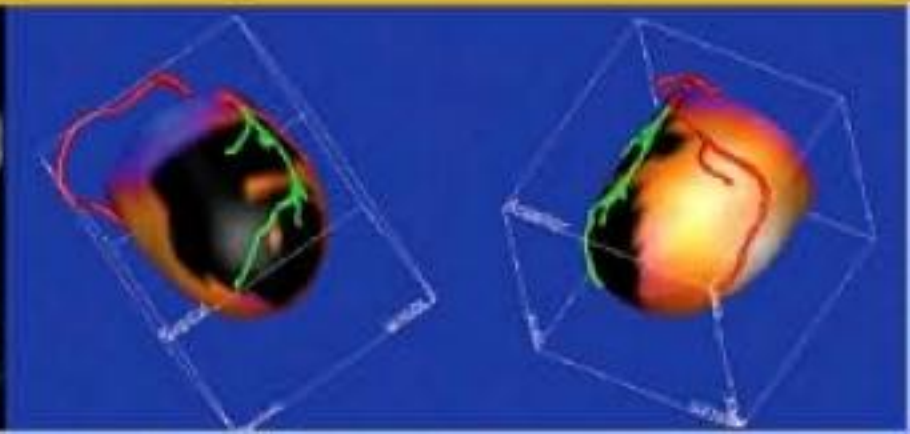
CLINICAL NUCLEAR CARDIOLOGY

State of the Art and Future Directions

FOURTH EDITION

Barry L. Zaret · George A. Beller



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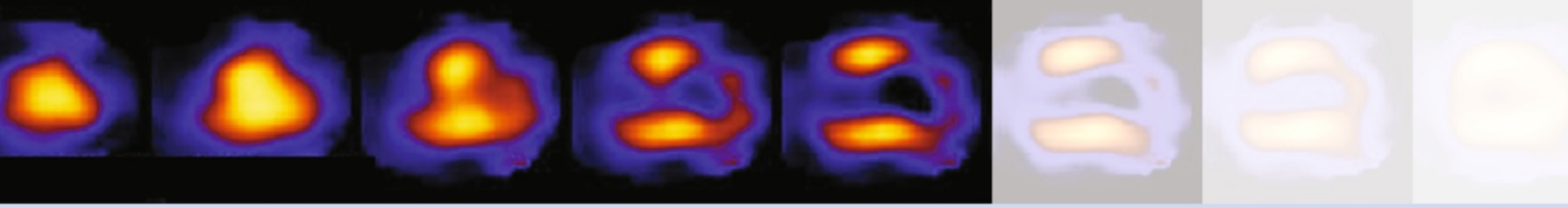

Clinical Nuclear Cardiology

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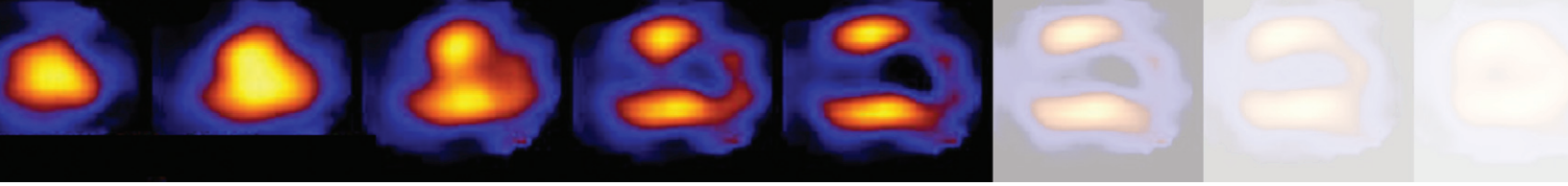
To Myrna Zaret, my wife of almost 50 years, my muse, my companion, my love.

Barry Zaret

To my wonderful and supportive wife, Katherine Brooks, and my six delightful grandchildren, Max, Pietro, Giacomo, Emily, Colin and Grace.

