Evaluation of Cardiac Function and Structure with Radioactive Tracer Techniques

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RADIOACTIVE TRACERS have been used for the evaluation of cardiac structure for over 50 years, since the initial application of Blumgart et al. of Radon for the measurement of the circulation time in man, using a cloud chamber as the radiation detection device. Many improvements in both instrumentation and radiopharmaceuticals have been introduced to make measurements of regional wall motion and ventricular volumes of both the right and left ventricles, regional myocardial perfusion, and for the detection of acutely damaged tissues in the myocardium. Some of the current clinical applications are summarized in table 1.

The function measured with a radioactive tracer procedure will depend on the type of radiopharmaceutical administered, the time of observation, and the type of instrument employed to make the measurement. For example, the initial, distribution of a radio-labeled albumin radiopharmaceutical as it courses through the cardiac chambers after intravenous injection is primarily a function of blood flow, while the distribution sometime later is a function of regional blood volume and is unrelated to flow. If the measurement of initial tracer passage through the heart is made with a device of low frequency response, a radiocardiogram type of curve is recorded. This can be used to determine cardiac output and estimate shunting. If a high fidelity recording device is employed, then a measurement of ejection fraction can be made at the same time and a more precise measurement of shunting is possible.

There are three classes of nuclear instruments commonly employed to record data from patients undergoing cardiovascular investigation: 1) a scintillation probe system; 2) rectilinear scanner; and 3) scintillation camera. Each of these systems employ 1) sodium iodide crystal for the gamma photon to interact in and cause a light flash; 2) photomultiplier tubes to detect the light and convert it to an electronic signal; 3) associated amplifiers; and 4) readout devices. The instruments differ in the spatial resolution and sensitivity they offer: 1) the probe is usually used with a flat field collimator which results in very high sensitivity to a gamma photon originating anywhere in the field of view; 2) the rectilinear scanner localizes the origin of photons by viewing one point in space at a time — using a focused collimator and mechanically moving the detector over the object. The arrangement results in lower sensitivity than the probe (due to the collimator) but is quite useful for evaluating the static spatial distribution of tracer; and 3) the scintillation camera (either single crystal or multicrystal type), which has less sensitivity than the probe (again due to the collimator) but offers high spatial resolution and can detect rapidly changing patterns of activity in a field of view because the location of photons entering the crystal is determined electronically.

There is an increasing tendency to tailor the radiopharmaceutical to both the physiology under investigation and to the instrument employed to make the measurement. The measurement of myocardial perfusion for example can be approached with several monovalent cations which have similar (but by no means identical) biological properties, but diverse physical properties in terms of physical t½ and the number and energies of photons. The Anger type scintillation camera has a 1.25 cm thick sodium iodide crystal as the photon detector; this equipment has limited photon stopping abilities: at 140 keV, photopeak sensitivity is almost 100%; at 300 keV, it is less than 40%, and at 500 keV, less than 10%. To use this instrument with optimum efficiency and resolution, the tracers employed should have energies of 100-200 keV. In addition, the collimators used to exclude photons coming from outside the field of view have the best combinations of resolution and sensitivity with low energy.
Table 1. Current Clinical Applications

