Original Article

Role of Myocardial Perfusion Study in Differentiating Ischemic versus Nonischemic Cardiomyopathy Using Quantitative Parameters

Preeti Singh, Bhairavi Bhatt[1], Shwetal U Pawar, Ashish Kamra, Suruchi Shetye, Mangala Ghorpade

Department of Nuclear Medicine and PET-CT, Seth GS Medical College and KEM Hospital, [1]Department of Nuclear Medicine, BYL Nair Hospital, Mumbai, Maharashtra, India

Abstract

Purpose: Ischemic cardiomyopathy (ICM) and non-ICM (NICM) causes of dilated cardiomyopathy with similar clinical presentation have different management and prognosis. This study employed myocardial perfusion imaging (MPI) to differentiate between the two using quantitative parameters in Indian population. **Methods and Materials:** Fifty patients prospectively underwent MPI and ^{18}F-fluorodeoxyglucose metabolism studies. *P* values (0.05 as significant) were calculated for the left ventricular ejection fraction (EF), end diastolic volume (EDV) at rest and stress, end systolic volume (ESV) at rest and stress, summed rest score (SRS), summed difference score (SDS), and eccentricity. On 6-month follow-up, rate of hospital admission, change in management and death was correlated for ICM and NICM. Coronary angiography (CAG) being gold standard, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and level of agreement were calculated for MPI. **Results:** MPI and CAG had a moderate level of agreement ($\kappa = 0.463$) for differentiating ICM and NICM. The sensitivity, specificity, PPV, NPV, and diagnostic accuracy were 79.31%, 66.67%, 76.67%, 70.0%, and 74% for ICM and 66.67%, 79.31%, 70%, 76.67%, and 74% for NICM, respectively. Significant differences were seen in EDV stress ($P = 0.045$), EDV rest ($P = 0.031$), ESV rest ($P = 0.034$), SRS ($P = 0.004$), Left ventricular EF rest ($P = 0.049$) and SDS in ICM and NICM, respectively. **Conclusion:** EDV at rest and stress, ESV at rest, SRS, SDS, and EF at rest obtained using MPI provides precise quantitative information to differentiate ICM and NICM. It is wide and easy availability, noninvasiveness, objectivity, and near absence of complications favors it as a preferable diagnostic tool with its given sensitivity, specificity, and accuracy for the purpose.

Keywords: *Cardiac viability, heart failure, ischemic cardiomyopathy, myocardial perfusion imaging, nonischemic cardiomyopathy*

Introduction

Dilated cardiomyopathy refers to a large group of heterogeneous myocardial disorders that are characterized by the left ventricular dilatation and impaired systolic function.[1-3]

In general usage, the phrase ischemic dilated cardiomyopathy (ICM) is sometimes applied to describe diffuse dysfunction occurring in the presence of multi-vessel coronary artery disease, and nonischemic dilated cardiomyopathy (NICM) to describe cardiomyopathy from other causes. Worldwide, dilated cardiomyopathy, with its high morbidity and mortality rate, is the primary indication for heart transplantation.[4] Multiple etiologies as described above lead to an insult to the myocyte. In case of ischemia, it is due to repeated ischemic events which lead to myocyte damage. In case of nonischemic cause, every etiology has its own mechanism for the damage, for example, toxins from virus in case of viral dilated cardiomyopathy.

ICM may produce a clinical picture virtually indistinguishable from NICM. The cardinal symptoms are fatigue and shortness of breath. As myocardial infarcts may be both symptomatically and electrocardiographically silent, the absence of historic evidence for ischemic heart disease does not exclude an ischemic etiology for heart failure in a given patient.[5] The differentiation between ischemic and NICM is important since prognosis and therapy of the two conditions differ. Furthermore, according to studies, the 5-year survival rates by Kaplan–Meier analysis have come out to be different with nonischemic patients having better survival.[6] Many a times, a nonischemic dilated cardiomyopathy is associated with

How to cite this article: Singh P, Bhatt B, Pawar SU, Kamra A, Shetye S, Ghorpade M. Role of myocardial perfusion study in differentiating ischemic versus nonischemic cardiomyopathy using quantitative parameters. Indian J Nucl Med 2018;33:32-8.