George Beller



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Comparison of Noninvasive Techniques for Myocardial Perfusion Imaging

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Cardiac Neurotransmission Imaging: Positron Emission Tomography

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Digital/Fast SPECT: Systems and Software

Regional and Global Ventricular Function and Volumes from SPECT Perfusion Imaging

Prognostic Implications of MPI Stress SPECT

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Imaging of Myocardial Metabolism

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Myocardial Blood Flow Measurement: Evaluating Coronary Pathophysiology and Monitoring Therapy

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Cost Effectiveness of Myocardial Perfusion Single-Photon Emission Computed Tomography

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Role of Intact Biological Models for Evaluation of Radiotracers

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Cardiac Performance

Imaging in Patients Receiving Cardiotoxic Chemotherapy

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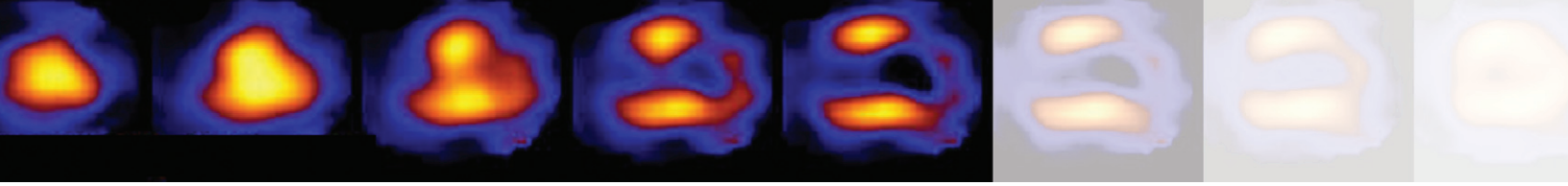

PREFACE

INTRODUCTION: INTEGRATED CARDIOVASCULAR IMAGING—THE FUTURE

This book first appeared in 1993; the preceding third edition was published in 2005. Each new edition has been associated with significant expansion, revision, and updating, as well as significant changes in orientation that reflect new advances in the field. At the time of this fourth edition, nuclear cardiology is firmly established as a key noninvasive modality for the clinical evaluation of patients with cardiovascular disease. Concomitantly, there have been further advances in instrumentation, radiopharmaceutical development, and new clinical research, leading to additional understanding of clinical utility, cost-effectiveness, appropriateness, and relationship of imaging findings to patient outcomes. Nuclear cardiology has been incorporated into major large multicenter clinical trials. In addition, as other modes of cardiovascular imaging have approached maturity, there has been movement toward integrating the various imaging modalities under the broad umbrella of cardiovascular multimodality imaging. The cardiovascular imager of the future will likely be trained in more than one modality and will be housed in dedicated imaging centers that offer a variety of imaging approaches. It will be the imager's job to determine the study most appropriate for answering the posed clinical question. In recognition of this trend, new chapters are included in this edition that provide additional focus on non-nuclear cardiovascular imaging modalities such as computed tomography, magnetic resonance imaging, and contrast echocardiography.

The fourth edition continues to focus on nuclear cardiology and represents a major effort to incorporate new advances in clinical nuclear cardiology, thereby providing a road map for up-to-date clinical use. In addition, we seek to point out the new directions in which nuclear cardiology as well as integrated cardiovascular imaging are headed. Our goals in the fourth edition continue to be twofold: first, to present the most up-to-date and comprehensive clinically applicable data available in the field, thereby offering both the practitioner and student/trainee the current clinical state of the art; and second, to present the newest and most exciting directions in the field that reflect both technologic and biological advances. To meet these combined goals, the book has once again expanded—now to a total of 45 chapters—and also includes a totally new and expanded atlas of case presentations to provide concrete examples of the clinical relevance of nuclear cardiology. Once again, the book is grouped into nine specific sections. Twenty of the 45 chapters, as well as the atlas, are totally new. An almost equal number of chapters have been eliminated, and, all remaining chapters have been revised, updated, and, in certain instances, consolidated.

