

Nuclear Cardiology: A New Medical Specialty

H. N. Wagner, Jr. and L. G. Knowles

To evaluate a patient's circulation, information is required about pressure gradients, flow rates, vascular volumes, and the structure and efficiency of the heart and blood vessels. Although radioactive tracer techniques do not let us dispense with established techniques or rigorous analysis of data obtained by other methods, it now seems clear that nuclear medicine will play a major and increasingly important role in cardiology.

Introduction

The theoretical basis for using indicators to study the heart and circulation was well established in the early 1900's. That radioactive tracers would prove to be especially suitable for this purpose was a possibility entertained almost a half century ago, when Blumgart and Weiss used solutions of radium salts as tracers and a cloud chamber as a detector in circulatory studies. But the prospect became a reality only recently with the advent of safe and efficient radioactive tracers and with the invention of sensitive detection instruments. First, radioiodine and the rectilinear scanner, and later technetium-99m (^{99m}Tc) and especially the Anger camera brought to cardiovascular medicine an effective adjunct to established radiographic procedures, together with fresh approaches that seem more feasible for screening purposes.

To evaluate a patient's circulation, information is required about pressure gradients, flow rates, vascular volumes, and the structure and efficiency of the heart and blood vessels. In general, radioactive tracer techniques do not let us dispense with established techniques or rigorous analysis of data obtained by other methods. It is true that in some

cases the information provided by a tracer study may be enough to forestall a more complicated procedure such as cardiac catheterization. It is also true that, in certain types of tracer studies, new kinds of functional information are provided that are not readily obtained by other means. Some applications, while extremely promising, are still investigational and, at present, occupy an intermediate stage between development and routine use. It now seems clear, however, that nuclear medicine will play a major and increasingly important role in cardiology in the foreseeable future.

Scintigraphic Imaging

In nuclear imaging, devices referred to as gamma cameras portray the distribution within the patient of an administered radioactive tracer (a radiopharmaceutical). The gamma camera is a more recent development than is the moving detector device for radionuclide imaging, but its basic principle is older. In 1895, Roentgen reported using a pin-hole aperture and photographic film to make images of the anode of his X-ray tube. The trend toward the camera and

away from the rectilinear scanner as the preferred general imaging instrument primarily reflects the camera's speed and adaptability to a large number of clinical tasks. The need for dynamic information, which cannot be accommodated by the moving scanner, can be satisfied better by a camera. Other desirable features of the camera include the ease of placing the patient in positions that facilitate viewing of regions of interest within the body. In 1957, Anger¹ introduced a gamma camera that became the first stationary radiation-detector device that is practical for clinical diagnostic imaging (see Fig. 1). The camera uses a lead collimator to localize the gamma-ray flux emanating from the area of interest within the patient. Those photons that successfully transit the multiaperture collimator impinge upon a large thallium-activated sodium iodide scintillation crystal as shown in Fig. 2. The scintillator used in the Anger camera ranges in size from 11 to 16 inches in diameter and is usually one-half inch thick. The crystal converts relatively energetic gamma rays into visible light photons that are viewed by the photomultiplier

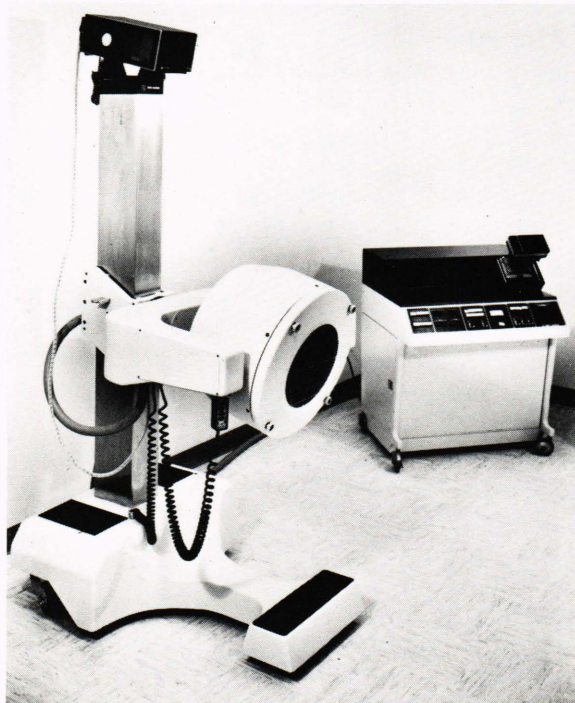


Fig. 1—Modern gamma camera system (courtesy Ohio-Nuclear Division, Technicare Corp.).

