Detection of Heart Disease: Promising New Methods

This is the fifth in a series of Research News articles examining recent developments in research on heart disease.

Many medical researchers believe that the only way to prevent deaths from heart disease is to prevent heart disease. Failing that, the next best thing is to devise effective treatments once heart disease occurs. In some cases, surgery may repair congenital damage or damage due to rheumatic fever. For those who have atherosclerotic heart disease, surgery or drugs may limit the extent of the damage by keeping alive areas of heart muscle that would otherwise die. (Some of these treatments will be discussed in future articles.) But before methods of treatment can be used or evaluated, certain questions must be answered: Are the patient's symptoms due to heart disease? If so, what is the extent and location of the damage? What are the effects of the damage on the heart's function? Does the therapy actually limit the extent of the damage?

To answer these questions, safe, accurate, and reliable techniques for detecting damage are necessary. Physicians now tend to rely on chest x-rays, electrocardiograms, and contrast angiograms. The chest x-ray indicates how large the heart is and provides a gross way of assessing the heart's function. For example, it can detect pulmonary edema due to congestive heart failure. The electrocardiogram often provides nonspecific information and is a relatively insensitive indicator of heart abnormalities. For example, when given to a person with symptoms of a heart attack, the electrocardiogram usually tells whether the person is having a heart attack but gives little information as to the size of the damaged area of the heart.

Contrast angiograms are generally performed when surgery or some other therapies are being contemplated for people who have chest pains (angina pectoris) or who have recently recovered from heart attacks. They provide an indication of the extent of the damage and of how the heart functions but are somewhat painful, dangerous, and expensive. When an angiogram is made, a catheter is inserted into a person's heart, a radiopaque medium is injected, and x-ray pictures and movies are made. The pictures show where arteries are blocked and how extensive the blockage is. The movies show how the heart functions.

In lieu of these standard methods of detecting damage, some promising new methods are being developed. Most, though, are not yet in clinical use. The newer techniques provide more information than chest x-rays and electrocardiograms and are safer and less uncomfortable than angiograms. Some of these methods involve indirect measurements of damage. For example, a radioimmunoassay developed by Robert Roberts and Berton Sobel of Washington University can be used to detect a specific enzyme, creatine phosphokinase (CPK), released into the blood when heart muscle dies. The most promising methods, however, produce pictures of the heart in which damaged heart tissue and its effects on heart function can be seen.

Pictures of the heart are obtained in several ways. The heart can be labeled with radioactive tracers that emit γ-rays and pictures taken with a scintillation camera that detects γ-radiation. Computerized methods can be used to build up a three-dimensional picture of the heart from x-ray or γ-ray pictures, or high-frequency sound can be beamed at the heart and a picture reconstructed from the reflections of the sound. These methods have different advantages and disadvantages, and they complement, rather than replace, each other. Together they are leading to improved diagnoses, to more accurate prognoses, and to better evaluations of treatments.

In the past few years, scintillation camera images have come into increasing use in diagnosing heart attacks. Some patients admitted to hospitals with symptoms of heart attack may have equivocal electrocardiograms, and the absence of serum enzymes, such as CPK, may not preclude heart damage. In these cases, scintillation camera images have proved extremely useful. Since these images also indicate the extent and location of damage, investigators at several medical centers, including Johns Hopkins University and the University of Texas Medical Center at Dallas, now routinely make images of patients' hearts to diagnose suspected heart disease.

Three ways to detect damage with a scintillation camera have been developed. The first results in a picture of areas of heart muscle that have recently died or been damaged. A radionuclide tracer, such as technetium-99m, is attached to a substance, such as pyrophosphate, that has an affinity for recently damaged heart muscle. Patients are injected intravenously with these tracers. The radionuclide lodges in and emits γ-rays from damaged areas, which then show up as bright areas in the scintillation camera image.

This method has several drawbacks. One difficulty is that small areas of damage, especially those that do not affect the full thickness of a wall of the heart, are not always detected. In recent years it has become clear that clinically important problems can occur when only part of the heart wall is damaged.

