Infarct Size Measured by Single Photon Emission Computed Tomographic Imaging With $^{99m}$Tc-Sestamibi
A Measure of the Efficacy of Therapy in Acute Myocardial Infarction

Raymond J. Gibbons, MD; Todd D. Miller, MD; Timothy F. Christian, MD

Background—Use of mortality as an end point in randomized trials of reperfusion therapy requires increasingly large sample sizes to test advances compared with existing therapy, which is already highly effective. There has been a growing interest in infarct size measurements by $^{99m}$Tc-sestamibi SPECT (single photon emission computed tomographic) imaging as a surrogate end point.

Methods and Results—We reviewed the reports published in English regarding infarct size measurements by $^{99m}$Tc-sestamibi. Four separate lines of published evidence support the validity of SPECT imaging with $^{99m}$Tc-sestamibi for determination of infarct size. This end point has been used in a total of 7 randomized trials—1 single center and 6 multicenter. The end point compares favorably with left ventricular function and infarct size measurements with the use of other radiopharmaceuticals. The most important limitation of this approach is the absence thus far of a randomized trial that has shown a corresponding decrease in mortality in association with a therapy that reduces infarct size.

Conclusions—SPECT imaging with $^{99m}$Tc-sestamibi is the best available measurement tool for infarct size. It has already served as an end point in early pilot studies to evaluate potential efficacy and in dose-ranging studies. It has the potential to serve as a surrogate end point to uncover advantages of new therapies that may be equivalent to existing therapies with respect to early mortality. (Circulation. 2000;101:101-108.)

Key Words: infarction ▪ radioisotopes ▪ tomography

Multiple end points, including global left ventricular function, regional left ventricular function, early arterial patency, and clinical outcomes, have been used in various randomized trials as measures of the efficacy of reperfusion therapy in acute myocardial infarction. Clearly, the most important clinical outcome is that of patient mortality, which has formed the basis for multiple megatrials comparing thrombolytic agents with placebo and with each other. However, use of mortality as an end point requires increasingly large sample sizes (Figure 1) to test advances compared with existing therapy, which is already highly effective. Such very large sample sizes limit the number of new therapies that can be tested and impose prohibitive financial barriers on the early testing of potentially promising therapies. End points that are potential “surrogates” for both early and late patient mortality are therefore attractive for several purposes: (1) to conduct very early pilot studies to demonstrate potential efficacy of a new agent, (2) to serve as end points for dose-ranging studies to select the “best dose” of a new agent, and (3) to indicate a possible late mortality benefit for a new therapy that may be “equivalent” to existing therapy with respect to early mortality.

As existing therapy improves, the third possibility may become more likely. It will be increasingly difficult to demonstrate an advantage in early mortality, even if one really exists, because of the decreasing mortality with existing therapy and the distinct possibility that the deaths that still occur in acute myocardial infarction may be related to phenomena that cannot be altered by reperfusion therapy. For example, some patients may die of embolic complications (cerebral or pulmonary) that are unrelated to therapy. Thus, at least a portion of the existing low mortality with reperfusion therapy may reflect an “irreducible foundation” of early mortality that is unlikely to be prevented with any new therapy.

In contrast, a new therapy might still reduce left ventricular damage and infarct size. Such a reduction might have favorable consequences for mortality over a much longer term (perhaps 5 to 10 years) than the short term (30 days) that has been used to date for megatrials of acute reperfusion therapy. Maintenance of a scientifically meaningful protocol over the long term to assess 5-year mortality in a megatrial (of 30 000 patients) would be extremely difficult. However, early measurements showing a reduction in infarct size are much more feasible and may indicate a potential benefit in late mortality.

There has been a growing interest in infarct size by $^{99m}$Tc-sestamibi single photon emission computed tomographic (SPECT) imaging as a surrogate end point for all 3 purposes listed earlier. Multiple animal studies have sup-
by electron-beam CT imaging.\textsuperscript{11} Despite the potential confounders of cardiomyopathic processes, ventricular loading conditions, and intervening silent reinfarction, the association between these 2 measures is quite strong.

