Circulation
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Circ Cardiovasc Imaging. 2013;6:790-799; originally published online August 9, 2013;
doi: 10.1161/CIRCIMAGING.113.000438
Circulation: Cardiovascular Imaging is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-9651. Online ISSN: 1942-0080

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circimaging.ahajournals.org/content/6/5/790

Data Supplement (unedited) at:
http://circimaging.ahajournals.org/content/suppl/2013/08/09/CIRCIMAGING.113.000438.DC1.html

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Myocardial Fibrosis as a Key Determinant of Left Ventricular Remodeling in Idiopathic Dilated Cardiomyopathy

A Contrast-Enhanced Cardiovascular Magnetic Study

Pier Giorgio Masci, MD; Robert Schuurman, MD; Barison Andrea, MD; Andrea Ripoli, PhD; Michele Coceani, MD; Sara Chiappino, MD; Giancarlo Todiere, MD; Vera Srebot, MD; Claudio Passino, MD; Giovanni Donato Aquaro, MD; Michele Emdin MD, PhD; Massimo Lombardi MD

Background—In idiopathic dilated cardiomyopathy, there are scarce data on the influence of late gadolinium enhancement (LGE) assessed by cardiovascular magnetic resonance on left ventricular (LV) remodeling.

Methods and Results—Fifty-eight consecutive patients with idiopathic dilated cardiomyopathy underwent baseline clinical, biohumoral, and instrumental workup. Medical therapy was optimized after study enrollment. Cardiovascular magnetic resonance was used to assess ventricular volumes, function, and LGE extent at baseline and 24-month follow-up. LV reverse remodeling (RR) was defined as an increase in LV ejection fraction ≥10 U, combined with a decrease in LV end-diastolic volume ≥10% at follow-up. ΔLGE extent was the difference in LGE extent between follow-up and baseline. LV-RR was observed in 22 patients (38%). Multivariate regression analysis showed that the absence of LGE at baseline cardiovascular magnetic resonance was a strong predictor of LV-RR (odds ratio, 10.857 [95% confidence interval, 1.844–63.911]; P=0.008) after correction for age, heart rate, New York Heart Association class, LV volumes, and LV and right ventricular ejection fractions. All patients with baseline LGE (n=26; 45%) demonstrated LGE at follow-up, and no patient without baseline LGE developed LGE at follow-up. In LGE-positive patients, there was an increase in LGE extent over time (P=0.034), which was inversely related to LV ejection fraction variation (Spearman ρ, −0.440; P=0.041). Five patients showed an increase in LGE extent >75th percentile of ΔLGE extent, and among these none experienced LV-RR and 4 had a decrease in LV ejection fraction ≥10 U at follow-up.

Conclusions—In patients with idiopathic dilated cardiomyopathy, the absence of LGE at baseline is a strong independent predictor of LV-RR at 2-year follow-up, irrespective of the initial clinical status and the severity of ventricular dilatation and dysfunction. The increase in LGE extent during follow-up was associated with progressive LV dysfunction. **(*Circ Cardiovasc Imaging*. 2013;6:790-799.)**

Key Words: cardiomyopathy, dilated ■ myocardial fibrosis ■ ventricular remodeling

In the past decades, the prognosis of patients with idiopathic dilated cardiomyopathy (IDCM) has improved after the advances in medical therapy and the introduction of device therapy, namely, cardiac resynchronization therapy and implantable cardioverter-defibrillator.[1–6] Nonetheless, 10-year survival remains <60%, with deaths often preceded by numerous heart failure exacerbations.[5,6] This reflects, at least in part, the difficulty in assessing the individual risk in patients with IDCM in whom clinical course varies widely, ranging from progressive heart failure and sudden cardiac death to left ventricular (LV) reverse remodeling (RR). The latter is characterized by a decrease in LV volumes, combined with a substantial improvement in systolic function. Studies in general heart failure populations and IDCM patients reported that approximately one third of patients treated with optimal medical therapy (OMT) experienced LV-RR at midterm follow-up, and this was associated with favorable long-term prognosis.[7–9] However, in clinical practice, the prediction of LV-RR after the optimization of medical therapy still remains particularly difficult. Two recent studies reported that late gadolinium enhancement (LGE) detected by cardiovascular magnetic resonance (CMR) may be a useful marker for predicting LV-RR in patients with nonischemic cardiomyopathy.[10,11] However, these studies had a

Received March 14, 2013; accepted August 6, 2013.

From the Fondazione CNR/Regione Toscana "G. Monasterio," Pisa, Italy (P.G.M., B.A., A.R., M.C., S.C., G.T., C.P., G.D.A., M.E., M.L.); Scuola Superiore Sant'Anna, Pisa, Italy (B.A., C.P.); University of Pisa, Pisa, Italy (G.T., V.S.); and Thoraxcentrum Twente, Enschede, The Netherlands (R.S.).

The online-only Data Supplement is available at http://circimaging.ahajournals.org/lookup/suppl/doi:10.1161/CIRCIMAGING.113.000438/-/DC1.

Correspondence to Pier Giorgio Masci, MD, Cardiac MRI and Cardiovascular Medicine Units, Fondazione CNR/Regione Toscana "G. Monasterio," via G. Moruzzi 1, 56124 Pisa, Italy. E-mail masci@ftgm.it

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short-term follow-up (5 and 12 months, respectively), and the recovery of LV function was likely prompted by the resolution of transient myocardial damage in a sizeable number of patients. Accordingly, it remains uncertain whether LGE is a predictor of LV-RR in patients with IDCM in response to OMT. In addition, at the moment, there are no data on the potential interplay between the changes in LGE over time and LV remodeling. Based on these premises, we conducted the current study with the following aims: (1) to assess whether LGE may be used to predict LV-RR at 2-year follow-up in patients with IDCM after optimization of medical therapy, and (2) to investigate the interaction between LGE variation and LV remodeling during follow-up.

Clinical Perspective on p 799

Methods

Study Population

Between May 2009 and July 2010, 112 consecutive patients with IDCM diagnosed in the preceding 12 months were prospectively evaluated at our institution (a tertiary referral hospital) for study enrollment. The diagnosis of IDCM was made according to World Health Organization criteria[12] and the evidence of an increased LV end-diastolic diameter indexed to body surface area at transthoracic echocardiography and a reduced LV ejection fraction based on published reference ranges.[13] Invasive coronary angiography was performed in all patients to exclude significant coronary artery stenosis.[14] Exclusion criteria included active myocarditis, peripartum cardiomyopathy, extracardiac systemic features of sarcoidosis, chemotherapy-induced cardiomyopathy, drug abuse or excessive alcohol consumption, tachycardia-induced cardiomyopathy, severe valvular disease, untreated hypertension, hypertrophic cardiomyopathy, cardiac amyloidosis, thyroid dysfunction, estimated glomerular filtration rate <30 mL/min, and contraindications to CMR. Active myocarditis was excluded by the absence of classical clinical feature and the increase in troponin I at study entry.

