Myocardial gallium-67 imaging in dilated cardiomyopathy

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Summary: The use of gallium-67, an isotope that is avid for areas of inflammation in patients with dilated cardiomyopathy, is described and compared with endomyocardial biopsy in 68 consecutive patients with dilated cardiomyopathy. Myocarditis was diagnosed in 8% on biopsy and the likelihood of a positive biopsy when the gallium scan was positive for inflammation, rose to 36%. It is concluded that gallium scanning is a useful adjunct to biopsy in detecting myocarditis in patients with dilated cardiomyopathy and in following patients with evidence of myocarditis on biopsy.

Disadvantages of gallium-67 imaging include the radiation dose accumulated with multiple scans and 72 h delay from initial injection of the isotope to imaging. It is suggested that definitive conclusions regarding the technique should await the results of a large multicentre trial evaluating gallium in comparison with endomyocardial biopsy in the diagnosis of myocarditis.

Introduction

In some patients with dilated cardiomyopathy (DC), identification of active myocardial inflammation may be of extreme clinical importance because of the disease's poor prognosis (Fuster *et al.*, 1981). Furthermore, there is a recent suggestion that modulation of immune responses by prednisone and azathioprine may induce dramatic clinical improvement (Mason *et al.*, 1980).

The clinical application of endomyocardial biopsy techniques to DC provides accurate histological diagnosis of myocarditis. Endomyocardial biopsy, although safe in experienced hands, is associated with small but significant morbidity, the increased cost of an invasive procedure and, although specific for the identification of myocarditis, it may lack sensitivity due to the focal nature of the pathological process. Because this technique is furthermore limited to tertiary referral centres, a sensitive and readily available non-invasive technique for screening the large population of patients with DC of recent onset is desirable.

Radioisotopic imaging techniques

Technetium-99m-pyrophosphate

Enthusiasm for the use of technetium-99m-pyrophosphate (Tc-99m-PYP) imaging in myocarditis arose from studies in the mouse model of Coxsackie virus B-3

myocarditis that lent support to the concept that it may be a valid tool in the screening of patients for myocardial inflammation (Kadota *et al.*, 1979). This interest was magnified by reports that patients with acute myocarditis have Tc-99m-PYP uptake over their myocardium (Mitsutake *et al.*, 1981). Serial histological studies revealed that the intensity of isotopic uptake correlated most closely with evidence of myocyte necrosis yet uptake was decreased when the cellular infiltration was prominent. This observation reinforces prior concepts that this radioisotope is avid for areas of myocardial damage and is not an inflammation-avid isotope (Matsumori *et al.*, 1980). It is, therefore, although a sensitive marker of myocyte damage, not a marker of inflammation and cannot be applied to dilated cardiomyopathy for screening for persistent inflammatory disease.

Gallium-67

Gallium-67 (⁶⁷Ga) was first used in clinical nuclear radiology as a bone scanning agent (Hoffer *et al.*, 1978). Because patients who undergo bone scans may frequently have tumours, the utility of this isotope in imaging soft tissue tumours and lymphomas was readily appreciated and ⁶⁷Ga is now the standard for staging many malignancies. Since patients with malignancies frequently have inflammatory disease, it was rapidly realized that ⁶⁷Ga is inflammation-avid. This isotope is now applied in the routine scanning for inflammation with a sensitivity of 90% but a specificity of only 64% (Ebright *et al.*, 1982). Acute

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inflammatory states of the myocardium such as myocardial abscess (Spies *et al.*, 1977) and bacterial endocarditis (Wiseman *et al.*, 1976) have been successfully imaged with this isotope. Gallium-67 imaging has been successfully applied to imaging chronic inflammation in myocardial sarcoidosis (Forman *et al.*, 1983) and pericarditis (O'Connell *et al.*, 1980). In the experimental animal model of isoproterenol-induced myocarditis, gallium-67 uptake proved to be a sensitive technique for identifying active inflammation (Reeves *et al.*, 1981). Chronic inflammatory diseases associated with cell-mediated immune responses such as interstitial pneumonitis (Niden *et al.*, 1976), non-infectious interstitial nephritis (Wood *et al.*, 1978), dermatomyositis (Smith *et al.*, 1979), and rheumatoid arthritis (McCall *et al.*, 1983) can be detected with ^{67}Ga . The ^{67}Ga uptake in cell-mediated chronic inflammatory states is dependent on its high avidity for activated lymphocytes (Merz *et al.*, 1974).