Address for correspondence:
Dr. Bhairavi Bhatt, Department of Nuclear Medicine, 218, OPD Building, BYL Nair Hospital, Mumbai Central, Mumbai, Maharashtra, India.
E-mail: bhairavibhatt@hotmail.com

Access this article online

Website: www.ijnm.in

DOI: 10.4103/ijnm.IJNM_118_17

Quick Response Code:

nonsignificant coronary artery disease. Revascularization in patients with low ejection fractions (EFs) and significant coronary artery disease (CAD) is strongly associated with improved survival[7-9] and should be considered in all patients with ICM.[10] Hence, it becomes very important to differentiate between ischemic and nonischemic causes of dilated cardiomyopathy so as to plan the management of the patient accordingly.

In addition to the existing quantitative parameters obtained using myocardial perfusion imaging (MPI), a new parameter of eccentricity (ECC) has been introduced. ECC is a measure of the elongation of the LV and varies from 0 (sphere) to 1 (line). The ECC/sphericity of the LV is a measurement tightly related to the amount of remodeling associated with the LV.

Coronary flow reserve (CFR) is the maximum increase in blood flow through the coronary arteries above the normal resting volume.[11] Noninvasive and simple methods are always preferred over invasive and complicated ones to diagnose any disease. MPI with perfusion radiotracers (gamma or positron emitters),[12] 2-dimensional (2D) echocardiography,[13,14] computed tomography, and cardiac magnetic resonance imaging[15] are some of the methods used. MPI performed using perfusion tracers and myocardial viability studies are simple, quantifiable, noninvasive, operator independent, and easily available. The purpose of the study was to test the effectiveness of MPI using gamma camera-based radiopharmaceutical to differentiate between the two types of cardiomyopathy. This included the use of widely available quantitative parameter measures provided by the standard processing softwares.

Materials and Methods

Fifty patients, who were referred to Nuclear Medicine Department between June 2015 and June 2016 for myocardial perfusion/viability studies, were included in this study having presenting symptoms as breathlessness on exertion (based on NYHA classification, Class II and III), reduced left ventricular EF (based on grading developed by Stanford University), and global hypokinesia with no regional wall motion abnormality on 2D-Echocardiography.[16,17]

Any patient with a history of myocardial infarction, history of revascularization of coronary arteries, patient unwilling to sign informed consent and pregnant were excluded from the study. Furthermore, patients with NYHA class I and IV and left ventricular EF (LVEF) <20% were excluded from the study. All patients were followed up for 6 months after the MPI study. Coronary angiography (CAG) was done in all the patients and taken as gold standard to diagnose ICM. The MPI was done on Siemens Symbia gamma Camera and myocardial viability study was done on GE Hawkeye Infinia^{vc} hybrid camera. All the parts of the studies were completed within 7 days. A 2-day protocol with rest first was followed throughout.[18]

Twenty-five patients selected as controls based on the absence of ischemia on MPI were used to calculate the mean ECC of the left ventricle. This was used as reference value to compare with the same of ICM and NICM patients.

On the day of rest myocardial perfusion studies, after confirming 4–6 h of fasting, the patient was injected with 24–26 mCi (888–962 MBq) of Tc-99m MIBI intravenously.[18] On the day of stress MPI, same amount of activity was injected mid infusion in 4 min protocol of injection adenosine (140 μg/kg/min). Following radiopharmaceutical injection 45 min poststress, Single Photon Emission Computed Tomography (SPECT) was acquired in gated mode, 8 frames/cycle in 64 × 64 matrix, cardiac mode angle from right anterior oblique to left posterior oblique in step and shoot manner with 74 views, 2.4° per step of 25 s duration with a photopeak at 140 with 15% window. After reconstruction with filter back projection, a Nuclear Medicine physician reviewed the scan using 17 segment model and step 10 scale [Figure 1].

On the basis of findings on rest MPI study patients were classified under two classes:

i. Severe perfusion defects on rest MPI in <2 contiguous segments
ii. Severe perfusion defects on rest MPI in ≥2 contiguous segments.