Another problem is that conditions other than acute damage to heart tissue can cause the tracers to accumulate. Several groups of researchers find that people with unstable angina pectoris—that is, angina pectoris in which the temporal pattern of pain changes—sometimes accumulate these tracers in their hearts. These people, however, may have no other signs of damage detectable by electrocardiograms or changes in concentrations of serum CPK. B. Leonard Holman and his colleagues at Harvard Medical School report that these tracers apparently bind to tissues that are deprived of oxygen whether or not those tissues are irreversibly damaged. This complicates the problem of separating patients with acute damage, who need intensive care, from those with less severe problems. Important therapeutic decisions may depend on this distinction.

An alternate way to see damaged heart muscle is to look at its complement—healthy heart muscle. In this case, a radioactive tracer consisting of a monovalent cation, such as potassium-43 or thallium-201, is injected intravenously into the patient. These tracers lodge in the heart in proportion to blood flow. Thus, portions of the heart that are deprived of blood as a result of blockage of the coronary arteries show up as blank areas in the scintillation camera image. These blank areas may indicate tissue damaged by a previous heart attack or recently damaged tissue. Once again, damaged areas that do not affect the entire heart wall may be missed. Recent damage can be distinguished from old when pictures taken with these monovalent cations are compared to pictures taken with radionuclides that concentrate only in recently damaged areas.

The third type of scintillation camera image provides information on how well the heart functions. To provide a radio-

active label, a blood pool tracer is injected into the patient. Such a tracer consists of a radionuclide attached to red blood cells or to a substance, such as albumin, that is carried along with the blood and does not lodge in heart tissue. The patient's cardiac cycle is recorded with an electrocardiograph, which, at specific points in the cycle, triggers the scintillation camera to record an image of the heart.

The resulting images of the heart at several points in the cardiac cycle provide information on whether the heart's left ventricle functions properly as a whole and whether all regions of the heart's walls move normally. The left ventricle is of greatest interest because it is the chamber that supplies blood to the major organs of the body and the one that is most commonly damaged by heart disease. Damage to heart muscle, including damage that does not involve the entire heart wall, often causes abnormal wall movements. Thus, determinations of wall movements can indicate dead or severely damaged areas of heart muscle that could not be detected with the other scintillation camera images.

Jeffrey Borer, with Stephen Bacharach and Michael Green at the National Heart, Lung, and Blood Institute (NHLBI) and the division of computer technology of the National Institutes of Health, and, independently, Bertram Pitt and William Strauss of Johns Hopkins University Medical School have recently refined this method of imaging the heart. These researchers now make movies of beating hearts rather than still shots. The movies are made with computers that store images taken at closely spaced intervals during the cardiac cycle. The Hopkins and NHLBI groups also use their computers to calculate and display graphically the volume of blood ejected from the heart when it contracts. This is possible because the blood is radioactively labeled and so the radioactivity of the heart at any time is a measure of the relative volume of blood in the heart. The ejection fraction—that is, the percentage of blood ejected in a single beat—is an indicator of left ventricular function.

In addition to using scintillation camera images to diagnose heart attacks, investigators are using these images to detect heart damage in people without symptoms who have normal resting cardiac functions and in people with angina pectoris. Borer and his colleagues are among those using their movies for this purpose. These researchers first make a movie of a person's heart and calculate the heart's ejection fraction while the person is at rest. Then they repeat the process while the person is exercising. When they compare the two movies, they can see previously undetected regions of left ventricular dysfunctions that occur only during exercise. Borer points out that this evaluation provides information that cannot be obtained from other methods, such as exercise electrocardiograms. He and others find that such electrocardiograms result in large proportions of both false positive and false negative diagnoses of coronary heart disease.

People with angina pectoris have coronary arteries that are so narrowed that, although they may carry enough blood to the heart when the person is at rest, they cannot supply the increased blood flow that is needed during exercise. When these people exercise, areas of their hearts are deprived of oxygen and they develop chest pain.

Pitt, Strauss, and Ian Bailey of Johns Hopkins University Medical School find that because thallium-201 labels only areas of the heart that are well supplied with blood, it can be used to diagnose people with angina pectoris. Patients whose hearts are labeled with this tracer exercise, then rest, during which time scans are made. Heart muscle that is deprived of blood during exercise then becomes evident.

