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Application of technetium-99m sestamibi single photon emission computed tomography in acute myocardial infarction: measuring the efficacy of therapy

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Infarct size and myocardial salvage measured by technetium (Tc)-99m sestamibi single photon emission computed tomography (SPECT) imaging have been applied as surrogate endpoints in clinical trials of acute myocardial infarction (MI). The major advantage of these endpoints over mortality is the ability to use much smaller sample sizes to compare different treatment strategies in acute MI. Multiple categories of evidence validate SPECT infarct size and myocardial salvage as surrogate endpoints, including: association with other variables used to measure infarct size; association with markers of myocardial perfusion; identification of myocardial fibrosis in pathology specimens; prediction of improvement in dysfunctional myocardial segments following revascularization; correlation between infarct size and mortality; and, demonstration that therapies which result in smaller infarct size also result in better clinical outcome in the same patients. These SPECT endpoints have been applied in over 30 clinical acute MI trials. Approximately one-third of these trials reported positive results in the intervention group or a subset of the intervention group. SPECT infarct size and myocardial salvage are the most extensively validated and widely applied surrogate endpoints in the setting of acute MI.

KEY WORDS: Myocardial infarction - Technetium Tc 99m sestamibi - Tomography, emission-computed, single-photon.

During the past quarter century, there has been a dramatic improvement in the treatment of patients with acute myocardial infarction (MI). Reperfusion therapy administered as either a thrombolytic agent or direct percutaneous coronary intervention has resulted in a significant reduction in acute and longer term mortality for patients with ST-segment elevation MI (STEMI).[1, 2] Despite these impressive advances, patients with MI continue to have a considerable early and later mortality rate. Early mortality rates in clinical trials where all patients were treated with reperfusion therapy have been 5% or lower,[2] but mortality rates in "real-world" settings are higher. Recent publications have reported in-hospital mortality for patients with STEMI of 12.1% for 126,172 patients in the National Registry of Myocardial Infarction database,[3] and a range of 4.2% to 13.5% across 21 countries in Europe with a median value of 9%.[4] The Canadian Assessment of Myocardial Infarction study reported a one-year posthospital discharge mortality of 7%.[5] Given these mortality rates, efforts should continue to try to lower mortality further.

The ultimate measure of success of any new treatment strategy or new therapy is a reduction in mortality. However, given the low mortality rates in clinical trials of patients treated with reperfusion therapy, it has become increasingly difficult to demonstrate a mortality advantage of a new treatment strategy or therapy *versus* standard care. Power calculations indicate that approximately 10 000 patients per treatment arm are required to demonstrate a statistically significant mortality difference between treatment strate-

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gies for STEMI trials where all patients are treated with reperfusion therapy.[6] Performing clinical trials that require these numbers of patients to test new therapies, especially devices, is often prohibitive from both a financial and logistical standpoint. In an attempt to overcome these barriers, several trials have used a composite clinical outcome measurement referred to as major adverse cardiac events, or MACE. In addition to mortality, major adverse cardiac events usually include nonfatal reinfarction, stroke, target vessel revascularization, and/or major bleeding complication. By increasing the number of expected outcome events, required sample sizes are smaller. However, the application of MACE has several limitations, including the use of heterogeneous endpoints which vary in terms of their clinical importance, the accurate adjudication of nonfatal events, and the use of highly subjective endpoints (target vessel revascularization).

Another disadvantage of examining only clinical endpoints to assess the efficacy of therapy is the limited information available for providing insight into the mechanism by which a therapy might be beneficial. Some deaths that occur in an MI trial are not directly due to the infarction (*e.g.* drug reaction, pulmonary embolus, suicide, etc.) Although these types of events should be randomly distributed in a clinical trial and may not impact the study results, they impair the accurate examination of the efficacy of treatment. Several important prognostic variables (age, infarct location, time to treatment, etc.) that may shed light on a mechanism can be easily acquired, but other important variables (amount of myocardium at risk) are not readily available through simple clinical assessment.

Given these limitations with the application of clinical endpoints in MI trials, there has been significant interest in the use of surrogate endpoints. One of the most important surrogate endpoints that has emerged is the measurement of infarct size. This variable has been most extensively measured through the use of technetium (Tc)-99m sestamibi single photon emission computed tomography (SPECT). This paper reviews the technical aspects, validation studies, and clinical trials experience with this technique.

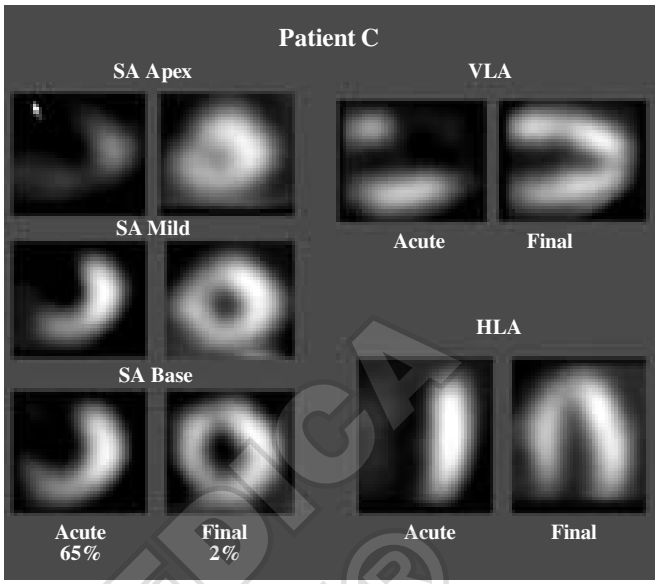

Figure 1.—Short-axis slices (SA) at the apical, mid, and basal levels of the left ventricle; vertical long-axis (VLA) slices; and horizontal long-axis (HLA) slices. The acute images were obtained on presentation to the emergency department before reperfusion therapy was administered. The final images were acquired at hospital discharge. The images were acquired from a patient who presented with an occluded proximal left anterior descending coronary artery who experienced significant benefit from reperfusion therapy with reduction in the myocardium at risk from 65% to a final infarct size of 2% at hospital discharge. Myocardial salvage was 63% of the left ventricle.

Properties of Tc-99m Sestamibi

Historically, the traditional radioisotope for measuring myocardial perfusion was thallium (T?)-201. Limitations of T?-201 include a relatively low peak energy window (80 kev) and redistribution of T?-201 between myocardial cells and the circulating blood pool. Due to these limitations there was a concerted effort put forth in the 1980s to develop a radioisotope with more favorable imaging properties for use in acute MI. Tc-99m sestamibi was discovered and released to a limited number of medical centers in the late 1980s. Tc-99m sestamibi is rapidly cleared from the blood stream following intravenous injection and taken up by the myocardium in direct proportion to myocardial blood flow.[7, 8] It localizes primarily within the mitochondria of the myocardial cells.[9, 10] Advantages of Tc-99m sestamibi over T?-201 include its higher peak energy window (140 kev) and its property of minimal redistribution over time.