Category I patients underwent stress myocardial perfusion study by pharmacological agent Adenosine. Category II patients underwent ^{18}F-fluorodeoxyglucose (^{18}F-FDG) glucose metabolism for cardiac viability [Figure 2].[19]

Patients were asked to come 8–10 h fasting on the day of the ^{18}F-FDG cardiac viability scan. Fasting blood glucose was measured, and the American Society of Nuclear Cardiology protocol for ^{18}F-FDG was followed for the administration of glucose load and insulin.[19] After 1 h, 5–6 mCi (186–222 MBq) of ^{18}F-FDG was administered intravenously, and acquisition was done 1 h postinjection on GE hawk-eye Infinia^{vc} hybrid camera with HSCS collimator in 128 × 128 matrix with 10% window on 511 KeV. The emission scan was of 10 min, 360° acquisition with reconstruction of 20 iterations, OSEM, normalize max pixel to 2000 using postfilter METZ.

Image interpretation: Images were reviewed by an independent nuclear medicine physician. Emory Cardiac Tool Box and Quantitative Gated SPECT-Quantitative Perfusion SPECT (QGS-QPS) were used for analysis for various parameters [Table 1]. On rest imaging, patient with ≥2 contiguous segment severe perfusion defect with low LVEF (<20%) was considered to be under the group of ICM.[20] ECC reference value was generated using MPI of 25 controls and was compared with the same of ICM and NICM which was found to be 0.85.

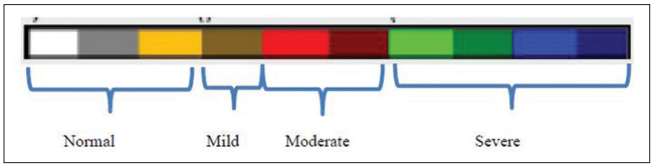

Figure 1: Step 10 scale showing mid, moderate and severe grading classification of myocardial perfusion

Specific interpretation criteria were used for defining ICM and NICM [Table 2, Figures 3 and 4]. The various quantitative parameters were calculated on MPI study using standard processing software for comparison in ICM and NICM [Tables 1 and 3].

All patients underwent CAG (Gold standard) and the final diagnosis was compared. On CAG any single or more vessel with >70% stenosis was considered to have significant CAD and was diagnosed to have ICM.

Follow-up of the patients was done for months. Each patient was either called or asked to visit the department and was asked the following details

1. Number of hospital admission due to cardiac cause
2. Any cardiac intervention done/change in management
3. Sudden cardiac death.

Statistical analysis

Descriptive statistical analysis has been carried out in the present study. Results on continuous measurements are presented and Mean and SD/STD DEV (Standard Deviation). Results on categorical measurements are presented in Number and percentage. Significance is assessed at 5% level of significance. Unpaired *t*-test, Mann–Whitney test, and Pearson Chi-square test have been used where found appropriate to determine the level of significance. The final diagnosis and all data for demographics were considered on the basis of CAG.

Results

Thirty-one out of 50 patients underwent rest-stress MPI and remaining 19 patients underwent viability using ^{18}F-FDG. Two patients underwent both MPI and viability studies. The final diagnosis was made using CAG. 29 and 21 patients belonged to ICM and NICM, respectively, considering the criterion mentioned in Table 2. The mean age of patient's in total was 52.64 ± 11.8 years; ICM had 52.59 ± 10.38 years and NICM of 52.71 ± 12.9 years as mean age. The ICM group comprised of 24 males and 5 females, whereas NICM group comprised of 13 males and 8 females. No statistically significant difference was found in between ICM and NICM group for mean age of presentation and gender [Table 3].

The level of agreement between MPI and CAG was moderate with kappa value of 0.43 to differentiate between ICM and NICM. The sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy were 79.31%, 66.67%, 76.67%, 70.0%, and 74% for diagnosis of ICM and 66.67%, 79.31%, 70%, 76.67%, and 74% for diagnosis of NICM, respectively. The difference in end diastolic volume (EDV) at rest, EDV at rest, end systolic volume (ESV) at rest, summed rest score (SRS) and LVEF at rest was found to be significant in the NICM and ICM groups using unpaired *t*-test and Mann–Whitney test appropriately except EDV at rest [Table 3]. The mean LVEF at rest in the ICM group