Evaluating Treatments

Another use of scintillation camera images is to evaluate treatments of heart disease patients. Borer is using his movies of beating hearts to see whether people who have coronary bypass operations subsequently have improved left ventricular functions and whether nitroglycerin improves heart function during exercise. Pitt and Strauss are using their movies to see whether nitroglycerin improves heart function at rest.

Scintillation camera images are also being used to obtain information that is useful for making prognoses. Robert Chisholm of Harvard Medical School and Holman evaluated 100 patients with suspected acute infarctions. They labeled the recently damaged muscle with a radionuclide. By determining how much of a patient's heart took up this tracer, Holman and Chisholm were able to distinguish low-risk from high-risk patients. These investigators claim that this ability should enable them to reduce the hospitalization times of low-risk patients and to identify the high-risk patients who would benefit from more intensive treatment.

Although the scintillation camera images of the heart have numerous advantages over electrocardiograms and angiograms, they also have drawbacks that limit their uses. For example, the radioactive tracers have half-lives on the order of hours. This makes it impossible to make serial images that show where the damage is located during the first few hours after a heart attack begins (when most damage occurs). Serial images would be most useful at that time since they would provide a means to monitor the progress of the damage. (Although the movies do constitute serial images, they indicate heart function but not the location of damage.) Another problem is that these images constitute two-dimensional projections of the three-dimensional heart. Thus, heart structures are superimposed, making the scintillation camera images difficult to interpret.

Some of these difficulties with scintillation camera images are avoided when images are reconstructed by computerized tomography (*Science*, 7 and 14 November 1975). This technique is still a research tool for imaging the heart, but indications are that it will soon come into clinical use.

Computerized tomography is based on a mathematical method for constructing a three-dimensional image from two-dimensional projections. The projections are taken from several angles, and then the information is processed by a computer to produce three-dimensional pictures in the form of a series of two-dimensional cross sections.

This method of computerized reconstruction has come into widespread use for making pictures of stationary organs, such as the brain. But it has had to be modified before it could be applied to moving organs, such as the heart. Difficulties with imaging the heart occur because, as the machine moves from position to position in order to take pictures from different angles, the shape and position of the heart changes. This movement results in a blurred picture.

The problem of the beating heart is not important to one type of computerized tomography that results in such low resolution pictures that heart movements are not noticed. The method, however, uses tracers with properties that compensate for this low resolution. This technique is used successfully by Michael Ter-Pogossian, Edward Weiss, Sobel, and their associates at Washington University, and independently, by Gordon Brownell and his associates at Massachusetts General Hospital.

These investigators label the heart with positron-emitting isotopes and then use a machine that scans the heart and detects γ-rays emitted when these positrons collide with electrons. Because of the low intensity of the emitted γ-rays, the resulting images have a resolution of

only 1 cm, as compared to 1 mm with conventional computerized x-ray techniques. Ter-Pogossian, Brownell, and their associates have, however, chosen positron-emitting isotopes that confer several advantages to make up for this lack of resolution.

The positron-emitting isotopes used are isotopes of carbon and nitrogen. These isotopes can be incorporated into organic compounds such as palmitate or ammonia, which are taken up more readily by healthy than by oxygen-deprived tissues. The compound ^{11}C-palmitate, which is used by the Washington University group, is taken up and metabolized almost exclusively by the heart.

Another advantage of the positron-emitting isotopes is that they have very short half-lives—about 10 minutes for ^{13}N and 20 minutes for ^{11}C. This means that serial images of the heart can be obtained and the progress of damage during the course of a few hours followed. The short half-lives, however, mean that the isotopes must be used almost as soon as they are produced. They are produced in cyclotrons, whose expense currently limits the number of medical centers where they are available.

More conventional computerized tomography relies on the transmission of x-rays through body tissues to produce the two-dimensional cross-sectional images of body organs. Structures and damaged areas of the heart can be seen because they differ in their attenuation of x-rays. (Patients are usually injected with a contrast medium before their hearts are imaged, though, so as to enhance these attenuation differences.) The x-rays are about 1000 times more intense than the positron-emitting isotopes, thus resulting in higher resolution images than emission tomography.

To get around the problem of the heart's movements and still produce clear pictures with transmission tomography, investigators are following two different strategies. The first is to monitor the cardiac cycle and to make images only at certain points of the cycle. This is a difficult technique, however, which is still being developed.

