Research Related to Noninvasive Instrumentation

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SUMMARY In the past three decades, techniques that permit noninvasive quantitation of the function of the heart have been developed. Exercise electrocardiography has been widely used to determine the presence or absence of ischemic heart disease. Echocardiography permits detection of valvular, congenital and arteriosclerotic disease and quantitation of its severity. Selective use of isotopes allows nuclear angiography, myocardial perfusion studies and detection of damage to cellular myocardium. New techniques such as computerized axial tomography, magnetometry, focused pulsed Doppler, and wider application of computer-enhanced image processing are important future directions for noninvasive monitoring.

Since 1947, interest in applying technology to measuring the function of the cardiovascular system has heightened. Much of what has been learned about the effects of hypertension and atherosclerosis on cardiac function has resulted from the application of technology for quantitatively assessing the function of the heart and blood vessels. Because systemic hypertension and atherosclerosis involving the coronary and cerebral blood vessels are the two most important cardiologic disorders, considerable emphasis has been given to developing instruments for studying the effects of these disorders. The sequence usually begins with the development of a new process or technique in a medical center for the purpose of scientific research. Once determined to be widely applicable in the field, the technique is disseminated to medical practitioners. The broad availability of quality instrumentation for studying the cardiovascular system has helped to bring high-quality medical care to a large majority of the American public. Unfortunately, the cost of developing and disseminating technology has been high, and when overzealous distribution occurs in areas of low use, the cost-effectiveness of technology has been questioned. However, the high technology still represents only a small part of the costs of health care, and cannot be blamed for the excessive costs we now face.

Concepts of Noninvasive Measurements

The term "noninvasive" refers to techniques that permit cardiovascular measurements to be made without the introduction of catheters or probes into the patient's body. While much of the basic information about the function of the cardiovascular system has come from cardiac catheterization and angiocardiography, new techniques and instruments that image structures and flows have been developed with increasing frequency during the past 30 years. The quality of the images that can be obtained noninvasively permits better quantitation of normal vs abnormal cardiovascular function. The patient undergoing noninvasive tests is subject to no or very low risk from repeated studies. Thus, noninvasive measurements can be used in mass screening for latent cardiovascular disease in clinical follow-up of a patient with clear-cut but asymptomatic disease and in determining the effects of treatment.

Basic Instrumentation Concepts

Important advances in cardiovascular monitoring include the development of smaller, low-cost, portable equipment that may be used not only in the hospital but also in the physician's office. Such equipment must sample data at a high rate because of rapid heart beating and the propelling of blood through the body's vascular channels at high velocities. Much attention has been focused upon developing instruments that are simple to operate and require little advanced technical training.

The equipment must provide direct copies of printed-out data for immediate examination by the physician or technician. The data must be processed and tabulated graphically so that decisions can be made quickly. Oscilloscopic presentation of images and video playback units are used with increasing frequency for viewing by the physician, and computer analysis and graphic outputs are being developed.

Recently, microelectronic devices and circuitry have been introduced into equipment for cardiovascular measurements, permitting marked reduction in the size of instruments. Most routinely sampled data require computer processing to facilitate interpretation by the physician. Significant progress in the use of computers in cardiology has been made during the past 20 years.

General Technologies

The basic principles for most noninvasive tests derive from physics or engineering concepts applied to medicine. The basic work that led to the development of these noninvasive techniques was usually performed in university laboratories affiliated with medical schools. Government laboratories, including those associated with the National Institutes of Health and with the National Aeronautics and Space Administration, have also developed some of the noninvasive technologies now being used in medicine. Industry

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adopted these techniques and mass-produced them for wide use by physicians throughout the country. Many of the technologies were developed for purposes other than medicine. For example, before the mid-1950s, ultrasound was used in industry and for submarine detection. Isotopes were used by nuclear physicists seeking to understand atomic structure and its application to military and scientific purposes.

The technologies developed during the 1940s and 1950s were recognized by biologists and physicians as having important applications for monitoring the function of the cardiovascular system in man. Therefore, the techniques were adapted for this purpose as “technology transfers” in the most general sense.

Many noninvasive cardiovascular techniques have been developed, but are not commonly used because of lack of validation, or because the highly technical nature of what they measure does not permit it. Some, such as quantitative pulse-contour analysis, impedance plethysmography and kinetocardiography, have been replaced by more advanced and easily applied techniques, such as echocardiography.

Electrocardiography1-3

Although the ECG has been available to physicians since the early 1900s, and the pathophysiology of heart disease reflected by changes in the ECG was documented in the 1920s and 1930s, the technique was not widely used because early ECG machines were cumbersome and records required photographic development. During the 1940s and 1950s, low-cost portable ECG machines were developed, and a new technique using a heat stylus on thermosensitive paper permitted the development of ECG machines that could be available in each physician’s office and in all hospitals. Together with improved knowledge about hypertension and atherosclerosis, resting ECG studies became a mainstay in understanding the effects of these diseases.