| Indications | Technique | Comments |
|-------------|-----------|----------|
| 1. Suspected acute myocardial infarction within 24 hr from onset of symptoms—no previous myocardial infarction | $^{201}$TI MPI and MUGA | The finding of a myocardial perfusion defect or regional myocardial wall motion abnormality suggests acute myocardial infarction under these circumstances. |
| 2. Suspected acute myocardial infarction—equivocal electrocardiographic and serum enzyme studies 24-96 hr after onset of symptoms | $^{99m}$Tc pyrophosphate | The finding of a localized left ventricular aneurysm suggests the patient is a candidate for cardiac catheterization and possibly surgery; diffuse left ventricular hypokinesis suggests continued conservative therapy. |
| 3. Recurrent congestive heart failure following myocardial infarction | $^{201}$TI MPI and MUGA | The finding of a dilated poorly contractile right ventricle with a small left ventricle raises the possibility of right ventricular infarction. |
| 4. Cardiogenic shock | $^{201}$TI MPI and MUGA | The finding of a dilated poorly contractile right ventricle with a small left ventricle raises the possibility of right ventricular infarction. |
| 5. Suspected ischemic heart disease in a patient with an abnormal resting electrocardiogram | Rest and Exercise $^{201}$TI MPI or MUGA | A positive $^{201}$TI MPI confirms the diagnosis of ischemic heart disease. A negative $^{201}$TI MPI raises the possibility of a false positive exercise electrocardiogram and suggests further diagnostic investigation. |
| 6. Positive exercise electrocardiogram in an asymptomatic patient | Rest and Exercise $^{201}$TI MPI | A positive $^{201}$TI MPI confirms the diagnosis of ischemic heart disease. A negative $^{201}$TI MPI raises the possibility of a false positive exercise electrocardiogram and suggests further diagnostic investigation. |
| 7. Development of a ventricular arrhythmia during exercise without the appearance of significant ST-T wave change | Rest and exercise $^{201}$TI MPI | A positive $^{201}$TI MPI confirms the diagnosis of ischemic heart disease. A negative $^{201}$TI MPI raises the possibility of a false positive exercise electrocardiogram and suggests further diagnostic investigation. |
| 8. The patient with systemic myocardial involvement such as sarcoidosis or tumor | $^{201}$TI MPI and MUGA | The finding of a myocardial perfusion defect 20% of the left ventricular circumference suggests ischemic cardiomyopathy. |
| 9. A patient with suspected idiopathic cardiac failure | $^{201}$TI MPI and MUGA | The finding of a myocardial perfusion defect 20% of the left ventricular circumference suggests ischemic cardiomyopathy. |
| 10. A patient with cor pulmonale or chronic obstructive pulmonary disease and suspected ventricular dysfunction | MUGA | The finding of a myocardial perfusion defect 20% of the left ventricular circumference suggests ischemic cardiomyopathy. |
| 11. Evaluation of a patient with cyanotic congenital heart disease | $^{201}$TI MPI and MUGA | Multiple projections are necessary to determine the presence of an intraventricular septum. |

Abbreviations: MPI = myocardial perfusion image; MUGA = multiple gated acquisition studies.

photon. Thallium-201 offers the best combination of biological and physical properties for imaging with the scintillation camera. This accounts for thallium’s popularity at this time: it represents the right match of radiopharmaceutical and instrument to evaluate an important clinical problem — myocardial perfusion.

New scanners and cameras have been designed and constructed to detect positron emitting radionuclides effectively. These instruments have thicker sodium iodide scintillation detectors, and because of the nature of positron interactions in matter (undergoing interaction with an electron which is transformed from matter into energy with the emission of two gamma photons 180° apart) permits a unique system of detection, using two sets of detectors placed 180° apart. Since the gamma photons are emitted simultaneously, it is possible to determine that they occurred from the same disintegration if they interact in the opposed detectors at the same time. Thus, extensive collimation is not required so that high sensitivity is possible. In addition, correction for the absorption of photons in tissue can be readily applied, and an accurate 3-dimensional reconstruction of the distribution of activity in the tissues performed. These devices require radiopharmaceuticals that emit positrons — hence, the popularity of nitrogen-13 labeled ammonia and rubidium-82 for measuring myocardial perfusion and $^{13}$C palmitate for evaluation of regional
myocardial substrate metabolism. Again, the right match of radiopharmaceutical and instrument is searched for to address the important problems of myocardial perfusion and substrate metabolism.

Three broad groups of problems that can be approached in patients with heart disease are 1) evaluation of myocardial perfusion and acute tissue damage; 2) measurement of ventricular function, and 3) measurement of transit times.

**Global Blood Flow Measurements**

The first tracer technique employed for measuring myocardial blood flow was the uptake measurement of Love et al., using a single probe placed over the chest and intravenous administration of ionic rubidium. This approach made a measurement of total tracer concentration in the heart, lungs, chest wall and blood in the field of view. To make the measurement more precise, attempts were made to correct for background with the positron emitting nuclide rubidium-82 and simultaneous measurements over both the left and right chests or with the simultaneous measurement of blood volume and cardiac output with iodinated albumin. At the same time these noninvasive approaches were being developed, Ross et al. utilized the direct intra-coronary injection of xenon and precordial measurements of activity to define coronary blood flow. This approach to the evaluation of myocardial blood flow was important because it eliminated background from surrounding lung, chest wall and intracavity blood pool and really defined whether gated measurements of perfusion could detect coronary disease. However, even with xenon, the separation of patients with coronary disease from those with totally normal coronary arteries was not possible. This suggested that measurement of regional myocardial blood flow with instruments of high spatial resolution would be better at separating patients with coronary disease from those with normal perfusion.

**Regional Inert Gas Clearance Method**

Cannon et al. employed a multicrystal scintillation camera to evaluate regional myocardial perfusion following the intracoronary injection of xenon and was able to detect alterations in the regional perfusion pattern of patients with abnormal coronary arteries in the basal state. These abnormalities in perfusion disappeared after successful coronary bypass graft surgery. This approach indicated the importance of measuring regional perfusion.

