MEDICAL PROGRESS

NONINVASIVE CARDIAC DIAGNOSIS (First of Three Parts)

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THE burgeoning appeal of noninvasive methods in the evaluation of patients with cardiovascular disorders is based not only on their diagnostic efficacy but also on their ease of application, ready repeatability, relative lack of expense and negligible patient risk. It is unfortunate that for these very reasons, some of these tests are at times indiscriminately used in place of a careful history and physical examination or in the hope of discerning lesions beyond the diagnostic capability of current noninvasive methods.

This review will emphasize effective use of noninvasive diagnostic procedures by underscoring their merits and limitations in the evaluation of commonly considered cardiovascular diagnoses. The mechanisms underlying the efficacy of specific methods will be emphasized, but the breadth of application of any one technic will not be stressed. Discussion will be directed particularly to the relative potential of several methods for contributing to the solution of diagnostic cardiac problems encountered most often in offices and hospitals.

METHODOLOGY — PHYSICAL AND PHYSIOLOGIC PRINCIPLES

Imaging Technics

Ultrasonic and radionuclide approaches demonstrate underlying gross anatomic abnormalities and thus have broad applicability and appeal in delineating lesions within the heart and great vessels.

Echocardiography. Sounds of frequency greater than 20,000 cycles per second (Hz) are beyond the upper-frequency limit of normal human hearing. Hence, they are called ultrasound. The ultrasound commonly used in examination of the heart has a frequency of 2.25 million Hz (2.25 MHz). It is emitted in extremely short pulses from a transducer that also acts as a signal receiver for reflected ultrasound waves. Ultrasound is reflected whenever tissue acoustic impedance changes; thus, it is possible to image the internal structure of the heart since the interfaces of cardiac structures such as valves, myocardium and pericardium present different acoustic impedances to the ultrasonic beam. The information is available almost instantaneously since ultrasound travels through soft tissues at the rate of 1500 meters per second.

Currently, echocardiography is most widely practiced by directing a single ultrasonic beam through the heart, and focusing on easily definable structures that have characteristic motion such as the mitral valve. The information is presented on an oscilloscope in time-motion (M mode) display wherein time is represented on the horizontal axis and reflected sound on the vertical axis in direct proportion to the depth of tissues from which the sound is reflected (Fig. 1). Once a known structure is identified, the beam can be redirected toward other portions of the intracardiac anatomy, allowing the visualization and identification of additional structures by characteristic motion and anatomic continuity. Structural continuity is a particularly helpful guide to anatomic relations. Normally, as the echo beam is directed superiorly and medially from the left ventricle, the interventricular septum is continuous with the anterior aortic wall, and the anterior mitral leaflet continues into the posterior aortic wall. Thus, the aortic root in normal subjects can be shown to overlie directly the left ventricular outflow tract. More detailed illustrated examples of this technic are available in several recently published textbooks.[1-3]

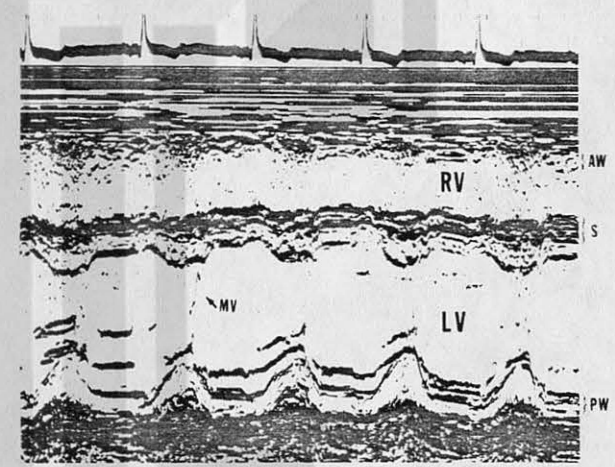

Figure 1. M-Mode Echocardiogram through the Body of the Right (RV) and Left (LV) Ventricles in a Normal Subject. Motion is recorded from the anterior right ventricular wall (AW), interventricular septum (S) and left ventricular posterior wall (PW) during systole. The ventricular cavities appear as relatively echo-free spaces. Note that the septum and posterior wall approximate during contraction. Some of the anterior leaflet of the mitral valve (MV) can be seen within the left ventricular cavity.

There is intense current interest in cross-sectional echocardiography, which produces a two-dimensional or planar image rather than the unidimensional time-motion display. Cross-sectional echograms of

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the heart are achieved in several ways. When the B-scan technic is used (Fig. 2*A*) the transducer is systematically moved across the precordium and pulsed at the same time in each cardiac cycle. Over a number of cycles an image of the heart is built up on a storage oscilloscope. By selection of the appropriate time in the cardiac cycle to activate the transducer a diastolic or systolic image can be constructed. The image produced is a retrospective average of the preceding beats chosen for analysis. However, the B-scan approach is time-consuming; in addition, arrhythmias can cause difficulty with proper image construction. For these reasons there is a strong momentum to produce cross-sectional cardiac echograms that portray "live" images — i.e., an instantaneous and continuous display of the heart's action in real time. Such images have been obtained with a linear array of 20 miniature transducer crystals (multicrystal echograph — Fig. 2*B*).[4] Each crystal in the array is fired in succession, and the activation process is rapidly repeated. Signals received by each crystal are displayed in a corresponding line on an oscilloscope. Because of the high velocity of ultrasound in the chest, the motion of specific portions of the heart that relate to each transducer element are received and displayed almost instantaneously.

"Live" cross-sectional echocardiograms can also be obtained by use of sector scanners. In these instruments the ultrasound beam is swept in an arc back and forth across the heart from a single point on the chest. The sweeping mechanism may be mechanical or electronic. In mechanical sector scanners a single crystal is rocked through a 30° to 45° arc on the chest wall (Fig. 2*C*).[5] Echoes from each position in the arc are simultaneously displayed on an oscilloscope. In electronic sector scanners a small multi-element transducer is maintained in a stationary position on the chest, and the ultrasound beam is swept back and forth electronically (Fig. 2*D*).[6-8] With electronic scanners, an expanded field over an 80° to 90° sector is possible.

Cross-sectional instruments are in a relatively early stage of development. Their cost is considerably higher and resolution lower than those of conventional echocardiographs. Furthermore, the entire adult heart is not encompassed in the field of many available instruments. Until these problems are overcome and specific diagnostic advantages are clearly demonstrated, the cross-sectional technic is unlikely to supplant conventional echocardiography in the near future. Nevertheless, considerable progress has been made since cross-sectional methods were introduced a few years ago. Since this technic portrays regional anatomy, it can provide information that clearly supplements time-motion studies. In particular, anatomic relations of the great vessels and ventricular chambers in complex congenital malformations may be readily defined. Quantitation of stenotic valve-orifice areas, detection of localized abnormalities of ventricular contraction and even imaging the ostia of the coronary arteries are additional applications where this technic has recently been used.

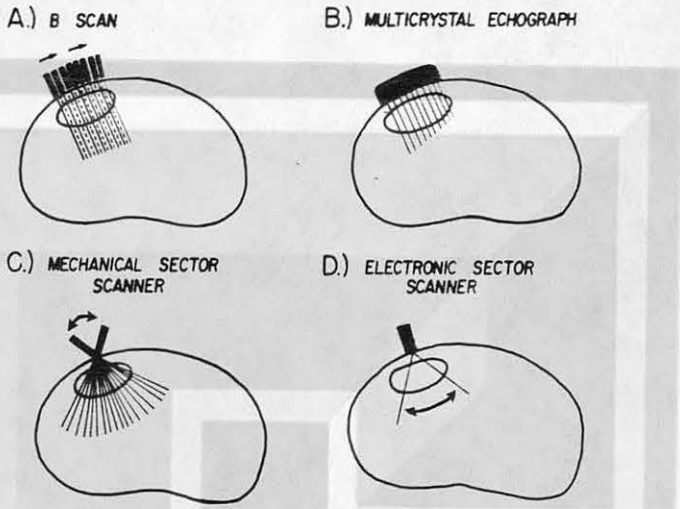

Figure 2. Schematic Illustration of Cross-sectional Echocardiographic Technics.

The heart is shown as an oval organ in a transverse section of the thorax as viewed from above. The transducer for each system rests on the left anterior chest wall. See text for details.

Radionuclides. Radionuclide imaging is achieved by the external detection of photons emitted from the body after the administration of radioactive pharmaceuticals. The radioactive agent may consist of a radionuclide alone, or, when specific localization cannot be achieved with a simple radionuclide, an agent can be radiolabeled to achieve this goal. In most cases the choice of a radiodiagnostic agent is a compromise between maximum amount of achievable information and minimum radiation dose to the patient. Much of the early work in cardiovascular diagnosis was accomplished by probe detectors that recorded time-activity curves over the designated area of interest. The advent of the high-speed scintillation camera, coupled to a computer system to produce images of the heart and blood vessels, has greatly broadened the uses of the available radionuclides in the cardiovascular field.

Important characteristics of radiopharmaceuticals used for diagnostic purposes include, first of all, specific localization in the organ of interest to achieve a good target-to-nontarget ratio. A second characteristic is the nature of radioactive decay, the ideal being without particulate emission, since particles — e.g., alpha and beta — contribute heavily to the radiation dose and nothing to external detection. The gamma ray, with a photon energy of 100 to 300 kilo electron volts (KeV), is the most suitable for the currently available instrumentation. Lower-energy photons have the problems of tissue absorption; higher-energy photons are difficult to detect efficiently. The final characteristic is a suitable half-life: the ideal half-life of a radiopharmaceutical has been shown by the-

Table 1. Common Radiopharmaceuticals in Cardiovascular Nuclear Medicine.*

Radiopharmaceutical	Physical Half-Life	Energy		Uses	Mechanism of Localization
	hr	*KeV*	*Abundance†* %		
Potassium ions (^{43}K)	22.4	373	85	Regional myocardial perfusion	Diffusion & exchange
		619	81		
Rubidium ions (^{81}Rb)	4.7	511	26	Regional myocardial perfusion	Diffusion & exchange
		190	65		
Cesium ions (^{129}Cs)	32.1	375	48	Regional myocardial perfusion	Diffusion & exchange
		416	25		
Thallium ions (^{201}Tl)	74	70 (Hg x-ray)		Regional myocardial perfusion	Diffusion & exchange
Xenon inert gas (^{133}Xe)	127.2	81	37	Regional myocardial blood flow	Diffusion
Technetium ions (^{99m}Tc)	6	140	90	Delineation of great vessels & cardiac chambers & assessment of ventricular function	1st passage through the central circulation
Indium ions (^{113m}In)	1.7	393	64	Delineation of great vessels & cardiac chambers & assessment of ventricular function	Intravascular substance
^{99m}Tc albumin				Delineation of great vessels & cardiac chambers & assessment of ventricular function	Intravascular substance
^{99m}Tc microspheres or macroaggregated albumin				Regional myocardial perfusion	Blockade of capillaries
^{113m}In macroaggregates				Regional myocardial perfusion	Blockade of capillaries
^{99m}Tc pyrophosphates				Delineation of acutely infarcted myocardium	Mitochondria of irreversibly damaged myocardial cells

*Nuclear data from Tables of Isotopes.[9a]

†This term indicates the frequency of radioactive decays resulting in emission of a given energy. It is also referred to as fractional decay, intensity, etc.

oretical consideration to be equal to 0.693 (natural logarithm of 2) times the duration of the biologic measurements.[9] The radionuclides commonly used in cardiovascular nuclear medicine are listed in Table 1.

Potassium-43 (^{43}K) and its analogues rubidium-81 (^{81}Rb), cesium-129 (^{129}Cs) and thallium-201 (^{201}Tl) have been used to delineate regional myocardial blood perfusion. Their mechanism of localization is through diffusion and exchange with potassium, the chief intracellular cation. The rate at which these isotopes concentrate in the myocardial tissues is determined by available coronary blood flow and by the rate of exchange of the isotope between the circulating blood and the viable myocardial cell. Of the four potassium analogues, ^{201}Tl, although most recently introduced, has enjoyed the widest use; the other three have the disadvantage of having high-energy photons and are thus inefficient for external detection.

