed within the same areas of interest and the same ratios were calculated. The data was analyzed with a Wilcoxon test for paired differences.

The time-activity graphs of the coronary arterial activity of krypton-81m were drawn and the changes seen were assessed by an

analysis of variance. At the end of each experiment the left anterior descending coronary artery and right aortic sinus activity of krypton-81m were measured while each dog was given intravenous potassium chloride to produce ventricular tachycardia or fibrillation.

Group 3.

Twenty mongrel dogs (weighing between 25 and 45 kg) were prepared as described in group one. In addition, a suitably sized Systems Electronic (S.E.) electromagnetic flow probe was fitted to the coronary vessel immediately proximal to the snare. The probe diameter varied between 3 and 5 mm. Pulsatile regional coronary flow was recorded by connecting the probe to a S.E. flowmeter (SEM 275). The flowmeter system has a carrier frequency of 285 Hz and the output is nominally flat (less than 3dB down) to 80 Hz. Numerous mechanical occlusions of the left anterior descending coronary artery were made by a distally placed snare to ensure an accurate zero level throughout the studies. Recordings were selected for analysis only if, in adjacent zero determinations, there was less than a 5% of peak flow change in zero level. The flow probe was calibrated in-situ at the end of the experiments by cannulating the main left coronary artery, tying off all the branches except the one of interest, and perfusing that artery with the dog's own blood from a continuous infusion pump. The areas under the systolic and diastolic portions of the phasic flow tracings were analysed by planimetry and using the calibration data, flow in ml/min was calculated. The mean of 6 measurements of flow in ml/min. for each control period and intervention was used. The dicrotic notch of the arterial pressure wave was taken as the beginning of diastolic coronary flow.

Protocol:

Each experiment started by positioning the dog's heart under the gamma camera. Krypton-81m in 5% dextrose was delivered by constant infusion into the aortic sinuses. The total and regional myocardial activity of the tracer was recorded for 20 minutes while heart rate, aortic pressure and phasic regional coronary flow were stable. The left anterior descending coronary artery was occluded for 30 seconds and a region of the heart on the visual display showing diminished krypton-81m activity was identified. The camera was rotated in relation to the heart so that the area affected by the snare was positioned on the edge of the image.

The interventions described in group one were used to increase and decrease regional and total myocardial perfusion. Regional perfusion (using the probe) also total and regional myocardial counts per minute of krypton-81m were recorded before, during and after each intervention, when heart rate, blood pressure and phasic regional coronary flow were stable. The random errors of the method were examined in two ways.

1. In each experiment the total and regional myocardial counts per minute of krypton-81m were recorded before, during and after each intervention. The animals were allowed to recover so that heart rate, blood pressure and coronary flow returned to control. At least 4 interventions were used in each experiment and at least 2 of these were repeated. The control myocardial krypton-81m activity before and after each intervention were compared using linear regression and a Wilcoxon

test for paired differences. The effects of the same interventions delivered twice on total and regional myocardial krypton-81m counts per minute were compared in the same way.

2. In each dog, the quantitative images of myocardial krypton-81m recorded before, during and after those interventions that affected the whole heart (pacing, isoprenaline, propranolol and pentabarbitone) were divided into 7 areas with an electronic light pen on the visual display unit. The activity in each area was expressed as a ratio of the total myocardial activity. Seven ratios from each heart were calculated before, during and after each intervention, (n = 20 dogs). A two way analysis of variance was used to test whether the control or intervention ratios changed during the experiments.

After the interventions each heart remained in position under the gamma camera and the left anterior descending coronary artery carrying the flow probe was occluded for 45 seconds. The regional decrease in activity of krypton-81m was recorded by the gamma camera and computer and outlined on the visual display unit with the electronic light pen. The position of each heart and the region affected by the snare were checked by comparing this area and the position to those outlined at the beginning of the experiment. Six areas of interest were constructed as described in group one. The computer then calculated the counts per minute of krypton-81m in each area during each 30 second period of the entire experiment.

At the end of each experiment Patent Blue 5 dye was selectively injected into the vessel carrying the flow probe. The heart was stopped within 3 seconds with intra-arterial potassium chloride. This outlined the area of supply for dissection. The heart was removed and weighed. The stained myocardial segment was dissected free and weighed.

Calibration of krypton-81m counts per minute and calculation of systematic errors

The purpose was to examine the changes in the myocardial signal $[Kr]$ which resulted from changes in myocardial blood flow. For any change in myocardial blood flow from F_1 to F_2 we have the following expressions for the corresponding myocardial counts per minute of krypton-81m,

$$F_1\,(Ca) = g.\,[Kr_1].\left(\frac{F_1}{V}\,P + 3.2\right) \quad \ldots\ldots\ldots\ldots\ldots 2.$$

$$F_2\,(Ca) = g.\,[Kr_2].\left(\frac{F_2}{V}\,P + 3.2\right) \quad \ldots\ldots\ldots\ldots\ldots 3.$$

where g is the relative detection efficiencies between counting the myocardial krypton-81m content $[Kr]$ and the concentration of krypton-81m in the arterial blood (Ca). If it is assumed that in any single experiment there are no significant changes in g or Ca then it is possible to solve F_2 by dividing 2 by 3.

$$F_2 = \frac{3.2\ F_1}{\frac{[Kr_1]}{[Kr_2]}\left(\frac{PF_1}{V} + 3.2\right) - \frac{PF_1}{V}}$$

This can be written:

$$\frac{F_2}{V} = \frac{3.2\,\frac{F_1}{V}}{\frac{[Kr_1]}{[Kr_2]}\left(\frac{PF_1}{V} + 3.2\right) - \frac{PF_1}{V}} \quad \ldots\ldots\ldots\ldots 4.$$

It follows that given a known value for $\frac{F1}{V}$ as measured by a reference technique and the corresponding krypton-81m signal $[Kr_1]$ it should be possible to convert subsequent tissue counts $\left(\text{IE. } [Kr_2]\right)$ into values of $\frac{F}{V}$ simply by insertion into equation 4. In effect, it should be possible to calibrate each preparation in order to convert changes in myocardial krypton-81m activity into absolute changes in $\frac{F}{V}$.

In each dog the resting reference regional coronary flow in ml/gm/min was calculated using the flowmeter data. The specific gravity of myocardium (1.05) was used to convert this to flow per unit volume $\frac{F_1}{V}$. This was related to the resting control regional counts per minute of krypton-81 in that area $[Kr_1]$. During each intervention a new value for flow per unit volume $\frac{F_2}{V}$ was calculated using the new regional counts per minute of krypton-81m $[Kr_2]$ and equation 4. This result was converted to ml/gm./min and compared to the new regional coronary flow measured using the probe and weighed myocardium supplied. The relationship was examined using linear regression analysis.

By calibrating the krypton-81m counts in this way it is possible to test the theoretical considerations, the stability of the arterial concentration of the tracer, mixing and streaming.[4] The regression analysis tested the technique using krypton-81m for measuring changes in regional myocardial perfusion.

Statistical Methods

Groups of results are expressed as a mean and one standard deviation or a mean and range. Comparison of groups was performed using a Wilcoxon test for paired differences. Significance was recorded if $P \leq .01$. If the data was parametically distributed the significance of sequential data was assessed in an analysis of variance. Linear regression was used to compare the range of values of two parameters when calculating systematic and random errors.

CHAPTER II

SECTION V

Results

Radiochemical purity

There was <0.1 μCi of rubidium-81 in 3000 ml of 5% dextrose eluted over 5 hours from the generators. The background of activity in the laboratory was less than 500 counts per minute at 190 kev and less than 600 counts per minute at 140 kev. If the camera's energy detection window was set at 500 to 600 kev for rubidium-81 during the experiments no activity above background was detected.

Elution from the rubidium-81 generators

Krypton-81m was continuously eluted in 10 ml/min of 5% dextrose. The gamma camera recorded the activity in the output tubing. Figure 7 shows the arrival of counts per minute and the output of krypton-81m during the 5 hours. This shows a constant decay due to rubidium-81 and when this is corrected the counts per minute of krypton-81m varied by $< \pm$ 5%.

The delivery of krypton-81m in dogs

Figure 8 shows the glass model of the aortic root used to design a catheter to deliver krypton-81m into the right and left sinuses. The basic design and variable dimensions are shown in figure 9. Three holes of unequal size on the outer surface of each loop allowed infusion of equal volumes into each sinus when between 5 and 15 ml/min of 5% dextrose was delivered to the catheter. Timed collections were used to check that the volumes differed by no more than $\pm$ 10%.

Myocardial scintigraphy using krypton-81m in dogs

Figures 6a and b show diagrams of the experiments. The specialised catheter was inserted using a guide wire as far as the ascending aorta. The wire was removed and the catheter was seated as shown in figure 10. Urovison (76%) was injected by hand (5 ml) to check this position.

Group 1: Figure 11 shows four images recorded at 5, 20, 40 and 60 minutes during the first hour of krypton-81m infusion. The aorta, aortic sinuses and myocardium (left lateral position) are shown. No interventions were used and heart rate and blood pressure varied by $< \pm$ 5%. During this hour the counts per minute of krypton-81m in areas of interest enclosing the catheter, aortic root, total and regional myocardium and background varied by less than $\pm$ 5% in the 10 dogs. The background counts were less than 4% of total myocardial counts per minute in all the dogs.

Figure 12 shows four images recorded before, during and after atrial pacing. The heart rate was increased from 120 $\pm$ 14 beats/min (mean $\pm$ SD) to 200 beats/min. Counts per minute of krypton-81m varied by $< \pm$ 5% in the catheter and $< \pm$ 5% in the aortic sinuses up to a heart rate of 180 beats/min. When the heart rate increased from 180 to 200 beats/min the counts per minute in the aortic root decreased by 12 $\pm$ 3.0% (mean $\pm$ SD). The total and regional myocardial counts per minute of krypton-81m increased by 110 $\pm$ 8%. Background activity did not change significantly.

Intravenous isoprenaline increased the heart rate from 118 $\pm$ 12 beats/min to 192 $\pm$ 10 beats/min. Mean aortic pressure decreased from

101 ± 4 to 74 ± 7 mmHg. Counts per minute of krypton-81m varied by < 5% in the catheter and in the aortic root up to a heart rate of 180/min. When heart rate increased from 180/min to 192/min the counts per minute in the aortic root decreased by 14 ± 2%. Total and regional myocardial counts per minute of krypton-81 increased by 131 ± 17%. Background activity did not change significantly.

Figure 13 shows an example of four images of the heart recorded before, during and after occlusion of the left anterior descending coronary artery for 5 minutes. The aortic root catheter and background varied by < ± 5% throughout.

Intravenous propranolol produced a decrease in heart rate from 121 ± 8 beats/min to 73 ± 4 beats/min. Mean aortic pressure decreased from 98 ± 4 mmHg to 91 ± 6 mmHg. Counts per minute of krypton-81m in the aortic root, catheter and background varied by < ± 5% throughout. The total and regional myocardial counts per minute of krypton-81m decreased by 21 ± 7%.

Figure 14 shows an example of the effects of intravenous pentabarbitone. This drug produced a decrease in heart rate from 120 ± 10 beats/min to 30 ± 4 beats/min and a decrease in mean aortic pressure from 97 ± 10 to 41 ± 12 mmHg. Counts per minute in the catheter and background varied by < ± 5% throughout. Counts per minute in the aortic root varied by < ± 5% until the heart rate reached 50 ± 10 beats/min. The aortic root counts per minute increased by 14 ± 4% as the heart rate fell from 50 ± 12 to 30 ± 10 beats/min. The total and regional myocardial counts per minute of krypton-81m decreased by 69 ± 7% during this intervention.

Intravenous methoxamine increased the mean aortic pressure from 101 ± 8 to 127 ± 19 mmHg. Heart rate decreased from 123 ± 12 to 118 ± 10 beats/min. Counts per minute of krypton-81m varied by < ± 5% in the catheter, aortic root and background. Total and regional myocardial counts per minute of krypton-81m increased by 7.4%.

Spatial resolution

The energy detection window of the camera was set to detect 190 ± 10 kev. Generators containing between 20 and 45 mCi of rubidium-81 were used. Between 7000 and 12000 counts per second were recorded from the total myocardium. Resolution at full width half maximum using a line source in various circumstances is shown below:

Position of line source:	open chest asystolic	open chest beating	closed chest beating
Back of heart, 7-9 inches from camera face	9 mm	1.3 cm	1.5cm
Front of heart 3-5 inches from camera face	7 mm	1.0 cm	1.2cm

These numbers represent a mean of 5 estimations.

Group 2

The delivered arterial concentrations of krypton-81m were recorded in each dog in groups a, b and c (n = 30) for 2 hours. Figure 15 shows the counts per minute of krypton-81m recorded in the 5 ml/min of blood continuously withdrawn from the left anterior descending coronary artery and the right aortic sinus during the 2 hours while heart rate, blood pressure and the myocardial counts per minute of krypton-81m varied by < ± 5%.

The inverventions listed in group one were then used to change heart rate and blood pressure. The control heart rate of 119 $\pm$ 14 beats/min and mean aortic pressure of 98 $\pm$ 7 mmHg were both treated as 100% as was the control counts per minute of krypton-81m in the left anterior descending coronary artery and right aortic sinus. The effects of each intervention on the delivered arterial activity of krypton-81m in these two sites are plotted as percentage change in figure 16.

Left anterior descending coronary artery occlusion and release produced $<\pm$ 5% changes in counts per minute of krypton-81m in the 5 ml/min withdrawn from the left anterior descending coronary artery and the right sinus in all the dogs. The snare was always distal to the sampling catheter. Similarly, the 27 $\pm$ 4% increase in mean aortic pressure produced by intravenous methoxamine produced no significant ($<\pm$5%) changes in the delivered arterial concentration of the tracer. An analysis of variance showed that the delivered counts per minute of krypton-81m were significantly changed ($P = <.01$) when heart rate increased by more than 60% or decreased by more than 50%. It was not possible to separate completely the effects of changes in blood pressure although the test using methoxamine showed that blood pressure had no significant effect.

A comparison with technicium-99m microsphere distribution

Figure 17 shows the regional myocardial distribution of krypton-81m infused into the aortic sinuses and the regional myocardial distribution of technicium-99m microspheres injected into the left atrium. These images were recorded from the same dog in the left lateral position

while all the haemodynamic parameters varied by $< \pm$ 5%. The regional and total myocardial counts per minute of krypton-81m and technicium-99m microspheres were calculated from the same 7 areas of interest in each dog. Ratios were calculated by dividing the counts per minute in each area by the total counts in the same image. The range of the ratios was 0.02 to 0.85. There were no significant differences between the krypton-81m and technicium-99m ratios from each area (Wilcoxon test for paired differences, $P = > .05$) The regional myocardial distribution of these two tracers were also examined during atrial pacing at 200 beats/min (n = 10, figure 18) and during left anterior descending coronary artery occlusion (n = 10, figure 19). Again a comparison of the ratios describing the regional myocardial distribution of the two nuclides showed no significant differences ($P > 0.05$).

Systematic errors

Group 3

Figure 20 shows the images, regional myocardial counts per minute and phasic regional coronary flow recorded before, during and after one of the interventions used to increase and decrease myocardial perfusion. The control measurement of regional flow per unit weight of myocardium was 0.80 $\pm$ 0.3 ml/gm/min. The increases and decreases in this parameter were compared to the increases and decreases in regional myocardial perfusion calculated from the calibrated changes in the regional counts per minute of krypton-81m in the area supplied by the left anterior descending coronary artery. Figure 21 shows a significant relationship between measured and calculated changes in flow ($P = < .001$; $r = 0.97$; $y = .908X + 0.105$; $n = 60$). The linear regression

analysis shows a random variability of 7%. When flow was increased above 3.0 ml/gm/min this was not followed by a further detectable increase in the regional myocardial activity of krypton-81m.

Random errors

When two interventions were repeated the control regional and total myocardial counts per minute of krypton-81m recorded before and after were compared as were the changes produced when the same intervention was used twice. Linear regression analysis was used to show adequate reproducibility when recording measurements with krypton-81m ($P = <.001$; $r = 0.98$; $Y = 0.982\ X + 0.257$; $n = 100$).

The ratios of regional to total myocardial activity of krypton-81m were calculated from the 7 areas of interest before, during and after using those interventions that affect the whole heart. The range of the ratios was 0.02 to 0.87. These results showed no significant changes in the distribution of krypton-81m activity in the images ($P = > 0.05$). There was no detectable redistribution of the tracer in the myocardial images with interventions that changed heart rate, blood pressure and cardiac output.

CHAPTER II

SECTION VI

Discussion:

The ability to measure moment-to-moment changes in regional myocardial perfusion in the intact subject would allow the clinical investigator to assess an important part of the effects of coronary artery disease. The requirements of any new technique must include a clear description of the systematic and random errors also its application in experimental and clinical studies.[1]

Methods for measuring coronary blood flow

The electromagnetic flow probe is now an acceptable method for measuring pulsatile or mean flow in arteries and veins.[2,3] The stability of the probe when placed on small arteries is a technical problem and except for perioperative investigation of arterial flow the technique cannot be used to investigate regional myocardial perfusion in patients.[3,4] In addition, the relationship between flow in large arteries and perfusion to ventricular myocardium is complex because of cross circulation, collaterals and shunting. The electromagnetic flow probe cannot be used in patients to study nutrient perfusion to ventricular tissue.[5,6,7,8,9]

The left atrial injection of radioactively labelled microspheres is a reference method in experimental practice. The results are quantitative and can separate endocardial and epicardial events. There is still some controversy about the behaviour and distribution of these foreign particles in the circulation and there is a limited

ability to see changes in perfusion. The method requires left atrial annulation and myocardial dissection and therefore cannot be used in patients.[10]

Long-lived and inert isotopes can be selectively injected into the coronary circulation. An analysis of the washout of these tracers is a widely used method to study myocardial flow per unit volume experimentally and in man. The technique is invasive but simple and quantitative. The 80 kev emissions of xenon-133 provide data of poor spatial resolution. The absorption into tissues, scattered radiation, changing partition coefficient, diffusional shunting and countercurrent exchange are all problems that produce systematic errors.[11] The bolus injection and method of detection mean that the technique will preferentially measure areas of high flow. Regional decreases of perfusion may be missed or underestimated because insufficient tracer reaches the area and the washout data may be statistically poor. It is also difficult to use this method to see changes in regional perfusion.[12]

Cations such as rubidium-81, cesium-131 and potassium-43 can be given by a peripheral intravenous injection and their distribution in the myocardium can be recorded as images. The myocardial activity of these tracers is determined by a complex interaction between perfusion, arterial concentration, energy dependent cellular extraction, tissue mass, fractional escape and recirculation. Thallium-201 has emerged as the cation of choice and the technique is non-invasive. Regional decreases in the activity of this tracer can identify myocardil infarction or acute ischemia depending on whether they appear to be

fixed or whether the defect is reversible and seen only during stress. The method is widely applicable, however, it is not quantitative, the background of activity is relatively high and the resolution of events is poor when compared to the 140 kev emissions of technicium-99m. The long half-life of this tracer makes the dose to the patient considerable and this prevents any dynamic studies of changes in regional perfusion.[13]

Methods using the inhalation of hydrogen, nitrous oxide or argon with coronary sinus sampling provide data about overall myocardial perfusion. These techniques will not identify any regional disturbances of myocardial perfusion and are therefore of limited value in patients with coronary artery disease.[14,15]

The term blood flow encompasses a number of possible measurements such as flow in arteries (ml/min), flow per unit volume in tissues (ml/V/min) and flow per known weight of tissue (e.g., ml/100gm/min). There are measures of perfusion that do not include physiological units, for instance the regional distribution of myocardial perfusion can assess the state of perfusion to segments of the heart supplied by stenosed arteries in relation to perfusion in segments supplied by normal vessels. Also, a reproducible and accurate measure of changes in perfusion or the distribution of perfusion within an organ can provide valuable dynamic information about the behaviour of the circulation in various physiological and pathological states.

Krypton-81m

These experiments have shown that the unique physical properties of krypton-81m provide scintigrams of the heart that have advantageous physical properties. For example, the background is negligible. The

spatial resolution of events and the statistically good count rates are all better than might be expected when using xenon-133 or thallium-201. Attenuation and scatter will be less of a problem when compared to nuclides of lower energies.

A specially designed catheter has been used to continuously infuse equal volumes of 5% dextrose and krypton-81m. The shape of this catheter means that it cannot engage the coronary ostia and it can be positioned in the aortic sinuses.

Bellhouse has investigated the pattern of pulsatile blood flow in the aortic sinuses and has described the accelerating and decelerating vortex pattern with each heart beat. Their studies suggest that these particular flow patterns aid coronary perfusion and aortic valve closure.[16,17] If krypton-81m is delivered as a constant infusion into this space there is likely to be a fluctuation in the arterial concentration with systole and diastole. A direct investigation of these changes is not yet technically possible. The method used so far looks at changes in the myocardial equilibrium of activity over 30 or 60 second periods. This will represent a mean estimation in the myocardial water space of an inert and freely diffusing tracer. This mean estimation will not be sensitive to the beat-to-beat regular fluctuations of krypton-81m in the much smaller intra-arterial vascular compartment. Nevertheless, if the regional myocardial equilibrium of krypton-81m is to be used to measure changes in regional myocardial perfusion then the mixing, streaming and the delivered arterial concentration during 30 second periods must be investigated.

These experiments have shown that within the limits imposed by using a gamma camera, the regional myocardial distribution of radioactively labelled microspheres injected into the left atrium was similar to the regional myocardial distribution of krypton-81m infused into the aortic sinuses. This relationship was maintained during changes in heart rate, blood pressure, cardiac output and coronary flow. This would suggest that the krypton-81m is adequately mixed in each sinus and delivered according to the distribution of coronary flow. The 13 second half-life of krypton-81m prevented more detailed tissue studies of distribution and mixing of the tracer.[18]

The theoretical basis for using krypton-81m to measure changes in regional myocardial perfusion demands that the delivered arterial concentration remains stable. This must be tested because a constant quantity of krypton-81m is delivered into a variable flow within the aortic sinuses. These experiments examined the delivered arterial concentration in the left anterior descending coronary artery and the right sinus and the results suggested that there is an adequate reserve of mixed tracer. This was because the arterial concentrations were stable during control periods and over a wide range of changes in heart rate, blood pressure and cardiac output. These experiments have defined some of the physiological limits within which the delivered arterial concentration remains stable. The arterial concentration should be measured in the right and left aortic sinuses and in all three major coronary arteries simultaneously. This was not possible technically and we have taken the left anterior descending coronary artery to represent the left circulation.

The vortex pattern of blood flow in each sinus might be expected to favour the mixing of an inert, freely diffusing gas in solution. It is not known if changes in cardiac output cause parallel and equal changes in flow through each aortic sinus and therefore changes in cardiac output may affect the delivered arterial concentration. In addition, changes in left and right coronary flow may affect the reservoir of tracer in each sinus. The direct measurements in the right sinus and left anterior descending coronary artery suggest that there is no significant effect on the coronary arterial concentration until heart rate is increased or decreased by more than 50%. The separate effects of blood pressure, cardiac output and coronary flow were difficult to assess but no significant changes in the arterial concentration of krypton-81m could be detected with interventions that change these parameters markedly.

Other workers have not shown good mixing of indicators in the aortic root. These experiments have used bolus injections under pressure, usually of particulate matter such as microspheres or macroaggregates. These experiments using krypton-81m are different in that a soluble, inert and freely diffusing gas in solution is slowly infused in small volumes into the base of each sinus.[18,19,20,21]

The comparison between changes in regional myocardial perfusion measured using an electromagnetic flow probe and krypton-81m showed excellent systematic and random errors. These results showed that the calibrated regional counts per minute of krypton-81m could be used to assess changes in regional myocardial perfusion between 0 and 3 ml/ml/minute. The physiological range for myocardial blood flow in man is 0.5 to 1.5 ml/gm/minute. This supports the theoretical concept and the experiments

showing mixing and stable arterial concentration.[22]

Disadvantages of using krypton-81m

This method clearly has a number of disadvantages. It is invasive and requires a cyclotron to produce rubidium-81. The images do not separate endocardial from epicardial events. An appreciation of depth is lost when the heart is represented in 2 dimensions by a gamma camera. Multiple views are therefore needed to understand the superimposition of structures and to assess the extent of lesions. Regional increases in the myocardial activity of krypton-81m will be affected by a physiochemical constant (i.e., the decay constant, 3.2/min). This will not vary but it is necessary to correct the effects of distorting the relationship between increased counts and increased flow.

Clearly, a number of further experiments are required to complete an investigation of krypton-81m. The partitioning of the indicator between the systemmic and coronary circulations might be measured directly in various circumstances by delivering tritiated water with krypton-81m. Single photon tomography would also help to quantitate the regional myocardial distribution of krypton-81m. An absolute measure of regional perfusion in physiological units may be possible by recording the washout of krypton-81m at the start and end of each experiment. The time constant (t $\frac{1}{2}$) could be used to calculate flow/unit volume. However, the rapid decay of krypton-81m will have a marked effect on this data and further experiments are needed.

These experiments have shown that it is possible to continuously infuse krypton-81m into the aortic sinuses of the dog. The equilibrium of activity distributed in the myocardium can be recorded as images

that have relatively good spatial and temporal resolution of events. The unique physical properties of krypton-81m mean that the activity in the heart is dominated by perfusion and radioactive decay. The experiments have shown that the mixing, distribution and arterial concentration are adequate and stable within a useful range of changes in haemodynamic parameters. The comparison with a reference method for measuring changes in regional myocardial perfusion between 0 and 3 ml/ml/min showed adequate systematic error and reproducibility.

The disadvantages of the method have been outlined and they include important logistic, theoretical and physiological limitations. However the specific feature is that the technique will measure moment-to-moment changes in regional myocardial perfusion in-vivo.

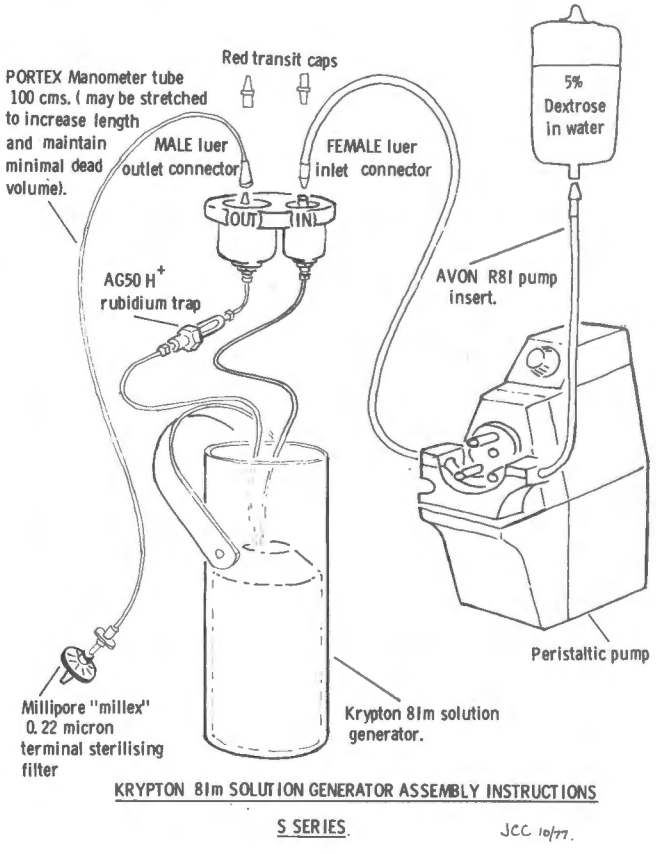


Figure 2: On the left is shown the portable, lead lined rubidium-81-krypton-81m generator with the inlet and outlet luer parts used to infuse 5% dextrose and elute krypton-81m.

On the right is shown schematically how the continuous infusion system is assembled.

