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ORIGINAL ARTICLE

# Validating an Idiopathic Dilated Cardiomyopathy Diagnosis Using Cardiovascular Magnetic Resonance: The Dilated Cardiomyopathy Precision Medicine Study

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**BACKGROUND:** Coronary angiography to identify coronary artery disease has been foundational to distinguish the cause of dilated cardiomyopathy (DCM), including the assignment of idiopathic or ischemic cardiomyopathy. Late gadolinium enhancement (LGE) with cardiovascular magnetic resonance (CMR) has emerged as an approach to identify myocardial scar and identify etiology.

**METHODS:** The DCM Precision Medicine Study included patients with left ventricular dilation and dysfunction attributed to idiopathic DCM, after expert clinical review excluded ischemic or other cardiomyopathies. Ischemic cardiomyopathy was defined as coronary artery disease with >50% narrowing at angiography of ≥1 epicardial coronary artery. CMR was not required for study inclusion, but in a post hoc analysis of available CMR reports, patterns of LGE were classified as (1) no LGE, (2) ischemic-pattern LGE: subendocardial/transmural, (3) nonischemic LGE: midmyocardial/epicardial.

**RESULTS:** Of 1204 idiopathic DCM patients evaluated, 396 (32.9%) had a prior CMR study; of these, 327 (82.6% of 396) had LGE imaging (mean age 46 years; 53.2% male; 55.4% White); 178 of the 327 (54.4%) exhibited LGE, and 156 of the 178 had LGE consistent with idiopathic DCM. The remaining 22 had transmural or subendocardial LGE. Of these 22, coronary angiography was normal (13), showed luminal irregularities (3), a distant thrombus (1), coronary artery disease with <50% coronary artery narrowing (1), or was not available (4).

**CONCLUSIONS:** Of 327 probands enrolled in the DCM Precision Medicine Study cohort who had LGE-CMR data available, an ischemic-pattern of LGE was identified in 22 (6.7%), all of whom had idiopathic DCM as adjudicated by expert clinical review.

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**Key Words:** coronary angiography ■ coronary artery disease ■ dilated cardiomyopathy ■ gadolinium ■ magnetic resonance imaging ■ precision medicine



Understanding the underlying cause of cardiomyopathy is essential as it greatly impacts the therapeutic strategy, disease course and prognosis. The appropriate classification of cardiomyopathy is particularly critical for clinical studies that aim to understand cause and disease mechanisms. This is especially the case for genetic studies of dilated cardiomyopathy (DCM) that aim to identify inherited abnormalities.[1] The DCM Precision Medicine Study, a multi-site study funded by the National Institutes of Health, aims to test the central hypothesis that most idiopathic DCM has a genetic basis.[2] Given the population prevalence of coronary artery disease (CAD), accurate phenotyping of probands and family members is essential to identify ischemic cardiomyopathy. This

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## WHAT IS NEW?

- Late gadolinium enhancement (LGE), commonly found at cardiac magnetic resonance imaging in idiopathic dilated cardiomyopathy (DCM), in most cases shows a nonischemic pattern of LGE, midmyocardial or epicardial.
- However, in some idiopathic DCM cardiac magnetic resonance exams where coronary artery disease has been excluded, ischemic-pattern LGE, subendocardial or transmural, can be observed.
- In this study of 327 patients with idiopathic DCM who had cardiac magnetic resonance exams with LGE imaging, 178 (54.4%) exhibited LGE, and 156 of the 178 had midmyocardial or epicardial LGE consistent with idiopathic DCM.
- The remaining 22 patients had ischemic-pattern LGE even though 16 of the 22 had no coronary artery disease.

## WHAT ARE THE CLINICAL IMPLICATIONS?

- Case reviews of 2 of the 22 patients suggest the ischemic-pattern LGE likely resulted from coronary artery embolus or subendocardial ischemia without flow-limiting coronary artery disease, both established causes of ischemic injury and myocardial infarction.
- Genetic etiologies of idiopathic DCM have also been shown to cause transmural LGE, consistent with an ischemic-pattern.
- Clinically well-validated idiopathic DCM with ischemic-pattern LGE may not necessarily reflect occult coronary artery disease.