Study Protocol

The study protocol consisted of the following baseline investigations: complete clinical evaluation, 12-lead ECG, echocardiography, and blood sampling, including amino-terminal probrain natiuretic peptide dosage and contrast-enhanced CMR. All the investigations were performed within 1 week from the study enrollment. Patients were treated with angiotensin-converting enzyme (or angiotensin II receptor inhibitors) and β-blockers, in addition to diuretics, when clinically indicated. Neurohormonal medications were titrated to maximally tolerated dose (within 3–6 months), which was defined as OMT. Medications at study entry and OMT are reported in Table 1. Patients underwent clinical follow-up at our outpatient clinic every 3 to 6 months up to July 2012. CMR was repeated at 24-month follow-up. The protocol was approved by our institution's ethical committee, and all patients gave written informed consent.

Transthoracic Echocardiography

Transthoracic echocardiography was performed in all patients and consisted of M-mode, 2-dimensional, and Doppler imaging. For LV diastolic function, from the apical 4-chamber view transmitral flow pattern was assessed by pulsed-wave Doppler echocardiography. Early (*E*) and late (*A*) diastolic filling velocities, *E*/*A* ratio, and *E* deceleration time were measured. For patients with atrial fibrillation, only E wave was considered. All studies were interpreted by an experienced operator (V.S.) blinded to clinical and CMR data. Left ventricular diastolic function was graded as (1) normal, (2) impaired relaxation, (3) pseudonormal, and (4) restrictive filling. Changes in the mitral flow pattern during Valsalva maneuver, pulsed-wave Doppler of pulmonary vein flow, or mitral annular velocities sampled by tissue Doppler imaging were used to differentiate a pseudonormal from a normal transmitral flow pattern.[15] LV diastolic dysfunction was defined by the presence of restrictive filling pattern. Mitral regurgitation was graded semiquantitatively as mild, moderate, or severe according to current recommendations.[16]

CMR Protocol

All patients were examined with 1.5-T unit (CVi; GE-Healthcare, Milwaukee, WI) at study enrollment and follow-up using the same protocol. Studies were performed using dedicated cardiac software, a phased-array surface receiver coil, and vectocardiogram triggering. Cine images in horizontal, vertical, and short-axis views were acquired using breath-hold cine steady-state free precession sequence. For the quantification of biventricular volumes, stroke volume, ejection fraction, and LV mass cine images were acquired in a stack of contiguous short-axis slices from base to apex. Sequence parameters were as follows: field of view, 350 to 400 mm; slice thickness, 8 mm; repetition time/echo time, 3.2/1.6 ms; flip angle, 60°; matrix, 224×192; phases, 30; no interslice gap. Ten to 20 minutes after intravenous administration of 0.2 mmol/kg gadolinium–DTPA, LGE images were acquired using segmented T1-weighted gradient-echo inversion-recovery sequence in the same views used for cine images. The inversion time was individually adapted to suppress the signal of normal myocardium (220–300 ms). Sequence parameters were as follows: field of view, 380 mm; slice thickness, 8 mm; repetition/echo time, 4.6/1.3 ms; flip angle, 20°; matrix, 256×192; no interslice gap.

Image Analysis

All CMR studies were analyzed off-line using a workstation (Advantage; GE-Healthcare, Milwaukee, WI) with a dedicated software (MASS 6.1; Medis, Leiden, The Netherlands). The analysis was started with postcontrast images. Presence of LGE was assigned by the consensus of 2 experienced operators (P.G.M. and A.B.) blinded to clinical data. A third blinded operator (M.L.) adjudicated LGE in case of disagreement (n=2). When present, LGE was automatically quantified on short-axis images by 1 operator (P.G.M.). For each short-axis slice, after tracing the endocardial and epicardial borders, a region of interest averaging 50 mm^2 was defined within normal myocardium with homogeneously nulled signal and without artifacts. Myocardial LGE was defined as areas with signal intensity >6 SD above the mean signal intensity of normal myocardium and expressed as percentage of LV mass.[17] LV and right ventricular (RV) volumes, stroke volume, mass, and ejection fraction were quantified using the stack of cine short-axis images. At least 2-week apart, in 15 anonymized and randomly chosen LGE-positive patients, LGE extent was quantified twice by the same operator (P.G.M.) to assess intraobserver variability. LV-RR was defined as an increase in LV ejection fraction ≥10 U, combined with a decrease in LV end-diastolic volume ≥10% at follow-up.[7]

Statistical Analysis

Continuous variables were expressed as mean±SD or median and 25th to 75th percentiles and categorical variables as frequency with percentage. For continuous variables, Δ expressed the difference between follow-up and baseline values. LGE expansion was defined as ΔLGE extent >75th percentile. Student independent *t* tests or Mann–Whitney tests were used as appropriate to compare continuous variables between patients with and without LV-RR. Comparisons between categorical variables was performed using the χ^2 or Fisher exact test, if the expected cell count was <5. Student dependent *t* test and Wilcoxon sign-rank test were used as appropriate to compare continuous variables at baseline and follow-up. Correlations between continuous variables were examined as appropriate by Pearson or Spearman ρ correlation coefficients. Univariate logistic regression analysis was used to study the association of baseline variables with LV-RR. Interactions between LGE

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Table 1. Baseline Characteristics of the Whole Study Population and Patients With and Without LV-RR

