Imaging Techniques for Myocardial Inflammation

JOHN B. O'CONNELL, M.D., ROBERT E. HENKIN, M.D., and JOHN A. ROBINSON, M.D.

Departments of Medicine and Radiology, Loyola University Medical Center, Maywood, IL 60153

ABSTRACT

Dilated cardiomyopathy (DC) represents a heterogeneous group of disorders which results in morbidity and mortality in young individuals. Recent evidence suggests that a subset of these patients have histologic evidence of myocarditis which is potentially treatable with immunosuppression. The identification of myocardial inflammation may therefore lead to development of therapeutic regimens designed to treat the cause rather than the effect of the myocardial disease. Ultimately, this may result in improvement in the abysmal prognosis of DC.

The currently accepted technique for identification of active myocardial inflammation is endomyocardial biopsy. This technique is not perfect, however, since pathologic standards for the diagnosis of myocarditis have not been established. Furthermore, focal inflammation may give rise to sampling error. The inflammation-avid radioisotope gallium-67 citrate has been used as an adjunct to biopsy improving the yield of myocarditis from 7 percent to 36 percent. Serial imaging correlates well to biopsy results. Future studies are designed to study the applicability of lymphocyte labelling techniques to myocardial inflammatory disease.

Introduction

Idiopathic dilated cardiomyopathy (IDC) is an important cause of morbidity and mortality in the young adult population. Although the therapy of congestive heart failure, a common manifestation of IDC, has improved substantially over the past 15 years with the addition of vasodilators and intravenous inotropic agents, there has been no effect on long term survival. The current therapies, therefore, are palliative at best because they are designed to treat the signs and symptoms (congestive heart failure, arrhythmia, or thromboembolic complications) and not the cause of this heart muscle disease. The only form of therapy proven to prolong life is cardiac transplantation.
The variable prognosis of IDC suggests that it is the end result of a heterogeneous group of conditions. When Mason and colleagues demonstrated that active myocardial inflammation could be identified histologically by using endomyocardial biopsy (EMB) in patients with advanced dilated cardiomyopathy, new hope for the development of therapies designed to treat the cause rather than the effect of the cardiomyopathic process emerged. Since then their observations have been confirmed and uncontrolled trials of immunosuppressive therapy suggest that a subset of patients with clinical IDC and inflammation on myocardial biopsy may respond with clinical and hemodynamic improvement by the addition of prednisone and azathioprine. A large randomized controlled trial must be completed before the effect of these agents on the natural history of IDC can be determined.

Although efficacy of immunosuppressive therapy in active myocarditis is not yet proven, identification of myocardial inflammation may be important to the clinician for other reasons. In animal models, there is compelling evidence that regular physical exercise results in marked worsening of inflammation and subsequent necrosis and may be detrimental to inflammatory heart diseases. Consequently, restricting activity in patients with active myocarditis may be therapeutically beneficial. Mural thrombi may form in the inflamed endomyocardium even in the absence of aki netic segments on echocardiograms, necessitating anticoagulant therapy in individuals with active myocarditis. For these reasons, a reliable tool for the identification of myocardial inflammation is desirable if optimal care is to be provided. Finally, if a patient with proven myocarditis clinically deteriorates, immunosuppression may be considered.

Identification of myocardial inflammation

Endomyocardial biopsy is the standard against which all other techniques of detection of myocardial inflammation are compared. This technique, although safe in experienced hands, is costly and may be associated with morbidity in inexperienced hands. Although widely available in tertiary care centers, it is not likely that endomyocardial biopsy will be a practical tool in smaller community hospitals, primarily because experience with histopathologic interpretation of biopsy samples may be limited in that setting. Although interpretation of myocardial biopsy at face value seems relatively straightforward, in fact, multiple reports describing the incidence of histologic myocarditis from five percent to 63 percent in dilated cardiomyopathy is strong evidence there are significant discrepancies in pathologic interpretation. For example: How many lymphocytes in the myocardial interstitium are necessary to establish a diagnosis of myocarditis? Is it important to quantitate lymphocytes since myocarditis may be only focal in a biopsy specimen? How important is demonstrable myocyte necrosis and how does one demonstrate myocyte necrosis? Does fibrosis alter the pathologic interpretation? Is immunohistochemistry of value? And finally: Can one establish a diagnosis of active myocarditis in the presence of myocyte abnormalities compatible with dilated cardiomyopathy? Before the specificity of endomyocardial biopsy can be ascertained, these questions need to be answered.