Section 1 addresses issues related to radiopharmaceuticals and tracer kinetics. The three chapters in this section provide information concerning tracer kinetics and cellular mechanisms of uptake, principles of myocardial metabolism as they relate to imaging, and the role of intact biological models in evaluating radiotracers.

Section 2 deals with instrumentation. The eight chapters in this section address issues relating to processing, quantification, and display of single-photon emission tomography (SPECT) data, SPECT artifacts, attenuation/scatter/resolution and correction from both physics and clinical standpoints, hybrid imaging, digital/fast SPECT imaging, radiation considerations of imaging technologies, and small-animal imaging.

Section 3, as in the previous edition, contains two chapters dealing with cardiac function and performance, as evaluated by blood-pool imaging and gated SPECT imaging.

Section 4 addresses major issues that relate to perfusion imaging and detection of coronary disease. The 12 chapters in this section address the issues of coronary artery disease detection by exercise and pharmacologic stress, their prognostic implications, assessment of myocardial perfusion imaging by magnetic resonance imaging, echocardiography, and positron emission tomography (PET), and hybrid imaging. Specific chapters deal with computed tomography angiography and use of computed tomography to assess coronary artery calcification. Chapters also address cost-effectiveness as well as the appropriate use criteria for nuclear cardiology. A chapter also compares the various noninvasive approaches for assessment of myocardial perfusion.

Section 5 focuses on disease- and gender-specific issues. Specific chapters focus on imaging in women, imaging for preoperative risk assessment, revascularized patients, patients with diabetes mellitus, imaging in

the heart failure population, imaging of patients receiving cardiotoxic chemotherapy, mental stress imaging, and the use of PET measurements of myocardial blood flow to evaluate cardiovascular pathophysiology and therapeutic efficacy.

Section 6 addresses acute coronary syndromes. The two chapters in this section deal with imaging in the emergency department and risk stratification of patients with acute myocardial infarction, based on new data from a multicenter randomized trial.

Section 7 contains four chapters focusing on myocardial viability. Viability assessment with SPECT studies, PET, and other techniques is addressed in three specific chapters, while an additional chapter focuses on the pathophysiologic basis of hibernating myocardium.

Section 8 contains three chapters on tracer-specific imaging techniques. These three chapters deal with imaging of myocardial metabolism and cardiac neurotransmission imaging with either SPECT or PET.

Section 9 deals with new molecular approaches and contains three chapters dealing with molecular imaging of angiogenesis matrix metalloproteases and cell death, vascular abnormalities, and imaging of gene expression and cell therapy. Such techniques are primarily being evaluated in preclinical experimental models but have already shown promise in early clinical studies.

The Atlas of Cases is the final section of the book and is designed to provide complementary information to the numerous clinical issues discussed in the text. It exemplifies the substantial clinical utility of nuclear cardiology and shows a variety of images set in their clinical context. This atlas is significantly expanded from the one included in the third edition.

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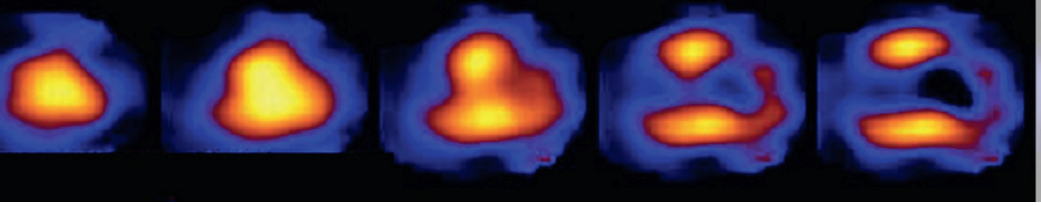

Chapter 1

Overview of Tracer Kinetics and Cellular Mechanisms of Uptake

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INTRODUCTION

The kinetics of tracer transport provides a skeletal framework that supports the body of clinical imaging using radionuclide tracers. This underlying framework provides an essential basis for understanding and clinical interpretation of tracers, including the sensitivity of different tracers to indicate reduction of coronary flow reserve, the use and limitations of redistribution and reinjection, and the applications of tracers for indication of myocardial viability and prediction of recovery of myocardial contractile function.

