REVIEW

Radionuclide-Based Insights into the Pathophysiology of Ischemic Heart Disease: Beyond Diagnosis

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Your vision will become clear only when you can look into your own heart. Who looks outside, dreams; who looks inside, awakes.

—Carl Gustav Jung (1875–1961)

ABSTRACT

This review article discusses the historical origin of cardiac radionuclide-based methods, the physiologic background that justifies their existence, as well as the basic pathophysiologic concepts of coronary artery disease and their connection with the technologic design and application of these methods. Most importantly, this review discusses the important insights that these methods have provided to the understanding of the mechanisms of ischemia, risk stratification, and both treatment choice and treatment efficacy in ischemic heart disease.

Nuclear cardiology originated as an attempt to provide complementary physiologic information to the anatomic information provided by coronary angiography. To comprehend the design and applications of nuclear cardiology methods, one must have a basic understanding of coronary artery disease as an inflammatory process that may manifest as acute or chronic states. Basic concepts on myocyte metabolic pathways, coronary blood flow, ischemic cascade, ventricular remodeling, and ejection fraction become critical for this purpose. Insights into risk stratification may permit patient-tailored therapy approaches. Insights into prognosis have made nuclear cardiology a robust tool for outcome predictions, with an exceptionally high negative predictive value. Evaluation of prognosis in special patient populations such as diabetics has originated important pathophysiologic concepts. Most insights into phenomena such as myocardial hibernation, myocardial stunning, and viability have been generated by nuclear cardiology techniques. Finally, new applications of radionuclide-based methods such as molecular identification of "vulnerable" atherosclerotic plaques, "ischemic memory" using fatty acid imaging, and myocardial innervation imaging provide new avenues for insightful research.

Key Words: radionuclide-based methods, coronary artery disease, pathophysiology

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HISTORICAL PERSPECTIVE

There was no clearly recognizable account of angina in a series of patients prior to William Heberden's in 1768.[1] The absence of descriptions of angina before 1768 could be due to one of two causes: either angina pectoris made its first appearance at about that time, or it was prevalent previously, but contemporary physicians lacked the clinical acumen to recognize it. The first cause seems to be the most likely. Furthermore, the first clinical description of a series of patients with coronary thrombosis is attributed to Herrick in 1912.[1] This makes ischemic heart disease a phenomenon of the industrialized society, brought on by the emergence of new risk factors that were rare before that time, possibly combined with an unprecedented pattern of survival into older ages. Despite such humble beginnings, ischemic heart disease is currently the leading cause of death in North America and Europe and has been the target of an unprecedented growth in medical diagnostic and therapeutic modalities made possible through ingenious biomedical engineering and technology. The accelerated development of modern cardiology has been driven by the quest for direct visualization of disease. Available technologies have been put to the task of making the disease process visible to the physician's eye. This quest has initially been anatomic, with a subsequent and necessary insight into physiologic processes being as important as and complementary to anatomy. There is no doubt that in modern cardiology, the discussion between anatomy and physiology has led to the conclusion that the truth lies not in either one but in the complementary combination of both.

Since coronary angiography became a reality by the 1960s, visual analysis of the anatomic information given

by coronary arteriograms is used to assess the clinical severity of coronary disease. The central dogma of clinical cardiology consists of relentlessly pursuing significant coronary stenoses to relieve angina and improve prognosis through both interventional and surgical techniques.[2] This dogma is based on the theory that a stenosis of a major epicardial vessel has the potential for causing ischemia that leads to angina and for closing completely, causing the death of myocardial tissue (myocardial infarction [MI]). The tighter the stenosis is, the worse the ischemia and, thus, the worse the perceived angina. The higher the number of vessels with stenoses, the higher the risk of myocardial cell death if the stenoses were to close completely. Unfortunately, the above theory, although intuitive, is not entirely true: patients without symptoms may have significant stenoses on angiography,[3] patients without identifiable stenoses may have symptoms,[4] and patients without significant stenoses may present with acute vessel thrombosis and occlusion.[5,6] These discrepancies were noted by physicians at that time and made it imperative for other diagnostic modalities, besides angiography, to exist. It was then recognized that coronary angiography failed to provide information concerning the adequacy of perfusion of myocardial cells, despite affording adequate visualization of major coronary branches.[7] There was a new necessity to assess the significance of coronary obstruction through direct visualization of myocardial perfusion. This led to the development of nuclear cardiology, an imaging technology based on the intravenous injection of small amounts of radioactive materials that are absorbed by the myocardial cells and then localized and measured using a scintillation camera, referred to as a gamma camera. Initially, calculations of blood flow per unit volume of heart muscle were developed; however, these were not diagnostically helpful. Localization of flow within regions of the myocardium was necessary to give clinical significance to the measurement of myocardial flow.[7] Localization was achieved through the addition of a collimator and a camera was designed that could efficiently detect low-energy photons emitted from radiopharmaceutical agents used at the time.[8]

Nuclear cardiology techniques have become indispensable in the evaluation of ischemic heart disease in the current state-of-the-art practice of cardiology. This review article attempts to address the basic principles and applications of nuclear cardiology and how these radionuclide-based methods have influenced our understanding of ischemic heart disease leading to the development of new concepts that go well beyond diagnosis.

BASIC PATHOPHYSIOLOGIC CONCEPTS

Atherosclerotic Coronary Artery Disease

Coronary atherosclerosis is a chronic, generalized inflammatory disease of the coronary arteries that can progress silently over many years.[9] It is initiated at an early age through endothelial dysfunction, which refers to an imbalance between the vasodilatory and vasoconstrictive properties of the endothelium, leading to a predominance of constriction. This imbalance is promoted by specific clinical and biochemical risk factors, such as smoking and hyperlipidemia. Endothelial dysfunction leads to an inflammatory process within the endothelium and adjacent tissues that ends in the formation of atheromatous ("gruel") plaque, which grows in size over time, leading to obstruction of the arterial lumen and causing ischemia and angina. An obstruction in an artery causes an increase in blood flow and a pressure drop across the stenosis.[10] These two factors are related in an exponential manner (Figure 1): beyond 70% of luminal obstruction, there is an exponential increase in resistance and in pressure drop across the stenosis (see Figure 1); this degree of stenosis (70%) proves to be blood flow limiting when myocardial oxygen demand is increased (ie, during exercise). The physiologic significance (degree of flow limitation) of mild (ie, 20%) and severe anatomic luminal obstructions (ie, 95%) is evident; however, that of intermediate lesions (ie, 50–70%) is variable[2] and remains unknown until it is evaluated by a physiologic method that can determine if the lesion is flow limiting in the setting of increased myocar-

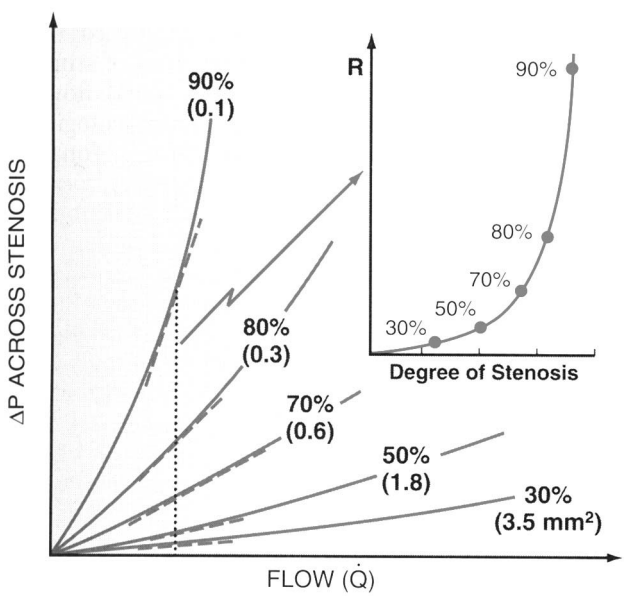

FIGURE 1 Relationship between pressure reduction across a stenosis and flow through the stenosis. Relationships are shown for concentric stenosis of 30%, 50%, 70%, 80%, and 90% internal diameter. The level of flow corresponding to basal metabolic needs is represented by the *vertical dotted line*. In the *inset* at the right, stenosis resistance is plotted as a function of the degree of stenosis. After 70%, there is an exponential increase in resistance and a drop in pressure across the stenosis. Reproduced with permission from Klocke FJ. Measurements of coronary blood flow and degree of stenosis: current clinical implications and continuing uncertainties. Newsletter of the Council on Clinical Cardiology of the American Heart Association 1982;7(3). In Braunwald E. Heart disease. 6th ed. WB Saunders Company; 2001. p. 1101.

dial metabolic demand. One physiologic method able to determine this is nuclear myocardial perfusion imaging.