Xenon-133 (^{133}Xe) is an inert gas that can be dissolved in physiologic saline for intravenous injection. Like that of the potassium analogues its main use has been to measure regional myocardial blood flow. Its mechanism of localization is simple diffusion. The major disadvantage of ^{133}Xe is that it has to be administered during coronary catheterization and thus is an invasive procedure. Technetium-99m (^{99m}Tc)-labeled microspheres or macroaggregated albumin or indium-113 (^{113m}In) macroaggregates have also been used primarily to determine regional myocardial perfusion. These particles localize in the heart because of entrapment in a small fraction of the coronary capillary bed. A disadvantage is that, like ^{133}Xe, they have to be administered during cardiac catheterization. Unlike that with ^{133}Xe, however, imaging can be performed away from the catheterization facility within the convenient time that the physical half-life of these radionuclides allows.

^{99m}Tc has an ideal energy characteristic and a suitable half-life. Its main use in the pertechnetate form has been in the delineation of the great vessels and the cardiac chambers (Fig. 3). This radiopharmaceutical is diffusible, and hence imaging after its injection must be accomplished on the first pass of the bolus through the heart. With a high-speed scintillation camera, coupled to a sophisticated computer system, ^{99m}Tc pertechnetate can be used for the assessment of left ventricular function. ^{113m}In is also suitable for the delineation of the great vessels and the chambers of the heart. Unlike the ^{99m}Tc pertechnetate, ^{113m}In, when injected intravenously, is bound to the transferrin molecule in circulating plasma, making it nondiffusible. Similarly, ^{99m}Tc-labeled serum albumin has been used as a labeled intravascular substance for the delineation of great vessels and cardiac chambers and the assessment of ventricular function, particularly the ejection fraction of the left ventricle.

Unlike all the above radiopharmaceuticals, ^{99m}Tc-labeled pyrophosphate delineates the acutely infarct-

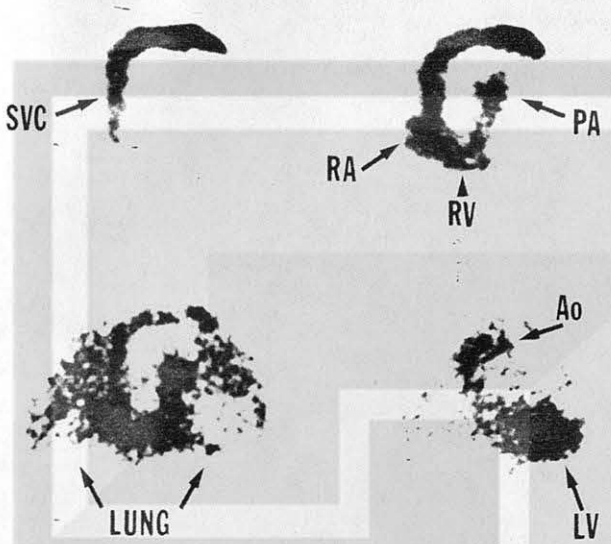

Figure 3. ^{99m}Tc Pertechnetate Flow Study through a Normal Heart.

By sequential imaging the superior vena cava (SVC), right atrium (RA), right ventricle (RV), pulmonary artery (PA), the lung, left ventricle (LV) and aorta (Ao) are outlined.

ed myocardium. The mechanism of localization is believed to be concentration of pyrophosphate in the mitochondria within the irreversibly damaged myocardial cells, where calcium deposition has been demonstrated in experimental myocardial-cell injury.[10]

In general, radionuclide studies of the cardiovascular system take one of two approaches. The first is recording the flow pattern through the heart and great vessels with a high-speed scintillation camera. In this regard, the technic is analogous to contrast angiography (Fig. 3). The second is selectively identifying normal or abnormal tissues with diffusible radiopharmaceuticals. Thus, ^{43}K distributes in normal but not in ischemic or infarcted myocardium, whereas ^{99m}Tc-labeled pyrophosphate and other labeled substances selectively accumulate in the acutely infarcted myocardium.

Deductive Technics

These methods rely on electrocardiography with or without simultaneous waveform recordings of pulsations and heart sounds from the body surface. Conclusions about underlying pathophysiology are inferred from changes observed during stress or from

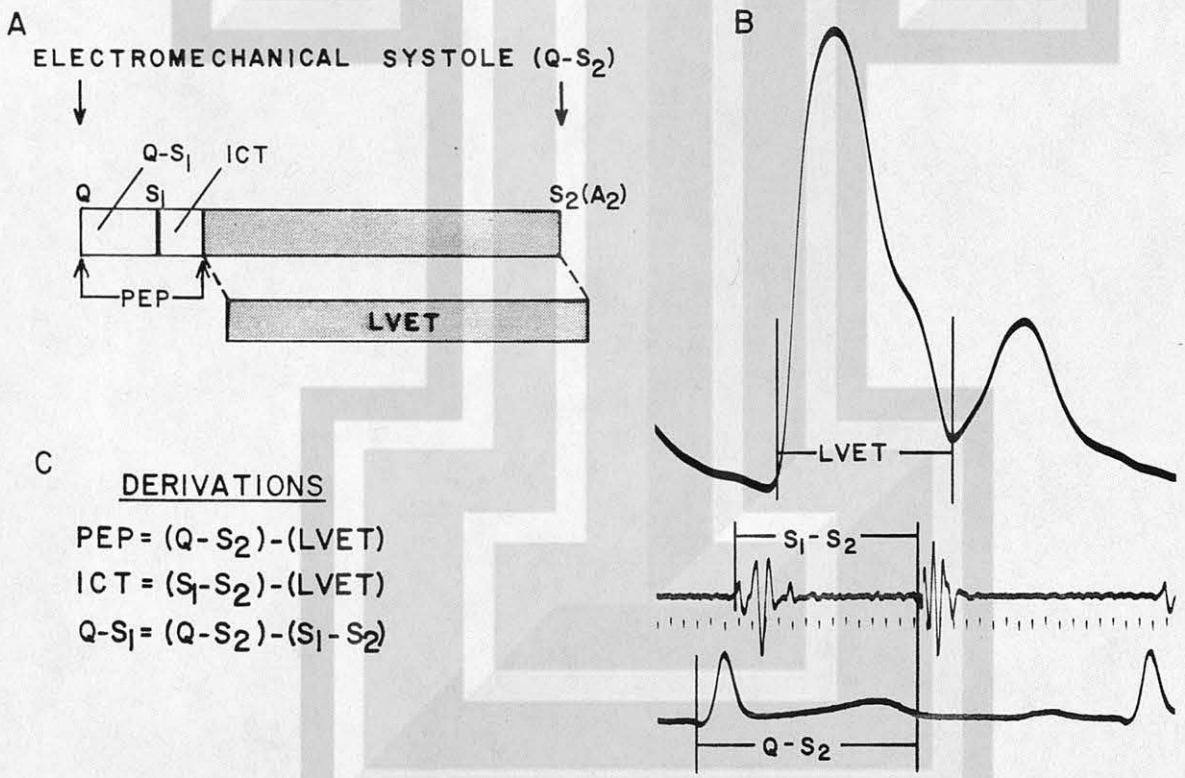

Figure 4. Schematic Drawing (A) Showing Major Intervals and Subintervals of Total Electromechanical Systole ($Q\text{-}S_2$).

LVET denotes left ventricular ejection time, PEP pre-ejection period, ICT isovolumic systole, and $Q\text{-}S_1$ Q wave to first-heart-sound interval.

B shows simultaneous carotid pulse, phonocardiogram and electrocardiogram and how intervals are measured; $S_1\text{-}S_2$ is the heart-sound interval.

C shows derivation of PEP; the PEP subintervals ICT and $Q\text{-}S_1$ are derived only if there is a well defined S_1.

measurements compared to values derived from a normal population. Although less direct than imaging technics they are in widespread use and can yield important diagnostic information about specific pathologic processes.

Exercise electrocardiography. This technic, now widely employed with graded bicycle or treadmill ergometry, permits continuous electrocardiographic monitoring during exercise as well as ready quantitation of the work load achieved. One can evaluate changes in the electrocardiographic ST segment during and after exercise. Such findings can be helpful in documenting ischemic heart disease. But there are problems in drawing conclusions from electrocardiographic ST-segment shifts.[11] The major difficulty lies in the widespread propensity to make definitive diagnostic decisions about serious coronary-artery obstructive lesions *in an individual patient* on the basis of the appearance or absence of minor (i.e., 1 mm) ST-segment depression during the test.

Exercise electrocardiography can be used to document the state of a subject's physical condition. In the absence of serious pulmonary disease, maximum exercise performance reflects maximum cardiac output. Graded exercise protocols have established endurance criteria over a wide age range for normal subjects.[12,13] The performance of patients with established heart disease can similarly be documented by exercise testing. This performance can be related to the approximate metabolic cost of common occupational and recreational activities in formulating therapeutic objectives.[14] After a base-line test, the influence of a given drug treatment, exercise rehabilitation regimen or surgical intervention can be assessed.

Exercise electrocardiography can also be used to unmask a propensity for ectopic cardiac rhythms to develop with exertion. Serious ventricular arrhythmias have been detected by this means.[15,16] However, in a large proportion of patients exercise electrocardiography will not show high-grade ventricular ectopy where prolonged tape recordings confirm their presence under other circumstances.[17] Conversely, in some patients ventricular tachycardia will be shown on exercise but not with prolonged monitoring.[17] It is not known whether there is a difference of prognostic importance in ventricular ectopy uncovered by exercise as opposed to prolonged monitoring.

Systolic-time intervals. Systolic-time intervals can be derived from a simultaneous recording of the electrocardiogram, phonocardiogram and carotid-pulse tracing. Commonly determined intervals are total electromechanical systole ($Q\text{-}S_2$), the left ventricular ejection time (LVET) and the pre-ejection period (PEP) (Fig. 4). The $Q\text{-}S_2$ interval is measured from the initial Q wave in the electrocardiogram to the first high-frequency component of the aortic second sound. LVET is taken from the initial rapid rise of the carotid upstroke to the trough of the incisura. PEP is derived from $Q\text{-}S_2$ and LVET by subtraction, thus compensating for the transmission time of the carotid pulse. These intervals are inversely related to heart rate. Regression equations have been derived from large groups of normal subjects, allowing comparison of a patient's intervals to predicted normal values at the same heart rate. Since LVET is the duration that the aortic valve is open, it also relates directly to stroke volume.[18] PEP is the sum of electrical and mechanical events that precede aortic-valve opening. In the presence of normal left ventricular conduction PEP relates inversely to the rate of rise of left ventricular pressure (dp/dt).[19] A short LVET with a prolonged PEP is often seen in congestive heart failure and suggests the low stroke volume and slower dp/dt that commonly accompany this state.

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CLINICAL APPLICATIONS

Coronary-Artery Disease

Acute myocardial infarction. One of the striking developments in the past two years has been the ability to identify acutely infarcted myocardium with radiopharmaceuticals. Using ^{99m}Tc stannous pyrophosphate, Bonte, Parkey et al. have shown a high correlation between acute myocardial infarction confirmed by electrocardiography and enzyme studies and the appearance of a radioisotopic "hot spot" in the heart within five days after the acute event.[20,21] Canine experiments involving coronary-artery ligation indicate that radiopharmaceuticals of this class accumulate in ischemic regions as well as infarcted areas after a threshold reduction in coronary blood flow is reached. An inverse relation exists between accumulation and the reduction of coronary blood flow.[22] Using a somewhat different technic Buja, Parkey et al. showed that the radionuclide is taken up in irreversibly injured cells on the edge of the infarct, presumably by being complexed with mitochondrial calcium deposits.[10] Other radiopharmaceuticals labeled with ^{99m}Tc have also been demonstrated to localize in acutely infarcted myocardium. With ^{99m}Tc tetracycline, Holman, Lesch and their co-workers showed an excellent correlation of positive and negative scans with the presence or absence of documented myocardial infarction. These investigators found peak activity within the heart one to three days after the clinical onset of chest pain. Moreover, the scintigraphic size of the infarct correlated grossly with maximum creatine phosphokinase activity in 16 patients.[23] A disadvantage of this agent is that it requires a 24-hour delay before imaging.