¹ H. O. Anger, "Scintillation Camera," *Rev. Sci. Instrum.* **29**, 27-33 (1958).

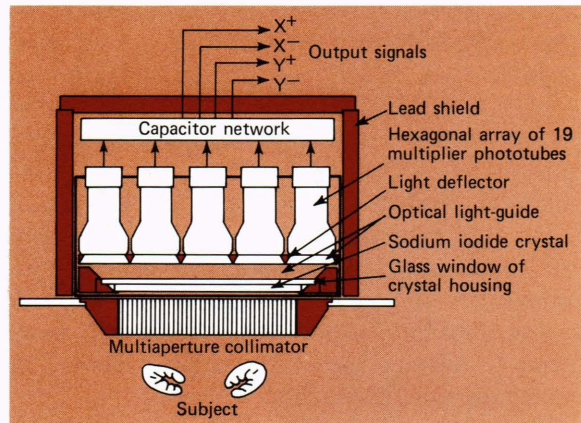


Fig. 2—Detector head of Anger gamma camera.

array. Gamma rays interact with the crystal in two important ways: by photoelectric and by Compton interactions. The photoelectric process within the crystal transfers the kinetic energy of an incoming gamma ray to a photoelectron that is almost equally energetic. A flash of light then appears at the site as ionization occurs along the electron path. An efficient phosphor can convert about 10% of the absorbed gamma-ray energy to light, so a ^{99m}Tc gamma-ray having 140 keV energy produces an average yield of 4.7×10^3 optical photons, each having approximately 3 eV energy. The path length of this scintillation is 0.1 to 0.2 millimeter and the ionization time is so short that the thousands of events can be considered a single spot of light at a single location. The short path also ensures a high probability that the photoelectron will deposit all its energy in the crystal.

The Compton process confronts the Anger camera design with a special problem that has been resolved at the expense of limiting the thickness of its crystal and thereby its sensitivity—a significant compromise. Unlike the photoelectric phenomenon where the incoming photon completely disappears, a Compton event is characterized by a division of the energy between an electron and a degraded photon. As before, the electron produces a flash but at an intensity proportional to its share of the incident energy. The deflected photon will either undergo photoelectric absorption or escape from the crystal with no further energy exchange. The low-to-moderate amount of light generated by the event will probably not be accepted by the pulse-height analyzer as a legitimate gamma ray even though in many cases it would be proper and beneficial to do so.

A thicker crystal could be used to increase greatly the probability that the scattered photon would also be captured and converted to light. However, Anger and Davis showed in 1964 that this approach would be undesirable because the scattered photon has an appreciable mean free path and is likely to produce a second flash of light at a location distant from the initial interaction. Both scintillations would appear to the analyzer to be coincident in time and summing to the proper energy, but the position-sensing electronics would tend to average the two positions, thereby degrading spatial resolution.

In modern scintillation cameras, an array of 37 photomultiplier tubes views the scintillation crystal. (There are lower resolution cameras that use only 19 photomultipliers.) In general, each photomultiplier intercepts a different fraction of the total light, resulting in different electrical pulse outputs. An electronic network designed to find the centroid of the signals converts the 37 separate pulses into three fundamental quantities: an X signal, a Y signal, and a total energy pulse (the Z signal). The total energy is derived by summing the outputs from all photomultipliers. If the pulse-height analyzer accepts the energy level, a standard pulse is generated that is used to unblank a cathode ray tube (CRT) beam previously positioned by the X and Y signals. The CRT face is viewed by a camera with an open shutter. The many individual flashes of light (typically a million or more) are integrated over time by the film. This results in a spatial mapping of the radionuclide concentration within the patient.

When a digital computer is used to process the data (as is becoming commonplace), the X, Y, and Z signals are entered into analog-to-digital converters and the resultant digital representation of their values is stored in a memory system for later playback and analysis.

