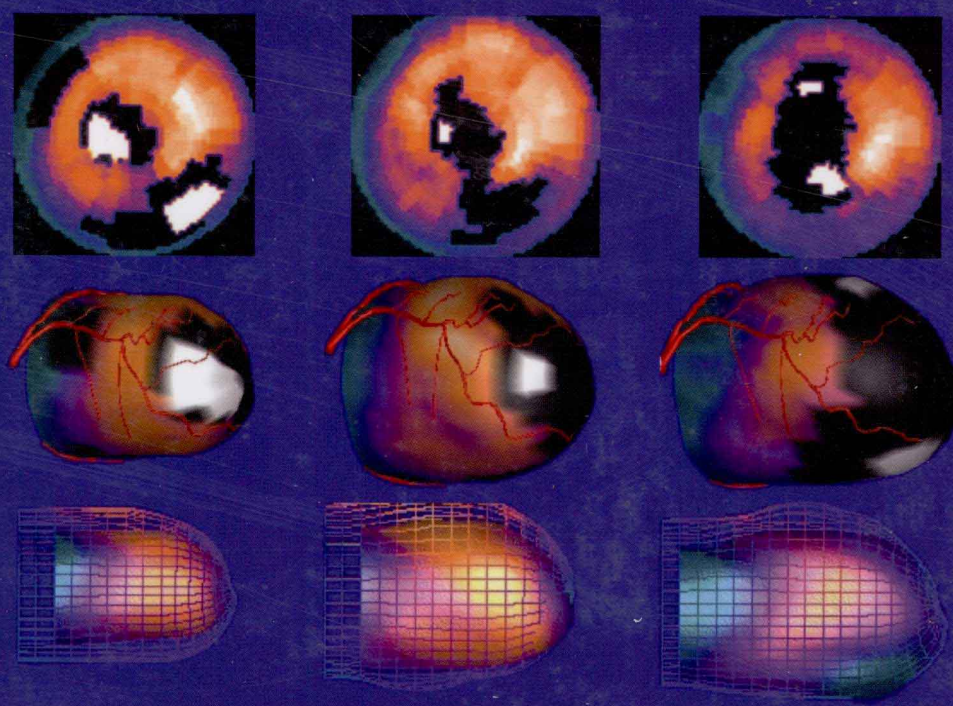
NUCLEAR CARDIAC IMAGING

FOURTH EDITION



Principles and Applications

AMI E. ISKANDRIAN
ERNEST V. GARCIA

NUCLEAR CARDIAC IMAGING
PRINCIPLES AND APPLICATIONS

Fourth Edition

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To our wives,
Greta P. Iskandrian
and *Terri Spiegel,*

and to our children,
Basil, Susan, and Kristen Iskandrian and *Meredith and Evan Garcia*
and to their spouses and children.

Preface

You are probably thinking, "Who needs another book in nuclear cardiology?" After all, there are many excellent nuclear cardiology books written or edited by leaders in the field. This is the fourth edition of the book; the third edition was previously edited by Iskandrian and Verani and published in 2003. For the well-established, mature field of nuclear cardiology, what possible innovations or changes in clinical practice would warrant a new edition in just five years? The answers to these questions are exactly what motivated us to come out with this edition.

In keeping with the original objective of this book, we sought out to edit a volume that would be the most comprehensive and definitive source of detailed information in nuclear cardiology for years to come. Most of the 26 chapters from the third edition have been retained and updated with new technical and clinical information. To keep up with the significant progress in our field, 11 new chapters have been added. Some of the new topics include perfusion quantitation, PET/CT and SPECT/CT hybrid imaging, equilibrium SPECT MUGA, Rb-82 perfusion PET, image fusion, screening asymptomatic subjects, infarct sizing, artificial intelligence for decision support, and molecular imaging.

As in previous editions, we selected as contributors, as much as possible, the leaders in the specific topic of each chapter. We are both grateful and impressed by their contributions. As both of us read each and every word the authors wrote, we were impressed by how well-explained and detailed the chapters were and by how much new information we were discovering in each of these topics, even the ones we thought we had mastered. We are very grateful to our contributors because as authors ourselves, we realize how much time and effort it takes to produce such a high-quality contribution.