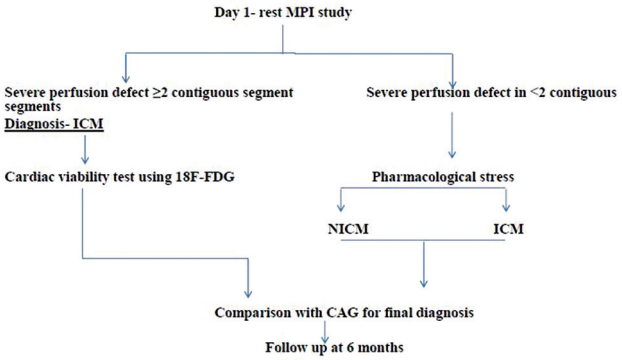

Figure 2: Flowchart demonstrating patient selection and course of action

Table 1: Parameters and softwares used

Parameter	Software
Eccentricity (rest and stress), EDS at rest and stress, ESV, at rest and stress, EF at rest and stress	QGS-QPS
SRS, summed stress score (SSS) and SDS, % of severe perfusion defect, % of viable and nonviable myocardium	ECTB

EDS: End diastolic volume, ESV: End systolic volume, EF: Ejection fraction, SRS: Summed rest score, SDS: Summed difference score; QGS-QPS: Quantitative gated SPECT-quantitative perfusion SPECT, ECTB: Emory Cardiac Tool Box, SPECT: Single photon emission computed tomography

Table 2: Interpretation criteria for ischemic cardiomyopathy, nonischemic cardiomyopathy, viable and nonviable myocardium in ischemic cardiomyopathy

Criteria	Diagnosis
Any evidence of inducible ischemia on stress seen in MPI	ICM
Presence of severe myocardial perfusion defects or transmural infarcts in 2 or more than 2 contiguous segments	ICM
Absence of inducible ischemia with <2 severe myocardial perfusion defects	NICM
In ICM, presence of ^{18}F-FDG in severely hypoperfused segments/ transmural infarct segments	Viable myocardium in ICM
In ICM, absence of ^{18}F-FDG in severely hypoperfused segments/transmural infarct segment	Nonviable myocardium in ICM

ICM: Ischemic Cardiomyopathy, NICM: Nonischemic cardiomyopathy, MPI: Myocardial Perfusion Imaging, ^{18}F-FDG: 18-Flourine-Fluro-de-oxy Glucose

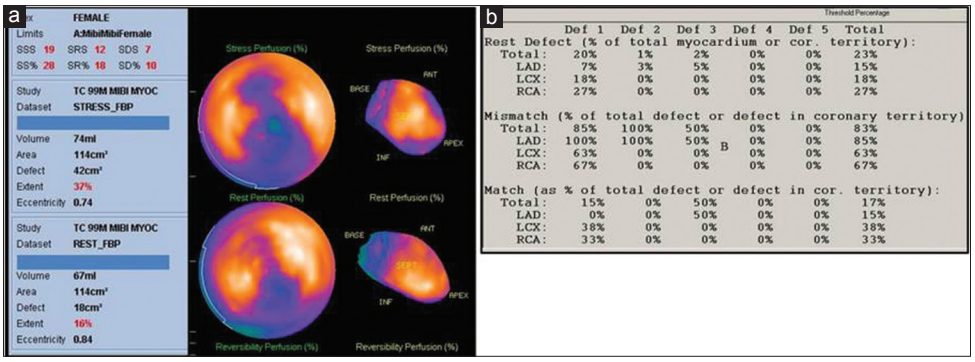

Figure 3: Sixty years female with dilated cardiomyopathy showed rest perfusion defect in >2 contiguous segment with reversible ischemia corresponding to left anterior descending territory (a: Summed difference score = 7) on myocardial perfusion imaging and presence of viability in all three territories . The total 83% of infracted myocardium was viable on Emory Cardiac Toolbox quantification. At 6 months, she had 1 hospitalization and was alive