Regional Blood Volumes and Flow

Volume Studies

Measurements of total red blood cell and plasma volumes were among the earliest applications of tracer techniques. Such measurements entail injecting a tracer, allowing enough time for it to be distributed throughout the circulation, and then comparing the diluted radioactivity with a standard to permit calculation of the volume of

distribution. Such procedures require no more complicated an instrument than a simple well counter.

But the ability to image the distribution of a radioactive tracer within the body adds a new dimension of considerable value. It is now possible to measure and compare the volumes of various compartments and regions of the circulation after the injection of labeled albumin, red blood cells, or substances bound by plasma proteins. While the spatial resolution of images so obtained is below that of conventional radiographs, such imaging of global and regional heart function is now widely used in medical practice.

Pericardial effusions resulting from such diseases as tuberculosis or myxedema can be detected within minutes after an intravenous injection; they are characterized by an abnormally small intracardiac blood pool and a zone of decreased activity surrounding the heart. For detection of pericardial effusion, we use ^{99m}Tc -labeled albumin and the scintillation camera to observe the passage of the tracer through the great vessels directly after intravenous injection. Ionic indium-111m or -113m can also be used.

One of the newer applications of tracer studies of regional blood volumes is in diagnosing peripheral vascular disease. Safe, simple, and rapid, such studies are useful in an initial diagnostic work-up and in evaluating the response to therapy. In the case of the venous pools of the legs, the procedure consists of intravenously injecting a radioactive label and monitoring both relative changes in the blood volume of the calf and the times required for the changes. In normal subjects, a Johns Hopkins Medical Institutions study² found that, with a rapid positional change from supine to 45° upright, the blood volume of the calf rises to $145 \pm 14\%$ of the horizontal value, taking an average of 21 seconds to reach half the figure and more than 90 seconds for equilibrium. With exercise, the calf muscle drains the calf blood to $76 \pm 6\%$ of its volume at rest. On inverting subjects to 45° head-down position, the pool is reduced to $70 \pm 12\%$ of the horizontal volume. The magnitude and rates of change of these relative volumes are altered in venous disease. With incompetent cardiac valves, the size of the calf blood pool is increased and positional changes are

² R. B. Rutherford, C. M. K. Reedy, A. G. Walker, and H. N. Wagner, Jr., "A New Quantitative Method of Assessing the Functional Status of the Leg Veins," *Am. J. Surg.* **122**, 594 (1971).

accompanied by more rapid filling and larger volume changes. Decreased size of the vascular blood pool, slowed drainage, and reduced volume changes are seen unilaterally in thrombophlebitis and bilaterally in congestive heart failure.

Flow Studies

Radioactive tracers make it possible to study directly the phenomenon of flow by clocking the arrival or transit of injected tracers and by observing the pathways and perfusion patterns of such indicators in various regions of the body. Being able to do this with indicators that are detectable externally has obvious advantages. In experimental animals, for example, the surgical insertion of flowmeters at appropriate sites is a procedure that may itself introduce circulatory alterations, although recent improvements in flowmeter technology seem to offer promise of avoiding such alterations.

Several agents are appropriate for flow studies, depending on the region under investigation. The soluble gas xenon-133, an excellent tracer for many studies of the circulation, has the combined advantage and disadvantage of being eliminated rapidly by the lungs. The advantage is that it is rapidly cleared from the system, allowing procedures at frequent intervals. The disadvantage is that to study the systemic circulation, either the afferent artery must be injected or a complicated correction for lung radioactivity must be made. Thus, an intracarotid injection is needed for a cerebral study and a coronary artery injection is needed for a myocardial study, both involving significant medical risk. On the other hand, ^{99m}Tc-pertechnetate and indium-113m, which are confined to the vascular compartment, can be administered with only a bolus intravenous injection to determine the time-course of the arrival of the activity in various organs.

Another technique for studying regional blood flow, one of growing importance, uses radioactive microspheres. The advantage of such labeled spheres is that they provide superior images of perfusion patterns by becoming lodged in the microvasculature. The microspheres can be mixed uniformly with blood, they have the same rheology as red blood cells, and they do not induce alterations of flow. The lung, which is rich in collateral circulation, can easily tolerate arteriolar and capillary obstruction, although an obstruction becomes a matter of concern with regard to the myocar-

dium or brain. The ability to label microspheres with short-lived isotopes like ^{99m}Tc combines the advantages of minimal radiation doses with higher photon yields; making them of metabolizable human serum albumin assures that their lodgment will be temporary.