NUCLEAR REACTIONS	BEAM NATURE	TARGET MATERIAL	BEAM ENERGY (MeV)	BEAM CURRENT (uA)	^{81}Rb YIELD ($mCiuAhr^{-1}$)	PRODUCTION CENTRE
$^{79}Br(\ ,2n)^{81}Rb$	^{4}He	NaBr (thick target)	30	50	1.5-2.5	M.R.C. Cyclotron Unit Hammersmith.
$^{79}Br(\ ,2n)^{81}Rb$	^{4}He	Cu_2Br_2 (thick target)	30	50	2.0	Argonne Cyclotron, Argonne National Lab., U.S.A.
$^{81}Br(\ ,4n)^{81}Rb$	^{4}He	NaBr (thin target)	30	15	2.9	Lawrence Radiation Lab., 88" Cyclotron Berkeley, U.S.A.
$^{81}Br(^{3}He,3n)^{81}Rb$	^{3}He	NaBr (thick target)	21	25	0.035	Sloan Kettering Institute, New York, U.S.A. (Cs-15 Cyclotron)
$^{79}Br(^{3}He,\ n)^{81}Rb$	^{3}He	NaBr (thick target)	21	15	0.035	Sloan Kettering Institute, New York, U.S.A. (Cs-15 Cyclotron)
$^{80}Br(^{3}He,pn)^{81}Rb$	^{3}He	37% enriched ^{80}Kr	20	5	0.226	Franklin McLean Memorial Research Institute, Chicago. (Cs-15 Cyclotron)
$^{80}Kr(d,\ n)^{81}Rb$	^{2}H	37% enriched ^{80}Kr	8	5	0.7	Franklin McLean Memorial Research Institute, Chicago.

Table I: This table lists some of the nuclear reactions and details for the cyclotron production of rubidium-81.

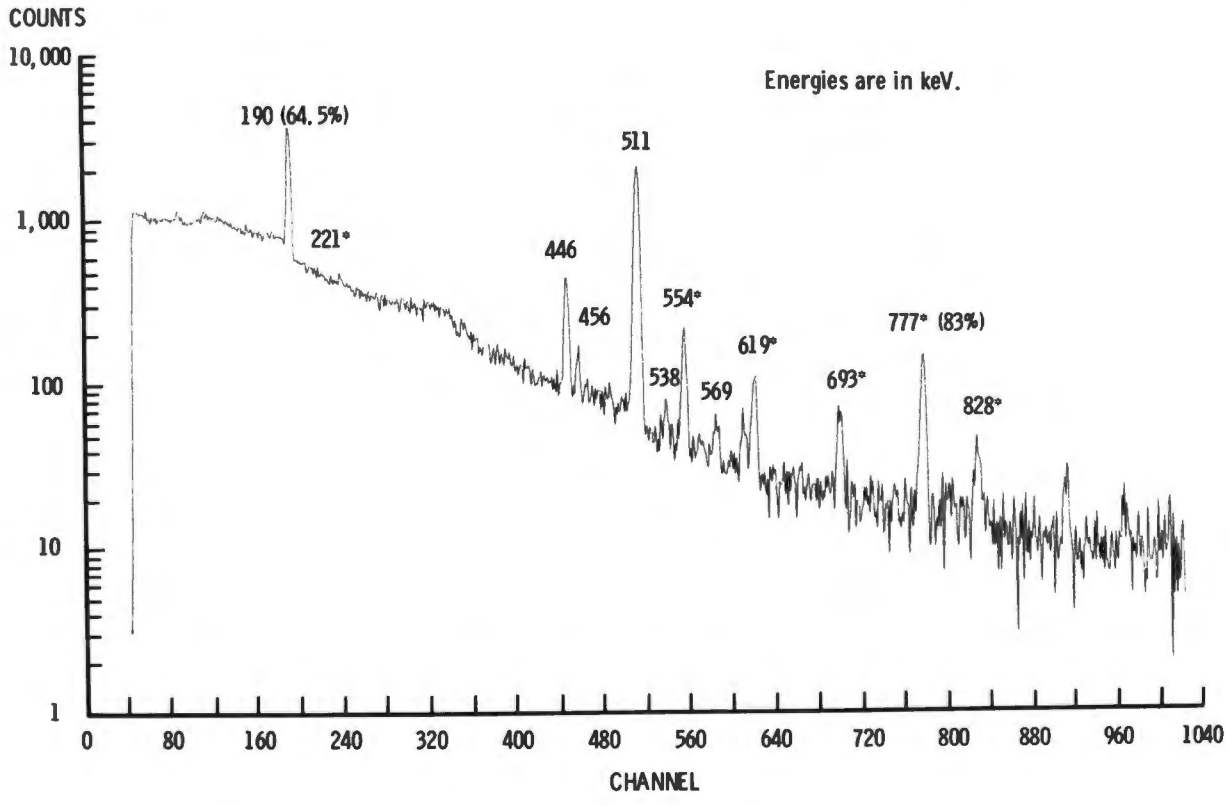


Figure 3: This graph of counts in different channels shows a typical spectrum of gamma energies obtained when rubidium-81 is examined in a gamma ray spectrometer.

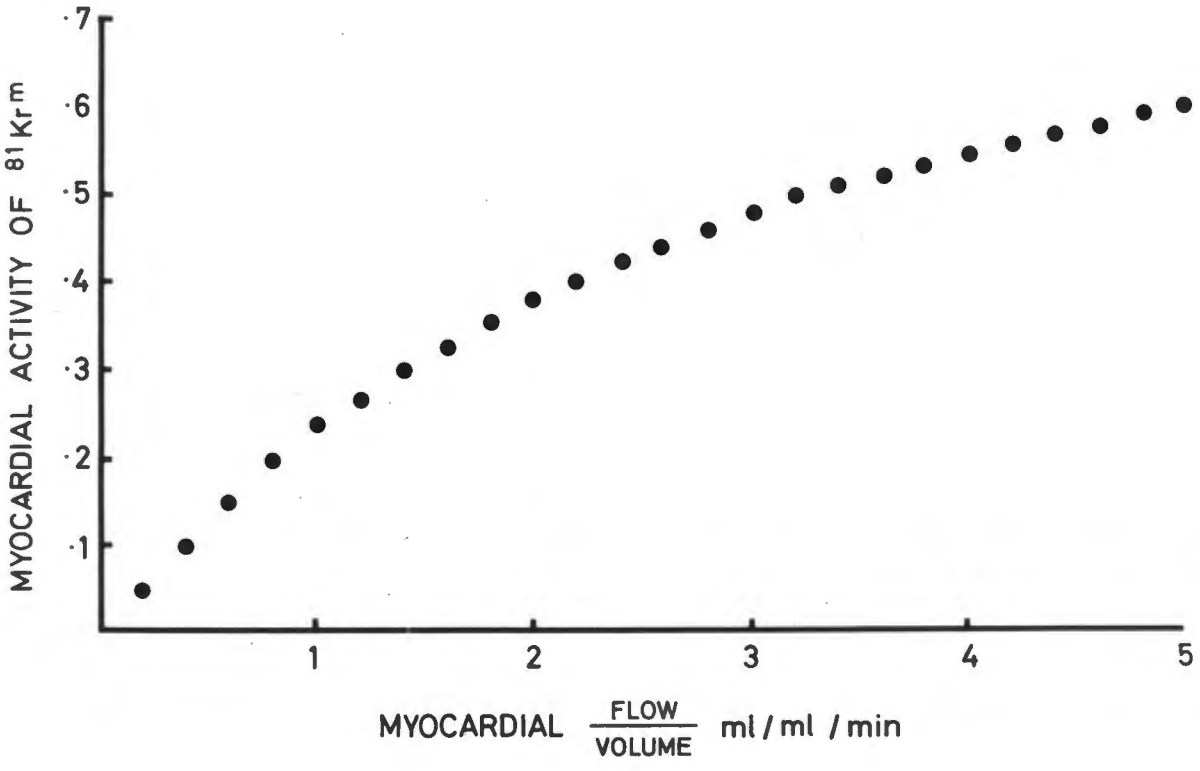


Figure 4: This graph plots the theoretical activity of krypton-81m in the myocardium at different values of flow per unit volume. This assumes mixing and a stable arterial concentration. At low flow activity is linearly related to flow. As flow per unit volume increases above the physiological range and approaches the decay constant for krypton-81m (3.2/min), washout of tracer systematically distorts the relationship between perfusion and activity.

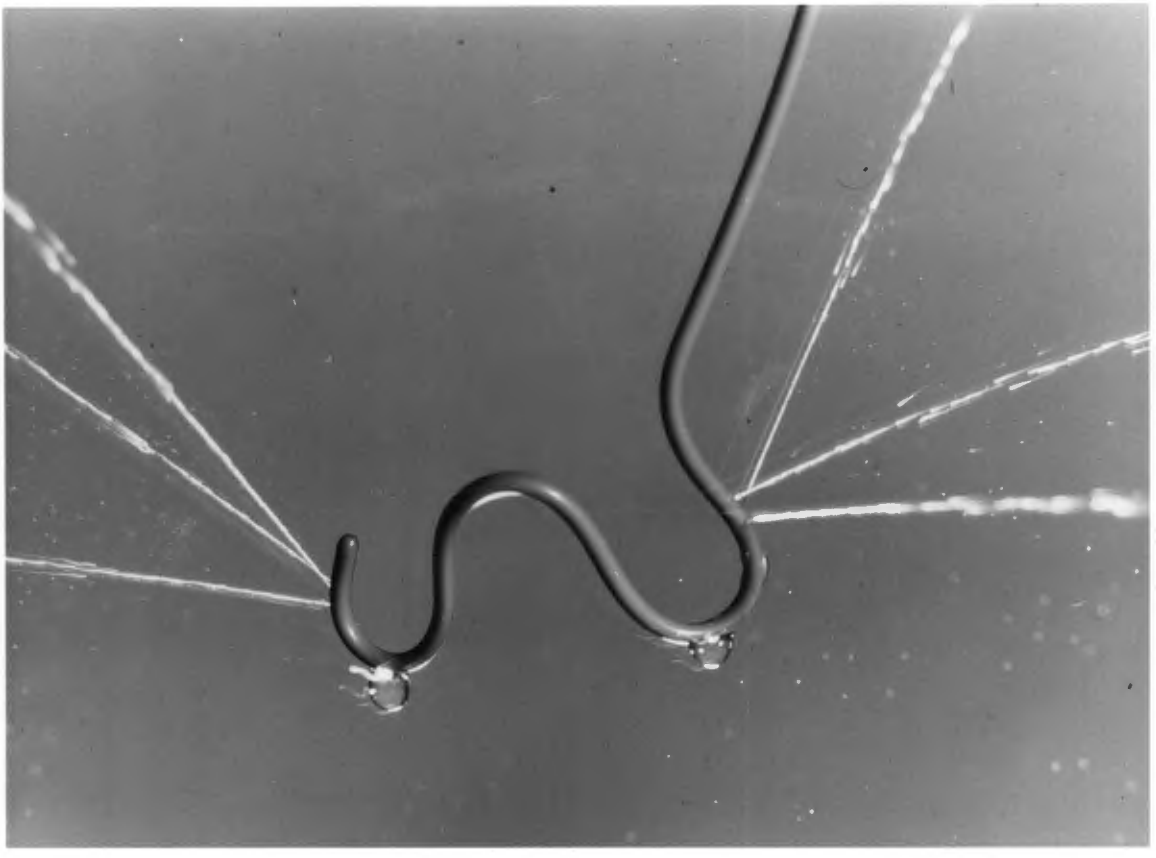


Figure 5: This photograph shows the specialized catheter. The distal loop seats in the left aortic sinus and the proximal loop seats in the right aortic sinus. Unequal holes on each loop allow equal volumes of 5% dextrose plus krypton-81m to be infused into each sinus.

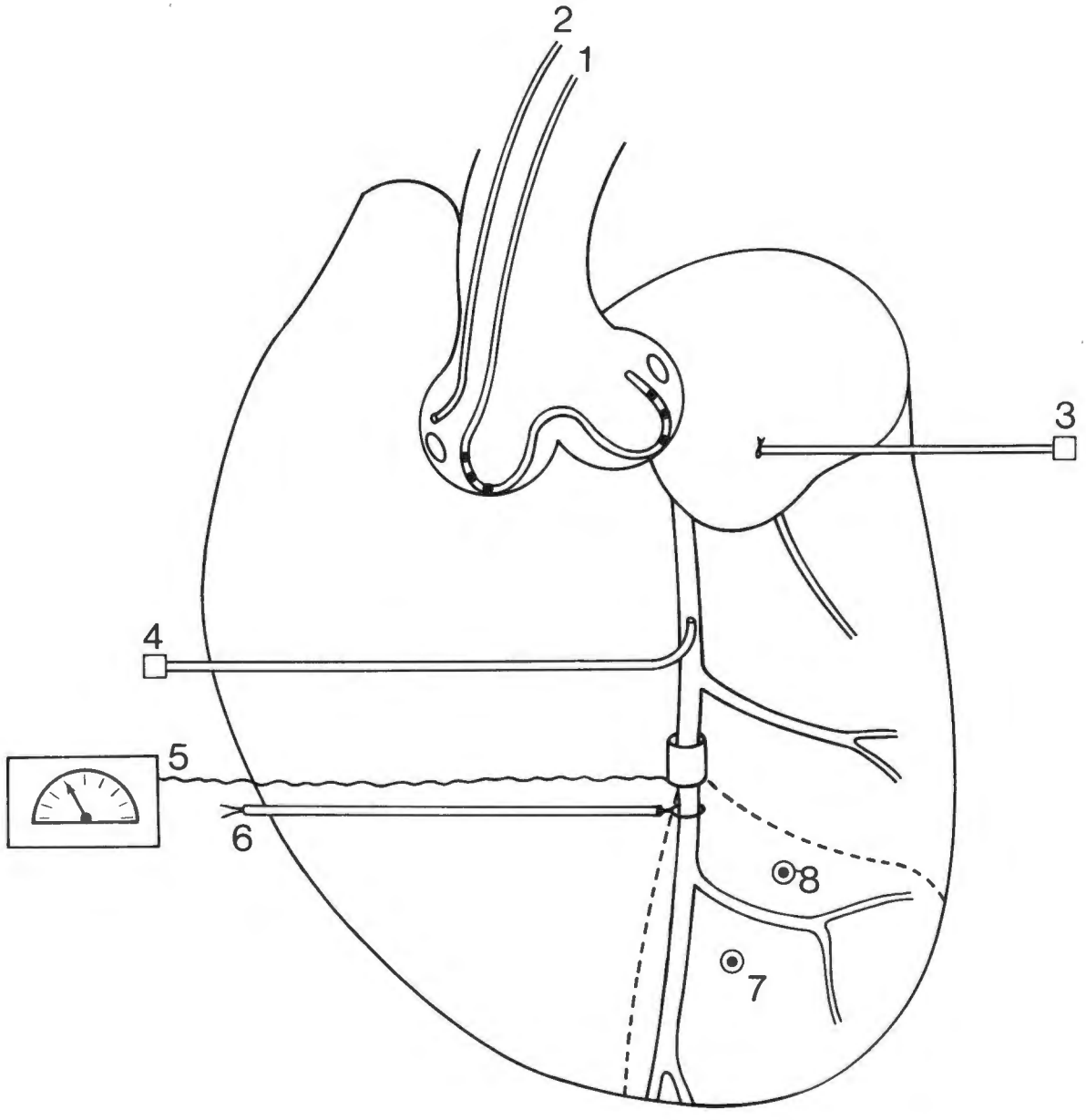


Figure 6a: This schematic diagram shows the experimental design.

1. The catheter used to infuse krypton-81m.
2. The catheter used to monitor the delivered arterial concentration.
3. The left atrial catheter.
4. The catheter used to monitor the arterial concentration of tracer in the coronary artery.
5. The electromagnetic flow probe and meter.
6. A reversible remote controlled snare.

7 and 8 Epicardial sites for recording the electrocardiograph.

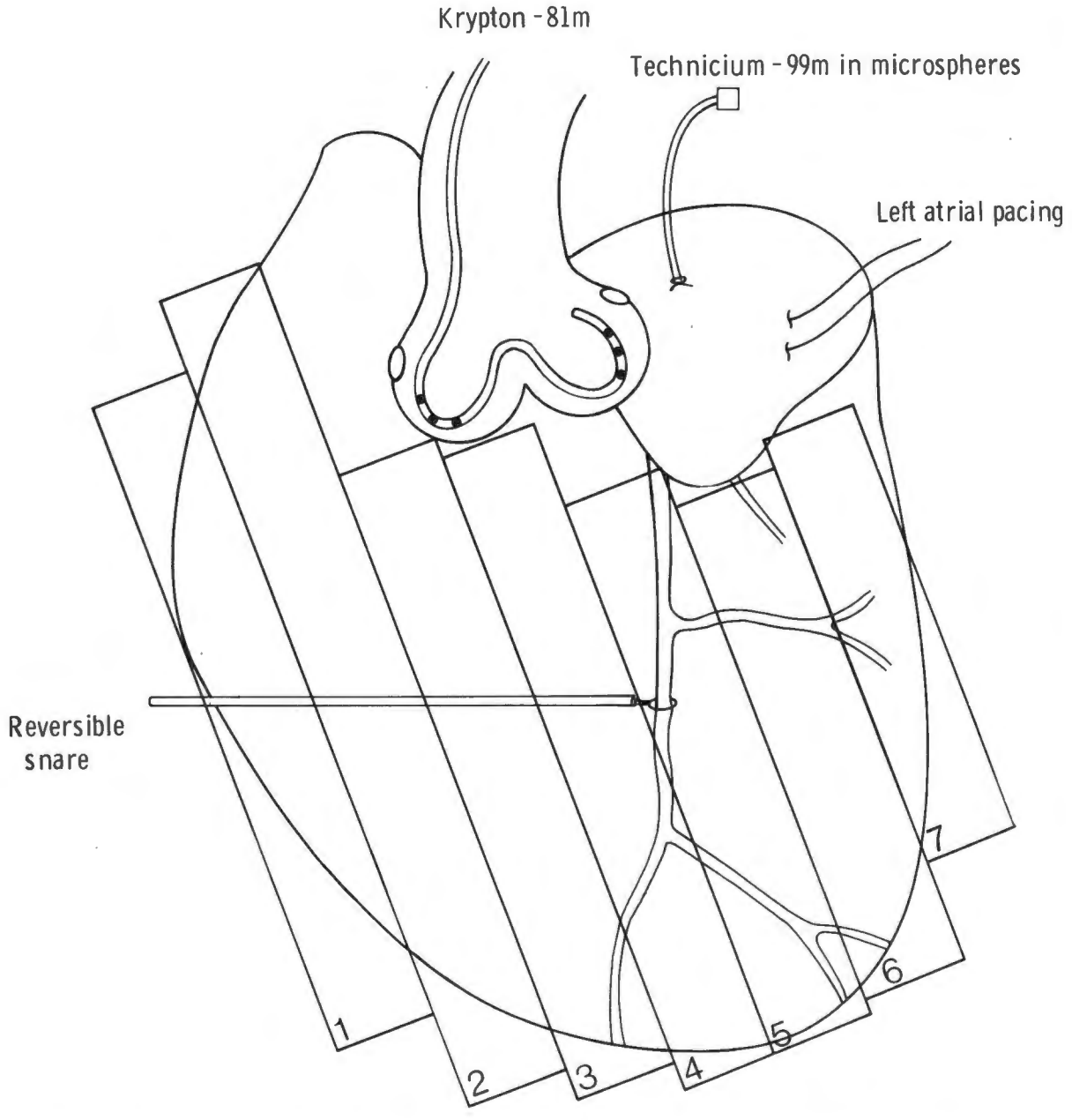


Figure 6b: This schematic diagram of the experiments shows the krypton-81m catheter, the left atrial catheter and the myocardial areas of interest (1-7). These were used to compare the regional myocardial distribution of krypton-81m infused into the aortic sinuses and the regional myocardial distribution of technicium-99m labelled microspheres injected into the left atrium.

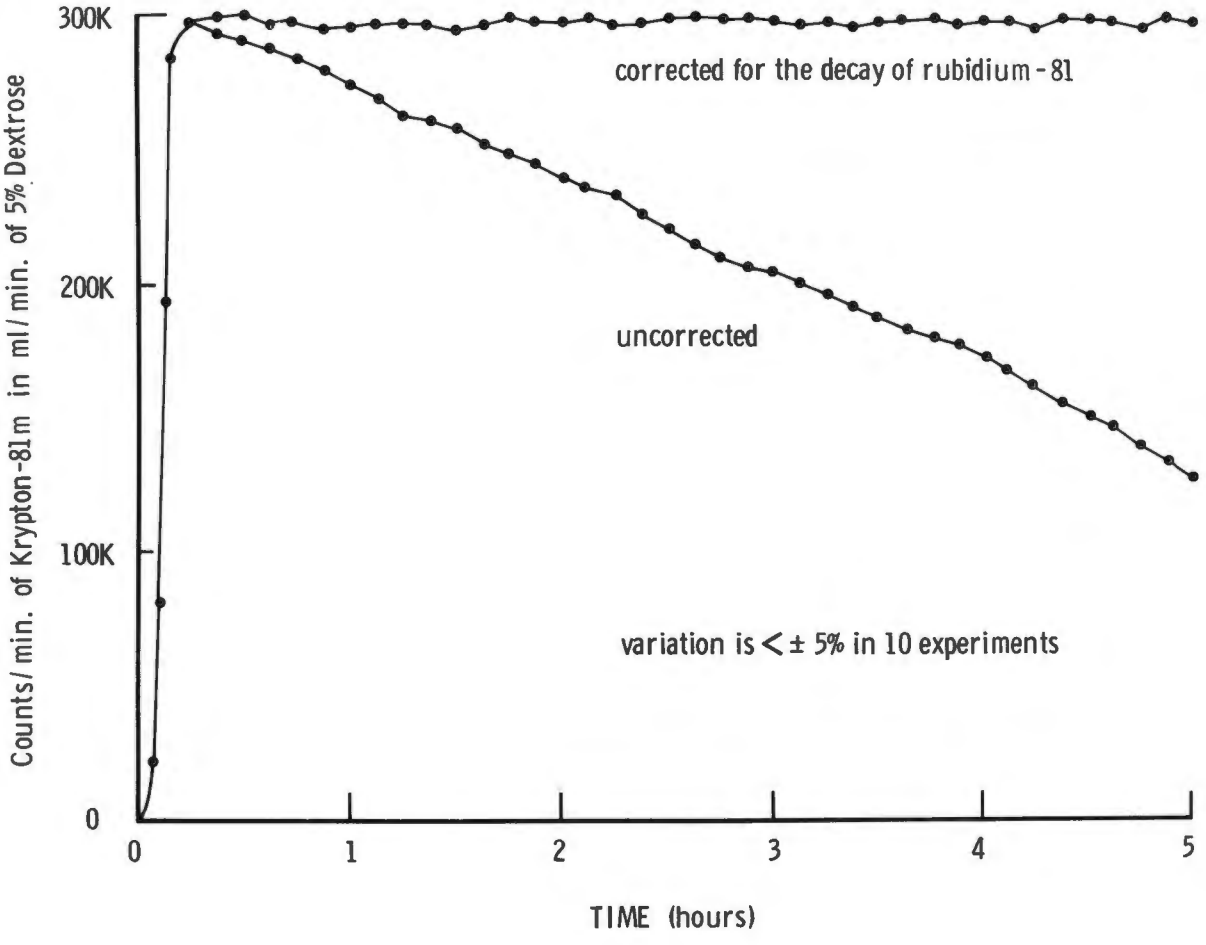


Figure 7: Ten ml/min of 5% dextrose was continuously eluted from a generator and the activity in the output tubing was measured using a gamma camera. When the output activity is corrected for the decay of the parent (IE ^{81}Rb) a constant supply of krypton-81m is available.

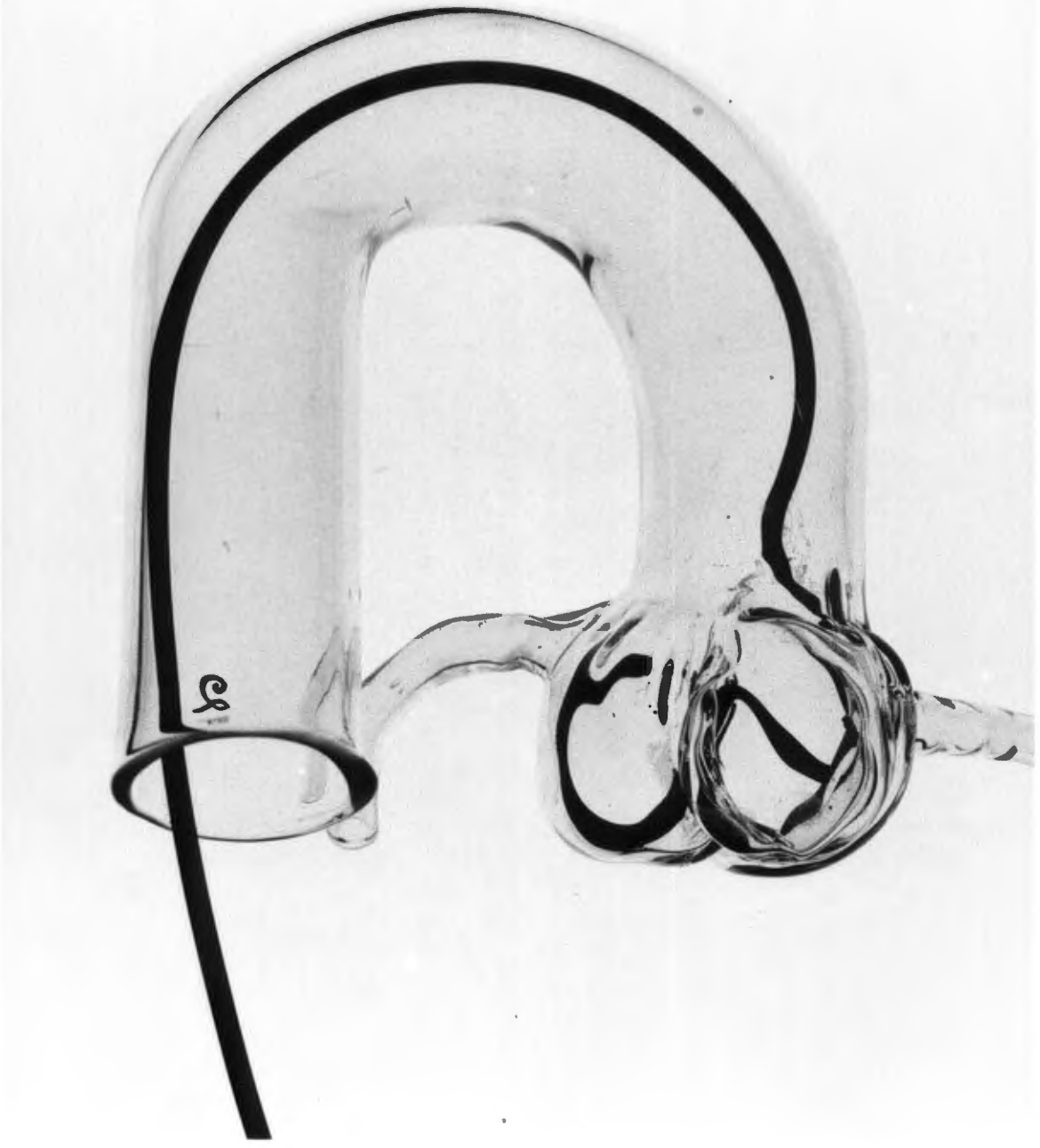


Figure 8: This glass model of the aortic root was used to design a catheter that seats in the left and right aortic sinuses.