Although there remain many theoretical and practical problems about the xenon measurements of blood flow such as 1) relatively poor spatial resolution of the scintillation camera so that the zone seen in the image reflect, more than one full wall thickness of myocardium and 2) xenon-133 (the usual isotope of xenon employed) has a low energy gamma photon which is subject to Compton scatter — which even the best scintillation camera cannot exclude — and 3) the partition coefficient of xenon in myocardium may change between healthy muscle and diseased tissue, the method will still have its utility. Some of the physical problems associated with the xenon technique can be readily overcome when a higher energy tracer such as xenon-127 is employed. A particularly exciting area of research at present involves the use of krypton-81m as the inert gas for making measurement of coronary perfusion. This ultra short-lived inert gas, (½: 13 seconds) with an energy of 190 keV, offers an opportunity to make continuous measurements of regional perfusion. Since the physical half-life of the nuclide is shorter than the myocardial clearance half-time, a continuous infusion of the nuclide dissolved in saline produces an image which reflects the initial flow-related distribution of tracer. Instantaneous changes in the regional distribution of flow can be readily defined by changes in the appearance of the continuous infusion image.

**Regional Perfusion with Particulate Injection**

Quinn et al. suggested the use of macroaggregated albumin injected into the coronary artery as an indicator of regional myocardial perfusion in dogs. The images recorded reflected regional perfusion at the time of tracer administration, but images could be performed up to several hours later. Four years later, Endo in Japan, and Ashburn in the United States reported their experience with the technique in patients. Extensive safety studies were carried out by Jansen and his colleagues which revealed that as long as the size of particles was kept below 50 microns and less than 50,000 particles were injected into the coronary arteries, no hemodynamic changes occurred even in patients with triple vessel disease. The vast clinical experience gathered with this method by Judkins and Jansen in several thousand patients revealed that the technique could readily separate patients with infarction from those with viable myocardium. Usually particles with one radio-nuclide tag are injected into the left system (usually labelled with technetium-99m) and with another label (usually Iodine-131) into the right system. Zones of collateral flow could then be identified by observing which nuclide supplied the area. Gould et al. suggested an improvement in this concept: the study of the distribution of myocardial perfusion in two states — basal blood flow and maximum flow — to determine whether a specific narrowing of a coronary artery was hemodynamically significant. This was accomplished by administration of radio-opaque contrast material in the coronary system as a potent coronary vasodilator followed in 15 seconds by administration of the particles with one tracer label. The vasodilator response was permitted to subside over several minutes, and a second injection of a particle with a different tracer label administered. Subsequent images revealed the changes in regional perfusion induced by the marked alteration in coronary flow. Normal subjects had no significant change in the distribution of the two tracers, while patients with hemodynamically significant coronary artery narrowings had marked decrease in tracer concentration distal to the lesions after the vasodilator.

Although the microsphere method reflects regional flow, it is not dependent on the fraction of cardiac output/unit of tissue, a significant difference from the xenon technique. Although the tracer is administered in the coronary arteries in both cases, the xenon method requires coronary flow for clearance of tracer from the myocardium, while the microsphere method administered 100% of the dose is also in the coronary bed, and its distribution will reflect the distal regional distribution of that flow but is not dependent on the.

*Most investigators use 25μ particles.*
fraction of cardiac output delivered to that vessel. It is possible with the microsphere method that a normal right coronary artery (RCA) and a RCA with a 99% proximal stenosis might appear similar since the entire dose will travel down the vessel and distribute in the distal capillary bed. In contrast, in the xenon method, the clearance from the zone distal to the 99% stenosis will be delayed compared to the normal zone.

Myocardial Imaging with Ionic Tracers

The measurement of regional perfusion is usually performed with tracers that follow the Sapirstein Principle:39

1) They are rapidly cleared from the blood — t½ of less than 30 seconds.
2) They are extracted by the myocardium at least as avidly as by the rest of the body — extraction of at least 50% (arteriovenous myocardial difference).
3) They remain in the heart with a relatively unchanging distribution long enough to permit the measurement — redistribution of nuclide begins within seconds of administration, but a significant change in regional tracer concentration should take minutes to hours.

Imaging of the myocardium with intravenously administered nuclides was first accomplished by Carr and his colleagues in the early 1960s.21 Carr relates that he was working in the emergency room and was asked to see a patient exposed to excess cesium. In his reading on cesium toxicity he found that cesium concentrated in muscles. Since the heart is a muscle, he reasoned that a radioisotope of cesium could be employed for myocardial imaging. He utilized cesium-131 for his initial studies in animals and patients, and found it possible to image myocardial infarctions. However, cesium-131 has many physical properties that are undesirable for imaging, including a long half-life (9.7 days) and low energy xenon X-rays (about 30 keV). In addition, cesium is poorly extracted by the myocardium (35%/pass),22 so that the distribution of cesium in the heart is not truly related to flow.