Variables	All (n=58)	LV-RR (n=22)	No LV-RR (n=36)	*P* Value
Age, y	55±12	58±14	52±13	0.167
Female, n (%)	39 (67)	10 (45)	9 (25)	0.151
BMI, kg/m^2	26±4	26±4	26±3	0.483
Heart rate, bpm	66±12	74±13	62±8	<0.001
Systolic BP, mm Hg	116±15	114±15	119±17	0.333
Diastolic BP, mm Hg	71±11	70±10	74±11	0.275
Previous HF hospitalization, n (%)	15 (26)	7 (32)	8 (29)	0.715
Duration of CM, mo	5±2	4±3	6±2	0.282
Family history of CM	15 (30)	6 (27)	13 (36)	0.572
Hypertension, n (%)	24 (41)	9 (41)	15 (42)	0.955
Diabetes mellitus, n (%)	7 (12)	2 (9)	5 (14)	0.698
Smoking, n (%)	23 (40)	9 (41)	14 (39)	0.897
NYHA class I/II/III/IV	33/20/5/0	6/11/5/0	27/9/0/0	<0.001
NYHA class >I	25 (43)	16 (73)	9 (25)	<0.001
NT-proBNP, ng/L	668 (222–1739)	1292 (481–1866)	433 (118–1038)	0.038
eGFR, mL/min	92±31	83±32	97±29	0.158
Serum sodium, mEq/L	138±2	138±2	139±2	0.895
Atrial fibrillation, n (%)	2 (3)	1 (4)	1 (3)	0.938
LBBB, n (%)	14 (23)	7 (32)	7 (21)	0.529
QRS duration, ms	120±25	125±30	116±20	0.317
Diastolic dysfunction	8 (14)	4 (18)	4 (11)	0.462
Moderate/severe MR	16 (28)	7 (32)	9 (25)	0.694
LGE, n (%)	26 (45)	3 (14)	23 (64)	<0.001
LGE extent, % of LV	5.94 (3.33–10.21)	5.97 (3.26–10.53)	5.45 (3.38–8.50)	0.821
LV-EDVi, mL/m^2	125±28	134±34	113±14	<0.001
LV-ESVi, mL/m^2	81±31	106±34	65±15	<0.001
LV-Mi, g/m^2	90±20	97±21	86±19	0.044
LV-SVi, mL/m^2	46±12	40±14	49±10	0.006
LV-EF, %	37±10	28±10	43±8	<0.001
LV-EF <35%, n (%)	22 (38)	16 (73)	6 (17)	<0.001
RV-EDVi, mL/m^2	76±17	78±22	75±13	0.640
RV-ESVi, mL/m^2	32±15	39±20	28±9	0.008
RV-SVi, mL/m^2	44±10	39±10	47±9	0.002
RV-EF, %	59±11	52±13	63±8	<0.001
ACEi/ARBs, n (%)	29 (50)	12 (54)	17 (47)	0.447
Dosage*	0.30±0.17	0.25±0.00	0.33±0.21	0.623
β-blockers, n (%)	32 (55)	10 (45)	22 (61)	0.146
Dosage*	0.26±0.26	0.18±0.09	0.32±0.32	0.191
Spironolactone, n (%)	8 (14)	4 (18)	4 (11)	0.336
Furosemide, n (%)	26 (45)	10 (45)	16 (41)	0.742
ACEi/ARBs, n (%)	53 (91)	19 (86)	34 (94)	0.287
Dosage*	0.70±0.29	0.70±0.30	0.70±0.28	0.988
β-blockers, n (%)	49 (84)	19 (86)	30 (83)	0.757
Dosage*	0.57±0.25	0.60±0.26	0.55±0.24	0.614
Spironolactone, n (%)	20 (34)	9 (41)	11 (31)	0.421
Furosemide, n (%)	21 (36)	6 (27)	15 (42)	0.268

ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II inhibitor; BMI, body mass index; BP, blood pressure; CM, cardiomyopathy; EDVi, end-diastolic volume index; EF, ejection fraction; eGFR, estimated glomerular filtration rate; ESVi, end-systolic volume index; HF, heart failure; LBBB, left bundle branch block; LGE, late gadolinium enhancement; LV, left ventricular; Mi, mass index; MR, mitral regurgitation; NT-pro-BNP, amino-terminal probrain natiuretic peptide; NYHA, New York Heart Association; RR, reverse remodeling; RV, right ventricular; and SVi, stroke volume index.

*Dosage expressed the ratio between the daily dose and the maximum recommended dose of medication.

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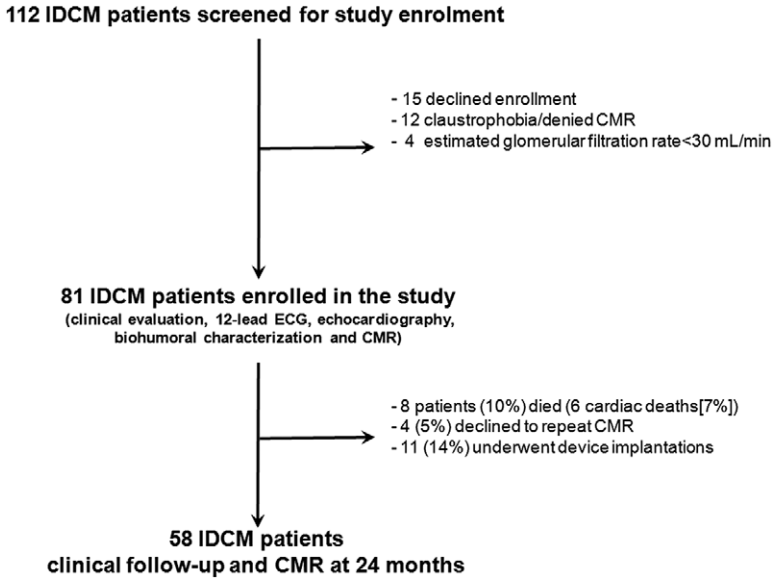

Figure 1. Study protocol. CMR indicates cardiovascular magnetic resonance; and IDCM, idiopathic dilated cardiomyopathy.

and other baseline variables were evaluated ($P<0.10$ was considered statistically significant for interaction). Multivariate logistic regression analysis with stepwise selection procedure ($P<0.05$ for entry; $P>0.10$ for removal) was used to assess the influence of covariates on LV-RR. Variables with $P<0.10$ at univariate analysis were introduced in the multivariate model as covariates. Considering the correlation between LV ejection fraction and LV end-systolic volume ($r=-0.875$; $P<0.001$) and the importance of the latter on LV remodeling, LV end-systolic volume (model 1) and LV ejection fraction (model 2) were introduced separately in the multivariate analysis. Because RV ejection fraction and end-systolic volume were strongly related ($r=-0.827$, $P<0.001$), only RV ejection fraction was introduced in the 2 models. For each model, the incremental value in predicting LV-RR by the stepwise inclusion of CMR functional parameters (RV ejection fraction, LV volumes, and ejection fraction) and LGE, in addition to clinical parameters (age, heart rate, and New York Heart Association class >I), was assessed by the χ^2 test using omnibus test of model coefficients. In addition, we also performed Bayesian model averaging to address model uncertainty, producing a posterior probability for each possible model and predictor, implemented with R package (R project for statistical computing).[18] Intraclass correlation coefficient and Bland–Altman analysis (MedCalc, Belgium) were used to assess intraobserver variability for LGE extent.[19] All tests were 2-tailed, and $P<0.05$ was considered statistically significant. With the exception of Bland–Altman and Bayesian model averaging, analyses were performed using SSPS version 15 (SPSS, Chicago, IL).