## Nonstandard Abbreviations and Acronyms

| | |
|---|---|
| **CAD** | coronary artery disease |
| **CMR** | cardiovascular magnetic resonance |
| **DCM** | dilated cardiomyopathy |
| **EF** | ejection fraction |
| **LGE** | late gadolinium enhancement |
| **LV** | left ventricular |

is key for the DCM Precision Medicine Study so that patient and family outcomes attributed to genetic cause would not be contaminated with unknown and undetected underlying ischemic cardiomyopathy.

The final assignment of an etiology of a myocardial abnormality depends on the integration of multiple types of medical information, including the patient's medical history of prior myocardial infarction, exposure to cardiotoxic agents including most commonly chemotherapeutic agents, other medical conditions that can affect cardiac function such as thyroid disorders, structural heart disease, history of arrhythmia, and other conditions.[3] Cardiac-specific functional studies are essential and include electrocardiography to assess heart rate, rhythm and conduction, echocardiography to measure ventricular size, function and wall thicknesses, and in those at risk for CAD, the exclusion of obstructive CAD by coronary angiography.

Cardiovascular magnetic resonance (CMR) can also contribute to this etiologic assessment. Prior studies have noted that late gadolinium enhancement (LGE) patterns consistent with a potential ischemic etiology may be present in as many as 13% of patients classified as nonischemic DCM by coronary angiography.[4] What is not clear are the appropriate etiological implications of LGE patterns, especially in patients who have normal or minimally obstructed coronary arteries and have no known risk factors, and even those ages 20s to 30s who have minimal CAD risk.

Considerable effort has been devoted to understanding the cause and significance of LGE, with the early consensus that ischemic-pattern LGE classically manifests as subendocardial or transmural scar.[5] This typical ischemic-pattern LGE can be explained by the pathophysiology of ischemia with the wavefront of necrosis beginning in the subendocardium and moving towards the epicardium to become transmural. Ischemic-pattern LGE should always involve the subendocardium and should localize to a perfusion territory of an epicardial artery. Although CMR may suggest the cause of ischemic-pattern LGE from myocardial infarction associated with CAD or from embolic phenomena, history and clinical data are crucial to make such distinctions. Additionally, ischemic-pattern LGE may also be observed in nonischemic cardiomyopathies such as sarcoidosis, amyloidosis, Fabry disease and others, in which case other key CMR features and clinical data help establish the final cause.[5] Moreover, LGE patterns have not been fully integrated with the breadth of DCM genetics, although gene-specific studies with *LMNA* cardiomyopathy have shown transmural LGE.[6,7]

The DCM Precision Medicine Study recruited patients considered to have idiopathic DCM after examining all clinical data. In a subset of patients enrolled who had prior CMR LGE studies, we undertook a comprehensive evaluation to further phenotype the study cohort and assess DCM cause, including LGE patterns for possible prior ischemic events.

# METHODS

## Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## The DCM Precision Medicine Study

The DCM Precision Medicine Study is a multi-site consortium study that aims to test the hypothesis that idiopathic DCM has substantial genetic basis and to evaluate the effectiveness of a

family communication intervention in improving the uptake and impact of family member clinical screening.[2] The study aimed to recruit 1300 individuals (600 non-Hispanic Blacks, 600 non-Hispanic Whites, and 100 Hispanics) meeting rigorous diagnostic criteria for idiopathic DCM and 2600 of their relatives. These idiopathic DCM patients (probands) were identified by heart failure and cardiac transplant cardiovascular physicians and clinical research personnel in heart failure/heart transplant programs at multiple sites in the DCM Consortium.

The project was approved by a single institutional review board at the University of Pennsylvania. All participants gave written informed consent but were allowed to withdraw the consent after clinical screening. The current analysis used available data from eligible probands enrolled in the study as of March 23, 2020 and who did not withdraw their informed consent after recruitment.