^{99m}Tc stannous pyrophosphate has been widely used as an agent to detect acute transmural as well as subendocardial myocardial infarction.[24] In one report of a series of 202 patients, equally divided between those with and those without acute infarction, scan results correlated with electrocardiographic and enzymatic data in over 90 per cent of cases.[25] Preliminary reports from several centers suggest that a similarly high success rate may not be universally achieved.[26] Discrepancies may in part be due to variation in rigidity and in uniformity of criteria in interpreting scintiscans. Although this approach appears to be valuable for the recognition of acute myocardial infarction, more experience is needed to reach consensus about its sensitivity and specificity.

The majority of patients with acute myocardial infarctions do not present diagnostic problems. Thus, imaging infarcted myocardium is not pertinent to the current management of most patients with this illness. However, in certain circumstances this technic may be extremely helpful in recognition of damaged myocardium — for example, after coronary-artery bypass operations (Fig. 5). In this setting acute myocardial infarction has been reported to vary between 5 and 40 per cent.[27] Under such circumstances, in a setting in which electrocardiographic ST-segment and T-wave changes and routine serum enzymes can yield confusing results, the development of a diagnostic "hot spot" appears to offer additional evidence of myocardial damage.[28-30] This imaging technic may also prove helpful in diagnosis of recurrent infarction in patients with pre-existing Q-wave abnormalities. Similarly, in patients who are comatose or confused (e.g., from trauma or alcoholism) and have nonspecific electrocardiographic abnormalities and enzyme rises for reasons other than acute infarction, a negative scan will help to clarify an otherwise equivocal diagnostic situation.

The ability to radiolabel the infarcted myocardium is a procedure qualitatively different from the traditional approaches of recognizing myocardial infarction in the living patient. In addition, this method affords the opportunity to quantify the amount of myocardium injured.[23,31-33] Therapeutic limitation of myocardial-infarct size is currently under investigation by other noninvasive studies such as serial creatine phosphokinase determinations and ST-segment map-

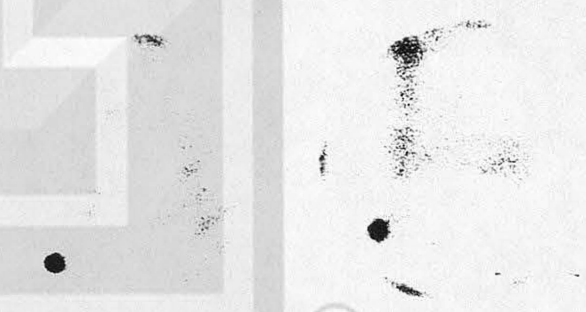

Figure 5. Left Anterior Oblique ^{99m}Tc Sn Pyrophosphate Scintiscans before (Left) and after (Right) Cardiac Operation on a Patient in Whom a Postoperative Myocardial Infarction Developed.

The accumulation of radioactivity in the image after operation occurred concomitantly with appreciable new Q waves in the electrocardiogram.

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ping,[34-36] since in-hospital survival of acute myocardial infarction in the majority of patients appears to be related to the amount of myocardium damaged.[37,38] Whether or not radionuclide quantitation of myocardial-infarct size will yield additional helpful information for a complex problem for which there are many potential and some hazardous interventions will be the subject of intense clinical study over the next few years.

Angina pectoris. Diagnosing clinically important coronary-artery disease in patients who have recurrent chest pain is considerably more difficult than recognizing acute myocardial infarctions. The high correlation of the syndrome of "classic" angina pectoris with angiographically demonstrable obstructive coronary-artery disease leaves little room for improvement by noninvasive diagnostic tests.[39,40] However, a large number of patients have recurrent chest pain with one or more atypical features[39]; in this group it is often difficult to establish a diagnosis of ischemic heart disease on objective noninvasive grounds.

Over the past five years, there has been renewed and increasing interest in exercise testing, particularly the use of graded-stress protocols on the bicycle or treadmill to diagnose ischemic heart disease. The diagnosis is usually based on the appearance of 1 mm or more of ischemic (horizontal or downsloping) ST-segment depression during or immediately after exercise.[41] Exercise-induced ischemic electrocardiographic changes are clearly useful in identifying patient populations at increased risk of subsequent angina pectoris or acute myocardial infarction.[42] The ability of exercise testing to establish the presence of coronary-artery disease in an individual patient has been less striking.[43] As the degree of exercise-induced ST-segment depression increases to 2.0 mm or more, the test becomes more specific but simultaneously less sensitive.[44] A number of reports correlating the results of exercise testing with coronary angiographic studies have attributed widely variable sensitivities and specificities to the procedure.[43,45-51] The disparities appear to stem in part from the nature of the groups studied. Thus, in asymptomatic patients selected for angiography on the basis of a positive exercise test specificity is considerably lower than in patients with classic angina studied similarly.[43,47]

Positive exercise tests will commonly lead to coronary angiography. If angiography shows high-grade obstructive coronary lesions — i.e., the exercise test was "truly positive" — appropriate medical or surgical management can be advised with an accurate knowledge of underlying pathologic anatomy. If normal coronary arteries are demonstrated — i.e., the test was "falsely positive" — the patient can be reassured of a normal coronary circulation — a finding that is correlated with an extremely low incidence of coronary disorders in the ensuing five years.[52,53] More disturbing are reports of false-negative tests in more than one half to two thirds of patients with high-grade angiographically demonstrated obstructive coronary lesions.[43,51] Excessive reliance on an exercise test that fails to show ischemic ST-segment depression is fraught with the risk of misdiagnosis and inappropriate management. As a consequence, some have seriously questioned the diagnostic application of exercise testing to the clinical problem of detecting coronary-artery disease.[43] Suffice it to say that the procedure of exercise testing in search of ischemic ST-segment depression is as yet an imperfect method for a large number of patients, particularly in view of the overall prevalence of coronary-artery disease.

Studies by Zaret and his co-workers, using ^{43}K, have suggested that clinically important coronary-artery disease can be detected with radiopharmaceuticals.[54,55] Potassium is the chief intracellular cation in the body. The potassium in healthy cells exchanges readily with its radionuclide analogues. Since the heart is an organ of high cell density in the mid-chest ^{43}K will accumulate in high concentration in normally perfused myocardial cells. A homogeneous myocardial scintigram will result. By injecting this radionuclide during exercise into patients with angina pectoris, Zaret and his co-workers have shown the failure of uptake in areas of the heart supplied by coronary arteries with high-grade obstruction. Presumably, under ischemic conditions, less radionuclide is available to poorly perfused cells or the sodium-potassium pump fails. A resulting "cold spot" appears on the myocardial scintigram. Thus, the ability to localize and define ischemic areas of myocardium on the basis of failure of uptake of a radiolabel in compromised muscle has been demonstrated. The method has considerable appeal because of its ability to detect and theoretically to quantify ischemic areas of myocardium.

It should be emphasized that a "cold spot" can result from a myocardial infarct as well as from acute ischemia. The heart with a previous scar from infarction will show a "cold spot" at rest; in contrast, ischemia is demonstrated by a normal perfusion scintiscan at rest and the appearance of a "cold spot" after exercise.

Owing to its high-energy characteristics (619 KeV), ^{43}K is a difficult radionuclide to collimate. Presumably for this reason, some groups have been unable to confirm the original observations of Zaret and his coworkers in localizing ischemic zones with ^{43}K.[56] However, results similar to those of Zaret et al. have been reported with another Group 1 radionuclide, ^{81}Rb, which, like potasium, is actively pumped intracellularly. Using ^{81}Rb and postexercise scintigraphy in 33 patients with obstructive coronary lesions, Berman and his colleagues[57] detected ventricular ischemia in 29 (88 per cent) whereas stress electrocardiography was positive in 19 (58 per cent). More recently, ^{201}Tl, another potassium analogue, has been introduced and has rapidly gained acceptance in imaging of ischemic myocardium.[58-61] ^{201}Tl has suitable half-life and energy characteristics for collimation (see Table 1). Preliminary evidence indicates that ^{201}Tl imaging is highly reproducible and may be superior to exercise

electrocardiography in detecting coronary-artery disease.[62-66]

The ability to recognize a threatened myocardial-cell population with a lack of radiolabel or a "cold spot" promises to be a future alternative or supplemental method to measuring ST-segment shifts in the electrocardiogram and should prove helpful in diagnosis of coronary disease with a negative exercise test. Pending further validation and more widespread acceptance of exercise scintigraphy, in patients with a history of "classic" angina pectoris, an electrocardiographic exercise test that fails to show ischemic ST-segment depression must be regarded with skepticism.

Valvular Heart Disease

In contrast to coronary disease, in which normal results on physical examination of the heart are commonplace, the identification of murmurs usually suggests the presence of a valvular heart disorder, whereas the absence of murmurs makes clinically important valvular disease unlikely. Murmurs may be inaudible in the presence of advanced heart failure; on rare occasions the murmur of mitral stenosis is "silent." Nuclear technics have not been as helpful as echocardiography or phonocardiography and pulse recordings for producing objective evidence of the presence and severity of a specific valvular disorder. Echocardiography can be particularly helpful in recognition of valvular heart disease in those circumstances when murmurs are not prominent.

An echocardiogram showing normal mitral-valve action is shown in Figure 6*A*. In early diastole, when there is normal mitral flow, the leaflets separate widely and rapidly from their position of systolic coaptation. The leaflets partially reapproximate after rapid ventricular filling and are definitely reseparated by atrial systole. Complete closure ensues with the next systole, during which the leaflets remain together, showing no major motion toward or away from the chest wall. Objective confirmation by the echocardiographic technic of the presence of mitral stenosis can usually be made with a specificity that approaches 100 per cent. The echocardiographic pattern of the abnormal mitral motion in mitral stenosis is shown in Figure 6*B*. The intense echoes from the mitral leaflets indicate increased acoustic impedance consistent with thickening or calcification (or both) of the valve. Since mitral stenosis involves leaflet fusion there is poor diastolic separation. The anterior leaflet of the valve, which is usually larger than the posterior leaflet, tends to hold the posterior leaflet parallel to its diminished

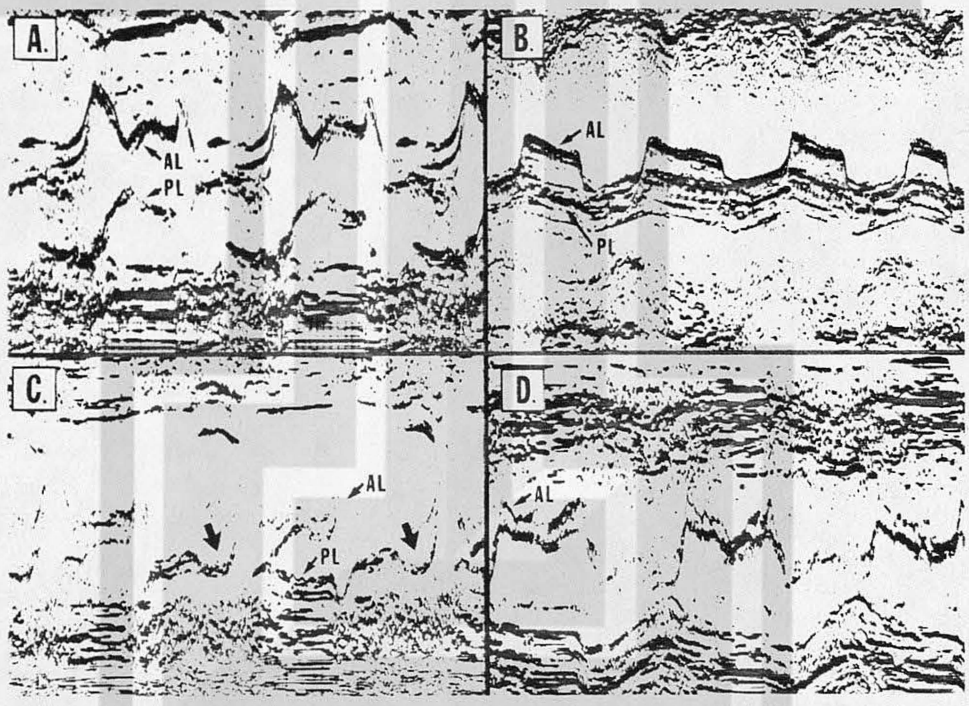

Figure 6. Echocardiograms.