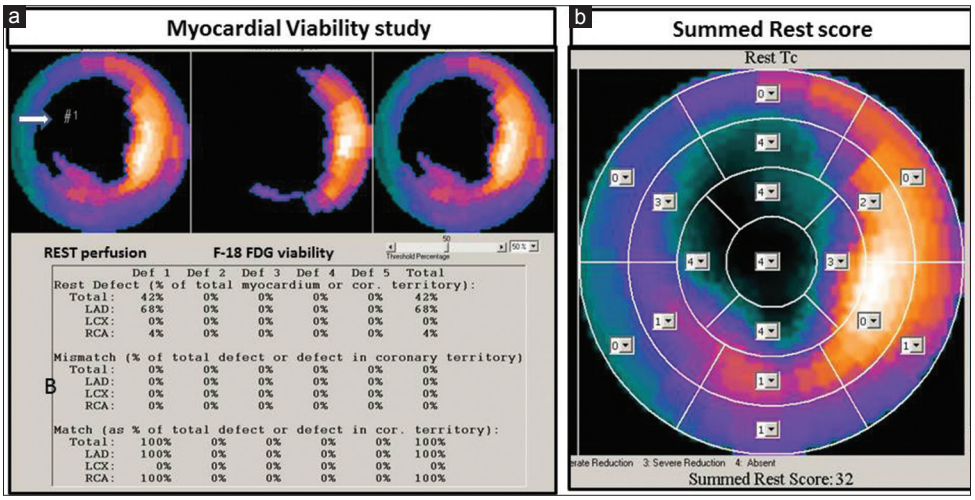

Figure 4: A 55-year-old male had Summed rest score of 32 (b) with >2 segment severe perfusion defect on rest study and was assumed to be due to ischemic cause and was confirmed on angiography. He underwent rest myocardial perfusion imaging and viability study a) which demonstrated severe perfusion defect (white arrow) with 100% nonviable myocardium in the perfusion deficit area. There was no change in his management and had 1 hospital admission due to cardiac cause during 6 months

Table 3: Quantitative parameters of ischemic cardiomyopathy and nonischemic cardiomyopathy group

Parameter	ICM	NICM	*P*	Significance
Age	52.59±10.38	52.71±12.91	0.96#	No
Male	24	13	0.097#	No
Female	5	8		
ESV rest	136.21±70.62	97.76±45.74	0.034#	Yes
EDV rest	186.34±72.25	145.52±50.08	0.031#	Yes
EDV stress	171.50±57.47	131.88±47.56	0.045#	Yes
ESV stress	122.36±52.31	88±41.71	0.051#	No
EF	28.45±9.93	35.86±13.72	0.049*	Yes
SRS	15±11.54	6.15±7.21	0.004*	Yes
SDS (>3)	8	3	0.039	Yes
ECCE at rest	0.779±0.05	0.773±0.04	0.637#	No
ECCE at stress	0.771±0.04	0.778±0.05	0.639#	No

#Unpaied *t*-test, *Mann–Whitney. ECCE: Eccentricity, ESV: End systolic volume, SRS: Summed rest score, SDS: Summed difference score, EDV: End diastolic volume, EF: Ejection fraction, ICM: Ischemic Cardiomyopathy, NICM: Nonischemic cardiomyopathy

was found to be lower than the NICM group, 25.45% and 35.86%, respectively. Eccentricity (Ecce) had no significant difference in rest or stress in ICM and NICM. Mean ECC was found to 0.77 in 50 patients (Normal 0.85). ECC had no significant variation with LVEF.

After 6-month follow-up [Table 4], the number of hospital admission in two groups differed significantly with higher chances of hospitalization due to cardiac cause in ICM group with a $P = 0.03$. The hospitalization rate for cardiac-related cause was significantly related to the LVEF ($P = 0.021$). Patients with LVEF <25% were found to have more chances of hospitalization. In ICM group, LVEF <25% predicted the possibility of increased number of hospital admissions for cardiac cause with $P = 0.024$; however, the same did not prove true for the NICM group. Summed difference score (SDS) could not predict the increased number of hospital admission due to cardiac cause in either group [Figure 3 and 5]. It was not significantly related to the death/alive status in either group. In addition, SDS did not differ significantly in the