Tracer transport kinetics are most compactly and simply understood in terms of "models." A *model* is a mathematical function that defines a relationship. An example would be the curve that relates tracer uptake as a function of myocardial blood flow. There are certain basic relationships that govern the extraction, washout, and recirculation of tracers. These basic generic relationships facilitate the understanding of many different tracers used in various ways.

As an introduction to perfusion tracers, the first part of this chapter will review the basic properties and cellular uptake mechanisms of a few of the single-photon emission computed tomography (SPECT) myocardial perfusion agents. Next, we will present the "bare bones" of tracer extraction, retention, and recirculation. We will employ a common solute absorption model to help understand the relationship of tracer extraction to capillary perfusion and use a simplified compartmental exchange model to help understand tracer redistribution. Comparing model predictions to experimental data will add some fascinating light to the mechanism of myocardial vasoregulation. Following this introduction, and in the light of our improved understanding of tracer kinetics, we will discuss specific clinical applications of the tracers commonly used for myocardial imaging.

CELLULAR UPTAKE OF MYOCARDIAL PERFUSION AGENTS

Before delving into a modeling approach to better understand the complex behavior of a myocardial perfusion imaging agent after intravenous injection, we will briefly review the physical and/or chemical properties of a few classes of these agents that play a role in their cellular uptake in the myocardium.

Thallium-201

Thallium-201 (^{201}Tl) is a radioactive potassium analog. The initial myocardial uptake of ^{201}Tl is dependent upon myocardial blood flow and its first-pass extraction fraction, which is approximately 85% under resting flow conditions.[1,2] At higher flow rates, such as those obtained during pharmacologic vasodilation, the extraction of ^{201}Tl is not linear with respect to flow.[3] The plateau in extraction results in an underestimation of the true maximal flow. This phenomenon is true of all diffusible flow tracers and will be discussed in detail in the next section of this chapter.

The intracellular uptake of ^{201}Tl predominantly involves active exchange across the sarcolemmal membrane of the myocytes via the Na^+/K^+ adenosine triphosphate (ATP) transport system.[4] Because this system is energy dependent, thallium transport can only occur in viable myocardium. Once inside the myocyte, ^{201}Tl is not bound intracellularly and can diffuse back out into the circulation. As will be discussed in detail later, these uptake and redistribution kinetic properties form the basis of clinical assessment of myocardial perfusion and viability using ^{201}Tl. Although the introduction of ^{201}Tl in the mid-1970s represented a major advance in

nuclear cardiology, its physical properties are not ideal for gamma camera imaging. The low-energy 69- to 80-keV x-ray photopeak can result in attenuation artifacts and the relatively long 73-hour half-life limits the maximal dose that can be safely administered.

Monovalent Cationic Technetium-99m-Labeled Tracers

Technetium-99m (^{99m}Tc) is a generator-produced isotope that is readily available and has a number of advantages over ^{201}Tl for gamma camera imaging. The higher-energy 140-keV principle photopeak is ideal for detection using standard collimated gamma cameras with less attenuation, and its short 6-hour half-life allows for a higher administered dose yielding improved count statistics.

Over the years, there have been a number of ^{99m}Tc-labeled myocardial perfusion imaging agents that have been investigated as replacements for ^{201}Tl. The most successful ones to date are the lipophilic monovalent cationic agents, ^{99m}Tc-sestamibi (sestamibi, Cardiolite) and ^{99m}Tc-tetrofosmin (tetrofosmin, Myoview), that are now widely used for clinical studies. Following an intravenous injection, the first-pass extraction fractions of sestamibi and tetrofosmin are approximately 65% and 54%, respectively, under basal resting flow conditions.[5,6] Because of their lower extraction fractions compared with ^{201}Tl, the plateau in tracer uptake observed during hyperemia occurs at lower flow rates. The effect of this "roll-off" in extraction at lower flow rates is to diminish the relative difference in tracer activities between high-flow regions and those myocardial regions subtended by a coronary stenosis, making it more difficult to detect milder stenoses.