It is also very difficult to quantitate the sensitivity of endomyocardial biopsy since the identification of a "false negative" population cannot be achieved. There is, once again, controversy regarding the potential for sampling error of endomyocardial biopsy.
focality of significant myocarditis was first brought to light on autopsy study of patients dying of varicella infection by Haeckel. He showed that when routine histologic specimens of the myocardium were obtained at autopsy, the incidence of myocarditis was quite low. In addition, when careful histologic serial sections were performed, myocarditis was uniformly present in these hearts, suggesting that multiple sections must be obtained in order to minimize the sampling error even when the entire heart is available. Since most cardiologists in the United States who perform endomyocardial biopsy use the safest procedure, one that involves biopsy of the septal portion of the right ventricle, left ventricular subendocardium is not available for examination. Although four or five specimens may be obtained from various areas of the septum, the patchy nature of myocarditis may result in significant sampling error. Proof of this can only be performed if the entire heart is available for histologic evaluation; however, these autopsy analyses represent a skewed population, that is, presumptively patients with more fulminant, end-stage forms of the disease die of their disease. Therefore, the sensitivity of endomyocardial biopsy will never be ascertained; however, one can assume that the specificity is far greater than the sensitivity.

It was hoped that careful evaluation of clinical, hemodynamic, and non-invasive parameters in patients with biopsy-proven myocarditis would sort out clinical clues retrospectively that could be utilized in screening for individuals with a high incidence of myocarditis at biopsy. In fact, that has not been the case. In patients with recent onset of congestive heart failure, there are no clinical, hemodynamic, or non-invasive parameters than can reliably help in the identification of a subset of patients with active myocarditis. Furthermore, since the autoimmune nature of this process is postulated to involve cell-mediated immune responses, the non-specific indicators of inflammation, such as erythrocyte sedimentation rate and white blood cell count, has proven to be useless in identifying those patients with active myocarditis. Antiheart antibodies, although common in active myocarditis, have not been shown to be specific for that condition. In summary, the identification of active myocarditis currently relies upon the use of endomyocardial biopsy, a technique which is potentially specific but lacks the necessary sensitivity to identify patchy myocardial inflammation. The use of clinical and laboratory tools to identify a population likely to have myocarditis on biopsy has been frustrating to date since no clear-cut difference has been identified between patients with active myocarditis and those without. Therefore, a safe, reliable, reproducible, highly sensitive technique is desirable as an adjunct to biopsy in the diagnosis of myocarditis.

**Imaging Techniques**

**Technetium-99m Pyrophosphate (99mTc PYP)**

Investigators in Japan were the first to identify that this 99mTc PYP, commonly used as a "hot spot" imaging agent for myocardial infarction, may show diffuse uptake in myopericarditis. This observation was verified with studies in the animal model of Coxsackie virus B3 myocarditis in BALB/c mice. When sequential studies of myocardial uptake were performed, the myocardial 99mTc PYP uptake correlated with the extent of myocardial necrosis but decreased with the progression of cellular infiltration documenting that, although an excellent marker of myocardial damage, this imaging technique does not mark active myocardial inflammation. Furthermore, other investigators have demonstrated
similar diffuse myocardial uptake in patients with IDC who have no evidence of active myocarditis suggesting that many forms of myocardial damage may non-specifically result in $^{99m}$Tc PYP uptake.\textsuperscript{9,36}