Our objective was also to produce a book that was easy to read and understand, both from the aesthetic and intellectual points of view. In this edition, for the first time, we are presenting most figures in color. We edited the chapters to be more consistent with each other in both form and function. We encouraged the authors, in addition to providing us with up-to-date information, to also indicate to the reader their honest appraisal of the status of each specific topic. This proved to be particularly useful in controversial and in fast-changing topics. Finally, in the last chapter, we provide straightforward answers to the most commonly asked questions regarding practical, technical, and clinical issues in nuclear cardiology.

This book validates the concept that the whole is greater than the sum of its parts. Although each chapter can be considered an excellent reference source for any specific topic, this book is not meant to be sitting on your shelf. We encourage neophytes and experts alike to read it cover to cover. We expect that you will get as much pleasure from reading it as we have in bringing it to you. As in any book with so many chapters and authors, some degree of repetition and controversy exist. We purposely have allowed that to give the readers different perspectives or even different viewpoints.

We are grateful to the staff of Oxford University Press and especially to the efforts of William Lamsback for advice and flexibility.

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Nuclear cardiac imaging

1 A brief historical perspective on nuclear cardiology

BARRY L. ZARET

Nuclear cardiology is generally considered a clinical phenomenon of the past three decades. However, the field has its roots in earlier times. This chapter focuses on these historical roots as they have evolved into the present era. Space constraints mandate focusing solely on the highlights. My apologies to the many highly productive investigators and laboratories whose contributions helped the field grow to its current level but who could not be included.

HEART FUNCTION AND CIRCULATORY DYNAMICS

The initial application of radioisotopes to the study of the circulation occurred in the mid-1920s (Table 1.1). The famous cardiologic investigator of that era, Hermann Blumgart, in an elegant series of studies employing radon gas dissolved in saline as the radionuclide marker and a modified Wilson cloud chamber as the radiation detector, measured central circulation transit times in humans [1]. These studies, which were well ahead of their time, resulted in substantial improvement in the general understanding of cardiovascular function in a variety of disease states. They were early forerunners of the studies of the 1950s and 1960s, in which substantial attention was given to hemodynamic characterization in both health and human disease states. Blumgart's laboratory in Boston also served as fertile ground for training the next generation of cardiovascular investigators.

Not until the 1940s did Myron Prinzmetal build on this concept for potential clinical use, employing a simple sodium iodide probe to record transit of radiolabeled albumin through the central circulation. Prinzmetal, a practicing cardiologist, made important clinical observations using nonimaging Geiger tubes and scintillation detectors in a procedure called "radiocardiography" to define cardiac output, pulmonary blood volume, and pulmonary transit time [2].

However, the major impetus for the development of nuclear medicine technology occurred when Hal O. Anger, working in Berkeley, California, developed the first practical widely used high-resolution dynamic imaging device, the gamma (Anger) camera [3]. With this device, early pioneers in the field (such as Joseph Kriss) demonstrated the ability to visualize cardiac structures from rapid sequential radionuclide images following injection of a bolus of technetium-99m (Tc-99m)–labeled radioactive tracers [4,5]. From these serial images, a number of inferences could be made concerning cardiac pathophysiology and cardiac chamber and great vessel size. Following these qualitative studies, quantitative techniques were developed for assessing left and right ventricular ejection fraction as well as the degree of left:right intracardiac shunting [6,7]. For over a decade, first-pass approaches to ejection fraction were widely used. Extensive studies were subsequently performed by many laboratories, particularly at Duke and Yale Universities, establishing efficacy and clinical utility [8–11].

