Clinical Nuclear Cardiology

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Preface

"Nuclear Cardiology" is a rapidly expanding and growing field that has made quantum leaps in the past several years. The purpose of this book is to describe and place in proper perspective those radionuclide techniques that presently aid the clinician in the elucidation of the nature of various forms of heart disease. We have attempted to emphasize theory, practice, clinical usefulness, and interpretation of the radionuclide tests that are presently most utilized and of greatest value in the evaluation of patients with suspected heart abnormalities. We hope that this approach will make this textbook useful for students, house officers, and practicing physicians interested in nuclear cardiology.

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Contents

1
Introduction

Frederick J. Bonte, M.D.

The first use of radioactivity in the study of the cardiovascular system was in a brilliant experiment reported by Blumgart and Weiss in 1927.[5] Utilizing the principles of the radioactive tracer method described by Hevesy,[24] these investigators determined the circulation time in man by injecting a dose of radium C salt into an arm vein and timing the arrival of radioactivity in the artery of the opposite arm, using the response of a Wilson cloud chamber. This technique was revived with the newer technology of the Atomic Age by Prinzmetal and his associates in 1948,[42] with a Geiger-Muller counter and recorder and the artificial radionuclide Na-24. These investigators repeated the experiment of Blumgart and Weiss on determination of circulation time and also made recordings over the heart and lungs. Thus was devised the radiocardiogram, which Prinzmetal et al. suggested might be used for such purposes as studying the function of the left ventricle in health and disease and for the detection of shunting.[20] Almost simultaneously, this group[42] and Kety[28] learned to determine blood flow by measuring the rate of clearance of Na-24 from a subcutaneous or intramuscular injection site.

Veall et al.[54] and MacIntyre et al.[36] learned how to derive the cardiac output from the left ventricular portion of the radiocardiographic curve. Donato et al.[18] and Van Dyke and his associates[53] refined the single-probe recording technique to yield pulmonary blood volume and ejection fraction. Although image-based methods have largely replaced the single-probe radiocardiogram, this technique is quite capable of yielding valuable information, and this original nuclear-cardiologic procedure survives into the present era.

Radionuclide imaging of the cardiovascular system originated with the blood pool scan, first described by Rejali and his colleagues in 1958.[44] Using a rectilinear scanner, these investigators made images of

the blood pools of the thorax and abdomen, after allowing intravenously injected I-131-labeled human serum albumin to come to equilibrium in the body vascular space. Other investigators, such as Bonte et al.,[6-9] MacIntyre et al.,[34,35] Sklaroff et al.,[49] and Wagner et al.,[56] found that blood pool imaging could be used for two general purposes: (1) identification of pericardial effusions and (2) the differential diagnosis of midline thoracoabdominal masses between aneurysms and solid tumors, based upon apparent blood content.

Important changes came to blood pool imaging technology with the availability of the large-crystal scintillation camera[1] and Tc-99m-labeled tracers, developed by Richards and his associates and by Harper et al.[22] It then became possible to view the passage of a tracer bolus through the central venous and arterial circulations as a dynamic series of events in multiple serial scintillation camera images.[7,21,31,47] The test that evolved came to be called "radionuclide angiocardiography," and it remains useful to the present time as a convenient, accurate means of appraising the status of mediastinal great veins and the existence of pericardial effusion, as well as for a number of other purposes.

Earlier, the concept of storage of radionuclide image data on magnetic tape for reprocessing and display had been developed by MacIntyre et al.[35] and by Bonte et al.[8] Data processing was advanced by Brown in 1964,[12] when he described the use of a digital computer to analyze and display images derived from rectilinear scanner. These techniques were rapidly adapted to the processing of scintillation camera images, leading to the development of sophisticated nuclear angiocardiographic systems by Ashburn et al.,[3] Kriss et al.,[30] and Wellman et al.[57] Capabilities of nuclear physicians had advanced to such a degree that it was now possible to appraise volume changes in individual cardiac chambers, and utilizing a variation of the classic roentgenographic method of Chapman et al.,[17] Mullins et al.[38] employed radionuclide angiocardiography for the determination of left ventricular volume. This discovery rapidly led to the development of techniques for the estimation of cardiac output and left ventricular ejection fraction by Strauss et al.[50]

Further refinement in image processing technology made possible the cinematographic display of radionuclide tracer images of chambers obtained with the aid of gating mechanisms triggered by the patient's electrocardiogram. Now, in addition to determining changes in the ventricular volume and ejection fraction, the nuclear physician could appraise the pump function of the left ventricle by observing evidence of contractility of the chamber wall, as seen in several projections.[59] This procedure, often termed "wall motion study," provides useful information by identifying poorly functioning segments of ventricular wall such as may exist following myocardial infarction. The formation of ventricular aneurysms may also be demonstrated.