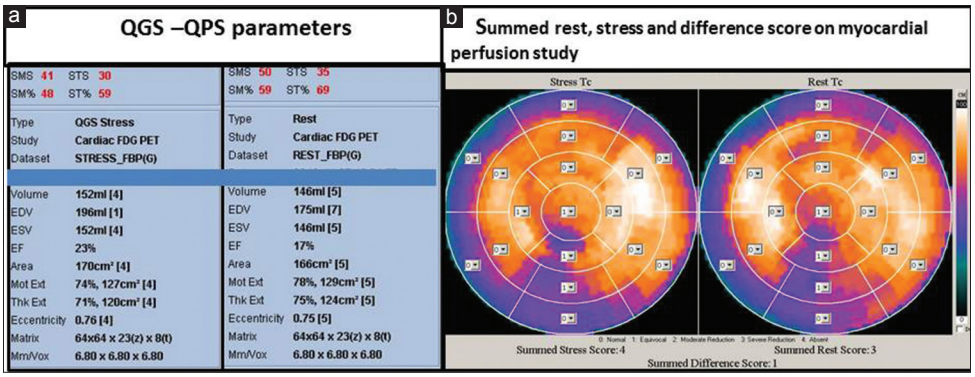

Figure 5: A 50-year-old male on pharmacological stress myocardial perfusion study with adenosine. He had fixed perfusion deficit involving inferior wall, low eccentricity (a) with no evidence of inducible ischemia with summed difference score of 1 (b). The patient was diagnosed with no coronary artery disease on coronary angiography correlating with our diagnosis. He had 3 admissions in 6 months due to cardiac cause and is alive

Table 4: Follow-up parameters

Parameter	*P*	Significance
Number of hospital admission related to cardiac cause	0.030*	Yes, ICM had more hospitalization rate
EF <25% and >25% relation with hospitalization rate	0.021$	Yes, <25% EF predicted more hospitalization rate
EF <25% relation with hospitalization rate in ICM	0.024$	Yes
EF <25% relation with hospitalization rate in ICM	0.950$	No
SDS >3 and rate of hospitalization in ICM	0.766$	No
SDS >3 and rate of hospitalization in ICM	0.432$	No
SDS >3 and death/alive status	0.769$	No

*Mann–Whitney, $Pearson Chi-Square test.
SDS: Summed difference score, EF: Ejection fraction, ICM: Ischemic Cardiomyopathy

two groups, however, the test was not appropriate as the values of SDS was <5 in many subsets.

Discussion

There has always been an interest in differentiating the patients with ischemic and NICM using noninvasive techniques. The ideal study for this would be one with objective criteria to differentiate ICM and NICM. In this study, an attempt was made to objectify and quantitate the differences and prognosticate the ICM and NICM patients. In our study, EDV at rest and stress, ESV at stress, EF at rest, SDS and SRS had statistically significant different values and hence could differentiate ICM from NICM. On the other hand, ESV rest, ECC at rest and stress failed to establish the difference between ICM and NICM statistically. The MPI led to change in management in 40% patients. In follow-up parameters, it was observed that ICM had statistically significantly increased number of hospital admissions due to cardiac cause. EF <25% correlated positively with the increased number of hospital admission due to cardiac cause whereas SDS did not influence hospitalization rates due to cardiac cause. ECC value was found to have no prognostic value in our study.

In this study, Tc-99 m MIBI radioisotope was used. Bulkley *et al*. used Tl-201 for differentiating ICM and NICM. Tc-99 m MIBI has better imaging properties and resolution than Tl-201. The study population was small (n = 35) and no significance was calculated for demographic parameters. No quantitative parameters were defined to differentiate ICM from NICM other than the percentage of perfusion defect. The viability of myocardium and prognostication of patients were the areas which were not attempted. However, they found one patient to have large perfusion defect with regional wall motion abnormality diagnosed as NICM on CAG.[21] Similarly, in our study, 4 patients were assumed to belong to ICM group due to severe perfusion defects in ≥2 contiguous segments, eventually had NICM on CAG. The reason for this could be embolic event in undiagnosed myocardial infarction or CAD with subcritical stenosis as a cause. Furthermore, there can always be an overlap between ICM and NICM, and this group might be reflective this overlap zone.[21] This gray zone needs further studies to be distinguished.

We did not find a significant difference between the presenting age group in the NICM and ICM. The mean age was found to be 52.64 years and 52.59 years in ICM and NICM respectively. Bart *et al*. found ICM with older age 45 group in their study of 3,787 patients.[6] A small study group in our study could be one of the reasons for this different finding as compared to the literature. Yao *et al*.[22] studied 144 patients retrospectively and 89 patients prospectively and found significant age difference in the presenting age group with ICM group being the older one. In contrast to our study, Yao *et al*. did not find any significant difference in the EDV and ESV in their study population.

