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Diagnostic Accuracy of Cardiac Magnetic Resonance Imaging in the Evaluation of Newly Diagnosed Heart Failure with Reduced Left Ventricular Ejection Fraction

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Abstract

The aim of this study is to determine the diagnostic value of cardiac magnetic resonance imaging (CMR) with late gadolinium enhancement (LGE), cine imaging, and resting first-pass perfusion (FPP) in the evaluation for ischemic (IC) versus non-ischemic (NIC) cardiomyopathy in new onset heart failure with reduced (40%) left ventricular ejection fraction (HFrEF). A retrospective chart review analysis identified 83 patients between January 2009 and June 2012 referred for cardiac magnetic resonance imaging (CMR) evaluation for new onset HFrEF with coronary angiography performed within 6 months of CMR. The diagnosis of IC was established using Felker's criteria on coronary angiography. CMR sequences were evaluated for the presence of patterns suggestive of severe underlying coronary artery disease as the cause of HFrEF (subendocardial and/or transmural LGE, regional wall motion abnormality on cine, regional hypoperfusion defect on resting FPP). Discriminative power was assessed using receiver operator characteristics curve analysis. Coronary angiography identified 36 patients (43%) with IC. Presence of subendocardial and/or transmural LGE alone demonstrated good discriminative power (c-statistic 0.85, 95%

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confidence interval 0.76–0.94) for the diagnosis of IC. The presence of an ischemic pattern on both LGE and cine sequences resulted in a specificity of 87% for the diagnosis of IC, while the absence of an ischemic pattern on both LGE and cine sequences resulted in a specificity of 94% for the diagnosis of NIC. Addition of resting FPP on a subset of patients did not improve diagnostic values. In conclusion, CMR has potential value in the diagnostic evaluation of IC versus NIC.

Keywords

Cardiac magnetic resonance imaging; late gadolinium enhancement; heart failure reduced ejection fraction

> Heart failure affects 5.1 million people in the United States, and the prevalence is expected to rise as the population ages and the prognosis after acute coronary events improves [1]. Over 650,000 new diagnoses of heart failure are made yearly, more than half of which are associated with a reduced ejection fraction [2]. Heart failure with reduced ejection fraction (HFrEF) may be secondary to severe coronary artery disease (CAD) in up to two thirds of cases, leading to the categorization of ischemic (IC) versus non-ischemic (NIC) cardiomyopathy. Early diagnosis and identification of etiology is crucial because the prognosis of patients with IC may improve following revascularization. Current guidelines recommend invasive coronary angiography in all patients presenting with new onset heart failure [3]. However, as invasive angiography presents a small risk of serious morbidity, alternative non-invasive strategies to diagnose IC versus NIC should be explored [4]. Cardiac MRI (CMR) has superior safety profile and the ability to identify myocardial fibrosis or scar. In this study, we aimed to evaluate the utility of CMR in the diagnosis of IC versus NIC in patients presenting with newly diagnosed HFrEF.

Methods

This was a retrospective study of patients undergoing CMR within 2 months of a new diagnosis of heart failure with left ventricular ejection fraction ≤40% and a coronary angiogram within 6 months of the CMR scan. Consecutive patients were included from January 2009 to June 2012 at 2 tertiary care sites, New York University (NYU) Langone Medical Center and Bellevue Hospital Center (BHC). The former is a private academic tertiary referral center, while the latter serves as the cardiac referral center for the underserved population within the New York City Health and Hospital Corporation system. Both hospitals are affiliated with the NYU School of Medicine. CMR images and coronary angiograms were interpreted by the same group of cardiac radiologists and interventional cardiologists at both sites. Patients were excluded if they met one of the following criteria: (1) known history of severe CAD, prior myocardial infarction, or prior coronary revascularization; (2) known history of structural heart disease such as hypertrophic cardiomyopathy or congenital heart disease; (3) evidence of severe left-sided valvular disease; or (4) diagnosis of ST-segment elevation myocardial infarction on admission. The study was approved by the NYU School of Medicine and BHC Institutional Review Boards.

Baseline demographic, clinical, and CMR variables were recorded from review of the electronic medical record (EMR). Obesity was defined as a body mass index 30 kg/m^2 . History of hypertension was defined per prior documentation in the EMR. Dyslipidemia was defined as a low-density lipoprotein-cholesterol >130 mg/dL or prior documentation in the EMR. Diabetes mellitus was defined HbA1c 6.5% or prior documentation in the EMR.