2. There is close association between SPECT sestamibi infarct size and actual fibrosis in human hearts. Medrano et al.\textsuperscript{14} have reported a close correlation between the actual amount of pathological fibrosis in human hearts explanted at the time of cardiac transplantation from patients with ischemic heart disease and the perfusion defect measured by ex vivo SPECT imaging after intravenous vivo injection of \textsuperscript{99m}Tc sestamibi (Figure 3). They reported excellent correlation ($r=0.94$) between their polar map technique (used in Figure 3) and a fixed threshold of 60% of peak counts (used by our laboratory). The regression line in Figure 3 is shifted upward from the line of identity, indicating that sestamibi imaging slightly overestimated the amount of fibrosis, presumably because some hibernating myocardium was misclassified as infarcted. However, in this highly selected series of patients with severe left ventricular dysfunction, hibernating myocardium should be more prevalent than in less selected patients. Because the mean overestimate by sestamibi in these highly selected patients was only 8% of the left ventricle, the error in less selected patients should be even smaller. These published data on fibrosis have been confirmed by 2 studies that used myocardial biopsies at the time of CABG.\textsuperscript{15,16}

![Figure 1. Total patient (Pt) enrollment in selected major randomized therapeutic trials in acute myocardial infarction displayed by year of publication. GISSI, GISSI-2, and GISSI-3 indicate Gruppo Italiano per lo Studio della Streptochinasi nell’Infarto miocardico I, II, and III; ISAM, Intravenous Streptokinase in Acute Myocardial Infarction; ISIS-2, ISIS-3, and ISIS-4, International Study of Infarct Survival 2, 3, and 4; ASSET, Anglo-Scandinavian Study of Early Thromblyosis; AIMS, APSAC Intervention Mortality Study; LATE, Late Assessment of Thrombolytic Efficacy; EMERAS, Estudio Multicentrico Estreptoquinasa Republicas de Americas del Sur; and GUSTO, GUSTO-II, and GUSTO-III, Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries, Global Use of Strategies To Open occluded arteries, and Global Use of Strategies To Open occluded coronary arteries.](http://circ.ahajournals.org/)

![Figure 2. Correlation between tomographic \textsuperscript{99m}Tc infarct size at hospital discharge and end-systolic volume (ESV) of left ventricle (LV) measured by electron-beam CT 1 year later (reprinted with permission from Reference 11).](http://circ.ahajournals.org/)

**Evidence Supporting the Validity of Spect Infarct Sizing**

Multiple lines of evidence now support the validity of SPECT imaging with \textsuperscript{99m}Tc sestamibi for determination of infarct size:

1. There is close association between this measurement and other parameters that have traditionally been used clinically to estimate infarct size. Table 1 summarizes the published comparisons of SPECT sestamibi infarct size and multiple other parameters, including global left ventricular function (ejection fraction),\textsuperscript{8–10} end systolic volume,\textsuperscript{11} regional left ventricular function (regional wall motion),\textsuperscript{8,9} creatine kinase release,\textsuperscript{12} and \textsuperscript{20}TI infarct size.\textsuperscript{13} Figure 2 shows the relationship between sestamibi infarct size measured at discharge and end-systolic volume of the left ventricle measured 1 year later.
The relationship between the sestamibi SPECT perfusion defect and fibrosis demonstrated in these studies is superior to that previously reported for regional wall motion (Table 2). The data in these 4 studies are voluminous and beyond the scope of this article. Contrast left ventriculography, radionuclide angiography, and 2-dimensional echocardiography have all been shown to have a significant major error rate; at least 15% of segments judged to be akinetic or dyskinetic have proved not to have major fibrosis on pathological examination. Two-dimensional echocardiography, which should be the optimal modality because of its tomographic properties, has a reported correlation coefficient of only 0.53 between regional wall motion assessment and fibrosis.20

