Gallium-67 imaging in patients with dilated cardiomyopathy and biopsy-proven myocarditis

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ABSTRACT Current standards for detection of myocarditis in a clinical setting rely on endomyocardial biopsy for accurate diagnosis. With this technique a subset of patients with dilated cardiomyopathy show unsuspected myocarditis histologically. Endomyocardial biopsy, despite its specificity, may lack sensitivity due to sampling error if the inflammation is patchy or focal. Therefore, inflammation-sensitive radioisotopic imaging may be a useful adjunct in the diagnosis of myocarditis. This study was designed to evaluate the applicability of gallium-67 (67Ga) myocardial imaging as an adjunct to endomyocardial biopsy in the diagnosis of myocarditis. Sixty-eight consecutive patients referred for evaluation of dilated cardiomyopathy underwent 71 parallel studies with 67Ga imaging and biopsies that served as the basis of comparison for this study. Histologic myocarditis was identified in 8% of biopsy specimens. Clinical and hemodynamic parameters could not be used to predict the presence of myocarditis. Five of six biopsy samples (87%) with myocarditis showed dense 67Ga uptake, whereas only nine of 65 negative biopsy samples (14%) were paired with equivocally positive 67Ga scans (p < .001). The single patient with myocarditis and no myocardial 67Ga uptake had dense mediastinal lymph node uptake that may have obscured cardiac uptake. The incidence of myocarditis on biopsy with a positive 67Ga scan was 36% (5/14); however, the incidence of myocarditis with a negative 67Ga scan was only 1.8% (1/57). Follow-up scans for three patients showed close correlation of 67Ga uptake with myocarditis on biopsy. In conclusion 67Ga may be a useful screening test for identifying patients with a high yield of myocarditis on biopsy, and serial scans may eliminate the need for frequent biopsies in patients with proven myocarditis.


DILATED CARDIOMYOPATHY is a clinical syndrome that frequently culminates in progressive congestive heart failure and premature death. The etiology of dilated cardiomyopathy is obscure by definition; consequently, current therapy is neither specific nor life prolonging.1 The recent development of safe techniques of endomyocardial biopsy has led to the realization that patients with dilated cardiomyopathy may have unsuspected myocarditis and that the inflammatory infiltrates are potentially reversible.2 Immunosuppressive therapy may ultimately lead to improvement of clinical symptoms and prognosis if the myocardium has not been irreversibly damaged. Although safe when performed by experienced hands, endomyocardial biopsy is not the ideal diagnostic tool because of its morbidity, cost, and potential for sampling error, which may cause low sensitivity when the inflammatory infiltrate is patchy or focal — a common finding in myocarditis.

The ideal noninvasive screening test should have high sensitivity, low morbidity, and low cost. Inflammation-sensitive radioisotopic imaging has great potential for this role. Gallium-67 (67Ga) is a radioisotope that is routinely used to identify chronic inflammatory reactions with a reported sensitivity of 90%3 and specificity of 98%.4 We have previously described 67Ga uptake over the cardiac region in patients with pericardial inflammation,5 and more recently we have identified a subset of patients with dilated cardiomyopathy who have 67Ga uptake over the myocardium.6 Forty percent of these patients showed clinical and hemodynamic improvement after the initiation of immunosuppressive therapy.4 Changes in myocardial 67Ga avidity paralleled the clinical re-
spontaneous immunosuppression. This study was designed to compare $^{67}$Ga imaging with endomyocardial biopsy in identification of inflammation in patients with dilated cardiomyopathy.

**Materials and methods**

**Patients.** All patients referred to Loyola University Medical Center for evaluation of dilated cardiomyopathy from January 1981 through December 1982 underwent endomyocardial biopsy and $^{67}$Ga scintigraphy within 72 hr of the biopsy. Diagnoses other than dilated cardiomyopathy were excluded by left ventricular and coronary angiography in all patients over 25 years of age. The criteria included a dilated, hypococontractile left ventricle with normal coronary arteries and no evidence of valvular or pericardial disease. All patients underwent two-dimensional and M mode echocardiographic and electrocardiographic examinations as well as gated blood pool imaging by standard techniques with technetium-99m-labeled red blood cells.