## Diagnostic Criteria for Idiopathic DCM

Idiopathic DCM is defined as the presence of both left ventricular (LV) enlargement and systolic dysfunction but without evidence of ischemic or known causes.[2] Specifically, diagnostic criteria for idiopathic DCM include the presence of (1) LV ejection fraction (EF) <50% and (2) LV enlargement defined by echo-derived LV end-diastolic dimension (≥95th percentile for gender/height).[8] The study excluded patients with the following conditions at the time of idiopathic DCM diagnosis: CAD causing ischemic cardiomyopathy, primary valvular disease, cardiotoxic drug exposure (including anthracyclines and other cancer chemotherapeutics), other forms of cardiomyopathy (eg, hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, restrictive cardiomyopathy, Chagas cardiomyopathy), congenital and structural heart disease, sarcoid, amyloid, iron overload, other active multisystem disease that may plausibly cause nonidiopathic DCM (eg, hypereosinophilic syndrome, cardiac involvement with connective tissue disease, Loeffler endocarditis, endomyocardial fibrosis), and severe and untreated or untreatable hypertension.[2]

Patients needed to be able to communicate in English (or in Spanish at sites approved to recruit Hispanic participants), be able to give informed consent (or assent and parental consent for children), and be willing and able to participate in a family-based study. Risk factors considered conventional for idiopathic DCM, such as obesity, routinely treated hypertension, alcohol use/abuse, peripartum cardiomyopathy, or the presence of left ventricular noncompaction, are not used as exclusion criteria.

## Clinical and Demographic Information

A patient interview questionnaire was used during the clinical visit to collect information on patient demographic information (eg, age, sex, race, ethnicity), medical history (eg, diabetes, high cholesterol, hyperlipidemia, lung disease, thyroid disease, rheumatic fever, amyloid, asthma, chemotherapy, hypertension, CAD, heart failure, stroke, myocardial infarction, arrhythmia, etc), symptoms of heart failure, past cardiovascular procedures and diagnostic tests, and previous molecular genetic testing, or genetic evaluation. The questionnaire also asked patients about lifestyle factors such as tobacco and alcohol use, amphetamine and cocaine use, and pregnancy history.

A structured medical record query form was used to abstract information on cardiovascular disease history; data from diagnostic testing performed at the date closest to the idiopathic DCM diagnosis (echocardiograms, electrocardiograms, coronary angiography, nuclear imaging, stress testing, endomyocardial biopsy, Holter monitoring, CMR, and other cardiac testing); medication history related to idiopathic DCM diagnosis; laboratory data (eg, sodium, creatinine, hemoglobin, uric acid, BNP and NTproBNP, etc); and primary and secondary diagnoses.

## CMR Report Analysis

The DCM Precision Medicine Study database was queried to identify patients who underwent comprehensive contrasted CMR exams with LGE imaging. Each CMR report was evaluated for the following parameters: LV end-diastolic and end-systolic volumes, LVEF, the presence of LGE, and the pattern of LGE. Patterns of LGE were classified as (1) no LGE, (2) ischemic-pattern LGE: subendocardial and transmural, and (3) nonischemic LGE: midmyocardial and epicardial. Although direct access to CMR images was unavailable, the reported LGE details along with the clinical interpretation allowed classification into the 3 LGE patterns. Right ventricular indices were not included in the analysis given lack of uniform data.

## Statistical Analysis

Frequency distributions of the study patients who had CMR with LGE imaging were described by demographic and clinical characteristics, and compared with the distributions of the patients who did not have CMR imaging. Differences in percentages and means were tested by Pearson $\chi^2$ test (or Fisher exact test for small numbers) and *t* test (or ANOVA) as appropriate based on the significance level of 0.05. Counts and the percentage of patients who had any evidence of myocardial infarct scar identified by LGE were described. Missing values were excluded from the analysis as noted in the table footnote. The SPSS statistical software was used to analyze and summarize the results.