The higher energy window of Tc-99m *versus* T?-201 results in less soft tissue attenuation and better image contrast, which permit greater accuracy in defining the boundaries of a perfusion defect.[11, 12] Although most of the work with Tc-99m sestamibi in MI has focused on the perfusion defect demonstrated by SPECT, the higher energy window also results in high-

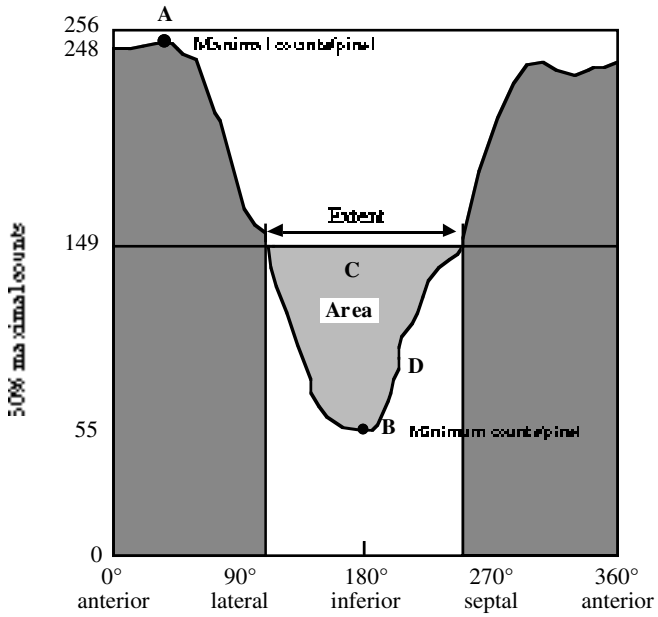

Figure 2.—Acute tomographic sestamibi short-axis count profile starting at the anterior wall and progressing clockwise at 6° intervals. A) highest counts per pixel in this slide. B, lowest counts per pixel. C, area of perfusion defect (<60% maximal counts). D, maximum potential perfusion defect area for the extent of the defect. Collateral flow was estimated by three methods relating to the depth of the perfusion defect: 1) nadir, B/A; 2) severity index, C/(C+D); and 3) area (C). Extent, reflects myocardium at risk on the acute image and infarct size on the image obtained at discharge.

er count density, thereby allowing the images to be gated for assessment of left ventricular ejection fraction (LVEF) and regional wall motion. The contribution of gated SPECT in the setting of acute MI has not been extensively evaluated.

The property of minimal redistribution possessed by Tc-99m sestamibi is especially important for measuring myocardium at risk. In the earliest stages of acute coronary occlusion, myocardium at risk represents the region that would ultimately become infarcted in the absence of timely restoration of coronary blood flow. The hypoperfused myocardium that is present several days after the acute event represents final infarct size. The difference between the size of myocardium at risk and final infarct size represents salvaged myocardium (Figure 1). Salvaged myocardium can be expressed as a percentage of the left ventricle or as a "salvage index" (determined by dividing salvaged myocardium by myocardium at risk). Since Tc-99m sestamibi undergoes minimal redistribution,[8, 13, 14] this agent can be injected intravenously when a patient with MI first presents to the emergency room. Imaging can then be delayed for up to 6 hours while the patient undergoes acute treatment and still reflect myocardium at risk when the patient first presented. This approach allows for accurate assessment of myocardium at risk without any delay in initiating acute therapy.

The most common method of quantitating the perfusion defects applies an absolute threshold technique. This method identifies all pixels that fall below 50% or 60% of peak counts (different thresholds have been applied by different laboratories) as infarcted myocardium (Figure 2).[15-17] Circumferential count profile curves can be generated for a representative number of slices of the left ventricle extending from apex to base. Computer software techniques can be applied to quantitate the percentage of hypoperfused myocardium in each slice adjusted for the radius of the slice to calculate a total defect size expressed as a percentage of the left ventricle. Early phantom studies with first generation SPECT cameras showed that a threshold of 60% of peak counts is optimal for accurately identifying infarcted myocardium.[18] Subsequent studies using improved SPECT cameras suggested that 55% of peak counts was preferable.[11] Another method that has not been as extensively validated identifies infarcted myocardium as a resting perfusion defect that falls below the lower limit of normal distribution derived from a population of patients with low likelihood of coronary artery disease.[19-22] This method, which has not been as extensively validated, yields many more non-zero values in patients with normal left ventricular function and no history of MI.

The use of Tc-99m sestamibi for measurement of myocardium at risk and final infarct size was initially validated in a number of animal experiments. In a model of permanent coronary occlusion, Verani *et al.*[23] reported a close correlation (r=0.95) between the perfusion defect measured ex vivo on Tc-99m SPECT images and the histologic area of infarction measured by triphenyl tetrazolium chloride staining. In a model of reperfusion, Sinusas *et al.*[24] reported that the perfusion defect size measured by autoradiography when Tc-99m sestamibi had been injected during coronary artery occlusion was tightly correlated (r=0.94) with the area of myocardium at risk assessed by post mortem coronary angiography. In this same experiment the myocardial uptake of Tc-99m sestamibi injected during coronary artery occlusion was

also closely correlated (r=0.91) with myocardial blood flow measured by microspheres. However, when Tc-99m sestamibi was injected after reperfusion was restored, its uptake (measured by autoradiography) at this stage did not correlate with flow but instead the perfusion defect did correlate with histologic infarct size (r=0.98).

At the same time that these animal studies were being performed, the first case report [25] and small series [15, 16, 26] in humans established the proof of concept of using Tc-99m sestamibi SPECT for measuring myocardium at risk and infarct size. This early work in humans showed that measurement of final infarct size should be delayed 120 hours or longer. Assessment of Tc-99m sestamibi uptake at 48-78 hours overestimates final infarct size.[27] In selected patients there may be a modest ongoing reduction in infarct size measured days to weeks extending to several months after the acute event.[20, 28]

Tc-99m SPECT as a surrogate endpoint

The use of a surrogate endpoint in clinical trials does have limitations. In a classic article, Fleming and DeMets [29] outlined the requirements for a surrogate endpoint. These requirements should include biological plausibility and demonstration of an association between the surrogate endpoint and the clinical outcome endpoint of interest. However, the most stringent criterion is the demonstration that the effect of an intervention on the surrogate endpoint reliably predicts the effect on the desired clinical outcome. Examples of clinical trials where this criterion was not met include the Cardiac Arrhythmia Suppression Trial (CAST) [30] and the Investigation of Lipid Level Management to Understand its Impact in Atheroscle-rotic Events (ILLUMINATE) [31] trials. In CAST anti-arrhythmic therapy successfully suppressed ventricular ectopy in patients with recent MI, but actively treated patients had a higher mortality rate than patients treated with placebo. Similarly, in the ILLUMINATE trial patients treated with torcetrapib experienced a significant increase in HDL cholesterol levels but paradoxically had a higher mortality rate than patients assigned to placebo. Although multiple lines of evidence support the use of Tc-99m SPECT as a surrogate endpoint for MI trials (see below), no trial to date has shown that a therapy that results in smaller infarct size also results in improved mortality as a single endpoint.