Results

Study Population

Of the 81 patients initially enrolled in the study, 8 patients died (6 for cardiac causes), 4 declined to repeat CMR, and 11 underwent device implantation during the study period. The final study cohort was made up of 58 patients, and all patients had an increased LV end-diastolic volume indexed to body surface area and reduced LV ejection fraction at baseline CMR compared with published reference ranges normalized for age and sex[20] (Figure 1). Twenty-two patients (38%) experienced LV-RR at follow-up. Baseline characteristics of the overall study population and patients with and without LV-RR are reported in Table 1. At baseline, patients with LV-RR had higher heart rate, were more symptomatic, and showed higher amino-terminal probrain natiuretic peptide levels than patients

Table 2. Changes in CMR Parameters During Follow-Up in Patients With and Without LGE at Baseline

	Patients Without LGE			Patients With LGE		
Variables	Baseline/Follow-Up	Δ Value	*P* Value	Baseline/Follow-Up	Δ Value	*P* Value
LV-EDVi, mL/m^2	134±32/98±17	−36±6	<0.001	115±16/116±26	+1±4	0.828
LV-ESVi, mL/m^2	89±37/47±12	−42±7	<0.001	70±14/75±29	+5±5	0.385
LV-Mi, g/m^2	91±19/76±20	−14±4	0.001	90±22/87±20	−3±3	0.408
LV-SVi, mL/m^2	45±14/51±8	+6±2	0.021	46±11/44±9	−2±2	0.316
LV-EF, %	35±13/52±7	+17±3	<0.001	40±10/39±11	−1±2	0.646
RV-EDVi, mL/m^2	79±19/77±15	−2±2	0.320	72±13/72±17	+0±2	0.866
RV-ESVi, mL/m^2	35±18/27±11	−9±3	0.004	29±8/31±14	+2±2	0.320
RV-SVi, mL/m^2	44±11/51±9	+7±2	0.002	43±10/43±10	0±2	0.961
RV-EF, %	57±13/66±8	+9±2	0.001	60±9/60±10	0±2	0.932

Data are expressed as mean±SD. Δ value is the difference between follow-up and baseline values and is expressed as mean±SE. CMR indicates cardiovascular magnetic resonance; EDVi, end-diastolic volume index; EF, ejection fraction; ESVi, end-systolic volume index; LGE, late gadolinium enhancement; LV, left ventricular; Mi, mass index; RV, right ventricular; and SVi, stroke volume index.

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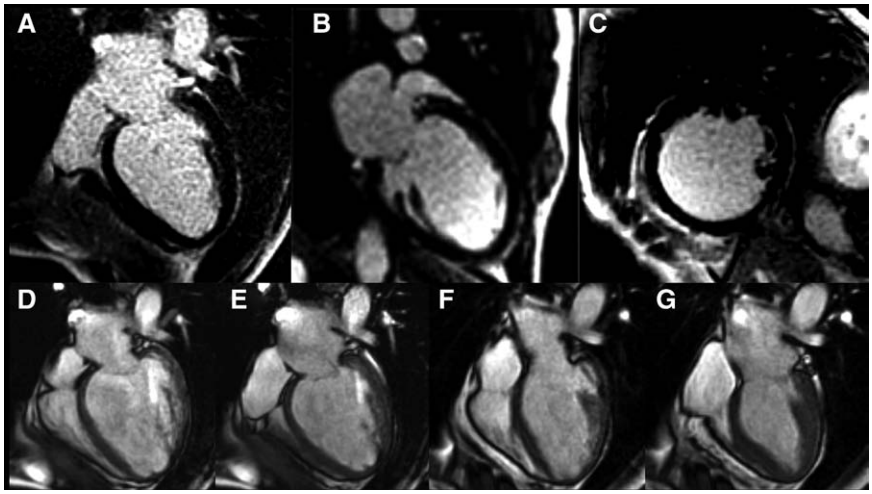

Figure 2. A 52-year-old woman with 8-month history of idiopathic dilated cardiomyopathy, left bundle branch block, and dyspnea on exertion (New York Heart Association class II). Baseline postcontrast cardiovascular magnetic resonance images in horizontal (**A**) and vertical long axis (**B**) and midventricular short axis (**C**) did not show late gadolinium enhancement. End-diastolic (**D** and **F**) and end-systolic (**E** and **G**) horizontal long-axis images at baseline (**D** and **E**; Movie I in the online-only Data Supplement) and follow-up (**F** and **G**; Movie II in the online-only Data Supplement) showing a reduction in left ventricular (LV) volumes (end-diastolic volume from 208 to 112 mL/m^2; end-systolic volume from 169 to 61 mL/m^2) and improvement in function (LV ejection fraction from 18% to 46%).

without LV-RR. Myocardial LGE was observed less commonly in patients with LV-RR than in those without LV-RR. Patients with LV-RR had larger LV volumes and mass but lower stroke volume and ejection fraction than those without LV-RR. In addition, RV end-systolic volume was higher, but stroke volume and ejection fraction were lower in patients with LV-RR.

Relationship Between LGE at Baseline and LV-RR

All patients with LGE at baseline (n=26; 45%) showed LGE at follow-up with the same pattern (midwall [n=18]; patchy [n=7]; subendocardial [n=1]), and none of the patients without LGE at baseline developed LGE at follow-up. Changes in CMR parameters during follow-up are shown in Table 2. Patients without LGE at baseline showed significant reduction in LV volumes and mass with a concurrent increase in stroke volume and ejection fraction (Figure 2). In this group, a consistent reduction in RV end-systolic volume was observed, leading to an improvement in stroke volume and ejection fraction. Conversely, patients with LGE at baseline experienced neither a decrease in LV and RV volumes nor an improvement in stroke volume and ejection fraction (Figure 3). As a result, 3 (11%) and 19 (59%) patients with and without LGE at baseline CMR experienced LV-RR at follow-up (P<0.001). During follow-up, normalization of LV volumes, mass, and function[20] occurred only in 6 patients, none of which had LGE at baseline.

LGE Variation During Follow-Up and LV Remodeling

The extent of LGE increased significantly during follow-up (from 5.94% [3.33%–10.21%] to 6.76% [3.79%–10.80%]; P=0.034). The median value of ΔLGE extent was 0.95% (0.00%–3.42%). There was an inverse relationship between ΔLV ejection fraction and ΔLGE extent (Spearman ρ, –0.440; P=0.041). Five patients (9%) showed LGE expansion during follow-up (ΔLGE extent >3.42%), and among these none experienced LV-RR and 4 had a decrease in LV ejection fraction ≥10 U at follow-up (Table 3; Figure 4).