The disposition of microspheres injected into the bloodstream depends on their size, the injection site, and the system's circulatory characteristics. The first two factors can be manipulated by the investigator according to the objectives of the study. Particles or microspheres smaller in diameter than the capillaries are removed from the circulation by phagocytosis, primarily in the liver but also in the spleen and bone marrow. When larger than the capillaries, the microspheres are trapped in the arterioles and capillaries in the first vascular bed downstream from the injection site unless they are diverted through shunts large enough to permit their passage. The fraction that bypasses a capillary bed is related to the fraction of blood shunted. Microspheres shunted through the systemic circulation are subsequently trapped in the lungs; particles shunted through the heart or lungs are ultimately deposited in systemic vascular beds. Inert particles such as gold, glass, or carbon (which have been used in animals) remain almost indefinitely where they finally become lodged, but particles of albumin, gelatin, and amylose are biodegradable and are eventually metabolized. Spherical albumin microspheres are now commercially available in graded sizes ranging from 7 to 65 microns; they are very stable in the dry state and can be labeled when needed.

Computer-Aided Cerebral Flow Studies

With the advent of computerized tomography, most of the nuclear studies of the brain are concerned with the cerebral blood flow. The ability to relate the known vascular patterns of the brain to the configuration of the abnormalities seen on the image often makes it possible to assess the probable nature of a disorder, that is, to distinguish between a mass lesion and a circulatory impairment.

One limitation of the conventional "equilibrium" brain scan, apart from the fact that it cannot be expected to provide the spatial resolution available from computerized tomography, is that it gives essentially a static picture of the distribution of the tracer after equilibration has occurred.

If the physician can view not only the final

distribution of the radioactive tracer in the brain and surrounding structures but also the manner and rate by which that distribution was achieved, his diagnostic ability can become both more sensitive and more specific. Using computerized data acquisition, processing, and display systems, many dynamic studies of the cerebral blood flow were analyzed to determine the normal variants of blood flow in the head. For instance, regional cerebral perfusion may be evaluated by imaging the first circulation of a relatively nondiffusible intravenous bolus labeled with ^{99m}Tc . The data can be interpreted quantitatively by generating time/activity curves from selected regions of interest in the brain.

These radiotracer methods for evaluating patients with ischemic strokes have been shown³ to have a sensitivity of about 50% with visual interpretation alone, and of up to 74% when the data are also quantified. This improvement in sensitivity is attributable to the ability to generate time/activity curves within selected regions of interest, to measure associated parameters with good reproducibility, and to establish normal ranges for the parameters.

A well-known medical axiom states that there is more similarity in function between paired organs (e.g., the lungs or kidneys) of a particular person than there is between the same organ of two different people (e.g., the left kidneys of any two randomly chosen persons). This basic principle has been applied to evaluate regional abnormalities in the brain. Paired and symmetrical regions of interest, in the brain, as illustrated in Fig. 3, can be expected to exhibit essentially identical blood-flow patterns when subjected to the same bolus of radioactive tracers, so that regions in the left side of the brain can reasonably be compared with similar areas in the right side.

The time/activity curve generated by detecting the passage of the radionuclide through the region of interest is related to the injected dose and cardiac output by the Stewart-Hamilton equation

$$Q = F_{co} \int_0^{\infty} C(t) dt.$$

It states that if a given amount of tracer, Q , is injected into the proximal circulation and under-

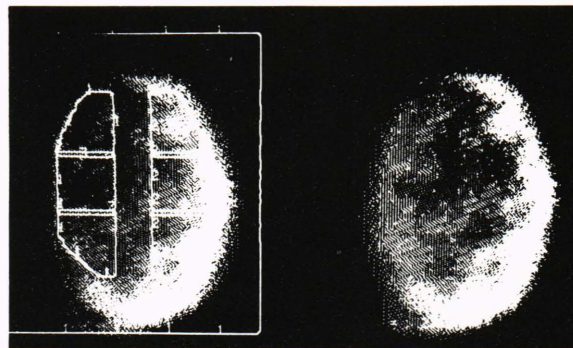


Fig. 3—Six regions of interest defining areas in a vertex radionuclide image of the brain. The abnormal distribution is due to metastatic lesions caused by a primary cancerous prostate gland.