The major advantage of using Tc-99m sestamibi infarct size in place of mortality as a clinical endpoint is the ability to use a much smaller sample size in a clinical trial. A statistically significant difference in infarct size can be demonstrated between two therapies enrolling only 300-400 patients per treatment arm.[6] Available evidence suggests that a fairly modest difference in infarct size of 5% of the left ventricle between two treatment arms is clinically meaningful.[32]

Tc-99m SPECT variables that can be used as endpoints include infarct size or myocardial salvage. Infarct size alone is logistically easier to perform. Patients only need to undergo one imaging session at day 5 or later. At this time point their clinical status has usually been well stabilized, allowing significant flexibility for performing imaging electively. To apply myocardial salvage as an endpoint, myocardium at risk must be measured. The intravenous injection of a bolus of Tc-99m sestamibi in the emergency room is a simple procedure that does not delay treatment. However, a dose of Tc-99m sestamibi must be readily available for injection when the patient arrives in the emergency room. Based upon the half life of Tc-99m sestamibi, isotope needs to be prepared by a nuclear medicine technologist every 12-24 hours, and imaging must be performed within 6 hours following injection. These requirements place increased demands on nuclear medicine departments. In addition to smaller sample size,[6] another advantage of the use of myocardial salvage over infarct size as an endpoint includes greater insight into the mechanism of response to treatment in an individual patient. Studies in both animals [7, 33] and humans [34-37] have demonstrated that there is tremendous variability in myocardium at risk even for infarcts that involve the same coronary distribution. One could erroneously assume that 2 patients with the same final infarct size responded the same to therapy if myocardium at risk is not measured. Since myocardium at risk is one of the major determinants of final infarct size,[38] using myocardial salvage incorporates myocardium at risk and reduces some of the variability in the final infarct size measurement, thereby allowing smaller study groups in each treatment arm. However, the degree to which sample size can be reduced by using myocardial salvage instead of final infarct size is fairly modest.[6] A novel application of prolonged stunning detected by gated SPECT may be helpful in this setting. A recent study suggested that the extent of abnormal wall thick-

ening on gated SPECT 5 to 10 days after admission could be used to estimate myocardium at risk measured by SPECT perfusion at presentation.[39]

Validation of SPECT imaging as a surrogate endpoint

Over the past 2 decades ample evidence has been generated from clinical studies supporting the validation of SPECT infarct size and myocardial salvage as surrogate outcome endpoints for studies of MI. This evidence can be summarized into 6 categories (Table I).

TABLE I.—*Evidence validating Tc-99m SPECT infarct size.*

Association with other parameters used to measure infarct size: • Biomarkers – total creatine kinase, creatine kinase-MB, troponin I and T • Mechanical indices - left ventricular ejection fraction, end systolic volume, extent of regional wall motion abnormality • Perfusion defects measured by magnetic resonance imaging (delayed hyperenhancement) and computed tomography
Association with markers of myocardial reperfusion: • Electrocardiographic ST-segment resolution • Angiographic myocardial blush grade • Angiographic TIMI myocardial perfusion grade
Accurate identification of myocardial fibrosis by pathology
Prediction of improvement following revascularization for hypokinetic/akinetic myocardial segments
Correlation between larger infarct size and higher mortality
Demonstration that therapies which result in smaller infarct size also result in improved clinical outcome in the same group of patients

TIMI: thrombolysis in myocardial infarction.

Association with other parameters used to measure infarct size in clinical studies

Other parameters that have been used to measure infarct size include cardiac biomarkers, mechanical indices of left ventricular function, and more recently perfusion abnormalities detected by cardiac magnetic resonance or computed tomographic imaging.

Biomarkers. Creatine kinase and creatine kinase-MB have been the traditional biomarkers used to detect acute MI. Older studies in animals [40] and humans [41, 42] indicated that creatine kinase and/or creatine kinase-MB correlate with infarct size. More recent studies have shown that creatine kinase release correlates with infarct size measured by SPECT imaging.[22, 43, 44] Creatine kinase has more recently been supplanted by measurement of cardiac troponin for diagnosis of acute MI. Troponin kinetics and release are not well defined and may be more complex than creatinine kinase release. These properties may differ for troponin T and troponin I. A small number of studies suggest that troponin T levels are associated with SPECT infarct size measured by T2-201 [45] or Tc-99m sestamibi.[22, 46, 47] In a study that applied multiple biomarkers (total creatine kinase, creatine kinase-MB, troponin I, and troponin T), the highest correlation between a single time point biomarker measurement and SPECT infarct size occurred with the 72-hour troponin I measurement.[22] Another study using Troponin I reported that high levels measured on admission were associated with larger myocardium at risk but not infarct size or myocardial salvage measured by Tc-99m sestamibi in patients treated with primary angioplasty and abciximab.[48]

Mechanical indices. SPECT infarct size is closely correlated with mechanical indices of infarction, including LVEF,[15, 49-55] left ventricular volumes,[50, 52, 55] and the extent of regional wall motion abnormality,[15, 49] measured at various time points (between hospital discharge to one year). The first study to report this association demonstrated that SPECT infarct size correlated with both LVEF (r=-0.82) and wall motion score in the infarct segment (r=-0.74 for anterior infarction and r=-0.975 for inferior infarction) with all variables measured at hospital discharge.[15] The most robust evidence demonstrating an association between SPECT infarct size and LVEF was generated in the Collaborative Organization for RheothRx Evaluation (CORE) trial.[54] In this multicenter international study 753 patients with STEMI treated with thrombolytic therapy had measurement of both infarct size by SPECT and LVEF by gated equilibrium radionuclide angiography (assessed by separate core laboratories) performed between days 6 and 16. Infarct size was significantly correlated with LVEF (r=-0.67) and end systolic volume index (r=0.57). Chareonthaitawee *et al.*[52] reported a close correlation (r=0.80) between SPECT infarct size measured at hospital discharge and end systolic volume measured 1 year later by computed tomography (Figure 3). The correlation coefficients in most of these studies have been in the range of 0.6-0.8. Nonetheless, it is important to appreciate that these mechanical indices, especially when performed early, are much more influenced by conditions surrounding the acute

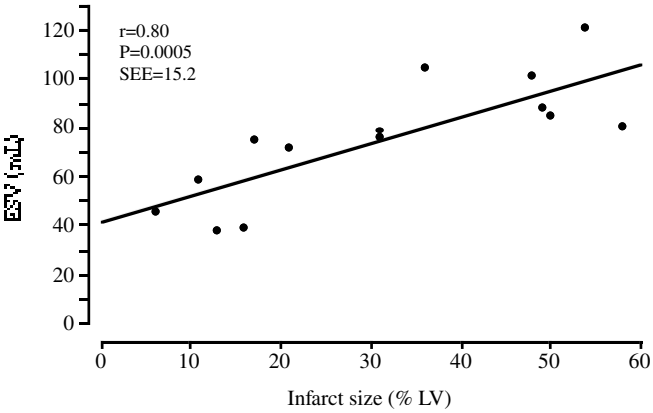

Figure 3.—Correlation between SPECT Tc-99m sestamibi infarct size at hospital discharge and left ventricular (LV) end-systolic volume (ESV) by electron beam computed tomography at 1 year.