These problems led Love and his colleagues to develop an improved collimator to image the myocardial distribution of potassium-41, (half-life 12.6 hours-major gamma at 1.5 meV).22 In their work, they too demonstrated zones of myocardial infarction but found that zones of myocardium supplied by narrowing coronary vessels appeared normal on the scan. Thus, even with this "improved" tracer a major clinical problem remained the detection of regional ischemia. Two proposals for its detection were evaluated:

1) Administration of radionuclide with the patients in the basal state, and subsequent exercise to induce ischemia. The reasoning was that tracer would enter a large intracellular pool; with ischemia, potassium loss from the affected tissue would occur, and a zone of diminished tracer concentration would result. Unfortunately, the amount of potassium lost from the ischemic cells represents a relatively small proportion of the total intracellular potassium pool in that area and this approach did not work.

2) Administration of the tracer at the time of peak stress with immediate imaging.24,36 This approach takes advantage of physiology that is better suited to nuclear imaging: a relatively large difference in perfusion to the normal and abnormal areas results in a marked difference in regional tracer delivery to the myocardial cells. This hypothesis was tested by Prokop et al.36 who compared the relationship of regional potassium-43 distribution in the myocardium to microspheres in animals with normal flow, ischemia induced by partial occlusion and pacing, and infarction induced by coronary ligation. A linear relationship was found between the distribution of potassium-43 and tracer microspheres under these circumstances. Thus, scans performed immediately following intravenous administration of potassium represent the regional distribution of flow at the time of injection, not the regional rate of potassium loss. If the ischemia is sufficiently severe to induce a flow difference in excess of 25%, and if the ischemia is maintained for the interval of time during which 70-80% of the radionuclide is cleared from the blood (2 circulation times with potassium, rubidium and thallium), an image performed immediately after injection will reflect the distribution of nuclide at the time of administration.

The type of stress used to induce this regional difference in flow does not appear to be a significant factor. Bicycle, treadmill, pacing and pharmacologic stress have all been utilized with success. The examination is performed by starting an intravenous line prior to the exercise procedure. The patient is instructed to exercise to his self-determined maximum. This is important since the maximum difference in regional flow distribution is desired to maximize the probability of both an abnormal exercise electrocardiogram and an abnormal scan. At subanginal exercise levels, ischemia is not present, and the scan remains normal. At the peak of stress, the tracer is injected as a bolus intravenously. The patient is instructed to continue exercising (at a lower level), if at all possible, for at least 30 seconds following tracer administration, to permit the activity to deposit in tissues in relation to flow while the patient is still ischemic. If exercise is terminated prematurely, the ischemia may clear while the tracer is still being distributed in tissue. The tracer distribution will then reflect some intermediate distribution.

Coronary angiographic studies revealed that the combination of exercise stress and potassium imaging could identify zones of myocardium perfused by significantly narrowed vessels. Injection of radionuclide with the patient in a basal state can identify zones of normal myocardial perfusion and the presence of myocardial scar. The comparison of scans of tracer injected at rest to that injected at maximum stress permits the separation of patients into normal, those with transient ischemia, and those with infarction by the relative scan patterns. This approach to imaging has been used to investigate patients with coronary bypass grafts,24 and patients with false positive exercise tests.36

The development of thallium-201, a cyclotron produced radiopharmaceutical, which has biological properties similar to potassium has spurred the application of myocardial imaging in many hospitals.10-12 Thallium-201 has photon energies which are low enough to be well collimated

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*Potassium is a particularly well suited radionuclide for this purpose since it is the major intracellular cation in muscle but is virtually absent in scar.
and to permit high efficiency detection with the 1.25 cm thick crystal of most Anger type scintillation cameras. Like potassium, the regional distribution of thallium in the myocardium reflects blood flow in the initial interval following injection. In patients examined with thallium administration at the time of maximal exercise stress, and at rest, the myocardial perfusion images were more sensitive than simultaneous stress electrocardiograms for the detection of myocardial ischemia.