3. Sestamibi uptake predicts the response of myocardial regions with abnormal function to subsequent revascularization. 201TI has commonly been used to assess myocardial viability. As shown by Medrano et al,14 99mTc-sestamibi might be expected to misclassify viable myocardial segments with decreased resting blood flow as infarcted. In a series of 31 patients with left ventricular dysfunction, Udelson et al21 compared regional sestamibi activity (as a percent of peak counts) with 201TI activity (as a percent of peak counts) determined on a redistribution image after a resting 201TI injection (Figure 4). The overall correlation between the 2 radiopharmaceuticals with respect to regional activity was highly significant (r=0.78). More importantly, the regional ventricular function of these segments was assessed by 2-dimensional echocardiography both before and after subse-quent coronary revascularization with either PTCA or CABG. Segments that were abnormal at baseline and improved after revascularization had higher initial values of both sestamibi and thallium. Segments that were abnormal at baseline and did not improve after revascularization had lower initial uptake of both radiopharmaceuticals. A value of 60% of peak counts on resting sestamibi imaging separated those segments with reversible dysfunction (which were presumably viable at baseline) from those segments with irreversible dysfunction (which were presumably fibrotic at baseline). This 60% threshold is the same threshold developed independently by our laboratory to separate infarct from viable tissue.

These findings were confirmed by Maes et al.15 Although the optimal sestamibi threshold for predicting functional improvement was 50% in their study, a 60% threshold did nearly as well.

4. Sestamibi infarct size is associated with subsequent patient mortality. Miller et al22 reported a 2-year follow-up of 274 patients at the Mayo Clinic (86% with reperfusion therapy) who underwent predischarge imaging with sestamibi to measure infarct size (Figure 5). The measured infarct size in this series was quite small, with a median of 12% of the left ventricle. Approximately 25% of the patients had no measurable infarct by this technique, which is valid down to about 3% to 4% of the left ventricle.23 Despite the low 2-year mortality rate of 3%, sestamibi infarct size was highly associated with both overall mortality (χ2=8.66, P=0.003) and cardiac mortality (χ2=11.89, P<0.001). Miller et al24 have also shown a significant association between sestamibi infarct size at discharge and 1-year mortality in a separate multicenter study of 249 patients. These published data from relatively small patient series have been confirmed by preliminary data from Burns et al,25 who have demonstrated a similar association between discharge sestamibi infarct size and 6-month mortality in a much larger series of 1184 patients.

**TABLE 2. Assessment of Fibrosis in the Human Heart by Regional Left Ventricular Wall Motion**

<table>
<thead>
<tr>
<th>Wall Motion Technique</th>
<th>Institution</th>
<th>Reference</th>
<th>Percent of LV Segments</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>With Akinasia/Dyskinesia</td>
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<tr>
<td>Contrast ventriculography</td>
<td>Duke</td>
<td>17</td>
<td>32</td>
</tr>
<tr>
<td>Radionuclide angiography</td>
<td>Vermont</td>
<td>18</td>
<td>24*</td>
</tr>
<tr>
<td>Radionuclide angiography</td>
<td>Yale</td>
<td>19</td>
<td>24</td>
</tr>
<tr>
<td>Echocardiography</td>
<td>Mayo</td>
<td>20</td>
<td>15†</td>
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LV indicates left ventricular.
*Wall motion graded as “abnormal”; additional gradations not used.
†Correlation of regional wall motion score to fibrosis (r=0.53).

**Figure 3.** Correlation between perfusion defect measured by SPECT perfusion imaging with 99mTc-sestamibi and amount of fibrosis measured by histology in human hearts explanted at time of cardiac transplantation (reprinted with permission from Reference 14).

**Figure 4.** Correlation between sestamibi activity on resting image and thallium activity on redistribution image after resting injection. Segmental values are expressed as percent of peak counts. There is reasonable correlation between the uptake of the 2 radiopharmaceuticals. Segments shown had abnormal regional function before revascularization. It is evident that a sestamibi threshold of 60% of peak counts separated segments with reversible from those with irreversible dysfunction (reprinted with permission from Reference 21).
Experience With SPECT Sestamibi Imaging in Clinical Trials

Measurement of myocardial salvage and infarct size by 99mTc-sestamibi has now been used as end points in several randomized trials, discussed below.

1. A randomized trial comparing tissue plasminogen activator and PTCA.26 In this single-center trial, there was no detectable difference in myocardial salvage assessed by sestamibi between the 2 therapies. After adjustment for baseline inequalities, the difference in myocardial salvage was 0% of the left ventricle, with 95% confidence limits of ±6% of the left ventricle. There was also no difference between the 2 therapies with respect to ejection fraction at discharge or 6 weeks.