Panel A shows normal mitral motion. The anterior leaflet (AL) moves anteriorly in diastole, then floats partially closed and is reopened by atrial systole. The result is "M"-shaped pattern. The posterior leaflet (PL) shows an opposite shallow "W"-shaped motion.

In B (mitral stenosis) the anterior leaflet (AL) is thickened and has diminished excursions. The posterior leaflet (PL) is thickened and its motion parallels the anterior leaflet during diastole when both leaflets are separated.

In C (mitral prolapse) there is sudden posterior buckling of the mitral leaflets (AL and PL) during late systole (heavy arrows).

In D (aortic regurgitation) there is high-frequency diastolic vibration of the anterior mitral leaflet (AL) during diastole.

anterior diastolic excursion. Although parallel anterior diastolic motion of the anterior and posterior leaflets of the mitral valve is not present in the echocardiogram in every case of mitral stenosis, more than 90 per cent of patients with mitral stenosis have this particular finding.[67-69]

Although the presence of mitral stenosis is confirmed relatively easily by echocardiography, its severity is difficult to determine by the single-beam technic. There have been no published prospective series evaluating the accuracy with which the severity of mitral stenosis can be graded by M-mode scans. The considerable variability of measurements of anterior-leaflet motion — particularly the initial rate of diastolic closure (EF slope) — relating to severity[70] has recently been reaffirmed.[71] With the single-beam technic, maximal diastolic leaflet separation has been correlated with mitral-valve area determined at heart catheterization with an r value of 0.81.[72] Imaging of leaflet separation, however, is critically dependent on the echo-beam path. In an individual study, separation can vary from beat to beat (Fig. 6*B*). As a result, predicting valve area from leaflet separation by means of single-beam studies is unlikely to be consistently rewarding.

Using a mechanical sector scanner in the transverse position, Henry et al. have shown that it is possible to image the mitral orifice directly.[73] The correlation coefficient of the echo-image area with the surgically determined mitral-valve area was 0.92. In 12 of 14 patients the echo-orifice area was within 0.3 cm^2 of the valve area measured at operation. This approach has considerable promise in accurately predicting the severity of mitral stenosis by noninvasive means, and further confirmation of the validity of these observations appears to be forthcoming.[74]

Mitral regurgitation may or may not be directly recognized from the echocardiographic pattern of mitral-leaflet motion, depending on the specific form of regurgitation present. The severity of regurgitation is usually inferred from combined left atrial and left ventricular dilatation[75] in the presence of normal or exaggerated left-ventricular-wall motion. Echocardiography has provided excellent evidence of late systolic prolapse of either or both mitral leaflets in the click-murmur syndrome as well as showing flail leaflets in cases of ruptured chordae.[76-80] The finding of late systolic posterior buckling of mitral leaflets appears to be more specifically indicative of prolapse than a pansystolic "hammock-like" posterior movement of the valve (Fig. 6*C*). The latter pattern may be artifactually produced by inferior transducer angulation.[81] Echocardiography, however, has shown that mitral prolapse is more prevalent than has previously been appreciated. Ninety-one per cent of a series of 35 patients with Marfan's syndrome[82] had findings consistent with mitral prolapse,[83] as did 6.3 per cent of a series of 1169 healthy young women. The prognostic value of echocardiographically demonstrated mitral prolapse in otherwise healthy persons remains to be established. Hence, in the absence of other substantiating data the physician should have considerable reservations in equating this finding with important heart disease.

Echocardiography is also helpful in defining the presence of other left-sided cardiac valvular lesions. Two of the three aortic cusps are normally seen separating widely, with a "box-like" motion within the aortic root as it is thrust anteriorly with each systole (Fig. 7*A*). The third cusp is usually not seen since its motion lies perpendicular to the echo beam. Dense additional echoes within the aortic root in the area of the aortic leaflets suggest sclerosis or calcification of the valve and hence favor the presence of aortic stenosis (Fig. 7*B*); however, its severity cannot be determined from this finding alone.[84,85] The additional presence of concentric left ventricular hypertrophy, however, strongly favors a severe degree of obstruction at the aortic valve.[86] Cross-sectional echocardiography appears to offer further aid in establishing the severity of aortic stenosis. Weyman et al. were able to separate 28 consecutive patients with varying degrees of aortic obstruction proved at cardiac catheterization into mild, moderate and severe subgroups, on the basis of aortic-valve diameters derived from cross-sectional images of the valve orifice.[87] The additional value of cross-sectional echocardiography in predicting aortic-orifice area awaits confirmation from other centers. Confirmatory observations are likely to be forthcoming as the imaging with cross-sectional instruments is technically improved and experience with this technic increases.

Simultaneous pulse tracings and phonocardiography can provide objective confirmation of severe aortic stenosis. In the absence of heart failure, the left ventricular ejection time is usually prolonged, the carotid upstroke slowed, and the peak of the basal ejection murmur delayed.[88-90] Bonner, Sacks and Tavel reported the combination of the above three findings to be 96 per cent specific for the presence of severe aortic stenosis.[89] However, although the presence of one of these three findings is usually indicative of severe stenosis, their complete absence does not exclude severe aortic obstruction. Older patients with heart failure can have an unremarkable carotid upstroke, a normal ejection time and an unsustained murmur.

Aortic regurgitation can also be recognized with echocardiography, but severity must once again be inferred from associated findings. High-frequency diastolic vibration of the anterior mitral leaflet is commonly present in all degrees of aortic regurgitation[91] (Fig. 6*D*). In acute, severe aortic regurgitation, early coaptation of the anterior and posterior mitral leaflets indicating premature mitral closure is a highly reliable sign of wide-open regurgitation.[92,93] Acute, severe regurgitation is not the most common form of aortic insufficiency encountered clinically, and hence the sign is of limited value. In chronic aortic regurgitation, the amount of left ventricular dilatation determined from the left ventricular internal diastolic dimension provides an index to the severity of the regurgitant lesion.[94]

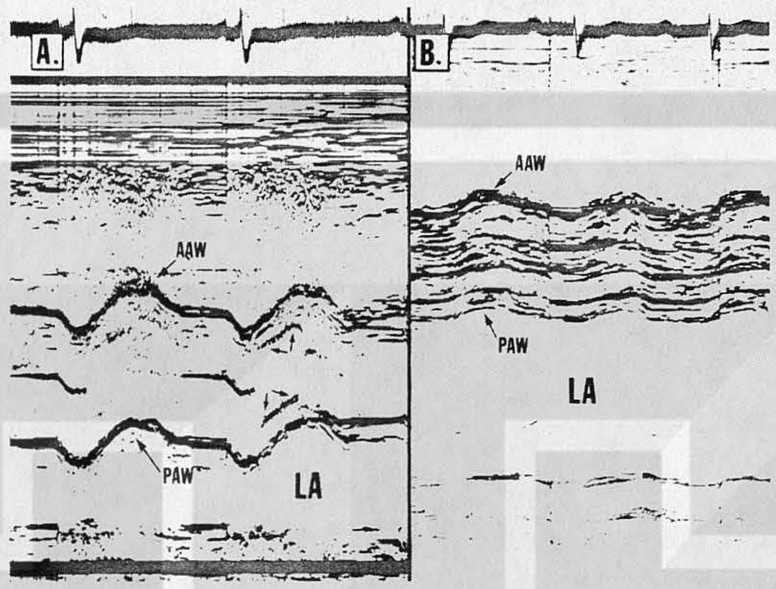

Figure 7. Echocardiograms.

Panel A is a normal aortic root (A), demonstrating "box-shape" opening of aortic leaflets (arrows) as the root is thrust anteriorly in systole.

The anterior aortic wall (AAW) and posterior wall (PAW) are labeled in systole. LA denotes left atrium.

In B (aortic root from a patient with severe aortic stenosis) dense parallel echoes are present between the aortic walls, and leaflets could not be visualized.

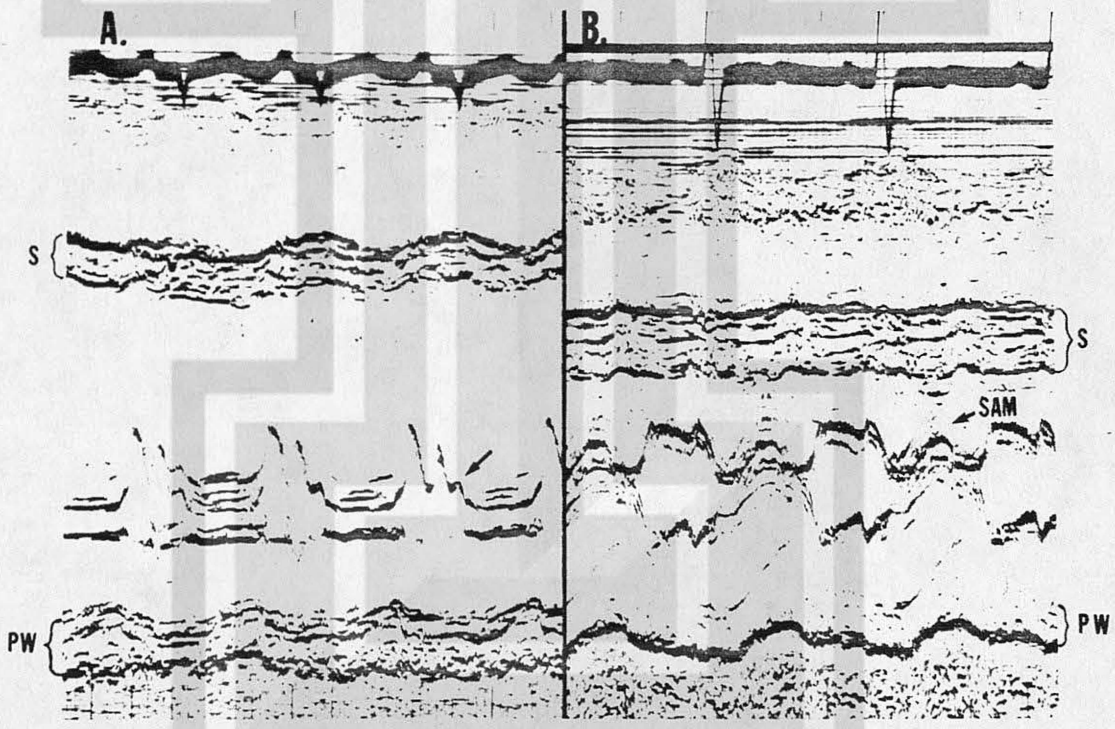

Figure 8. Echocardiograms.

Panel A shows congestive cardiopathy. The left ventricle is large, and the distance from the septum (S) to the anterior mitral leaflet is increased. Both the septum and the posterior wall (PW) show poor motion. The presystolic notch in the mitral motion (arrow) is thought to indicate a high left ventricular end-diastolic pressure.

In B (hypertrophic subaortic stenosis), in contrast to A, the left ventricular cavity is not dilated. The septum (S) is disproportionately thickened as compared to the posterior wall (PW) and has poor motion. There is systolic anterior motion (SAM) of the anterior mitral leaflet, which approximates the septum in midsystole.

Cardiomyopathy

Echocardiography is particularly useful in evaluating cardiomegaly. In full-blown form congestive cardiopathies present a stereotyped pattern of left ventricular dilatation associated with poor motion of both the interventricular septum and the left ventricular posterior wall. With chamber dilatation the distance from septum to the anterior leaflet is increased, and the mitral apparatus becomes eccentrically located in the oversized ventricle.[95] Concomitantly, the posterior mitral leaflet is more readily distinguished than in normal hearts. A secondary notch in mitral motion immediately before the valve closure point is often present and is thought to indicate a high left ventricular end-diastolic pressure[96] (Fig. 8*A*). Severe congestive cardiopathies present some of the largest left ventricular internal dimensions recorded by echocardiography. Cases of coronary-artery disease in which there have been multiple infarctions, or advanced cases of hypertensive heart disease with heart failure, can present a similar echocardiographic pattern,[97] but these conditions will quickly be recognized from other, associated clinical findings.