MI, including stunning, varying loading conditions on the ventricle, and/or arrhythmias, as well as myopathic processes and/or valvular heart disease that may coexist with coronary artery disease. SPECT infarct size is either not influenced or influenced to a much smaller degree by these conditions.[49, 56]

Perfusion abnormalities measured by magnetic resonance imaging and computed tomographic imaging

Infarct size can be measured by magnetic resonance late gadolinium hyper-enhancement.[57-59] An advantage of magnetic resonance imaging over other cardiac imaging modalities is its superior spatial resolution. Phantom studies demonstrated that the smallest infarct size that could be detected by SPECT imaging was 3% of the left ventricle.[18] Magnetic resonance imaging is superior to SPECT imaging for detecting small amounts of infarcted myocardium, especially nontransmural infarction that involves less than 50% of left ventricular wall thickness.[60] It is not clear at the present time if the ability to detect smaller infarcts will translate into an advantage for comparison of 2 different treatment strategies in clinical trials. In 2 clinical studies where infarct size was measured by both magnetic resonance imaging delayed hyper-enhancement and SPECT, infarct size was equivalent with nearly the same standard deviation (Table II).[61, 62] A potential disadvantage of cardiac magnetic resonance imaging compared to SPECT is the exclusion of certain patients from this type of imaging, including those with pacemakers, renal impairment, or arrhythmias. Additionally, myocardium at risk cannot be practically measured using conventional magnetic resonance imaging, since this approach would require interrupting acute treatment to proceed with imaging in patients, some of whom likely would be clinically unstable. However, recent work has suggested that cardiac magnetic resonance imaging may be able to measure myocardium at risk for several days post MI by applying T2-weighted imaging to detect myocardial edema.[63, 64] The details and validity of this approach are not yet established. Although not as extensively investigated, preliminary work has shown that cardiac computed tomography perfusion imaging can identify infarcted myocardium as hypo-enhanced defects on delayed imaging.[65, 66] The correlation for quantified infarct size measured by tomography and SPECT in one small study was only modest (r=0.48).[65]

TABLE II.—*Infarct size measured by both SPECT and magnetic resonance imaging.*

Study	Patients	SPECT (%LV)	MRI (%LV)
Mahrholdt [61]	15	14±7%	14±6%
Ibrahim [62]	33	15±15%	15±13%

LV: left ventricle; MRI: magnetic resonance imaging; SPECT: single photon emission computed tomography.

Association with other markers of successful myocardial reperfusion

The demonstration of successful myocardial reperfusion requires not just restoration of blood flow in the infarct-related artery but also adequate perfusion at the tissue level. Techniques for demonstrating adequate perfusion at the tissue level include ST-segment resolution by electrocardiography [67] and angiographic myocardial blush grade [68] or Thrombolysis in Myocardial Infarction (TMI) myocardial perfusion grade.[69] SPECT infarct size and myocardial salvage have been shown to be associated with these variables.[44, 70] In the Limitation of Myocardial Injury following Thrombolysis in Acute Myocardial Infarction (LIMIT AMI) trial,[44] median infarct size was 13% in patients with TIMI myocardial perfusion grades 0 or 1 compared to 7% in patients with TIMI myocardial perfusion grade 2 or 3 (P=0.004). In the same trial median infarct size was 15% in patients with no ST segment resolution *versus* 11% in those with incomplete resolution *versus* 6% in those with complete resolution (P=0.0001).

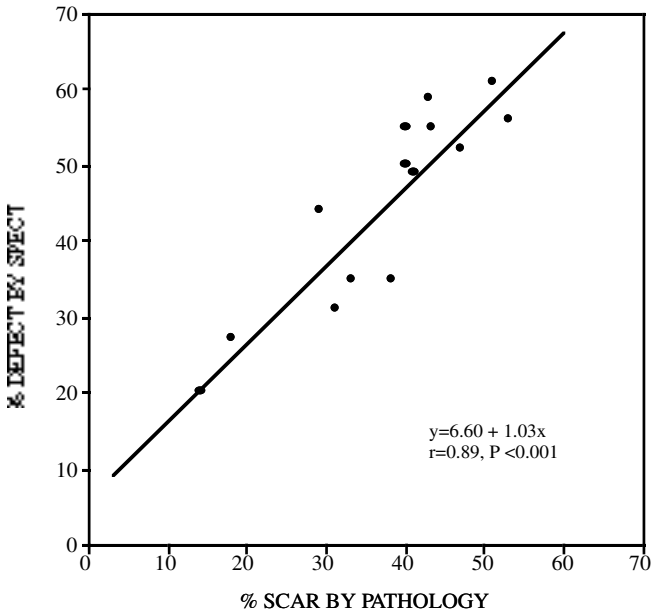

Figure 4.—Linear regression analysis of SPECT defect size vs pathological scar size.

Myocardium identified as infarcted myocardium by SPECT imaging accurately identifies myocardial scar in pathologic specimens

Evidence from animal studies demonstrating this association has been cited above.[23, 24] There are also supporting data from human studies. Medrano *et al*.[71] applied a clever study design to demonstrate this association in patients undergoing cardiac transplantation. Fifteen patients with ischemic cardiomyopathy were injected with Tc-99m sestamibi just prior to explantation of their native hearts. The *ex vivo* SPECT infarct size demonstrated a very close correlation (r=0.94) with the amount of pathologic fibrosis in the explanted hearts (Figure 4). Two additional studies have also demonstrated a close association between Tc-99m sestamibi uptake and the amount of myocardial fibrosis measured in myocardial biopsy specimens obtained at the time of patients undergoing coronary artery bypass surgery.[72, 73]

Tc-99m sestamibi uptake predicts the response to revascularization. Myocardial regions with abnormal wall motion fail to improve following revascularization if Tc-99m sestamibi uptake in these regions is below the infarct threshold; conversely, dysfunctional segments with uptake above the infarct threshold will generally improve following revascularization.[72-74]