goes uniform mixing in a central chamber, measurement of the concentration of the tracer, $C(t)$, at some distal point during the first circulation will permit determination of the cardiac output, F_{co} . When the equation is modified to evaluate the relative regional perfusion to symmetrical paired regions of interest within the brain, the equation reduces to a simple relationship: relative flow equals relative volume divided by the relative mean transit time of the tracer through the region of interest.⁴

A group of 50 patients who did not have organic brain disease at the time of discharge (or follow-up) was studied this way. An automated data acquisition and processing system was used to determine the time course of the radioactive bolus through six regions of interest within the brain. Computer programs were developed to calculate objectively a number of physiological parameters. The values of the injection-to-first-arrival times, injection-to-peak-activity times, and mean transit times for these normal patients are given in Table 1.

There are nine possible combinations of normal, increased, or decreased relative regional blood volume and normal, increased, or decreased relative mean transit time of the bolus through the region of interest. When the two physiological parameters are compared, a pathophysiological interpretation relating to regional blood flow can be constructed (see Fig. 4) that proves disease states by relating local flow patterns.

³ W. H. Oldendorf and M. Kitano, "Radioisotope Measurement of Brain Blood Turnover Time as a Clinical Index of Brain Circulation," *J. Nucl. Med.* 8, 570-587 (1957).

⁴ W. C. Klingensmith III, M. G. Lotter, L. G. Knowles, A. Motazedi, and H. N. Wagner, Jr., "Modification of the Stewart-Hamilton Principle for Clinical Evaluation of Regional Cerebral Circulation," (submitted for publication in *J. Nucl. Med.*).

Table 1
NORMAL ABSOLUTE VALUES FOR TIME PARAMETERS
(MEAN \pm 1 STD DEV)

Time (s)	Hemisphere	Anterior	Middle	Posterior
T_1 : Injection-to-first arrival time	Right	11.3 \pm 2.5	11.4 \pm 2.5	11.2 \pm 2.5
	Left	11.3 \pm 2.5	11.4 \pm 2.5	11.2 \pm 2.5
T_2 : Injection-to-peak-activity time	Right	18.0 \pm 3.5	18.3 \pm 3.9	17.6 \pm 3.3
	Left	18.0 \pm 3.5	18.3 \pm 3.9	17.6 \pm 3.3
T_3 : Mean transit time	Right	22.3 \pm 3.8	22.4 \pm 4.3	21.8 \pm 3.8
	Left	22.3 \pm 3.8	22.4 \pm 4.3	22.0 \pm 4.1

Evaluation of Cardiac Structure and Function

The main cause of death in the United States is coronary artery disease. It is so widespread that experts predict that nearly 20% of the male population will sustain a myocardial infarction. Clearly, progress in this area can aid a vast number of people.

In addition to measuring the volume of blood within a compartment of the cardiovascular system, tracer images help evaluate regional as well as global functions of the walls of the compart-

ment itself. For example, nuclear techniques offer a way to visualize cardiac wall motion that, although lacking the fine detail of contrast angiography, can be used on a screening basis to provide more definite indications for invasive procedures or, occasionally, to forestall them. Also, the radiation dose is less than that associated with fluoroscopy, an important advantage for a screening procedure.

With nuclear angiocardiology, enlarged, hypertrophic, and malpositioned cardiac structures can be identified and their abnormalities suggested for angiographic verification. The immediate