**Endomyocardial biopsy.** Endomyocardial biopsy was performed by standard techniques with the Stanford biotome (Scholten Surgical Supply, Redwood City, CA) through the right internal jugular vein. A minimum of four samples were obtained with attempts to vary the sampling site. Tissue was immediately immersed in paraformaldehyde. All specimens were embedded in paraffin and stained with hematoxylin-eosin and Masson’s trichrome stains. A minimum of nine sections of each of the four specimens were reviewed. Myocarditis was considered to be present if more than five lymphocytes per high power field or focal clusters of lymphomononuclear cells were noted. Myocytic necrosis along with cellular infiltration aided the confirmation of the diagnosis of myocarditis.

**$^{67}$Ga imaging.** $^{67}$Ga imaging was routinely performed 72 hr after the intravenous injection of 8 mCi $^{67}$Ga citrate. Patients were scanned in the anterior, 45 and 60 degree left anterior oblique, and left lateral projections, with most of the liver excluded from the region of interest. Images were performed with a latest-generation, large-field-of-view gamma camera with a medium-energy collimator capable of detecting the 93, 185, and 300 keV $^{67}$Ga peaks to 625,000 counts. The images were then processed in a nuclear medicine computer with a 256 x 256 matrix and enhanced by less than 20% of the maximal pixel. Scans were interpreted by a nuclear medicine physician who was blinded to the clinical and pathologic data. Density of gallium uptake was compared with the density of the sternum. Scans were interpreted as positive if the density was equal to or greater than that of the sternum and equivocal if density was less than that of the sternum.

**Data analysis.** Evidence of active myocarditis by endomyocardial biopsy was considered the standard to which $^{67}$Ga images were compared. Patient populations were compared by a chi-square analysis or unpaired Student’s t test where appropriate; data are expressed as mean ± SD.

**Results**

Sixty-eight patients underwent 71 parallel studies with $^{67}$Ga imaging and right ventricular endomyocardial biopsy. The biopsy results and patient characteristics are presented in table 1. Of the 68 patients, five (7%) had biopsy-proven myocarditis. The five patients with active myocarditis were similar to the other 63 patients with respect to age, duration of symptoms before biopsy, incidence of an antecedent viral syn-

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Characteristics of patients with and without biopsy-proven myocarditis*</th>
</tr>
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<tbody>
<tr>
<td>n</td>
<td>EMB +</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>46.4 ± 19.2*</td>
</tr>
<tr>
<td>Duration (mo)</td>
<td>9.5 ± 14.8</td>
</tr>
<tr>
<td>Antecedent virus</td>
<td>2 (40%)</td>
</tr>
<tr>
<td>ESR (mm/hr)</td>
<td>27.4 ± 13.5</td>
</tr>
<tr>
<td>CI (l/min/m²)</td>
<td>2.2 ± 0.4</td>
</tr>
<tr>
<td>PAW (mm Hg)</td>
<td>14.4 ± 5.0</td>
</tr>
<tr>
<td>EF (%)</td>
<td>23.6 ± 8.0</td>
</tr>
<tr>
<td>LVEDD (mm)</td>
<td>62.6 ± 12.4</td>
</tr>
</tbody>
</table>

*EMB = endomyocardial biopsy; CI = cardiac index; PAW = mean pulmonary arterial wedge pressure; EF = ejection fraction; LVEDD = left ventricular end-diastolic dimension. *p = NS in all categories. *Data expressed as mean ± SD.

drome, erythrocyte sedimentation rate (ESR), cardiac index, pulmonary arterial wedge pressure, radionuclide ejection fraction, and echocardiographic left ventricular end-diastolic dimension. In this population, myocarditis could not be predicted on the basis of clinical or hemodynamic parameters.

After the initial biopsy, three patients underwent subsequent biopsies, which provided a total of 71 paired biopsies and $^{67}$Ga scans to serve as the basis of comparison for this study. Five of the six biopsy specimens with myocarditis had corresponding densely positive $^{67}$Ga scans. An example of $^{67}$Ga uptake in the presence of active myocarditis is demonstrated in figure 1. One of the patients with biopsy-proven myocarditis had a negative $^{67}$Ga myocardial scan and dense $^{67}$Ga uptake in posterior mediastinal lymph nodes. Of the 65 biopsy specimens with no evidence of active inflammation, 56 (86%) were accompanied by no $^{67}$Ga uptake over the myocardium. Nine, however, had $^{67}$Ga uptake over the myocardium, although not as dense (equivocal grade) as those with biopsy-proven myocarditis.