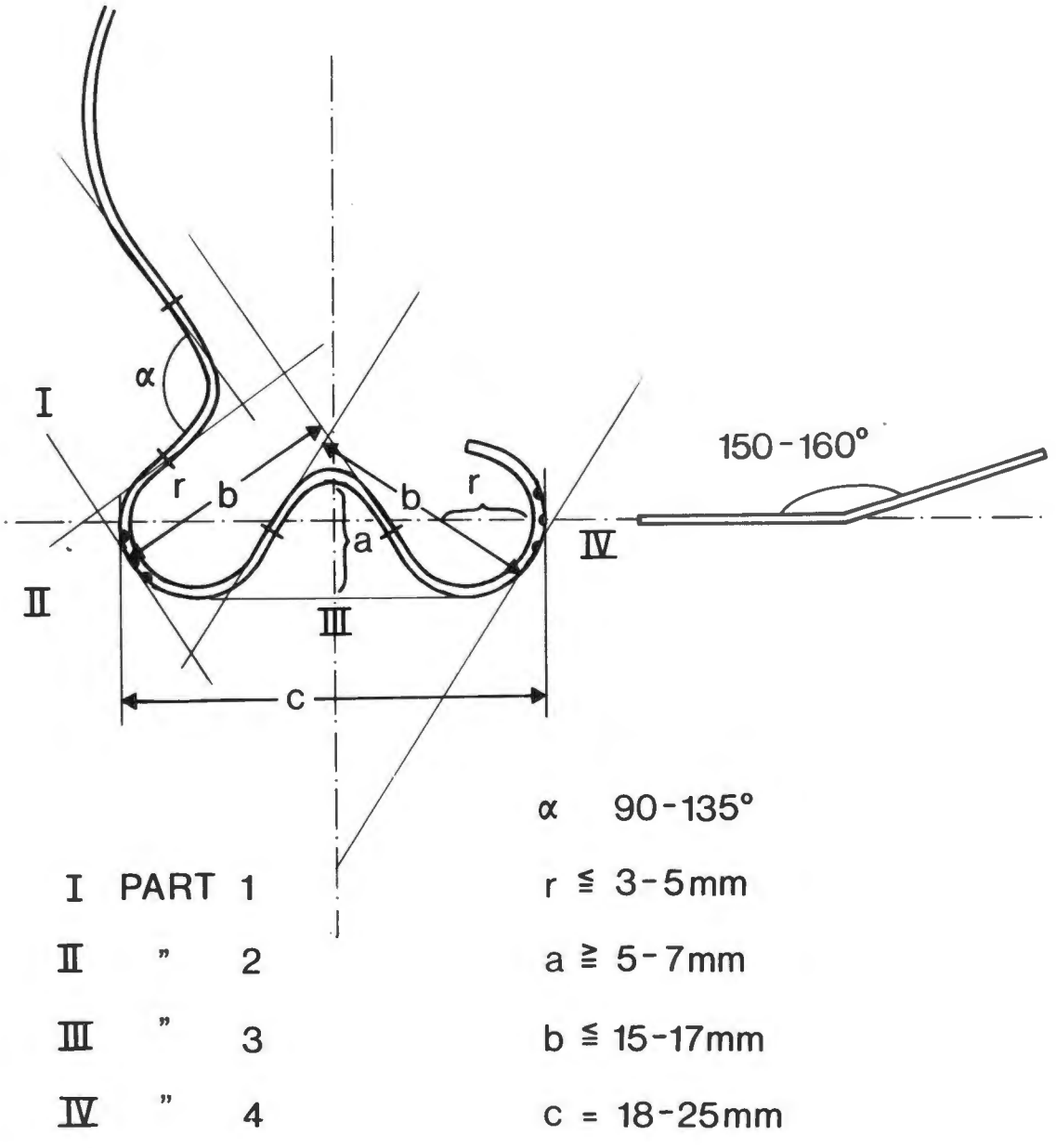


Figure 9: This diagram shows the dimensions of the specialized catheter that were required to seat in the left and right aortic sinuses of the dog.

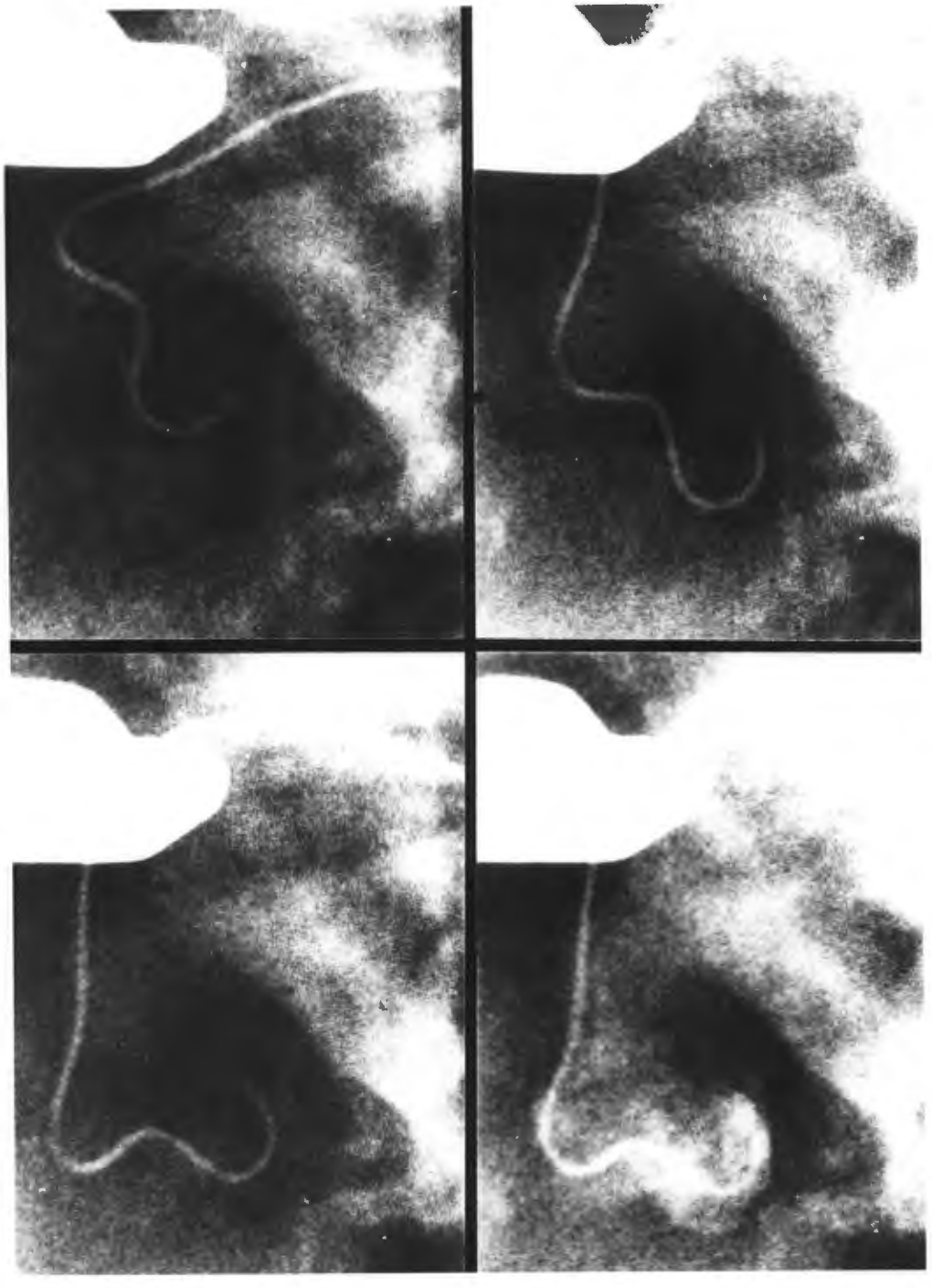


Figure 10: These radiographs show the krypton-81m catheter in the ascending thoracic aorta (top left), the distal loop in the left sinus (top right) and advanced so that the proximal loop enters the right aortic sinus. A hand injection of iodine contrast liquid shows the mixing of contrast in each sinus without the selective injection of the coronary arteries.

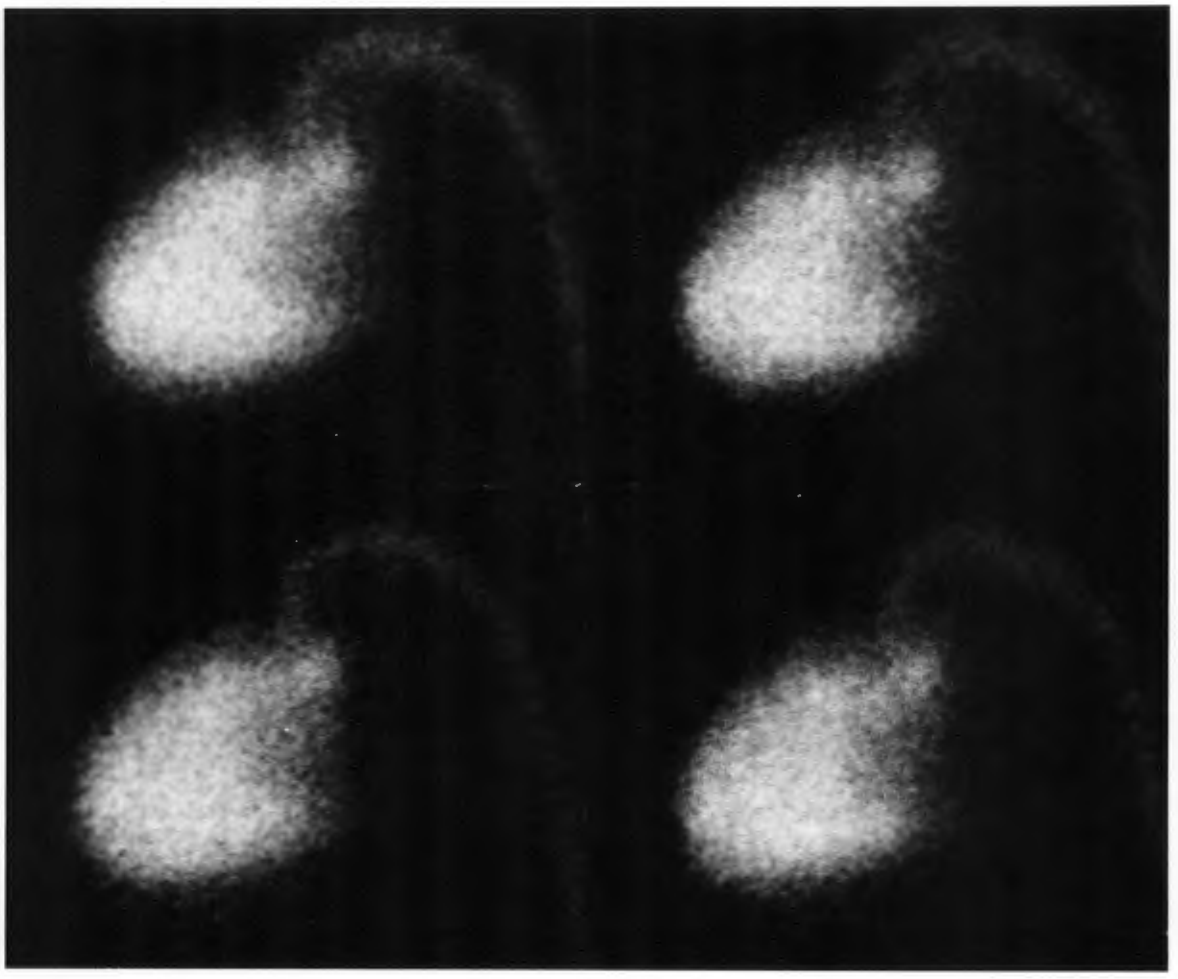


Figure 11: These images show the aorta containing the krypton-81m catheter, the aortic sinuses and the regional myocardial equilibrium of krypton-81m with the dog in the left lateral position. Cardiovascular and haemodynamic parameters remained constant for 1 hour. The serial images were recorded at 15 minutes (top left), 30 minutes (top right), 45 minutes (bottom left) and 60 minutes (bottom right) during that period. These images demonstrate the stability of delivery, mixing and the myocardial equilibrium of krypton-81m.

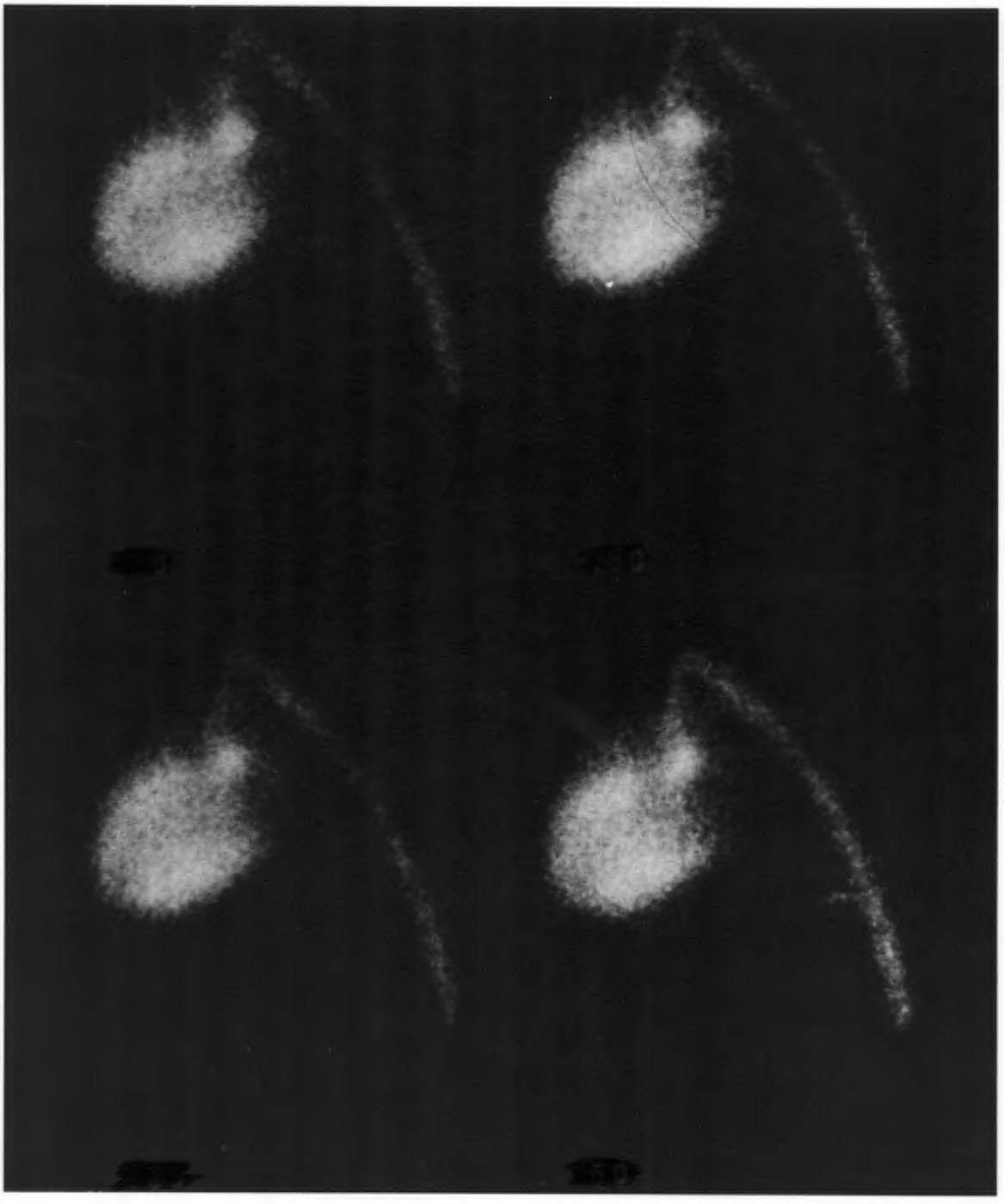


Figure 12: These serial images were recorded in one dog (left lateral position) while the heart rate was 120/min (top left), 180/min (top right), 200/min (bottom right) and 120/min (bottom left). The coronary circulation was intact and each image consists of 250,000 counts. The images and subsequent count rate analysis showed no redistribution of the regional myocardial activity with this intervention, suggesting that mixing of the tracer was stable.

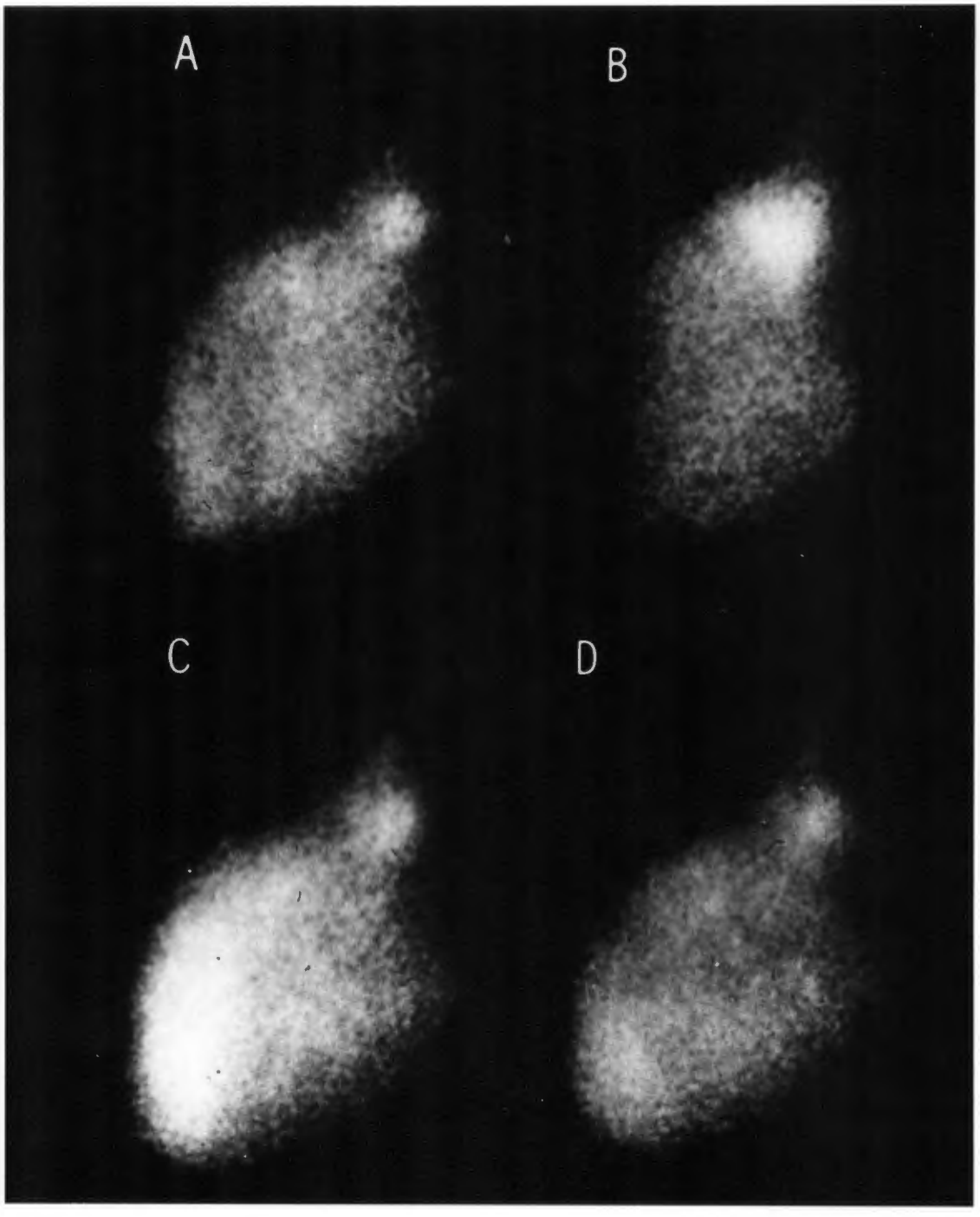


Figure 13: These serial images from one dog (left lateral position) show the aortic sinuses and the regional myocardial distribution of krypton-81m during a control period (A). Occlusion of the left anterior descending coronary artery caused a regional decrease in activity within 30-60 seconds (B). Release of the coronary artery shows reperfusion and reactive hyperaemia (C) with a slow return to the control state over 20 minutes (D). The myocardial equilibrium of krypton-81m is able to respond to changes in regional myocardial perfusion.

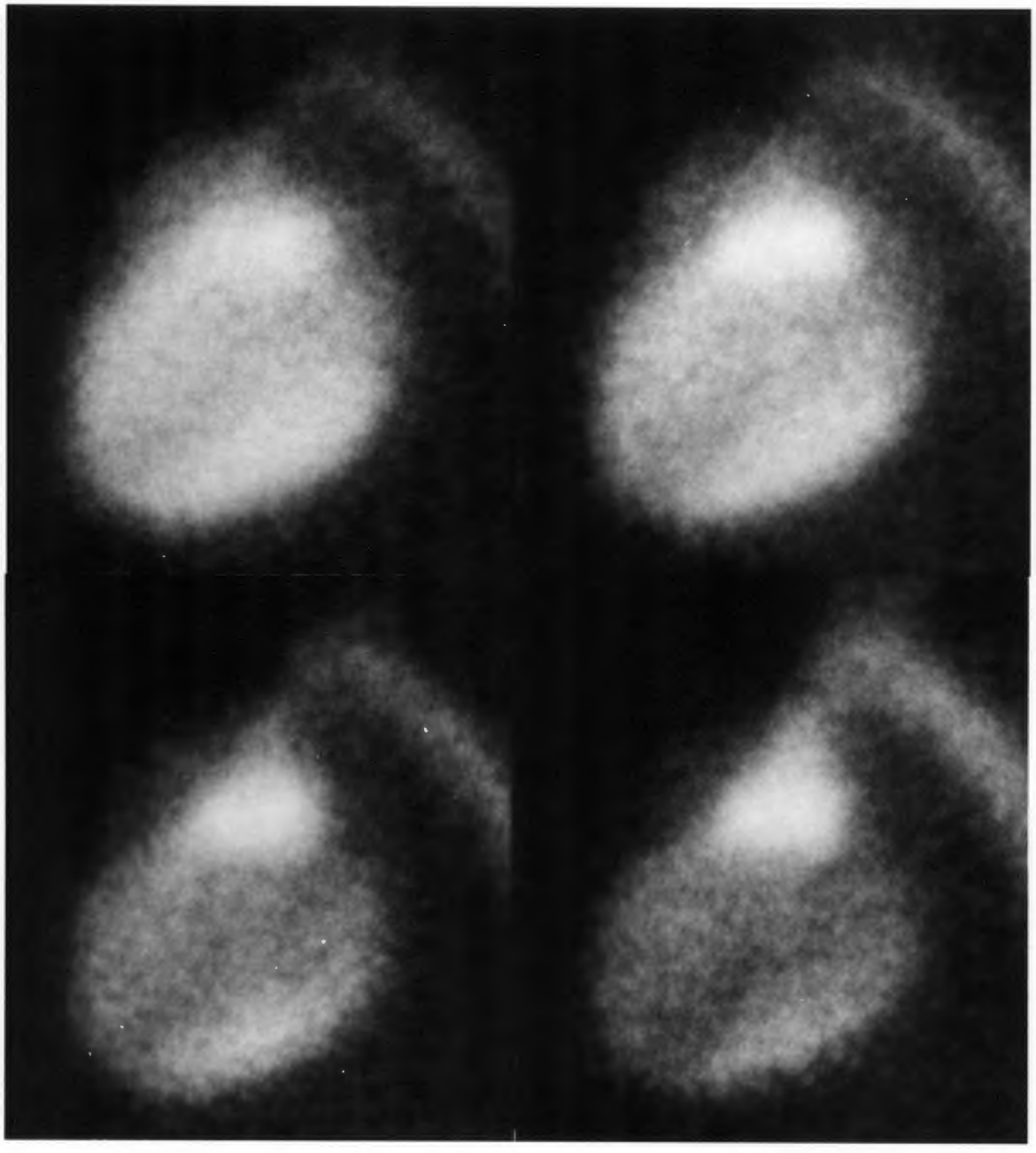


Figure 14: These serial images in one dog (left lateral position) were recorded before (top left) and during (top right, bottom left and right) an intravenous infusion of pentabarbitone (2-7 mg/kg/min) over 30 minutes. The images show a progressive overall decrease in myocardial activity as heart rate and blood pressure decreased due to the drug. The delivered arterial concentration represented in the aortic sinuses did not change. This demonstrates the use of krypton-81m to follow overall as well as regional decreases in myocardial perfusion.

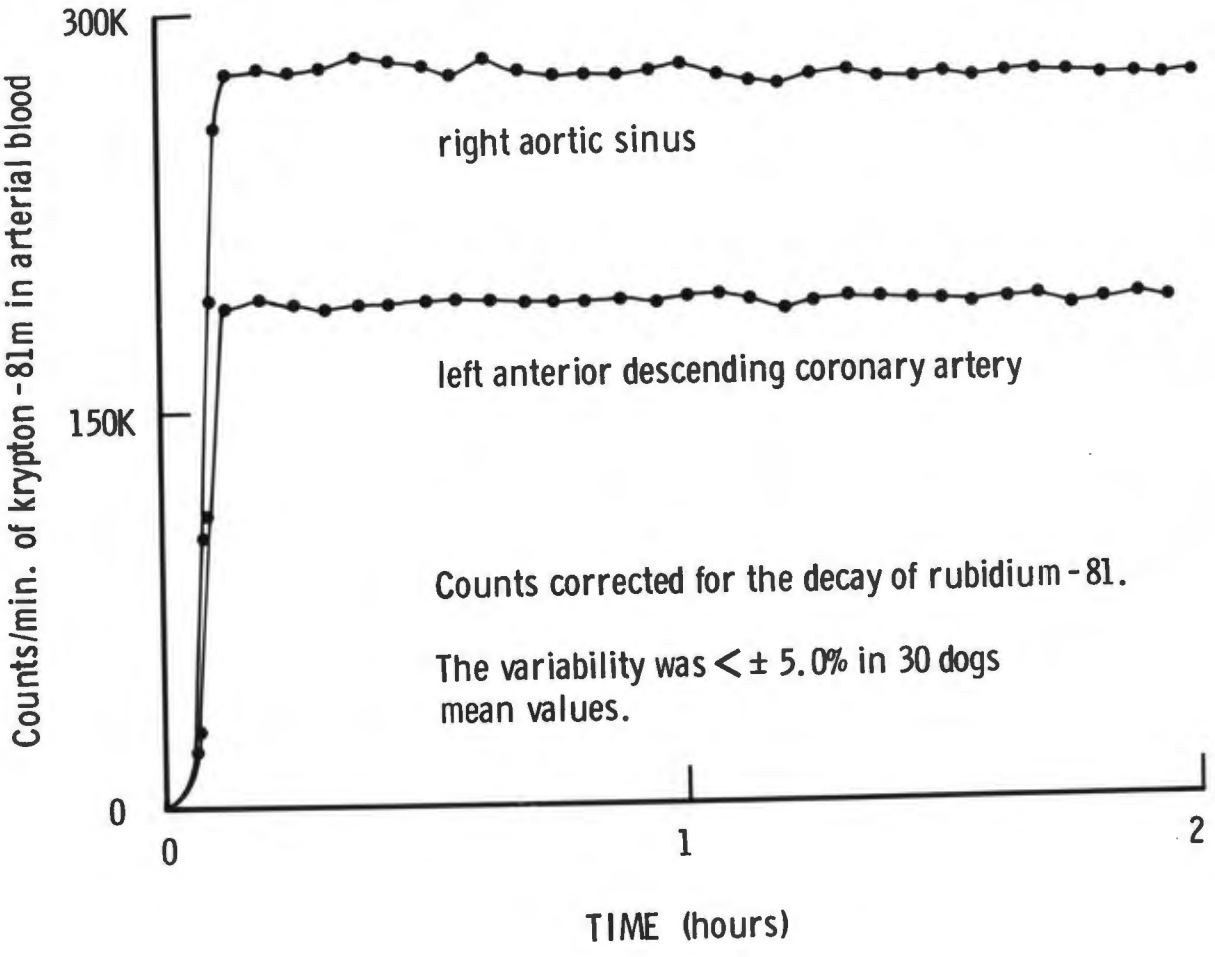


Figure 15: Five ml/min of arterial blood was continuously withdrawn from the right aortic sinus and the LAD coronary artery during a continuous infusion of krypton-81m. The graph shows that during a control period the delivered arterial concentration of the tracer was stable.