# RESULTS

## Clinical Characteristics

Of the 1204 patients enrolled in the DCM Precision Medicine Study and available for analysis, 396 (32.9%) had a prior CMR exam; 327 (82.6% of 396) of those patients had a CMR with LGE imaging. Clinical characteristics of patients with LGE-CMR imaging were well balanced between men and women with substantial non-European ancestry represented (Table 1). The clinical and demographic characteristics of patients with LGE-CMR exams were comparable with those who did not have an LGE-CMR exam. Patients who underwent LGE-CMR imaging were younger and more likely to be non-Hispanic White (55.4% versus 47.3%). The mean echo-based LVEF was slightly higher for patients who underwent LGE-CMR than for those who did not (25.1% versus 22.6%, *P*=0.002). Nearly two-thirds of patients in both groups underwent a coronary angiogram to exclude CAD.

**Table 1. Distribution of the Study Idiopathic DCM Patients by Demographic and Clinical Characteristics**

| Characteristic | Patients who had LGE-CMR, N (%) | Patients who did not have LGE-CMR, N (%) | *P* value |
|---|---|---|---|
| Total number | 327 (100.0) | 877 (100.0) | |
| Mean age, y (mean, SE) | 45.8 (0.75) | 53.3 (0.44) | <0.001 |
| Age at enrollment, y | | | <0.001 |
| <45 | 152 (46.5) | 216 (24.6) | |
| 45–64 | 142 (43.4) | 471 (53.7) | |
| 65+ | 33 (10.1) | 190 (21.7) | |
| Male | 174 (53.2) | 501 (57.1) | 0.223 |
| Race and Hispanic origin | | | 0.046 |
| Hispanic | 25 (7.6) | 76 (8.7) | |
| Non-Hispanic Black | 121 (37.0) | 386 (44.0) | |
| Non-Hispanic White | 181 (55.4) | 415 (47.3) | |
| Current or prior tobacco use | 132 (40.4) | 353 (40.3) | 0.971 |
| Obesity (BMI ≥30 kg/m$^2$) | 158 (48.3) | 426 (48.6) | 0.937 |
| High cholesterol* | 78 (23.9) | 248 (28.3) | 0.124 |
| Hypertension* | 151 (46.2) | 485 (55.3) | 0.005 |
| Diabetes* | 57 (17.4) | 239 (27.3) | <0.001 |
| Echo LVEF(%), mean (SE) | 25.1 (10.5) | 22.6 (9.5) | 0.002 |
| ECG | | | |
| Atrial fibrillation | 14 (4.3) | 57 (6.5) | 0.391 |
| LBBB | 56 (17.1) | 101 (11.5) | 0.057 |
| Inferior MI | 8 (2.4) | 41 (4.7) | 0.171 |
| Anterior MI | 11 (3.4) | 45 (5.1) | 0.463 |
| Septal MI | 7 (2.1) | 29 (3.3) | 0.579 |
| Coronary angiogram | | | |
| Yes | 235 (71.9) | 654 (75.1) | 0.020 |
| Medications | | | |
| ACE inhibitor/ARB | 231 (70.6) | 522 (59.5) | 0.01 |
| Beta blocker | 270 (82.6) | 616 (70.2) | 0.001 |
| Loop diuretics | 194 (59.3) | 574 (65.5) | 0.155 |
| Mineralocorticoid antagonist | 191 (58.4) | 439 (50.1) | 0.071 |

Percentages may not sum to 100 due to rounding. ACE indicates angiotensin converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; CMR, cardiac magnetic resonance; DCM, dilated cardiomyopathy; Echo, echocardiogram; LBBB, left bundle branch block; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; and MI, myocardial infarction.

*Excluded 2 missing values.

## CMR Characteristics

A total of 327 CMR reports with LGE imaging were evaluated (Table 2). LGE was identified in 178 (54.4%) of the 327 patients, of which 22 patients (6.7%) exhibited LGE patterns (subendocardial and transmural) classically considered to represent an ischemic event, while 156 (93.3%) patients had LGE considered nonischemic (midmyocardial and epicardial).

Patients with an ischemic-pattern LGE were older at DCM diagnosis and at time of CMR examination, and had a shorter duration of DCM. Additionally, patients with ischemic-pattern LGE tended to have larger indexed LV volumes and lower LVEF than those with nonischemic LGE.