Few clinical differences were noted when patients with $^{67}$Ga uptake over the myocardium and no evidence of myocarditis on endomyocardial biopsy were compared with those without $^{67}$Ga uptake (table 2). Patients with positive $^{67}$Ga scans in the presence of a negative biopsy had a higher ESR ($p < .01$) and a higher mean ejection fraction ($p < .05$) than the population with negative scans. In this series, false-positive $^{67}$Ga scans did not correlate with parameters of left ventricular hypertrophy as was observed initially. 6

Three of the 68 patients whose initial biopsy results showed active myocarditis underwent serial biopsies
and $^{67}$Ga scans because the initial biopsy showed active myocarditis. Results of the initial biopsies of these patients showed extensive inflammatory infiltration and all three were placed on prednisone (1 mg/kg) and azathioprine (2.5 mg/kg). Two of the patients showed conversion of the $^{67}$Ga scans to negative within 3 months, when both biopsies showed resolution of the infiltrate. Serial studies in the third patient during immunosuppression revealed a change in $^{67}$Ga uptake from a diffuse pattern to a more localized pattern; however, the density did not change. In one of the four biopsy samples obtained, dense lymphomononuclear infiltration was observed.

**Discussion**

That inflammation might play a role in the development of chronic dilated cardiomyopathy is a concept that had little relevance until the advent of endomyocardial biopsy provided the opportunity to detect inflammatory infiltration. Because inflammation is potentially reversible, early identification of the infiltrates before the development of irreversible damage is of the utmost importance if modification of the natural history of this illness is attempted. Lack of reversibility of cardiac dysfunction because of late recognition of inflammation may explain why current clinical immunosuppressive regimens do not uniformly reverse the hemodynamic abnormalities in patients with dilated cardiomyopathy and biopsy-proven myocarditis.

The availability of safe endomyocardial biopsy allows serial histologic evaluation of the myocardium. By this technique, myocarditis has been identified in 8% to 25% of patients with dilated cardiomyopathy.

**TABLE 2**

<table>
<thead>
<tr>
<th>Characteristics of patients without myocarditis on biopsy: comparison based on $^{67}$Ga uptake</th>
<th>$^{67}$Ga +</th>
<th>$^{67}$Ga –</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>9</td>
<td>54</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>47.2 ± 10.4$^a$</td>
<td>47.0 ± 13.7</td>
</tr>
<tr>
<td>Duration (mo)</td>
<td>12.8 ± 13.4</td>
<td>13.0 ± 15.8</td>
</tr>
<tr>
<td>ESR &gt; 20 mm/hr$^b$</td>
<td>6 (75%)</td>
<td>8 (19%)</td>
</tr>
<tr>
<td>CI (l/min/m$^2$)</td>
<td>3.0 ± 1.1</td>
<td>2.4 ± 0.6</td>
</tr>
<tr>
<td>PAW (mm Hg)</td>
<td>19.6 ± 9.4</td>
<td>18.3 ± 10.9</td>
</tr>
<tr>
<td>EF (%)$^c$</td>
<td>24.8 ± 9.8</td>
<td>17.3 ± 8.9</td>
</tr>
<tr>
<td>LVEDD (mm)</td>
<td>71.3 ± 10.2</td>
<td>70.1 ± 9.5</td>
</tr>
<tr>
<td>LVFW (mm)</td>
<td>8.6 ± 2.1</td>
<td>9.7 ± 2.0</td>
</tr>
</tbody>
</table>

$^a$Data expressed as mean ± SD.

$^b$p < .01.

$^c$p < .05.

LVPW = left ventricular posterior wall thickness. For other abbreviations see table 1.
Critics of myocardial biopsy cite the morbidity, cost, and sampling error as disadvantages. Although quantification of sampling error cannot be accurately calculated, focal or patchy inflammation may be missed by biopsy, and this technique may lack the sensitivity of an ideal screening test.

The specificity of myocardial biopsy is contingent on the definition of myocarditis. The number of lymphocytes in the interstitium necessary to justify histologic diagnosis of myocarditis and the significance of myocyte necrosis remains controversial. Our working definition of myocarditis is conservative, requiring both lymphocyte quantitation and myocyte necrosis. Although the lack of defined specificity and sensitivity of endomyocardial biopsy diminishes its utility, this remains the only reference point for comparison of techniques.