2. A pilot study assessing the potential efficacy of poloxamer-188 as adjunctive therapy in patients receiving thrombolytic therapy.27 In this randomized, multicenter trial of 114 patients, poloxamer-188–treated patients demonstrated a 38% reduction in median myocardial infarct size compared with placebo (Figure 6) and a 13% improvement in median ejection fraction.

3. A pilot study of poloxamer-188 used as adjunctive therapy with PTCA.28 In this randomized, multicenter trial of 150 patients, there was no significant difference in final infarct size or ejection fraction between the poloxamer-188– and placebo-treated groups.

4. CORE (Collaborative Organization for RheothRx Evaluation) trial. This was a large (n=2948) international, multicenter, dose-ranging study29 that tested the hypothesis that poloxamer-188 plus standard therapy would improve patient outcome. Infarct size was measured with 99mTc-sestamibi as part of a substudy (n=1184). The dose of poloxamer-188 was adjusted downward during the course of the trial because of unacceptable renal toxicity. The subsequent lower doses were not associated with any significant reduction in infarct size or improvement in ejection fraction, despite a persistent increase in measured renal toxicity. Thus, the drug unintentionally targeted the kidney.

5. Pilot study comparing CY-1503 (P-selectin blocker) with placebo as an adjunct to PTCA.30 In this multicenter, randomized trial (CALYPSO: Cylexin as an Adjunct to LYtice therapy to Prevent SuperOxide reflow injury) enrolled 150 patients with sestamibi imaging as a primary end point before termination by the data and safety monitoring committee because of lack of efficacy.

6. Single-center pilot study of 45 patients examining the efficacy of adenosine used as ancillary therapy with PTCA.31 Early predischARGE images in this study did not show an increase in myocardial salvage compared with historical controls, but later (6 weeks after discharge) images did demonstrate greater myocardial salvage. Ejection fraction data were not reported.

7. Phase 2 study of the efficacy of adenosine used as ancillary therapy with thrombolysis.32 In this randomized, multicenter trial of 236 patients, the patients treated with adenosine demonstrated a significant reduction in infarct size. The benefit was striking in the prespecified subgroup of anterior infarcts; median infarct size was 45.5% of the left ventricle in the placebo group compared with 15% of the left ventricle in the adenosine group (P=0.014). Ejection fraction was not measured.

Sestamibi infarct size measurements have therefore been used to assess potential efficacy in these randomized trials and to assess the potential “best dose” in a larger dose-ranging trial (the CORE trial). In all the multicenter studies, images were acquired by each individual center but processed by a single central laboratory (Mayo Clinic). The results have generally been confirmed by similar findings with respect to ejection fraction.

Comparison With Left Ventricular Function

Compared with left ventricular function measurements, perfusion imaging provides a number of advantages. Perfusion images are not influenced by the presence of arrhythmias, cardiomyopathies, valvular heart disease, or ventricular loading, which have a substantial effect on left ventricular function. Infarct sizing by perfusion imaging is less affected by the presence of myocardial stunning or hibernation.9,32 Finally, perfusion imaging permits detection of treatment benefit with much smaller sample sizes. Although a detailed...
Discussion of this issue is beyond the scope of this article, the main advantage of infarct sizing by perfusion imaging is the absence of any variability when there is no measurable infarct, i.e., when infarct size is 0%, which occurs in about 25% of the patients who have received reperfusion therapy. In contrast, ejection fraction measurements have a considerable variability in such patients, in whom the normal ejection fraction ranges from 50% to 75%.

Comparison With Other Radiopharmaceuticals

Infarct size has been measured in experimental models with a variety of other radiopharmaceuticals, including 201 Tl, 99m Tc-pyrophosphate, and indium-111 antimyosin antibody. Clinical studies have shown an association between these measurements and left ventricular function, cardiac enzymes, cardiac pathology, and subsequent outcome. The largest such clinical study demonstrated the prognostic value of infarct size assessed by SPECT 201 Tl imaging. Cerqueira et al reported the 5-year survival of 618 patients enrolled in multiple studies performed by the Western Washington Trials Group. There was a highly significant association (P = 0.002) between thallium infarct size and subsequent mortality.