Coronary angiograms were evaluated by 2 independent board-certified practicing interventional cardiologists blinded to all clinical, echocardiographic, and CMR data. Significant CAD was defined as a 20% diameter stenosis in a coronary artery 2 mm in caliber by visual assessment of coronary angiogram or pressure gradient <0.80 if fractional flow reserve measurement was performed. The gold standard etiology of IC was determined using the definition established by Felker et al: presence of 70% diameter stenosis in the left main coronary artery, proximal left anterior descending (LAD) artery, or ≥2 epicardial coronary arteries [5]. For those angiograms not categorized to the same IC or NIC classification by the 2 readers ($n=5$), a 3rd independent blinded interventional cardiologist served as the final reader.

Patients were imaged using a 1.5 or 3.0 Tesla MRI system (Avanto, TimTrio, or Verio; Siemens, Erlangen, Germany). CMR was performed using a standard clinical protocol for evaluation of patients with cardiomyopathy, including use of late gadolinium enhancement (LGE) sequences, cine images, and, when applicable, resting first-pass perfusion (FPP). Imaging was performed in standard 2-chamber, 3-chamber, and 4-chamber long axis views and a short-axis series (base to apex) that was acquired every 10 mm to cover the entire left ventricle.

Per standard clinical protocol, CMR images were analyzed using the American Heart Association 17-segment model, and each segment was evaluated qualitatively on LGE and cine sequences [6]. LGE sequences were used to identify myocardial scar in a pattern suggestive of significant coronary artery disease (ischemic pattern with subendocardial and/or transmural LGE) versus other etiology (non-ischemic pattern with midwall and/or subepicardial LGE or absence of LGE). Since prior reports differ regarding the optimal number of segments used to diagnose IC, separate analyses of LGE were performed using both 1 and 3 segment thresholds. Cine sequences were used to identify regional versus global abnormal myocardial wall motion, with each segment reported as normal, mild/ moderate/severe hypokinesia, akinesia, or dyskinesia. In the subset of patients who underwent FPP, resting FPP sequences were used to identify presence versus absence of regional myocardial perfusion defects. All imaging data were obtained from retrospective review of clinical CMR reports, which were generated by the same group of CMR readers at both sites.

CMR sequences were evaluated independently and in combination to diagnose IC versus NIC. A diagnostic algorithm incorporating all 3 sequences, in accordance with current clinical practice, was also used (Figure 1). In this clinically-based CMR algorithm, a third category, termed "mixed" cardiomyopathy, was created for patients with 1 or 2 ischemic LGE segments without perfusion defect on resting FPP and without regional wall motion abnormality on cine [7].

All continuous variables were evaluated for normality using the Shapiro-Wilkes test and determined to be normally distributed. Continuous variables, presented as mean ± standard deviation, were compared between IC and NIC groups using independent sample t-test. Categorical variables, presented as proportions, were compared between IC and NIC groups using Fisher's exact or Chi Square test. To evaluate CMR's diagnostic utility in differentiating IC versus NIC, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), diagnostic accuracy, and discriminative power were calculated for different CMR sequences using Felker's criteria on coronary angiography as the gold standard for diagnosis. Diagnostic accuracy was calculated as a percentage of diagnoses that were equivalent between CMR and coronary angiography. Discriminative power was assessed using receiver operator characteristics curve analysis.

Results

Eighty three consecutive patients met inclusion/exclusion criteria. Approximately 61% $(n=51)$ were from the BHC site, and the proportion of patients with IC was similar between both sites (45% at NYU Langone Medical Center and 41% at BHC, p=0.86). The majority of patients had a coronary angiogram performed before CMR in the IC and NIC groups (69% and 55%, p=0.28). Baseline characteristics are shown in Table 1.

All 83 patients had results available for LGE and cine sequences, while 68 (82%) had a resting FPP sequence performed as part of their CMR protocol. Left ventricular characteristics by CMR are shown in Table 2. Among the 4 patients in the IC group who did not demonstrate an ischemic pattern on LGE, 3 had nonproximal coronary artery stenoses and 1 had a severe stenosis in the proximal LAD artery.