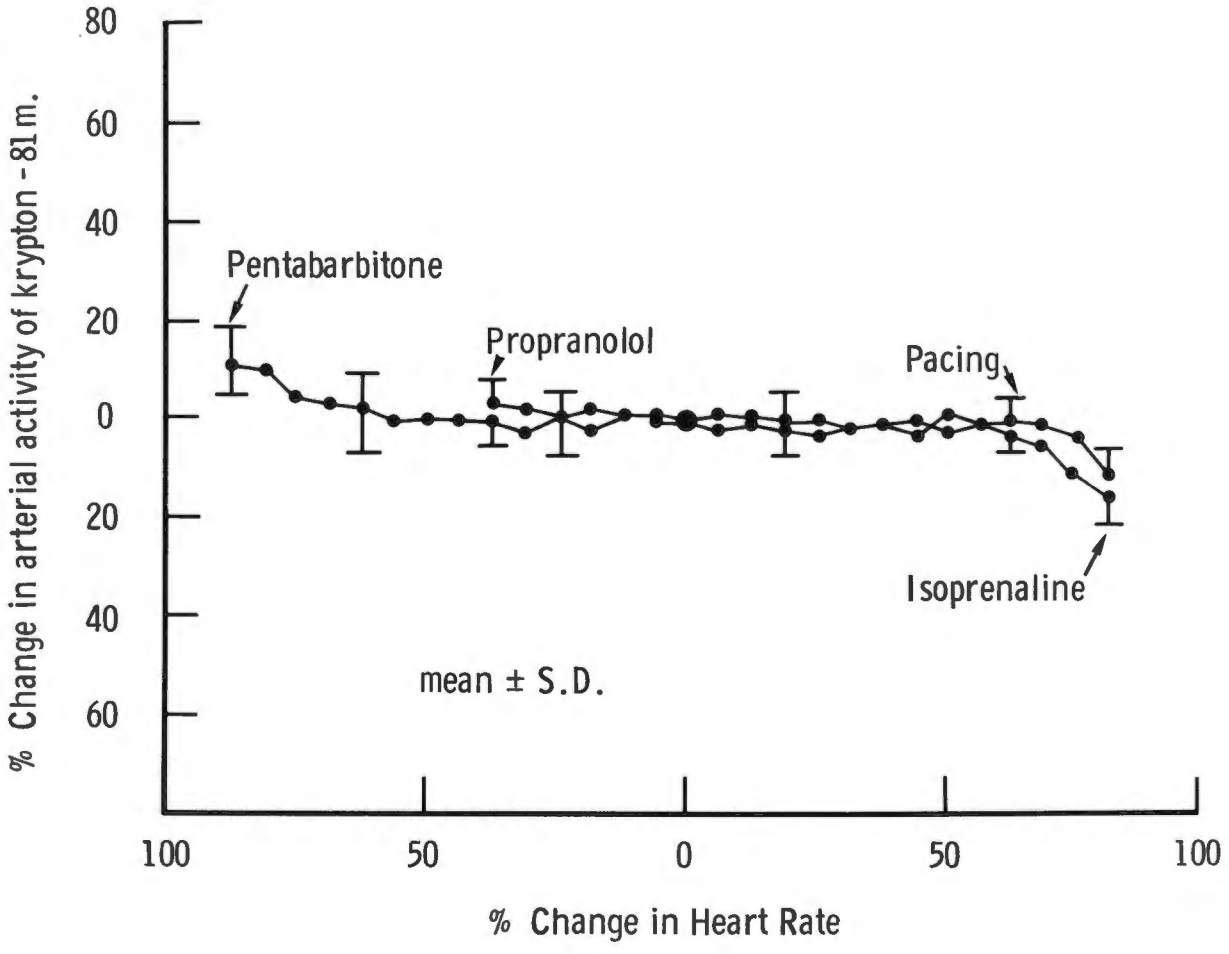


Figure 16: This graph shows the percentage changes in the delivered arterial concentration of krypton-81m using a variety of interventions that affect heart rate, blood pressure, cardiac output and coronary flow. As it was difficult to separate the relative importance of each physiological change caused by the interventions, changes in arterial concentration are plotted against changes in heart rate. The arterial concentration of krypton-81m was stable until pentabarbitone, pacing and isoprenaline caused gross ($\geq \pm$ 50%) changes in heart rate. This supports the theoretical basis and defines the limitations for using krypton-81m to follow changes in myocardial perfusion.

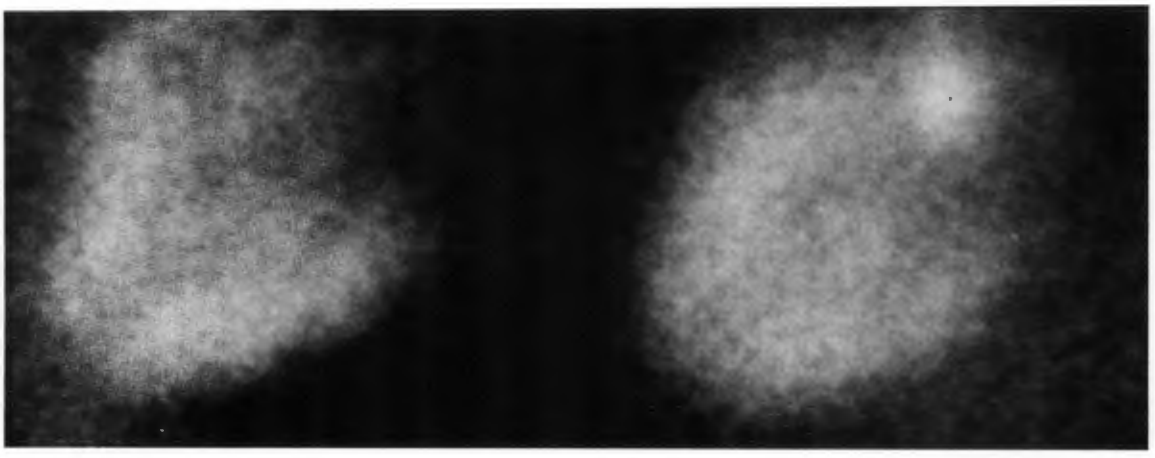


Figure 17: The regional myocardial distribution in images of krypton-81m infused into the aortic sinuses (right) was not significantly different from the regional myocardial distribution of technicium-99m labelled microspheres injected into the left atrium (left).

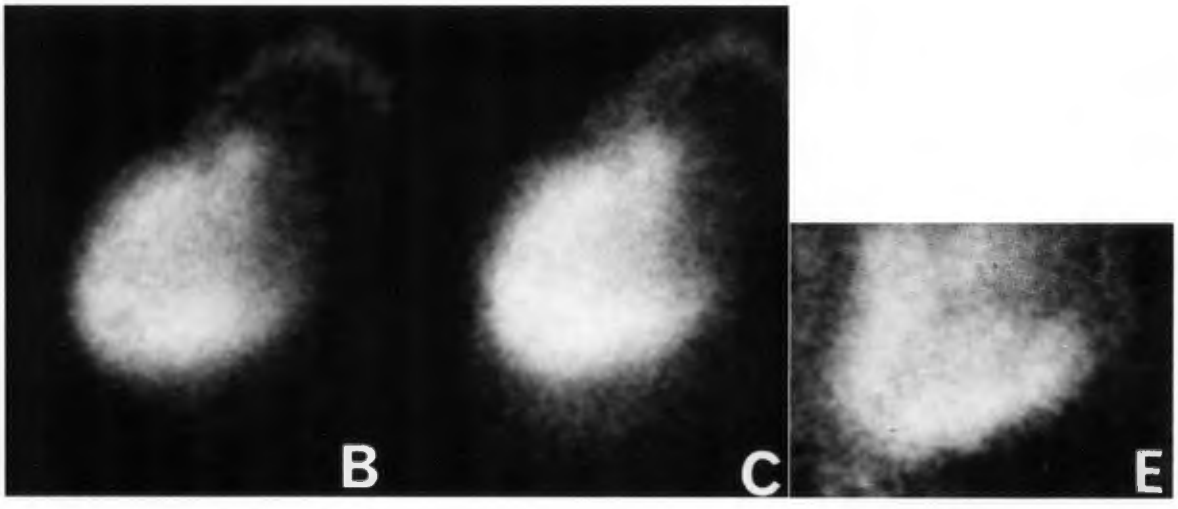


Figure 18: The krypton-81m scintigrams show in one experiment the distribution of myocardial perfusion before (B) and during (C) right atrial pacing. The technicium-99m labelled microspheres were injected into the left atrium during the pacing (E). These two tracers showed a similar distribution to the myocardium suggesting that the krypton-81m is adequately mixed.

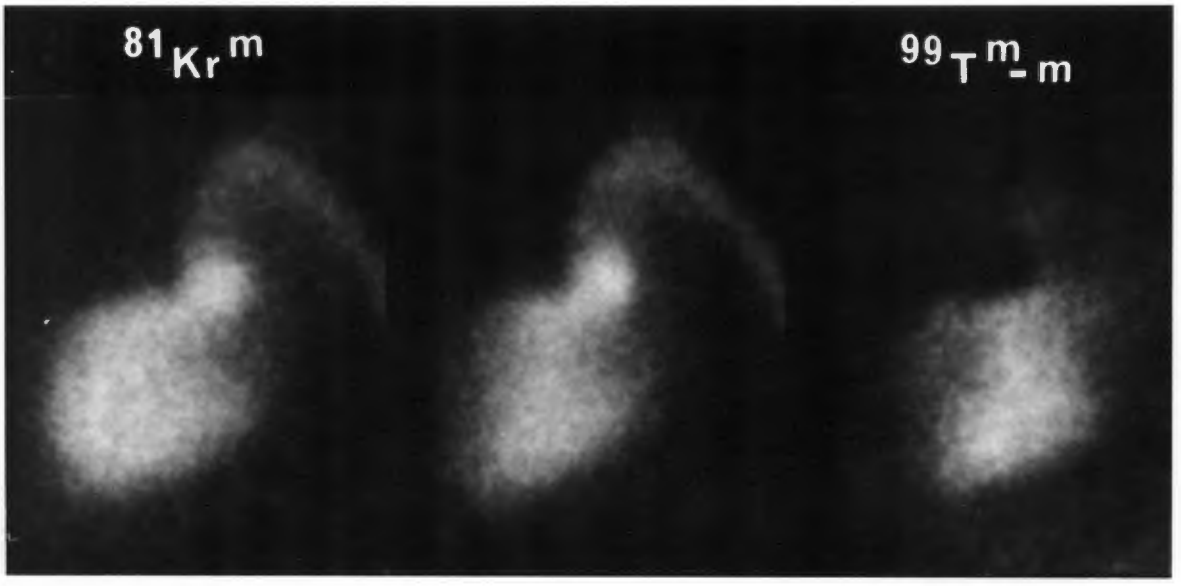


Figure 19: This example from one experiment shows two krypton-81m scintigrams, one recorded before (left) and one after (middle) severe narrowing of the LAD coronary artery. The technicium-99m microspheres were then injected into the left atrium and (right) the regional myocardial distribution of krypton-81m was similar to the distribution of the microsphere reference method. These findings support the evidence that krypton-81m is adequately mixed and distributed according to coronary flow.

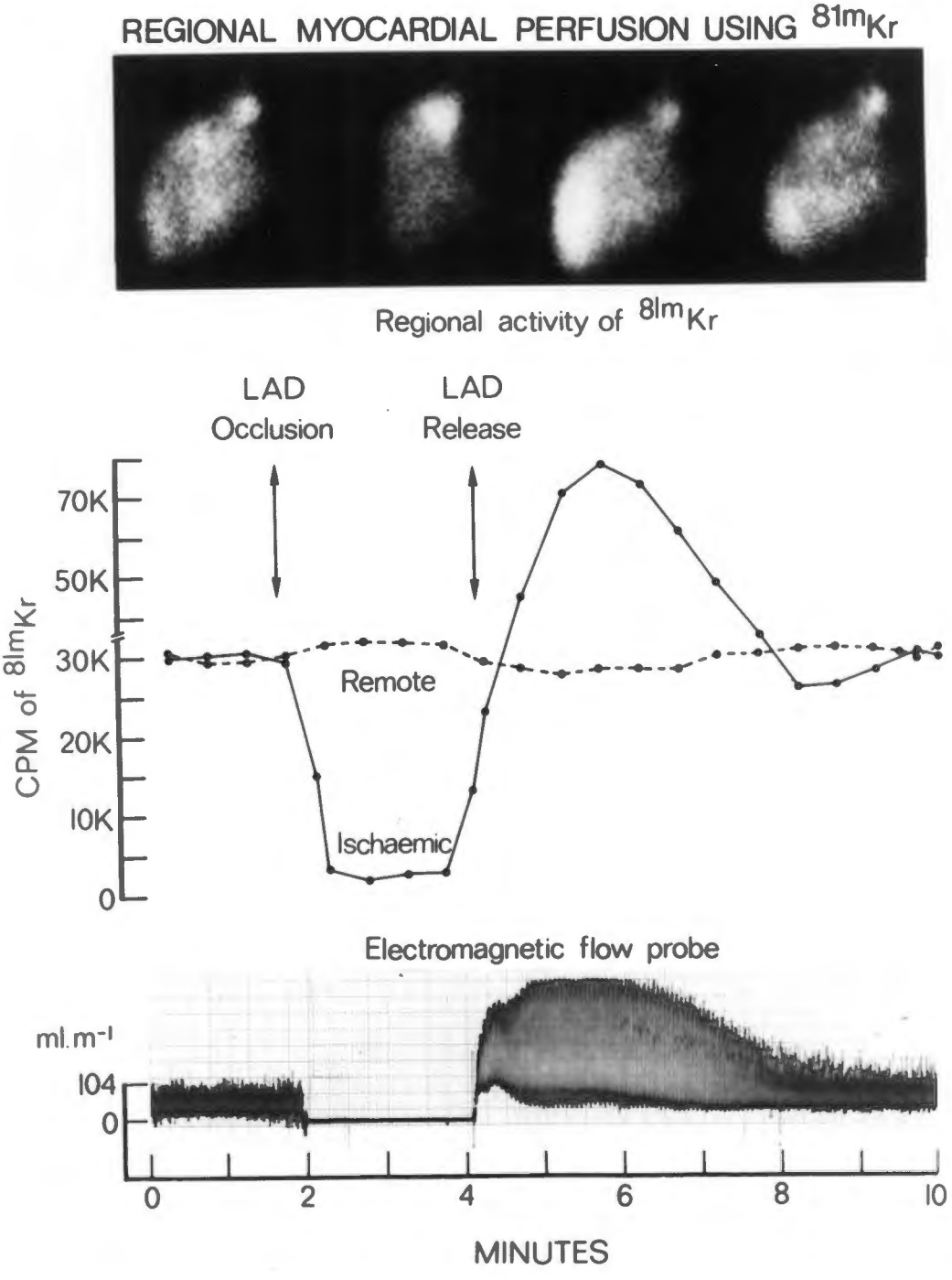


Figure 20: The myocardial images (top) show the distribution of perfusion before (left), during (second), immediate after (third) and 20 minutes after (fourth) occlusion of the LAD coronary artery.

The graph (middle) shows the regional changes in krypton-81m activity in the affected (ischaemic) and unaffected (remote) myocardium calculated by the computer from areas of interest on a visual display. The reference measure below shows the regional phasic coronary flow in the snared artery recorded simultaneously with the images.

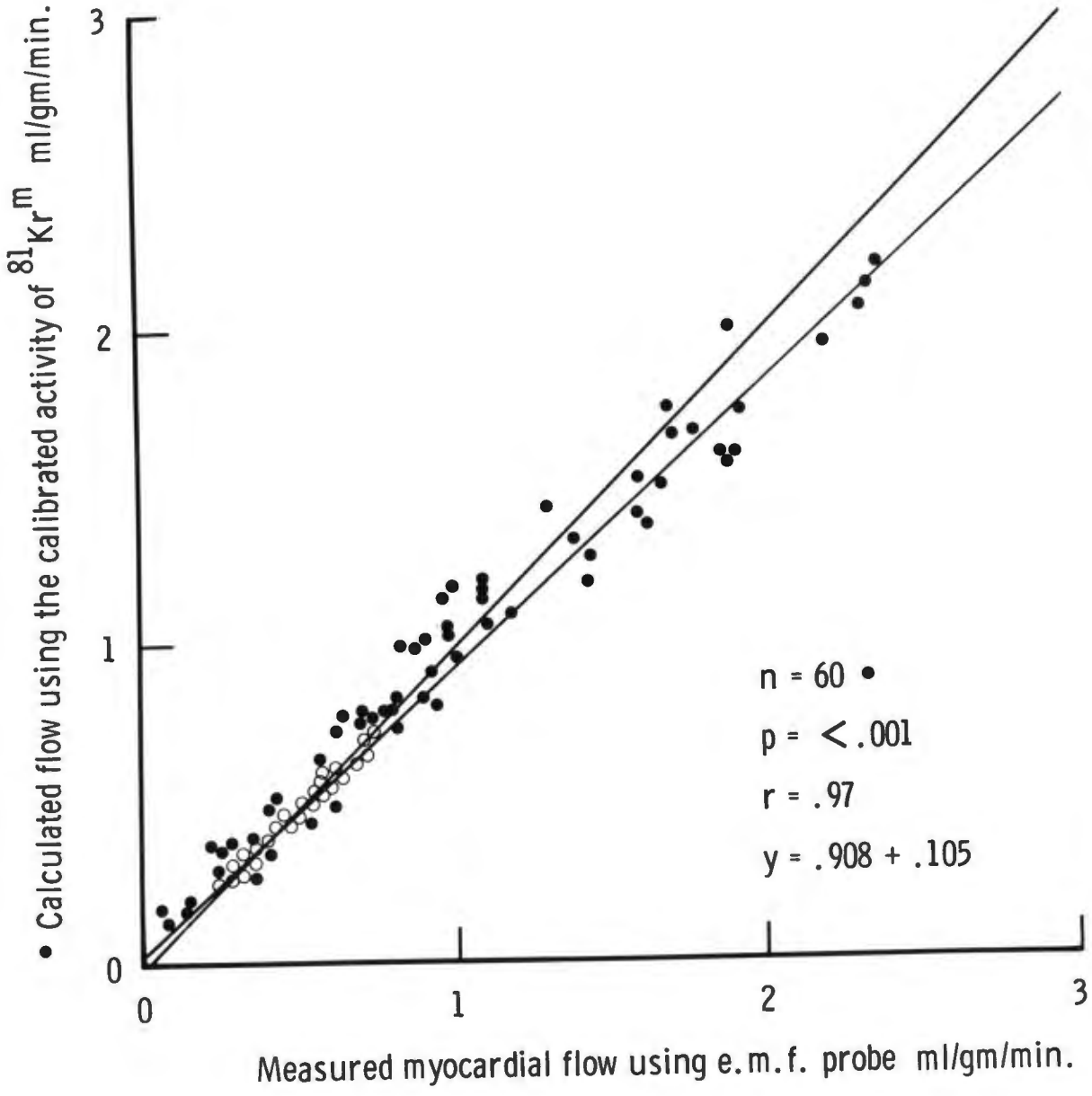


Figure 21: The regional myocardial activity of krypton-81m was calibrated using initial measurements of flow per unit weight with the electromagnetic flow probe and weighed myocardial segments. Interventions were used to change flow (solid dots). There was a significant relationship between the reference measure and the measure using krypton-81m.

CHAPTER III

SECTION I

Clinical Studies - Assessment of regional myocardial perfusion in patients with coronary artery disease.

Introduction

Atherosclerotic narrowing of coronary arteries in patients is known to be associated with angina pectoris, acute myocardial infarction and premature death.[1,2,3] Coronary artery disease is thought to produce these effects by disturbing regional myocardial perfusion and limiting the adaption of coronary flow required to meet changing myocardial metabolic requirements.[4,5,6,7] Clinical research in patients with ischaemic heart disease should consider the coronary anatomy, haemotological and haemodynamic factors, also coronary vasomotor tone. A detailed understanding of the disturbances of regional perfusion has been difficult to obtain because of methodological problems.[8]

The coronary arteriogram does not provide a physiological assessment of the haemodynamic significance of coronary artery stenosis. A technique is required to describe the disturbances of regional perfusion and so identify jeopardized segments of ventricular myocardium.[9,10,11] The exercise electrocardiogram and various methods using radionuclides have been introduced in an attempt to identify regions of the myocardium permanently damaged and regions that are reversibly damaged by transient ischaemia during stress.[9,10,11,12]

The survival of working myocardium will depend on the relationship between regional perfusion and myocardial metabolic requirements. Most of the methods available in clinical research cannot measure a dynamic sequence of changes in regional perfusion in patients with coronary artery disease at rest and during stress.[13, 14]

Krypton-81m can be continuously eluted from its cyclotron-produced parent compound, rubidium-81. A constant infusion of this radionuclide has been developed in the dog for continuous imaging and measurement of changes in regional myocardial perfusion.

The purpose of this chapter is to introduce the use of rubidium-81-krypton-81m generators in patients. A catheter has been designed to allow the delivery of this nuclide into the right and left aortic sinuses following routine catheterization. The aims are to use the unique physical properties of krypton-81m to image and measure changes in regional myocardial perfusion in patients with and without coronary artery disease. The temporal and spatial nature of any changes in perfusion will be related to the stenosed coronary arteries identified in the arteriogram, chest pain and electrocardiographic signs of ischaemia.

Any regional changes in myocardial perfusion will also be correlated with the precordial electrocardiographic signs of ischaemia and infarction recorded during standardized exercise tests. In this way an invasive and specific method using radionuclides will be used in an attempt to increase our understanding of pathophysiology and of non-invasive and more available methods using the electrocardiogram.

CHAPTER III

Section I

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CHAPTER III

SECTION II

Patients and methods:

Eighty patients (60 males and 20 females) aged 32 to 59 years were admitted to Hammersmith Hospital because of angina pectoris.[1] Fifty-eight of these patients complained of pain on effort (1-15 episodes/day, range) and 22 of the 58 also complained of pain at rest, during the night and not related to effort. Fifteen patients were in class I, 51 were in class II and 14 patients were in class III of the New York Heart Association functional classification describing the severity of angina pectoris. Fifteen of the 80 patients had a history, electrocardiographic and enzyme evidence of past myocardial infarction. Only two patients had maturity onset diabetes controlled by diet alone and 12 patients were known to be hypertensive (for 2 to 4 years). Thirty-one of the 80 patients smoked between 10 and 40 cigarettes per day. Twenty-one of the 80 patients had a family history (one parent or one sibling) of ischemic heart disease. None of the patients had a history that suggested familial hyperlipoproteinaemia.

On examination 9 patients had xanthelasmata, none showed any other physical signs suggesting hyperlipidaemia. Twelve of the 80 patients had systolic blood pressures over 170 mmHg and diastolic blood pressure between 110 and 115 mmHg. Twenty-five patients (out of 80) had systolic blood pressure between 140 and 170 mmHg with the diastolic blood pressure between 95 and 110 mmHg. Forty-three of the 80 patients had blood pressures at or below $\frac{140}{95}$ mmHg. All blood pressures were measured supine after 10 minutes rest.

Seventeen of 80 patients had atrial (4th) sounds heard on ausculation of the precordium. None of the patients showed other signs of congestive heart failure. None of the patients had physical signs of aortic stenosis, anaemia, cor pulmonale, murmurs, coarctation of the aorta, thyrotoxicosis or any other condition that might cause angina pectoris.

Fourteen of the 80 patients were taking nitroglycerine alone, 39 were also taking 80-160 mg of propranolol orally TDS and 28 were taking propranolol (40-120 mg 0 TDS) and nifedipine (10-20 mg 0 TDS).

On routine haematological and biochemical screening the haemoglobin was 14 to 16 g/dl (range), the blood urea was 3.1 to 6.5 mmol/l and the blood sugar was 4.1 to 5.6 mmol/l. After overnight fast the serum cholesterol was 5.2 to 6.6 mmol/l and the triglycerides were less than 2.3 mmol/l.

The chest X-ray (postero-anterior and lateral) showed modest cardiac enlargement in 12 of the 80 patients but no other signs of pulmonary oedema or heart failure. The 12 lead electrocardiogram showed anterior infarction in 10 and inferior infarction in 5 patients.[2] All patients were in sinus rhythm and the QRS duration was <110 msec with a mean frontal axis between -30° and $+120^{\circ}$.

During the period of this study 4 patients were considered but were excluded because 3 had left bundle branch block in the electrocardiogram and one had left ventricular failure with pulmonary venous congestion. No other exclusions were made.

Precordial mapping of the electrocardiogram in exercise tests

Sixteen precordial electrocardiogram leads were positioned on the chest in order to cover the left hemithorax (Figure 22). Each patient

performed an increasing work load on a bicycle ergometer using a standardized procedure. The exercise tests were limited by chest pain, dyspnoea, fatigue, or multiple ventricular ectopic beats. A recording of the 16 leads was made before exercise, immediately after, and then 1,3,5,8 and 10 minutes later. The electrocardiogram was continuously monitored and recorded during the test.[3,4]

The criteria established by the Scandinavian Committee on ECG classification (1967) were used to interpret the electrocardiographic changes.[2] ST segment changes were measured in 3 complexes and an average calculated. The method, reproducibility, sensitivity and specificity of this technique have already been published.[4] The following measurements were calculated from each exercise test:

1. The total workload achieved was recorded (Joules).
2. The onset and duration of chest pain was noted.
3. The total number of precordial positions showing significant ST segment depression.
4. The sum of all the ST segment depression in mm.

Angiocardiography and krypton-81m scintigraphy

The group were referred for cardiac catheterization either because a firm diagnosis of ischemic heart disease was in doubt (4 patients) or because the symptoms were not satisfactorily controlled on medical treatment (76 patients).

Left ventricular angiography and selective coronary arteriography were performed using the Judkins technique.[5] The surface electrocardiogram (lead I, II and aVF) was monitored throughout the investigation. At the end of this procedure all the patients were free of chest pain

and the electrocardiogram had returned to the control pattern.

A 5 french pacing wire was inserted intc the right femoral vein using a percutaneous puncture and sheath. This was advanced tc the right atrium and the pacing threshold was tested until this was less than one volt.

A glass model and casts of the aortic root and thoracic aorta in man were used to design a catheter that would seat in the right and left aortic sinuses (figure 23). The catheters were manufactured from Kifa polethylene tubing and moulded using heat (Cooks, Europe). A range of catheters were made with the width of the specialized end (marked in figure 24) varying from 25 to 40 mm. Three holes were punched on the outer surface of each loop and these were unequal in size. The diameter of each hole was varied so that when 7 to 15 ml/min of 5% dextrose was infused into the catheter equal volumes of infusate were delivered by each loop. A constant infusion pump and timed collections from each loop were used to check that equal volumes were delivered into the right and left sinuses.[6,7,8]

A guide wire and vessel dilater were used to insert a number 7 french sheath into the right femoral artery. Eight thousand units of heparin sulphate were given by intravenous injection. This sheath, with an adaptor (Cooks, Europe) were used to introduce the specialized 6 french cardiac catheter (figure 25). This catheter was straightened with a guide wire prior to insertion and then advanced to the ascending thoracic aorta. The guide wire was removed and an infusion of heparinized saline (1000 $iu.l^{-1}$) was delivered via this catheter at 5 $ml.min^{-1}$. The distal loop of this specialized catheter was advanced into the left aortic sinus with the patient in the supine position. A hand injection of 5 ml of

sodium diatrizoate (76%) and X-Ray screening were used to check the position. The patient was moved into the 45^{o} left anterior oblique position and the proximal loop of the catheter was advanced into the right aortic sinus (figure 25).

Protocol

Krypton-81m was continuously eluted in sterile 5% dextrose from a portable pyrogen free store of rubidium-81 (20 to 35 mCi). This solution was passed through a millepore filter (Millex, Millepore SA) and then delivered to the cardiac catheter at between 10 and 15 $ml.min^{-1}$ by a roller pump (Watson-Marlow MRHE 88). The activity delivered at the aortic sinuses was calculated to be 5 to 7 $mCi.min^{-1}$ during the continuous infusion.[7,8]

The patient's chest was positioned within the field of a mobile gamma camera (EKCO N668FO). The energy detection was set at 190 kev $\pm$15% and images of the myocardial distribution of krypton-81m were recorded by collecting 200,000 counts on polaroid film. Two areas of interest were enclosed on the visual display unit in order to record regional counts per minute of krypton-81m.

Images of the regional myocardial distribution of counts were recorded (250,000 counts per image) and considered satisfactory if the activity in an area enclosing the total myocardium was $\geqslant$ 5000 counts per second and if the activity in an equal sized area adjacent to the heart in the lung fields was less than 5% of the total myocardial activity. The patient was then moved and positioned within the field of a General Electric MaxiCamera 400T linked to a control module (Model 49-200) and digital computer (Deltron-Nova 1220). Images of the heart were recorded

by collecting 250,000 counts on X-ray film and the computer collected the counts in 30 second frames as quantitative images automatically correcting for the decay of rubidium-81.

Images of the myocardium were collected with the patient in the anterior, also right and left anterior oblique positions. The left anterior oblique position was then chosen for continuous recording of images and counts before, during and after transvenous atrial pacing. A control period of 15 minutes was used to record images and counts from the myocardium. Atrial pacing was then used to increase the heart rate by 10 beats per minute at 2 minute intervals until the patient complained of chest pain, shortness of breath, discomfort or reached a heart rate of 140 beats per minute. Images were recorded throughout the procedure and for 10 minutes thereafter. The maximum time taken for krypton-81m scintigraphy was 40 minutes. After the catheter and sheath had been removed 40 mg of protamine sulphate was given by intravenous injection over 10 minutes.[6]

Analysis of data

At the end of each study the serial images were independently assessed by a radiologist, a cardiologist and a nuclear medicine technician. Areas of the myocardium in the images showing decreases in activity during stress were identified and chosen as areas of interest. The digital images of the regional myocardial activity of krypton-81m were recalled from the computer onto a visual display unit within a 128 x 128 matrix of squares. Up to 6 areas of interest were chosen using an electronic light pen. These areas enclosed:

1. The total myocardium
2. The aortic root
3. The region or regions showing abnormal changes during the stress test
4. The rest of the myocardium
5. The activity in the descending thoracic aorta
6. Background activity from an area adjacent to the heart with the same number of pixels found in the image of the total myocardium.