In 1971, the principle of electrocardiographic gating of the stable labeled (equilibrium) blood pool to evaluate cardiac performance was first proposed by Zaret and Strauss [12,13] (Table 1.2). This forerunner of current equilibrium radionuclide angiocardiography (ERNA) required separate manual gating of end-systole and end-diastole for subsequent measurement of left ventricular ejection fraction and assessment of regional function. This was a cumbersome and time-consuming procedure. However, once efficacy had been established, it was only a short time before automation of this technique occurred; using relatively simple computerized techniques, the entire cardiac cycle could be visualized in an endless loop display with automated calculation of ejection fraction and visualization of the entire ventricle volume curve. For over a decade, this technique was the standard for measuring ventricular function noninvasively. In 1977, Borer and colleagues at the National

TABLE 1.1 *Major Advances: Before 1970*

Decade	*Investigator*	*Advance*
1920s	H Blumgart	Circulation times with radioisotopes
1940s	M Prinzmetal	Radiocardiography
1960s	EA Carr	Perfusion imaging in experimental MI
	EA Carr	Hot spot imaging in experimental MI
	HO Anger	Development of scintillation camera
	J Kriss	Quantitative FPRNA

FPRNA = First-pass radionuclide angiocardiography.
MI = Myocardial infarction.

Institutes of Health first reported combining ERNA with exercise to evaluate regional and global LV function under stress conditions in coronary artery disease as well as other disease states, such as valvular heart disease [14]. In large part, echocardiography has superseded ERNA in this context. However, for precise serial measurements of ejection fraction, such as in the situation involving monitoring cardiotoxicity in patients receiving chemotherapy, the radionuclide technique remains the procedure of choice [15].

Newer evolutionary advances in ventricular function assessment involve single-photon emission computed tomography (SPECT) studies of the cardiac blood pool. This allows a more comprehensive assessment of right and left ventricular regional function [16]. Presently, with the marked advances in gated SPECT perfusion studies, ventricular function is often evaluated concomitantly with assessment of myocardial perfusion, and this has frequently obviated the need for separate studies [17].

MYOCARDIAL PERFUSION IMAGING

In the early 1960s, Carr, in a pioneering set of experiments, demonstrated the localization of radioactive potassium and other radioactive potassium analogs, such as cesium and rubidium, in the myocardium of experimental animals [18]. He also demonstrated that under conditions of acute coronary ligation, there was a decreased accumulation of these radioactive tracers in the evolving infarct zone. However, it was not until 1973 that the ability to image the site and extent of myocardial ischemia was demonstrated by combining physiological stress with static cardiac imaging (Table 1.2). In these initial studies, performed directly in humans, Zaret, Strauss, and colleagues, working in Travis Air Force Base in California, established the paradigm of imaging ischemia induced by treadmill exercise stress, utilizing potassium-43 (K-43) as the tracer and the rectilinear scanner as the imaging device [19]. This relatively simple observation formed the clinical and physiological basis of nuclear cardiology and stress imaging as practiced today. These investigators were able to demonstrate a pattern of relatively decreased perfusion in an ischemic area only under conditions of stress, with homogeneous radioactive tracer uptake under resting conditions. The kinetics of K-43 mandated separate injections for rest and stress studies. The authors were also able to establish direct relationships between perfusion patterns and coronary stenosis as demonstrated by coronary angiography. Following the initial demonstration, subsequent clinical studies demonstrated the utility of this approach, again using K-43 and the rectilinear scanner, in assessing the patency of bypass grafts following cardiac surgery [20] and the presence of false positive exercise tests [21]. These studies, which set the stage for the rapid development of the field, clearly employed a suboptimal radioactive tracer in the form of K-43. Its high-energy spectrum, which was not a problem for the rectilinear scanner, was a significant problem for the gamma camera. Of note, this same group, in the early 1970s, demonstrated that with appropriate pinhole collimation and shielding, one could obtain acceptable planar cardiac images using these high-energy, positron-emitting agents and a conventional gamma camera [22]. This study was a forerunner of current hybrid gamma camera technologies.