Acute Coronary Syndromes

Atherosclerotic plaques can rupture at any time and cause acute thrombosis of a vessel, which may lead to total occlusion of the artery and MI or partial occlusion, leading to unstable angina; together, these are the so-called "acute coronary syndromes." The "vulnerable" plaques tend to rupture and are characterized by a large lipid core and abundance of macrophages with a small number of smooth muscle cells.[11] Vulnerable plaques that cause MI and unstable angina tend not to cause severe anatomic stenosis; in fact, in 68 to 75% of cases, MI evolves from plaque disruption in plaques that are only mild to moderately obstructive,[5,6,12] that is, less than 70% of luminal stenosis. It is important to recognize, however, that 25% of acute thrombosis leading to MI occurs in plaques that are severely obstructive through plaque erosion.[12] These observations suggest that although it is vital to address the physiologic significance of coronary stenoses through perfusion imaging methods, these are not likely to identify a subpopulation of nonobstructive vulnerable plaques. These plaques are responsible for MI and ischemic sudden death in some patients not known to have coronary artery disease (CAD). Therefore, a clear necessity to image vulnerable plaques has emerged. Radionuclide-based methods may serve as a tool to identify this patient population.

Ventricular Remodeling and Ejection Fraction

Left ventricular remodeling is the process by which mechanical, neurohormonal, and possibly genetic factors alter ventricular size, shape, and function.[13] After MI, the acute loss of myocardial cells results in abnormal loading conditions that involve not only the border zone of the infarction but also the remote myocardium. These abnormal loading conditions induce dilatation and change the shape of the ventricle, rendering it more spherical (as opposed to physiologically "bullet shaped"), as well as causing hypertrophy. Remodeling continues for months after the initial insult. The eventual change in the shape of the ventricle becomes deleterious to the overall function of the heart as a pump, contributing to the development and/or worsening of heart failure.[13] One of the ways to assess systolic function (pump function) is through the measurement of the ejection fraction (EF). The EF is the percentage of blood ejected by the left ventricle in systole, assuming that the blood volume (which equals ventricular cavity volume) at the end of diastole is 100% (end-diastolic volume − end-systolic volume/end-diastolic volume [EDV − ESV/EDV]). The normal ejection fraction is 60% ± 10. EF is the single most important determinant of prognosis in CAD. Several studies have confirmed that the EF is the strongest independent predictor of survival in patients who have suffered an MI.[14,15] A complete assessment of coronary atherosclerosis must include an accurate EF determination. Radionuclide-based methods have the capability of simultaneously measuring myocardial perfusion and EF.

Metabolic Pathways

The heart is an aerobic organ; it relies almost exclusively on the oxidation of substrates for the generation of energy and can develop only a small oxygen debt.[10] Long-chain fatty acids are the principal energy source for the normoxic myocardium and are rapidly metabolized by β-oxidation. Approximately 60 to 80% of adenosine triphosphate (ATP) produced in aerobic myocardium derives from fatty acid oxidation, whereas the remaining ATP is obtained from glucose and lactate metabolism.[16] In ischemia, the electron transport chains in the mitochondria cannot function properly owing to decreased oxygen availability, and energy is obtained in an anaerobic manner from the oxidation of glucose to lactate. Thus, alteration of fatty acid oxidation is considered to be a sensitive marker of both ischemia and myocardial damage.[16] In the same manner, an increase in glucose uptake may indicate a switch from aerobic to anaerobic metabolism owing to ischemia. Nuclear imaging techniques that can identify and localize abnormalities in myocyte metabolism represent a valuable tool for early diagnosis of blood flow impairment. Furthermore, imaging techniques capable of identifying and localizing normal metabolic pathways may "point out" areas of live myocardium in the midst of surrounding myocyte necrosis, that is, differentiate "viable" (live) tissue from dead tissue.

Ischemic Cascade

The development of an ischemic event, whether silent or painful, represents the cumulative impact of a sequence of pathophysiologic events.[17] Each ischemic episode is initiated by an imbalance between myocardial oxygen supply and demand that may ultimately be manifested as angina pectoris. This sequence of events is termed the "ischemic cascade." The significance of this concept resides in the fact that it redirects the focus from the end result, angina, to the more fundamental, underlying pathophysiologic factors that precede it.[17] Specifically, these events are temporally determined and include, in chronologic order, ischemia, perfusion abnormality, diminished left ventricular compliance (diastolic dysfunction), decreased myocardial contractility (systolic dysfunction), increased left ventricular end-diastolic pressure, ST segment changes in the electrocardiogram, and, occasionally, angina pectoris.[17] Therefore, there is a spatiotemporal disparity between abnormal perfusion and abnormal function.[18] Detection of an early pathophysiologic step in the ischemic cascade, such as abnormal myocardial perfusion

as in radionuclide-based methods, will offer great sensitivity for the diagnosis of ischemia.

The "Heart" of the Matter: Coronary Blood Flow

Coronary blood flow occurs in diastole and in resting conditions is approximately 1 to 2 cc of blood per kilogram per minute. This flow can be increased approximately 2 to 2.5 times its baseline value with exercise and 4 to 5 times with the use of pharmacologic agents that produce coronary vasodilatation, such as adenosine and dipyridamole. This "extra"coronary flow in response to physiologic or pharmacologic stimuli is termed coronary flow reserve (CFR).[10] The physiologic effect of a coronary stenosis on blood flow depends on the degree to which the resistance to flow caused by the stenosis can be compensated for by dilation of arterioles distal to the stenosis.[10] As a stenosis develops, the microvessels distal to it dilate to compensate for the reduced distal arterial perfusion pressure, maintaining normal resting blood flow.[19] Consequently, when most patients with coronary arterial obstruction are resting, they have no ischemia and therefore no angina. During exercise, however, the capacity of the microcirculation to dilate further (CFR) in response to increased metabolic demand is limited, and ischemia results. The same phenomenon can be observed with the use of intravenous dobutamine, which increases cardiac metabolic demand through augmentation of cardiac output and heart rate. When a pharmacologic vasodilator, such as adenosine or dipyridamole, is used, the CFR is activated, not owing to increased metabolic demand but through direct vasodilatation of the coronary system; this will enhance perfusion mismatches (because the normal arteries dilate maximally and the stenosis of the affected artery is a fixed obstruction to flow followed by an already maximally dilated microcirculation) but generally not cause ischemia. Coronary stenoses that stimulate compensatory dilatation of the microcirculation and limit the maximal blood flow achievable are termed "physiologically important." Hyperemic blood flow (CFR) falls significantly when 70% of the cross-sectional area of an artery is stenosed, and the resting blood flow falls when the stenosis reaches more critical levels. Gould and Lipscomb demonstrated that resting coronary blood flow is not altered until at least 85% of luminal narrowing is attained.[20] Therefore, resting coronary blood flow is not impeded by mild to moderate stenoses and is an insensitive measure of CAD, thus the need for exercise or pharmacologic tests that elicit the CFR.