Echocardiography has been particularly useful in the recognition of the obstructive form of idiopathic hypertrophic subaortic stenosis, in which the systolic anterior motion of the anterior mitral leaflet apposing an hypertrophied ventricular septum has been considered pathognomonic[98-100] (Fig. 8*B*). The proximity of the anterior mitral leaflet to the interventricular septum in early systole also distinguishes most patients with the obstructive from those with the nonobstructive form of the disease.[101] Echocardiography has allowed a further appreciation of the spectrum of this disease since it has been shown that many relatives of patients with the obstructive form of idiopathic hypertrophic stenosis have asymmetric septal hypertrophy.[102] It has been claimed that asymmetric septal hypertrophy may be the fundamental pathologic abnormality in both obstructive and nonobstructive forms of the disease.[103,104] This anatomic abnormality is also accompanied by functional asymmetry since the septum is hypodynamic and the posterior wall shows excessively rapid motion.[105] More importantly, this lesion, which can be confused with mitral regurgitation, ventricular septal defect or even aortic stenosis, can objectively be defined without the need of cardiac catheterization. At present, it would be reasonable to avoid cardiac catheterization for diagnostic purposes in patients with unequivocal echocardiographic evidence of idiopathic hypertrophic subaortic stenosis unless such cases prove refractory to medical management.

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any greater value than clinical impressions. Although recognizing the lack of definitive data, we believe there is an inconsistency in the networks' attitude, which questions the effect of television violence while championing the impact of television advertising.

Our basic premise in approaching the networks was — and is — that the burden of proof that violence on television does no real harm lies with those who introduce such a potent force into the societal brew. We obviously reflect the current responsibility placed on the medical profession when it is introducing new modes of therapy. Some of the network representatives found this approach to a social issue unfamiliar and irritating. They instead reflected the approach of criminal law, which insists that innocence exists until proof to the contrary is established.

Although we were impressed with the concern and effort currently expended by the networks in evaluating the impact of television violence, we also believe that profit is one of the most important factors, if not the most important, in determining program policy. Therefore, public pressure that would have an effect on advertising and network pocketbooks, directly as in boycott movements, or indirectly in terms of concern for image, seems to offer the most effective way to influence program content. We believe that both the sponsors and the networks are currently sensitive to the "violence problem," and will be responsive to intelligent efforts directed to their consciences and coffers. However, we also believe that continuing public pressure is absolutely essential in maintaining such responsiveness.

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MEDICAL PROGRESS

NONINVASIVE CARDIAC DIAGNOSIS (Third of Three Parts)

Alfred F. Parisi, M.D., Donald E. Tow, M.D., W. Robert Felix, Jr., M.D., and Arthur A. Sasahara, M.D.

Assessment of Ventricular Function

A number of noninvasive technics have been advocated as reflecting left ventricular performance. These methods include systolic-time intervals, echocardiography and imaging of the left ventricular chamber with radionuclides during systole and diastole.

The determination of systolic-time intervals is noninvasive, extremely rapid and simple.[106,107] A long preejection period with an accompanying short left ventricular ejection time is typically associated with a low ejection fraction and heart failure. In some circumstances, such as edematous states, the intervals have proved helpful in distinguishing the heart failure of cardiomyopathy from constrictive pericarditis.[108] The latter condition is usually associated with normal systolic-time intervals.

Systolic-time intervals, however, have not achieved widespread popularity for the assessment of ventricular function. The technic has been extensively evaluated in patients with acute myocardial infarctions[109-111] with the expectation of predicting clinical deterioration — particularly severe heart failure and shock — in this setting. In patients with acute infarction, however, the hemodynamic variables upon which the pre-ejection period and left ventricular ejection time depend can rapidly change in opposite directions in a manner that offsets the ability of the intervals to relate to any single hemodynamic measurement. The net result is that systolic-time intervals, taken by themselves, are not useful in managing or predicting the outcome of patients with acute myocardial infarction. In addition, since the 1968 study of Garrard, Weissler and Dodge, there has been little confirmation of the diagnostic accuracy of systolic-time intervals for predicting ventricular function in large groups of patients with chronic coronary disease.[112] The technic also is further limited by its dependence on normal intraventricular conduction as well as normal sinus rhythm.[113]

Several studies have shown echocardiographic measurements to correlate with ventricular volumes and ejection fraction.[114-116] However, this approach in predicting ventricular function in individual patients, derived from approximately transverse diastolic and systolic measurements of the left ventricle, has been open to criticism.[117] In particular, coronary-artery disease often involves localized disorders of left ventricular contraction that can alter systolic chamber dimensions in either direction, depending on whether or not a hypocontractile or hypercontractile area of the ventricle is traversed by the echocardiographic beam. As a result the correlation of echocardiographic and angiographic ventricular volumes in coronary disease is poor when left ventricular asynergy is present.[118]

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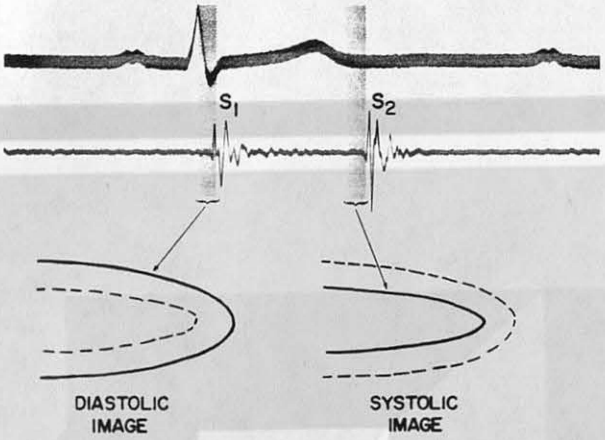

Figure 9. Schematic Illustration of the Technic of Gating.
The images of diastole and systole are integrated over several cardiac cycles. As indicated by the shaded bars the electrocardiographic QRS complex is used to time the formation of diastolic images while systolic imaging is accomplished immediately before S_2.

When abnormalities of anterior or anterolateral wall motion (which are not traversed by the echocardiographic beam) exist, echocardiographic ejection fractions are often overestimated.[117,120] Despite current limitations, however, the echocardiographic approach has potential for overall rapid noninvasive assessment of left ventricular function. The results of recent studies of Teichholz et al., which accurately predicted ejection fractions by using the B-scan technic, indicate that a fuller image of the left ventricle is likely to have more reliable information than can be obtained by conventional M-mode technics.[121] With the development of multiscan and sector-scan approaches to the left ventricle, echocardiography may indeed prove to be the most practical, rapid means of assessing left ventricular function in the future.[122,123]

Radionuclide evaluation of left ventricular function by means of the gamma camera and gating currently appears to be the most reliable noninvasive means of approximating angiographic evaluation of left ventricular performance. Several independent studies have shown correlation coefficients of 0.9 or better when ejection fractions determined by radionuclides are compared to angiographic ejection fractions.[124-127] In these studies, images of the left ventricle during systole and during diastole are separately obtained after intravenous injection of a labeled intravascular substance such as ^{99m}Tc albumin. The build-up of the images involves electronic switching of the gamma camera controlled by electrocardiographic or phonocardiographic monitoring of the heartbeat. Thus, radioactivity only during systole or diastole is recorded. This method is commonly known as gating (Fig. 9). The images obtained represent composites of many beats. Ejection fraction is calculated from the systolic and diastolic images by planimetry or computer data processing.

More recently, assessment of left ventricular function by the first radionuclide transit through the heart has been advocated (Fig. 10). This purpose is achieved with a high-speed scintillation camera coupled to a computer system.[128,129] The resulting images are reported to be superior in both spatial and temporal resolution to those obtained by the gating method.[130] Insufficient reports are available at present for a critical evaluation of this first-pass approach.

Radionuclide imaging of the left ventricle can also be used to evaluate regional left ventricular function. Abnormally contracting segments can be detected by this means, providing an important clue to the likeli-

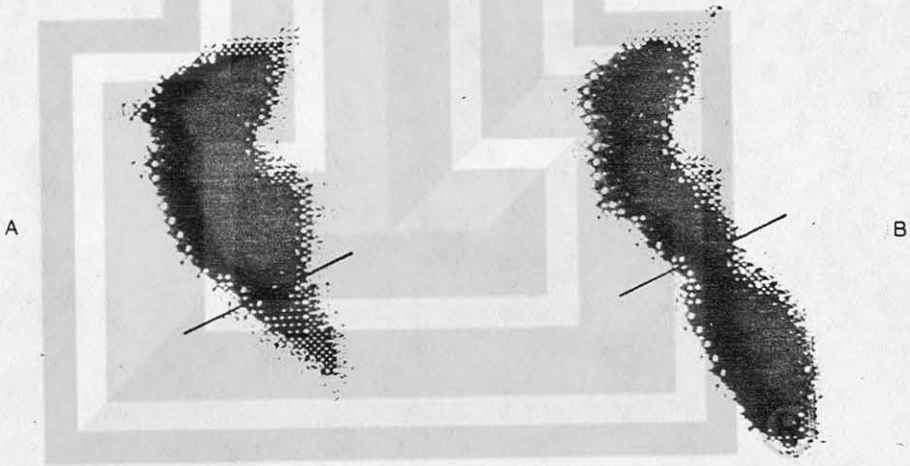

Figure 10. ^{99m}Tc Scintiscans from First Pass of Radionuclide through the Left Ventricle in Left Anterior Oblique View Obtained with a Multicrystal Gamma Camera.
The systolic (left) and diastolic (right) outlines of the left ventricle can be seen below the plane of the aortic valve (solid line).

hood of coronary-artery disease.[131] Because resolution is not ideal, the method is less sensitive for this purpose than for evaluating overall ventricular function. However, this approach appears to be the best noninvasive means of recognizing ventricular aneurysms, to which the chest roentgenogram, electrocardiogram and echcardiogram are relatively insensitive.[132]

The imaging achieved with radionuclides, at present, can by no means be compared to the more detailed information obtainable by angiocardiographic evaluation of the left ventricle. In particular, the margins of the left ventricular cavity and areas of transition between poorly functioning and normally functioning segments of ventricular myocardium are poorly resolved. To those versed in the traditional angiographic evaluation of left ventricular performance, radionuclide evaluation of left ventricular contractility remains suboptimal. However, this method appears reasonable in its ability to distinguish patients with grossly poor ventricular function (ejection fraction less than 25 per cent) from those with fair or good overall ventricular function. Furthermore, preoperative assessment of left ventricular performance is a meaningful index of the likelihood of surviving coronary-artery operation.[27,133-135] In view of the increasing readiness with which coronary angiography and bypass are pursued to relieve angina pectoris, initial evaluation of patients' ventricular performance by the radionuclide approach is useful. For those who have clearly poor ventricular function, it would be reasonable to defer considerations of angiography and operation until the results of intensive trial of medical therapy are known.

Congenital Heart Disease

Both nuclear technics and echocardiography are used routinely to detect a large number of congenital heart lesions. Nuclear approaches are particularly useful in detecting the presence, direction and magnitude of intracardiac shunts. Echocardiography offers the advantage of further resolution within the heart. Thus, the relation of each of the ventricular chambers to the great vessels and the details of valve action can be imaged.

