Review Article

# Late gadolinium enhancement in Non ischemic dilated cardiomyopathy

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**Abstract:** Non ischemic cardiomyopathy (NICM) refers to varied myocardial conditions that are featured by a decline in left ventricular (LV) systolic function in the absence of considerable coronary artery disease. Late gadolinium-enhanced (LGE) cardiac MRI is known as a non invasive method that is used to establish the principal reason of dilated cardiomyopathy (DCM). The existence of LGE on CMR considerably deteriorates the prognosis for unfavourable cardiovascular events in patients suffering with DCM, and the absence refers to left ventricular reverse remodelling. Thus the present review was done to assess the role of Late gadolinium enhancement in Non ischemic dilated cardiomyopathy.

**Key words:** Nonischemic cardiomyopathy; Late gadolinium-enhanced; Cardiac MRI

Dilated cardiomyopathy (DCM) is a clinical condition that is featured by dilation and impaired contraction of left ventricular or biventricular parts, which is not being explained by abnormal loading conditions like valvular heart disease and hypertension or coronary artery disease.[1] DCM is defined by WHO as a severe cardiac disorder characterised by structural or functional abnormalities of muscles of heart leading to considerable morbidity and mortality causing various complications like arrhythmia and heart failure.[2] Nonischemic cardiomyopathy (NICM) is defined as a varied myocardial condition featured by a decrease in left ventricular (LV) systolic function in the absence of evident coronary artery disease.

Various research studies have revealed different aetiological factors for DCM, like infections, genetic mutations, autoimmune diseases, inflammation, endocrine or neuromuscular causes and exposure to toxins. A correct and timely diagnosis is challenging because of the heterogeneous nature of aetiological factors and varied clinical presentation of DCM.[2] In the general population the prevalence rate of NICM is observed to be ≈40 to 50 cases per 100,000.[3]

Different non-invasive and invasive examinations are required to precisely recognize the aetiology of DCM.[4-5] Globally an extensive variability exists in terms of the accessibility of advanced diagnostic tools like comprehensive cardiac imaging and genetic testing for inborn metabolic errors. Echocardiography and other imaging techniques are generally used to evaluate unfavourable myocardial remodelling and ventricular dysfunction. When an inflammation or infection is predicted, immunological and histological analyses of an endomyocardial biopsy sample is generally indicated.[4]

It has been found that around one-third of patients suffering with heart failure have nonischemic dilated cardiomyopathy (NIDM). Fibrosis or Myocardial scar in patients suffering with NICM is known to be a substrate for re-entrant circuits leading to remodelling and ventricular dilatation, predisposing the patient to heart failure and sudden cardiac death (SCD).[6]

Five-year mortality rate from NIDM is observed to be as high as 20% with sudden cardiac death (SCD), leading to mortality in 30% of cases. Thus, detecting scar/fibrosis by imaging technique has the capability to identify the elevated cardiovascular risk in patients suffering with cardiomyopathy. Now-a-days, the left ventricular ejection fraction (LVEF) is being used as the important criteria to risk stratify patients who require an implantable cardioverter defibrillator (ICD) to avert SCD.

However, LVEF does not inevitably show myocardial propensity for electrical instability causing ventricular tachycardia (VT) or ventricular fibrillation (VF).[7]

Late gadolinium enhancement is an effective and reproducible method for assessing myocardial fibrosis and has previously demonstrated prognostic use in patients with ICM and hypertrophic cardiomyopathy.[8] Currently, there is a lack of prognostic data in patients with NICM involving studies with uniform end points and large patient populations. Therefore, the present review was done to assess the role of Late gadolinium enhancement in Non ischemic dilated cardiomyopathy.

## Epidemiology of NIDM

DCM is a heterogeneous condition that occurs in a diverse group of patients because of factors like underlying genetic susceptibility and environmental insults. The patients suffering with DCM has poor prognosis and more accurate risk stratification and personalised therapy may improve outcomes significantly.

The Global Burden of Disease study in 2015, has estimated the global prevalence of cardiomyopathy being 2.5 million cases, showing an increase of 27% in just 10 years. The causes of heart failure occurring from DCM arise from failure of pump (70%) due to dilatation, and sudden cardiac death from arrhythmias accounts for the rest of 30%. In developed countries patients with DCM who develop heart failure showed an improved survival with time.[9] It has been observed that mortality rate in women is lower than men even after adjusting different key prognostic variables, including implanted devices. Research in patients suffering with DCM secondary to specific genetic mutations also revealed that men have a poor prognosis as compared with women. But it has remained unclear that whether this is genotype-specific or more general.[10]

The DANISH (Danish Study to Assess the Efficacy of ICDs in Patients with Non-ischemic Systolic Heart Failure on Mortality) revealed that implantation of a cardioverter-defibrillator (ICD) did not decrease the overall mortality in patients. More accurate patient's selection for ICD in patient having DCM is needed.[11] Subgroup analysis of the DANISH has demonstrated a mortality advantage with ICD implantation in patients aged <59 years and outcome worsen in patients aged more than 68 years. The reason for these findings still remains unclear but it has been observed that a higher death rate in later years of life due to competing causes can dilute the benefits of an ICD.[12]

## Diagnosis

The accuracy of diagnostic techniques is dependent on the combination of various conventional non-invasive and invasive cardiological examination using molecular and non-cardiac parameters that consists of genetic analyses, which is also required to analyse the aetiology of DCM.