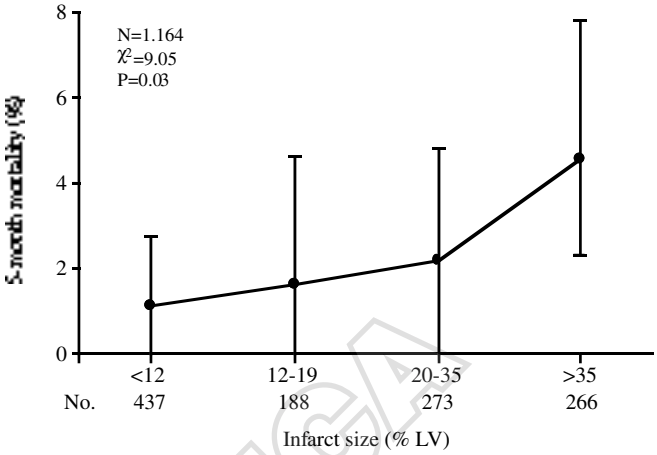

Figure 5.—CORE trial 6-month mortality plotted against quartiles of infarct size. LV = left ventricle.

Positive and negative predictive values for recovery of function in these studies were 79%-82% and 78%-100%, respectively. Another study of patients with acute MI treated with acute coronary angioplasty reported that the severity of reduced Tc-99m sestamibi uptake in the infarct zone at one week predicted improvement in LVEF at 6 months.[75]

SPECT infarct size is significantly associated with mortality

Larger infarct size and smaller myocardial salvage are associated with higher mortality.[54, 76-78] The largest patient population (N=1 164) in whom this finding was demonstrated came from the CORE trial.[54] In this study 6-month mortality was 1% for patients with the smallest quartile of infarct size (<12% of the left ventricle) compared to nearly 5% for patients with the largest quartile of infarct size (>35% of the left ventricle) (Figure 5).

Treatment strategies which result in greater myocardial salvage and smaller infarct size also result in better clinical outcome in the same patients

In the Stent *versus* Thrombolysis for Occluded Coronary Arteries in Patients with Acute Myocardial Infarction (STOP AMI) trials,[17, 79] treatment strategies that resulted in smaller infarction and greater myocardial salvage were associated with an improvement in MACE (consisting of death, reinfarction, or stroke) at 6 months. STOP AMI-1 [17] compared patients treated

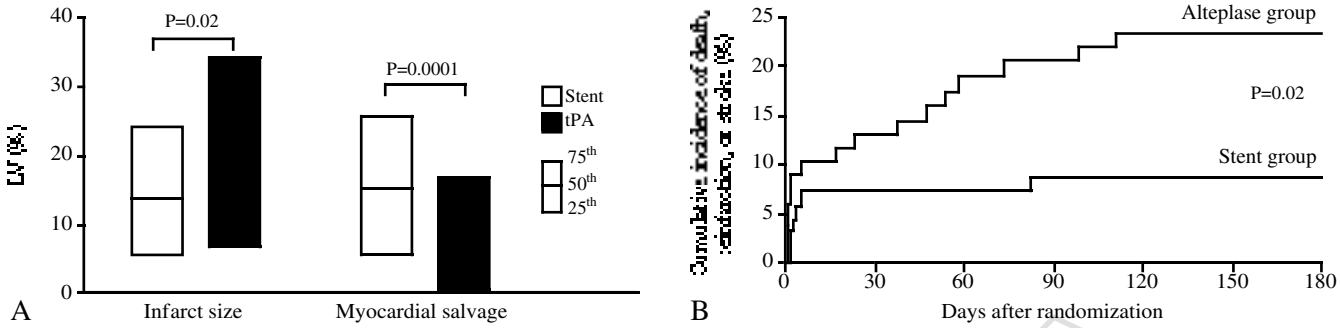

Figure 6.—A) STOPAMI-1 infarct size and myocardial salvage. Patients treated with stenting and abciximab had smaller infarct size and greater myocardial salvage than patients treated with alteplase. B) STOPAMI-1 MACE. The event rate was significantly lower in the stent group compared with the alteplase group. LV: left ventricle.

with coronary stenting plus abciximab *versus* intravenous alteplase. Patients in the stenting group had higher myocardial salvage index (0.57 *versus* 0.26, P=0.001) and smaller infarct size (14.3% *versus* 19.4% of the left ventricle, P=0.0002). In these patients, the percentage of MACE was 8.5% *versus* 23.2% for those treated with thrombolysis (P=0.02) (Figure 6). In STOP AMI-2 [79] the comparative treatment strategies included coronary stenting plus abciximab *versus* fibrinolysis plus abciximab. Once again the SPECT parameters were better in the patients treated with stenting (salvage index 0.60 *versus* 0.41, P=0.001; infarct size 8% *versus* 16% of the left ventricle, P=0.01). The patients treated with stenting had a trend toward lower MACE at 6 months (8.6% *versus* 18.5%, P=0.06).

These multiple categories of evidence provide strong support for the use of Tc-99m sestamibi SPECT infarct size and myocardial salvage as surrogate end points in clinical trials of acute MI. No other surrogate end point has been as extensively validated for use in MI trials.[80] Although no data yet exists demonstrating within the same trial that a treatment strategy which results in smaller infarct size is also associated with improved mortality, these multiple categories of evidence have all produced consistent findings demonstrating the benefit of smaller infarct size.

Tc-99m sestamibi SPECT endpoints in clinical trials

Infarct size and/or myocardial salvage measured by Tc-99m sestamibi SPECT have been used as endpoints in over 30 clinical trials (Table III). The results of most of these trials have been published. These studies can be classified into 3 groups: comparisons of different strategies of reperfusion/antiplatelet therapy;[17, 21, 79, 81-90] pharmacologic agents intended to limit reperfusion injury;[91-101] and, devices designed to provide distal cardioprotection,[102] to deliver myocardial cooling,[103-105] or to super oxygenate the blood perfusing infarcted myocardium.[106, 107]

Strategies of reperfusion/antiplatelet therapy

The first randomized clinical trial to apply Tc-99m SPECT endpoints compared treatment with tissue plasminogen activator *versus* direct coronary angioplasty in 108 patients at the Mayo Clinic.[81] There were no significant differences in infarct size or myocardial salvage between treatment groups. The STOPAMI-1 and 2 studies are summarized above.[17, 79] The reperfusion strategy that applied stenting combined with a glycoprotein IIb/IIIa agent resulted in smaller infarct size and greater myocardial salvage compared to thrombolytic therapy alone (Figure 6) [17] or thrombolytic therapy combined with a IIb/IIIa agent.[79] STOPAMI-3 enrolled 611 patients who were ineligible for thrombolysis (contraindication, no ST-segment elevation, or late presentation) and randomized them to stenting or balloon angioplasty.[82] Although patients treated by either approach had significant myocardial salvage, there were no differences between treatment arms for infarct size, degree of myocardial salvage, or salvage index. In STOPAMI-4 181 patients who failed thrombolysis within the preceding 24 hours were randomly assigned to rescue coronary stenting or balloon angioplasty.[83] The stent group had a bet-