Historically, nuclear technics have been used successfully in a manner analogous to indicator-dilution ("green-dye") curves for the detection of intracardiac shunts. A radionuclide, which remains within the vascular system, such as ^{99m}Tc albumin, is injected intravenously in one limb while a single probe to detect its passage through the arterial system is placed over another limb. The early appearance of radioactivity in a detector situated over a systemic artery would indicate shortened transit that bypassed the pulmonary bed and, hence, the presence of a right-to-left shunt. Many prefer to use substances completely excreted or trapped by the lung for this purpose such as radioactive krypton or macroaggregated albumin.[136,137] In these cases more than 1 per cent of the injected radioactive substance will appear in the systemic circulation only if there is a reversal of flow from a right-sided to a left-sided cardiac chamber. If ^{99m}Tc albumin is injected intravenously and the probe is selectively placed over a right-sided cardiac chamber or the lung, initial passage as well as recirculation of the isotope can be demonstrated. Under these circumstances *early reappearance* of radioactivity suggests left-to-right shunting.[138,139]

Nuclear angiocardiograms can aid considerably in the definition of selective cardiac-chamber enlargement as well as in the recognition of complex interrelations of the great vessels and of intracardiac shunts.[140,141] This technic is particularly useful in evaluating cyanotic neonates, in whom the risk of catheterization is considerable. Although a single precordial probe monitoring the time activity curve of a peripherally injected tracer has provided much of the present knowledge, the gamma scintillation camera interfaced with a computer system has enhanced the applicability of radionuclide technics. Sequential images of flow patterns can be obtained, and, in addition, time activity curves from selected regions of the image can be displayed. As with contrast angiography, anatomic abnormalities are detected by observation of variation from the normal flow pattern through the central circulation. Analysis of the time activity curve allows quantification of flow abnormalities. In right-to-left shunts there will be early appearance of the radioactivity in the left side of the heart and the systemic circulation and less than average concentration of radioactivity in the lung. Because of early recirculation, clearance of radioactivity from the central circulation will be prolonged. Sequential imaging is characterized by early appearance of the left chambers or the aorta (or both) before the lung image reaches a maximum, and by poor delineation of the pulmonary outflow tract. In the left-to-right shunts, there is rapid transit of the tracer through the lung because of increased pulmonary blood flow, early reappearance of the tracer in the right side of the heart distal to the shunt, and prolonged clearance from all the chambers in the central circulation distal to the site of shunt owing to recirculation.[128,142-145] By computer analysis of nuclear angiocardiograms, left-to-right shunts have been detected with considerable sensitivity and quantified accurately. In a series of 105 patients, shunts involving pulmonary systemic flow ratios as low as 1.2 to 1.0 were detected; the pulmonary systemic flow ratio calculated from cardiac catheterization data agreed with the radionuclide angiographic ratio with an r value of 0.94.[146]

Echocardiography plays an important part in the diagnosis of congenital heart lesions. Since the technic delineates anatomic continuity of intracardiac structures, the relations of the great vessels with the ventricular chambers can be determined. Atrial septal defects are often suspected from detection of an enlarged right ventricular internal dimension. Occasionally, ventricular septal defects are detected directly. As in adults, valvular dysfunction has been recognized by characteristic motion abnormalities.

In tetralogy of Fallot an enlarged aorta over-rides the right ventricular outflow tract. As the echocardiographic beam is directed superiorly, this over-riding is detected as septal-aortic discontinuity — i.e., the anterior aortic wall is misaligned, lying in front of rather than in the plane of the interventricular septum. A thickened anterior right ventricular wall and septum often suggest accompanying right ventricular hypertrophy.[3,147] Ventricular septal defects are directly detected by the absence of echoes from the upper interventricular septum. As a rule, only large defects are detected; the diverging tendency of ultrasound waves and the anatomic position of small defects in relation to transducer position on the chest wall make detection difficult. Ventricular septal defects are most often demonstrated accompanying tetralogy of Fallot.[1,3,148]

Many valvular lesions in children have echocardiographic features analogous to those found in adults. Aortic stenosis is somewhat more difficult to recognize because the leaflets rarely calcify in children. Valvular atresia — e.g., of the tricuspid and pulmonic valves — is characterized by absence of characteristic motion from these structures. An experienced pediatric echocardiographer must make a considerable effort before accepting these diagnoses. Other valvular abnormalities peculiar to childhood such as Ebstein's anomaly and endocardial-cushion defects also have typical echocardiographic features. To date, over 30 distinct congenital abnormalities detected by echocardiography have been reported.[149]

In an adult population the congenital lesion that most often passes unnoticed is an atrial septal defect. Although such a lesion usually requires catherization of the right side of the heart to confirm its presence and quantify the shunt, echocardiography appears to be extremely sensitive in detecting evidence of noteworthy left-to-right shunting with this defect.[150-152] Thus, the presence of an enlarged right ventricular internal dimension should routinely raise the question of right ventricular volume overload. In the majority of cases there is associated abnormal septal motion — i.e., the septum usually shows a "paradoxic" anterior movement parallel to, rather than opposite, the left ventricular posterior wall in systole; less frequently, the septum is "flat," with no apparent motion. These findings are not specific for an atrial septal defect since they may occur with other lesions that produce right-sided volume loading such as tricuspid regurgitation and anomalous pulmonary venous connections, and occasionally are found in patients with pulmonary hypertension. However, the absence of a substantially increased right ventricular internal dimension would appear to exclude more than 90 per cent of clinically serious left-to-right shunts on the basis of an uncomplicated interatrial septal defect.[153]

Miscellaneous Problems

Both echocardiography and radionuclide technics are very useful in evaluating an enlarged cardiac silhouette. With this roentgenographic finding the presence of a pericardial effusion is a common differential diagnostic problem. Echocardiography is particularly sensitive to this condition. The separation by fluid of a nonmoving posterior pericardium from a moving adjacent epicardium can be detected with minor effusions[154,155] (Fig. 11). By routinely performing echocardiography 24 hours before cardiac operations, Horowitz et al. showed that effusions as small as 15 ml could be detected.[156] The overlap of negative and positive patterns in their group of 41 patients was small, attesting to the specificity of the method as well.

Features of cardiac tamponade have also been demonstrated by echocardiography. With inspiration there is an increased right ventricular dimension, consistent with increased filling of this chamber. Concomitantly, excursion of the anterior mitral leaflet and left ventricular dimension are diminished, indicating decreased transmitral flow.[157] These findings accord with the physical finding of a paradoxic pulse.

By radiolabeling of the intracardiac blood pool, large effusions can be inferred by contrast of the size of this blood mass to the apparent size of the cardiac silhouette. In addition, the intracardiac blood pool is widely separated from the liver.[158] Effusions have also been demonstrated by studies of ^{99m}Tc pertechnetate flow when the cardiac blood pool is widely separated from the lungs by the fluid-filled pericardium.[159] Nuclear technics, however, are less sensitive[160] and less versatile than echocardiographic technics that can be performed at the patient's bedside.

The diagnosis of left atrial myxoma was virtually impossible to establish by noninvasive means before the advent of echocardiography. Such tumors, al-

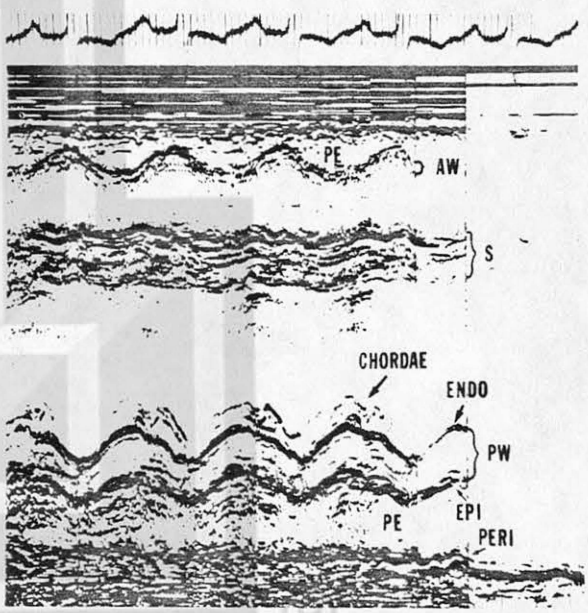

Figure 11. Pericardial Effusion.
The moving anterior (AW) and posterior (PW) heart walls are separated by pericardial effusion (PE) from the nonmoving pericardium (PERI) (S denotes interventricular septum). The endocardium (ENDO) and epicardium (EPI) of the left ventricular posterior wall are also shown.

though rare in occurrence, have been detected repeatedly by this method by a number of independent observers.[161-164] The presence of a multilayered radiodense area within the left atrium, particularly prolapsing into the mitral-valve orifice during diastole, appears to be pathognomonic for the presence of such a tumor. With appropriate attention to proper instrumental settings the false-positive detection of such a lesion by an experienced echocardiographer should be quite rare. False-negative results can occur, but their true frequency may never be known in view of the relative rarity with which this lesion is encountered. Right atrial myxomas have also been recognized particularly when prolapsing into the right ventricle.[161] Atrial myxoma has also been detected by scintiphotographic imaging.[165,166]

Dissecting aneurysm of the ascending aorta is an acute medical emergency. Recent reports have shown that the cavity of the dissecting hematoma can be delineated from the true aortic lumen by ultrasound.[167-169] However, in none of these studies has the series been large enough from a single institution to establish definitively the diagnostic accuracy of the method. Moreover, false-positive results have been reported.[170] Further evaluation will be necessary before one can be certain of the reliabilty of ultrasound as a screening technic for the presence of this lesion.

Intracardiac thrombosis such as left atrial clots in mitral stenosis and left ventricular thrombi in ventricular aneurysms and cardiopathies have also been detected by the use of ^{131}I fibrinogen as well as radiolabeled fibrinolytic agents.[171] Here once again, the reported series are too small to permit definitive statements about the clinical usefulness of such radionuclide screening technics.

Conclusions

The past decade has seen many meaningful advances in the development of diagnostically accurate noninvasive cardiovascular procedures for recognition of major problems that occur in adult medicine.

These tests should not be undertaken as a primary diagnostic step to exclude possible forms of heart disease. The physician should synthesize into a logical diagnostic formulation the information gleaned from a carefully taken history, physical examination and such routine studies as an electrocardiogram and chest roentgenogram. If this initial evaluation clearly does not indicate heart disease no further testing is necessary. If heart disease is present or suspected, the physician should request the noninvasive tests most likely to confirm his suspicions or clarify his doubts. If a surgically approachable lesion is demonstrated — as is commonly the case in valvular heart disease — and the patient's symptoms warrant, cardiac catheterization and angiography should be undertaken to provide confirmatory evidence that surgical palliation is likely to prove successful. If noninvasive testing fails to clarify potentially important symptoms angiography should also be considered to guide patient management. This course of action commonly occurs in the evaluation of relatively young adults with chest pain whose features suggest angina pectoris.

Most cases of cardiopathy, whether congestive or hypertrophic, can be readily confirmed by echocardiography. In these cases catheterization of the left side of the heart should be avoided unless one is contemplating a myectomy for the patient with obstructive hypertrophic subaortic stenosis that has proved refractory to medical management. Similarly, echocardiography and radionuclide technics are highly sensitive in detecting important left-to-right shunting in congenital heart disease. If these studies prove negative, cardiac catheterization is not necessary to exclude such shunt lesions, particularly an atrial septal defect.

Reliance on invasive tests in the future should prove to be more highly selective and directed because of recent progress in noninvasive cardiac diagnosis. As imaging technics improve, particularly for quantifying the severity of valvular heart lesions, omission of cardiac catheterization as a step toward valvular heart surgery is likely to become accepted practice.

A comparable situation does not exist for evaluation of coronary-artery lesions in anticipation of bypass. Angiography, at present, is the only accurate means of identifying normal coronary arteries and high-grade obstructive coronary lesions. However, there is considerable observer variability in reading coronary angiograms,[172] particularly when there are lesions of intermediate severity (50 to 75 per cent narrowing). In assessing lesions whose severity is questioned at angiography, myocardial scintigraphy may prove to be a helpful adjunct. Although direct noninvasive imaging of the coronary circulation is conceivable, and has even been achieved in selected patients with left-main-coronary lesions,[173] there is little prospect of its clinical implementation for a complete evaluation of the coronary-artery system in the immediate future.

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Apollo Space Crew Cardiovascular Evaluations

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HOFFLER, G. W., R. A. WOLTHUIS, and R. L. JOHNSON. *Apollo space crew cardiovascular evaluations.* Aerospace Med. 45(8):807-820, 1974.