Several studies have demonstrated that 201 Tl and 99m Tc-sestamibi provide similar results for determination of infarct size. However, 99m Tc-sestamibi provides higher count images that are more accurately quantified and the option to do short-term imaging to assess myocardium at risk. Compared with sestamibi, infarct-avid agents (pyrophosphate and antimyosin) have the potential advantage of distinguishing new from old infarction. However, their uptake depends more on the timing of administration after the acute event, they do not allow the option of assessing myocardium at risk, and there is less experience with their use in the setting of acute reperfusion therapy. There are relatively few clinical data regarding the use of 99m Tc-tetrofosmin in acute infarction. It has not been studied in experimental models. Thus, compared with other radiopharmaceuticals, sestamibi has technical advantages and has been much more extensively studied.

Limitations of This Approach

This approach has 5 major limitations:

1. SPECT imaging of a beating heart has definite technical limitations for the purposes of quantification. The 2 major limitations are degradation of image quality resulting from the effects of scatter and attenuation and the partial volume effect related to severely abnormal wall motion. The threshold of 60% of peak counts used by our laboratory to identify infarction was established on the basis of cardiac phantom studies. It provided the highest correlation coefficient (r = 0.98) and the slope of the regression line between true and measured infarct size that was closest to unity (slope = 1.01). Both the correlation coefficient and slope were better with a 60% than with a 50% threshold, which theoretically should be optimal if scatter and attenuation did not exist. In a later cardiac phantom study that used a newer-generation gamma camera with enhanced energy resolution and hardware software to perform scatter correction, the optimal threshold proved to be 55%, closer to the theoretical ideal. The normal limits of activity distribution in the basal inferior wall may extend below the 60% threshold in some patients whose body habitus leads to greater attenuation. In a consecutive series of 100 overweight (89 ± 19 kg) patients with a normal resting ECG and no history of infarction who were referred for sestamibi imaging, 81 had no measurable defect and 8 had trivial defects measuring between 1% and 3% of the left ventricle. Although the remaining 11 patients had inferior wall defects that measured between 4% and 21% of the left ventricle, 7 of these, including all 4 patients with defects of >10% of the left ventricle, had further cardiac evaluation that suggested that the measured inferior defects were real. Thus, tissue attenuation can certainly lead to “false-positive” infarctions, although these should be quantitatively small. Both of the aforementioned effects of attenuation—the nonoptimal threshold and false-positive infarctions—could theoretically be removed with attenuation correction, but this has not yet been widely applied in clinical imaging.

2. Sestamibi infarct size measurements are less commonly available and more technically demanding than left ventricular function measurements. Although this is true, the availability of SPECT imaging is certainly improving. Medicare data from 1994 show that nearly 1 million SPECT myocardial perfusion imaging studies were performed nationally and that this procedure is increasing at a rate of >10%/y. Although the procedure is technically demanding, we have used a quality control study and a phantom experiment to assess the technical performance of laboratories. Most laboratories are capable of acquiring high-quality SPECT images of a phantom that when processed in a central laboratory, provide measured “infarct” sizes that are very closely correlated with the actual defect size, with an average absolute error of <3% of the left ventricle.

3. There may be late recovery of myocardium which will alter the measurement of infarct size over time. Galli et al carefully studied 71 patients with anterior myocardial infarction by sestamibi SPECT imaging at 5 weeks and 7 months after acute infarction. Using a polar map “normal limits” technique, they reported a late decline in measured infarct size. Their study design incorporated a number of features—use of a polar map technique, restriction to anterior infarcts, and inclusion of patients who did not receive reperfusion therapy and had occluded arteries by angiography—that would be expected to produce a larger perfusion defect at 5 weeks and therefore greater potential for a late decrease. Nevertheless, the change in extent of the defect was relatively modest (6% of the left ventricle). Given the difference in measurement technique and image timing used by Galli et al,
applicability of their findings to the approach we have developed is questionable. Although this late change might argue for performing perfusion imaging after a longer delay following myocardial infarction, it would probably be much more difficult from the standpoint of patient compliance and patient dropout because of deaths, recurrent infarction, or other intervening clinical events. All the data validating infarct size measurements by SPECT sestamibi described previously were based on measurements performed at the time of hospital discharge. Clearly, further data are needed on serial determinations of defect size with the use of this technique in an unselected population of postinfarction patients to determine the overall magnitude of late change.