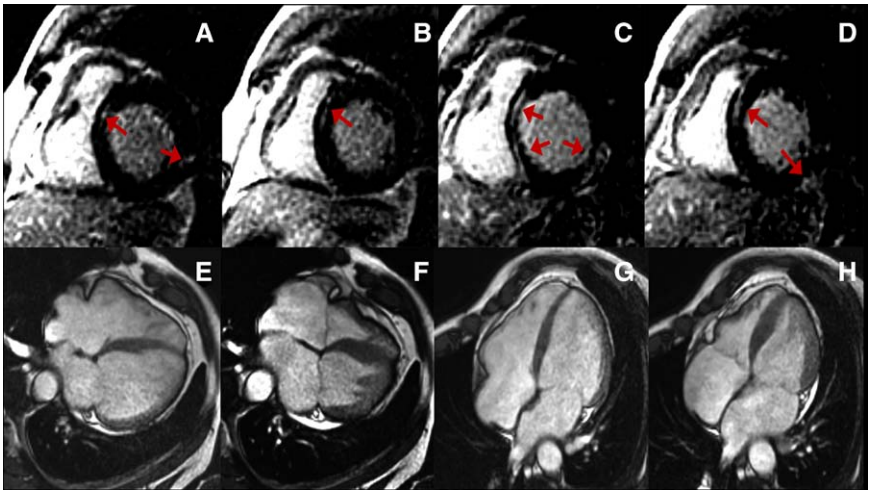

Figure 3. A 51-year-old man with 11-month history of idiopathic dilated cardiomyopathy complaining of episodes of palpitation and asthenia. Baseline postcontrast basal (**A**) and midventricular (**B**) short-axis images showed late gadolinium enhancement (LGE) of the septum and left ventricular (LV) inferolateral wall (arrows). At follow-up, postcontrast basal (**C**) and midventricular (**D**) short-axis images showed an increase in LGE extent (from 4.43% to 7.52%; Δ value, 3.09%). End-diastolic (**E** and **G**) and end-systolic (**F** and **H**) horizontal long-axis images at baseline (**E** and **F**; Movie III in the online-only Data Supplement) and follow-up (**G** and **H**; Movie IV in the online-only Data Supplement) showed no significant changes in LV volumes (end-diastolic volume from 108 to 107 mL/m^2; end-systolic volume from 55 to 54 mL/m^2) and function (ejection fraction 49% at baseline and follow-up).

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Table 3. Characteristics of Patients With LGE Expansion

Patients	Age, y	Sex	CM Duration, mo	NYHA Class	LV-EDVi b/FU, mL/m^2	LV-ESVi b/FU, mL/m^2	LV-EF b/FU, %	LGE Extent b/FU, % of LV
1	64	Female	8	1	108/113	61/77	44/33	5.97/10.66
2	30	Female	6	2	122/136	73/97	40/29	23.92/28.57
3	61	Male	7	3	137/144	87/109	36/24	17.51/23.08
4	55	Female	8	2	89/92	50/51	44/45	17.11/23.08
5	29	Female	11	1	112/136	73/97	40/29	23.92/28.57

b indicates baseline; CM, cardiomyopathy; EDVi, end-diastolic volume index; EF, ejection fraction; ESVi, end-systolic volume index; FU, follow-up; LGE, late gadolinium enhancement; LV, left ventricular; Mi, mass index; and RV, right ventricular.

Reproducibility of LGE Extent

Intraobserver variability for LGE extent was low, showing a mean bias of 0.92% (95% confidence intervals, 1.97% to −1.3%; limits of agreement, 4.62% to −2.78%). The intraclass correlation coefficient between the repeated measurements was high (intraclass correlation coefficient, 0.930 [0.793–0.977]; $P<0.001$).

Univariate and Multivariate Analyses for Baseline Predictors of LV-RR

At univariate analysis, the absence of LGE at baseline was strongly associated with LV-RR at follow-up (Table 4). No interaction was observed between LGE and other baseline variables. Multivariate analysis showed that the absence of LGE and decreased LV ejection fraction were the only 2 predictors of LV-RR at follow-up after correction for other baseline covariates, including age, heart rate, New York Heart Association class >I, LV end-diastolic volume, and LV and RV ejection fractions. This result was also confirmed when LV end-systolic volume replaced LV ejection fraction in the multivariate model (Table 5). Compared with the model containing only the clinical variables, the addition of CMR functional parameters to the model enhanced significantly the value in predicting LV-RR. Furthermore, when LGE was added to the model containing clinical and CMR functional parameters, there was a further significant improvement of the model in predicting LV-RR (Figure 5). In Bayesian analysis, the lack of LGE at baseline was the best predictor of LV-RR, remaining significant in all selected models in association with one of the other selected variables (Figure I in the online-only Data Supplement).

Discussion

The main findings of this study can be summarized as follows. First, we demonstrated that the absence of LGE at baseline CMR was a strong and independent predictor of LV-RR in patients with IDCM at 2-year follow-up, irrespective of the initial clinical status and the severity of LV dilatation and dysfunction. Second, in patients with LGE at baseline, there was an increase in LGE extent during follow-up, and this variation was inversely related to the change in LV ejection fraction. Noteworthy, 5 patients (9%) showed a marked increase in LGE extent (LGE expansion), which was almost always associated with a decrease in LV ejection fraction ≥10 U at follow-up.

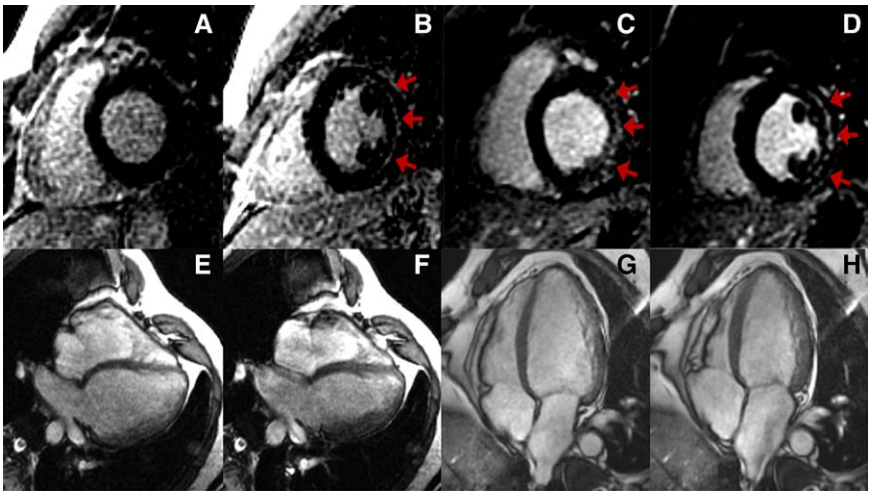

Figure 4. A 64-year-old woman with a 7-month history of idiopathic dilated cardiomyopathy and dyspnea on exertion (New York Heart Association class II). Baseline postcontrast basal (**A**) and midventricular (**B**) short-axis images showed late gadolinium enhancement (LGE) in the midventricular lateral wall (arrows). At follow-up, postcontrast basal (**C**) and midventricular (**D**) short-axis images showed an increase in LGE extent involving also the basal left ventricular (LV) lateral wall (from 5.97% to 10.66%; Δ value, 4.69% [LGE expansion]). End-diastolic (**E** and **G**) and end-systolic (**F** and **H**) horizontal long-axis images at baseline (**E** and **F**; Movie V in the online-only Data Supplement) and follow-up (**G** and **H**; Movie VI in the online-only Data Supplement) showed an increase in LV volumes (end-diastolic volume from 108 to 113 mL/m^2; end-systolic volume from 61 to 77 mL/m^2) and reduction in function (ejection fraction from 44% to 33%).