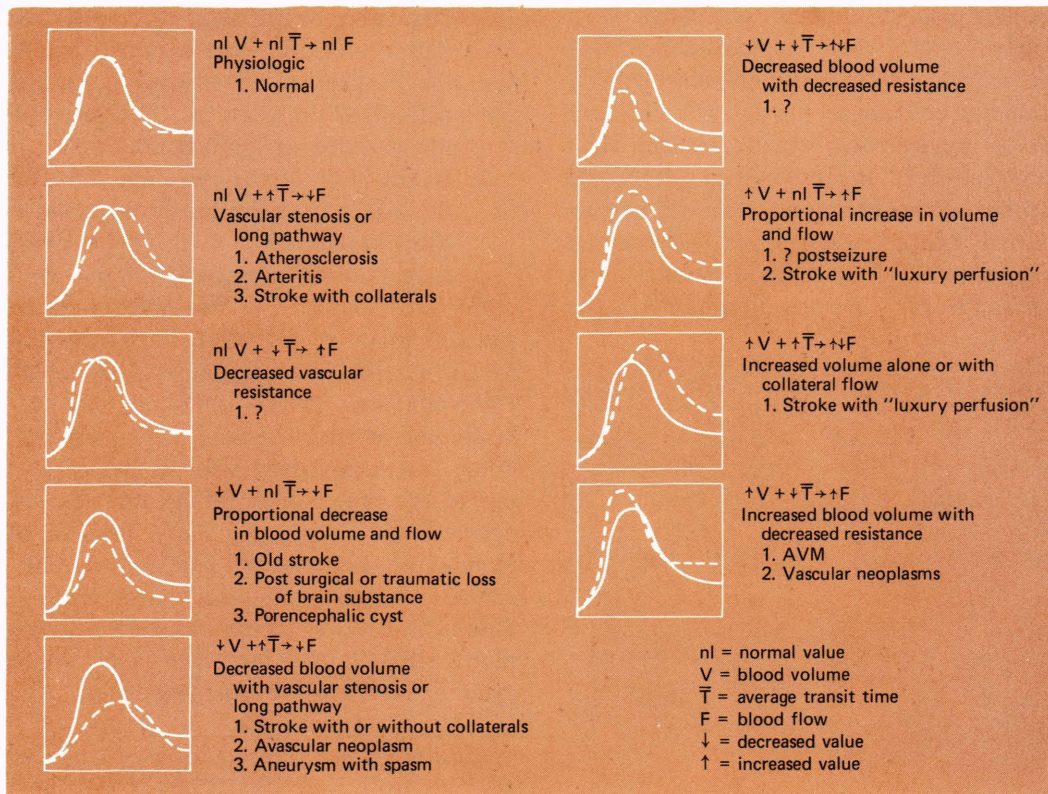


Fig. 4—Pathophysiological interpretations of time/activity curves from paired regions of interest in the brain.

demonstration of an abnormality such as transposition of the great arteries considerably expedites cardiac catheterization. In combination with "gating" and other techniques to be described later, information can be obtained about the contractility of the heart, the rate of forward and backward blood flow, or areas of poor myocardial contractions. Such studies have proved useful in detecting ventricular aneurysms in patients after myocardial infarction. When confirmed by X-ray contrast angiography, these lesions can sometimes be treated successfully with surgery.

Nuclear angiocardigraphy can help differentiate cardiac from noncardiac cyanosis, especially in newborns, who run considerable risk during the catheterization procedures required for definitive diagnosis. If the physician can be reasonably certain that the infant is suffering from respiratory distress syndrome, myocardial disease, or central nervous system disease, invasive methods can be avoided and the chance for survival increased. If the infant does have congenital heart disease, the institution of more definitive studies can be lifesaving. At the Johns Hopkins Hospital, we have found that continuous camera monitoring of the passage through the heart and lungs of an intravenous bolus of ^{99m}Tc -pertechnetate or ^{99m}Tc -albumin (see Fig. 5) makes it possible to identify with reasonable confidence the integrity of such structures as the superior vena cava, the right atrium and ventricle, the pulmonary artery and lungs, and the left ventricle and aorta. In a structurally normal heart, a clear space between the superior vena cava and the pulmonary artery that is evident in the early frames disappears as the

ascending aorta fills. The lungs fill immediately after the pulmonary artery is visualized, but no activity is seen in the abdominal aorta. After the lung vessels begin to fill, activity is discernible in the region of the left ventricle. The technique may also prove helpful in differentiating patients with so-called innocent murmurs from those with heart disease.

While blood pool agents outline or silhouette the heart chambers, it is often desirable to view the myocardial muscle itself. This can be done with thallium-201, permitting detection of the areas of infarction, for example. To detect areas of diminished blood flow before infarction has occurred, thallium-201 is injected at the peak of exercise on a treadmill or on an in-place bicycle.

Left Ventricular Function

Recent advances⁵ have been made using a computerized scintillation-camera system with the following distinctive characteristics:

1. It has an EKG-synchronized data-acquisition capability that uses a buffer memory to separate the gamma-camera data into as many as 64 individual matrices. Each data field (image) contains only the events recorded during a discrete, predetermined portion of the cardiac cycle. However, the data accumulated in each of the time slots are integrated over 1000 heart beats.
2. It can display the resultant data matrices as images of the beating heart and recycle them repeatedly on a color-TV monitor as an endless-loop motion picture.