Invasive techniques that physiologically evaluate stenoses have been designed for use in the catheterization laboratory. Using blood velocity across the stenosis as the variable, an index can be generated that estimates the physiologic significance of the stenosis. This is achieved using special fiberoptic wires that have a miniaturized Doppler crystal placed at the tip.[21] Velocity is measured at rest and after maximal hyperemia, usually induced by intracoronary administration of adenosine. CFR velocity is then calculated as the ratio of maximum to baseline flow velocity. Patients with a ratio equal to or less than 2 usually have other corroborating evidence of myocardial ischemia. There is a strong correlation between a ratio equal to or less than 2 and the detection of ischemia with myocardial perfusion imaging.[21] This type of invasive physiologic assessment may also be achieved with the use of intracoronary "pressure wires" that record pressures before and after the obstruction and can detect the amount of pressure drop across the lesion.[22] Because these methods are not currently used in day-to-day clinical practice, radionuclide-based applications for assessing perfusion represent the current state-of-the-art method for the noninvasive evaluation of the coronary plaque physiologic significance. Furthermore, nuclear myocardial perfusion not only identifies coronary flow limitation, it can also localize it, quantify the myocardial area affected, and assess the severity.

Coronary Angiogram: Limitations

Visual assessment of coronary stenoses by angiography is achieved by comparing the obstructed segment with a "normal" reference segment. The problem is that atherosclerosis is primarily a disease of the arterial wall, whereas an arteriogram is an image of the lumen.[19] Intravascular ultrasound technology has demonstrated that in patients with atherosclerotic CAD, the great majority of angiographic "normal" segments are diffusely diseased.[2] Mintz and colleagues studied 884 angiograms and found that only 6.8% of normal reference segments were actually normal; the rest had diffuse atherosclerosis, with a mean cross-sectional narrowing of 51% in normal segments.[23] Besides the potential to give an overall "wrong impression" of the severity of the disease, angiography relies on the estimation of obstruction by the physician, and this is subject to error. Quantitative coronary angiography[24] increases the accuracy of the estimation, but this modality has technical limitations and is time consuming; furthermore, it is generally not used in clinical practice. Coronary angiography visualizes medium to large epicardial vessels; therefore, a large part of the coronary circulation is not assessed. Mild coronary stenoses and severe stenoses can be accurately assessed by visual analysis; however, intermediate stenoses do not correlate with the physiologic significance of the stenosis[2]; in fact, one study suggests that the majority of coronary stenoses cannot be determined accurately by angiography.[25] Coronary angiography is invasive.

Despite these limitations, coronary angiography remains the "gold standard" method for atherosclerotic coronary disease evaluation because it provides the exact location and an estimate of the severity of the coronary plaque, allowing direct anatomic corroboration of noninvasive information and therapeutic planning. Further-

more, invasive catheter-based techniques have made it possible to percutaneously revascularize epicardial vessels, and this represents one of the greatest therapeutic breakthroughs of the last century.

BASIC PRINCIPLES OF RADIONUCLIDE-BASED METHODS APPLIED IN CARDIOLOGY

Based on the previous observations, the ideal method to evaluate atherosclerotic CAD should have the following characteristics: noninvasive; capable of eliciting the CRF; capable of localizing flow to specific regions of the myocardium; able to identify perfusion to its ultimate destination, the myocardial cell; able to identify an early pathophysiologic step in the ischemic cascade to guarantee sensitivity; capable of assessing metabolic changes in the myocardium; capable of simultaneously measuring other important variables, such as EF; able to minimize error through a systematic, semiquantitative method of analysis that is reproducible and time-efficient; and have the potential to develop intelligent solutions to its own limitations. These virtues are currently present in nuclear cardiology techniques.

In cardiac radionuclide-based methods, whether the radioactive materials are "taken up" by the myocardium or just pass through the cardiac chambers, their localization is most commonly accomplished using a scintillation camera or a gamma camera. A gamma camera consists of one or more high-density scintillation detectors (typically sodium iodide), whose function is that of converting incoming gamma rays into light photons. The photons are, in turn, converted into electrons by a photocathode and amplified into an electric current by a set of contiguous photomultiplier tubes directly coupled to the scintillation crystal.[26] A collimator allows the determination of the x and y coordinates of where a gamma ray arose in the patient. Collimators are metal devices (usually lead) that sit on top of the detector and let only a small part of the incoming radiation pass. The reason for this is that most radiation is scattered inside the patient and therefore must be eliminated because it carries inaccurate information as to the location of the emitting isotope. The gamma camera accumulates the coordinates of each gamma ray interaction in an image matrix. The camera rotates and takes "snapshots" at different angles; these are two-dimensional images referred to as planar images. A three-dimensional image is tomographically reconstructed[27] by filtered back-projection or iterative techniques. This reconstruction process is called single-photon emission computed tomography (SPECT), and it has revolutionized nuclear cardiology because it allows for complete reconstruction of the perfusion pattern of a complex three-dimensional structure (the left ventricle) based on the acquisition of two-dimensional images (Figure 2). Powerful processing computerized workstations allow for processing, analysis, and display of data.[26] Figure 3 shows a standard display of perfusion images from our laboratory.

This technology can generate many potential artifacts. Artifacts may be due to human error or technology based. Common artifacts include patient motion (which leads to reconstruction of distorted images), soft tissue attenuation (patients' tissues between the heart and the camera can interfere with the amount of radiation detected by the camera, thus producing low-count areas that are not real), "low counts" (owing to loss of isotope through intravenous infiltration or giving a low radiotracer dose to a large patient), inappropriate reconstruction (erroneous spatial constraints that result in "clipping" of myocardial areas, erroneous axis reconstruction), inappropriate normalization owing to intracardiac or extracardiac "hot spots" that

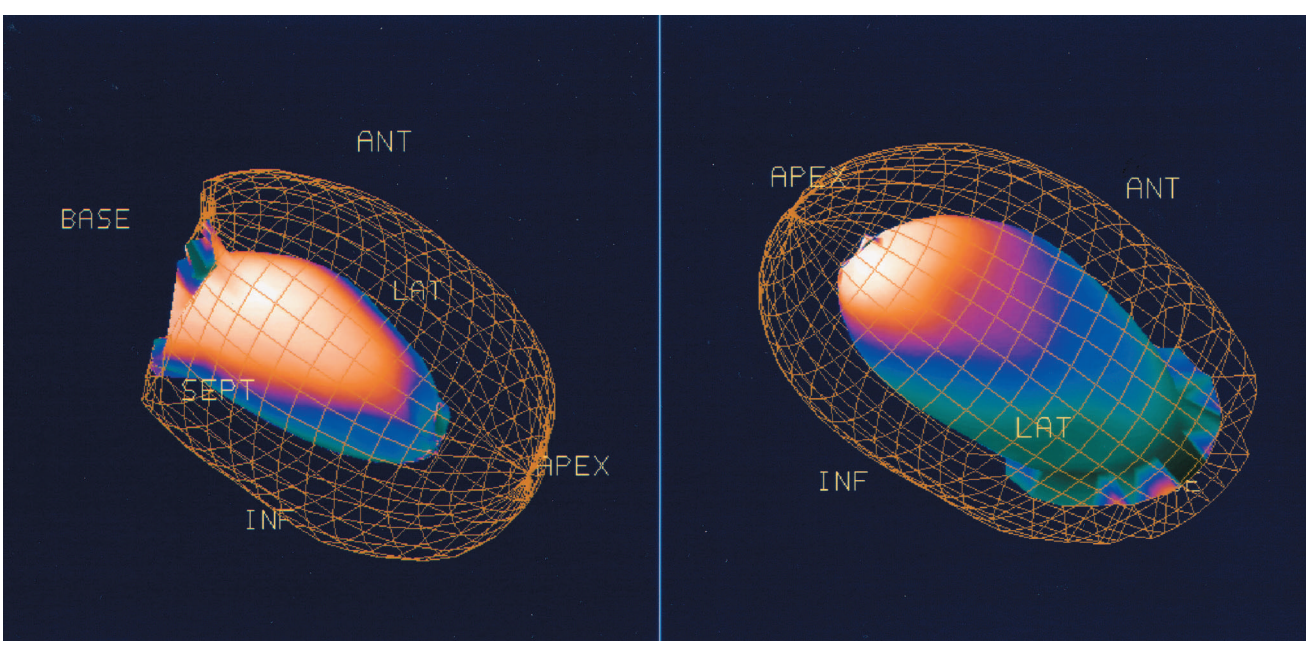

FIGURE 2 Three-dimensional reconstruction of the left ventricle by single-photon emission computed tomography.