When no abnormalities were identified, the myocardial images were simply divided into the free wall of the left ventricle, the inferior wall of the left ventricle, the interventricular septum and the wall of the right ventricle. Time activity graphs were constructed by recalling from the computer the counts per minute that occurred in each area throughout the study.

The angiocardiograms were assessed by a radiologist and cardiologist. They recorded normal pattern of left ventricular contraction, regional dyskinesia or aneurysm. Each investigator was asked to report whether the coronary arteries were normal or showed $\leq 50\%$ stenosis or $\geq 70\%$ stenosis. These reports were made by inspection of the coronary arteriograms by doctors who routinely report more than 200 arteriograms per year.

It was agreed beforehand that the recordings and analysis of all data would be done separately by a staff cardiologist, a radiologist and a technician. They were unaware of the others findings and the clinical details. Disagreement was settled by an independent assessor.

Statistics

All results are expressed by a mean and one standard deviation unless otherwise stated. Myocardial and background activity and ratios of regional to total myocardial activity were compared using a Wilcoxon test for paired differences. An analysis of variance was used to assess changes in the regional myocardial activity of krypton-81m.

Ethical considerations

The nature, intention and potential dangers of the procedure were explained to each patient before each study. Signed consent was obtained as required by the hospital ethics committee and isotope panel clearance was obtained before the studies commenced.

CHAPTER III

Section II

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CHAPTER III

SECTION III

Results

The history, physical examination and routine laboratory tests describing the 80 patients are in Section II of this chapter.

Precordial mapping of the electrocardiogram with exercise

Figure 26 shows the 16 precordial positions and the unipolar electrocardiographic complexes recorded from each position before and after maximal exercise. The baseline stability was satisfactory when skin preparation, prejelled electrodes and micropore strapping were used. Figure 27 shows the arbitrary regions chosen to describe anterior, inferior and lateral precordial areas. Figure 28 and figure 29 are examples showing the precordial positions of pathological ST segment depression after exercise and the temporal sequence of events for 10 minutes after the exercise test.

Fifteen patients had pathological Q waves in the precordial map before and after exercise. The Q waves were found in the anterior leads in 9 and inferior leads in 6 patients.

Sixty-five of the 80 patients had positive exercise tests.

The following results were obtained from the exercise ECG tests.

1. Fifteen patients had no significant ST segment changes during or after exercise. Thirteen patients experienced no pain and two complained of chest discomfort. This group achieved a workload of 43000 to 56000 Joules (mean = 48000 Joules) and exercised for 8 to 10 minutes (range).

2. Sixteen patients complained of chest pain and performed a workload of 30000 to 43000 Joules (mean = 37000 J). These patients developed ST segment depression at 4 to 6 precordial positions (range) measuring 7 to 15 mm in total immediately after exercise.

3. Twenty-three patients developed chest pain and performed a workload of 26000 to 32000 Joules (mean = 29000 Joules). These patients developed ST segment change at 5 to 11 precordial positions (range) measuring 12 to 21 mm in total immediately after exercise.

4. Twenty-six patients developed chest pain and performed a workload of 7000 to 22000 Joules (mean 18000 Joules). These patients developed significant ST segment depression at 9 to 12 precordial positions measuring 16 to 28 mm in total immediately after exercise (Table 2).

Table 3 summarizes the relationship between the site of ST segment changes in relation to the findings at coronary arteriography.

Left ventriculograms and coronary arteriograms

Nine patients were reported as showing anterior dyskinesia and 6 were reported as showing inferior dyskinesia on the left ventriculogram. These findings corresponded with the anterior and inferior Q waves reported above in the electrocardiograms. None of the patients were reported to have diffuse failure of ventricular contraction.

None of the patients had stenosis of the main stem of the left coronary artery.

The findings at angiocardiography are shown in tables 2 and 3. Two patients with $\leqslant 50\%$ stenosis and two with $\geqslant 70\%$ stenosis of coronary arteries had negative exercise ECG tests. Eight patients reported to have $\leqslant 50\%$ stenosis of coronary arteries had positive ECG tests (see table 3).

Regional Myocardial Perfusion and Atrial Pacing

Images of the heart using krypton-81m during a continuous infusion are shown in Figure 30. No other structures could be seen in the scintigrams and counts were recorded from equal sized areas of interest over the heart and on background. This showed that the background activity was always less than 5% of the myocardial activity of krypton-81m.

Figure 31 shows the krypton-81m scintigrams recorded before, during and after cardiac pacing in a patient with normal coronary arteries. Figure 32 shows the same sequence of images recorded from a patient with a negative ECG exercise test but 70% stenosis of the left anterior descending coronary artery. Both these sequences showed no significant redistribution of myocardial activity with atrial pacing.

Group 1. In the 15 patients with negative exercise tests 11 were reported to have normal coronary anatomy, 2 had $\leq 50\%$ stenosis and two were reported to have $\geq 70\%$ stenosis of coronary arteries (Table 3). All showed no redistribution of regional myocardial perfusion with atrial pacing. They also did not have ST segment changes or chest pain during the atrial pacing. Figure 33 shows the changes in regional count rates with atrial pacing. The aortic root and descending thoracic aorta showed changes in activity that were $< \pm 7\%$ throughout the study. The counts per minute in the 5 areas of interest (see methods) all increased by the same percentage. The analysis of variance showed no significant differences at any time. Background activity remained $\leq \pm 5\%$ of the total myocardial activity during pacing. Following the

end of atrial pacing the activity in all regions of the myocardium returned to the control levels.

In these patients the regional activity in each area of interest was also expressed as a ratio of the total activity. The range of the ratios was 0.02 to 0.90. No change in these ratios could be detected with atrial pacing from 81 $\pm$ 15 beats per min (b/min) to 140 b/min. (Wilcoxon test for paired differences.)

Figure 34 shows a sequence of images recorded from a 52 year old male patient with a 3 month history of angina pectoris. The precordial ECG maps showed ST segment changes in inferior leads following exercise and the coronary arteriogram showed $\geq$70% stenosis of all 3 major coronary arteries. The sequence of images shows the distribution of myocardial perfusion in the left anterior oblique position at rest (a). There was no obvious redistribution of regional myocardial perfusion when the heart rate was increased from 72 to 100 beats/min (b). However, when the heart rate was increased from 100 to 140 b/min there was a decrease in regional myocardial activity of krypton-81m seen in the inferior and lateral wall of the left ventricle (c). This is accompanied by chest pain and ST segment depression. All these changes were reversed when the atrial pacing was turned off (d). Regional perfusion in the affected segment appears to be lost mostly in the endocardial layers. The planar imaging, however, prevents any confident separation of endocardial and epicardial events.

Group II. The graph in figure 35 shows regional changes in myocardial activity of krypton-81m in the 16 patients who had positive electro-

cardiograms and achieved between 30,000 and 43,000 Joules. One of the areas of interest encloses a region of the myocardium that the 3 reviewers agreed showed abnormalities during pacing. The second area encloses the remote myocardium and both areas show stable perfusion before pacing (variation during control = $< \pm$ 5%). During atrial pacing the remote myocardium showed significant and progressive increases in counts of krypton-81m ($P = <0.01$, 98.0 $\pm$ 14%). The abnormal area in each of the 16 patients showed increases in perfusion during the first 3.5 to 7 minutes (range) of 17.0 $\pm$ 8%. These increases were significant ($P = <.05$). The counts in this area then decreased rapidly and significantly ($P = <.01$) throughout the rest of the atrial pacing test. This regional decrease in counts per minute was 68.0 $\pm$ 9% for the 16 patients in this group. Following atrial pacing the regional activity in both areas returned to the control state.

Group III. The graph in Figure 36 shows the regional changes in myocardial activity of krypton-81m in the 23 patients who had positive exercise electrocardiograms and achieved between 26,000 and 32,000 Joules. One of the areas of interest encloses a region of the myocardium that the 3 reviewers agreed showed abnormalities during pacing. The second area encloses the remote myocardium and both areas show stable perfusion ($< \pm 5\%$) before pacing. During atrial pacing the remote myocardium showed significant ($P = <.01$) and progressive (102 $\pm$ 20%) increases in myocardial counts of krypton-81m. The abnormal areas in each of the 12 patients showed no significant changes in perfusion for 4 to 7 minutes after the onset of atrial pacing, ($P = >0.05$). Regional myocardial activity then showed a significant ($P = <.01$) and progressive

decreases of 89.0 ± 17% in the regional perfusion during the rest of the pacing test. When atrial pacing was stopped the regional activity in both areas returned to the control state.

Group IV. The graph in Figure 37 shows the regional changes in myocardial activity of krypton-81m in the 26 patients who had a positive exercise electrocardiogram and achieved between 7000 to 22000 Joules. One of the areas of interest encloses a region of the myocardium that the 3 reviewers agreed showed abnormalities during pacing. The second area encloses the remote myocardium and both areas show stable perfusion (≤ ± 5%) before pacing. During atrial pacing the remote myocardium showed significant ($P = <.01$) and progressive (91.0 ± 7%) increases in myocardial counts of krypton-81m. The abnormal areas in all the 26 patients showed a decrease in regional myocardial activity within 60 seconds of the onset of atrial pacing. This was significant ($P = <.01$) and progressive, decreasing below control values by 88.0 ±7%. When atrial pacing was stopped the regional activity in both areas returned to the control state.

The relationship between disturbances of regional myocardial perfusion and the findings at coronary arteriography are shown in Table 4. Two patients reported to have ≤50% stenosis and 2 reported to have ≥70% stenosis of coronary arteries showed no abnormal distribution of perfusion during pacing. Table 5 shows the relationship between the site of ST segment changes during exercise and the site of abnormal regional myocardial perfusion during pacing. The two patients with ≤50% stenosis and the two with ≥70% stenosis shown in tables 3 and 4 showed both negative ECG and radionuclide tests. There was close

agreement between these two physiological measures. Septal and apical disturbances of perfusion were related to a variety of precordial positions showing abnormal ECG signs (table 5).

The relationship between the disturbances of regional myocardial perfusion and the appearance of significant ST segment depression in the electrocardiogram is shown in all the graphs in the preceding 3 figures. Significant ST segment depression appeared 140 $\pm$ 18 sec (mean $\pm$ SD) after the decrease in regional myocardial perfusion in the affected segments.

Past myocardial infarction

The 15 patients with pathological Q waves in the precordial maps all showed regional defects of myocardial activity in the rest scintigrams identified by all the assessors. Antero-septal defects corresponded with the anterior Q waves in 9 patients (figure 38). During atrial pacing regions of the myocardium remote from the defects showed a 123 $\pm$ 17.0% increase in activity while no significant changes ($P = <.05$) in activity occurred within the infarcted area. During atrial pacing the 2 of the 6 patients with inferior infarcts developed new transient anterior defects of perfusion with chest pain and ST segment depression. Six of the 9 patients with anterior infarcts developed new transient inferior defects of activity during atrial pacing with pain and ST depression (figure 39). The analysis of variance showed that the regional increases and decreases in the myocardial activity of krypton-81m during pacing were significant ($P = <.01$).

No complications were encountered during these studies. The maximum total dose of radioactivity delivered during the studies was calculated to be 75 mrads.

TABLE 2

The findings at coronary and left ventricular angiocardiography

normal coronary arteriogram	11
⩽ 50% stenosis	
LAD alone	4
LAD + RCA	6
⩾ 70% stenosis	
LAD alone	7
LAD + ⩽ 50% of RCA	5
LAD + RCA	9
LAD + RCA + ⩽ 50% of Cx	6
RCA + 50% of LAD	4
LAD + RCA + Cx	28
anterior left ventricular dyskinesia	9
inferior left ventricular dyskinesia	6
normal left ventricular angiogram	65

LAD - left anterior descending coronary artery

RCA - right coronary artery

Cx - left circumflex coronary artery

TABLE 3. Site of ST segment changes in relation to the findings at coronary arteriography

Vessels involved	No change	Site of ECG changes: Anterior	Inferior	Anterior & Lateral	Anterior & Inferior	Inferior & Lateral	Anterior Inferior Lateral	Total
Normal arteriogram	11							11
< 50% stenosis:								
LAD alone		3		1				4
LAD + RCA	2	2			2			6
≥ 70% stenosis:								
LAD alone	2	1		2			2	7
LAD + ≤50% of RCA				2		2	1	5
LAD + RCA			1		4	1	3	9
LAD + RCA + ≤50% of Cx				1	2		3	6
RCA + <50% of LAD			1				3	4
LAD + RCA + Cx		1	1	3	4	2	17	28
TOTALS:	15	7	3	9	12	5	29	80

TABLE 4. Site of abnormal regional myocardial perfusion during pacing in relation to the findings at coronary arteriography.

Vessels involved	Site of abnormal perfusion during pacing				
	No changes	Inferior	Inferior & Lateral	Septal & apical	Total
Normal arteriogram	11				11
⩽ 50% stenosis					
LAD alone				4	4
LAD + RCA	2		1	3	6
⩾ 70% stenosis					
LAD alone	2			5	7
LAD + ⩽ 50% of RCA			1	4	5
LAD + RCA			3	6	9
LAD + RCA + 50% of Cx		1	2	3	6
RCA + ⩽ 50% of LAD		2	1	1	4
LAD + RCA + Cx		3	7	18	28
TOTAL:	15	5	15	44	80

TABLE 5. Site of ST segment changes in relation to the site of abnormal regional myocardial perfusion.

Site of abnormal perfusion	Site of ECG changes							
	No changes	Inferior	Inferior Lateral	Anterior & Lateral	Anterior & Inferior	Anterior	Anterior Inferior Lateral	Total
No changes	15							15
Inferior		3	2		1			6
Inferior & lateral			3		5		7	15
Septal & apical				9	6	7	22	44
TOTAL:	15	3	5	9	12	7	29	80

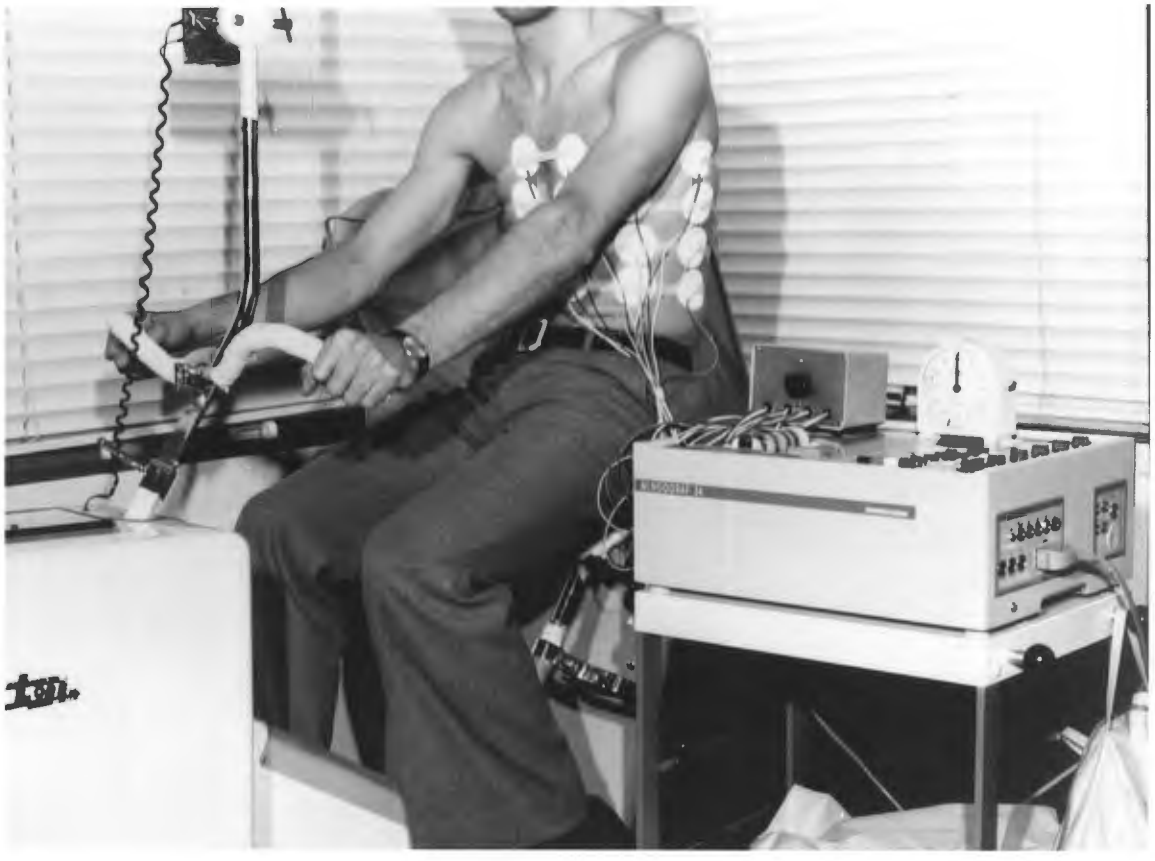

Figure 22: This shows the electrodes, equipment and technique used in 16 point precordial mapping of the ECG before, during and after a maximum exercise test.

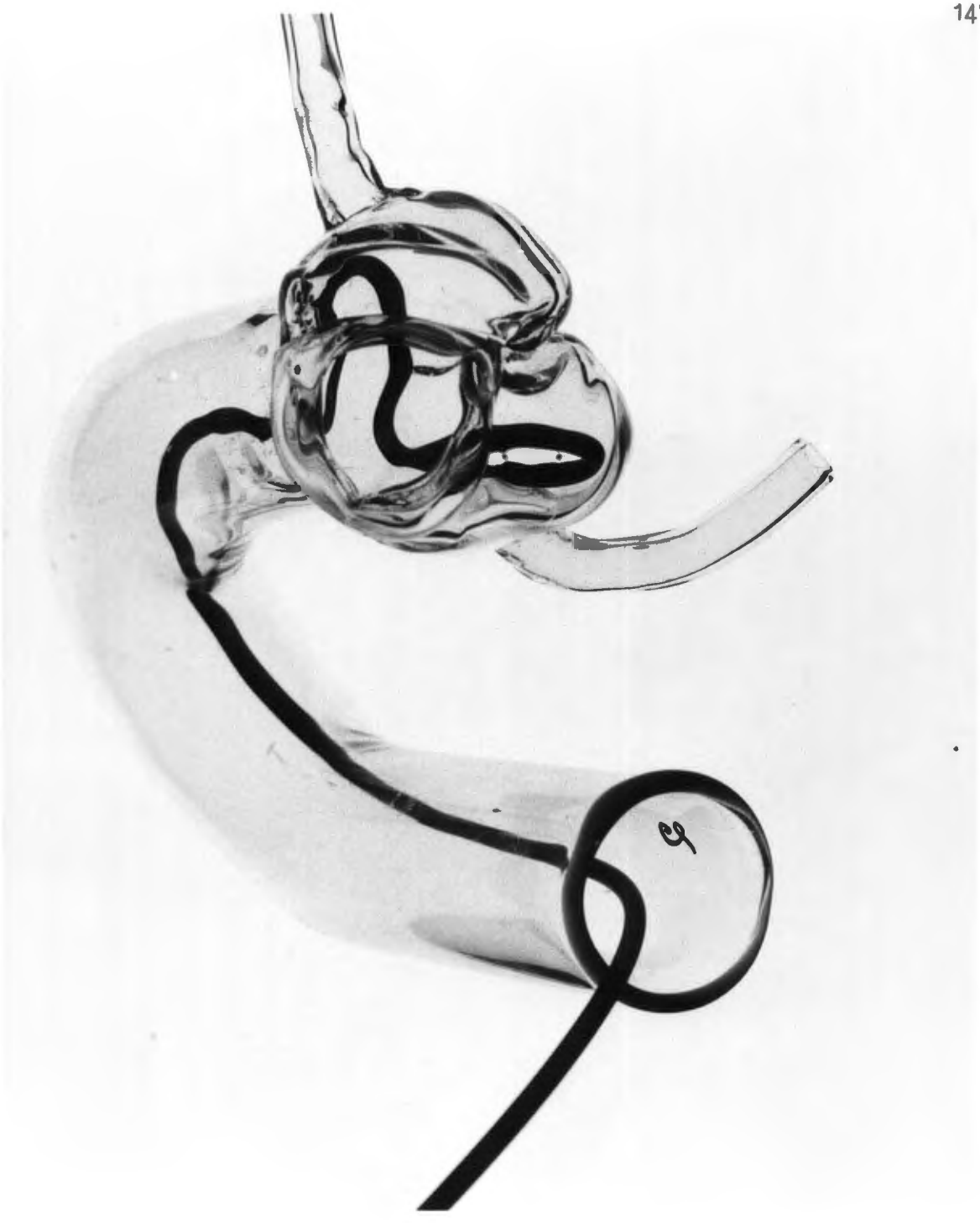

Figure 23: This glass model was used to design a catheter that allowed the continuous infusion of krypton-81m into the right and left aortic sinuses.

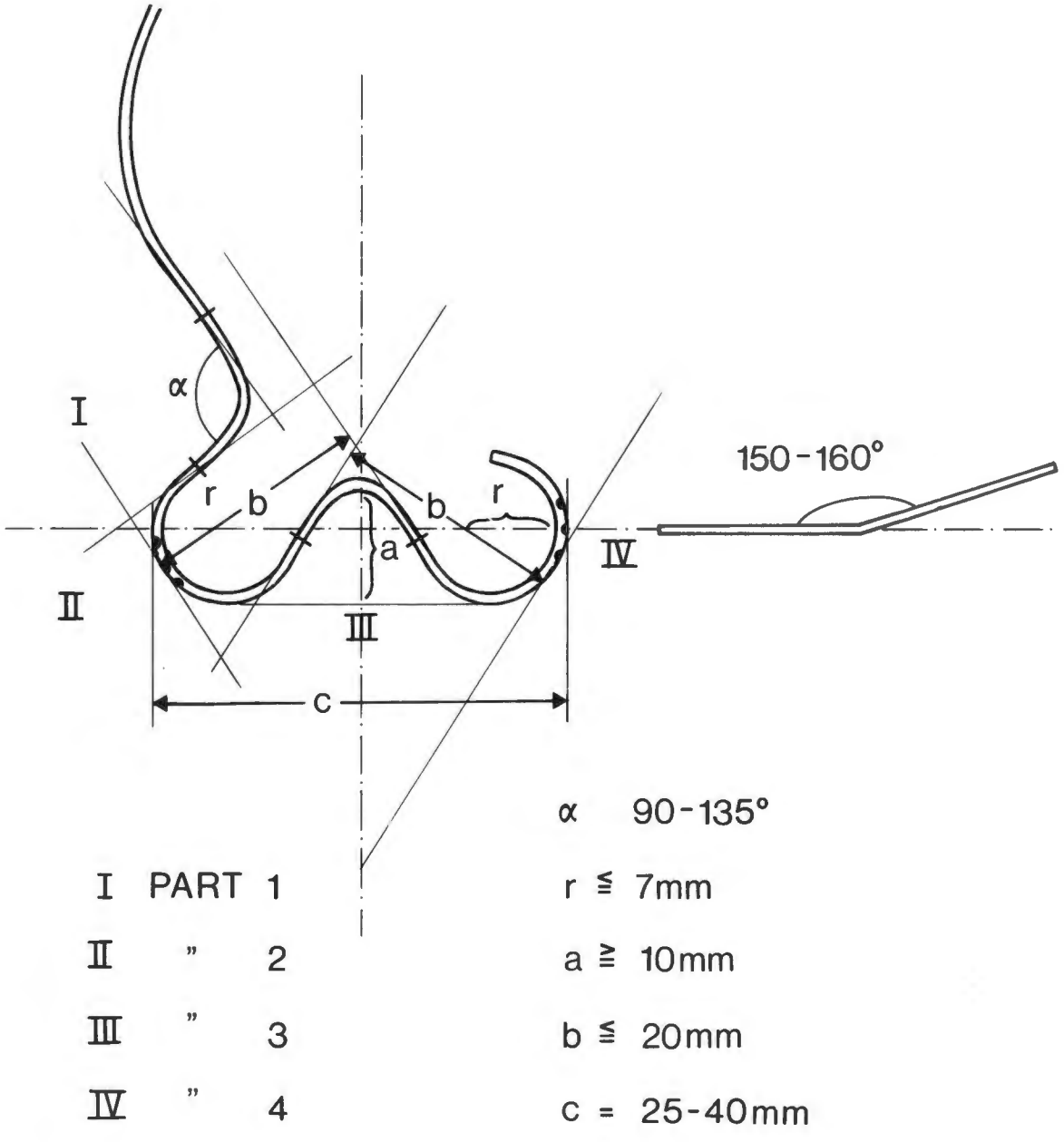

Figure 24: This scale drawing indicates the variable dimensions of the krypton-81m that were required in order to seat the catheter in the right and left aortic sinuses.

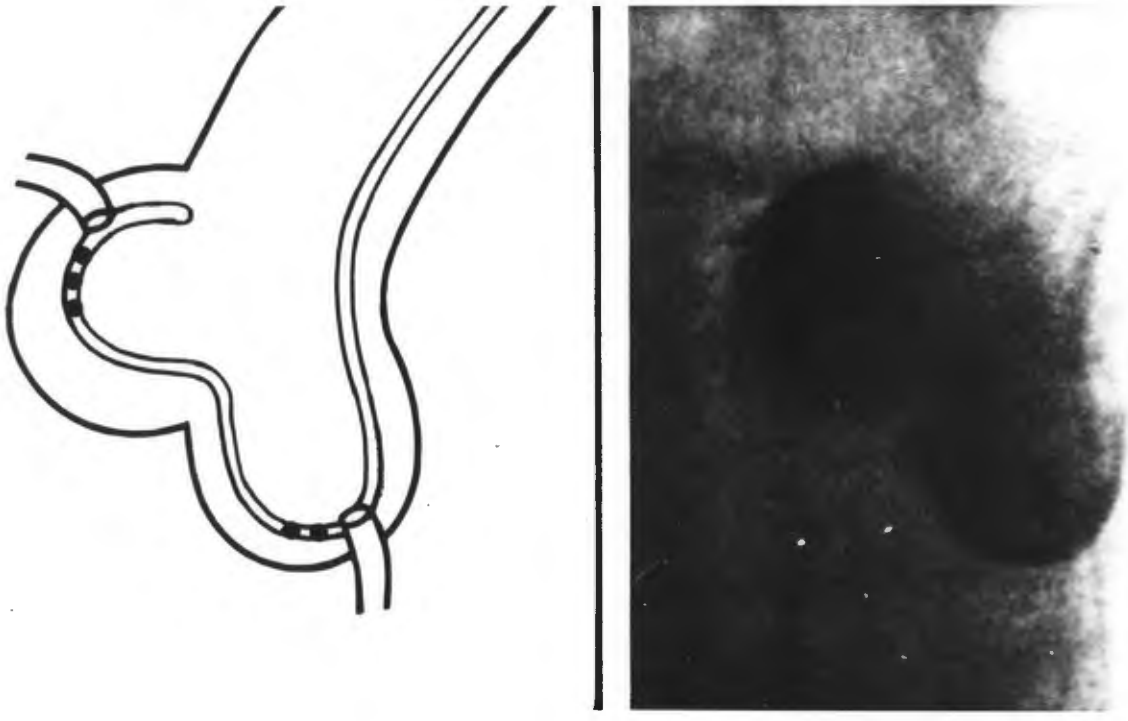

Figure 25: The diagram on the left indicates the shape and position of the krypton-81m catheter in the aortic sinuses.

The radiograph on the right shows the catheter in-situ. When iodine contrast is infused this is mixed in the sinuses without any selective coronary filling as shown in this figure.