It was recognized quite early that a stress test such as exercise might reveal abnormalities, even though the resting ECG might be normal. This led to the development of the Master’s two-step exercise test, which related body size, age and the likelihood of disease to an exercise rate in a given patient with ECGs recorded before and after the exercise. Since recordings were not possible during the test, and the heart-rate response of each patient could not be individualized, bicycle ergometry and treadmill tests were devised. The introduction of treadmill and graded exercise programs led to the concept of stress testing now widely used in cardiology. Frequently, the resting records are completely normal, but become grossly abnormal, showing the presence of latent coronary atherosclerosis and myocardial ischemia during exercise. They then recover after a period of rest. Such techniques now permit the screening of asymptomatic patients with suspected coronary artery disease before catastrophic events, and the documentation of disease in mild forms so that appropriate treatment can be recommended.4-6 Many problems with interpretation of exercise ECGs in asymptomatic patients have been reported6-7 recently because of a low prevalence of disease in some populations, and only a 60% sensitivity and a 90% specificity for the tests.8 As the prevalence of disease rises in a population, the percentage of false-positive tests declines and the predictive value of the tests increases.9 In some instances, vectorcardiographic techniques to examine the electrical pattern of conduction in the heart give a more precise understanding of some abnormalities produced by myocardial necrosis.

Once a patient experiences an acute myocardial infarction and is admitted to the coronary care unit, the ECG may be recorded continuously and analyzed by beat by beat by computers programmed to recognize rhythm abnormalities. Such computer systems not only recognize the arrhythmia, but also provide a series of priority alarms, based upon the seriousness of the arrhythmia detected, to alert the staff of the coronary care unit to a potential hazard for a patient. These monitoring techniques have led to the early use of drug therapy and the prevention of death in patients experiencing myocardial infarction.

If a patient with atherosclerotic coronary artery disease is found to have abnormal rhythms, it is necessary to quantitate their number during daily activities. Small recorders continuously tape 24 hours of heart beats. The resultant recording may represent more than 100,000 heart beats, and requires computer analysis to provide quantitative data that can be rapidly reviewed by the physician to determine whether the patient needs therapy.10-12 A number of cardiology centers have developed such ambulatory monitoring systems for quantitating arrhythmias, which are now being used to determine the influence of arrhythmias on susceptibility to sudden cardiac death, which accounts for more than 50% of all cardiac deaths in the U.S. each year (fig. 1).10

Recently, the development of techniques that may limit the size of necrosis in acute myocardial infarction has emphasized the need to know the amount of irreversibly damaged myocardium. Precordial ECG mapping techniques using an array of electrodes attached to the chest have proved promising in the effort to quantify the size of infarction. This noninvasive technique is now being used to study ways in which infarct size may be limited.

Ultrasound Applications13-14

The use of sound waves reflected from various cardiac tissues and border zones was recognized as a noninvasive method for studying the motion of valves, chambers and blood vessels in the heart (fig. 2). In the past decade, M-mode echocardiography with a single transducer has been widely applied to study the movement of cardiac structures. Initially, M-mode echocardiograms were recorded by means of polaroid photography from the face of an oscilloscope. Subsequently, strip chart recorders were developed to use the single transducer to direct beams of sound at several areas within the heart and continuously record the movement of intracardiac structures (fig. 3). These
techniques permit detection of abnormalities of wall motion and areas of thickened myocardium that might result from hypertension. Studies of the effects of hypertension on left ventricular mass have been performed using such echocardiographic techniques.

Linear arrays of transducers for emitting sound waves and detecting reflected sound waves have been investigated but have not been widely adopted by cardiologists. Mechanical sector scanners were then developed to direct the sound beams in an arc of 30° to record a number of structures in the heart. Sector scanners have permitted investigators to determine images of coronary arteries and to demonstrate the process of atherosclerosis. Most recently, phased-array sector scanning using an electronic switching device for directing beams of ultrasound over an arc of 90° has been developed. The phased-array sector scanners can image the ventricular walls of coronary arteries (fig. 4), as well as valves, ventricular walls and other vascular structures. This technique permits detection of wall motion abnormalities that occur with acute myocardial infarction. The abnormalities in mechanical motion of the wall occur early and in some instances may precede the electrical changes recorded on the ECG. Preliminary studies at Stanford have shown that abnormal mechanical events may occur before electrical abnormalities when sudden occlusion of a coronary artery is produced. These changes reflect the wall motion abnormalities produced by ischemia.