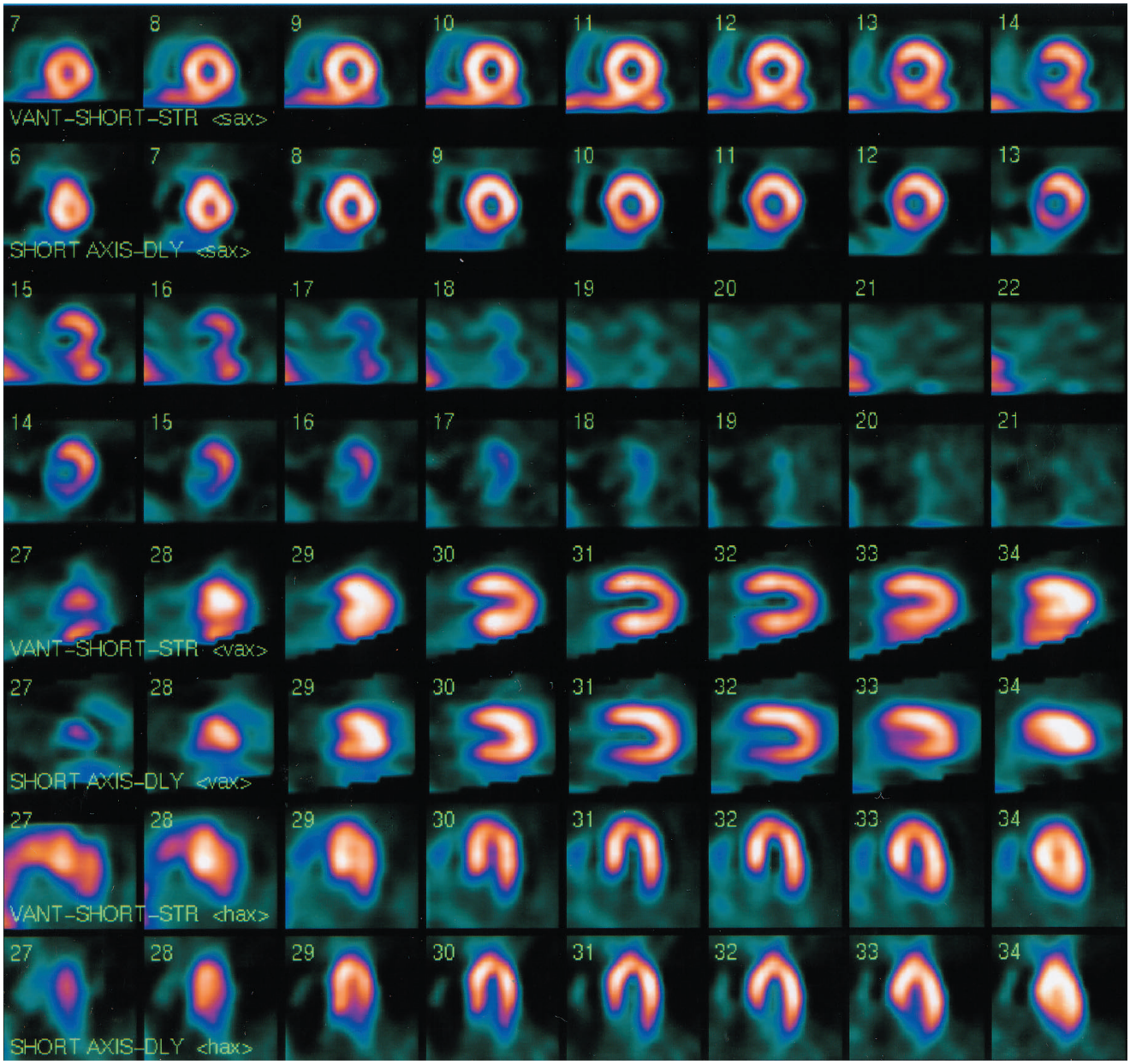

FIGURE 3 Standard tomographic projections: typical display of perfusion images. From top to bottom and left to right, the first two rows represent the short axis from apex (*left*) to base (*right*) during stress and rest, respectively. Rows 3 (stress) and 4 (rest) are the continuation of the first 2 rows toward the base of the heart. Rows 5 (stress) and 6 (rest) represent the vertical long axis from the septum (*left*) to the lateral wall (*right*). Rows 7 (stress) and 8 (rest) represent the horizontal long axis from the inferior wall (*left*) to the anterior wall (*right*). This is a normal perfusion study with technetium 99m tetrofosmin.

add or "steal" counts from the myocardium, physiologic artifacts (ie, false perfusion defects caused by intrinsic conduction abnormalities or enlarged ventricular cavities), and, finally, hardware artifacts (ie, photomultiplier tube malfunction). Fortunately, the technology allows for prevention, timely identification, and correction of most artifacts by the experienced nuclear technician and nuclear cardiologist. For example, motion artifact may be prevented by making the patient as comfortable as possible during image acquisition. Soft tissue attenuation, one of the major causes of false-positive results in SPECT, may be identified and corrected to a certain degree using "attenuation-correction" algorithms designed for that purpose.[28,29]

Regarding the assessment of ventricular function with radionuclide-based techniques, electrocardiographically gated planar acquisitions or gated SPECT is a form of dynamic imaging that can be obtained during perfusion imaging to evaluate left ventricular EF. During this type of imaging, data from several hundred different cardiac cycles are averaged into one cardiac cycle and EF is calculated based on volumetric analysis (EDV − ESV/EDV). Determining cavity volume depends on computerized detection of endocardial borders, which represents a

potential source of error; however, the technology allows for appropriate endocardial border detection verification by the physician (Figure 4). The nature of the calculation is geometric; this implies computerized reconstruction of three-dimensional images from two-dimensional ones; thus, the technique is subject to certain "software assumptions" on cavity size and wall motion that may create error. Despite these potential limitations, gated SPECT methods have been extensively validated. The advantage of this method is that it can be performed simultaneously with perfusion imaging.

Simultaneous assessment of perfusion and function has revolutionized the clinical application of nuclear cardiology and has generated new insights into the diagnostic and prognostic significance of ischemic heart disease. The methods described above allow for EF calculation and regional wall motion and wall thickening analysis; this increases the specificity of the perfusion images. For example, a perfusion defect in a stress image may represent attenuation, scar (previous MI), or ischemia (if reversibility is found on the rest image). If the wall motion and EF are normal, this would generally rule out the presence of a transmural, large scar.