The ability to derive quantitative information by processing stored image data has also led to the development by Rosenthall[46] of processes to identify left-to-right and right-to-left shunts. Investigators learned how to formulate flow curves derived from a region of interest generated within the stored, digitized image and gain from them information similar to that obtained with single-probe techniques.

Development of these capabilities led several groups of investigators to study the work of Kety and his associates,[28] who had utilized radionuclide tracers to determine blood flow in myocardium and other tissues.[28,29] This work was adapted by many groups into a procedure in which a diffusible tracer, such as Xe-133 or Kr-85 was injected into the coronary artery or into the heart muscle itself, and the disappearance or washout of radioactivity, an index of tissue blood flow, was measured with a radiation detection system. At first this procedure was carried out with single-probe detectors, but later investigators learned how to utilize data derived from serially tape-recorded images to estimate myocardial blood flow. By arbitrarily subdividing the recorded image into zones, investigators have been able to obtain reproducible values for regional myocardial blood flow. Cannon and his associates[14] employed a Bender-Blau multicrystal scintillation camera (autofluoroscope[4]) and were able to derive a myocardial blood flow value from regions corresponding to each of the camera's crystals. Bonte et al.[11] utilized an Anger large-crystal scintillation camera[1] and obtained similar results.

An alternative method for determining regional myocardial blood flow followed upon the observation by Sapirstein[48] that organ blood flow could be measured by the fractional distribution of particulate tracers, employing particles of slightly larger diameter than the body's capillaries.

Quinn et al.[43] showed that the radioactive particle method could be utilized to make pictures of the distribution of coronary perfusion following intracoronary-arterial injection. Quinn's method was developed further by Ashburn and his colleagues,[2] who performed particulate tracer studies for estimation of distribution of myocardial blood flow in a large series of patients, as did Jansen and his associates.[27]

However, both the diffusible and particulate tracer methods are invasive procedures. Although they are both valuable research tests, they must be carried out under the circumstances of cardiac catheterization, in which there is a certain inherent morbidity.

Nuclear physicians have long been eager to find radiotracers that would selectively label either normal or diseased myocardium. The distribution of such a tracer would also be an index of myocardial perfusion and myocardial cell function and would offer promise of a noninvasive procedure for eliciting this valuable information.

Considerable work has been done over the years by Carr et al.,[15,16] Nolting et al.,[39] Romhilt et al.,[45] and many other groups. A number of

radioisotopes of rubidium and cesium, analogs of the intracellular cation potassium, were employed without a great deal of success. At length, however, K-43 became available.[26] Although the photon emissions of this radionuclide were of relatively high energy, rectilinear scans of good quality could be made with proper collimation, and Strauss and his colleagues[51] used K-43 to demonstrate areas of transient ischemia occurring after exercise in a group of patients with coronary arterial disease.

Other agents for visualizing the perfused myocardium have been proposed and employed with partial success. In 1965, Evans et al.[19] showed that radioiodinated long-chain unsaturated fatty acids could be used as imaging tracers for perfused myocardium, since the myocardium utilizes such substances as prime energy sources. Poe and his associates[41] have more recently developed I-123-labeled fatty acids as a noninvasive myocardial perfusion marker. Recently Ter-Pogossian and his associates[52] have used the positron-emitting radionuclide, C-11, incorporated into CO or palmitate, to image myocardium with their positron-tomographic camera. Harper et al.,[23] on the other hand, have used the positron emitter N-13, as ammonia, with interesting results.

The present tracer of choice for imaging the perfused myocardium is Tl-201, introduced by Lebowitz and his colleagues[33] and utilized to advantage by many groups, chief among them Wackers et al.[55] With this agent nuclear physicians could now demonstrate areas of transient ischemia following exercise and could show unperfused areas representing fresh infarcts. Perfusion defects due to scarring by remote disease could be demonstrated as well.