Harjai *et al*. in their study of 112 patients, determined ECC index using 2D echocardiography and concluded that the ECC did not have any impact on prognosis in mean

follow-up of 17 months in their study. Hence, the degree of sphericity did not impact prognosis.[23] These similar findings were confirmed in this study using QGS-QPS for estimation of ECC. Considering the diagnostic ability to differentiate ICM and NICM, multiple other modalities have been used apart from MPI. Budoff *et al*. used electron beam computed tomography for this purpose and had 92% overall diagnostic accuracy and used ICM diagnosis with a cutoff of >50% stenosis in a vessel.[24] In our study as well the studies by Bulkley *et al*.[21] and Bart *et al*.,[6] a cutoff of 70% was used to define critical stenosis and diagnosing ICM.

Apart from all the morphological details provided by cardiac MRI, it can detect ischemia and viability in a single study. However, coronary MRI angiography has only moderate level of sensitivity (72%–77%) and specificity (71%–87%) as compared to CAG. Calcium scoring is not adequate for the differentiation between ICM and NICM; however, coronary CT angiography is a good alternative in patients with low clinical probability positive for ischemia to screen for coronaries. Nephrotoxicity is a common complication in both the studies. MPI with SPECT gives moderate sensitivity and specificity to differentiate ICM and NICM.[20]

CFR provides a view of the overall vascular health including epicardial and microvascular vessels. PET can measure absolute myocardial blood flow at rest and stress along with CFR. Quantitative MBF may offer a potential solution for one of the challenges of relative PET MPI-balanced ischemia. The most promising modality for this purpose is PET MPI which extends to the whole spectrum of cardiomyopathy including disease at the microvascular level. Absolute quantification of MBF and CFR is the best approach to plan the management of these patients.[12]

Thus, our study differentiated ICM and NICM using several quantitative parameters, used ECC in MPI study, prognosticated the patients on MPI findings, and provided information about myocardium viability in patients of ICM which influenced their management. The viability assessment has helped the management of patients more effectively in addition to the diagnosis of ICM.

In our study, the sample size was small and the follow-up period of 6 months was short.In addition, the criterion for selection of ICM patients was based on strict selection criterion of perfusion defects involving 2 or more than 2 contiguous segments might have led to bias. No further attempt was made to determine the etiology of NICM in this study.

Conclusion

Myocardial perfusion study as a noninvasive cardiac diagnostic tool to differentiate ICM and NICM has fairly good sensitivity, specificity, and accuracy with a moderate level of agreement (0.463) with CAG. EDV at rest and stress, ESV rest, EF at rest, SRS and SDS values can differentiate ICM from NICM. Further, EF can prognosticate the patient groups in terms of increased rate of hospitalization due to cardiac cause. MPI is a well-established, noninvasive method with acceptable method for this purpose.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Rakar S, Sinagra G, Di Lenarda A, Poletti A, Bussani R, Silvestri F, *et al.* Epidemiology of dilated cardiomyopathy. A prospective post-mortem study of 5252 necropsies. The heart muscle disease study group. Eur Heart J 1997;18:117-23.
2. Report of the WHO/ISFC task force on the definition and classification of cardiomyopathies. Br Heart J 1980;44:672-3.
3. Roberts WC. Defining idiopathic dilated cardiomyopathy: A courtroom discussion. Am J Cardiol 1989;63:893-6.
4. Sugrue DD, Rodeheffer RJ, Codd MB, Ballard DJ, Fuster V, Gersh BJ, *et al.* The clinical course of idiopathic dilated cardiomyopathy. A population-based study. Ann Intern Med 1992;117:117-23.
5. Burch GE, Giles TD. Ischemic cardiomyopathy: Diagnostic, pathophysiologic, and therapeutic considerations. Cardiovasc Clin 1972;4:203-20.
6. Bart BA, Shaw LK, McCants CB Jr., Fortin DF, Lee KL, Califf RM, *et al.* Clinical determinants of mortality in patients with angiographically diagnosed ischemic or nonischemic cardiomyopathy. J Am Coll Cardiol 1997;30:1002-8.
7. Alderman EL, Fisher LD, Litwin P, Kaiser GC, Myers WO, Maynard C, *et al.* Results of coronary artery surgery in patients with poor left ventricular function (CASS). Circulation 1983;68:785-95.
8. Gersh BJ, Kronmal RA, Schaff HV, Frye RL, Ryan TJ, Mock MB, *et al.* Comparison of coronary artery bypass surgery and medical therapy in patients 65 years of age or older. A nonrandomized study from the coronary artery surgery study (CASS) registry. N Engl J Med 1985;313:217-24.
9. O'Connor CM, Puma JA, Gardner LH, Califf RM, Jones RH. A 25-year experience in patients with coronary artery disease and chronic heart failure: Outcomes with medical therapy and bypass surgery. J Am Coll Cardiol 1995;27 Suppl A: 142A.
10. Packer M, O'Connor CM, Ghali JK, Pressler ML, Carson PE, Belkin RN, *et al.* Effect of amlodipine on morbidity and mortality in severe chronic heart failure. Prospective randomized amlodipine survival evaluation study group. N Engl J Med 1996;335:1107-14.
11. Collins P. Coronary flow reserve. Br Heart J 1993;69:279-81.
12. Majmudar MD, Murthy VL, Shah RV, Kolli S, Mousavi N, Foster CR, *et al.* Quantification of coronary flow reserve in patients with ischaemic and non-ischaemic cardiomyopathy and its association with clinical outcomes. Eur Heart J Cardiovasc Imaging 2015;16:900-9.
13. Diaz RA, Nihoyannopoulos P, Athanassopoulos G, Oakley CM. Usefulness of echocardiography to differentiate dilated cardiomyopathy from coronary-induced congestive heart failure.