The second strategy is to position numerous x-ray sources around the chest and then to produce the two-dimensional images from all the requisite angles simultaneously. A prototype of a machine that would do this was built by Earl Wood and his associates at the Mayo Clinic. They are currently using the machine on dogs but plan to use it soon on people. With this machine, they can produce 60 three-dimensional images of a dog's heart per second and display the images as a movie of various cross sections of a beating heart. They will use this technique to measure blood flow through the coronary arteries of patients and to see, with a 1-mm resolution, which areas of patients' hearts are supplied with and which deprived of blood.

Despite its advantages for viewing heart structures and movements, computerized tomography is an expensive technique. In some cases, similar information may be obtained at much less expense with ultrasound imaging.

Ultrasound—that is, sound with frequencies greater than 20,000 hertz—has come into extensive clinical use within the past few years (*Science*, 18 October 1974). Heart structures and movements can be detected when pulses of ultrasound are beamed at the heart. Most of this sound passes through body tissues, but some is reflected back each time the beam hits the interface between soft tissues of different compositions. By recording the time required for a beam to enter the body and be reflected back from a particular structure, medical scientists can estimate the distance of that structure from the source of the sound and chart how the structure moves with time. In that way, they can diagnose such things as congenital heart defects, enlargement of the heart due to congestive heart failure or hypertension, and defects in heart valves.

Ultrasound Sees the Moving Heart

Almost all current ultrasound techniques in cardiology result in one-dimensional images. The beam is moved from place to place and provides information on the matter in which different points on the heart move. The graphs of these movements are useful in assessing the overall structure and function of the heart but most often do not show segmental damage, such as that resulting from coronary artery disease.

Several groups of investigators have developed means of obtaining two-dimensional images of the heart with ultrasound. A problem in going from one to two dimensions comes from the heart's movements, which make it difficult to move a transducer across a person's chest, store the information as it is obtained, and finally display the information in two dimensions. Instead, it is necessary to sweep a beam across the heart more rapidly than the heart beats. Walter Henry and his associates at the NHLBI and Harvey Feigenbaum and his associates at the University of Indiana do this with a transducer that mechanically sweeps through an arc of 30° to 45° at a rate of 30 times per second. An alternate method is to use an array of transducers to electronically produce a wedge of sound. This is the method of Joseph Kisslo and his associates at Duke University and of James Meindl of Stanford University.

The two-dimensional images look like slices of the heart. Investigators can see valves open and close and can produce slices perpendicular to the long axis of the heart. These images are especially useful in the diagnosis of congenital heart defects in which the structures of the heart are displaced from their normal positions. Kisslo and his associates are also using their two-dimensional pictures to detect abnormal movements of the left ventricular walls produced by areas of dead or damaged heart muscle.

Since ultrasound can be used to produce two-dimensional images of the heart from a number of different angles, it is possible to gather enough information to construct a three-dimensional image of the heart. Although they are not yet able to display three-dimensional images, Meindl and his associates can collect two-dimensional images from all the necessary angles to construct them. At present, they use a computer to calculate heart volumes during the cardiac cycle from this information. Heart volumes in turn provide estimates of the volume of blood ejected when the heart contracts, which indicates left ventricular function.

Ultrasound, as used diagnostically, does not seem to harm subjects and its technology is progressing rapidly. This technique cannot be used on everyone, however. Good images can be made of children's hearts, but images of adult hearts vary in quality. As much as 15 to 20 percent of the adult population have physiological traits, such as chest wall configurations, that preclude the use of ultrasound.

All of the newer methods of viewing the heart represent attempts to detect damage, but the methods differ as to what effects of damage they detect. The monovalent cation tracers detect biochemical changes that occur when heart muscle is damaged. Radionuclide tracers such as thallium-201 detect defects in blood flow to damaged areas. Positron emission tomography that utilizes labeled palmitate detects changes in the metabolism of damaged tissue. Transmission tomography detects changes in the attenuation of x-rays by damaged myocardium. And ultrasound measures the movements and the dimensions of the heart. Which combination of these variables is most useful for the assessment of damage is not yet clear. However, these newer techniques together yield more information less dangerously than any combination of techniques used in the past.—GINA BARI KOLATA