Myocardial imaging offers information that is significantly different from that recorded with a coronary arteriogram: the arteriogram supplies detailed information about structural abnormalities of the coronary arteries while the scan supplies information about perfusion at the level of the muscle cell. The scan can be normal in the face of a totally obstructed coronary artery, if collateral flow is sufficient. Similarly, the scan may be abnormal in the face of a patent coronary vessel if recanalization of a coronary vessel has occurred following an infarct. In patients with multivessel disease, it is difficult to detect all the disease sites on a stress injected scan. One zone frequently becomes ischemic before the others and causes the patient to cease exercising, while other areas that might become ischemic if the patient had exercised longer are not identified because at the time of injection they had adequate flow. Thallium myocardial imaging appears to be most helpful in the evaluation of patients with suspected ischemic heart disease who have abnormal resting electrocardiograms, since the stress electrocardiograms in these patients are frequently difficult to interpret.

Although thallium-201 myocardial imaging has been advocated for the detection of acute myocardial infarction, it appears to have only a limited clinical role in evaluation of these patients. In patients with a history of infarction in the past, the scan will have diminished thallium concentration and it is impossible to determine if the zone of decreased tracer concentration seen on the scan is the result of acute infarction, severe ischemia, or a reflection of chronic changes. However, even with this limitation, Wackers et al. found thallium imaging to be useful in selecting patients with suspected infarction for admission to the Coronary Care Unit. However, it is possible that the recent observation of Pohost et al. will permit a better assessment of the zone of peri-infarction ischemia in patients with acute infarction or unstable angina. Pohost observed that in some patients images performed after tracer injection at stress changed over time. A lesion seen on the initial post injection scan, which concentrates activity late (so that the zone of decreased tracer concentration is no longer visible in 2–4 hours after injection), is strongly suggestive that the patient has ischemia. If the same observation holds true in patients with infarction and peri-infarction ischemia, then thallium imaging in acute infarction may be more valuable. If the extent of abnormality changes from the initial to the delayed image, the possibility of ischemia is high, whereas, if the lesion remains fixed over this interval of time, the likelihood of infarction without peripheral ischemia is high. In patients with coronary spasm, Maseri et al. observed these types of changes with tracer injection during the episode of spasm.

It should be emphasized that the physiology of thallium-201 redistribution is not fully understood, but probably depends on residual activity in the blood, increased extraction by the tissue on recovery from ischemia, and decreased loss from the previously ischemic zone. The optimum time for recording images to define redistribution is not known. Conversely, while some patients with ischemia have scans that improve, others appear to have a rapid loss of thallium from zones that were well perfused on the initial images. The significance of this finding is uncertain. It is clear that images recorded immediately after thallium-201 administration and at several later times offer a sensitive means of defining regional perfusion on the initial images, and possibly viable myocardial mass on the later studies.

Detection of Acutely Damaged Myocardium

The first successful images of acute infarction in dogs were obtained by Carr et al. using chloromeridrin labeled with mercury. The concept employed was that irreversibly damaged tissue would have an excess of sulfhydryl groups which would bind to the mercury of the radiopharmaceutical. Subsequent investigation by Gorten et al. in pigs verified these findings but suggested the study might not be clinically useful because of the excessive dose of the radiopharmaceutical required to record the image. Malek and his colleagues then demonstrated that the antibiotic tetracycline concentrated in acutely infarcted tissues. He reasoned that this could be labeled and used as a radiopharmaceutical. However, the labeling process was difficult, and mercury labeled fluorescein analogs were used instead. Although initial results in animals appeared encouraging, data in patients were not diagnostic. In 1973, Holman and his colleagues succeeded in labeling tetracycline with Technetium-99m and demonstrated the ability of this radiopharmaceutical to localize in acutely infarcted myocardium. Tetracycline imaging, however, has several drawbacks: 1) due to the slow blood clearance of the tracer, diagnostic images cannot be recorded for 24 hours after tracer administration; 2) the differentiation of residual activity in the blood pool from activity in an infarct is frequently difficult; 3) excess tracer concentration in the liver makes detection of inferior infarction difficult; and 4) there are no landmarks in the chest to localize any areas of abnormal tracer concentration. In 1973, Rossman and his associates evaluated glucophonea labeled with technetium-99m for myocardial imaging. This tracer had many of the disadvantages of tetracycline, but it also had one major advantage: the scan became abnormal immediately following infarction. However, the target background was not adequate in many patients.

The observation by Bonte et al. that the bone imaging radiopharmaceutical, technetium-labeled pyrophosphate, concentrates in acutely damaged tissue has hastened the application of this technique to the evaluation of patients with suspected myocardial infarction. Pyrophosphate and its congeners have several advantages over tetracycline: 1) they concentrate in bone so that landmarks are available to localize the lesion; 2) they rapidly clear from the blood, so that high quality images can be recorded within 1–3 hours following tracer administration; and 3) the ratio of normal to damaged myocardium is sufficiently high to permit ready
identification of even nontransmural infarction in the majority of cases. Although many questions about the mechanism of tracer localization remain to be answered, several facts appear clear; 1) residual blood flow into the damaged area is required for tracer localization, 2) acutely damaged tissue will concentrate the radiopharmaceutical, 3) the concentration of the radiopharmaceutical in infarction is not only a function of calcium deposition in the acutely damaged tissue. Although the concentration of both increase in the infarct, they do so at different times and in different concentrations.