TABLE III.—*Clinical acute MI trials applying Tc-99m SPECT infarct size/myocardial salvage as endpoints.*

Category	Trial Name or Site	Patients	Single/ MultiCenter	Reperfusion treatment	Experimental strategy	Result	Reference
Reperfusion/ Antiplatelet	Mayo	98	S	T or PCI	tPA *vs.* PTCA	(-)	81
	STOPAMI-1	123	S	T or PCI	stent + abciximab *vs.* tPA	(+)	17
	STOPAMI-2	141	S	T or PCI	Stent + abciximab *vs.* tPA + abciximab	(+)	79
	STOPAMI-3	501	S	PCI	Thrombolysis ineligible Stent *vs.* PTCA	(-)	82
	STOPAMI-4	146	S	T or PCI	Failed thrombolysis stent *vs.* PTCA	(+)	83
	BRAVE-1	228	M	T half PCI all	Reteplase + abciximab *vs.* abciximab alone	(-)	84
	BRAVE-2	347	M	Late (>12 hours) PCI in half	Delayed invasive (stent + abciximab) *vs.* conservative	(+)	85
	BRAVE-3	756	M	PCI	Upstream clopidogrel + abciximab *vs.* clopidogrel alone	(-)	86
	AIMI	402	M	PCI	Rheolytic thrombectomy + stent *vs.* stent alone	(-)	21
	Florence	100	S	PCI	Rheolytic thrombectomy + PCI *vs.* PCI alone	(+)	89
	ACE	228	M	PCI	Stent + abciximab *vs.* stent alone	(-)	87
	Florence	133	S	PCI	Upstream clopidogrel *vs.* ticlopidine	(-)	90
Adjunctive pharmacology	Poloxamer-188/ Lysis	100	M	T	Poloxamer-188 *vs.* placebo	(+)	91
	Poloxamer-188/ PTCA	127	M	PCI	Poloxamer-188 *vs.* placebo	(-)	92
	CORE	1164	M	T	Poloxamer-188 *vs.* placebo	(-)	93
	ALIVE	46	M	PCI	Adenosine *vs.* placebo	(-)	—
	AMISTAD-I	214	M	T	Adenosine *vs.* placebo	(-)	94
	AMISTAD-II	266	M	T	Adenosine *vs.* placebo	(-)	95
	ADMIRE	290	M	PCI	AMP579 (adenosine agonist) *vs.* placebo	(-)	96
	FESTIVAL	58	M	PCI	Hu23F2G (antibody to neutrophil CD18) *vs.* placebo	(-)	97
	HALT-MI	397	M	PCI	Hu23F2G (antibody to neutrophil CD18) *vs.* placebo	(-)	98

(Continue)

TABLE III.—*Clinical acute MI trials applying Tc-99m SPECT infarct size/myocardial salvage as endpoints. (Continue).*

Category	Trial Name or Site	Patients	Single/ MultiCenter	Reperfusion treatment	Experimental strategy	Result	Reference
	LIMIT AMI	355	M	T	RhuMAB CD18 (antibody to neutrophil CD18) *vs.* placebo	(-)	99
	RAPSODY	544	M	T	rPSGL-lg (P-selectin antagonist) *vs.* placebo	(-)	100
	REVIVAL	255	S	T or PCI	Glucose-insulin-potassium *vs.* placebo	(-)	101
	CALYPSO	149	M	PCI	CY1503 (p-selectin blocker) *vs.* placebo	(-)	—
Devices	EMERALD	437	M	PCI	PCI with distal protection *vs.* PCI line	(-)	102
	ICE-IT	204	M	PCI	PCI with hypothermia *vs.* PCI alone	(-)	103
	COOL-MI	325	M	PCI	PCI with hypothermia *vs.* PCI alone	(-)	104, 105
	LOW TEMP	18	M	PCI	PCI with hypothermia *vs.* PCI alone	(-)	103
	AMIHOT-1	243	M	PCI	PCI plus supersaturated oxygen *vs.* PCI alone	(-)	106
	AMIHOT-2	281	M	PCI	PCI plus supersaturated oxygen *vs.* PCI alone	(+)	107

ACE: abciximab and carbostent evaluation; ADMIRE: AMP579 for delivery for myocardial infarction reduction; AIMI: AngloJet rheolytic thrombectomy in patients undergoing primary angioplasty for acute myocardial infarction trial; ALIVE: adenosine and lidocaine infarct viability enhancement; AMIHOT: acute myocardial infarction with hyperoxemic therapy; AMISTAD: acute myocardial infarction study of adenosine; BRAVE: Bavarian reperfusion alternatives evaluation; CALYPSO: Cytel/CIA phase 2 study in the prevention of reperfusion injury in patients with AMI treated with primary angioplasty; COOL-MI: cooling as an adjunctive therapy to percutaneous intervention in patients with acute myocardial infarction; CORE: collaborative organization of RheothRx evaluation; EMERAL: enhanced myocardial efficacy and recovery by aspiration of liberalized debris; FESTIVAL: an anti-CD11/CD18 monoclonal antibody in patients with acute myocardial infarction having percutaneous transluminal coronary angioplasty; HALT MI: Hu23F26G anti-adhesion to limit cytotoxic injury following acute MI; ICE-IT: intravascular cooling adjunctive to percutaneous coronary intervention; LIMIT AMI: limitation of myocardial injury following thrombolysis in acute myocardial infarction; LOW-TEMP: lowering adverse outcomes with temperature regulation; RAPSODY: recombinant p-selectin glycoprotein ligand-lg in combination with thrombolytic therapy in acute myocardial infarction; REVIVAL: reevaluation of intensified metabolic support for acute infarct size limitation; STOPAMI: stent *versus* thrombolysis for occluded coronary arteries in patients with acute myocardial infarction. a) Single = ≤3 centers. b) Positive study defined as experimental group had smaller infarct size or greater myocardial salvage or salvage index. c) Overall study results negative; patient subset with anterior MI significantly smaller infarct size adenosine vs placebo. d) Overall study results negative; patient subset treated with high dose adenosine significantly smaller infarct size vs placebo. e) Overall study results negative; diabetic patients treated with GIK better myocardial salvage index vs placebo. f) Results not published in a separate manuscript but included in a summary article.[103] g) Early results (36 patients) published separately.[104] Complete results included in summary article.[103] h) Non-randomized (feasibility study). i) Overall study results negative; patient subset with anterior MI treated by PCI within 6 hours smaller infarct size supersaturated oxygen vs placebo. Other abbreviations: S = single; M = multicenter; T = thrombolysis; PCI = percutaneous coronary intervention; tPA = tissue plasminogen activator; PTCA = percutaneous transluminal coronary angioplasty.