Recently, Lima and colleagues demonstrated that adjunctive assessment of function in perfusion scans by gated SPECT enhances the detection of defects in multiple vascular territories in patients with severe three-vessel disease.[30] This increase in sensitivity comes without adversely affecting specificity. Postexercise EF is different (lower) from resting EF in patients with ischemia.[31] Exercise-induced (ischemia induced) left ventricular dysfunction, also called "myocardial stunning" if it persists into the postexercise period, is proportional to the amount of ischemia and is a marker of poor prognosis.[32]

Positron emission tomography (PET), although similar to SPECT, uses positron-emitting isotopes of elements naturally occurring in the human body. The obvious advantage of this approach is that substrates and drugs can be labeled with those isotopes without having their biochemical or biologic properties altered.[26] This allows PET to use metabolic markers, such as glucose (^{18}F-fluorodeoxyglucose), for the assessment of metabolic pathways in the myocyte. Second, two high-energy (511 keV) gamma rays are emitted simultaneously as a result of positron annihilation; these two gamma rays travel in opposite directions and are detected electronically by

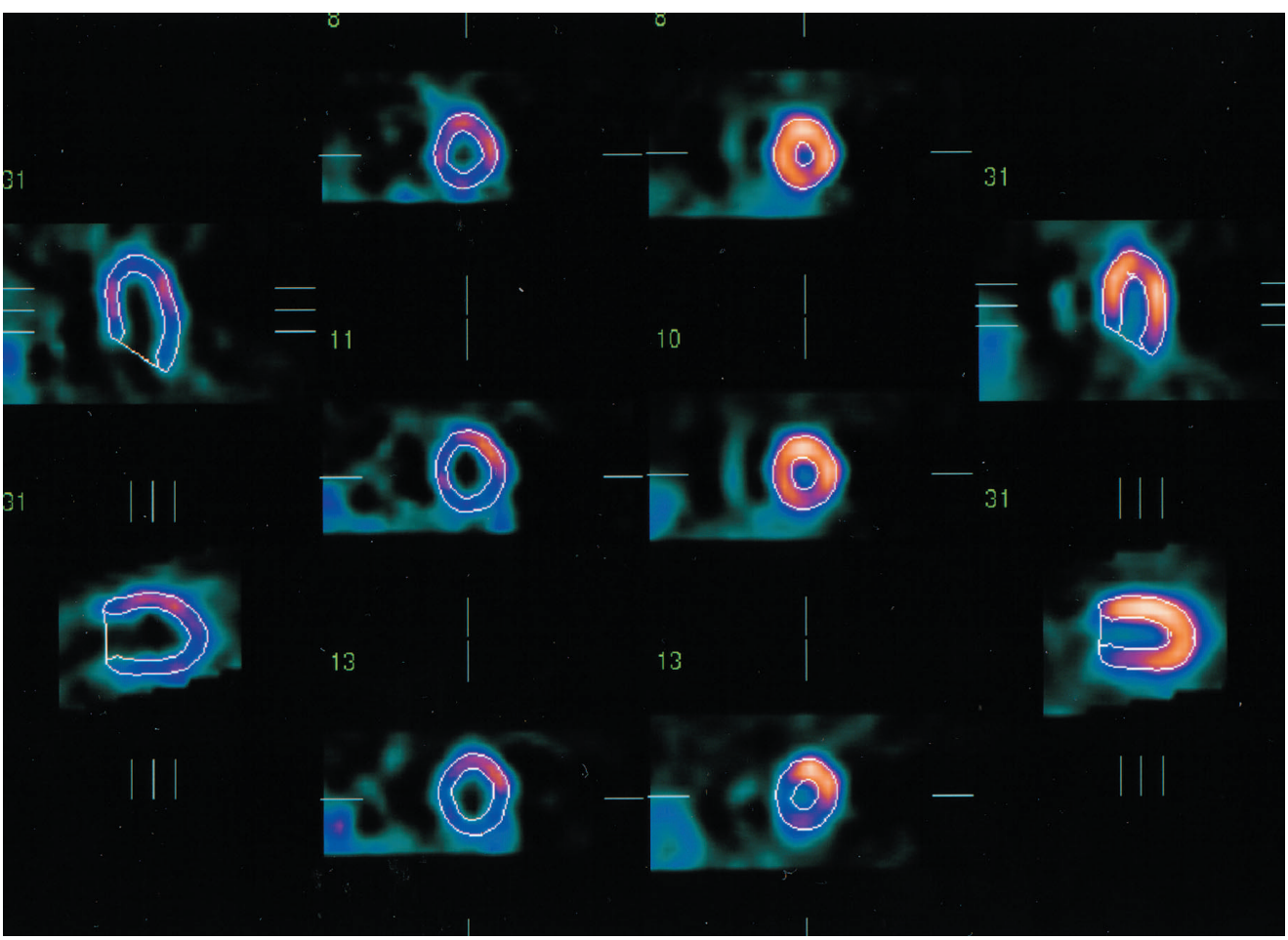

FIGURE 4 Gated single-photon emission computed tomographic analysis for geometric determination of ejection fraction. Endocardial borders are delineated by "contours," a quality control measure that allows the nuclear cardiologist to verify proper border detection.

opposing detectors instead of a collimator. This reduces the chance of attenuation artifact and increases sensitivity and specificity. The limitation of this technique lies in the fact that the radiotracers have a very short half-life; thus, the cyclotron that generates them has to be within the premises, and this results in excess cost and space use. PET is currently the gold standard technique for evaluating viable myocardium.

BEYOND DIAGNOSIS

The radiopharmaceutical agents most commonly used in nuclear cardiology are thallium 201 and technetium 99m. They are both "taken up" by the myocardial cell. The sensitivity of myocardial perfusion SPECT for the detection (diagnosis) of obstructive CAD is, on average, 87 to 89%, with a specificity of 73 to 75% (91% when corrected for referral bias), regardless of the technique (exercise or pharmacologic) or radiopharmaceutical agent (thallium 201 or technetium 99m) used.[33] Thallium 201 may be slightly more sensitive than technetium 99m because of a greater initial extraction by the myocytes, and technetium 99m may be slightly more specific owing to decreased attenuation artifact.

Insights into the Mechanisms of Ischemia

False-positives have taught us several points. Referral bias (specificity determinations in patients with normal angiograms) is a cause of apparently decreased specificity. The limitations of the technology itself (ie, attenuation) are a true cause of decreased specificity. But are all false-positives really false-positives, or may they represent exquisite sensitivity? Abnormal perfusion scans in patients with normal coronary arteries or nonobstructive CAD on angiography may carry important information because CFR is determined not only by the patency of the conduit but also by endothelial function, which translates into vasodilatory capacity. One important observation supporting this concept is the fact that after successful percutaneous revascularization, perfusion scans may remain abnormal (ischemic) for a period of time before returning to normal.[34,35] This phenomenon is probably related to severe residual endothelial dysfunction (decreased vasodilatory capacity) of the affected vessel despite a patent lumen. This may explain, in part, why exercise SPECT provides independent and incremental prognostic information even when catheterization data are available.[36] It may also explain why patients with angina and normal or near-normal coronary angiograms may exhibit perfusion abnormalities, the so-called "syndrome X." In syndrome X, those with perfusion abnormalities and mild nonobstructive CAD by angiography have a mildly decreased 7-year survival (96% in patients with normal angiograms versus 92% in mildly abnormal angiograms; $p < .0001$).[37] These observations suggest possible coronary artery endothelial dysfunction in the absence of epicardial obstructive disease, which is recognized by nuclear perfusion. Furthermore, it has been shown that endothelial dysfunction in humans may be associated with perfusion abnormalities in patients with minimally obstructive CAD.[38] This exquisite sensitivity explains why the most valuable feature of myocardial perfusion imaging is, perhaps, its excellent negative predictive value for predicting a low combined cardiac death and nonfatal MI rate in patients with completely normal perfusion.[33] The notion that normal angiographic coronaries may coexist with myocardial vascular dysfunction leading to ischemia has been supported indirectly by nuclear techniques: phosphorus 31 nuclear magnetic resonance spectroscopy can be used to measure myocardial high-energy phosphates and thus identify decreases in these energy compounds suggestive of ischemia. Using this technology, Buchthal and colleagues provided direct evidence of an abnormal metabolic response to handgrip exercise in some women with chest pain and no angiographically significant coronary stenoses.[39] Recently, Ammann and colleagues showed a significant incidence of left ventricular hypertrophy and left anterior fascicular block in patients with reversible perfusion defects without significant CAD on angiography.[40] This finding suggests the presence of other mechanisms other than epicardial vessel obstruction as causes of abnormal myocardial cell perfusion. Together, this evidence suggests that the flow-limiting coronary stenosis (> 70%), although an expression of severe, advanced CAD, represents only a part of the spectrum of a disease that is determined not only by anatomy but also by complex, dynamic pathophysiologic processes, which include biochemical and metabolic alterations. These pathophysiologic processes are susceptible to direct and indirect characterization by radionuclide-based methods applied in cardiology. This way, we are able to classify CAD into obstructive (flow limiting) and nonobstructive, which basically highlights the importance of nonobstructive CAD as an active disease process that warrants aggressive management. As mentioned earlier, a large number of atherosclerotic plaques prone to disruption and thrombosis are nonobstructive lesions.