The clinical features of DCM are normally not linked to the underlying aetiological factors. They generally range from fatigue, dyspnoea, swollen legs, pain in ankles, stomach, and chest due to decreased oxygen levels causing the heart to undergo conditions like cardiogenic shock, arrhythmia, or acute decompensation. The signs and symptoms of DCM are generally associated with the degree of LV or biventricular systolic dysfunction causing pump failure; and heart failure. The signs and symptoms may be chronic, acute, or subacute in nature. Features like palpitations, atypical chest pain may also be present. Echocardiography is used to observe dilated chambers. The diagnostic criteria are LV end-diastolic volumes or diameters >2 deviating from normal according to normograms.[13]

Cardiac catheterization technique is used to rule out the coexisting coronary artery disease, whereas the cardiac MRI is used to assess the occurrence of oedema and/or fibrosis, (suggestive of inflammation) with the help of imaging dilatation. In patients with DCM, Electrocardiography (ECG) may be remarkably normal, but abnormalities can be observed as changes in isolated T wave and left bundle branch block to prolongation of atrioventricular conduction. Sinus tachycardia and supraventricular arrhythmias are commonly observed; ~20–30% of patients have non-sustained ventricular tachycardia.[1]

In myocarditis and autoimmune DCM, different serum autoantibodies to cardiac-specific and muscle-specific autoantigens have been found, and these autoantibodies are observed to have a direct pathogenetic role.[14]

## Imaging techniques

The imaging methods like Doppler and 2D echocardiography remains the chief techniques to evaluate the cardiac function and these help to make the diagnostic criteria for most of the heart muscle diseases.

Echocardiogram characteristics usually show a specific aetiology; however, echocardiography cannot establish the underlying cause of DCM definitively.

The technique of CMR has become increasingly used in clinical practice, representing as the best method for morphological as well as functional assessment and characterization of myocardial tissue in patients suffering with DCM. Late gadolinium enhancement (LGE) cardiac magnetic resonance imaging is a specific tissue-based marker that, in single-centre studies, shows a strong prognostic value.[15]

## Late gadolinium enhancement (LGE) in patients with NIDM

The role of late gadolinium enhancement (LGE) in cardiac MRI (CMR) as prognostic marker in NIDM is evolving. Late gadolinium enhancement is a technique used in CMRI for cardiac tissue characterization, in particular, the assessment of myocardial scar formation and regional myocardial fibrosis.

LGE recognises the patients who are having NIDM and are at high risk for SCD. LGE also enables the optimized patient selection for ICD placement, whereas the LGE absence may decrease the need for ICD implantation in patients having NIDM who are at low risk for future VF/VT or SCD.[7] In patients with NICM, the use of LVEF <35% alone has limited capability in predicting SCD. As a prognostic variable, the use of LGE in addition to LVEF, may also help to improve the risk stratification of patients suffering with NICM and prove to be as a better guide for using cardiac resynchronization therapy, ICD, and other therapies in such patients.[16]

CMR technique has developed as a powerful and useful method, providing a comprehensive cardiac assessment involving evaluation of LV function, structure, perfusion, and tissue characteristics, along with the presence or absence of fibrosis by LGE. A recent study conducted by enrolling patients having ICM or NICM showed the presence of both LGE and LVEF <30% has increased the occurrence rates of SCD or ICD discharge as compared with the event rates in patients with LVEF <30% alone.[17] The prevalence of LGE in NIDM patients in a study conducted in Indian subcontinent found to be 39%.[18] The LGE presence recognises the subjects suffering with NICM who are generally at a higher risk of hospitalization for heart failure. This generally permits the identification of patients with NICM requiring a closer follow-up and evaluation after diagnosis. This may help reduce the significant costs incurred because of repeat admissions in this patient population.[15]

Recent studies that examine LGE by CMR in patients suffering with NICM use different definitions to explain the presence and extent of LGE. The presence of LGE is determined by various thresholds of signal intensity above that of the remote myocardium, but recently there is a limited consensus available on an acceptable threshold for diagnosing the LGE. This is especially more challenging in NICM in which the LGE intensity is much more varied than that in ischemic heart disease.[19]

## Limitations of LGE use in NICM

An important limitation of using the LGE by CMR is that it only identifies the focal fibrosis but not diffuse fibrosis. Various new techniques like T1 mapping have shown a promising result in diagnosing the diffuse fibrosis, thus providing additional valuable prognostic information in patients with NICM.[19] The observations from T1 mapping may add prognostic value to that observed by using LGE-CMR in both the ICM and NICM patients.

A recent study evaluated whether late gadolinium enhancement (LGE) can be assessed by CMR imaging as a prognostic marker in patients having newly diagnosed non-ischemic cardiomyopathy. The authors revealed that in consecutive patients showing with newly diagnosed non-ischemic cardiomyopathy, LGE-positive patients had bad prognosis.[21] Moreover, only traditional risk parameters like cardiac biomarkers and left ventricular performance but not presence of LGE were independent risk predictors.

LGE positive patients in CMR revealed significantly higher combined major cardiac events having all-cause mortality, VT, SCD, and heart failure hospitalisations. LGE extent, having LGE >14% of LV volume shows an additional prognostic information beyond LVEF. Even in patients having mild to moderate LV dysfunction (LVEF 35%–50%) presence of LGE shows poor cardiac outcome. Any pattern, location or distribution of LGE is considerable for adverse cardiac outcome occurrence.[22]

The occurrence of LGE by CMR shows excellent prognostic risk stratification for all-cause mortality, SCD, and HFH in patients with NICM. The addition of the presence or absence of LGE to LVEF may add to the overall prognostic power to forecast SCD in patients suffering with NICM and better recognise those subjects

who find the best benefit from ICD placement and other options of aggressive heart failure management. Future research, especially randomized control trials are required to assess whether CMR guided therapeutic intervention like ICD/CRT implantation or anti heart failure medicines can decrease the morbidity and mortality rate of NIDM patients.

Conflict of interest: Not declared

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