For most patients, a conventional nuclear angiocardigram is recorded in 1-second frames for 30 seconds after the intravenous injection of ^{99m}Tc -albumin. These frames provide a visual evaluation of the "first-pass" characteristics as the bolus enters the right side of the heart, passes out to the lungs, back to the left side, and out again to the rest of the body. Overall sluggish circulation, left-to-right and right-to-left inter-chamber shunts, and lung transit times can be noted. An EKG-synchronized study of the cardiac blood pool is then acquired with the cardiac cycle divided into 16 time segments.

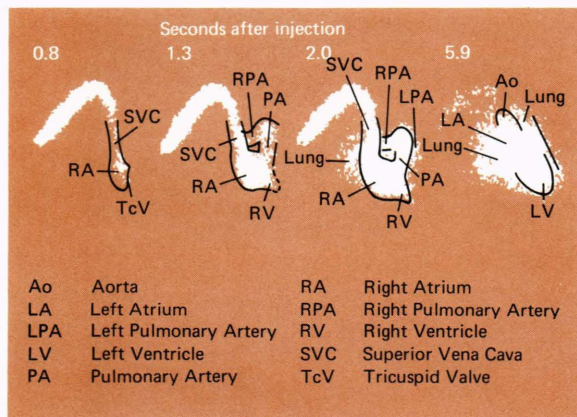


Fig. 5—Gamma camera monitoring of the passage through heart and lungs of an intravenous radioactive bolus.

⁵ M. G. Lotter, K. H. Douglass, L. G. Knowles, E. L. Nickloff, and H. N. Wagner, Jr., "A Technique for the Evaluation of Global and Regional Ventricular Function," *Proceedings of the Symposium on Computer Assisted Data Processing in Nuclear Medicine*, January 1977.

Following the acquisition phase, the data are corrected for inherent spatial nonuniformities in sensitivity found in the camera's detection system. Additionally, a data-bounding process is applied that sets to the value of two standard deviations any element that differs from its immediate neighbors by more than two standard deviations. Next, the left ventricle is outlined as the cardiac region of interest, and a periventricular area is defined as a background region of interest, as shown in Fig. 6. The activity within these regions of interest is plotted as a function of time within the cardiac cycle. The background curve is subtracted from the ventricular curve to yield the corrected blood-pool data. These data are further analyzed to yield the ejection fraction of the left ventricle, the pre-ejection period (which is a measure of the time from the maximum values of the heart's electrical trigger—the Q-R-S complex in Fig. 7—to the beginning of contraction), the emptying and filling times of the left ventricle as a fraction of the cardiac cycle, and the ejection fraction divided by the emptying time. Figure 7 shows the time relationship of some of the important cardiac parameters. Figure 8 gives several clinical examples of left ventricular volume curves as determined by EKG-synchronized scintigraphy.

In addition to the quantitative data, the ma-

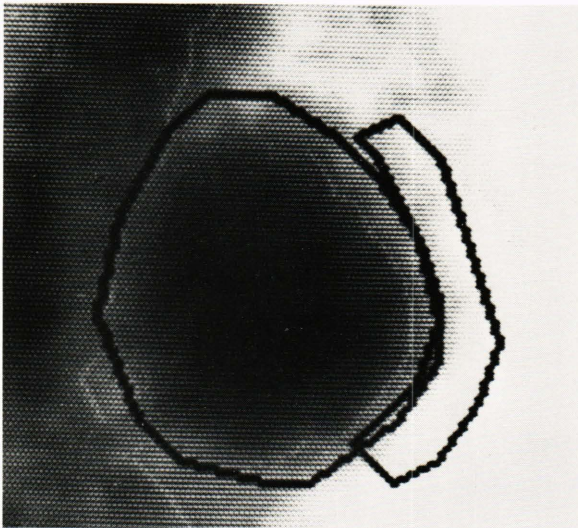


Fig. 6—Regions of interest superimposed on a radio-nuclide image of the heart at end diastole. The larger region encircles the left ventricle; the smaller region defines a background area in this left anterior oblique view. These regions are used in a computer program to generate time/activity curves of the activity within the left ventricle.