Before imaging patients with DC to detect active inflammation, we modified the ^{67}Ga technique (Table I). Conventionally, 5 mCi of gallium-67 citrate is administered intravenously and imaging is performed 72 h after injection. If imaging is performed at 24 h in patients with low cardiac output, the ^{67}Ga may not have successfully cleared the blood pool. At 48 h, the background counts remain fairly high decreasing the sensitivity of identification of uptake over the myocardium. Our patients are imaged in the anterior, 45° and 60° left anterior oblique, and left lateral projections to 625,000 counts. Most of the liver must be excluded from the field of view since the sensitivity of the technique could be significantly altered by accumulating most of the counts from the dense normal liver uptake. Breast uptake in lactating females will also decrease the sensitivity of detection of myocardial uptake and impair visual identification due to the close proximity of breast tissue to the heart. The patients are imaged on a gamma camera with

Table I Gallium-67 imaging technique

Dose	–	5 mCi ^{67}Ga citrate
Timing	–	72 h post injection
Positioning	–	anterior, 45° LAO, 60° LAO, left lateral – most of liver excluded
Equipment	–	gamma camera with medium energy collimator covering 93, 185, and 300 keV peaks to 625,000 counts
Computer	–	256 × 256 matrix enhanced less than 20%

medium energy collimation covering the 93, 185 and 300 keV peaks of ^{67}Ga . The images are then computer processed on a 256 × 256 matrix that is enhanced less than 20% of the maximal pixel.

Subsequent to our initial identification of ^{67}Ga uptake in a small series of patients with DC (Robinson *et al.*, 1979), we systematically scanned 39 patients with idiopathic dilated cardiomyopathy (O'Connell *et al.*, 1981) (Figure 1). Nineteen of these patients had ^{67}Ga uptake over the myocardium. There were no discriminating clinical or haemodynamic features to separate ^{67}Ga positive from negative patients. When 15 of the 19 ^{67}Ga positive patients were treated with immunosuppression, 6 showed resolution of the uptake within 3 months. These patients uniformly had improvement in functional class and ejection fraction with no mortality. Nine of the patients had persistent myocardial ^{67}Ga uptake and showed no haemodynamic or functional improvement with a 2 year mortality of 67%. These preliminary studies suggested that ^{67}Ga may be avid for the myocardium in some patients with active inflammatory disease but in other individuals uptake appeared unrelated to inflammation, in that uptake persisted despite immunosuppression. These findings prompted a study comparing gallium-67 imaging and endomyocardial biopsy in patients

Figure 1 Anterior and 45° LAO projections of ^{67}Ga myocardial scan showing uptake over the heart at the arrows. (From *Heart Transplant*, 2, 13, 1984 – reprinted with permission.)

with idiopathic dilated cardiomyopathy (O'Connell *et al.*, 1984). Seventy-one paired ^{67}Ga myocardial scans and endomyocardial biopsies were performed on 68 consecutive patients. The incidence of myocarditis on biopsy was 8%. The likelihood of a positive biopsy when the ^{67}Ga scan was positive rose to 36% (Figure 2). Therefore, a positive ^{67}Ga scan improved the yield of endomyocardial biopsy four-fold. Only 1 of 57 negative ^{67}Ga scans had a parallel positive myocardial biopsy. In this individual, there was very dense posterior mediastinal lymph node uptake, perhaps obscuring the ^{67}Ga uptake over the myocardium. Nine patients had a positive gallium scan in the absence of biopsy-proven myocarditis. These patients had an abnormal erythrocyte sedimentation rate (75% versus 19%) suggesting the possibility that these did not represent false positive ^{67}Ga scans but may, in fact, represent false negative myocardial biopsies due to sampling error. When serial biopsies and gallium scans were performed on patients with biopsy-proven myocarditis, the change in ^{67}Ga uptake paralleled the resolution of inflammatory infiltration. These studies suggest that gallium-67 imaging may be useful in screening patients with dilated cardiomyopathy who have a high yield of myocarditis on biopsy and that gallium-67 imaging is useful in non-invasively following patients with documented myocarditis on biopsy. Gallium-67 uptake in biopsy-proven myocarditis has been confirmed by other investigators (Strain *et al.*, 1983; Shanes *et al.*, 1983). Definitive conclusions, however, await the results of a large multi-centred trial evaluating ^{67}Ga in comparison with endomyocardial biopsy in the diagnosis of myocarditis.

Future prospects

The technical difficulties associated with gallium-67 imaging, the radiation dose accumulated with multiple scans, and the 72 h delay from the initial injection of the isotope to imaging are disadvantages of this technique. More recently, cell labelling techniques

Figure 2 Endomyocardial biopsy from patient whose ^{67}Ga scan is shown in Figure 1 showing a lymphomononuclear cell infiltration with myocyte necrosis compatible with myocarditis. Haematoxylin-eosin original magnification $\times 20$. (From *Heart Transplantation*, 2, 13, 1984 – reprinted with permission.)

using autologous indium-111-labelled leucocytes or technetium-99m-labelled lymphocytes may prove valuable in the evaluation of chronic myocardial disease (Thakur, 1982; Doly *et al.*, 1983). Experimental use of these isotopes in myocardial disease, however, is limited to identifying rejection by indium-111-labelled leucocytes and platelets in experimental cardiac transplantation (Wang *et al.*, 1982). It is hoped that clinical studies evaluating the use of these isotopes will be forthcoming so that greater application of radioisotopic techniques to the problem of detection of inflammatory cardiomyopathy subsets may prove practical in the near future.

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