Recently, several reports have appeared about other causes of increased pyrophosphate concentration in the heart — calcified valves and unstable angina, cardiac version, aneurysm, and persistence of an abnormal scan weeks to months following infarction. Recently, another radiopharmaceutical, radioiodinated antimyosin, has been developed for acute infarct imaging in animals. This agent holds the promise of increasing specificity for infarct identification. Further work is necessary to determine if the preliminary results obtained in animal studies will be as useful in man.

Once it is recognized that the myocardial concentration of these radiopharmaceuticals is not pathognomonic of infarction, the test can take its place with others for the diagnosis of infarction and be used wisely. The data thus far in series of patients with documented infarction suggest that imaging with the bone-seeking radiopharmaceuticals 24–48 hours after the onset of pain will demonstrate the presence of infarction in almost all subjects with transmural infarction, and in the majority of patients with nontransmural infarction. A totally normal scan suggests that there is a less than a 5% chance that the patient has infarction and that some other cause of pain should be sought. One of the major reasons for the differences in sensitivity of the infarct avid-imaging procedure that have been reported from different laboratories relates to the methods used to image patients: Parkey and his co-investigators image patients daily for the first 2-4 days until they are certain that the scan is either changing and definitively abnormal or normal. This enhances the specificity of the technique in comparison with that of laboratories that employ a single examination. Recent work by Holman et al. suggests that if the scan is definitively abnormal early and either the lesion remains unchanged or appears to get smaller over time the patient has not extended the infarct, whereas if the scan becomes more abnormal over time the extension has occurred.

Sizing the infarct with these agents has not proved to be as simple as originally hoped, nor as useful. The requirements for imaging hours to days after the onset of infarction imply that the ability of the technique to evaluate acute interventions to reduce infarct is limited. Anterior infarcts can frequently be viewed en face in at least one view, and can have their maximum size defined on the images. Inferior infarcts, on the other hand, usually are seen on end in all the common views employed for imaging. Thus in the latter the maximum extent of the lesion is difficult to define, and sizing is almost impossible. Attempts at sizing infarction by the amount of tracer in the lesion have been unsuccessful, due to the relationship of tracer concentration and residual blood flow. A large infarct with poor residual flow can have a relatively low tracer concentration, whereas if a similar lesion occurred in a vessel that recanalized, or in an area that is relatively well supplied with collateral vessels, it will have a greater concentration of tracer. The extent of the lesion, on the other hand, should be similar in the two patients. Thus, quantification of the lesion with this method must be done by geometric means (i.e., showing boundaries and calculating volumes).

The best use of infarct-avid imaging is in the determination of whether infarction has occurred, what its approximate location is, and provision of a qualitative assessment of size. This approach is helpful after coronary bypass grafting and in patients admitted with equivocal ECGs.

The Use of Transit Time Measurements in Cardiology

Transit time measurements have been used in cardiology since the measurement of the circulation time in man by Blumgart in 1927. Prinzmetal used a more sophisticated device to define precordial curves of the radiocardiogram following intravenous injection of tracer sodium-22, and was able to define cardiac output, shunts, and changes in chamber size. However, it was not until the development of the autofluoroscope by Bender and Blau in 1963 that images could be recorded with the transit time data. Since that time, there has been renewed interest in these transit time determinations. This is particularly evident in the work of Steele and his colleagues, who defined the relationship of a shortened pulmonary transit time to the presence of pulmonary embolus, and in the work of Maltz, who defined the relationship of a prolonged pulmonary curve to the amount of left-to-right shunting. Recently, efforts have been made to quantify regurgitant lesions in patients by the relationship of forward stroke volume to total stroke volume. The transit time measurement by itself is far less useful than previously hoped because many factors can affect the measure in the same way that the cardiac output can be influenced. However, when taken in concert with images of the cardiac chambers and measurements of ejection fraction and end-diastolic volumes, the transit time determinations can serve as a check on the quality of the gated images, e.g., a normal transit time and diffuse hypokinesis suggest a technical error, while a large end-diastolic volume, high stroke volume, and prolonged transit time through a chamber might mean valvular regurgitation.