Cardiovascular responses associated with pre- and postflight orthostatic tolerance evaluations of Apollo crewmen, primarily using lower body negative pressure (LBNP) are here summarized and presented with a brief historical overview and some interpretations and implications for future manned space flight. Heart rates were increased while systolic and pulse pressures were decreased during the immediate postflight orthostatic evaluation. A postflight elevation in resting heart rate was a less frequent finding. There was considerable variability in the magnitude of these changes between individual crewmembers and in the persistence of these changes over subsequent postflight evaluations. Postflight changes in leg volume during LBNP were equal to or less than those seen during preflight baseline evaluations. Body weight, resting calf girth, supine leg volume, and cardiothoracic ratios were all diminished immediately postflight and their return to preflight values was not complete within the postflight testing time frame. The reported changes in orthostatic tolerance and other related measurements must be interpreted with care in view of the conditions under which the data were obtained. The cardiovascular adaptation of man to the space environment and his readaptation upon return to earth have been difficult to assess within the constraints imposed by this and previous American manned space flight programs. This fact does not diminish the operational success of these earlier programs since each contributed to the ultimate achievement of landing man on the moon, allowing him to conduct important lunar explorations, and then returning again safely to earth. But a more complete understanding of the physiologic role, especially for missions of longer duration, will require a thorough analysis of the effects of the space environment, with special emphasis upon inflight evaluations, control of environmental conditions, and interrelating findings from many study disciplines.

THE APOLLO PROGRAM was designed to fulfill the specific operational goals of landing man safely on the moon, allowing him to explore the lunar surface, and returning him successfully to earth. The engineering and operational complexity of this program necessarily limited inflight physiologic studies of man to those few measurements (i.e., ECG, respiration, and oral temperature) which were considered vital to crew safety and health assessment. The bulk of physiological data on Apollo crewmembers was obtained during pre- and postflight medical evaluations. These evaluations, centered about a standard clinical examination, were augmented by more specific physiological tests which included an assessment of orthostatic tolerance with the lower body negative pressure (LBNP) technique.

Reductions in orthostatic tolerance following space flight were observed following the later flights of the Mercury Program. Tilt table tests revealed moderate orthostatic hypotension in the Mercury 9 pilot after only 34 h of orbital flight. Because of this finding, 70° upright tilt table tests for orthostatic tolerance were incorporated into routine pre- and postflight evaluations and continued throughout the Gemini Program. Results from these tests confirmed variable but consistent losses of orthostatic tolerance following flights lasting from 3 to 14 d. This was evidenced by an elevated heart rate, reduced pulse pressure, and increased pooling of fluid in the lower extremities within the early postflight period. Responses to this stress returned to normal, usually within 50 h or less after splashdown, regardless of flight duration (6,10).

The advent of the Apollo Program presented new questions and uncertainties. Fundamental differences in the Apollo spacecraft, its operational environment, and Apollo Program goals might alter physiological responses from those previously seen after Gemini flights. For example, the two-gas atmosphere and the ability to move about in the spacecraft led to speculation that returning Apollo crewmen might exhibit smaller decrements in orthostatic tolerance. On the other hand, headward acceleration ($+G_z$) incurred by crewmembers during descent to the lunar surface after 3 to 4 d of weightlessness and an ascent profile imposing nearly 1G ($+G_z$) acceleration, following one or more days in a one-sixth gravity environment, added new variables that warranted concern for crewmember well being. Additionally, it seemed reasonable to expect that the crewmen who walked on the moon might show important differences in postflight tests from their counterparts who remained in weightless flight continuously. These speculations and many other unanswered questions emphasized the urgency of understanding adaptation of the cardiovascular system to weightlessness and subsequent re-

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adaptation to earth's gravity. Obviously the former could only be inferred from physiological changes observed following space flight.

For several years prior to the first manned Apollo flight, a number of investigators had studied the cardiovascular effects of LBNP. Evaluations of its use both as a simulator of orthostatic stress (4,7,8,11,13,14) and as a countermeasure against cardiovascular deconditioning had been made (15,16). In most individuals, LBNP at levels ranging from −40 mm Hg to —60 mm Hg produced changes in heart rate and blood pressure which were quite similar to those resulting from upright tilting. While qualitatively similar to tilt responses, differences in the magnitude of cardiovascular compensatory responses induced by LBNP were also reported. Stevens and Lamb (14,17) found a greater increase in heart rate during upright tilting then during LBNP adjusted to produce the same reduction (−19%) in cardiac output. The smaller heart rate responses during LBNP were attributed in part to the absence of stimulation of carotid and other baroreceptors by gravity-induced hydrostatic pressure and flow changes. While the cardiovascular responses induced by either stress procedure depended upon displacement of blood from central blood volume reservoirs toward the lower extremities, LBNP probably produced a somewhat different pattern of pooling within the lower body than tilting. Nevertheless, it appeared that LBNP could be adjusted to produce cardiovascular responses quantitatively similar to those produced by the upright tilt.

In addition to the similarity of cardiovascular responses to LBNP and to orthostasis, certain technical considerations prompted the use of LBNP during the Apollo program. Movement of the subject was not required; instrumentation was thus not only easier to apply and maintain, but physiological signals remained more stable. Further, LBNP permitted adjustment of the stress to any desired level of magnitude with greater ease and precision than in the case of tilting. Of perhaps equal significance was the fact that, unlike tilting, LBNP could be used under weightless conditions and this early experience with Apollo crewmen could thus contribute to planning for later inflight use of LBNP during the Skylab program. LBNP testing would therefore not only assess pre- and postflight orthostatic responses of Apollo crewmen but would also furnish data of value to the interpretation of Skylab results.

The primary purpose of this report is to present the large volume of data obtained during LBNP and passive stand tests from the Apollo program, henceforth collectively referred to as orthostatic evaluations, along with associated cardiovascular measurements and other pertinent data. Many answers will be required before the entire picture of man's cardiovascular adaptation to space flight can be clarified and understood. The Apollo cardiovascular studies constitute a small but important step in the acquisition of this knowledge.

MATERIALS AND METHODS

The type and duration of each of the 11 Apollo missions are described in Table I. Total mission duration varied from 143 to 302; length of crew time in one-sixth gravity during the lunar landing missions varied from 22 to 75 h. Also shown is the type of orthostatic tolerance evaluation completed pre- and postflight. An LBNP protocol was used in conjunction with missions not encumbered by postflight quarantine restrictions. A simple, passive stand protocol was used in addition to LBNP for the crew of Apollo 9 to assess the comparability of this procedure with that of LBNP. The passive stand protocol alone was used for evaluating orthostatic tolerance on the crews of Apollo 10 and 11. Postflight quarantine operations of missions 10 through 14 precluded use of the LBNP protocol.

Major preflight medical examinations were completed on Apollo crewmen at approximately 30, 15, and 5 d (F-n days) prior to launch. Orthostatic tolerance evaluations, as an integral part of these medical examinations, provided baseline information for comparison with subsequent postflight evaluation results. These preflight orthostatic tolerance evaluations were made at the NASA-JSC Cardiovascular Laboratory, Houston, Tx, and at the Medical Operations Facility, Kennedy Space Center, Fl. Postflight orthostatic tolerance evaluations, again a part of major medical examinations, took place shortly after splashdown and at approximately 24-h intervals thereafter. The number of postflight evaluations and the time after splashdown of their performance (see

TABLE I. APOLLO MISSIONS—CHARACTERISTICS AND ORTHOSTATIC EVALUATIONS.

Apollo Mission	Type of Mission	Time to Lunar Landing, H	Length of Lunar Stay, H	Lunar Liftoff to Splash-down, H	Total Mission Duration HOURS	DAYS	Type of Orthostatic Evaluation Performed
7	earth orbital				260.1	10.8	LBNP
8	lunar orbital				147.0	6.1	LBNP
9	earth orbital				241.0	10.0	LBNP, STAND
10	lunar orbital				192.0	8.0	STAND
11	lunar landing	102.7	22.2	70.9	194.0	8.1	STAND
12	lunar landing	110.5	31.5	102.0	244.5	10.2	—
13	lunar-abort				142.9	6.0	—
14	lunar landing	108.2	33.5	74.3	216.0	9.0	—
15	lunar landing	104.7	67.0	123.6	295.0	12.3	LBNP
16	lunar landing	104.5	71.0	90.3	265.8	11.1	LBNP
17	lunar landing	110.3	75.0	116.5	301.8	12.6	LBNP

TABLE II. TIME (HOURS) FOLLOWING SPLASHDOWN FOR ORTHOSTATIC EVALUATIONS.

Apollo Mission	Crew-member	Time of Postflight Evaluations (hours following splashdown) First	Second	Third	Fourth
	CDR	3	34		
7	CMP	2	35		
	LMP	5	32		
	CDR	3	26	51	
8	CMP	4	27	53	
	LMP	5	26	52	
	CDR	2	31	53	
9	CMP	4	33	55	
	LMP	3	32	54	
	CDR	2	26		
10	CMP	3	27		
	LMP	2	28		
	CDR	6	25		
11	CMP	7	25		
	LMP	8	26		
	CDR	3	43	73	122
15	CMP	4	42	71	121
	LMP	5	44	72	137
	CDR	4	24	68	162
16	CMP	6	26	70	162
	LMP	5	25	71	162
	CDR	6	24	48	90
17	CMP	5	26	50	91
	LMP	7	25	51	91

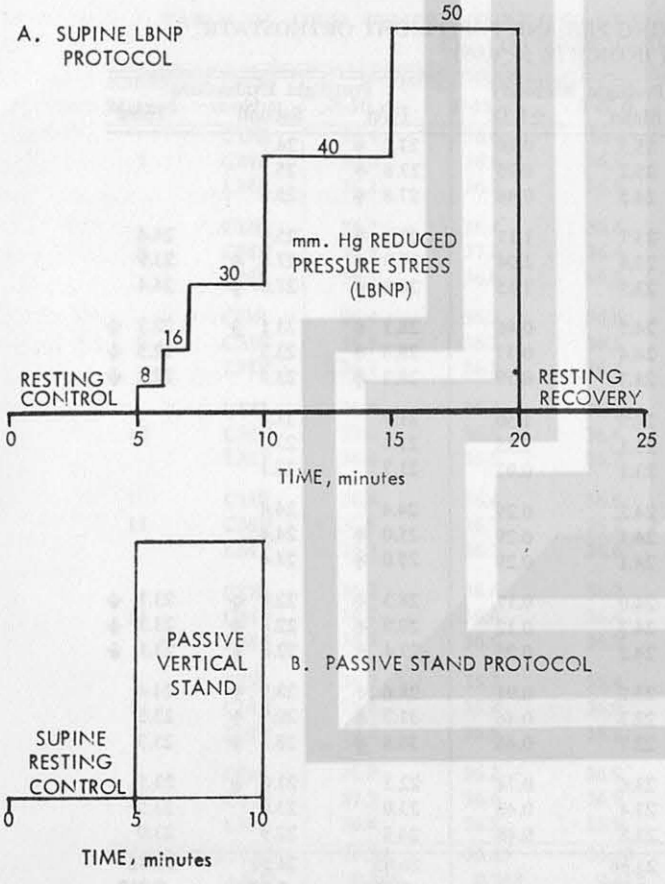

Fig. 1. Types of orthostatic stress protocol used for pre- and postflight evaluations. (A—Apollo 7-9, 15-17; B—Apollo 9-11).

Table II) were dictated in part by operational constraints and in part by the length of time it took individual crewmembers to regain their preflight status. As indicated in Table II, either two or three postflight orthostatic evaluations were completed on each crewman; a fourth evaluation on crewmembers of Apollo 15, 16, and 17 did not in every case include orthostatic stress. "Immediate" postflight evaluations took place on the recovery ship, at Kennedy Space Center or at the JSC Cardiovascular Laboratory.

In an effort to assure comparability of test conditions and operability of test equipment, several members of the attending medical support team assigned to each mission participated in pre- and postflight orthostatic evaluations identical to those used on crewmembers. These individuals, or "control" subjects, were evaluated a day or two before the indicated Apollo crew evaluation day. Data provided by these evaluations helped to assure the validity of postflight changes observed in space flight crewmembers and the operational readiness of test teams and equipment.