Risk Stratification Based on Perfusion: A Guide to Therapy

Prognostication has always been essential to the art of medicine. The increasing emphasis on the right of patients to be involved in decisions about their care clearly requires the generation and communication of "predictions" by physicians.[41] Prognostication allows for stratifying patients by risk, permitting the application of different levels of therapy for each case. The 12-year follow-up of survival in the randomized European coronary surgery study and the 11-year follow-up of survival in the Veterans Administration randomized trial of coronary bypass surgery for stable

angina both showed a significant survival benefit with revascularization over medical therapy via the use of coronary bypass surgery (92% vs 83% at 5 years; $p < .0001$ and 77% vs 70% at 7 years; $p = .043$, respectively).[42,43] The benefit of surgical revascularization tended to be greater in the highest-risk patients (left main or three-vessel coronary critical disease) and declined over time. With the clear exception of patients with left main critical obstruction (who fare better with surgery), the method of revascularization does not seem to matter: King and colleagues reported that the survival benefit associated with revascularization therapy in high-risk patients was independent of the use of angioplasty or surgery.[44] This finding was later corroborated in the larger Bypass Angioplasty Revascularization Investigation (BARI), with the exception of diabetic patients with multivessel disease, who benefited more from surgery as the means for revascularization.[45] Unfortunately, these trials were performed before current state-of-the-art medical therapy (angiotensin-converting enzyme inhibitors and 3-hydroxy-3-methylglutaryl coenzyme A [HMG-CoA] reductase inhibitors) was fully implemented; thus, they represent a somewhat "unfair" comparison between medical therapy and revascularization. However, recently, Hachamovitch and colleagues reported a comparison of the short-term (mean follow-up 1.9 years) survival benefit attained with current medical management compared with revascularization in a large population of patients whose disease severity was pre-evaluated by nuclear perfusion.[46] They found a statistically significant survival benefit (mortality 2.8% vs 1.3%; $p < .0001$) with revascularization only in patients with moderate to large amounts of inducible ischemia on perfusion SPECT (high-risk patients). Survival was greater in the medical therapy arm only for patients with mild or no ischemia detected by perfusion imaging. These trials suggest that it is useful to risk-stratify patients to allocate them to the best therapy (ie, medical therapy versus medical therapy plus revascularization). However, the potential benefits of current medical therapy over revascularization are still being evaluated, and radionuclide-based methods have been indispensable in this task: several trials have shown improvement of SPECT myocardial perfusion in patients with obstructive CAD after treatment with HMG-CoA reductase inhibitors without mechanical revascularization.[47–49] Interestingly, improvement in perfusion sometimes is not related to the amount of lipid lowering, suggesting an improvement in endothelial function and/or other mechanisms.[50] An improved prognosis has been observed after normalization of the perfusion scans in ischemic patients treated with these medications.[51] For now, medical therapy and revascularization should be viewed as complementary rather than opposing strategies and nuclear perfusion not only as a prognostic aid in the decision making[52] but also as a way to "follow up" the progression or regression of disease and the effectiveness of therapy.

Prognostic Significance of Nuclear Myocardial Perfusion

Uncovering a physiologically significant coronary lesion has a high diagnostic value, but does it have prognostic value? Does a coronary lesion confer additional risk because it has become flow limiting?[19] If so, how would we reconcile that with the fact that a considerable number of acute coronary artery occlusions occur in non–flow-limiting lesions (vulnerable plaques)?[5,6,12]

Nuclear perfusion imaging has made the prima facie case for a higher risk in patients with flow-limiting stenoses. This notion represents at least a partial challenge to the concept of non–flow-limiting stenoses being the most vulnerable. Hachamovitch and colleagues evaluated prospectively the incremental prognostic value and role in risk stratification of myocardial perfusion SPECT in 2,200 patients without previously documented ischemic heart disease.[53] Based on Bayes's theorem, the accuracy of any test that is not 100% sensitive and 100% specific depends on the pretest probability of disease in the patient population being studied.[54] Based on this premise, the authors concluded that in a patient population at overall low risk (low pretest probability), myocardial perfusion SPECT adds incremental information and risk-stratifies patients even after clinical and exercise information is known: in patients with a high-risk exercise stress test, the presence of a normal scan decreased the rate of hard events (MI or cardiac death) from 7.7%/year to 3.5%. In patients with a low-risk exercise stress test but a high-risk scan, the rate of events increased from 0.9%/year to 7.8%. Pamelia and colleagues studied the prognosis of 349 patients with chest pain who underwent thallium 201 scintigraphy.[55] After a mean follow-up of 34 months, the combined incidence of cardiac deaths and nonfatal MIs was 1.1%/year in patients with a normal perfusion scan. This risk increases only to 2 to 3%/year in patients with known CAD and normal perfusion scans[56,57] versus up to 33%/year if severe ischemia is detected in a patient with known CAD.[56] In patients with no known CAD and positive ST depressions on exercise, a normal scan portends a good prognosis, making many of the ST depressions be ultimately classified as false-positive responses.[55] In general, the combined annual death or nonfatal MI rate is approximately 0.6% in patients with normal perfusion scans and 7.4% in patients with abnormal scans.[33] Iskandrian and colleagues followed 316 medically treated patients with angiographically defined CAD and previous SPECT perfusion imaging for 28 months.[36] They reported the size of the perfusion abnormality to be the single most important prognosticator. Transient ischemic left ventricular dilatation further enhanced the prognostic power. If the outcome is ischemic events, such as unstable angina and nonfatal MI, the amount of ischemia (reversible defect size) is the most important predictor. If the outcome is cardiac death, then the amount of ischemia plus total perfusion abnormality (fixed and reversible) is the most important predictor.[58]

The latter predictor is directly related to EF; the more scar there is, the lower the EF and the greater the mortality. Myocardial scars create an electrically unstable environment around them that predisposes the patient to the development of ventricular arrhythmias. Scars also lead to ventricular remodeling and heart failure. Heart failure and ventricular arrhythmias are the causes of death in ischemic heart disease. The incremental prognostic value of left ventricular EF over perfusion has been studied by Sharir and colleagues.[59] One thousand six hundred eighty consecutive patients undergoing SPECT myocardial perfusion imaging were followed for a mean of 569 days. Patients with an EF of > 45% had a mortality rate of < 1%/year regardless of perfusion defect sizes. Patients with an EF < 45% had high mortality rates, even with only mild to moderate perfusion abnormalities (9.2%/year; $p < .00001$).[59]

Within the previous discussion, the prognostic significance of EF and normal and markedly abnormal perfusion is well established; however, what is the importance of minimally abnormal perfusion scans? The importance of mildly abnormal scans has been studied by Hachamovitch and colleagues, who reported a low risk of death but an increased risk of MI (from 0.7%/year in normal scans to 2.6%/year in mildly abnormal scans) in 5,183 consecutive patients undergoing SPECT myocardial perfusion imaging.[60]

Why does identification of obstructive CAD by SPECT predict the occurrence of acute coronary syndromes and confer a worse prognosis if the most vulnerable plaques are generally nonobstructive? Obstructive lesions cause ischemia; thus, it would seem logical to think that active ischemia may predispose patients to cardiac death by inducing lethal ventricular arrhythmias. However, it has been shown that there is only a small relationship between transient ischemia and ventricular arrhythmias,[61–63] so ischemia per se (without infarction) is probably not a cause of death. Therefore, the most likely explanation is that the presence of obstructive lesions is a marker of atherosclerotic burden, so that for every obstructive stenosis, there are many nonobstructive or vulnerable lesions that predispose the patient to acute vessel thrombosis. However, if the obstructive lesions are revascularized and the perfusion scan normalizes, then the risk decreases (although not to the level of non-CAD patients),[56,57] suggesting that the obstructive lesion itself may carry a risk of rupture and thrombosis that is greater than thought. In fact, some autopsy studies have revealed that plaque rupture in fatal acute MI occurs more commonly than thought at sites of severe narrowing.[64,65] Also, logically, there is probably a worse outcome if a nonobstructive lesion becomes unstable (plaque rupture) in a vessel that already has a critically obstructive lesion. Another possible explanation is that after diagnosis and revascularization of the obstructive lesions, the intensive medical treatment that follows has the ability to stabilize the less obstructive, more vulnerable lesions still present, preventing plaque rupture and acute coronary syndromes and, thus, improving prognosis. Another possible explanation for obstructive CAD as a marker of bad prognosis is the fact that chronically underperfused myocardium or myocardium exposed to recurrent ischemic episodes may develop a state of "hibernation" that may lead to advanced cell degeneration[66] and, thus, a worse prognosis.