The sensitivity, specificity, PPV, NPV, and diagnostic accuracy of the individual CMR sequences and in combination are shown in Tables 3 and 4. LGE-CMR had the highest diagnostic accuracy for the diagnosis of IC, with good discriminative power (c-statistic 0.85, 95% confidence interval 0.76–0.94).

Four patients (4.8%) were categorized as "mixed" cardiomyopathy by the clinically-based CMR algorithm (Figure 1). Two of these patients were categorized as IC by Felker's criteria. The diagnostic value of the individual and combination CMR sequences did not differ when these 4 "mixed" cardiomyopathy patients were excluded from the analyses.

Discussion

This is a real world, all-comers study of a racially and ethnically diverse group of patients with newly diagnosed HFrEF, which demonstrated a combination of CMR sequences to have excellent discriminative power for the diagnosis of IC versus NIC. LGE alone was a powerful tool such that the presence of subendocardial and/or transmural LGE on at least 3 myocardial segments provided 77% specificity in the diagnosis of IC, while the absence of subendocardial and/or transmural LGE provided 89% specificity in the diagnosis of NIC. Diagnostic concordance on cine images provided incremental discriminative value such that the addition of an ischemic pattern on cine images increased specificity for the diagnosis of IC to 87%, while the addition of a non-ischemic pattern on cine images increased specificity

for the diagnosis of NIC to 94%. Addition of resting FPP, however, did not further improve diagnostic values. Finally, although only present in one-fifth the study cohort, the presence of only midwall and/or subepicardial LGE provided 97% specificity for the diagnosis of NIC. Thus, CMR is an attractive tool in the evaluation of patients with a new diagnosis of HFrEF.

In the current study, 43% of patients with a new diagnosis of HFrEF had IC, a proportion that is consistent with data from European sites [8]. The lack of underlying severe CAD in more than half of new HFrEF cases highlights the need to investigate non-invasive alternatives to coronary angiography in this setting. The majority of prior studies evaluating the diagnostic utility of CMR in HFrEF had several notable differences from the current study, including: (1) data primarily from European sites, (2) inclusion of patients with longstanding HFrEF, (3) exclusion of patients with any signs or symptoms of CAD, and (4) evaluation of LGE alone [7, 9–11]. Given that the United States has among the highest rates of obesity and diabetes mellitus in the developed nations, the prevalence of these comorbidities is higher than reports from outside the United States [7, 9–13]. Indeed, diabetes mellitus is associated with cardiomyopathy independent of CAD, possibly through interstitial fibrosis and/or protein glycosylation, though the precise contribution of diabetes mellitus in the absence of CAD to CMR findings remains unclear. Also, given our study did not exclude patients presenting with chest pain or elevated cardiac biomarkers, the current findings are more generalizable than prior reports.

The reported 89% sensitivity of an ischemic pattern on LGE to diagnose IC in the current study is similar to that seen in prior studies (81% to 86%) [9, 11]. However, these prior studies also report a much higher specificity for ischemic patterns on LGE in the diagnosis of IC than the current report. This discrepancy may arise from not only the more selective populations evaluated in prior studies, but also the definition of IC used. The majority of prior reports determined IC by the presence of any angiographically severe CAD, instead of the currently accepted Felker's criteria [5]. This distinction is important for 2 reasons: (1) survival outcomes in patients with single-vessel disease and HFrEF without proximal LAD involvement are similar to those in patients with no significant CAD and HFrEF, and (2) a significant portion of patients with single-vessel disease without proximal LAD involvement do not have subendocardial/transmural LGE [10]. A more recent study from the United Kingdom demonstrated greater diagnostic accuracy of LGE patterns when compared to a "gold standard" consensus panel, which assembled a diagnosis based on the same CMR findings, along with clinical history and findings on invasive coronary angiography [7]. However, there are currently no standardized diagnostic criteria that integrate clinical and imaging data for the diagnosis of IC versus NIC.

Prior reports suggested different optimal numbers of myocardial segment involvement for the diagnosis of IC [7, 11]. However, regardless of whether 1 or 3 segments were used as the LGE threshold, the diagnostic accuracy of CMR for ICM in our study was similar. Our evaluation also included cine sequences. As both sequences are typically performed as part of routine clinical protocol, it is appropriate to evaluate LGE and cine in combination rather than just LGE alone. A third sequence, FPP, is sometimes performed in CMR protocols to evaluate IC, although perfusion defects have also been reported in NIC [14, 15]. Our study

was consistent with prior reports such that resting FPP did not improve diagnostic accuracy of the other 2 CMR sequences. Finally, as a non-invasive modality that can also identify areas of myocardial viability and scar, as well as structural abnormalities, without the use of iodinated contrast media, CMR adds valuable information in the diagnosis of the underlying etiology of HFrEF.