The protocols for the two orthostatic stress procedures are depicted in Fig. 1. The supine LBNP protocol consisted of a 5-min resting control period, 5 min each at three discrete levels of reduced pressure, and a 5-min recovery period. Beginning with Apollo 9 the first 5-min period of reduced pressure was modified to include a minute each at -8 and -16 mm Hg followed by 3 min at -30 mm Hg; these two relatively low levels of reduced pressure were used in an effort to define the responsiveness or tone of lower limb capacitance vessels. The three levels of sequentially applied reduced pressure were chosen on the basis of previous experience in this Laboratory (18). As reported, the use of an incremental LBNP protocol produces physiological responses whose magnitudes increase with each increment of reduced pressure. This protocol provided assurance that measurable, quantitative stress responses could be obtained both for the normal preflight and for the relatively ortho-

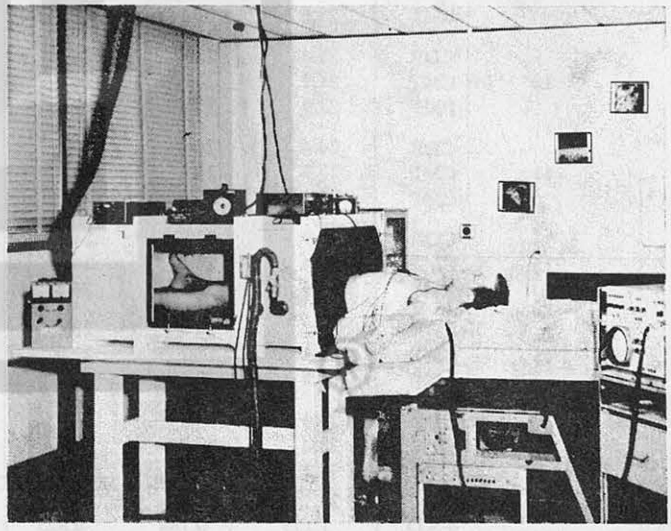

Fig. 2. LBNP device and instrumentation used in Apollo LBNP orthostatic evaluations.

statically intolerant postflight conditions.

The LBNP device is shown in Fig. 2; its construction and operation have been described elsewhere (19,20). The physiological measurements made during the LBNP protocol varied slightly from mission to mission. Measurements made in conjunction with the Apollo 7 to 9 missions included continuous axillary and sternal lead electrocardiograms (ECG), indirect blood pressure every 30 s (NASA Gemini blood pressure measuring system) (12), and changes in calf circumference by double stranded mercury-in-silastic strain gauges. For Apollo 15 to 17 evaluations the bipolar chest lead ECG was replaced with a Frank lead vectrocardiogram (VCG) which was modified slightly by placing the ground and positive Y-axis electrodes on the right and left sacral areas, respectively, rather than on the corresponding legs. Additionally, precordial heart sounds (vibrocardiogram) were recorded with a wide band capacitance microphone system (LTV, Research Center, Anaheim, Ca). For crewmen of Apollo 16 and 17, respiration rate was obtained from another mercury strain gauge attached to the lower thorax. The carotid pulse trace was recorded on crewmen of Apollo 17. Vectorcardiographic data and phonocardiographic findings, derived from the vibrocardiogram, have already been published in preliminary form (2,9).

The passive stand protocol involved a 5-min resting supine control period following by a 5-min passive stand. For the passive stand the subject leaned against a wall in a relaxed manner with his heels spaced 6 in. away from the wall. Physiological measurements made during this protocol included continuous sternal and axillary lead electrocardiograms and indirect blood pressure at 30-s intervals.

Certain accessory cardiovascular and related measurements were made in conjunction with orthostatic evaluations. Circumference of the calf at its maximum girth was measured during supine rest prior to orthostatic evaluations of crewmen of Apollo 7 to 11 and 15 to 17. On crewmen of Apollo 16 and 17, multiple measurements of leg circumference were made at discrete intervals from the ankles to the groin with subjects supine but extended legs slightly elevated. Limb volume was computed by summing sequential, circular truncated cones. Additionally, standard 6-ft. posterior/anterior chest X-rays were taken on every cerwmember at his last major preflight medical examination and first postflight evaluation. The cardiothoracic ratio was determined by standard clinical methods. Further refinement was obtained for crewmen of Apollo 16 and 17 with an ECG device used to trigger X-ray exposures at the termination of systole and diastole.* Ambient and oral tem-

*Custom designed system by Dr. R. J. Gowen, Lt. Col, USAF Academy, Co.

TABLE III. AMBIENT TEMPERATURE (°C) DURING PRE-AND POSTFLIGHT ORTHOSTATIC EVALUATIONS. (ARROWS INDICATE $p<0.05$).

Apollo Mission	Crew-member	Preflight Evaluations F-30 d	F-15 d	F-5 d	Preflight Summary Mean	±S.D.	Postflight Evaluations First	Second	Third
	CDR	26.1	24.9	25.6	25.5	0.60	27.8 ↑	24.7	
7	CMP	26.1	24.8	24.8	25.2	0.75	27.8 ↑	25.1	
	LMP	24.4	25.0	24.1	24.5	0.46	27.8 ↑	25.0	
	CDR	22.8	23.3	25.0	23.7	1.15	27.9 ↑	25.8	24.4
8	CMP	23.1	23.3	25.0	23.8	1.04	27.9 ↑	27.8 ↑	23.9
	LMP	23.3	22.8	25.0	23.7	1.15	28.8 ↑	27.0 ↑	24.4
	CDR	24.0	24.8	24.8	24.5	0.46	28.3 ↑	23.1 ↓	22.3 ↓
9	CMP	23.8	24.6	24.9	24.4	0.57	28.3 ↑	23.3	22.5 ↓
	LMP	23.6	24.5	24.7	24.3	0.59	28.3 ↑	23.1	22.2 ↓
	CDR	21.4	22.8	24.4	22.9	1.50	21.7	23.2	
10	CMP	21.7	23.2	24.4	23.1	1.35	21.1	23.3	
	LMP	22.0	23.3	23.9	23.1	0.97	21.7	23.1	
	CDR	24.4	24.4	23.9	24.2	0.29	24.4	24.4	
11	CMP	23.9	24.4	23.9	24.1	0.29	25.0 ↑	24.4	
	LMP	23.9	24.4	23.9	24.1	0.29	25.0 ↑	24.4	
	CDR	23.9	23.9	24.2	24.0	0.17	28.3 ↑	22.8 ↓	23.1 ↓
15	CMP	24.4	24.4	24.2	24.3	0.12	28.9 ↑	22.8 ↓	23.1 ↓
	LMP	24.4	23.9	24.2	24.2	0.25	29.4 ↑	22.8 ↓	23.1 ↓
	CDR	22.2	23.9	23.6	23.2	0.91	28.6 ↑	28.9 ↑	24.4
16	CMP	22.8	22.2	21.9	22.3	0.46	31.7 ↑	29.9 ↑	23.3
	LMP	22.8	23.1	22.2	22.7	0.46	30.6 ↑	28.3 ↑	23.3
	CDR	23.0	23.3	24.4	23.6	0.74	22.5	21.0 ↓	23.5
17	CMP	23.0	23.3	23.9	23.4	0.46	23.0	23.0	23.5
	LMP	24.2	23.3	23.9	23.8	0.46	24.8	22.9	23.0
GROUP MEAN		23.55	23.83	24.20	23.86		26.65	24.59	23.32
	±S.D.	1.175	0.784	0.825	0.760		2.981	2.270	0.712
					t-Test		$p<0.001$	n.s.	n.s.

peratures and body weights were recorded at each evaluation.

The priority of operations during Apollo missions prevented optimal control over several important variables during pre- and postflight orthostatic evaluations. Preflight evaluations had to be scheduled and completed within narrow time frames and in competition with crewmember training and preparations for launch. Postflight evaluations took place amid intensive debriefing sessions, public appearances and other ceremonies. As noted, group mean ambient temperature (Table III) for the first postflight evaluation was significantly elevated, reflecting both the recovery zone climate (usually tropical) and inadequate air conditioning on board the recovery ships. Group mean ambient temperatures for succeeding postflight evaluations were not significantly different from preflight values. Table IV shows a similar elevation at the first postflight evaluation in group mean oral temperature which, however, remained elevated for succeeding postflight days.

Certain additional variables complicated the interpretation of orthostatic evaluations. For example, while most crewmen reported a nominally sufficient amount of sleep prior to each preflight evaluation, there was a significant group mean reduction in the amount of sleep for the night prior to splashdown. Further, the interval between venipuncture for biochemical analysis (30-80 cc withdrawn) and diurnal time of orthostatic evaluation varied widely (15 min to many hours) within pre- and postflight time frames. Finally, the interval between the time a crewmember ingested food and time of orthostatic evaluation also varied widely (15 min to 17 hours).

The various physiological measurements were recorded in real time on a strip chart recorder and on FM magnetic tape. The strip chart data were used for real time monitoring. Tests were terminated at the first appearance of presyncopal symptoms. Analog tape data were subsequently digitized and the digital data were analyzed by specially developed software on a Sigma 3 Computer System. Minute heart rates were derived from an analysis of ECG or VCG R-R intervals; systolic and diastolic blood pressure values were read at the appearance of the first and last Korotkov sounds, respectively, on the calibrated descending arm cuff pressure ramp. Percentage change in calf volume during LBNP was obtained using the method of Eagan (5). Two successive heart sound complexes were analyzed from the vibrocardiogram each minute; computation of stroke volume followed the method of Agress, et al. (1).

Mean values for heart rate, systolic blood pressure, diastolic blood pressure, pulse pressure, and stroke volume were calculated for each of the five 5-min periods of the LBNP protocol and the two 5-min periods of the passive stand protocol. These mean values for each physiological variable were subsequently used as the best measure of crewmember response in the compilation of

TABLE IV. ORAL TEMPERATURE (°C) AT INDICATED PRE- AND POSTFLIGHT ORTHOSTATIC EVALUATIONS. (ARROWS INDICATE $p<0.05$).

Apollo Mission	Crew-member	Preflight Evaluation F-30 d	F-15 d	F-5 d	Preflight Summary Mean	±S.D.	Postflight Evaluations First	Second	Third
	CDR	36.4	36.6	36.4	36.5	0.12	37.6 ↑	36.8 ↑	
7	CMP	36.6	36.8	36.8	36.7	0.12	36.6	37.0 ↑	
	LMP	36.1	36.7	36.8	36.5	0.38	37.4	36.8	
	CDR	36.7	36.4	36.4	36.5	0.17	37.1 ↑	36.6	36.8
8	CMP	36.9	37.0	36.4	36.8	0.32	37.1	37.1	36.9
	LMP	36.8	36.6	36.3	36.6	0.25	36.8	36.6	36.7
	CDR	36.4	36.3	36.6	36.4	0.15	36.4	36.2	37.2 ↑
9	CMP	36.3	36.2	36.5	36.3	0.15	36.6	36.2	36.5
	LMP	36.7	36.8	36.4	36.6	0.21	36.8	37.2 ↑	36.8
	CDR	36.9	36.4	36.2	36.5	0.36	36.2	36.3	
10	CMP	37.0	36.8	36.4	36.7	0.31	36.8	36.8	
	LMP	36.4	36.5	36.7	36.5	0.15	37.1 ↑	36.6	
	CDR	36.4	36.4	36.6	36.5	0.12	36.4	—	
11	CMP	35.9	36.7	36.8	36.5	0.49	36.7	—	
	LMP	36.7	36.7	36.6	36.7	0.06	37.1 ↑	—	
	CDR	36.2	36.6	36.2	36.3	0.23	—	36.1	36.3
15	CMP	36.7	36.4	36.4	36.5	0.17	—	—	37.3 ↑
	LMP	36.3	36.6	36.7	36.5	0.21	—	36.7	36.6
	CDR	36.2	35.7	35.4	35.8	0.40	—	—	36.5
16	CMP	36.1	35.9	36.0	36.0	0.10	—	—	36.6 ↑
	LMP	36.2	35.6	35.3	35.7	0.46	—	—	37.1 ↑
	CDR	36.9	36.2	36.9	36.7	0.40	36.7	36.6	36.7
17	CMP	37.3	36.6	36.9	36.9	0.35	37.3	36.7	37.4
	LMP	36.8	36.2	35.9	36.3	0.46	36.8	36.9	36.2
GROUP MEAN		36.54	36.45	36.40	36.46		36.86	36.66	36.77
±S.D.		0.346	0.348	0.417	0.287		0.370	0.316	0.353
					t-Test		$p<0.005$	n.s.	$p<0.005$