Prognosis in Diabetic Patients

The evaluation of a perfusion imaging–derived prognosis in diabetic patients has led to important pathophysiologic insights in this population. Giri and colleagues followed 4,755 patients with angina for a mean of 2.5 years after perfusion scans were done.[67] Nine hundred twenty-nine patients were diabetic. Diabetic patients, despite an increased revascularization rate, had 8.6% cardiac events (MI, cardiac death) versus 4.5% in the nondiabetic cohort ($p < .0001$). Several pathophysiologic mechanisms are likely to be related to these findings. Insulin resistance decreases fibrinolytic activity.[68] Diabetes is also associated with increased oxidative stress and inflammation[69] and platelet dysfunction.[70] These pathophysiologic states lead to a rheologic milieu that promotes both atherosclerosis and instability of the atherosclerotic plaques and may explain why diabetic patients have a worse prognosis. High-risk diabetic patients likely fare better with surgical revascularization[45] than with angioplasty, thus the importance of risk stratification in the population.

From the previous analysis, we may conclude that, pathophysiologically, the prognosis of ischemic heart disease depends on the following:

1. Factors related to the atherosclerotic plaque itself, with the "vulnerability" of the plaque and the severity or extent of luminal obstruction being equally important. Nonobstructive vulnerable plaques require aggressive risk factor modification and medical treatment. Obstructive lesions may require a combination of revascularization and medical treatment.
2. Factors related to the environment that surrounds the plaque, the rheologic milieu. These factors are also susceptible to risk factor modification and medical therapy.
3. Left ventricular function. This factor is susceptible to medical treatment that may prevent and regress remodeling and prolong life.[13]

Vulnerable Plaque Identification

From the previous discussion, it is evident that recognizing nonobstructive lesions as bearers of vulnerability to plaque rupture is not essential for the management of known obstructive CAD; however, it becomes essential for understanding why some patients with normal perfusion develop acute coronary syndromes. This population of patients without known CAD or symptoms of ischemia

and the presence of vulnerable nonobstructive plaques may present with sudden cardiac death without warning. Attempts to visualize vulnerable atherosclerotic plaques in experimental settings have been successful. Narula and colleagues have shown the feasibility of imaging atherosclerotic lesions with radiolabeled antibodies directed against components of the atherosclerotic plaque.[71] Directing radiolabeled antibodies against proteins involved in the generation of vulnerable plaques, such as matrix metalloproteinase and annexin V, has been achieved in animal models and holds promise for imaging in humans.[72] These methods are not used clinically at this time. Appropriate, early risk factor assessment that includes clinical and biochemical risk factors such as blood lipids and C-reactive protein measurements is warranted.[73] Aggressive risk factor modification and treatment of these markers in an effort to stabilize vulnerable plaques are an appropriate primary prevention strategy at this time.[74]

Hibernation, Stunning, and Viability

Over the past two decades, pathophysiologic paradigms concerning the relationship between myocardial perfusion and left ventricular function have changed considerably with the introduction of the hibernating and stunned myocardium concepts.[75] In 1971, Rees and colleagues reported the positive influence that aortocoronary bypass surgery had on left ventricular performance in patients with CAD.[76] There was postsurgical improvement in the function of myocardial segments that were "hypokinetic" or "akinetic" before surgery. This led to the insight that ischemic noninfarcted myocardium can exist in a state of functional hibernation.[77] Up to 50% of patients with previous infarction may have areas of hibernating tissue mixed with areas of scar tissue, even in the presence of Q waves on the electrocardiogram. Hibernation is an adaptive response of the myocardium in which viable (live) but hypocontractile myocardium arises from prolongued myocardial hypoperfusion at rest, derived from severely stenosed lesions. In contrast, stunned myocardium refers to the state of delayed recovery of regional myocardial dysfunction after a transient period of ischemia that has been followed by reestablishment of flow.[75] Post-stress EF nuclear SPECT measurements are based on the concept of detecting stunning after ischemia. In acute vessel occlusions, there is postrevascularization stunning, which may take days to weeks to recover.

Noninvasive quantification of myocardial perfusion by PET, considered the most accurate method of measuring blood flow in humans, has provided evidence that blood flow in hibernating myocardial segments may not be decreased to an extent that would account for the degree of cardiac dysfunction. This suggests that in some patients, the state of hibernation is the result of multiple episodes of demand-induced ischemia that have caused "repetitive stunning," which has become cumulative, not allowing full recovery of function.[77] Independent of the pathophysiologic mechanism, hibernating myocardium is characterized histopathologically by loss of contractile proteins (sarcomeres), the presence of multiple small mitochondria, nuclear abnormalities, and loss of sarcoplasmic reticulum in a substantial number of myocytes.[78,79] There is a direct correlation between the severity of the histopathologic changes and the possibility of recovery after revascularization.[80] Identifying hibernating viable myocardium in areas of decreased myocardial function offers the potential of reinstituting blood flow to areas of the myocardium that may recuperate function, thus increasing EF and improving the prognostic outlook.

The diagnostic approach consists of comparing the function, perfusion, and metabolic activity of the myocardium; if we can prove that a hypokinetic or akinetic myocardial region has decreased perfusion but retains metabolic activity, we can restore perfusion to that region via revascularization in the hope of terminating the hibernation state and restoring contractile function to that region. Radionuclide-based techniques are capable of generating information on function, perfusion, and metabolism. The gold standard technique is the combined analysis of myocardial perfusion and glucose use in corresponding myocardial segments obtained by PET.[81] Using ^{13}N-ammonia to identify perfusion and ^{18}F-fluorodeoxyglucose to identify viability (ischemic cells decrease fatty acid oxidation and increase anaerobic glucose use), three possible combination patterns may result (Figure 5):

1. Normal. There is normal blood flow and glucose use.
2. Mismatch. There is a reduction in blood flow, with maintained or augmented glucose use.
3. Match. There is a concordant reduction in blood flow and glucose use, which usually indicates scar.