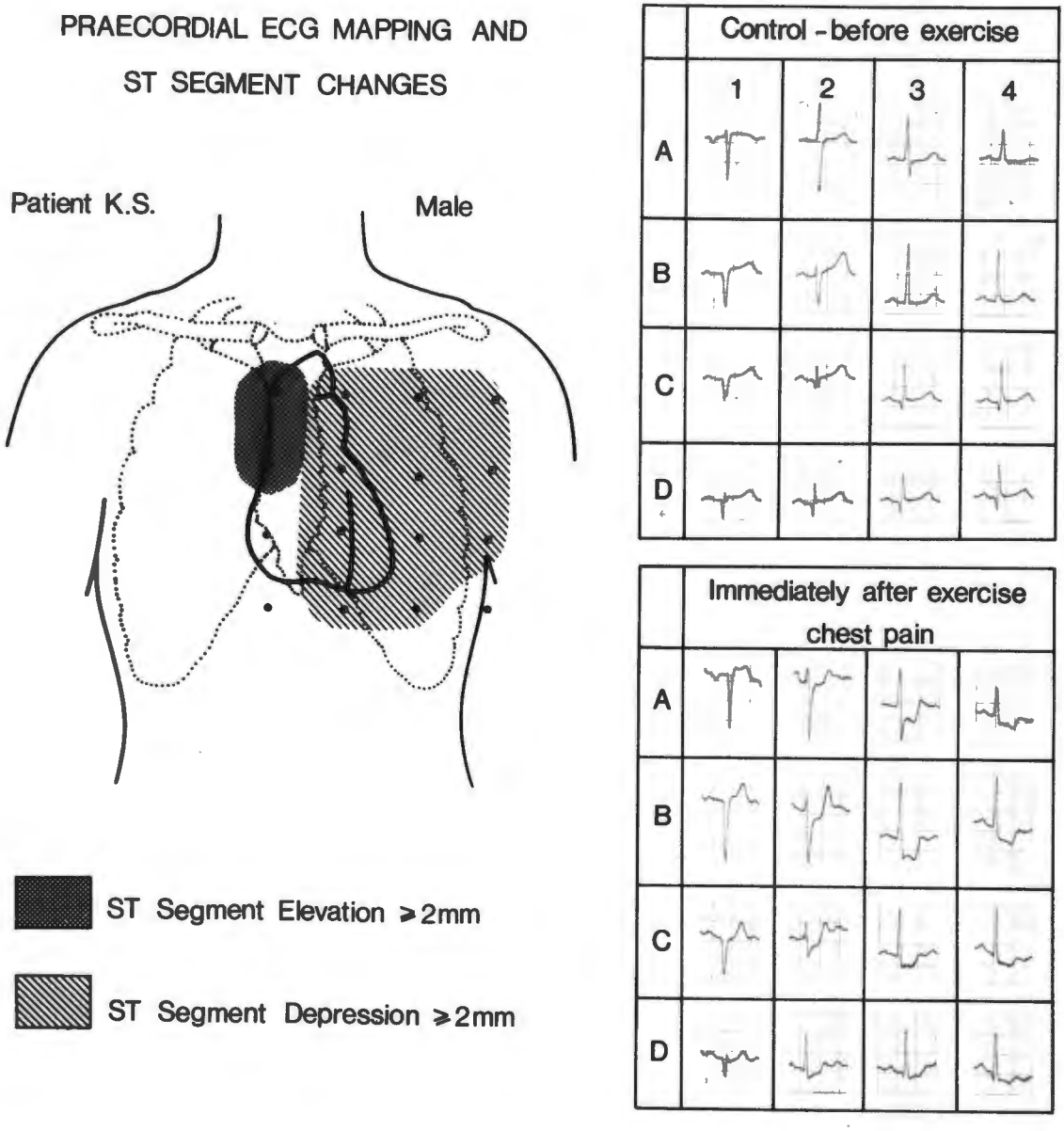

Figure 26: This example shows the 16 precordial positions, the precordial areas of abnormal ECG signs and the unipolar complexes at each position before and immediately after exercise.

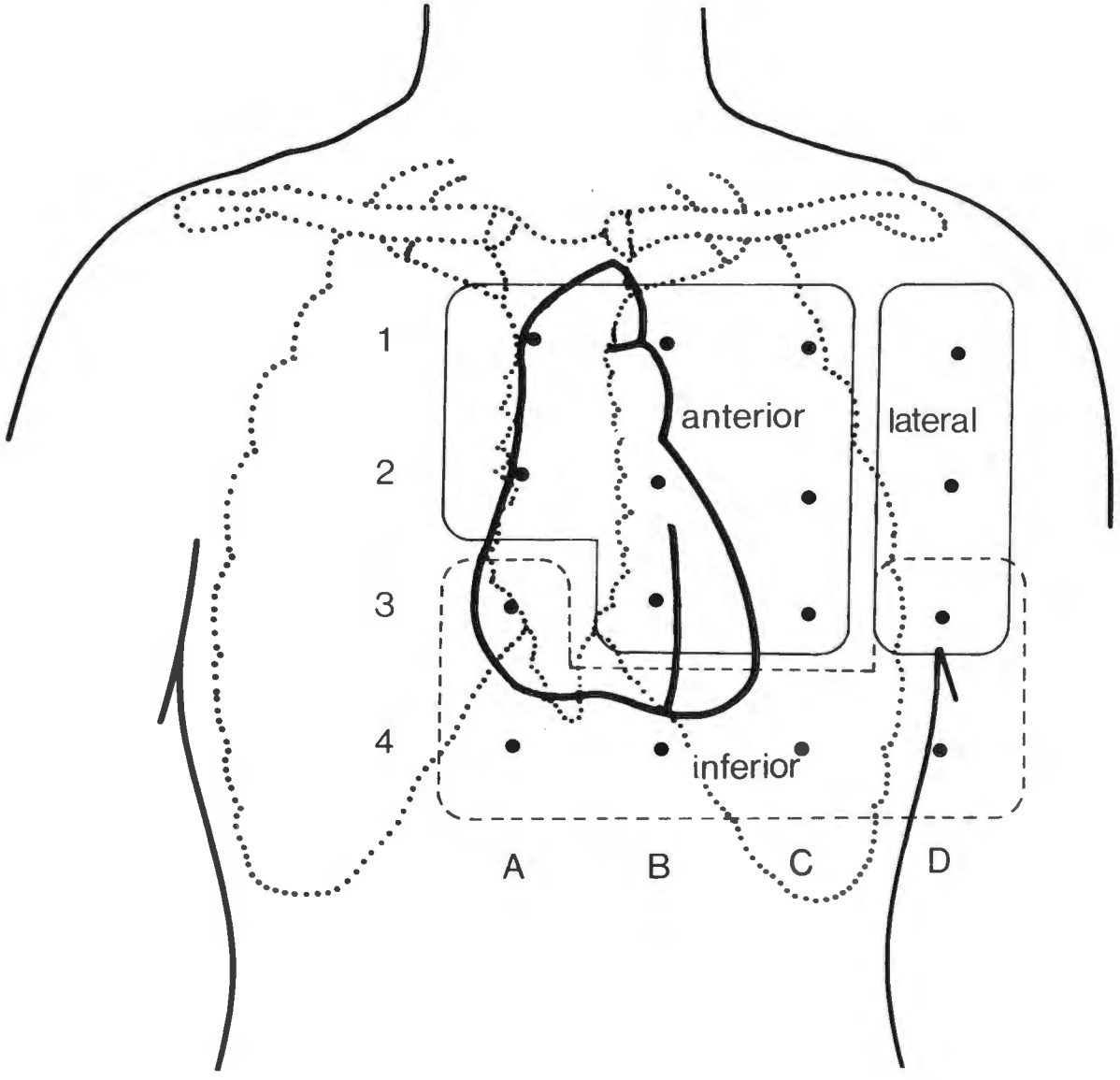

Figure 27: This diagram shows the precordial positions chosen for the 16 point maps and the arbitrary areas (anterior, inferior and lateral) chosen for the description of the clinical findings.

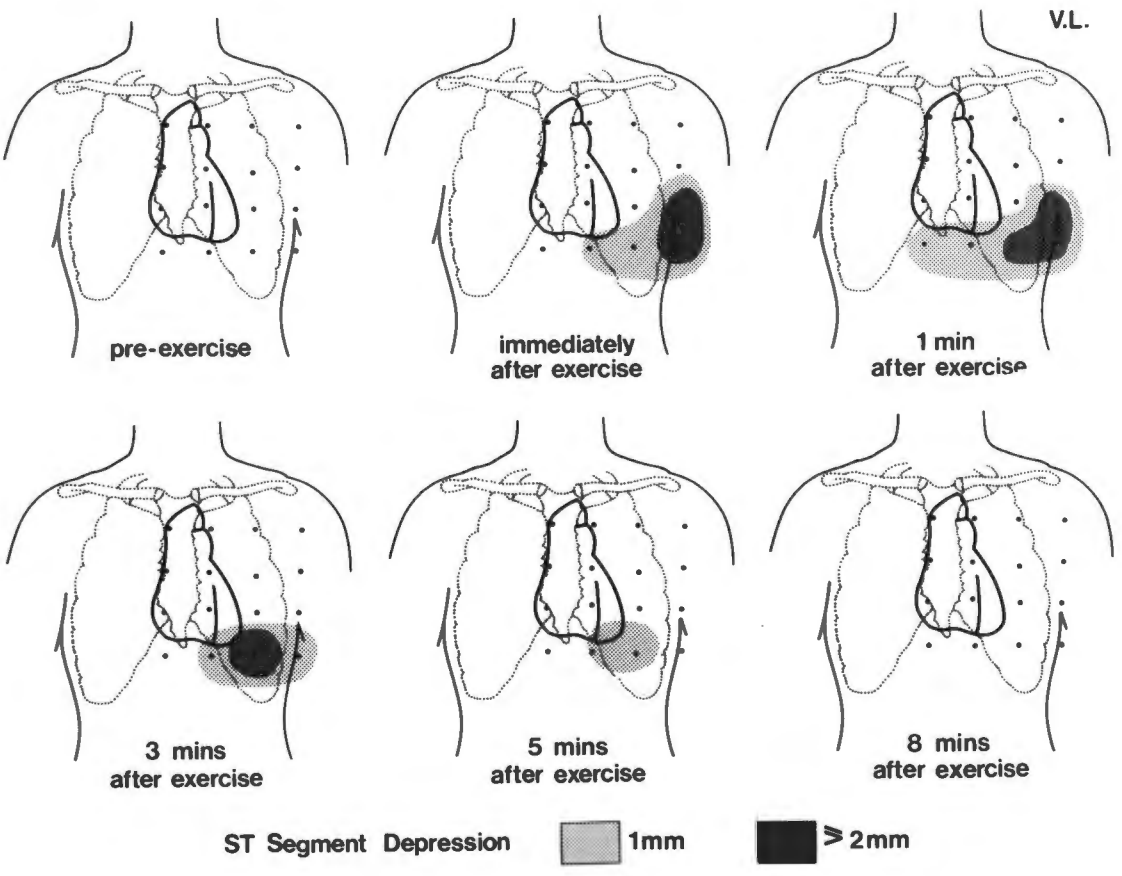

Figure 28: This series of maps represent a single exercise test showing the precordial areas of abnormal ECG signs that manifest after an exercise test. The maps show involvement of inferior precordial leads.

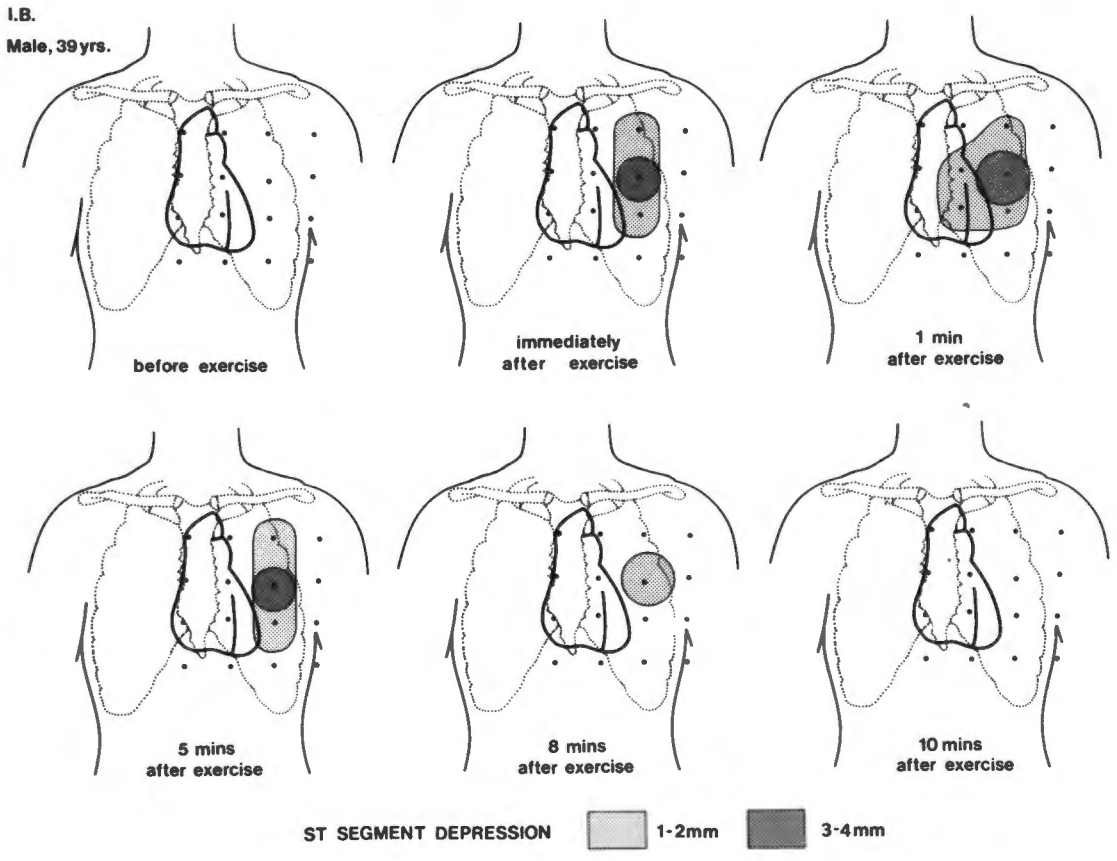

Figure 29: This series of maps represent the anterior precordial areas that manifest abnormal ECG signs after an exercise test.

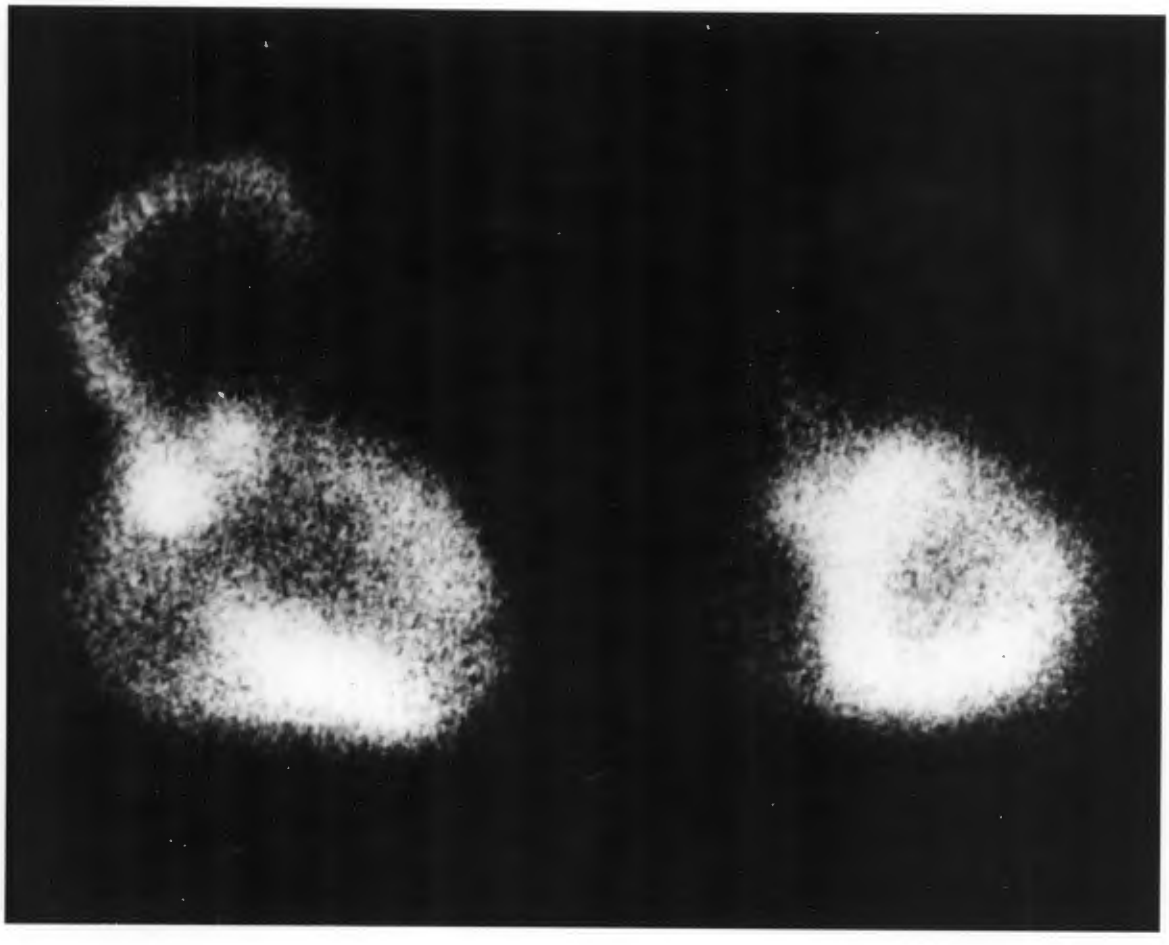

Figure 30: These are examples of krypton-81m scintigrams recorded in a patient at rest. The anterior view (left) shows the aorta, aortic sinuses also the anterior apical and inferior portions of the left ventricular myocardium. The increased inferior activity results from the relationship between the interventricular septum and the camera. The left anterior oblique (LAO) view (right) shows the aortic sinuses, the free wall and base of the left ventricle and the septum. The defect in the lateral wall seen represents the mitral orifice. These analog images were not processed.

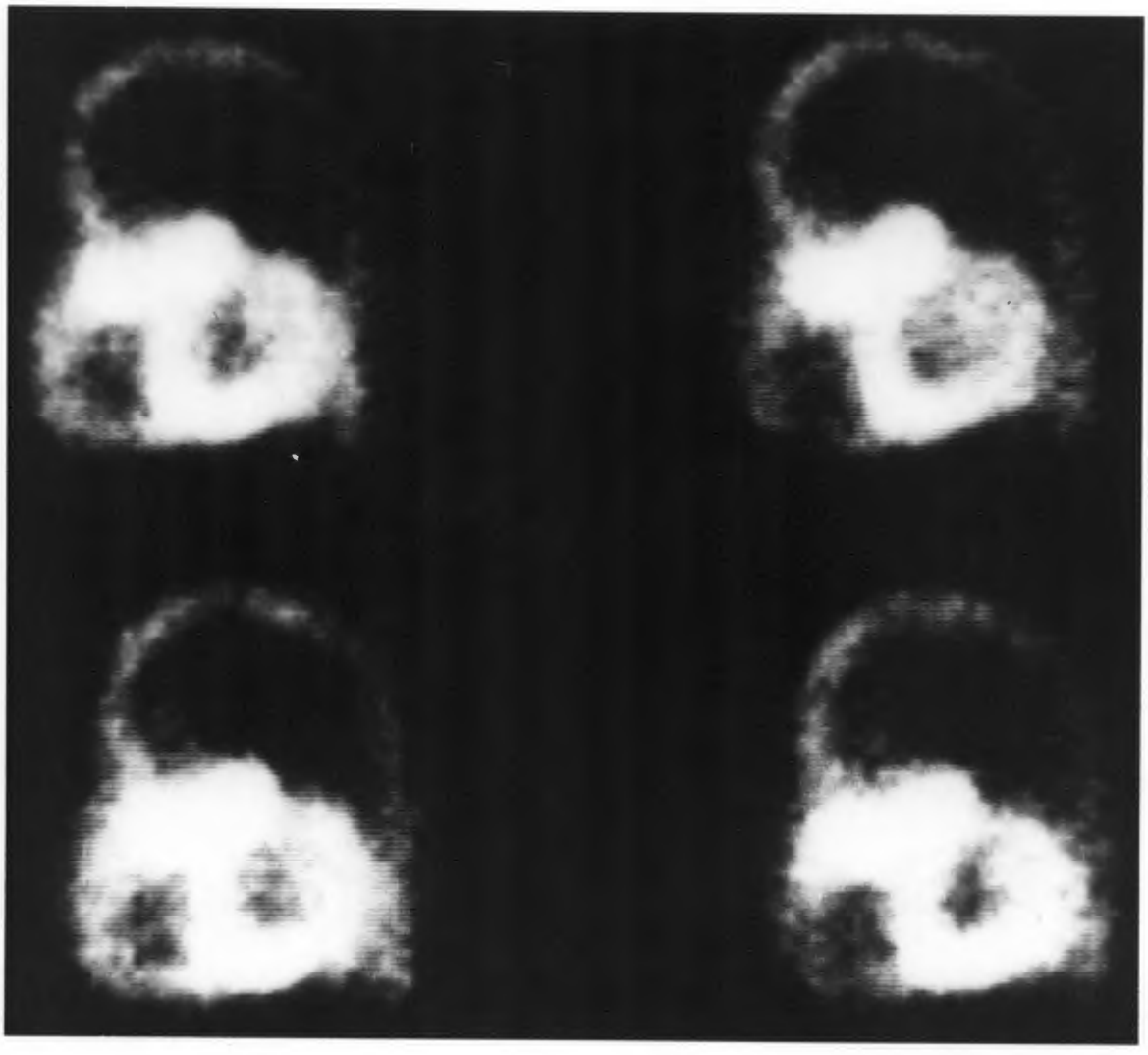

Figure 31: The examples above are from a patient with normal coronary arteries and a negative ECG test. The images were recorded at rest (top right), during pacing at 100/min (bottom right), during pacing at 140/min (bottom left) and again at rest (heart rate 70/min). During pacing the left ventricular cavity appears to decrease in size, the aortic sinus concentration remains stable and all regions of the myocardium show a similar increase in the activity of krypton-81m.

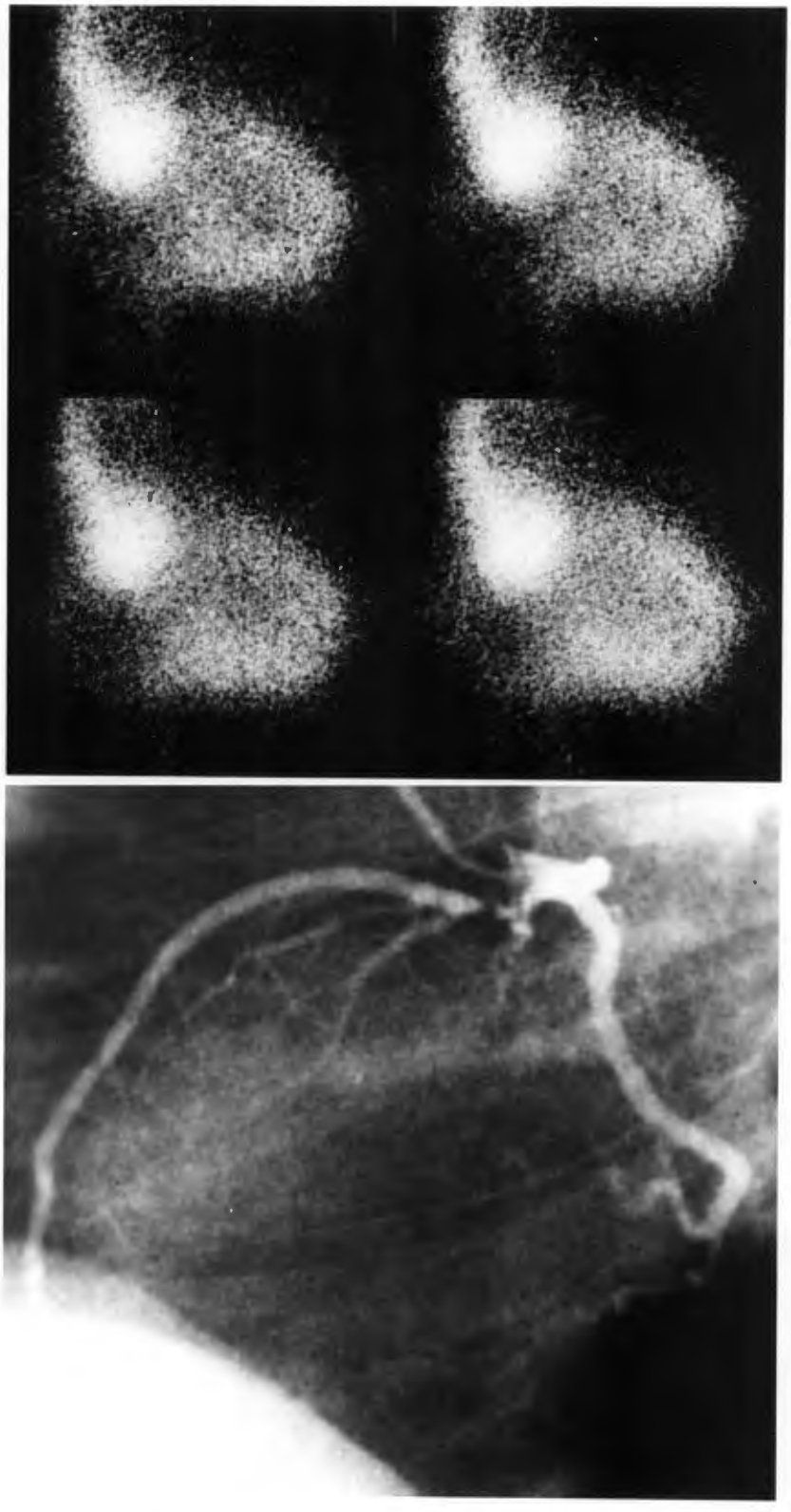

Figure 32: The patient studied above presented with chest pain, had a negative ECG exercise test but showed a 70% stenosis of the LAD coronary artery shown in the left coronary angiogram above (lower panel) in the LAO projection. The serial krypton-81m scintigrams (anterior position) showed uniform perfusion at rest (heart rate 80/min; upper panel, top left), also uniform perfusion during pacing at 110 (top right) and 140/min (bottom right) and again at rest (bottom left).

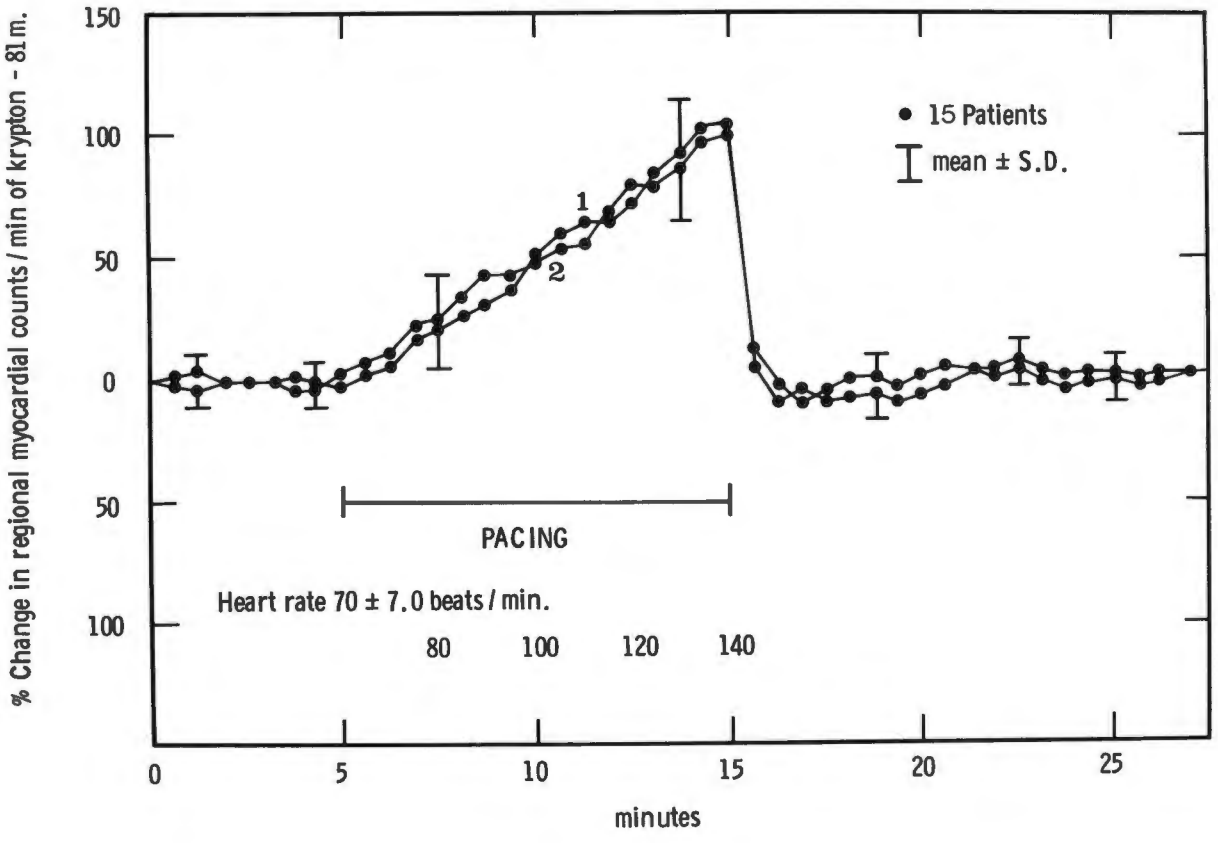

Figure 33: This graph plots the changes in regional myocardial activity of krypton-81m in the patients with negative exercise tests. Pacing produced similar increases in perfusion in two separate regions of the left ventricular myocardium. The aortic sinus activity changed by $\pm$ 5% throughout.