ter myocardial salvage index (35% *vs.* 25%, P=0.005). The Bavarian Reperfusion Alternatives Evaluation (BRAVE) acute MI trials compared reteplase plus abciximab *versus* abciximab alone in patients undergoing percutaneous coronary intervention (BRAVE-1),[84] examined mechanical reperfusion in patients presenting >12 hours after symptom onset (BRAVE-2),[85] and evaluated the potential benefit of adding abciximab to clopidogrel loading in patients scheduled for primary percutaneous coronary intervention (BRAVE-3).[86] In BRAVE-2 patients assigned to the invasive group had a significantly smaller median infarct size than the conservative group (8.0% vs 13.0%, P<0.001). BRAVE-1 and 3 reported no differences in infarct size between treatment arms. In the Abciximab and Carbostent Evaluation (ACE) [87] trial, the investigators from Florence reported a trend toward smaller median infarct size in 228 patients treated with stenting plus abciximab vs stenting alone (12.5% *vs.* 16.6%, P=0.067). Similar to STOPAMI-1, the composite MACE endpoint at 30 days in this study was significantly lower in the abciximab group (10.5% *vs.* 4.5%,

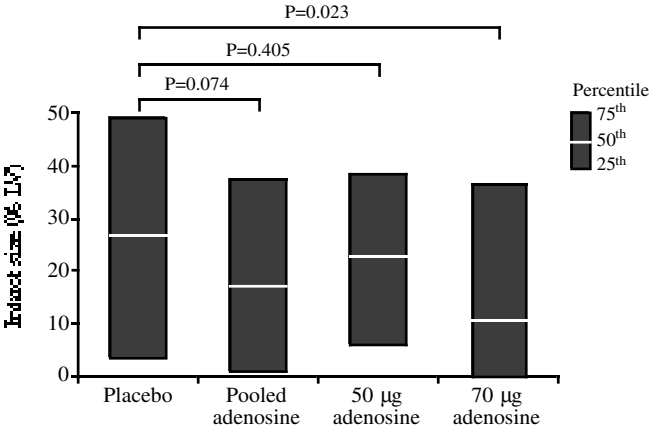

Figure 7.—AMISTAD-II infarct size substudy. Infarct size was significantly smaller in the 70 µg/kg/min adenosine dose group *vs.* placebo (11% *vs.* 27%, P=0.023).

P=0.023). A subsequent sub study of 182 of these patients who completed gated SPECT reported smaller infarct size in those treated with abciximab vs control (14.3% *vs.* 18.1%, P<0.02).[88] In another study the Florence investigators reported that rheolytic thrombectomy before infarct stenting resulted in smaller infarct size compared to stenting alone (13.0% *vs.* 21.2%, P=0.010),[89] but a different group of investigators who evaluated rheolytic thrombectomy reported no benefit.[21]

Adjunctive pharmacologic agents

The two most promising agents were poloxamer-188 (Rheothx) and adenosine. Poloxamer-188 is a surfactant with hemorheologic and antithrombotic properties that improves microvascular blood flow by reducing blood viscosity. An initial pilot study of 114 patients treated with thrombolytic therapy demonstrated that poloxamer-188 resulted in a 38% reduction in median infarct size compared to placebo (P=0.031).[91] This study was followed by the CORE trial.[93] In CORE 2,948 patients treated with thrombolytic therapy were randomized to poloxamer-188 or placebo. Poloxamer-188 had an unintended adverse effect on renal function. The dose of poloxamer-188 needed to be adjusted downward during the trial due to renal toxicity. In these patients treated with lower doses of poloxamer-188, there was no difference in infarct size for actively treated patients *versus* placebo. A small pilot study of 45 patients treated with coronary angioplasty and adjunctive adenosine demonstrated better salvage measured at 6 weeks compared to historical controls (unpublished data). This finding led to the Acute Myocardial Infarction Study of Adenosine (AMISTAD) trials. AMISTAD-1,[94] a Phase II study, enrolled 236 patients treated with thrombolytic therapy who were randomized to adenosine or placebo, 197 of whom underwent infarct size measurement. In the entire imaging group there was a trend towards smaller infarct size in patients treated with adenosine (13% *vs.* 19.5%, P=0.085). For the subset of patients with anterior MI, there was a significant reduction in infarct size from 45.5% to 15% of the left ventricle (P=0.014). A subsequent Phase III trial, AMISTAD-II,[95] randomized 2 118 patients with anterior STEMI treated with thrombolysis or primary angioplasty to low (50 µg/kg/min) or high (70 µg/kg/min) adenosine or placebo. In a subset of 243 patients who underwent infarct size imaging, there was a trend towards smaller median infarct size in the pooled adenosine patients (17% *vs.* 27%, P=0.074) with a significant difference *vs.* placebo in the 70 µg/kg/min dose subset (11% *vs.* 27%, P=0.023) (Figure 7). Clinical outcomes were also improved in this patient subset but the difference was not significant, probably reflecting inadequate statistical power. In the REVIVAL study [101] there was no overall benefit with glucose-insulin-potassium, but the subset of patients with diabetes did have greater salvage index *vs.* controls randomized to active treatment (mean difference, 0.19; 95% CI, 0.01 to 0.37). The other trials of novel adjunctive pharmacologic therapies were negative.[96-100]

Devices

Devices designed to provide distal microcirculatory protection [102] or to provide myocardial cooling [103-105] reported negative results. The Acute Myocardial Infarction with Hyperoxemic Therapy (AMIHOT) trials evaluated the effectiveness of hyperoxemic vs normoxemic reperfusion for reducing infarct size. AMIHOT-I [106] enrolled 269 patients with anterior or large inferior MI treated with percutaneous coronary intervention. For the entire study group there was no difference in median infarct size (hyperoxemic 11% *vs.* control 13% of the left ventricle, P=0.30). Post-hoc analysis of the patient subset with anterior MI treated within 6 hours demonstrated smaller infarct size in the hyperoxemic group *vs.* control (9% *vs.* 23%, P=0.04). These results led to the performance of AMI-