**Gallium-67-Citrate ($^{67}$Ga)**

Initially developed as a bone scanning agent but later shown to be an excellent marker for identification of extent of lymphoma and some selected soft tissue tumors, $^{67}$Ga was noted to be an excellent imaging agent for chronic inflammation.\textsuperscript{13} In fact, several autoimmune conditions such as sarcoidosis,\textsuperscript{1} interstitial pneumonitis,\textsuperscript{26} Crohn’s disease,\textsuperscript{13} non-infectious interstitial nephritis,\textsuperscript{43} dermatomyositis,\textsuperscript{37} and rheumatoid arthritis,\textsuperscript{24} have all been imaged successfully with $^{67}$Ga. Initial interest in the use of $^{67}$Ga imaging in myocardial lesions was its use as a “hot spot” imaging agent in acute myocardial infarction;\textsuperscript{18} however, with the development of $^{99m}$Tc PYP, this interest rapidly tapered. The present authors first became interested in studying the role of $^{67}$Ga imaging in active myocarditis when a young woman presented to our institution with a malignant thymoma and congestive heart failure. In an attempt to stage her thymoma, a $^{67}$Ga scan was performed which demonstrated no uptake over the known pleural neoplasm but very dense uptake over the myocardium. Despite aggressive therapy for her lymphoma, she expired several months later; at autopsy, evidence of myocarditis was identified.

This stimulated us to study $^{67}$Ga as a tool in imaging the myocardium for inflammation; however, the available techniques for gallium scanning were not adequate to image the myocardium and modifications of that technique had to be made. Currently, $^{67}$Ga heart scans are performed 72 hours after intravenous injection of 5mCi of $^{67}$Ga citrate. Our patients are imaged in the anterior, left lateral, and 45° and 60° left anterior oblique projections. It is tried to exclude all but the superior portion of the liver so that the 625,000 counts accumulated will not be of hepatic origin. Images are performed with a latest generation large field of view gamma camera with medium energy collimator capable of detecting the 93, 185, and 300 keV $^{67}$Ga energy peaks. Our images are processed in a nuclear medicine computer with a $256 \times 256$ matrix, enhanced less than 20 percent of the maximal pixel, and the scans are interpreted by a nuclear medicine physician (REH) who is blinded to the clinical and pathologic data. Scans are interpreted as positive if their density is equal to or greater than that of the sternum and equivocal if the density is less than that of the sternum. Utilizing this technique, it was possible to identify gallium uptake (figure 1) over the myocardium in three individuals with IDC, two of whom were treated with immunosuppressive therapy with encouraging results.\textsuperscript{35}

Since myocardial inflammation frequently occurs in the presence of pericardial inflammation, it was possible to identify active uptake over the pericardium in three patients with proven pericardial inflammation, one of whom had a thin pattern of uptake that was visually much different than those patients with myocardial inflammation.\textsuperscript{28} Thirty-nine unselected patients with IDC were scanned. It was found that in 19 of those individuals there was active uptake over the myocardium.\textsuperscript{29} When comparing clinical, hemodynamic, and non-invasive parameters of myocardial dysfunction, those individuals with gallium uptake could not be separated from those who were gallium negative.

When offered immunosuppressive therapy, 15 of the 19 $^{67}$Ga positive patients accepted and received predni-
sone and azathioprine for two years. Nine (60 percent) had persistently positive gallium scans despite immunosuppressive therapy and no clinical nor hemodynamic improvement as a result of this treatment. Six (40 percent) showed conversion of the gallium scan from positive to negative by three months with substantial improvement in ejection fraction and no mortality in the follow-up period. These patients have been followed for seven years (five years after discontinuation of immunosuppression), and, to date, all of the patients remain alive and well. This prompted us to postulate that in the 60 percent of patients who received immunosuppression and whose gallium scan did not convert to negative, perhaps the scan was positive for reasons other than inflammation because it was not possible to alter the process causing the myocardial uptake with the potent immunosuppressive regimen. It was our hope that the 40 percent of patients who responded and had gallium scan conversion to negative represented a population of patients with active myocarditis who improved on immunosuppressive therapy. Endomyocardial biopsies were not available for that study and, therefore, these conclusions were not firm.