While the search for a tracer useful in labeling normal myocardium was progressing, many of the same investigators were also looking for a compound that would selectively label a myocardial infarct. Although infarcts could be demonstrated as defects within the distribution patterns of the previously mentioned radiopharmaceuticals, these tracers could not discriminate between defects caused by ischemia, infarction, or scarring from some remote process. Therefore, a parallel search was conducted for a tracer that would specifically label infarcted myocardium.

It is likely that the first successful myocardial infarct scan was made in 1962 by Carr, Beierwaltes, and their associates[16] with Hg-203 chlormerodrin, an agent which was thought to label necrotic tissue. This tracer proved unsatisfactory for clinical use, however, and other investigators continued the search for useful agents. Malek et al.[37] reported a degree of success with Hg-203 fluorescein and subsequently experimented with labeled tetracycline. In 1973, Holman and his colleagues[25] developed a Tc-99m compound of tetracycline and found it to be the best agent thus far reported for direct infarct imaging, but optimum concentration of tracer in infarct occurred late after administration, an un-

fortunate circumstance when the radiopharmaceutical is labeled with a short-lived emitter such as Tc-99m.

In 1973 and 1974, Bonte, Parkey, Willerson, and their associates[10,40,58] reported the successful use, first in animals and then in patients, of Tc-99m stannous pyrophosphate. These investigators, working with Buja,[13] have shown that this radiopharmaceutical indicates whether necrotic myocardium has been produced by an infarct or some other cause, such as chronic ischemia (unstable angina pectoris) or trauma.

At the present time, the diagnosis and estimation of the consequences of myocardial infarction by nuclear imaging methods are usually carried out with some combination of testing with Tl-201 and Tc-99m phosphate tracers, together with ventriculography performed with Tc-99m-labeled human serum albumin or red cells. From the latter testing, such important information as ejection fraction and evaluation of wall motion may be derived. The nuclear physician now has at his command an impressive battery of diagnostic tests that can be done under noninvasive circumstances with the aid of mobile imaging equipment at the patient's bedside in the coronary care unit.

The future of myocardial imaging may well lie with three-dimensional image reconstruction, a concept originally introduced into nuclear medicine by Kuhl and Edwards in 1964.[32] Ter-Pogossian and his associates[52] have been able to accomplish this objective with their positron-tomographic camera and positron-emitting tracers. However, a positron-based technique requires expensive detection equipment and the ready availability of a cyclotron, formidable requirements which place these techniques beyond the reach of the average institution at the present time. What is therefore needed for full implementation of the three-dimensional image in cardiovascular nuclear medicine is a tomographic instrument utilizing single photon emissions from such radionuclides as Tc-99m and Tl-201. The introduction of such detectors may actually be near at hand. Further, it seems likely that the ultimate agent for the direct labeling of myocardial infarcts for imaging has not yet been identified, but a vigorous search is underway in many laboratories. It is, therefore, evident that although much has been accomplished in the way of productive research and useful clinical application in cardiovascular nuclear medicine, important work remains to be done, affording splendid research opportunities to the interested and vigorous mind.

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2
Physics and instrumentation

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PHYSICS

The discipline of nuclear cardiology is concerned with the use of radioactive pharmaceuticals (also termed radiopharmaceuticals, radionuclides, or isotopes) to evaluate the physiologic and morphologic status of the central circulation. Nuclear cardiographic procedures are based upon the following concepts:

1. If an injected radiopharmaceutical is completely mixed with the blood, the rate of passage of that radiopharmaceutical through the circulation is exactly the same as that of the blood. Detection of the arrival and disappearance of that radiopharmaceutical at various points in the circulation can then be used to evaluate circulatory hemodynamics. This technique can be used for calculating cardiac output or ejection fractions, for determining the existence of a cardiac shunt, or for evaluating myocardial blood flow.
2. If an injected radiopharmaceutical is completely mixed with the blood, the spatial distribution of that radiopharmaceutical is identical to that of the blood. The external visualization of the changing spatial distribution of that radiopharmaceutical is then analogous to visualizing the deformations of the blood itself. High-speed imaging of the changing spatial distribution of such a radiopharmaceutical on its initial or subsequent passage through the central circulation can then be used for such purposes as diagnosing intracardiac tumor, differentiating pericardial effusion from cardiac hypertrophy or cardiac dilatation, identifying the presence of aneurysms of either the left ventricle