Determination of Ventricular Function

First Pass

Mullins and his colleagues described the validation of the nuclear angiocardiogram for the measurement of the end-diastolic and end-systolic volumes in 1969. These investigators recorded the initial passage of a nuclide through the heart in synchrony with the electrocardiogram. They then replayed the data and added up several cycles at end-diastole and several at end-systole. The added images were then projected and the outlines defined, and the volumes of the chambers determined. Since then, in addition to the geometric approach, Schelbert and his colleagues have defined methods of calculating the ejection fraction directly from the activity in the cardiac chambers. This method has the advantage of being independent of geometric assumptions. During the initial passage of tracer through the heart, data from the scintillation camera are recorded in a computer. Thus, from the patient's point of view, the measurement is
completed in less than one minute. This type of rapid data recording is particularly useful in patients with rapidly changing or unstable conditions. Much has been made of the importance of recording as many counts as possible during the procedure. Although this is important, all modern scintillation cameras can achieve a count rate suitable for this measurement. To have the best curves for analysis, the injected bolus should be kept as small as practicable: less than 3 ml. The bolus should be administered with a central venous injection or a peripheral injection in the basilic vein with good technique (the Oldendorf method is very useful in our experience). The ejection fraction is measured subsequently by identifying the region of the left ventricle from the computer display and asking the computer to generate the activity versus time histogram as the bolus transverses this chamber. The time versus activity curve can be generated for both the right and left ventricles with this method so that ejection fraction and ejection rates can be measured from both. The temporal resolution of the recording device must be sufficiently short to permit details of the ejection rate to be measured (at least 20 frames per cardiac cycle resolution). However, at these high frame rates, the number of events recorded in each frame decreases to a point where statistical noise becomes a significant factor with the radiopharmaceuticals employed. To obtain reliable data, several cardiac cycles are usually summed in phase and the ejection fraction and ejection rates recorded from this representative cycle, or root mean square analysis applied to the curves. Regional wall motion is evaluated from an image of this representative cycle. The images from these frames are usually converted by the computer into a cine film format, and evaluated for wall motion abnormalities. It is common for the cumulative image to have only 5000–6000 events recorded in the region of the ventricle at end-diastole for a count density of about 100 ct/cm² in the region of the ventricle. With this count density, the borders of the chamber can be defined grossly, but precise delineation of a small zone may be difficult. This is a particular problem when attempts are made to define small changes in regional wall motion in patients undergoing therapeutic interventions. To fully evaluate wall motion, multiple views are needed. With the first pass method, only one view is recorded with each injection: multiple views require multiple injections. When measuring the effects of drug on a patient, it is prohibitive from a dosimetric point of view to record more than three or at the most four evaluations in a single sitting.

Because the measurements of ventricular function are made during the initial passage of tracer through the heart, a radiopharmaceutical that remains in the vasculature is not mandatory for the measurement. These determinations are frequently carried out with 99mTc-labeled sulfur colloid for the first measurement, which is rapidly cleared from the blood by the reticuloendothelial system (most of which resides in the liver) and technetium-99m pertechnetate for the second determination. It is possible to employ technetium chelates which are cleared by the kidneys if additional measurements are to be made.

**Equilibrium**

Measurements of ventricular function can also be made after a blood pool tracer equilibrates in the vasculature. This technique relies on the assumption that, although in any one cardiac cycle events take place rapidly, if several consecutive cardiac cycles are recorded the number of events recorded will be sufficient to produce high spatial resolution images at specific points in the cardiac cycle with an electronic switch (gated) synchronized to the patient's cardiac cycle. Initially, gated scans were recorded at end-systole and end-diastole, were manually outlined, and ejection fractions determined. Now computers are employed to record the data, and the cardiac cycle is usually divided into as many as 64 segments for evaluation. The time employed for recording the data can be controlled by the operator; may be as short as 100 cycles or as long as several thousand cycles, depending on the quality of the data required; and the stability of the patient at the time of the measurement.

Gated imaging at two points in the cardiac cycle (end-systole and end-diastole) has already proved to be of value in determining the ejection fraction and end-diastolic volumes of patients with acute myocardial infarction, differentiating aneurysm from diffuse hypokinesis of the left ventricle, determining whether right ventricular dysfunction is a cause of low cardiac output in patients with inferior wall infarction, and detecting the presence of intra-atrial masses. Following a single injection of radiopharmaceutical, measurements of ventricular function can be made for up to four hours. This means that multiple views can be readily recorded and that measurements before and after an intervention can be made several times. In addition, the radiation burden from this procedure is no greater than that from the initial pass method performed in two views. With the computer, multiple gated acquisition (MUGA) images are usually recorded for a ten-minute period at a temporal resolution of 20–30 frames/cardiac cycle following intravenous administration of 20 mCi of Tc-albumin. In an average adult with a normal sized heart, about 800 cardiac cycles will be recorded and the average count density over the left ventricle will be 600 counts/cm² (fig. 1). This will permit much more precise definition of the borders of the cardiac chambers. However, since tracer is present in all the chambers, overlap may at times make borders difficult to define. This problem can usually be overcome by recording data from a different position and employing cephalad or caudal tilt. In addition to counts, other factors such as the resolution of the collimator and intrinsic resolution of the imaging device are important in determining the quality of the image.