Thereafter Lebowitz et al. introduced thallium-201 (Tl-201) for imaging [23]. The ease of using the lower-energy Tl-201 with the gamma camera heralded a major breakthrough in the development of nuclear cardiology as a clinically viable discipline. In 1975, Pohost and colleagues defined the phenomenon of redistribution on thallium imaging [24]. This allowed the use of a single radionuclide injection and sequential imaging to assess transient ischemia or heterogeneity of blood flow that was normalized in a subsequent resting state several hours later. In the late 1970s, Gould, who had already made important contributions to understanding the pathophysiologic basis of perfusion imaging, developed the concept of detection of heterogeneity of coronary perfusion in the presence of stenosis by using vasodilator pharmacological stress as opposed to exercise stress [25]. This was first performed with dipyridamole. Thereafter it became apparent that more optimal studies could be obtained by using adenosine directly. More recently, attention has turned to more specific adenosine receptor agonists, with focus on the adenosine A2a receptor [26]. For patients who could not tolerate adenosine because of bronchospastic disease, dobutamine

was introduced as a stressor, comparable to its use in stress echocardiography [27]. These advances established the utility of the field of perfusion imaging for individuals incapable of exercising. In the same decade, Wackers et al., in Amsterdam, demonstrated the potential utility of thallium imaging for detecting acute infarction [28]. This study was a forerunner to current imaging approaches in the emergency department setting.

The late 1980s and 1990s saw the development of technetium-99m (Tc-99m) perfusion agents as important new radiopharmaceuticals for identifying ischemia and infarction. The initial two agents were Tc-99m-labeled sestamibi and teboroxime [29,30]. Whereas sestamibi has survived and remains a major clinical tracer today, teboroxime is no longer employed. The reason resides in the very rapid transit of teboroxime from the myocardium. Consequently, for purposes of imaging ischemia clinically, it remains a suboptimal agent. In the mid-1990s, tetrofosmin became available as an alternative to sestamibi for perfusion imaging [31]. The Tc-labeled perfusion agents have provided a more optimal situation for tomographic imaging employing SPECT. The more efficient energy spectrum and ability to use higher doses have led to substantial improvement in resolution. However, it must be noted that the optimal perfusion imaging agent has not been defined as yet. Such an agent would, while using Tc-99m as the radionuclide, provide better myocardial uptake and kinetic characteristics and not have excessive subdiaphragmatic tracer accumulation.

More recently, positron emission tomography (PET) perfusion studies using rubidium-82 generators and pharmacological stress have received increasing attention. These studies allow direct quantification of blood flow, provide high-resolution studies, and are well suited for markedly obese patients [32].

TABLE 1.2 *Major Advances: After 1970*

Date	*Investigators*	*Advance*
1971	B Zaret, HW Strauss	ECG gating of cardiac blood pool in humans (ERNA) for LVEF and regional wall motion abnormality
1973	B Zaret, HW Strauss	Exercise perfusion imaging (K-43) in humans
1970s–1980s	Multiple	Quantitative FPRNA for LVEF, RVEF
1973	E Lebowitz	Development of Tl-201
1974	R Parkey, J Willerson	Hot spot imaging of acute F Bonte MI with Tc-PYP
1976	F Wackers	Imaging acute MI with Tl-201
1976	B Khaw, E Haber	Antibody imaging of acute MI
1977	J Borer	Exercise ERNA
1977	G Pohost	Tl-201 redistribution
1978	KL Gould	Pharmacological stress imaging
1980s–1990s	Multiple	Development of Tc perfusion agents
1980s–1990s	Multiple	Development of SPECT
1986	J Tillisch, H Schelbert	PET viability
1980s–1990s	Multiple	SPECT viability
1990s and after	Multiple, in particular GA Beller, D Berman, R Hachomovitch, A Iskandrian	Studies of prognosis with nuclear cardiology
1990s	Multiple	Development of attenuation correction
1995	J Narula, B Khaw	Vascular plaque imaging
1998	H Blankenberg, HW Strauss	Imaging apoptosis in vivo
2000 and beyond	Multiple	Development of molecular imaging
2000 and beyond	Multiple	Development of hybrid imaging systems
2000 and beyond	Multiple	Development of microSPECT and PET system

ERNA = Equilibrium radionuclide angiocardiography.
FPRNA = First-pass radionuclide angiocardiography.
MI = Myocardial infarction.
PYP = Pyrophosphate.