The mismatch pattern is associated with reversible myocardial dysfunction: viability.[81] It is important to recognize that mismatch does not necessarily imply recovery of contractile function because scar and viable tissue frequently coexist in a given myocardial segment; therefore, dead tissue may be near viable tissue and preclude contractile recovery. Because thallium 201 and technetium 99m depend on myocyte viability to be taken up from the bloodstream and their initial uptake reflects perfusion, whereas their later "redistribution" reflects viability, these two agents are used in SPECT viability determinations with acceptable sensitivity.[77] An uptake of more than 50 to 60% of that in the normal area on redistribution (thallium 201) images or residual uptake (technetium 99m) is the best predictor of functional recovery after revascularization.[77]

Allman and colleagues performed a meta-analysis of 24 viability trials resulting in 3,088 CAD patients with a mean EF of 32% who underwent viability studies, followed for a mean of 25 months.[82] In patients with viability, revascularization was associated with a 79.6% reduction in annual mortality (16% vs 3.2%; $p < .001$) compared with medical

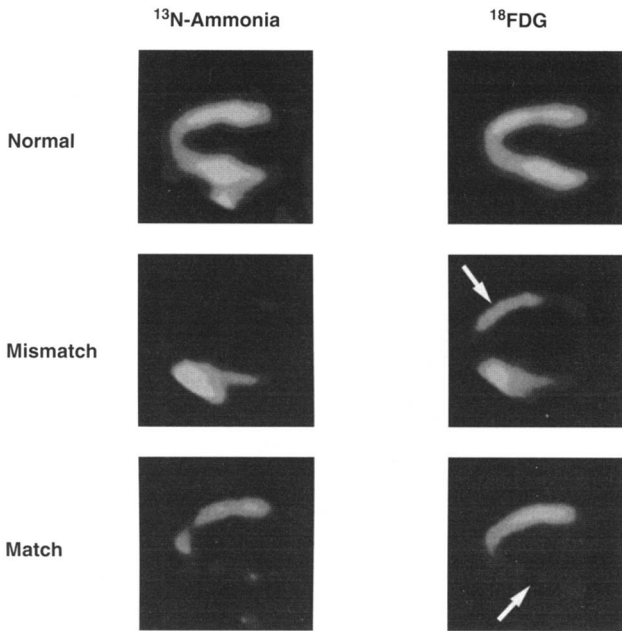

FIGURE 5 Vertical long-axis positron emission tomographic images are shown for ^{13}N-ammonia and ^{18}F-fluorodeoxyglucose. The top panel shows a normal pattern. The middle panel shows discordance between ^{13}N-ammonia and ^{18}F-fluorodeoxyglucose uptake (mismatch) in the anterior wall (*arrow*), indicating viability. The inferior panel shows concordance (match) in the inferior wall, indicative of scar (*arrow*). Reproduced with permission from Arrighi JA, Dilsizian V. Myocardial viability, radionuclide-based methods. In: Pohost GM, O'Rourke RA, Berman DS, Shah PM, editors. Imaging in cardiovascular disease. Philadelphia: Lippincott Williams & Wilkins; 2000. p. 224.

treatment. Patients without viability undergoing revascularization had the same intermediate mortality as medically treated patients. The techniques used in these studies were thallium 201 SPECT, ^{18}F-fluorodeoxyglucose PET, and dobutamine echocardiography. The latter technique identifies "contractile reserve" with the use of an inotrope (dobutamine) as a surrogate for identifying live myocardium. There was no performance difference for predicting revascularization benefit among the three techniques.

Chronic hibernation may lead to myocyte degeneration,[66] which may eventually be irreversible. This occurs by necrosis or by programmed cell death (apoptosis).[75] Recently, Bax and colleagues studied 85 CAD patients with low EF and substantial viability to determine if timing of revascularization influences prognosis.[83] The patients were divided into early (< 1 month) and late (> 1 month) revascularization. On long-term follow-up (up to 2 years), the mortality rate in the early group was 5% versus 20% in the late group ($p < .05$), which waited a mean of 85 days for revascularization. These findings confirm that chronic hibernation may lead to irreversible cell damage and highlight the importance of timely revascularization. Identifying the "point of no return" in chronic hibernation is of critical importance in avoiding the risk of revascularization in patients whose recovery potential is minimal. We believe that this is a fertile research area.

Fatty Acid Imaging

Radionuclide-based methods in cardiology allow for imaging of physiology and metabolism. Based on the metabolic principles discussed previously, radiolabeled fatty acid tracers represent potential probes to evaluate differences in myocardial oxidative metabolism. Fatty acid PET is a well-established method to probe myocardial metabolism.[16] Iodine 123 is an excellent radionuclide for labeling fatty acids. Labeled fatty acids have been studied for use with SPECT and appear to be as good as more conventional radionuclides for imaging ischemia and myocardial viability.[16] The branched-chain fatty acid ^{123}I-βmethyliodophenylpentadecanoic acid is possibly the most studied.

In a similar manner, as glucose uptake increases during "PET ischemia," fatty acid use decreases. Therefore, in hibernating myocardium, viability will be marked by a perfusion-metabolism mismatch; this time, both perfusion and fatty acid uptake will be decreased, but the fatty acid uptake decrease will be greater than the perfusion decrease. This represents a persistent metabolic abnormality that is out of proportion to the perfusion abnormality. Matsunari and colleagues showed that this metabolic abnormality may be reversible after appropriate revascularization.[84] Taki and colleagues studied 34 patients with chronic CAD who underwent conventional viability studies and fatty acid SPECT before and 2 to 5 weeks after revascularization.[85] EF improvement after revascularization correlated best with the area of improved fatty acid uptake after revascularization. Areas of discordant fatty acid uptake less than perfusion before revascularization were a good predictor of improvement in EF. Nakajima and colleagues studied 32 patients with vasospastic angina and compared resting perfusion versus resting fatty acid uptake after induction of vasospasm in the catheterization laboratory.[86] Of 32 patients with induced vasospasm, 25 (78%) had reduced fatty acid uptake and only 10 patients (31%) had perfusion abnormalities. These findings suggest that in the ischemic cascade, metabolic alterations may precede detectable perfusion abnormalities; thus, metabolic assessment of ischemia may be highly sensitive.

Finally, Naruse and colleagues, studying patients after revascularization for acute MI, showed that abnormal fatty acid uptake correlated best with wall motion defects observed during the acute event (active ischemia) than after revascularization, making SPECT fatty acid uptake a candidate for providing a "memory image" of ischemic damage.[87] The ability to uncover an "ischemic memory" may be of great value in localizing target or culprit vessels after ischemia has occurred (ie, spontaneously recanalized

epicardial vessels after acute thrombosis) or in correlating previous symptoms with true ischemia.

Myocardial Innervation Imaging

The primary route of communication between the brain and the heart is through the sympathetic nervous system. The heart is densely innervated with sympathetic nerves.[88] Metaiodobenzylguanidine (MIBG), an analogue of the false adrenergic transmitter guanethidine, shares similar uptake and storage mechanisms with norepinephrine; thus, it localizes to myocardial sympathetic nerve endings. ^{123}I-labeled MIBG is currently used experimentally to identify sympathetic innervation heterogeneity within the heart. After MI, sympathetic denervation occurs and areas of innervation heterogeneity develop within and around the scar that may predispose the patient to the initiation of ventricular arrhythmias.[89]

It has been shown that areas of denervation become supersensitized to catecholamines,[90] which predisposes the patient to generation of cardiac arrhythmias and explains partially why β-blockade reduces arrhythmogenicity in ischemic heart disease. These observations have opened another pathophysiologic area of investigation in the study of sudden death in ischemic heart disease.

SUMMARY

Radionuclide-based methods applied in cardiology have played a critical role in the quest for visualization of pathophysiologic processes in ischemic heart disease. These methods have aided in the generation of important insights that go well beyond diagnosis and represent an expansion of the medical intellect into the physiologic, metabolic, and molecular bases of ischemic heart disease. Technologic advances in bioengineering have revolutionized these methods, conferring high accuracy, feasibility, and the potential for multiple applications. Assessment of prognosis and risk stratification in ischemic heart disease by nuclear cardiology techniques has enabled cardiologists to provide accurate outcome predictions and patient-tailored therapeutic approaches. Furthermore, these techniques allow adequate follow-up of ischemic heart disease and can evaluate the efficacy of interventions. Metabolic nuclear cardiology techniques may timely identify appropriate candidates for mechanical revascularization and may provide an ischemic memory of past events to the ischemic heart. Molecular nuclear cardiology techniques hold the potential of identifying asymptomatic populations at high risk of ischemic cardiac events.

Radionuclide-based methods represent one of the basic experimental tools for the generation and study of new pathophysiologic insights that have changed our understanding of ischemic heart disease. These insights hold the potential for generating new therapeutic approaches that may increase the quantity and quality of life of our cardiac patients.

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