Upon detailed evaluation of the 22 patients with ischemic-pattern LGE (Table 3), 18 had coronary angiographic data available. Of these 18, 3 had luminal irregularities, one exhibited moderate CAD (up to 50% stenosis), one had a distal coronary thrombus without CAD, and the remaining 13 had normal coronary angiography. Three cases deserve further comment. Patient 1 (Table 3) who had luminal coronary irregularities at angiography and at CMR had midmyocardial and subendocardial LGE also had a 1.3 cm thrombus in her left ventricle and met criteria for noncompaction cardiomyopathy. In addition to a LVEF of 10%, her right ventricular ejection fraction was 17% and she had marked biventricular enlargement, consistent with advanced biventricular DCM. The clinical conclusion was that of nonischemic cardiomyopathy due to the dramatic biventricular systolic dysfunction out of proportion to the coronary luminal irregularities and most consistent with idiopathic DCM. The presence of the LV thrombus raises the question of a possible prior embolic infarct responsible in part for the LGE findings. Patient 2 had a transmural scar consistent with a prior myocardial infarction but had had coronary angiography at ages 51, 65, and 68 years of age, all reported as having only coronary luminal irregularities. Based on this evidence, an ischemic cardiomyopathy due to CAD was considered unlikely with a clinical diagnosis most consistent with idiopathic DCM. Patient 6 presented in profound cardiogenic shock with advanced heart failure with a suspected acute myocardial infarction due to marginally elevated cardiac biomarkers. Coronary angiography was performed urgently on admission, but the coronary angiogram was reported as normal. At CMR, she was found to have severe biventricular dysfunction with biventricular enlargement and a LVEF of 17% and right ventricular ejection fraction of 30%. She also had diffuse subendocardial LGE that was read as consistent with amyloid cardiomyopathy. Following heart transplant 4 months later, pathological examination of her explanted heart was negative for amyloid, rather, she had striking dense circumferential subendocardial fibrosis with associated inflammation considered most likely secondary to global ischemia in setting of advanced nonischemic DCM and cardiogenic shock. Moderate atherosclerotic plaque of the major epicardial coronary arteries was also reported.

## DISCUSSION

The DCM Precision Medicine Study sought to enroll a cohort of patients (probands) with idiopathic DCM and their family members for genetic study.[2] A foundational aspect of the study was to include patients who met strict idiopathic DCM criteria, defined as the exclusion of all other clinically detectable causes of DCM, except

**Table 2. Characteristics of Idiopathic DCM Patients With LGE-CMR by LGE Pattern**

| Characteristic | LGE-CMR finding | | | *P* value |
|---|---|---|---|---|
| | No LGE | Ischemic | Nonischemic | |
| Total number (%) | 149 (100.0) | 22 (100.0) | 156 (100.0) | |
| Mean age at DCM diagnosis (SE), y | 39.9 (1.12) | 48.1 (2.80) | 43.5 (1.09) | 0.008 |
| Mean age at time of CMR (SE), y | 41.5 (1.13) | 49.1 (2.76) | 44.9 (1.09) | 0.015 |
| Male, n (%) | 65 (43.6%) | 12 (54.5%) | 97 (62.2%) | 0.005 |
| Race and ethnicity, n (%) | | | | 0.728 |
| Hispanic | 15 (10.1%) | 1 (4.3%) | 9 (5.8) | |
| Non-Hispanic Black | 54 (36.2%) | 8 (34.8%) | 59 (37.8%) | |
| Non-Hispanic White | 80 (53.7%) | 13 (60.9%) | 88 (56.4%) | |
| Mean DCM duration (SE), y | 3.8 (0.44) | 2.0 (0.59) | 2.8 (0.25) | 0.073 |
| Obesity (BMI ≥30 kg/m$^2$), n (%) | 77 (51.7) | 7 (31.8) | 75 (48.1) | 0.215 |
| CMR measures, mean (SE) | | | | |
| Mean LVEDV, mL | 276.5 (8.86) | 306.2 (23.09) | 310.2 (9.65) | 0.034 |
| Mean LVEDVi, mL/m$^2$ | 132.0 (3.88) | 150.6 (9.61) | 145.9 (4.06) | 0.028 |
| Mean LVESV, mL | 200.4 (9.57) | 247.1 (22.9) | 229.6 (9.13) | 0.040 |
| Mean LVESVi, mL/m$^2$ | 94.7 (4.21) | 121.6 (10.28) | 108.6 (4.10) | 0.013 |
| Mean LVEF, % | 29.84 (1.08) | 22.1 (2.62) | 25.0 (0.92) | <0.001 |