Am J Cardiol 1991;68:1224-7.
14. Sharp SM, Sawada SG, Segar DS, Ryan T, Kovacs R, Fineberg NS, *et al.* Dobutamine stress echocardiography: Detection of coronary artery disease in patients with dilated cardiomyopathy. J Am Coll Cardiol 1994;24:934-9.
15. Assunção FB, de Oliveira DC, Souza VF, Nacif MS. Cardiac magnetic resonance imaging and computed tomography in ischemic cardiomyopathy: An update. Radiol Bras 2016;49:26-34.
16. David WA, Timothy CM, John FD, Jeremy D. Oxford Textbook of Medicine: Cardiovascular Disorders. 1st ed. Oxford, UK: Oxford University Press; 1983.
17. Stanford University: Echocardiography in ICU; Left Ventricular Systolic Function. Available from: https://www.web.stanford.edu/group/ccm_echocardio/cgibin/mediawiki/index.php/Left_ventricle_systolic_function. [Last accessed on 2017 Dec 06].
18. Henzlova MJ, Duvall WL, Einstein AJ, Travin MI, Verberne HJ. ASNC imaging guidelines for SPECT nuclear cardiology procedures: Stress, protocols, and tracers. J Nucl Cardiol 2016;23:606-39.
19. Dilsizian V, Bacharach SL, Beanlands RS, Bergmann SR, Delbeke D, Gropler RJ, *et al*. PET myocardial perfusion and metabolism clinical. J Nucl Cardiol 2009;16:651.
20. Beton O, Kurmus O, Asarcikli LD, Alibazoglu B, Alibazoglu H, Yilmaz MB, *et al.* The practical value of technetium-99m-MIBI SPET to differentiate between ischemic and non-ischemic heart failure presenting with exertional dyspnea. Hell J Nucl Med 2016;19:147-54.
21. Bulkley BH, Hutchins GM, Bailey I, Strauss HW, Pitt B. Thallium 201 imaging and gated cardiac blood pool scans in patients with ischemic and idiopathic congestive cardiomyopathy. A clinical and pathologic study. Circulation 1977;55:753-60.
22. Yao SS, Qureshi E, Nichols K, Diamond GA, Depuey EG, Rozanski A, *et al.* Prospective validation of a quantitative method for differentiating ischemic versus nonischemic cardiomyopathy by technetium-99m sestamibi myocardial perfusion single-photon emission computed tomography. Clin Cardiol 2004;27:615-20.
23. Harjai KJ, Edupuganti R, Nunez E, Turgut T, Scott L, Pandian NG, *et al.* Does left ventricular shape influence clinical outcome in heart failure? Clin Cardiol 2000;23:813-9.
24. Budoff MJ, Shavelle DM, Lamont DH, Kim HT, Akinwale P, Kennedy JM, *et al.* Usefulness of electron beam computed tomography scanning for distinguishing ischemic from nonischemic cardiomyopathy. J Am Coll Cardiol 1998;32:1173-8.