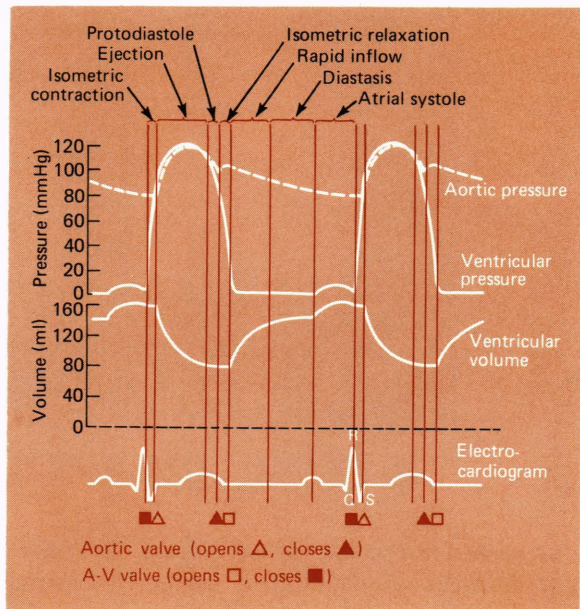


Fig. 7—Various physiological events that occur during the cardiac cycle. The shape of the left ventricular volume curve can be determined noninvasively using radiotracer techniques.

trices are displayed in a cine format; the images are essentially a scintigraphic movie of the beating heart. A visual evaluation of wall motion of both ventricles can be made by the physician. Areas of the heart wall that are improperly functioning or nonfunctioning are easily identifiable. In normal areas, the myocardial cells containing ^{201}Tl can be seen to spread apart during diastole and come together during systole. In a comparison of 27 paired studies, viewing only the synchronized ^{201}Tl cinematic display, six observers could accurately predict regions of wall-motion abnormalities demonstrated in subsequent $^{99\text{m}}\text{Tc}$ -albumin studies of wall motion. Thus, the cinematic display provides a significant improvement over the conventional method of viewing only static images of the distribution of ^{201}Tl within the ventricles.

Conclusion

Nuclear medicine has given cardiologists a significant tool for investigating the structure and function of the heart. These simple noninvasive procedures allow patient screening to a degree never possible before. Even those who are definitely surgical candidates are aided by the pre-

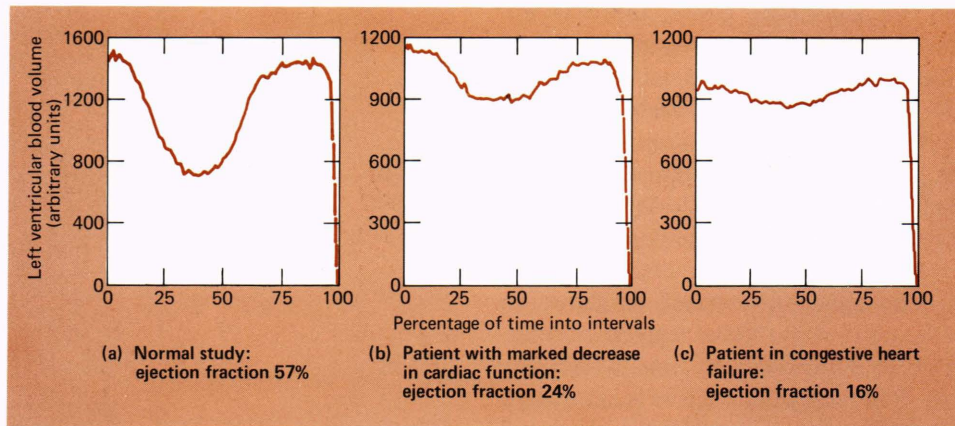


Fig. 8—Clinical examples of left ventricular volume curves as determined by EKG-synchronized scintigraphy.

operative information gleaned from the scintigraphic data. In addition to the heart, regional circulation throughout the body may be evaluated with a sensitivity never dreamed possible just a short time ago. Nuclear medicine was born in the 50's, survived its infancy in the 60's, and is now reaching a mature and highly accepted position among users and providers of our health systems.

Acknowledgments

This work was supported, in part, by U.S.P.H.S. Grants GM-10548 and 1R01 FD00815-01.

Part of this article was previously published in a series on nuclear medicine in *Hospital Practice*, whose permission to use the material is gratefully acknowledged.