BMI indicates body mass index; CMR, cardiac magnetic resonance; DCM, dilated cardiomyopathy; LGE, late gadolinium enhancement; LVEDV, left ventricular end-diastolic volume; LVEDVi, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; and LVESVi, left ventricular end-systolic volume index.

genetic.[9,10] Conditions excluded were other known types of cardiomyopathy, including ischemic DCM, valvular and structural heart disease, prior cardiotoxic exposure, and medical conditions such as iron overload or thyroid disease, among others.

While the definition of ischemic cardiomyopathy is straightforward (myocardial dysfunction that results from a prior myocardial ischemic insult), the implementation of an ischemic cardiomyopathy exclusion for clinical studies has been challenging.[11] Traditionally, DCM diagnoses have been supported and confirmed by a clinical triad of coronary angiography, echocardiography, and clinical history.[11] Coronary angiography has typically been the final arbiter in distinguishing nonischemic from ischemic cardiomyopathy,[4,11,12] with a well-established most-stringent standard of coronary artery narrowing of >50% of any of the 3 major epicardial branches defined as CAD.[11] While some patients with CAD and >50% narrowing may have preserved myocardial function without evidence of an ischemic insult, a 50% narrowing standard has been used as a conservative approach and a surrogate for ischemic cardiomyopathy, and has been used in the DCM Precision Medicine Study.[2] However, the converse, where angiographically normal coronary arteries or nonobstructive coronary disease (<50% stenosis) have been documented, may not necessarily exclude a prior ischemic insult that has caused ischemic cardiomyopathy. For example, a coronary artery thrombus, triggered from early CAD with <50% narrowing, can cause an acute myocardial infarction with subsequent recanalization of the culprit artery. Alternatively, a large acute myocardial infarction could result from a coronary artery embolus from a LV mural thrombus that was consequent to antecedent LV systolic dysfunction and dilatation of DCM. In that case, the cause would rightfully be assigned as idiopathic DCM with a subsequent and superimposed myocardial infarction not from CAD.

To these issues, CMR with LGE imaging has been proposed to assist with defining the cause of myocardial disease, as reviewed.[5,13] Prior studies have shown that LGE identifies replacement fibrosis from numerous causes, including prior myocardial infarction.[13] Myocardial fibrosis by LGE is commonly identified in various types of cardiomyopathy, including DCM, where there is no known CAD, no prior myocardial infarction, and coronary angiography has shown the coronary arteries to be normal, and thus with a low probability of CAD. LGE patterns have been proposed to assign cause as ischemic or nonischemic, with CAD-induced ischemic injury from myocardial infarction considered to be transmural LGE in a epicardial coronary artery distribution.[5] Subendocardial LGE has been commonly observed in patients with known CAD and is also considered representative of a nontransmural ischemic insult. In contrast, the usual pattern observed in DCM is midmyocardial or epicardial LGE.[5]

Using an LGE-based analysis of the 327 patients enrolled in the DCM Precision Medicine Study with LGE-CMR data available, 178 (54.4%) exhibited LGE with 156 (93.3%) consistent with an LGE pattern most commonly observed in idiopathic DCM. The high prevalence of no LGE finding or a mixed LGE pattern including the