Although these agents are members of two distinct chemical classes of compounds, isonitriles and diphosphines, respectively, they share several common properties. Unlike ^{201}Tl, which utilizes a specific membrane-active transporter, these tracers are passively drawn across the sarcolemmal and mitochondrial membranes along a large electronegative transmembrane potential gradient, owing to their lipophilicity and positive charge.[7] Once inside the mitochondria, these cationic tracers are tightly bound by the potential gradient such that there is a very slow net efflux resulting in prolonged myocardial retention times. Although ATP is not directly required for the intracellular sequestration of cationic tracers, as it is for ^{201}Tl, the influx and retention of these tracers are energy dependent because the presence of a normal electronegative transmembrane gradient is required. With irreversible injury, the mitochondrial and sarcolemmal membranes are depolarized, and the uptake of these cationic tracers is impaired.[8] Accordingly, like ^{201}Tl, the cationic ^{99m}Tc-labeled agents can be used to assess myocardial viability.

In addition to the lower plateau in extraction mentioned, another disadvantage to both sestamibi and tetrofosmin is the problem of photon scatter from the adjacent liver that can interfere with the interpretation of myocardial perfusion defects, particularly in the inferior left ventricular wall. Accordingly, there has been renewed interest in recent years to design improved cationic ^{99m}Tc-labeled tracers that exhibit more rapid liver clearance. ^{99m}Tc-(N)(PNP5)(DBODC5)$^{+}$ (DBODC5) is a lipophilic nitride that is rapidly taken up and retained by the myocardium in a manner that is mechanistically similar to sestamibi and tetrofosmin. However, studies in both rats and dogs demonstrated that DBODC5 cleared more rapidly from the liver than either of these other cationic tracers, with virtually no liver activity observed after only 1 hour.[9,10] The first-pass extraction fraction of DBODC5 is intermediate to that of sestamibi and tetrofosmin.[10] Although there is no improvement in the ability of DBODC5 to track myocardial blood flow at hyperemic flow rates, its more favorable biodistribution properties offer a potential advantage that warrants further investigation.

Another new lipophilic cationic tracer with improved biodistribution and very rapid liver clearance is ^{99m}Tc-[N(MPO)(PNP5)]$^{+}$ (MPO). The myocardial uptake of MPO in Sprague Dawley rats was reported to be between that of sestamibi and DBODC5 over 2 hours.[11] Interestingly, the heart-liver ratio of MPO at 30 minutes after injection was more than twice that of DBODC5 and approximately 4 times higher than that of sestamibi.[11] With such rapid liver clearance, clinically useful images might be obtainable as early as 15 minutes post injection. At the present time, the first-pass extraction fraction studies have not been conducted using MPO.

Neutral Lipophilic Tracers

^{99m}Tc-teboroxime (teboroxime) is a member of a class of neutral lipophilic molecules known as *BATOs* (*B*oronic acid *A*dducts of *T*echnetium di*O*xime). After intravenous injection, the initial instantaneous uptake of teboroxime is high, with a first-pass extraction fraction of approximately 90%—higher than even ^{201}Tl.[12,13] However, unlike the cationic ^{99m}Tc-labeled myocardial perfusion tracers discussed earlier that are retained in the myocardium, teboroxime exhibits rapid flow-dependent myocardial clearance in under 10 minutes. Thus, although the myocardial extraction fraction that is observed immediately after injection is very high, the rapid clearance of this tracer results in a loss of defect contrast within the first 5 minutes post injection.[14] Additionally, because the myocardial clearance rate of teboroxime is flow dependent, with slower clearance from ischemic versus normally perfused zones, the differential clearance rates give the scintigraphic equivalent of "redistribution," with an apparent filling-in of the initial perfusion defects over time, as is observed with ^{201}Tl.[15] The mechanism for such rapid clearance is that teboroxime is believed not to cross the sarcolemmal membrane into the intracellular space of the myocyte, remaining instead within the intravascular space in association with the endothelial layer.[16] Furthermore, its myocardial uptake is passive, not dependent on either active transport or other energy-dependent processes. Thus, teboroxime is considered to be a pure perfusion tracer.