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Table 4. Univariate Analysis for LV-RR at Midterm Follow-Up

Variables at Baseline	OR (95% CI)	*P* Value
Age, y	1.051 (1.004–1.101)	0.003
Sex (female)	2.500 (0.809–7.727)	0.111
Heart rate, bpm	1.125 (1.046–1.209)	0.001
Systolic BP, mm Hg	0.979 (0.938–1.022)	0.363
Diastolic BP, mm Hg	0.966 (0.908–1.027)	0.270
Family history of CM, mo	0.663 (0.208–2.114)	0.488
Diabetes mellitus	0.620 (0.110–3.509)	0.589
Hypertension	0.969 (0.330–2.847)	0.955
Smoking	0.855 (0.185–3.950)	0.841
Previous HF hospitalization	3.984 (0.879–18.616)	0.491
Duration of CM, mo	0.940 (0.840–1.051)	0.277
NYHA class >I	8.000 (2.400–26.665)	0.001
NT-proBNP, ng/L	1.003 (0.998–1.007)	0.112
Serum sodium, mEq/L	0.963 (0.729–1.271)	0.789
eGFR, mL/min	0.983 (0.961–1.007)	0.159
Atrial fibrillation	1.647 (0.097–28.094)	0.730
Presence of LBBB	1.733 (0.509–5.902)	0.379
QRS duration, ms	1.015 (0.989–1.042)	0.266
Diastolic dysfunction	1.407 (0.432–5.003)	0.538
Moderate/severe MR	3.694 (0.856–15.944)	0.187
Absence of LGE	11.205 (2.778–45.199)	0.001
LV-EDVi, mL/m^2	1.055 (1.024–1.088)	0.001
LV-ESVi, mL/m^2	1.065 (1.031–1.099)	<0.001
LV-Mi, g/m^2	1.028 (1.008–1.057)	0.152
LVEF, %	0.860 (0.799–0.925)	<0.001
RV-EDVi, mL/m^2	1.009 (0.977–1.041)	0.593
RV-ESVi, mL/m^2	1.054 (1.009–1.101)	0.017
RV-EF, %	0.905 (0.849–0.966)	0.003

BP indicates blood pressure; CI, confidence interval; CM, cardiomyopathy; EDVi, end-diastolic volume index; EF, ejection fraction; eGFR, estimated glomerular filtration rate; ESVi, end-systolic volume index; HF, heart failure; LBBB, left bundle branch block; LGE, late gadolinium enhancement; LV, left ventricular; Mi, mass index; MR, mitral regurgitation; NT-pro-BNP, amino-terminal probrain natiuretic peptide; NYHA, New York Heart Association; OR, odds ratio; RR, reverse remodeling; and RV, right ventricular.

Reactive (interstitial and perivascular) and reparative (replacement) myocardial fibrosis (MF) are 2 hallmarks of IDCM.[21–23] Contrast-enhanced CMR with LGE is an accurate technique for in vivo detection of replacement MF, and previous studies demonstrated that LGE was an independent predictor of heart failure–related deaths and hospitalizations contributing utmost to outcome in patients with IDCM.[24–26] In our study, we showed that patients without LGE were more likely to respond to OMT than patients with LGE, and LV-RR occurred irrespective of the severity of clinical status and the degree of LV dilatation and dysfunction at baseline. In fact, at initial evaluation, patients with LV-RR were more symptomatic and showed higher heart rate and amino-terminal probrain natiuretic peptide levels coupled with larger and more dysfunctional LV than patients without LV-RR. Noteworthy, the severity of LV dysfunction and the absence of LGE were independent predictors of LV-RR, although there was no interaction between the 2 variables. We also showed that the addition of LGE to the model including clinical and CMR functional parameters increased significantly the capacity of predicting LV-RR, underscoring the importance of this marker in the stratification of patients with IDCM. Our findings are in line with those of 2 recent CMR studies that have investigated the capacity of LGE in predicting LV remodeling in patients with recent-onset nonischemic cardiomyopathy. In a study including 44 patients, Kubanek et al[11] demonstrated that a lower extent of LGE at baseline CMR was an independent predictor of LV-RR at 12 months. However, in this study, one third of patients had increased troponin at study entry, and endomyocardial biopsy revealed myocardial inflammation and genomes of cardiotropic viruses in 34% and 66% of patients, respectively, indicating an inflammatory or viral cause of LV dysfunction in a sizeable number of cases. The transient nature of myocardial damage was also suggested by the dynamic behavior of LGE observed in the 30 subjects who repeated CMR at 12-month follow-up: LGE persisted in 13 patients (43%) but disappeared in 7 subjects (23%), whereas 2 patients (7%) who were LGE negative at baseline developed LGE at follow-up. In contrast, in our study, patients with suspected myocarditis were excluded. Also, all patients with baseline LGE showed LGE at follow-up, and no patient without LGE at baseline developed LGE at follow-up. In a cohort of 51 patients with new diagnosis of nonischemic cardiomyopathy, Leong et al[10] reported that the extent of LGE was independently associated with the lack of improvement in LV ejection fraction at 5-month follow-up (interquartile range, 4–7 months). Although Leong et al[10] excluded patients with suspected myocarditis, which differed from our study, tachycardia-induced cardiomyopathy was not considered an exclusion criterion. Importantly, this study evaluated the effect of baseline LGE on the variation of LV ejection fraction without taking into account the modification of LV end-diastolic volume, which is a crucial parameter in the assessment of LV remodeling. Our study expands the previous results by describing the occurrence of LV-RR during a 2-year follow-up in patients with a longer duration of cardiomyopathy in whom an acute or subacute transient myocardial damage was unlikely.