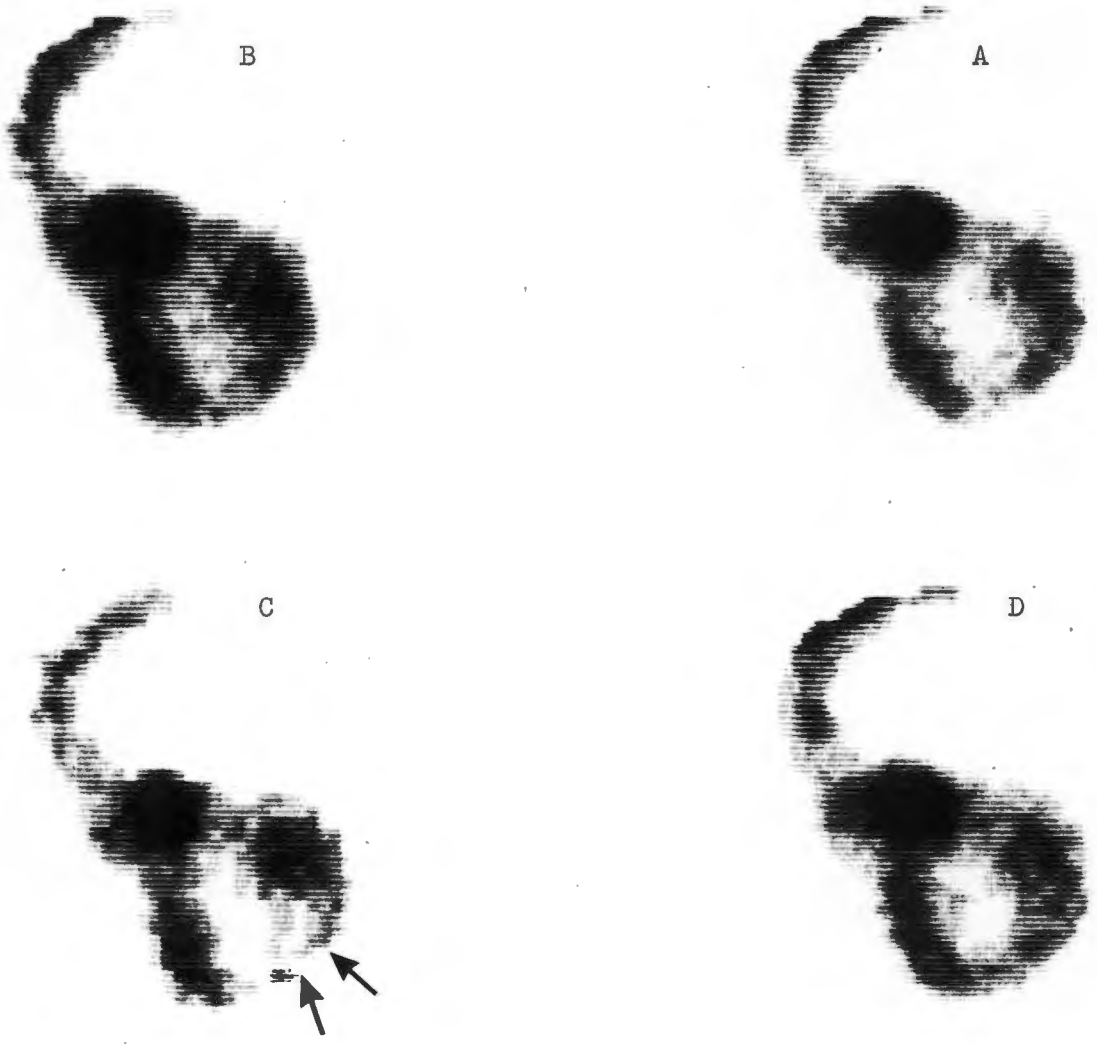

Figure 34: The patients shown here had a positive ECG test and $\geq$ 70% stenosis of the three major coronary arteries. The rest scintigram (A) in the LAO shows some decreased activity adjacent to the apex of the left ventricle. Atrial pacing from 75 to 110/min produced no pain, ECG change or obvious disturbances of perfusion (B). Pacing at 140/min produced pain, ST depression and an apical, inferior and lateral defect of activity seen in C. Ten minutes after atrial pacing the regional perfusion returned towards the conditions seen in the control image (A). The aortic sinus activity changed $<$ $\pm$ 5% throughout.

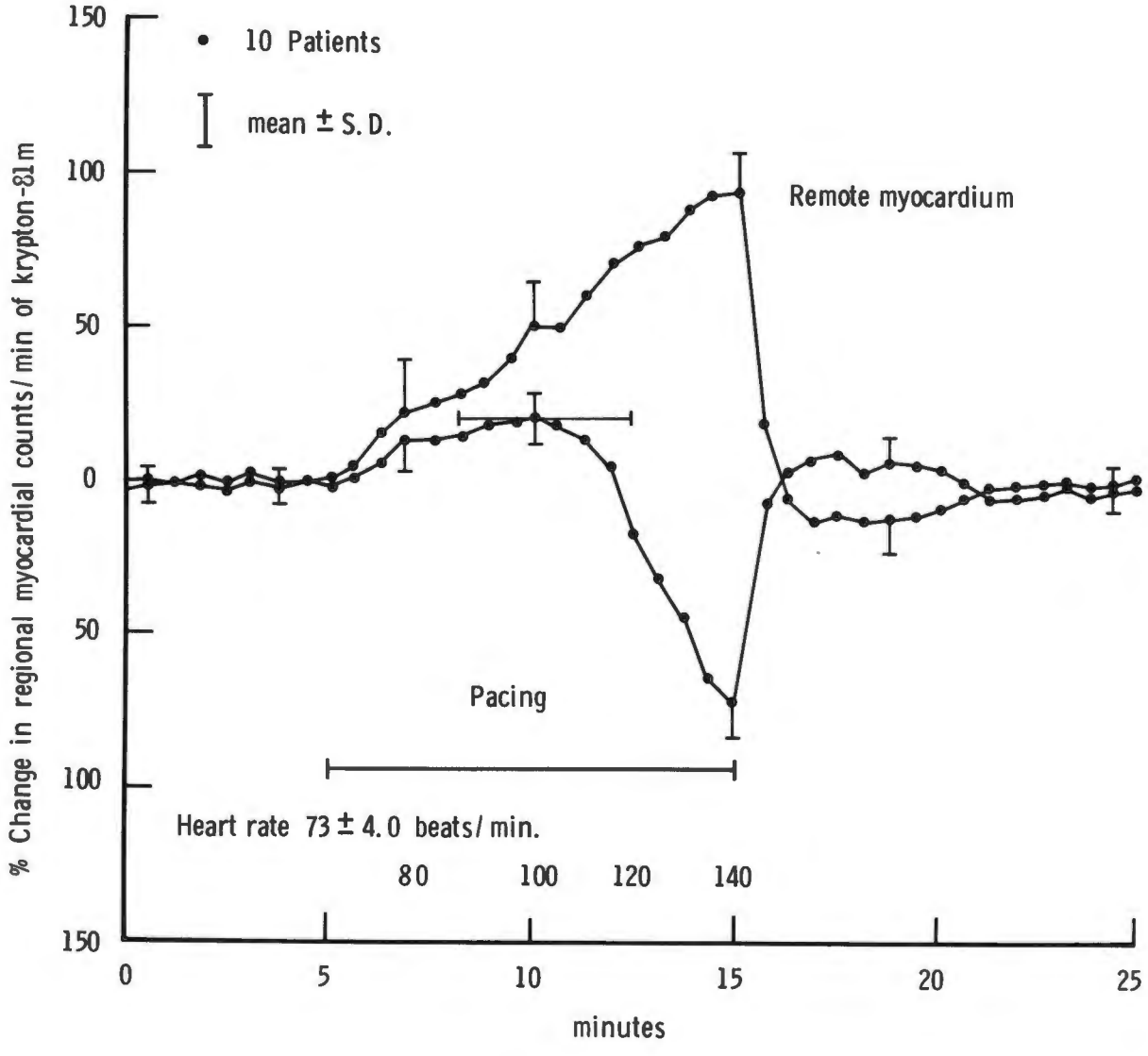

Figure 35: This graph shows the regional myocardial increases and decreases of krypton-81m activity before, during and after atrial pacing in 10 patients (Group 2, see text) with positive ECG exercise tests. Atrial pacing produced at first an increase in activity in the affected and remote areas. The affected area, however, changed during pacing and decreased rapidly until pacing was stopped. ST segment depression followed at 140 seconds (mean) after the regional decrease in activity.

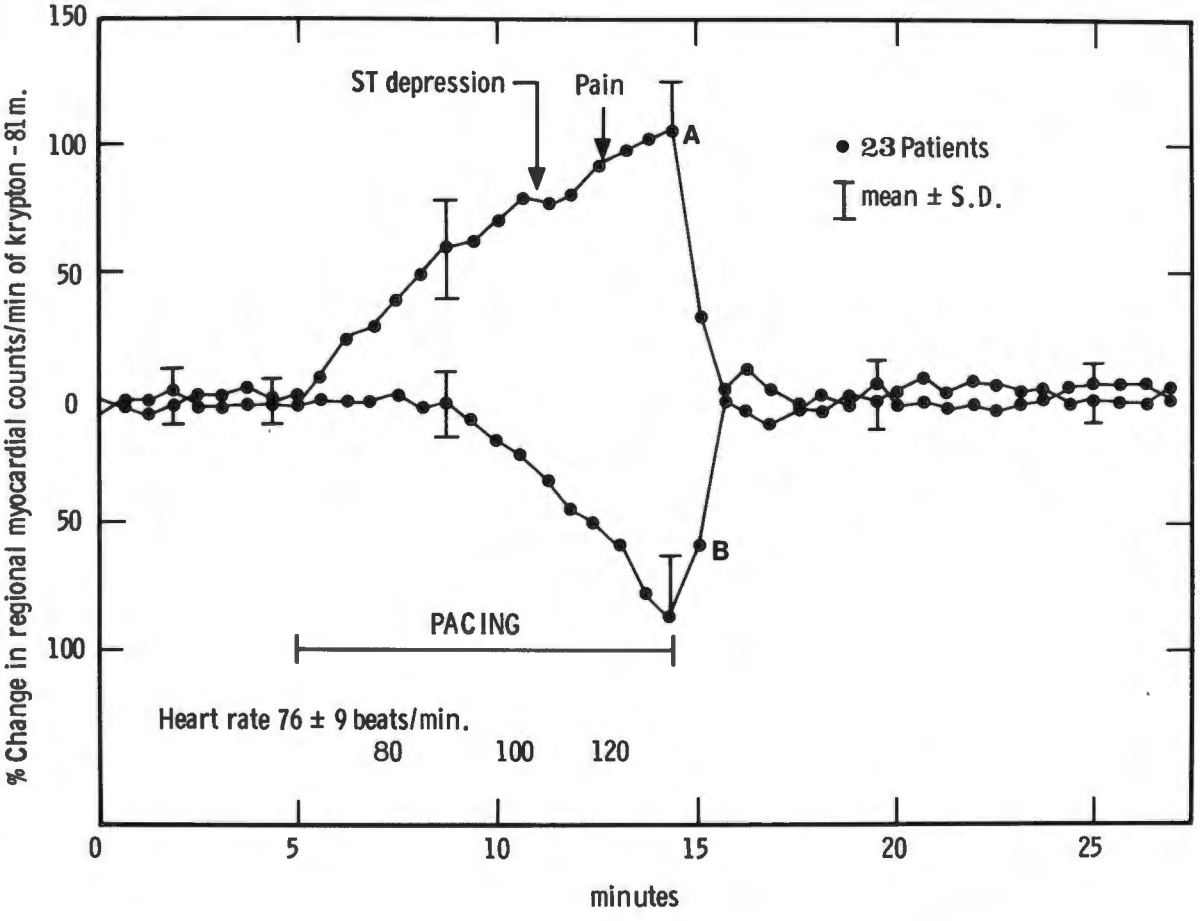

Figure 36: This graph shows the regional myocardial changes in krypton-81m activity with atrial pacing in 23 of the patients (Group 3, see text) with positive ECG exercise tests. The remote areas of myocardium (A) showed progressive increases in activity throughout the pacing. The affected area (B) showed at first no change with pacing and then a decrease in activity followed by ST depression and chest pain as shown in the graph.

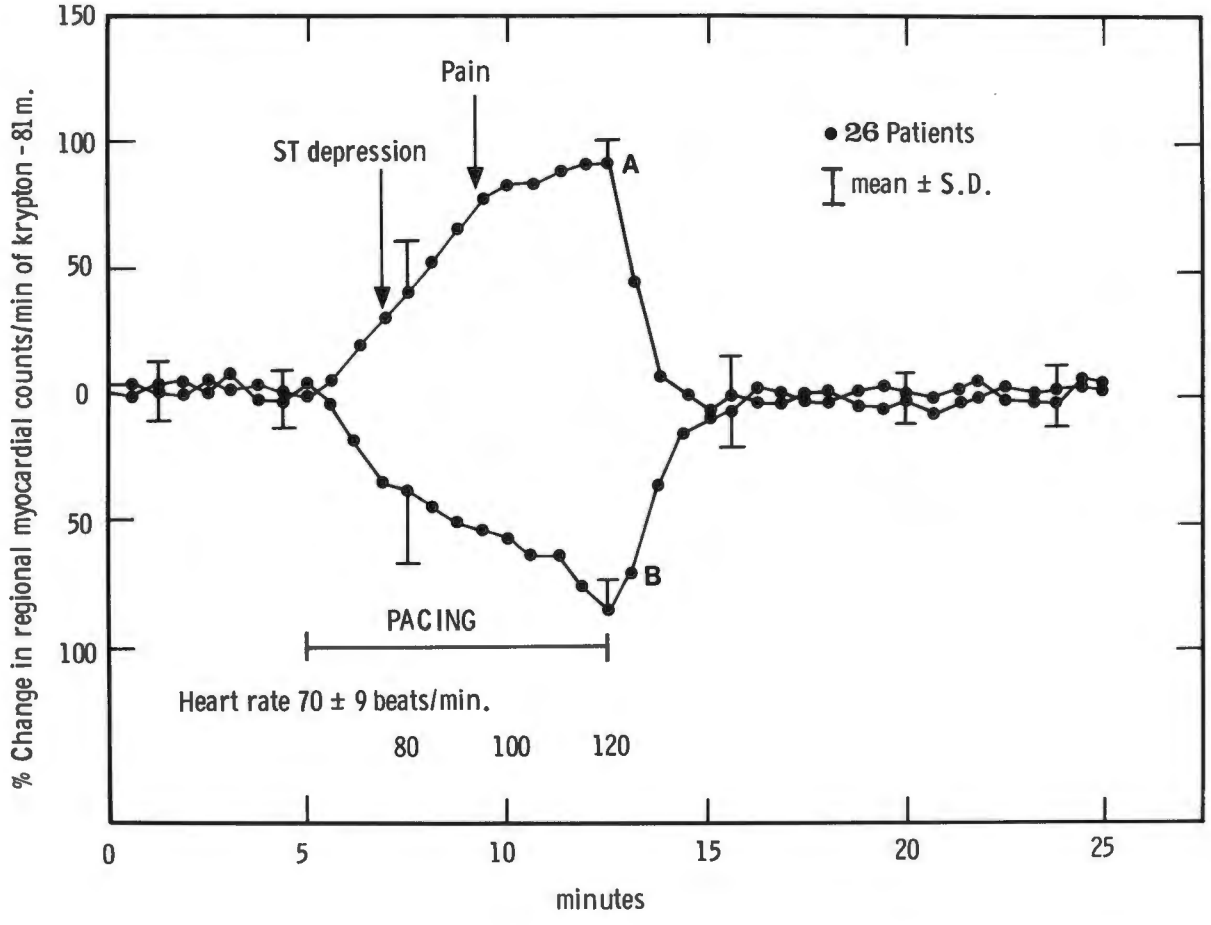

Figure 37: This graph shows the regional myocardial changes in krypton-81m activity with atrial pacing in 26 of the patients (Group 4, see text) with positive ECG exercise tests. The remote areas of myocardium (A) showed progressive increases in activity throughout the pacing. The affected area (B) showed within one minute an early and progressive decrease in activity followed by ST depression and chest pain as indicated in the graph.

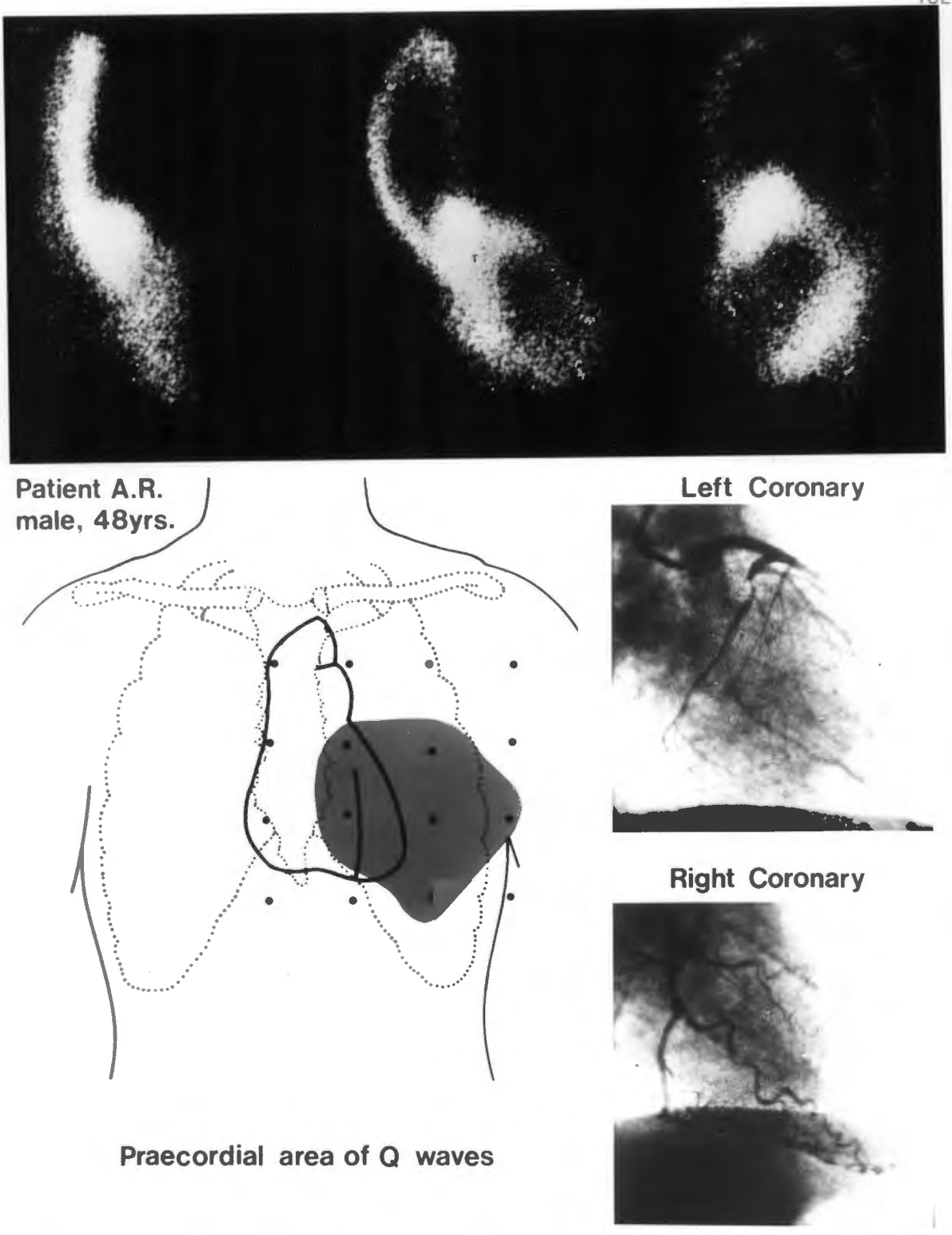

Figure 38: The patient shown above presented with chest pain with a past history and ECG evidence of anterior infarction. The scintigrams in the top panel (right anterior oblique, anterior and left anterior oblique) show a large anterior, apical and septal perfusion defect at rest. The praecordial ECG shows an anterior area of Q waves, extending to inferior and lateral leads (lower left panel). The coronary arteriograms (lower right panels) show $\geq$ 70% stenosis of the left circumflex and occlusion of the left anterior descending coronary artery.

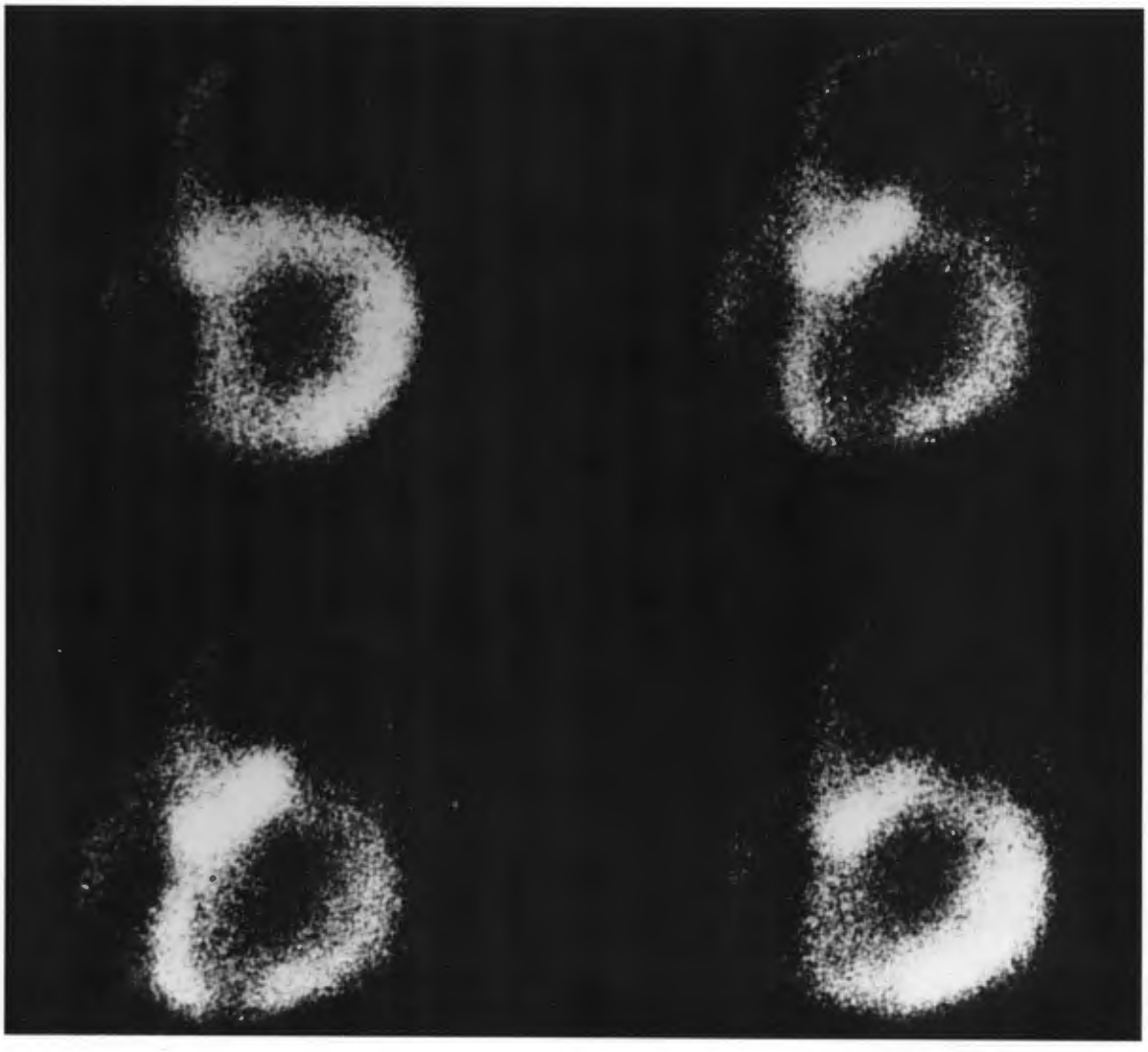

Figure 39: The patient studied above had a past history of anterior infarction with anterior Q waves in the precordial map. He also presented with chest pain and showed inferior ST segment depression in the ECG following exercise. The scintigram at rest (top left) shows diminished activity in the apex and septum. During pacing at 140/min (top right) the left ventricular (LV) cavity appeared to enlarge, counts in the lateral wall of the LV diminished and a marked regional defect appeared in an inferior segment. Three minutes after pacing the scintigrams showed some improvement (bottom left) and at 20 minutes the distribution of activity had returned towards the control state (bottom right).