Although teboroxime was approved for clinical imaging at the same time as sestamibi, its rapid dynamic myocardial clearance kinetics proved difficult to image

using the relatively slow, single-head gamma cameras that were standard in the early 1990s. With the exciting new generation of fast cardiac SPECT instrumentation that has recently become available on the market, there may be renewed interest in this tracer in the future.

Another neutral lipophilic perfusion tracer that has undergone Phase III clinical testing is ^{99m}Tc-N-NOET (NOET). Like teboroxime, NOET exhibits a first-pass extraction fraction that is higher than either sestamibi or tetrofosmin, with flow-dependent differential clearance of the tracer from the myocardium.[17,18] Because of the differential clearance from ischemic versus normal zones, NOET has been shown to undergo apparent redistribution like teboroxime, albeit at a slower rate.[18,19] Another similarity between NOET and teboroxime involves their mechanism of localization in the myocardium. NOET is also believed to remain within the intravascular space in association with the endothelial layer.[20] Because of its accessibility, NOET clearance can be affected by a host of intravascular factors. Experimental studies demonstrated that the myocardial clearance rate of NOET could be accelerated not only by increasing the flow rate but also by elevating the blood lipid concentration.[16,21] Like teboroxime, the uptake and retention of NOET does not involve active or energy-dependent processes, and thus it would also be considered a pure perfusion tracer.

In summary, the advent of the ^{99m}Tc-labeled myocardial perfusion imaging agents, particularly the lipophilic cationic tracers, sestamibi and tetrofosmin, represented a major advance by virtue of their superior imaging properties compared with ^{201}Tl. Some aspects of these tracers may not be ideal, but in general they have shown excellent diagnostic accuracy and have fueled the growth of the field of nuclear cardiology for nearly 20 years. New SPECT perfusion tracers that exhibit both improved myocardial first-pass extraction fraction and more favorable biodistribution properties are clearly warranted.

MODELING TRACER EXTRACTION

If a tracer is injected intravenously, the number of tracer atoms passing through a capillary bed will be proportional to the fraction of total cardiac output passing through the capillary bed. If all the tracer atoms were extracted in a single pass through the capillary bed, the number of tracer atoms per unit volume of tissue would then be proportional to the fraction of cardiac output perfusing the unit volume of tissue. The only tracers that approximate this ideal are microspheres.

The tracers used for clinical imaging of myocardial blood flow are not completely extracted. For these tracers, the fraction of tracer extracted on passing through a capillary bed depends on the blood flow through the capillary bed. A model based on the work of Gosselin and Stibitz [22] provides insight into this process. The model is that of a diffusible tracer traveling through a cylindrical capillary. The tracer can diffuse outward from the blood across the capillary endothelium, but it can also diffuse back into the blood from outside the capillary endothelium. The outward and back-diffusion coefficients can be different. The extraction coefficient reflects the net loss in tracer concentration between the arterial and venous ends of the capillary. This leads to a tracer "extraction fraction" of the form:

$$1 - e^{-\frac{PS}{b}} \qquad (1)$$

where *PS* is a product of capillary permeability and surface area, and *b* is the capillary blood flow. The relationship between blood flow and tracer extraction predicted by this model is shown graphically in Figure 1-1. The top curve with PS = 2 would represent a tracer with high first-pass extraction, such as ^{201}Tl. The lower curve with PS = 1 would represent a tracer with lower first-pass extraction, similar to sestamibi and tetrofosmin. The term *first-pass extraction* is often used to characterize radionuclide tracers, but it is not often carefully defined. Since the extracted fraction of tracer is flow dependent, the *first-pass extraction* indicates the fraction of extracted tracer measured at baseline resting blood flow. In Figure 1-1, the first-pass extraction of the two tracers shown would be about 86% for the upper line and about 64% for the lower line.