The identification of patients with LV-RR is of great importance for risk stratification and management of patients with IDCM. Several trials have shown the benefits of cardiac resynchronization therapy and implantable cardioverter-defibrillator treatment in selected patients with IDCM, but at a considerable cost and risk of complications.[1–5] Ideally, an effective risk stratification should allow early identification of high-risk patients likely to respond to OMT, in whom device implantation should be at least temporally withheld. Current guidelines recommended ≥3 months on OMT before proceeding to device implantation.[27] Based on our results, device treatment can be postponed beyond this time window in patients presenting with severe LV dilatation and dysfunction but without LGE because they are likely to recover ventricular function on OMT. Conversely, device implantation should be considered earlier in high-risk patients with LGE because they are unlikely to recover ventricular function on OMT. These findings, whether confirmed by larger

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Table 5. Multivariate Analysis for Prediction of LV-RR at Midterm Follow-Up

	Model 1		Model 2	
Variables at Baseline	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Age, y	…	…	…	…
Heart rate, bpm	…	…	…	…
NYHA class >I	…	…	…	…
Absence of LGE	10.857 (1.844–63.911)	0.008	23.743 (2.887–195.298)	0.003
LV-EDVi, mL/m^2	…	…	…	…
LV-ESVI, mL/m^2	1.071 (1.026–1.119)	0.002	N/A	N/A
LV-EF, %	N/A	N/A	0.830 (0.748–0.921)	<0.001
RV-EF, %	…	…	…	…

CI indicates confidence interval; EDVi, end-diastolic volume index; EF, ejection fraction; ESVi, end-systolic volume index; HF, heart failure; LBBB, left bundle branch block; LGE, late gadolinium enhancement; LV, left ventricular; Mi, mass index; NYHA, New York Heart Association; OR, odds ratio; RR, reverse remodeling; and RV, right ventricular.

prospective studies, may influence decisively the decision making of device implantation.

Furthermore, we observed that in patients with LGE there was a significant increase in LGE extent during follow-up, which was associated with a decrease in LV ejection fraction. Notably, 5 patients showed LGE expansion, and among these none experienced LV-RR and 4 had a decrease in LV ejection fraction ≥10 U during follow-up. Although an increase in LGE extent over time has been recently reported in hypertrophic cardiomyopathy,[28] to the best of our knowledge, this is the first study that indicates that LGE is not fixed but is rather a dynamic process in IDCM, and its increase is associated with progressive LV dysfunction. Cumulating evidence suggests that replacement MF, as detected by LGE technique, occurs as a result of progressive myocyte loss via necrotic, apoptotic, or autophagic cell pathway and alteration of extracellular matrix constituents,[29] which are, in turn, influenced by genetic predisposition, myocardial ischemia, increased wall stress, and activation of renin–angiotensin–aldosterone system.[29–31] One may speculate that MF is a marker of disease severity, reflecting the burden of initial damage and ensuing derangements as a result of adverse LV remodeling, explaining the poor response to OMT in patients with LGE. However, recently Thum et al[32] have shown that fibroblasts activation in rodents determined progressive LV dilatation and dysfunction, whereas fibroblast inhibition prevented this phenotype, supporting thereby the concept that MF might be a primary phenomenon in IDCM rather than a stereotyped response to myocardial damage.

Limitations

The study is limited by the small number of enrolled patients. In addition, patients were recruited in a tertiary referral center, and only patients repeating CMR at 24-month follow-up were included in the study, thus leading to a potential selection bias. However, we think that our study reflects real-life practice in which there are no ideal clinical or instrumental parameters capable of predicting LV-RR. Furthermore, we studied patients with a duration of cardiomyopathy <12 months and in whom neurohormonal therapy was optimized after enrollment. Therefore, our results cannot be extrapolated to patients with a longer duration of disease or already

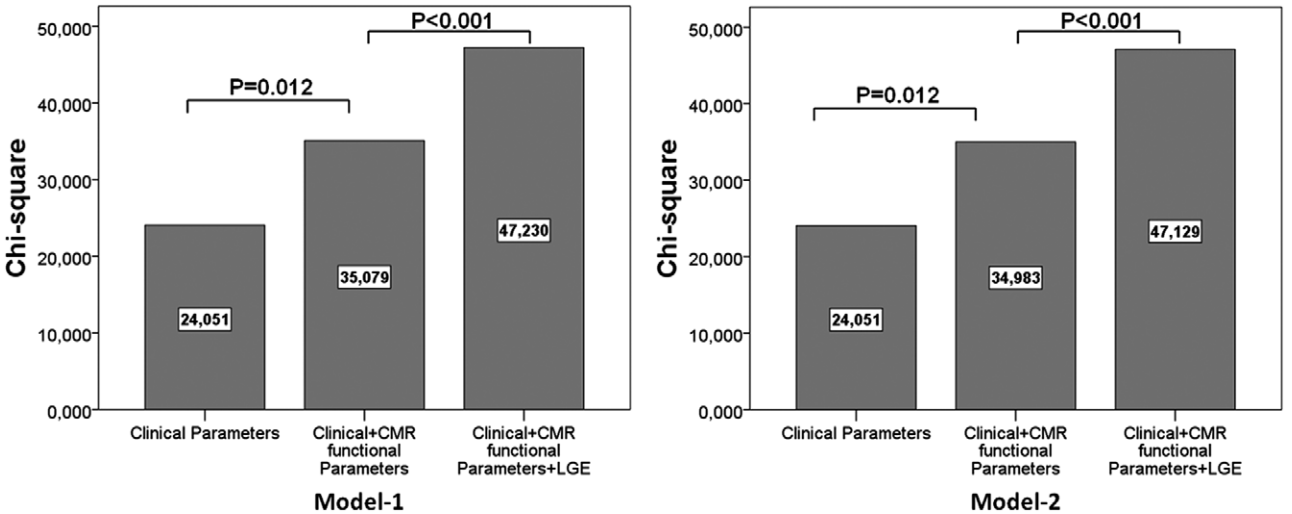

Figure 5. Multivariate analyses showing the incremental value of late gadolinium enhancement (LGE) in predicting left ventricular reverse remodeling compared with models including only clinical parameters or clinical plus cardiovascular magnetic resonance (CMR) functional parameters.

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on OMT. The LGE technique allows only the detection and quantification of replacement (gross) myocardial MF. The quantification of interstitial MF by T1 mapping may be of value in this setting.[33] The current study included a non-negligible number of patients at an initial phase of IDCM showing a mild degree of LV dilatation and systolic dysfunction. Furthermore, only a limited number of patients (n=5) presented a New York Heart Association functional class of III/IV at study entry. Finally, despite the fact that the stepwise procedure was used in the multivariate analysis to determine the independent predictors of LV-RR, overfitting could have occurred because 5 to 10 events should be used per each covariate.[34]

Conclusions

In patients with IDCM, the absence of LGE is independently associated with LV-RR at 2-year follow-up after optimization of medical therapy, irrespective of the initial clinical status and the severity of LV dilatation and dysfunction. Thus, LGE may have key role in the workup and management of IDCM with particular regard to decision making of device implantation. The increase in LGE extent over time was associated with progressive LV dysfunction at follow-up.