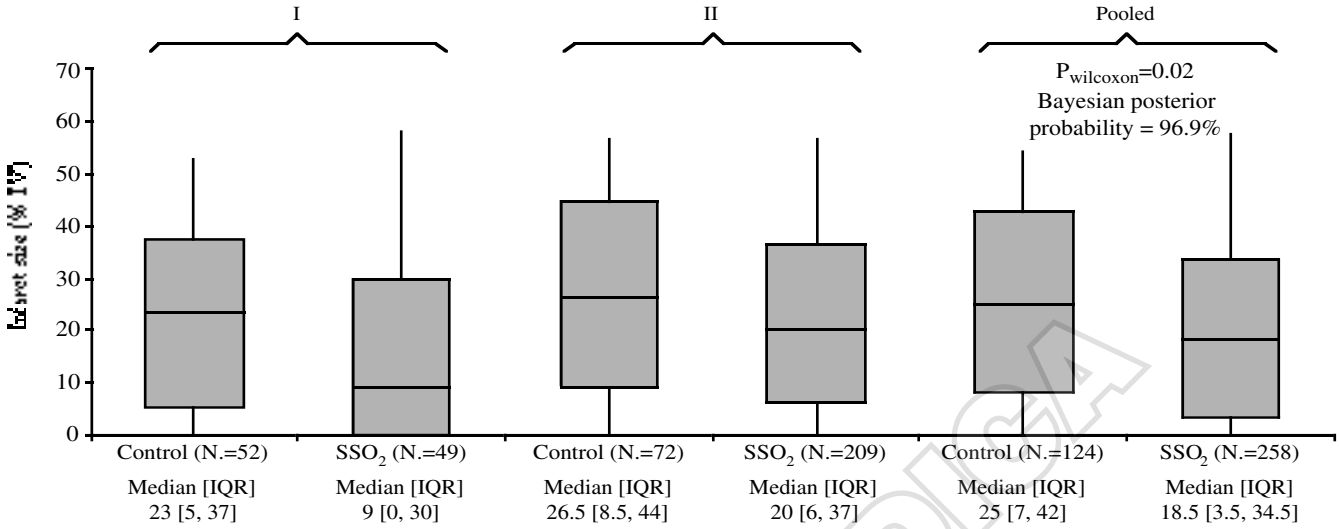

Figure 8.—Infarct size estimates from the AMIHOT-1 and AMIHOT-II trials. The adjusted pooled infarct size was significantly smaller in patients treated with supersaturated oxygen (SSO_2) therapy *vs.* controls (18.5% *vs.* 25%, P=0.02).

HOT-II.[107] In this study 301 patients with anterior MI treated with percutaneous intervention within 6 hours were randomized to 90-minute intracoronary infusion of supersaturated oxygen into the left anterior descending coronary artery or control. Using a statistical approach that permitted partial pooling of results from AMIHOT-1, infarct size was statistically smaller in actively treated patients (18.5% *vs.* 25%, P=0.02) (Figure 8). Approval of this device is currently under review by the Federal Drug Administration.

Summary of clinical experience

SPECT Tc-99m sestamibi endpoints have been used in 31 studies involving 8 676 patients (Table III). Seven of these trials [17, 79, 83, 85, 89, 91, 107] reported significantly smaller infarct size and/or greater myocardial salvage in the intervention arm. In 4 other trials [94, 95, 101, 106] the overall results were negative but additional analyses identified patient subsets who had a significant improvement with the interventional therapy. Some studies [103] were not adequately powered to be able to demonstrate a significant difference between treatment strategies. These results illustrate that SPECT endpoints can be applied in clinical trials to demonstrate statistically significant differences between treatment arms. Furthermore, the loss of data using SPECT endpoints has been minimal. In the CORE trial,[93] which represents the single largest study experience with this methodology, technically satisfactory studies for quantification of infarct size were available in 1 164 patients out of 1 181 patients who underwent imaging (98.6%).

Insights into the pathophysiology of AMI

Although the major role of Tc-99m sestamibi SPECT in acute MI has been as a surrogate endpoint to compare the efficacy of different therapies, this technique has also provided insight into the pathophysiology and mechanisms of disease. These studies have clarified that determinants of final infarct size are the initial size of the myocardium at risk, anterior location, baseline TIMI blood flow, time to reperfusion therapy, and residual flow to the infarct zone.[38, 104, 108-110] This latter variable depends upon both antegrade flow and collateral flow. The residual flow to the infarct zone can be estimated on the basis of the severity of the defect in the circumferential count profile curve (Figure 2).[38] A longstanding clinical observation is the improved outcome of patients with inferior wall myocardial infarction *versus* anterior wall myocardial infarction. SPECT imaging in the setting of MI has demonstrated that anterior wall defects are roughly twice the size of inferior wall infarcts.[37, 38, 104]

Studies with Tc-99m sestamibi SPECT have also helped to clarify why certain subsets of patients with

MI, such as the elderly and diabetic patients, have worse clinical outcome. The higher mortality in the elderly is not a result of larger infarct size.[111] Diabetic patients do have modestly larger infarct size, but their modestly larger infarcts do not fully account for their substantially higher mortality.[112, 113]

Christian *et al*.[114] provided important insights into the impact of symptoms on the response to therapy in acute MI. They reported a significant association between the magnitude of chest pain relief and the amount of myocardial salvage in patients receiving reperfusion therapy, although there was no correlation between chest pain severity and the extent of myocardium at risk. In patients in whom ST-segment elevation persisted after their chest pain resolved, the amount of myocardial salvage was 11% of the left ventricle following administration of reperfusion therapy, demonstrating that even in patients whose symptoms have resolved reperfusion therapy can result in significant myocardial salvage if ST segment elevation persists. The BRAVE-2 [85] trial confirmed the benefit of mechanical reperfusion therapy for reducing infarct size in patients presenting late (>12 hours) whose symptoms had resolved.

Limitations

Tc-99m sestamibi SPECT imaging in the acute MI setting does have several limitations. Some of these limitations have been mentioned already. The technique cannot reliably detect infarcts that comprise less than 3% of the left ventricle.[18] Imaging performed earlier than 120 hours for measurement of infarct size will overestimate infarct size.[27] Given the very short hospital stays in many patients with MI, delaying imaging to day 5 or beyond can occasionally create logistical difficulties. Imaging artifacts can interfere with accurate measurement of infarct size. The major imaging artifacts related to SPECT imaging include motion, scatter, and attenuation. In obese patients soft tissue attenuation can create small (< 5% of left ventricle) "false positive" infarcts or result in modest overestimation of infarct size.[76] This technique cannot identify the timing of infarction or distinguish old infarction from new infarction unless a prior SPECT study has been performed. Finally, it is important to remember that Tc-99m sestamibi SPECT provides an assessment of efficacy, but not the safety, of treatment, as demonstrated by the CORE trial.[93] The preliminary pilot study [91] demonstrated that poloxamar-188 was efficacious for reducing infarct size, but the adverse effect of this agent on renal function was only recognized when a large clinical trial was performed.

Conclusions

The value of Tc-99m SPECT in the setting of an acute MI has been extensively demonstrated in multiple studies over the past two decades. Infarct size and myocardium at risk are well-established surrogate endpoints for examining the efficacy of treatment in acute MI. Although other parameters are available for use as surrogate endpoints, Tc-99m sestamibi SPECT remains the most extensively validated method. The technical limitations of this approach must be recognized.

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