This study has the limitations inherent to a retrospective analysis. We addressed potential reader bias utilizing an expert panel blinded to all clinical and other imaging data to review the coronary angiograms. Second, while this is a small single center study, we enrolled a racially diverse population from a private and public city hospital. Third, the study only included patients who received both an invasive coronary angiogram and a CMR, potentially introducing selection bias. Finally, the criteria established by Felker et al in the diagnosis of IC does not account for whether or not the wall motion abnormalities present are concordant with the coronary anatomy distribution jeopardized, and it does not account for physiologic relevance of an anatomic stenosis. Felker's criteria also do not account for mixed CM. However, Felker's criteria are often considered the gold standard criteria for the diagnosis of IC, and sensitivity/specificity of CMR sequences did not differ significantly when mixed CM diagnosed using a clinically-based CMR algorithm were removed. Despite these limitations, this is a real-world study demonstrating the potential utility of 3 CMR sequences in the evaluation of newly diagnosed HFrEF.

This study further demonstrates the utility of CMR in the diagnosis of IC versus NIC. A CMR pattern suggestive of NIC may obviate the need for invasive coronary angiography, or at least allow for consideration of non-invasive coronary angiography. Taken together with prior studies, a consideration should be made to revisit the current guideline driven recommendation for routine invasive coronary angiography in all patients with newly diagnosed HFrEF.

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Figure 1.

Diagnostic algorithm used to determine ischemic versus non-ischemic cardiomyopathy on cardiac magnetic resonance imaging

 $FFP = first pass perfusion, LGE = late gadolinium enhancement$

Table 1

Baseline demographic and clinical characteristics by study group

*** Diagnosed using Felker's criteria on coronary angiography

† Ischemic versus non-ischemic cardiomyopathy cohort comparison

 $\dot{\phi}$ Obesity defined as body mass index 30 kg/m^2

§ Dyslipidemia defined as low-density lipoprotein-cholesterol >130 mg/dL or prior documentation in the electronic medical record

Continuous variables are presented as mean ± standard deviation and compared using independent sample t-test. Categorical variables are presented as n (proportion) and compared using the Fisher's exact test.

Table 2

Left ventricular characteristics on cardiac magnetic resonance (CMR) imaging by study group

*** Diagnosed using Felker's criteria on coronary angiography

† Ischemic versus non-ischemic cardiomyopathy cohort comparison

‡ Non-ischemic pattern is defined as midwall and/or subepicardial late gadolinium enhancement, and ischemic pattern is defined as subendocardial and/or transmural late gadolinium enhancement

§ Patients categorized as mixed cardiomyopathy by the clinical algorithm (see Figure 1) are categorized as ischemic cardiomyopathy by CMR

Continuous variables are presented as mean ± standard deviation and compared using independent sample t-test. Categorical variables are presented as n (proportion) and compared using the Fisher's exact test.

Diagnostic value of an ischemic pattern on different cardiac magnetic resonance imaging sequences in the diagnosis of ischemic cardiomyopathy Diagnostic value of an ischemic pattern on different cardiac magnetic resonance imaging sequences in the diagnosis of ischemic cardiomyopathy

 $\dot{\mathcal{L}}$
presence of subendocardial and/or transmural LGE in $\,$ 3 segments *†*Presence of subendocardial and/or transmural LGE in ≥3 segments

 $^{\not\prime}$ presence of regional wall motion abnormality in $\,$ 1 segment on cine imaging *‡*Presence of regional wall motion abnormality in ≥1 segment on cine imaging

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Absence of subendocardial and/or transmural LGE, but presence of midwall and/or subepicardial LGE in 1 segments of the American Heart Association 17-segment model *†*Absence of subendocardial and/or transmural LGE, but presence of midwall and/or subepicardial LGE in ≥1 segments of the American Heart Association 17-segment model

 $^{\neq}$
Absence of regional wall motion abnormalities on cine imaging *‡*Absence of regional wall motion abnormalities on cine imaging