Echocardiography now plays an important role in noninvasive evaluation of cardiac function, and in the future promises to be even more important for detecting and following the course of cardiac disease produced by atherosclerosis and hypertension. The quality of echocardiographic images now approaches that seen with high-quality angiography. With computer processing of the images, image enhancement and better instrumentation, it appears that much of the invasive evaluation now performed to determine the effects of infarction and hypertension upon ventricular function can be made noninvasively.

Noninvasive Nuclear Techniques15-19

In the past three decades, radioisotopes have been used with increasing frequency to study physiologic and biochemical processes in the body. Beginning with
early work to image the thyroid gland when cancer was suspected, it was recognized that radioisotopes offered noninvasive methods to determine alterations in structure and function in disease. For example, myocardial tissue concentrates radioactive ions and substances that bind to unique proteins in the heart. Using these concepts, a number of imaging techniques have been developed for studying the effects of atherosclerosis on the heart structures and blood flows.

The so-called cold-spot imaging was first developed using $^{40}$K. Potassium is a normal electrolyte found in high concentrations in heart muscle, and is taken up by heart muscle when administered to a patient. Because its concentration by muscle is related to the blood flow into the muscle, it serves as a marker for flow. Recently, thallium-201, an analog of potassium that is also taken up by normal myocardium, was substituted for $^{40}$K as a noninvasive means of assessing the status of the myocardium. Thallium-201 was chosen because of the ease of isotope preparation, the half-life of the isotope, and the quality of images that can be produced.

Such isotopes may be used to show the abnormalities of blood flow to infarcted or dead tissue (fig. 5) or, when combined with exercise studies that accelerate blood flow, the uptake of electrolyte into normal tissue (fig. 5), but result in a disproportionately low flow and low uptake in ischemic tissue not receiving adequate flow to meet the demands of the myocardium for increased flow. These techniques are widely used to study the effects of atherosclerosis that limit myocardial blood flow in coronary arteries. Spasm of the coronary arteries resulting from an im-

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**Figure 3.** Strip chart recording of an echocardiogram in which the single-beam transducer was moved from the body of the left ventricle (LV, position A) through the mitral valve (position B), up to the aorta and left atrium (LA). The right ventricular outflow tract (RVOT) is also shown. A standard electrocardiogram (EKG) is shown above for timing purposes. Thus, by using a single transducer and sweeping it across various chambers of the heart, continuous time-motion recording can be made.

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**Figure 4.** Photograph of an oscilloscopic display of a sector scan showing the aorta (Ao), left atrium (LA), pulmonary artery (PA), and a coronary artery; the arrows indicate the left main artery down to the bifurcation.
balance of neural control mechanisms governing them can also be demonstrated noninvasively by the use of thallium-201 imaging and drugs that induce spasm (fig. 6).

Another technique, the so-called hot-spot scanning, uses the concept that radioisotope-labeled substances bind to dead or severely damaged heart muscle cells. Technetium pyrophosphate — which binds to calcium inside damaged muscle cells — myosin antibodies labeled with radioactive iodine, and white blood cells labeled with indium are being used to image acutely damaged hearts and to attempt to define quantitatively the amount of dead heart muscle.

Nuclear cardiac techniques have allowed the development of nuclear angiocardiology. Isotopes are administered intravenously, and devices that detect and count radiation are placed over the heart. Either the gated blood pool scan or the first-pass technique may be used to measure volumes of the various chambers and ejection indices. High-speed cine filming devices and computer-processing techniques permit a study of wall motion abnormalities, which may develop during exercise because of blood flow limitation due to coronary atherosclerosis and the presence of intracardiac shunts occurring with various forms of congenital heart disease. Nuclear imaging is also valuable in noninvasively studying patients with rheumatic and congenital valvular disease.

Conclusions and Future Directions

Future directions for noninvasive monitoring will no doubt allow for higher quality imaging of cardiac and vascular structures and determination of their function. Applications of computer techniques for analysis, for graphically comparing sets of data to ascertain normal vs abnormal function, and for aiding with complex decisions seem likely. In examining new techniques for imaging, pulsed Doppler echocardiography, computerized axial tomography and positron-emission tomography are clearly devices that will permit high-quality studies in patients with heart disease. Other techniques that are likely to find widespread application are portable arrhythmia detectors, which may also be equipped with either devices warning the patient to seek medical advice, or treatment devices, which would terminate an abnormal rhythm when it occurred. For the management of hypertension, portable blood pressure recorders that could be used by patients seem essential. Finally, studying the effects of heart disease upon magnetic signals that can be recorded from the heart appears to be a promising area for future research. At Stanford,
we are attempting to use magnetocardiography to study patients whose ECGs do not provide sufficient differentiation between normal and disease states. In summary, the future for noninvasive measures of cardiovascular function appears to be bright. It seems likely that the technology to make such measurements will be available to physicians wishing to study patients routinely, and that such technology will contribute significantly to our understanding of atherosclerosis and hypertension.

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