Disclosures

None.

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CLINICAL PERSPECTIVE

We investigated the influence of myocardial fibrosis as detected by cardiovascular magnetic resonance using late gadolinium enhancement (LGE) technique on left ventricular (LV) remodeling in 58 consecutive patients with idiopathic dilated cardiomyopathy diagnosed in the preceding 12 months. Patients underwent cardiovascular magnetic resonance at study enrollment and 24-month follow-up after optimization of medical therapy. LV reverse remodeling was defined as an increase in LV ejection fraction ≥10 U, combined with a decrease in LV end-diastolic volume ≥10% at follow-up. We observed that the absence of myocardial LGE at baseline cardiovascular magnetic resonance was a strong and independent predictor of subsequent LV reverse remodeling at 2 years, irrespective of the initial clinical status and the severity of ventricular dilatation and dysfunction. Of note, all patients with baseline LGE demonstrated LGE at follow-up, and no patient without baseline LGE developed LGE at follow-up. However, in patients with baseline LGE, there was a substantial increase in LGE extent over time, which was inversely related to the variation in LV ejection fraction during follow-up. Five patients (9%) showed a marked increase in LGE extent (LGE expansion), and among these none experienced LV reverse remodeling and 4 had a decrease in LV ejection fraction ≥10 U at follow-up. On the basis of our results, LGE may become a useful tool when deciding which patients with idiopathic dilated cardiomyopathy should be implanted with a cardioverter-defibrillator or biventricular pacemaker. We also demonstrate that myocardial fibrosis is not a fixed but rather a dynamic process in idiopathic dilated cardiomyopathy, and its increase is associated with progressive LV dysfunction.

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Supplemental Material

Supplemental Figures

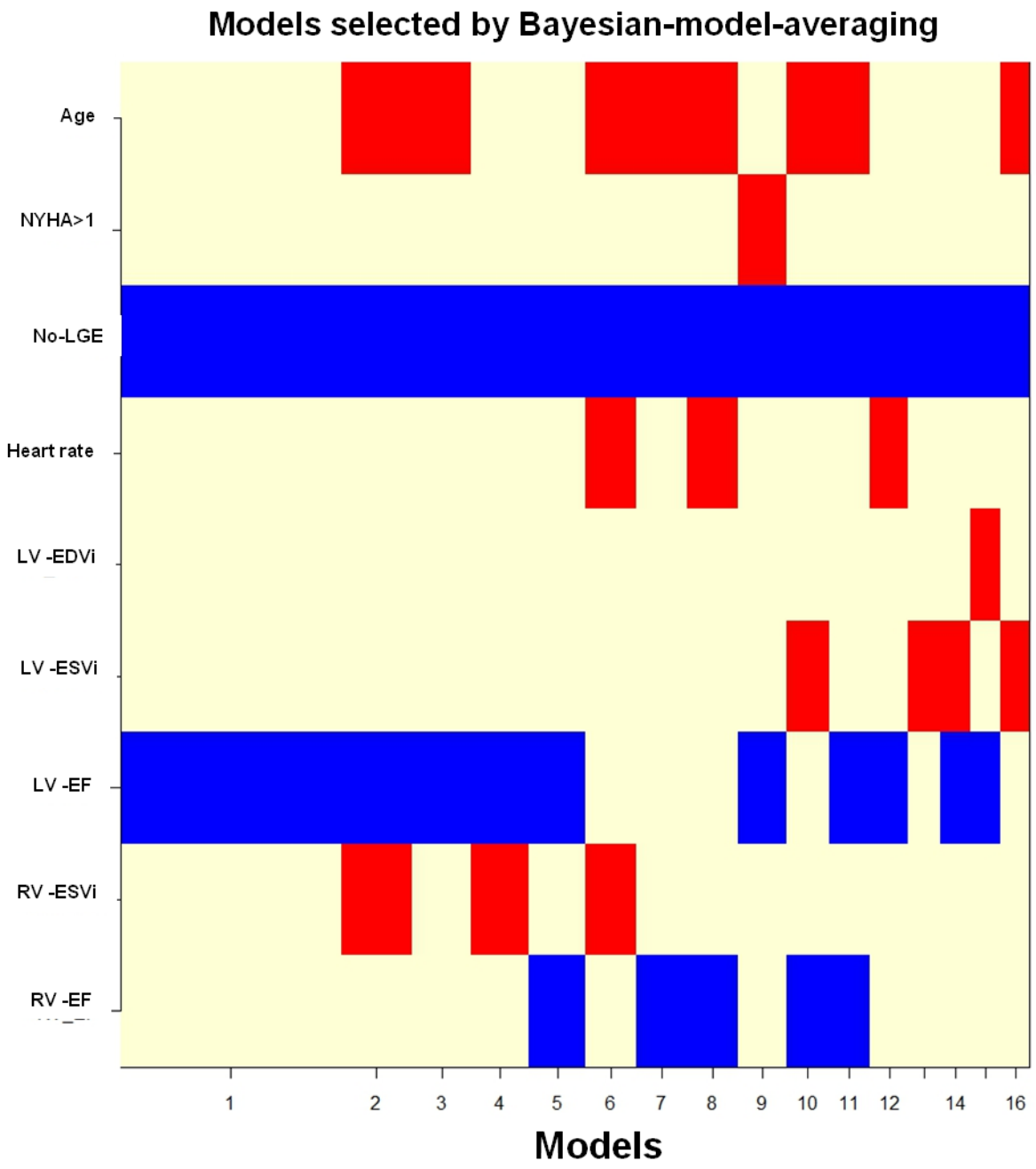

Figure 1. **The Bayesian–model-averaged selected 16 models. The absence of LGE (No-LGE) was statistically significant in each model.**

Video Legends

Video A: Cine balanced-steady state free precession images in horizontal long axis (4-chamber) view of the patient reported in Figure 2 at baseline.

Video B: Cine balanced-steady state free precession images in horizontal long axis (4-chamber) view of the patient reported in Figure 2 at follow-up.

Video C: Cine balanced-steady state free precession images in horizontal long axis (4-chamber) view of the patient reported in Figure 3 at baseline.

Video D: Cine balanced-steady state free precession images in horizontal long axis (4-chamber) view of the patient reported in Figure 3 at follow-up.

Video E: Cine balanced-steady state free precession images in horizontal long axis (4-chamber) view of the patient reported in Figure 4 at baseline.

Video F: Cine balanced-steady state free precession images in horizontal long axis (4-chamber) view of the patient reported in Figure 4 at follow-up.