The $^{67}$Ga imaging was compared to endomyocardial biopsy in patients in biopsy-proven myocarditis (figure 2). The overall incidence of myocarditis was seven percent in 68 patients with congestive heart failure of recent onset. As previously noted, clinical or hemodynamic parameters could not differentiate those patients who had biopsy evidence of myocarditis from those who did not. Fourteen gallium scans were positive. Five of the six patients with biopsy-proven myocarditis had a dense diffuse uptake of gallium. The single patient without gallium uptake had a probably hypersensitivity myocarditis and had dense uptake of posterior mediastinal lymph nodes which may have decreased our visual ability to detect myocardial uptake. Serial $^{67}$Ga imaging showed a direct correlation with resolution of histologic evidence of myocarditis. The
incidence of biopsy-proven myocarditis rose five-fold (7 to 36 percent) if the gallium scan was positive. True sensitivity and specificity of this technique cannot be calculated from these data because of the small patient numbers.

When $^{67}$Ga imaging was performed for detecting inflammatory lesions in other organ systems, the sensitivity was found to be 90 percent with a specificity of 64 percent, which would compare favorably to our myocardial data. Strain and others compared $^{67}$Ga imaging to endomyocardial biopsy and found that the sensitivity was quite low (44 percent) with a specificity of 100 percent. The rather marked difference in results between their study and ours is perhaps reflective of difference in pathologic interpretation of endomyocardial biopsy. When $^{67}$Ga was compared to $^{99m}$Tc PYP imaging in rabbit norepinephrine-induced myocarditis, diffuse cardiac uptake of $^{67}$Ga was found in 13 of 15 rabbits. There was no uptake of $^{99m}$Tc PYP in eight rabbits; yet, the histology of all 23 hearts showed similar levels of myocarditis.

Based on our current studies, it is felt that $^{67}$Ga imaging may, in fact, be a sensitive marker of active myocarditis although lacking specificity. Its utility is dependent upon meticulous attention to the details of the technical aspects of imaging the heart with this isotope. This technique has been very useful in following our patients with biopsy-proven myocarditis as a non-invasive marker of inflammation obviating the necessity of
multiple repetitive biopsies. The value of $^{67}$Ga as a screening tool for myocarditis will be evaluated in a large multi-centered trial of immunosuppression and biopsy-proven myocarditis.

**Future Prospects**

Although perhaps a sensitive marker of inflammation, $^{67}$Ga is not the ideal imaging agent. A 72 hour delay from injection to imaging is required to improve target to background ratios to enhance the ability to interpret the scans visually. This agent has an extremely long half life (96 hours); thus, serial scans require a minimum of a three to four week separation between studies. Furthermore, because this is a gamma emitter, safety in radiation dose dictates that injection to imaging is required to improve target to background ratios to result of congestive heart failure, techniques designed to identify active myocardium in myocarditis include cell labeling techniques utilizing indium 111 or technetium-99m to label autologous lymphocytes in an effort to follow their homing pattern into the myocardium indicating active inflammation.

**Summary**

Since active myocarditis is postulated as a cause of morbidity and mortality as a result of congestive heart failure, techniques designed to identify active myocarditis non-invasively are important so that therapy designed to alter the inflammatory response may be attempted. $^{67}$Ga may be a sensitive but non-specific indicator of active myocarditis which can be a useful adjunct in the diagnostic armamentarium of the clinical cardiologist when coupled with endomyocardial biopsy. Future studies are planned in which $^{67}$Ga imaging will be compared to endomyocardial biopsy in a randomized multi-centered trial. Although less than an ideal isotope, because of its radiopharmaceutical properties, isotopic studies involving lymphocyte labelling may be valuable in future studies of non-invasive identification of active myocarditis.

**References**

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