**Table 3. Characteristics of Idiopathic DCM Patients With Ischemic-Pattern LGE**

| Patient number | Age, y | Sex | LVEDVi, mL/m² | LVESVi, mL/m² | LVEF (%) | Coronary angiography | LGE description |
|---|---|---|---|---|---|---|---|
| 1 | 47 | F | 182 | 164 | 10 | Luminal coronary irregularities | Midmyocardial, subendocardial |
| 2 | 68 | M | 124 | 99 | 20 | Luminal coronary irregularities | Transmural |
| 3 | 58 | F | Not available | Not available | 40 | Luminal coronary irregularities | Transmural |
| 4 | 72 | M | 185 | 152 | 18 | Moderate CAD (up to 50% stenosis) | Midmyocardial, subendocardial |
| 5 | 43 | F | 143 | 115 | 20 | No CAD but distal coronary thrombus | Subendocardial |
| 6 | 66 | F | 133 | 110 | 17 | Normal | Diffuse subendocardial |
| 7 | 34 | M | 196 | 160 | 19 | Normal | Midmyocardial, subendocardial, transmural |
| 8 | 53 | F | 77 | 40 | 48 | Normal | Subendocardial |
| 9 | 25 | M | 171 | 144 | 16 | Normal | Subendocardial |
| 10 | 41 | M | 116 | 62 | 47 | Normal | Subendocardial |
| 11 | 47 | M | 163 | 116 | 28 | Normal | Subendocardial |
| 12 | 44 | F | 93 | 57 | 39 | Normal | Subendocardial, transmural |
| 13 | 52 | M | Not available | Not available | 20 | Normal | Transmural–small |
| 14 | 35 | F | Not available | Not available | 19 | Normal | Transmural |
| 15 | 52 | M | 123 | 107 | 13 | Normal | Transmural |
| 16 | 66 | F | 146 | 129 | 11 | Normal | Transmural, epicardial |
| 17 | 48 | M | 150 | 137 | 8 | Normal | Transmural |
| 18 | 57 | M | 213 | 188 | 12 | Normal | Transmural, subendocardial |
| 19 | 62 | M | 162 | 130 | 20 | Not available | Midmyocardial, small transmural |
| 20 | 41 | F | 102 | 63 | 38 | Not available | Midmyocardial, transmural |
| 21 | 27 | F | 140 | 127 | 10 | Not available | Midmyocardial, subendocardial, transmural |
| 22 | 43 | M | 243 | 210 | 14 | Not available | Midmyocardial, transmural |

CAD indicates coronary artery disease; DCM, dilated cardiomyopathy; F, female; LGE, late gadolinium enhancement; LVEDVi, left ventricular end-diastolic volume index; LVESVi, left ventricular end-systolic volume index; LVEF, left ventricular ejection fraction; and M, male.



epicardium support the role for LGE-CMR in the diagnosis of idiopathic DCM. The remaining 22 had transmural or subendocardial LGE considered consistent with ischemic scar. However, 15 had coronary angiography with 12 read as normal and 3 with minimal disease. Of these, 5 were ≤45 years without usual CAD risk factors, making even occult ischemic events from CAD unlikely. While the LGE pattern was consistent with prior ischemic injury and has been termed ischemic-pattern LGE in the cardiovascular literature, the pathophysiology of this LGE is unlikely to be related to epicardial CAD or occult antecedent myocardial infarction from CAD but more likely to some other injurious process. We suggest 3 possibilities for nonclassical CAD-induced myocardial ischemic events that may be relevant for these cases.

One well-established cause of myocardial ischemic injury in idiopathic DCM is coronary artery embolus[14–16] from LV or left atrial thrombus, with a frequency estimated at 3% of all myocardial infarctions,[15,16] and an overall rate of thromboembolism in heart failure patients of 3% to 5%.[17] Such a mechanism is plausible to explain many of the observed LGE findings in this cohort. In support of this suggestion, one of the 22 cases reported no CAD but a distal coronary artery thrombus.