CHAPTER III

SECTION IV

Discussion

The management of patients with angina pectoris must be based on a rational understanding of the underlying disturbances of myocardial perfusion and metabolism. At present there is no treatment for coronary atherosclerosis that is of clearly proven efficacy. The clinical investigator should therefore aim to relieve symptoms and preserve ventricular function by limiting ischemic damage. The efficacy of medical management and the timing of coronary artery surgery may be aided if the relationships between pain, electrocardiographic signs, disturbances of regional myocardial perfusion and coronary stenosis can be investigated.[1]

The coronary circulation

Chapter I has outlined the historical interest in the structure and function of the coronary circulation. Investigations of myocardial blood flow in patients have been encouraged by the need to evaluate in detail the disturbances that are thought to occur due to coronary artery disease.[2,3,4] Coronary atherosclerosis focally affects the large epicardial coronary arteries and affects the major branches and intramyocardial branches to a lesser extent.[5,6] The progressive narrowing of these vessels is thought to be associated with spatial and transmural disturbances of regional myocardial perfusion. These disturbances of perfusion in turn lead to ischemia with temporarily or permanent loss of contractile function.[4]

The applications for radionuclides in patients with coronary artery disease

In 1920 Blumgart and Weiss first used radon C to measure trans-pulmonary blood flow and velocity.[7,8] Since then the new radio-pharmaceuticals, methods of detection and computing have all developed over 50 years providing deeper insight into the physiology of the coronary circulation.[9]

The theoretical and basic studies of Kety and Schmidt encouraged the development of methods and clinical research using the washout of long-lived, inert and freely diffusing nuclides as a means of measuring regional myocardial perfusion.[10] Love and Carr first introduced the use of extracted cations for imaging the myocardium and Sapirsteins principles governing the fractional distribution of a tracer to organs according to flow have been extended by Donati and colleagues.[11,12,13,14] The peripheral intravenous injection of thallium-201 in patients is now widely used to image the heart and to identify regions of the myocardium permanently damaged by infarction or reversibly affected by ischemia during stress.[15]

There has been a limited application for direct intracoronary injection of radioactively labelled microspheres. This has been used to outline the distribution of the coronary circulation at rest and during pharmacological coronary vasodilitation.[16]

Left ventricular function and ejection fraction are affected in ischemic heart disease and the latter is considered a useful parameter in clinical practice. This measure can now be obtained by a peripheral intravenous injection of radionuclides that label the blood pool (e.g., technicium-99m stannous pyrophosphate and technicium-99m labelled to

albumin). The first pass and equilibrium methods are expertly described by Strauss, Pitt and colleagues.[17,18] These techniques will provide a measure of ejection fraction from the percentage change in radioactivity in the left ventricular cavity during each heart beat. Ashburn and colleagues have applied the method to study fixed regional dyskinesia at rest and, most important for this discussion, transient dyskinesia due to ischemic myocardium induced by stress in patients with coronary artery disease.[18]

The limitations of spatial resolution, planar scanning and quantitation can be partially overcome by positron and single photon tomography.[19,20] These new principles and methods are a rigorous and non-invasive way of examining tracer concentration in tissues quantitatively and in real space. Weiss and others have already measured the regional myocardial distribution of gases (oxygen-15, oxygen-15-labelled carbon dioxide, carbon-11-labelled carbon monoxide), cations (nitrogen-13-labelled ammonia, rubidium-82, potassium-38) and metabolic substrates (^{11}C - palmitate, ^{18}F - deoxyglucose). Schelbert has shown that it is possible to detect acute regional myocardial ischemia in patients with coronary artery disease.[21]

Krypton-81m and regional myocardial perfusion

The physiological range of myocardial perfusion in man at rest is probably between 0.5 and 1.5 ml/ml/min.[3] The half-life of krypton-81m ($t_{\frac{1}{2}}$ = 13 sec, decay constant = 3.2/min) is short in relation to this range for flow per unit volume (F/V). An equilibrium of activity of krypton-81m in the myocardial water space will depend mostly on perfusion, arterial concentration and radioactive decay. When

myocardial flow per unit volume approaches the time constant for the decay of the isotope (i.e., 3.2/min) then washout of krypton-81m will become significant. The physical constant would then have to be included in any quantitative calculation. This dynamic equilibrium means that if the aortic sinus infusion is constant, the regional myocardial activity of krypton-81m can be measured in order to investigate increases and decreases in regional myocardial perfusion.[22,23,24,25,26]

This work has introduced a cardiac catheter that can be seated in the right and left aortic sinuses, maintain a stable position and allow the constant infusion of equal volumes of 5% dextrose and krypton-81m into each sinus and not directly into the coronary arteries. This catheter cannot engage the coronary arteries because of the specialized curved ends seated in each sinus.[27]

Experiments in dogs have shown that the calibrated regional counts per minute of krypton-81m can measure changes in regional perfusion between 0 and 3.0 ml/ml of myocardium/minute. This satisfactory systematic error suggests that there is an adequate mixed reserve of krypton-81m in the aortic sinuses that is sufficiently stable within a range of physiological changes in heart rate, blood pressure and cardiac output. The particular vortex pattern of blood flow in the aortic sinuses would favour mixing and support this view. In addition, experiments have shown that the regional myocardial distribution of krypton-81m infused into the aortic sinuses is the same as the regional myocardial distribution of radioactively labelled microspheres injected into the left atrium. This evidence for the adequate and stable mixing of krypton-81m held during a useful range of changes in heart rate,

blood pressure, cardiac output and coronary flow.[25,26] Direct measurements in the right aortic sinus and the left anterior descending coronary artery showed no significant changes in the delivered arterial activity of krypton-81m with changes in heart rate, blood pressure and cardiac output. These findings would all suggest that within the defined limitations the theoretical considerations are correct and that the regional changes in the myocardial activity of krypton-81m can be used to measure regional changes in myocardial perfusion.

It is, clearly, important in this clinical study to know whether the regional myocardial (RM) increases and decreases in krypton-81m do represent increases and decreases in RM perfusion. If the delivered arterial concentration of krypton-81m changed significantly then the scans would assess RM flow differences or relative changes only. The preceding experiments in Chapter 2 and this discussion has shown that the RM signal is dominated by arrival of tracer (variable) and decay (a constant). Arrival is controlled by flow x arterial concentration. In these clinical studies the aortic sinus activity remained stable while the RM activity changed with the interventions.

If all the tracer were delivered directly into the coronary circulation the fixed supply of tracer would mean that the arterial concentration would alter with changes in flow. If flow increased to most areas of myocardium but remained constant in one area a greater percentage of the fixed supply of tracer might go to the regions of increased flow and the area of constant flow might show a decrease in RM activity simply because it received a smaller percentage of the total counts(i.e., a regional drop in the arterial concentration). However, the technique does not deliver the tracer into the coronary

arteries but proximally into the bases of the right and left aortic sinuses. A constant quantity of krypton-81m mixes and partitions between the systemic and coronary circulations at this site. Therefore, changes in coronary flow are met by changes in the partitioning of the mixed krypton-81m in the sinuses which act as an afferent mixing chamber similar to the role of the left atrium with radio-actively labelled microspheres. The flow through each sinus will vary with haemodynamic changes but these experiments have defined the limits within which the arterial concentration of krypton-81m remains insensitive and does not change. Within these limits the amount of krypton-81m reaching the coronary circulation and the myocardium will only vary with flow.

Patient studies using krypton-81m

In these patient studies the regional and total myocardial counts per minute were stable during the control periods. In addition, the patients with no evidence of coronary artery disease and negative exercise ECG tests showed no redistribution of myocardial activity during or after atrial pacing and the aortic root activity varied $\leq \pm 5\%$ throughout the studies in all the patients. Again, this would suggest that the delivered arterial concentration and mixing of the tracer were constant.

During the krypton-81m scintigraphy the background activity was less than 5% of the myocardial activity. This means that with the high myocardial counts (300,000 to 1 million counts per minute) there was adequate separation of regional myocardial structures and events. This finding also confirms that most of the krypton-81m decays in the myocardial water space.

Krypton-81m emits a single 190 kev gamma ray that is well suited to gamma camera detection. Attenuation and Compton scatter are less of a

problem than is encountered using nuclides with emissions of lower energy.[19] This study and experimental work have shown high count rates from the heart with good statistics aided by a negligible background of krypton-81m.

Disadvantages of using krypton-81m

The use of krypton-81m in this way clearly has a number of limitations. The method is invasive, prolonges the cathertization procedure and does not separate endocardial from epicardial events. Quantitation of flow in physiological units by calibrating the activity of krypton-81m is theoretically possible but was not tried in this patient study.[28] The geometrical relationship between the heart and gamma camera is complex and careful positioning with multiple views are required in order to identify regions of the heart. Any regional increases in myocardial activity due to flow must consider the decay constant (3.2/min) as this physicochemical constant will distort the relationship between counts and perfusion. Fortunately this effect is not significant within or below the physiological range for flow per unit volume. Aortic root activity must be stable throughout. If not, then changes in the regional myocardial activity must be expressed as being relative to total myocardial counts (as ratios). This will only assess the relative distribution of perfusion.

In this study the arterial concentration of tracer was assessed by measuring the aortic sinus activity. This was constant throughout. The results in this thesis show the percentage changes in the RM activity of krypton-81m. If these values are expressed in relation to the aortic sinus activity (i.e., ratios) which remained constant the results are unchanged.

Regional myocardial perfusion in patients

The images of the myocardium and equilibrium of counts per minute formed a familiar pattern of distribution in all the patients with no coronary artery disease.

Fifteen patients showed fixed regional defects of activity at rest and during stress identified by all 3 observers. These were all associated with regional ventricular dyskinesia reported in the angiocardiograms and pathological Q waves in the precordial electrocardiographic maps. These regions probably represent infarction and showed no significant changes in perfusion during the stress test.

The patients in this study all presented with chest pain and although every attempt was made not to distort the results by selection the numbers studied do not allow the author to make general statements about all disturbances of myocardial perfusion in patients with chest pain. Although 4 groups are shown in the results section, the author does not suggest that 4 separate conditions exist in the population of patients presenting with chest pain.

The patients with negative exercise tests had uniform increases of regional myocardial perfusion with atrial pacing. These patients either had no cardiovascular disease or had a transient condition causing myocardial ischemia that was not precipitated by pacing. The increases in perfusion with pacing are in accord with all the past research demonstrating a close relationship between the level of coronary perfusion and myocardial oxygen requirements.[29] This group of patients also demonstrated that the mixing and streaming of krypton-81m were stable before, during and after each intervention.

The remaining 65 patients with positive exercise tests all showed stable regional myocardial perfusion before atrial pacing. With pacing, the region of the myocardium thought to be supplied by a normal coronary artery (or the least severely affected vessel), showed progressive increases in regional perfusion with pacing. Even the patients with triple vessel disease always had at least one area of the myocardium showing significant increases in perfusion during pacing. Those regions of the myocardium showing abnormal changes or defects during pacing revealed on analysis a completely different sequence of changes in regional myocardial perfusion. Sixteen patients were able to increase regional perfusion in the jeopardized area but during atrial pacing this increase stopped and then perfusion decreased progressively. This decrease was accompanied by ST segment changes and chest pain. Twenty-three patients showed no changes in the jeopardized area following the onset of atrial pacing. During the pacing, all these patients also showed a significant decrease of perfusion accompanied by electrocardiographic changes and chest pain. The last group of 26 patients showed decreasing regional perfusion almost immediately following the start of pacing.

In all the patients there was a close temporal relationship between regional decreases of perfusion and ST segment depression.

These regional decreases in myocardial perfusion with chest pain in patients with coronary artery disease have been identified with difficulty using other techniques.[30,31] This study allows this pathophysiology to be examined in detail. It may be that the group showing increases in perfusion early in the pacing-test were still able to

regulate regional perfusion to a limited extent. The groups showing no regional increases in perfusion to jeopardized segments clearly had fixed limitations of blood flow, presumably imposed by the atherosclerotic coronary arteries. In addition, the collaterals if any, could not effectively diminish the total resistance to blood flow at arterial level.

When atrial pacing was continued the initial variable changes in regional myocardial perfusion were followed by progressive decreases of regional myocardial perfusion in the 65 patients. This was followed by ST segment changes and then chest pain. These decreases of perfusion may have been caused by the pacing which produced an inhomogeneous regional distribution of vascular resistances to blood flow with competition between the jeopardized segment which cannot diminish resistance and remote areas which can adapt. In addition, with the onset of ischemia the affected tissue fails to contract and relax normally, it changes shape, thickness, physical characteristics and is acted on by a raised left ventricular cavity pressure and volume. Oedema of ischemic myocardium, particularly capillary endothelial cells may also contribute with all the above factors by interferring with systolic and diastolic coronary flow during the ischemic event.[32-45] There are animal experiments that support this view.[46] In addition, functional factors such as changes in coronary vasomotor tone and platelet function must be considered as possible mechanisms.[47,48] Because these transient decreases of regional myocardial activity of krypton-81m during pacing occurred while the aortic root activity was constant the results suggest that the delivered arterial concentration

of tracer was stable and the regional myocardial changes are due to decreasing perfusion.

Clinical implications of changes in perfusion

The above dynamic changes in regional myocardial perfusion are difficult to examine using either xenon-133 or thallium-201.[44,49] Krypton-81m has shown different patterns of disturbed regional perfusion with stress and decreases in regional flow during the pacing test. This new finding means that the rational treatment of angina pectoris must consider that an increase in heart rate in patients with coronary artery disease may produce an immediate and inhomogeneous redistribution of myocardial perfusion as well as increases in myocardial oxygen requirements. This supports and extends the work of Cannon, Lichtlen, Maseri, Trobough and others who have simply stated that regional decreases of myocardial perfusion may occur during angina pectoris.[47] The washout of xenon-133 or krypton-85 and the extraction of cations have not been able to describe these dynamic changes of perfusion.[45-50]

The appearance of abnormal perfusion during stress always preceded the changes in the electrocardiograph and the onset of chest pain. This supports the work of Maseri and shows that alterations in myocardial oxygen requirements and perfusion are closely related.[47,49]

The interpretation of the coronary arteriogram

The coronary arteriograms in this study were assessed without knowledge of the clinical facts. Two of the patients reported to have $\leq 50\%$ stenosis and two patients with $\geq 70\%$ stenosis of coronary arteries did not have positive electrocardiograms on exercise and had

normal perfusion scans. In addition, 8 of the patients with $\leq$ 50% stenosis had positive exercise tests and abnormal perfusion during stress. These findings underline the difficulties of making physiological interpretations from the coronary arteriogram.[45,47,54,55,56]

The electrocardiogram during exercise

The electrical activity of the beating heart was first investigated by Kollechar, Muller, Donders and Bunden-Sanderson between 1855 and 1879. Waller first published electrocardiographic complexes from a human subject in 1887 and 1889. This was followed by Bayliss and Starling in 1892.[60,61] Between 1901 and 1913 Einthoven introduced the string galvanometer and standard limb leads.[62]

A variety of lead systems have been devised and following Einthoven, Goldberger introduced the augmented limb leads in 1942.[63] Wilson developed the chest leads in 1932 and 1944.[64] Frank introduced an orthogonal lead system in 1956 and Schmidt and Simoons advanced this aspect.[65-67]

The electrocardiogram during exercise has been widely used to diagnose coronary and ischemic heart disease. The difficulties of relating this test to symptoms (i.e., angina pectoris), pathophysiology (i.e., myocardial ischemia), and pathology (coronary artery disease) have been extensively reviewed along with the statistical analysis first introduced by Youden in 1950.[68] The correlation between the locality of ST segment changes and the site of coronary artery stenosis is poor.[69,70]

Isopotential precordial mapping of the electrocardiogram was first performed by Tacardi in 1963 using multiple recording sites on

the chest.[71] Horan recorded wave forms of the QRS complex across the chest and in 1971 and in 1972 Maroko used multiple epicardial and later precordial electrocardiographic recordings to study the distribution, time course and severity of ST segment elevation following occlusion of a coronary artery in the dog.[72,73,74] Reid, Pelides and Shillingford described precordial areas of ST segment elevation in patients during acute myocardial infarction and later Selwyn demonstrated the time course of changes in precordial ST elevation, loss of R and development of Q waves in acute uncomplicated anterior myocardial infarction.[75,76] Block developed 125 lead computer processed precordial mapping of the electrocardiogram during exercise.[77] This method has identified areas of abnormal electrocardiographic signs across the chest. The method developed by Fox and presented in this thesis uses 16 positions covering the left hemithorax and standard equipment.[78] The results provide the frequency, time course and severity of precordial ST segment changes before, during and after a standardized, maximum, symptom limited exercise test. This method had a sensitivity of 95% and a specificity of 92% for the diagnosis of coronary artery disease in a published series. In the same group of patients the 12 lead electrocardiogram gave a sensitivity of 85%, the orthogonal leads 80% and V_5, 65%.[74]

Transient disturbances of perfusion and the electrocardiogram

This thesis shows a close relationship in patients between a positive exercise precordial map and abnormalities of regional myocardial perfusion using krypton-81m. There was also a relationship between anterior Q waves and septal and/or apical defects of perfusion at rest

also inferior Q waves and inferior perfusion defects. This association has been described using the 12 lead electrocardiogram.[79,80]

The relationship between precordial areas of electrocardiographic changes and the size or severity of the underlying ischemic lesion must be complex. This is because of the poorly understood electrophysiological manifestations of ischemia, changing conduction between ischemic and normal myocardium, the variable spatial relationship between the ischemic lesion and the chest wall and finally the inhomogeneous conducting tissues between the electrode and the heart.[80,81,82] Nevertheless, the precordial maps may provide information about the presence of regions of ischemic or infarcted ventricular myocardium.

This agreement between precordial electrocardiographic signs and underlying disturbances of regional myocardial perfusion is better than the relationship between either of these two parameters and the coronary anatomy reported in the angiograms. This underlines again the difficulties of relating anatomical with physiological information.[47] The relationship between coronary artery stenosis and disturbances of regional myocardial perfusion is complicated by the difficulties in assessing the arteriogram, the variable cross circulation providing perfusion to any one segment of myocardium, the role of collaterals and the more debatable effects of coronary steal. The precordial electrocardiographic and scintigraphic findings both examine pathophysiology within the myocardial tissues. The former observing electrophysiology and metabolism and the latter assessing tissue blood flow. All of these parameters are interrelated and are disturbed in patients with coronary artery disease.

Conclusions

This chapter has demonstrated the limited use of a short-lived radionuclide for studying serial changes in regional myocardial perfusion in patients who presented with chest pain. Those patients with negative exercise electrocardiograms had uniform perfusion at rest and during stress. Patients with positive exercise tests showed different patterns of disturbed regional myocardial perfusion during ischemic events induced by atrial pacing. Those patients who achieved a poor workload showed immediate disturbances in regional myocardial perfusion. The study shows that myocardial perfusion and metabolism are closely related and both are disturbed during episodes of angina pectoris induced by pacing.

Although these studies have examined the coronary circulation in patients with coronary artery disease during stress, the atrial pacing used is not physiological and these results may not be relevant to the pathophysiology of angina pectoris during the patients active life. There may be a variety of causes of myocardial ischemia and the technique outlined in this thesis may be suitable to assess the relative importance of fixed atherosclerosis, coronary vasomotor tone and platelet malfunction.[47]

It is important to know if these changes also occur when a patient develops angina out of hospital. In addition, it may be useful to use the techniques outlined in this study to assess the effects of mental stress, exercise and coronary vasodilitation on regional myocardial perfusion in these patients. Lastly, krypton-81m could be used to investigate the mechanisms for the development of nocturnal and spontaneous angina pectoris with ST segment changes.

This study has shown that patients with chest pain, coronary artery disease and positive exercise tests suffer disturbances of regional myocardial perfusion immediately before and throughout episodes of angina and myocardial ischemia produced by atrial pacing. These regional disturbances of myocardial perfusion are closely related to, and always precede ST segment depression and the complaint of chest pain. Regional perfusion to jeopardized segments of myocardium increased temporarily, remained fixed or decreased at the onset of atrial pacing. This may be a physiological indicator of the severity of the coronary artery disease. Any rational treatment will have to affect both myocardial perfusion and metabolism as this study shows that both are involved in patients with angina and coronary artery disease.

Serial 16 point mapping of the electrocardiogram provided a measure of the precordial area, time course and severity of ischemic changes in a standardized exercise test. A positive result correlated with positive evidence of disturbed regional myocardial perfusion using krypton-81m. This finding strengthens the electrocardiographic method which is easily available, non-invasive and relatively inexpensive. Thus, a complex, and invasive method with considerable limitations has been used in an attempt to learn more about disturbed regional myocardial perfusion in patients with angina pectoris.

CHAPTER III

Section IV

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Conclusion of the thesis

The contents of this thesis have set out to discuss and investigate one aspect of coronary artery disease. The relationships between coronary atherosclerosis, disturbances of regional myocardial perfusion and damage to contractile myocardium have been discussed. Because there is a need to assess the effects of coronary atherosclerosis, a dynamic method using an ultra short-lived radionuclide has been introduced to image and measure serial changes in regional myocardial perfusion. Experiments in dogs using krypton-81m have shown the random and systematic errors for continuous measurement of changes in regional myocardial perfusion. However, the method has severe limitations related to the need for invasive catheterization, the two dimensional planar imaging and the limits for maintaining a stable arterial concentration of the tracer.

Eighty patients presenting with chest pain have been investigated by routine clinical methods, exercise electrocardiography and coronary arteriography. The technique using krypton-81m has been applied clinically to examine the changes in regional myocardial perfusion at rest and during stress using atrial pacing. The results show that patients with angina, positive exercise tests and coronary artery disease suffer complicated changes in regional myocardial perfusion with atrial pacing. The patients with poor exercise capacity showed immediate decreases in regional myocardial perfusion in a jeopardized segment. The patients with more exercise capacity showed either increases or no change in regional perfusion at the onset of pacing and then later in the pacing test they showed decreases in perfusion

in the jeopardized segment during the ischemic event. The three different patterns of changes in regional perfusion at the onset of atrial pacing may represent a useful physiological measure of the reserve function or adaptation remaining in the disease coronary circulation. This may increase the clinician's understanding of the stenotic lesions seen in the coronary arteriogram.

The 3 different patterns of disturbed perfusion were related to the maximum workload achieved during the ECG exercise test. There was, also, a close temporal relationship between ST segment depression and decreases in regional myocardial perfusion. These findings help to strengthen the clinical application of more available and less invasive techniques commonly used in clinical cardiology.

The thesis discusses the limitations of investigating patients in hospital using invasive methods. Atrial pacing is clearly not an ideal physiological stress. Although these findings are of interest it is important that these disturbances in regional myocardial perfusion related to coronary atherosclerosis be investigated during exercise, during spontaneous chest pain and during nocturnal angina pectoris.

List of Abbreviations

ADP	Adenosine diphosphate
AMP	Adenosine monophosphate
ATP	Adenosine triphosphate
Br	bromine
^{11}CO	carbon-11 labelled carbon monoxide
G.P.R.	General purpose reagent
Kev	kilo electron volts
M.R.C.	Medical Research Council
MeV	mega electron volts
µA	micro-amperes
µg	micrograms
mCi	mille Curies
mmHg	millemetres of mercury
mmol./l	millemoles per litre
mR/hr	mille rads per hour
MVO_2	myocardial oxygen requirements
$^{13}NH_4^+$	nitrogen-13 labelled ammonia
^{15}O	oxygen-15
$C^{15}O_2$	oxygen-15 labelled carbon dioxide
PaO_2	Partial pressure of oxygen in arterial blood
^{38}K	potassium-38
^{82}Rb	rubidium-82
Z.P.I.	Zirconium phosphate

EXTRACT OF LETTER FROM EXAMINER

MD Thesis : Dr. A.P. SELWYN

Before sending a report to you, however, I would need clarification of equation 1 on page 67. This equation is the basis of calculations which are used elsewhere in the thesis but, more importantly, it is the expression which defines the author's conceptual understanding of the method which he is using.

Would you please ask the author if he would kindly let me have, through you, a detailed mathematical derivation of this equation, together with the nature of the biological model on which it is based. Would he be certain to define all the symbols (the symbol "P" is not defined) and give their dimensions.

UNIVERSITY of LONDON

Royal Postgraduate Medical School

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Tel: 01-743 2030 Ext

Reply:

The equation to which you refer is derived from the law of thermodynamics that states that matter (energy) cannot be created or destroyed.

In the section of theoretical considerations I have defined P as the partition coefficient and drawn in a figure the biological model to which it relates. The detailed derivation of this equation has been repeatedly published in the medical literature (Fick, Zierler, Bassingsthwaighte, Jones, etc.) and you will find the references in the section . I did not include the derivation because it is not my own original work. Overleaf I have provided the derivation, biological model, definition of symbols with their dimensions.

The background and derivation of this particular equation has also been published. (Circulation Research, 42:771, 1978 and British Medical Journal, Vol 3, 673, 1975).

Yours faithfully,

Signed

Andrew Selwyn.

1. If we apply the first law of thermodynamics that deals with the conservation of mass then if any quantity of krypton-81m is delivered to the myocardium via the coronary circulation then that same quantity of krypton-81m must be found if we look in the heart and allow for any krypton-81m that has escaped or decayed.

2. We must now consider the situation where a constant quantity of krypton-81m is continuously delivered to the myocardium via the coronary circulation. This results in an equilibrium of activity in the myocardium $[Kr]$ mCi/ml/min. This myocardial equilibrium of activity is derived from a balance between the input to the myocardium and the output of activity from the myocardium. The input is made up of flow (F, ml/min) and the arterial concentration (A, mCi/ml). The output is made up of coronary venous flow, i.e., $\frac{F}{V}$ x venous concentration of $^{81}Kr^{m}$ (mCi/ml/min) plus decay ($t\frac{1}{2}$ = 13 sec: turnover 3.2/min) of krypton-81m in the myocardium $[Kr]$. If the myocardial activity is in equilibrium the input (F x A) must equal the out put $(\frac{F}{V} \cdot [Kr] + \lambda [Kr])$ where $[Kr]$ = the equilibrium activity of $^{81}Kr^{m}$ in the heart (mCi/ml/min) In other words when the myocardial activity is in equilibrium what goes in must come out.

If $^{81}Kr^{m}$ is inert and diffuses freely we can assume that at equilibrium

$$\frac{\text{mCi/ml of } ^{81}Kr^{m} \text{ in venous blood}}{\text{mCi/ml of } ^{81}Kr^{m} \text{ in myocardium}} = 1 = \text{partition coefficient}$$

Therefore the fractional escape of $^{81}Kr^{m}$ from the myocardium =

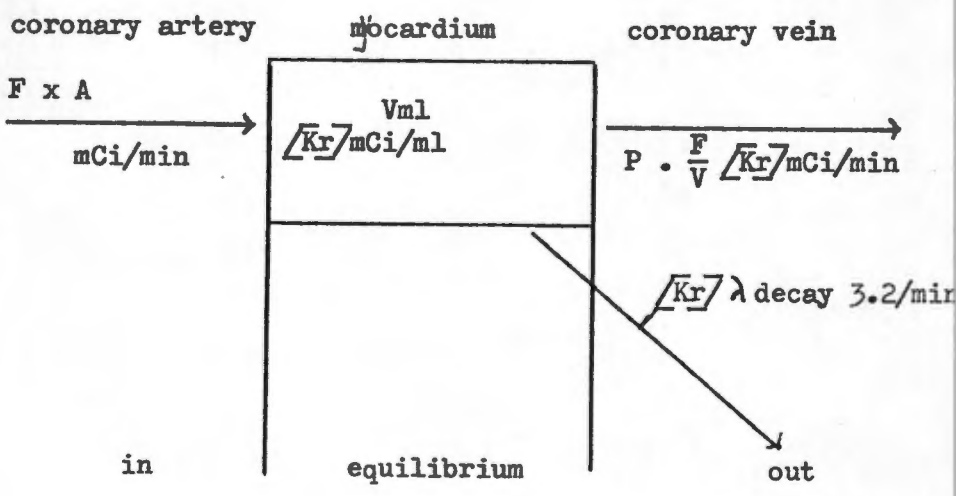
$$P \cdot \frac{F}{V}[Kr] + \lambda[Kr]$$

P = partition coefficient

$\frac{F}{V}$ = venous outflow from the heart ml/min

$[Kr]$ = mCi/ml of $^{81}Kr^{m}$ in the heart

λ = decay of $^{81}Kr^{m}$ = 3.2/min



We can now write an expression that states that input is equal to output of $^{81}Kr^{m}$ when the $[Kr]$ is constant:

$$F \times A = P \cdot \frac{F}{V}[Kr] + \lambda [Kr]$$

This can be re-written:

$$[Kr] = \frac{F \times A}{P \cdot \frac{F}{V}[Kr] + \lambda}$$

The activity in the myocardium is detected by the gamma camera within particular geometrical circumstaces (g). Therefore this activity of $^{81}Kr^{m}$ measured in the heart is equal to:

$$[Kr] = g \cdot \frac{F \times A}{P \frac{F}{V}[Kr] + \lambda}$$

The equation now says that at equilibrium of $^{81}Kr^{m}$ in the myocardium the equilibrium activity is equal to a balance between washin (F x A) and washout ($P \cdot \frac{F}{V}[Kr] + \lambda$).

Krypton-81m is delivered to the aortic sinuses where it is mixed and partitions. Within a broad physiological range a constant arterial concentration (A) is delivered to the coronary circulation.

The input therefore varies with variations in flow.

The equation now shows those factors (on the right) that determine the myocardial activity measured by a detector. Research is presented to show that A remains stable within certain physiological limits. The fast turnover of $^{81}Kr^{m}$ (3.2/min) means that the majority

of tracer decays in the myocardial space and the denominator is dominated by λ i.e., the constant decay. The myocardial signal $[Kr]$ should therefore vary with flow (F). The systemmatic influence of increasing washout with increasing flow also stability of arterial concentration and the problems of planar imaging are investigated further.

EXTRACT FROM EXAMINER'S LETTER — MD Thesis : Dr. A.P. SELWYN

Thank you for sending me the explanation by Dr. Selwyn of the equation on page 67 of his thesis. The equation which he derives in this explanation is not precisely the same as that which is given in the thesis. Neither is correct and neither balances in terms of its dimensions.

The correct equation is as follows :-

$$[Kr] = \frac{\frac{F}{V} \times A}{P \cdot \frac{F}{V} + \lambda}$$

EXTRACT FROM REPORT OF EXAMINER — MD Thesis : Dr. A.P. SELWYN

I have some reservations as to the candidate's appreciation of the theoretical basis of the technique in terms of the physics of trace-movement through tissues. The equation given on page 67 puzzled me since it did not balance in terms of physical dimensions. The written explanation which the candidate subsequently provided ended with a different equation. In fact, neither is correct. Mainly this is because the venous outflow has been expressed in terms of myocardial volume whereas the inflow is not. The correct expression should be :-

$$[Kr] = \frac{\frac{F}{V} \times A}{P \cdot \frac{F}{V} + \lambda}$$

The biological model on which this equation is derived is, I believe, too simple to be strictly biologically relevant. It takes no account of the distribution of transit times of tracer and changes in this distribution which may occur under physiological or pathological conditions.