$^{67}$Ga is useful clinically in the detection of noncardiac chronic inflammatory states. It has also been shown to be useful in the detection of inflammation in bacterial endocarditis, myocardial abscess, myocardial sarcoidosis, and pericardial disease. We initially described gallium uptake in three patients with dilated cardiomyopathy, two of whom showed response to immunosuppressive therapy. When our patient population was expanded it became obvious that $^{67}$Ga imaging may not be specific for active myocarditis. Yet, follow-up $^{67}$Ga uptake correlated closely with clinical improvement. This sequential correlation prompted us to compare results of $^{67}$Ga imaging with those of endomyocardial biopsy for detection of myocarditis.

In this study, consecutive patients without clinical evidence of myocarditis underwent endomyocardial biopsy within 72 hr of $^{67}$Ga imaging as part of the initial evaluation of dilated cardiomyopathy. Eight percent of these biopsy specimens showed myocarditis. When clinical and hemodynamic parameters were analyzed, no discriminating feature could identify those patients with myocarditis on biopsy. Eighty-seven percent (5/6) of positive biopsy results had associated dense $^{67}$Ga myocardial uptake. The sole patient without myocardial uptake had an abnormal $^{67}$Ga scan of the chest because of posterior mediastinal lymph node uptake that possibly obscured myocardial uptake. In patients with positive $^{67}$Ga scans, there was a 36% incidence of myocarditis on biopsy. The yield of myocardial biopsy therefore quadrupled if the $^{67}$Ga scan was positive. Conversely, when the $^{67}$Ga scan was negative, less than 2% (1/57) of patients had myocarditis in the parallel biopsy sample. $^{67}$Ga scanning therefore appears to be a useful adjunct in the screening of patients with dilated cardiomyopathy for identification of a subpopulation with a high yield of myocarditis on endomyocardial biopsy. Fourteen percent of patients without evidence of active myocarditis on biopsy had $^{67}$Ga uptake. The uptake of $^{67}$Ga in patients with positive biopsy results was obvious by our imaging techniques in all scans and subject to little variability in interpretation. However, in patients without evidence of myocarditis in biopsy specimens the uptake was not as dense (equivocal grade). When patients with positive $^{67}$Ga scans and negative biopsy results were compared with those with negative $^{67}$Ga scans and negative biopsy results, we noted elevated ESR and higher ejection fractions in the former. When viewed in the context of possible biopsy sampling error, perhaps some of these false-positive $^{67}$Ga scans may in fact represent false-negative biopsy findings. Serial endomyocardial biopsies and $^{67}$Ga scans were performed in three patients with initially positive biopsy results and $^{67}$Ga scans. The follow-up $^{67}$Ga scan correlated precisely to the follow-up biopsy in each.

Similar results have been reported recently by others. Shanes et al., in a small series, noted that a positive $^{67}$Ga scan usually correlated with the presence of inflammatory cells on endomyocardial biopsy. Strain et al., when comparing $^{67}$Ga scans with myocardial biopsy results in nine patients with biopsy-proven chronic myocarditis, found gallium to be highly specific but insensitive, with a predictive value of 58%. The discrepancy in utility of $^{67}$Ga scanning between their analysis and ours may stem from the pathologic interpretation of biopsy results.

Although $^{67}$Ga imaging is useful in the screening for inflammation in patients with dilated cardiomyopathy, there are several technique-dependent sources of error that could decrease the sensitivity. Scans should be performed 72 hr after injection of the isotope. If imaging is performed at 24 hr, $^{67}$Ga may not clear the blood pool and a false-positive $^{67}$Ga scan will result. If scanning is performed at 48 hr, the heart may be imaged but high background counts may decrease the sensitivity. Positioning of the gamma camera is very important. Scanning should be performed in the anterior as well as oblique projections so that localized uptake may be confirmed as myocardial in origin. In lactating or premenstrual women, breast uptake usually obscures the heart in the anterior projection, and if dense may totally obscure the heart. Most of the liver should be excluded from the field of view. The tendency to include more of the liver to cut down on the scanning time necessary to achieve the optimal 625,000 counts should be avoided because it reduces counts detected.
from the myocardium. Only latest-generation gamma cameras with good low-energy resolution should be used, and collimation should cover three $^{67}$Ga energy peaks. Computer background enhancement is important for improving the sensitivity of the examination, but enhancement should never be greater than 20% of the maximal pixel.

In summary, $^{67}$Ga imaging may be used as a screening tool to identify a population of patients with a high yield of myocarditis on endomyocardial biopsy. Once the correlation between $^{67}$Ga scanning and biopsy results is established in an individual patient, $^{67}$Ga imaging may be a useful technique for the serial evaluation of the patient, obviating the necessity for frequent endomyocardial biopsies.

References

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