4. No randomized trial has shown a corresponding decrease in mortality in association with a therapy that reduces infarct size. This requirement has assumed increasing importance because of the experiences with ventricular arrhythmias on ambulatory monitoring as a surrogate end point. Frequent premature ventricular contractions after myocardial infarction were known to be associated with increased subsequent mortality. Although it was hypothesized that their suppression with antiarrhythmic therapy could be used as a measure of efficacy, the CAST trial demonstrated that such therapy produced an increase rather than a decrease in mortality. The only published randomized trial to demonstrate a reduction in infarct size involved poloxamer-188, which was subsequently shown in the CORE trial to have unacceptable renal toxicity at the doses initially used in the pilot study.

However, randomized trial data are available that compare therapies that did not have a demonstrable difference in infarct size (Table 3). The Mayo trial comparing tissue plasminogen activator and PTCA mentioned previously did not show a significant difference in infarct size between these 2 therapies. The difference reported was 0% of the left ventricle, with 95% confidence limits of ±6% of the left ventricle. Although the randomized PAMI (Primary Angioplasty in Myocardial Infarction) trial reported a significant, large difference in reinfarction or death between these 2 therapies, the larger GUSTO Iib trial (Global Use of Strategies To Open occluded coronary arteries in acute coronary syndromes) found that the differences in reinfarction and death between these 2 therapies were significant but more modest. The modest difference in clinical outcome data observed in GUSTO Iib could not be excluded by the results of the Mayo trial.

A number of observational studies using sestamibi have reported treatment effects that are similar to those reported by a randomized trial using mortality as an end point (Table 3). Myocardial salvage by sestamibi is greater with tissue plasminogen activator than by conventional therapy without thrombolysis (13% versus 4% of the left ventricle, \( P<0.003 \)). Randomized clinical trials have clearly shown a reduction in mortality with tissue plasminogen activator compared with placebo.

When patients with patent arteries after reperfusion therapy have been compared with patients with occluded arteries after reperfusion therapy, patients with patent arteries have greater myocardial salvage (17% versus 0% of the left ventricle, \( P<0.001 \)) and smaller infarct size (9% versus 19% of the left ventricle, \( P<0.05 \)). The angiographic substudy of the GUSTO trial demonstrated a reduction in mortality associated with arterial patency.

Myocardial salvage by sestamibi is clearly greater in anterior infarcts than in inferior infarcts (24% versus 10% of the left ventricle, \( P<0.01 \)). A meta-analysis of randomized clinical trials showed that absolute mortality reduction was greater in anterior infarcts (3.7%) than in inferior infarcts (0.9%). Thus, the treatment effects on salvage and infarct size demonstrated by sestamibi have generally been consistent with the effects on mortality.

5. Sestamibi infarct size is a measure of efficacy, not safety. The demonstration of efficacy by this approach requires modest sample sizes, which are clearly not large enough to detect possible increases in adverse events that occur infrequently with existing therapy. The CORE trial demonstrated this principle.

This limitation is most relevant to the third purpose described earlier. From a regulatory standpoint, demonstration that a new therapy is “equivalent” to existing therapy with respect to early mortality will require a reasonably sized trial of perhaps 5000 to 10 000 patients. Such a trial should have sufficient power to assess other important safety concerns (strokes, renal insufficiency) that cannot be addressed by infarct size measurements. The development of reteplase
is a potential example of this approach; the RAPID (Recombinant plasminogen activator Angiographic Phase II International Dose finding study) trial3 demonstrated an advantage in patency compared with tissue plasminogen activator, and the INJECT (INternational Joint Efficacy Comparison of Thrombolitics) trial44 showed equivalence to streptokinase with respect to mortality.

Conclusions

On the basis of the available scientific evidence, SPECT imaging with 99mTc-sestamibi is the best available measurement tool for infarct size in clinical medicine. It has already served as an end point in early pilot studies to demonstrate potential efficacy of new therapies. It will likely be increasingly used in dose-ranging studies. Does the available evidence justify the use of this end point as a true “surrogate” to potentially uncover advantages of new therapies that may be “equivalent” to existing therapies with respect to early mortality? When this regulatory issue was last addressed by the Food and Drug Administration in 1992, the answer was clearly “no.”35 The large body of evidence that has emerged since would appear to justify a reexamination of this issue.

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