The amount of tracer taken up by the myocardium shortly after bolus injection is the product of extraction fraction and myocardial blood flow per unit volume, denoted by the letter *b*. This product is:

$$\textit{Myocardial Extraction} \propto b\,(1 - e^{-\frac{PS}{b}}) \qquad (2)$$

Although the equation was derived for solute exchange in a single capillary, it can be shown that the functional form remains unchanged for a generalized distribution of capillaries if the parameters are taken to represent the averages over the entire capillary distribution. The curve with the functional form shown has been ubiquitous in representing myocardial uptake as a function of myocardial blood flow. Figure 1-2 shows

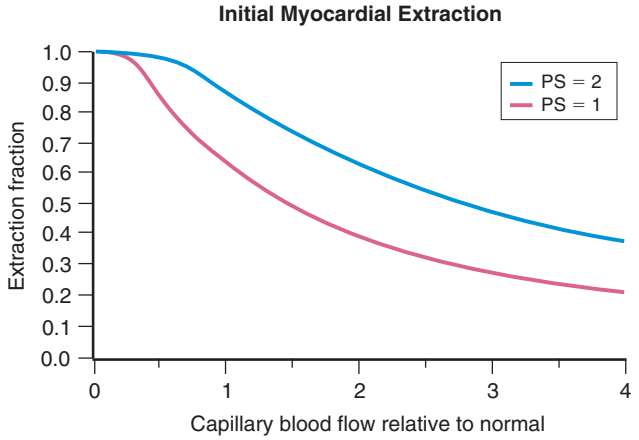

Figure 1-1 Tracer extraction fraction as predicted by the Gosselin and Stibitz model. Curves are shown for PS = 1, representing a tracer with first-pass extraction similar to the molecular Tc-99 m tracers, and PS = 2, representing a tracer with first-pass extraction of Tl-201.

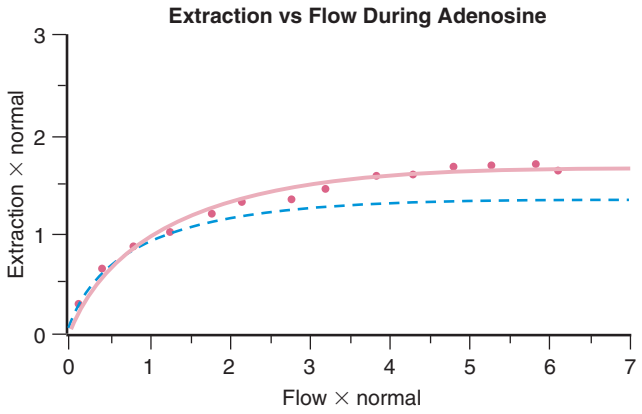

Figure 1-2 The *solid curve* shows the basic Gosselin and Stibitz model using the value of PS that produces the best fit for the extraction-versus-flow data. The *dashed curve* uses the value of PS that produces the best prediction of first-pass extraction. The model cannot simultaneously predict both sets of data using the same PS value. This indicates a flaw in the model.

some experimental data of sestamibi extraction versus blood flow. The solid line of Figure 1-2 has the functional form of Equation 2. It fits the experimental data quite well if the PS coefficient is chosen empirically to best fit the data. However, if we substitute the PS coefficient that best agrees with the first-pass extraction data, it results in the dashed line of Figure 1-2 and produces a poor fit for the flow-versus-extraction curve. The dashed line predicts a more extreme reduction of tracer extraction with increasing myocardial blood than experimentally observed.