A second possibility is that the dilated LV of idiopathic DCM is uniquely at risk for repeated ischemic insults due to elevated wall stress, myocardial oxygen demand and reduced subendocardial perfusion, even in the absence of obstructive CAD. These specific pathophysiological consequences of DCM and the heart failure clinical syndrome account for the elevated biomarkers of myocardial injury often seen in these patients, and may result in incidental infarction subsequent to the diagnosis of DCM.[18] Such conditions were present in Case 6 (Table 3) described above, who presented with DCM in profound cardiogenic shock, had elevated biomarkers suggestive of acute myocardial infarction, and the later LGE uptake identified at CMR showed extensive circumferential subendocardial ischemic-pattern LGE consistent with this mechanism.

A third possibility is the impact of genetic disease to cause LGE that could be otherwise attributed to an ischemic event. We recognize that this possibility—LGE that arises from genetic cause but fits usual ischemic-appearing patterns—has been only minimally investigated. We also note that the intersection of inflammation and resulting fibrosis that results from rare variant genetic disease is not well understood. While midmyocardial LGE is commonly seen in idiopathic DCM, as was the case in this study and has been shown previously to be the predominant finding for TTN-related cardiomyopathy,[19] most nonischemic cohorts have some fraction of individuals

found to have ischemic-pattern LGE that does not appear to result from CAD. For example, in a *TTN* study,[19] 2.5% were reported with a bystander myocardial infarction by CMR in patients with normal coronary arteries.

Although detailed segmental LGE analysis was not possible in our study given lack of direct access to CMR images, on review of the 22 CMR reports we also noted that 10 patients had ischemic-pattern LGE in ≤2 American Heart Association segments.[20] In these cases LV dysfunction appeared out of proportion to the small extent of ischemic-pattern LGE, hence also suggesting that the cardiomyopathy was likely of nonischemic cause. A recent study attempted to provide a definition for differentiating nonischemic DCM with incidental infarction from true ischemic cardiomyopathy by integrating LV geometric indices with LGE data.[21] They noted that the optimal cutoff value for detecting nonischemic DCM with incidental infarction was a ratio of indexed LV end-diastolic volume to the number of ischemic-pattern LGE segments >25 mL/m$^2$/segment resulting in a sensitivity and specificity of 100% and 91%, respectively.

The presence of ischemic-pattern LGE in idiopathic DCM is also important for accurate phenotyping and may also provide additional prognostic value.[22,23] In our cohort, patients with ischemic-pattern LGE had larger indexed LV volumes and lower LVEF than those with nonischemic-pattern LGE. No data exist on the prognostic value of LGE consistent with infarction specifically in an idiopathic DCM population where risk of infarction would be considered low. However, studies in patients with suspected CAD have demonstrated that those with unrecognized infarctions are less likely to receive guideline-directed medical therapies and have increased risk for heart failure hospitalization.[24] The presence of ischemic-pattern LGE in idiopathic DCM also has the potential to help predict clinical outcomes.

This study has limitations. The analysis was conducted among 327 patients who had had LGE-CMR reports available, only a fraction of the patients enrolled in the DCM Precision Medicine Study. Nevertheless, although only a modest sample size, the distributions of demographic and clinical characteristics were comparable between groups. As this study was a retrospective analysis of CMR written reports across multiple sites, actual CMR images were not able to be reviewed. Also, heterogeneity of image acquisition protocols and interpretation likely differed between the many sources of CMR reports. Nevertheless, a systematic approach by clinical (Dr Haas) and imaging (Dr Zareba) cardiologists was used to categorize clinical and CMR data to mitigate this limitation.

In summary, we have demonstrated that the phenotyping of the DCM Precision Medicine Study cohort using clinical criteria yielded a high fidelity nonischemic cohort with 7% prevalence of ischemic-pattern LGE, which by expert review was considered most consistent with nonischemic cause. This study validated the clinical diagnostic criteria used in the DCM Precision Medicine Study, demonstrating its accuracy in classification of ischemic and nonischemic causes of DCM. The study also provided an up-to-date approximation of LGE suggestive of ischemic cause in an otherwise carefully phenotyped cohort of nonischemic DCM patients.

## ARTICLE INFORMATION

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### Disclosures

None.

## APPENDIX

### DCM Consortium Institutions and Personnel Participating in This Study

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