The use of these images to define regional wall motion are greatly enhanced if the data are combined into a cine film, each frame representing a fraction of the cardiac cycle, which is displayed in real time as an endless loop. When the end of the last frame is reached, the computer cycles back to the first frame and begins showing the data over again. Viewing these "movies" allows doctors to define wall motion abnormalities by simple inspection. In addition, programs are presently under development to define the borders of the left ventricle automatically, so that objective determinations of wall motion will be possible without requiring operator interaction. From the MUGA data, both the ejection fraction and volumes of the left ventricle can be defined by either geometric means or from the changes in activity versus time in the left ventricle. These volume curve data have been correlated with contrast angiographic left ventricular volume curves with a correlation coefficient of $r = 0.94$.77
Recent work by Borer et al. combine the use of MUGA imaging and supine exercise stress testing to identify patients with coronary artery disease. In normal patients, ejection fraction increased with exercise, while in patients with coronary disease who developed ischemia ejection fraction fell and regional wall motion abnormalities were seen. Comparison of the rest and exercise MUGA examinations may permit a rapid evaluation of resting ventricular function and wall motion, and ventricular function reserve, and may prove to be as sensitive as thallium stress imaging for the identification of myocardial ischemia.

**Conclusion**

By careful selection of the study or studies performed, it is possible to obtain information about many facets of the myocardium and cardiac function. These measurements when coupled with those of the clinical evaluation, routine chemistry tests and electrocardiogram can frequently make diagnosis, confirm the site, and extent of abnormality and define if improvement has occurred following a therapeutic intervention. Radionuclide studies offer a particularly useful tool in cardiology because they measure physiological parameters, and through these measurements, give information about anatomy. In the future, specific metabolic substrates which are metabolized only in ischemic tissue may be developed, and it is not out of the realm of possibility that radiopharmaceuticals will be developed which will localize in atherosclerotic plaque and permit the identification of patients at risk of coronary disease long before they become symptomatic.

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Reporlation Abnormalities in Survivors of Out-of-Hospital Ventricular Fibrillation

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SUMMARY Survivors of out-of-hospital ventricular fibrillation (VF) are at high risk for recurrent VF, probably reflecting continued myocardial electrical instability. In this study 12-lead ECGs of 125 VF survivors with coronary heart disease were examined and compared to those of 98 ambulatory post-MI patients. The study was part of an effort to define clinical identifiers of patients likely to develop sudden cardiac death. Ventricular fibrillation survivors more commonly had premature ventricular complexes (PVCs): 30% versus 13% (P < 0.01). In addition, ECGs of VF survivors showed a significantly greater prevalence of ST-segment depression (46% versus 10%), T wave flattening (52% versus 26%), and QTc prolongation (35% versus 18%). It is proposed that these repolarization abnormalities represent asynchronous repolarization, which together with frequent PVCs, may set the stage for re-entrant ventricular dysrhythmias and ultimately VF. It is also possible that repolarization abnormalities together with premature ventricular contractions might serve as markers of patients with coronary heart disease who are at increased risk for sudden cardiac death.

VENTRICULAR DYSRHYTHMIAS are found both in healthy adult subjects as well as cardiac patients, and the mere presence of ventricular ectopy does not explain the increased risk of some groups of patients for sudden cardiac death. Hann and others have demonstrated that temporal dispersion of repolarization facilitates re-entrant ventricular tachydysrhythmias which would otherwise terminate when confronted with uniformly homogeneous refractoriness of the ventricles. Numerous conditions and pharmacologic interventions have been shown to enhance dispersion of refractoriness and lower ventricular fibrillation (VF) threshold. There is also considerable clinical evidence correlating prolongation of QT interval with sudden cardiac death; this includes two congenital syndromes associated with ventricular tachycardia and VF in children.

Survivors of out-of-hospital VF appear to have a sustained propensity for recurrent VF, reflecting a continuing state of myocardial electrical instability. The purpose of this study was to examine the ECGs of VF survivors for findings characteristic of this group. We directed particular attention to QT interval prolongation and to other repolarization abnormalities indicative of electrical heterogeneity.

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