The same PS product should predict both the measured first-pass extraction coefficient and the flow-versus-extraction curve. The fact that it does not indicates that something is wrong with the model. A possible problem with the simple Gosselin and Stibitz model is that it does not account for myocardial flow regulation by opening and closing of capillary channels. Selective opening and closing of parallel capillary channels is thought to be an important mechanism to regulate capillary resistance and myocardial blood flow. This has been experimentally demonstrated.[23,24] Further evidence for the role of capillary closure has been more recently found in the context of contrast echocardiography[25] and for sestamibi perfusion measurements in the dog model.[26]

To account for the effect of variable capillary volumes, we wish to extend the basic model as follows: The first factor in Eq. 2 is replaced by F, which represents flow per unit myocardial volume. The term b in the exponential represents flow per unit of *open* capillary volume. We now introduce a new relationship:

$$\frac{F}{b} = 1 - e^{-F} \qquad (3)$$

Equation 3 allows for flow in the open capillaries to be different from flow per unit myocardial volume determined by the arterial supply vessels. Equation 3 further introduces the assumption that capillary blood volume

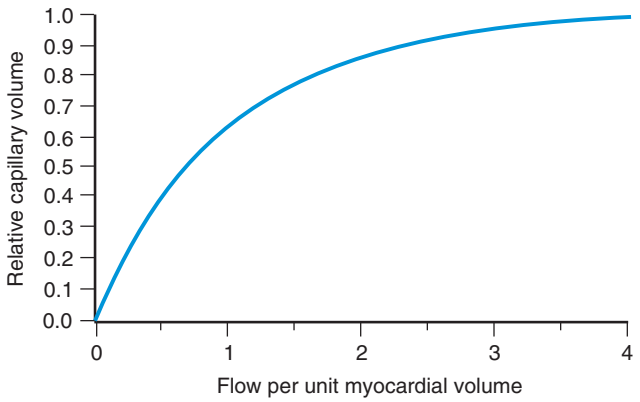

Figure 1-3 Relationship between the fraction of open capillary volume and myocardial blood flow per unit of myocardial volume.

decreases with decreasing flow due to capillary closure, and it increases to some maximum value when all the capillary channels are fully utilized at high flow. Figure 1-3 shows the relative capillary volume assumed by Eq. 3. This is in qualitative accord with the observations of Wu et al.[23] The exact way that capillary volume changes in the course of vasoregulation is unknown. Our purpose here is limited to that of showing what effect variable capillary volume would have on tracer extraction.

The effect of capillary closure can be seen in Figure 1-4. The curves of first-pass extraction become less blood-flow dependent. The first-pass extraction fraction at low flow is less than would be predicted by the basic model of Gosselin and Stibitz,[22] and the decrease of extracted fraction with increasing blood flow is less severe. The curves of Figure 1-4 are plotted for PS = 1.6 and 3.1, which represent the values that fit the experimentally measured extraction fractions of 0.64 and 0.86 for sestamibi and ^{201}Tl, respectively. These values, obtained from first-pass extraction data, were used to compute the myocardial uptake-versus-flow curves, and

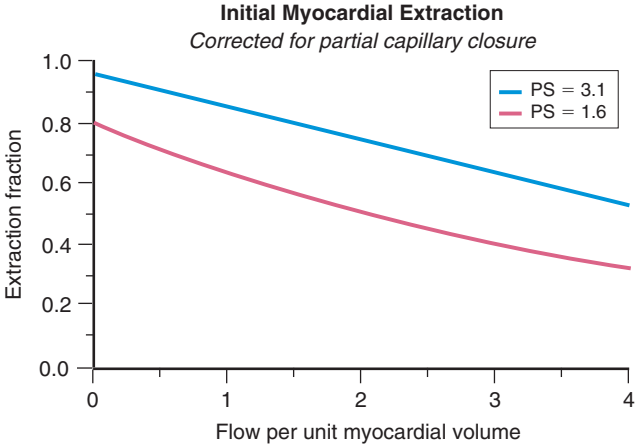

Figure 1-4 These curves show the changes in first-pass extraction caused by the introduction of variable capillary volume as assumed in Figure 1-2. Curves are for values of PS = 1.6 and PS = 3.1, which predict first-pass extractions of 0.64 and 0.86, respectively, for Tc-sestamibi and Tl-201.