Differentiation of Heart Failure Related to Dilated Cardiomyopathy and Coronary Artery Disease Using Gadolinium-Enhanced Cardiovascular Magnetic Resonance

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Background—Heart failure treatment depends partly on the underlying cause of the disease. We evaluated cardiovascular magnetic resonance (CMR) for the problem of differentiating dilated cardiomyopathy (DCM) from left ventricular (LV) dysfunction caused by coronary artery disease (CAD).

Methods and Results—Late gadolinium enhancement with CMR was performed in 90 patients with heart failure and LV systolic dysfunction (63 patients with DCM and unobstructed coronary arteries and 27 with significant CAD at angiography). We also studied 15 control subjects with no coronary risk factors and/or unobstructed coronary arteries. None (0%) of the control subjects had myocardial gadolinium enhancement; however, all patients (100%) with LV dysfunction and CAD had enhancement, which was subendocardial or transmural. In patients with DCM, there were 3 findings: no enhancement (59%); myocardial enhancement indistinguishable from the patients with CAD (13%); and patchy or longitudinal striae of midwall enhancement clearly different from the distribution in patients with CAD (28%).

Conclusions—Gadolinium CMR is a powerful technique to distinguish DCM from LV dysfunction related to CAD and yields new insights in DCM. These data suggest that using the coronary angiogram as the arbiter for the presence of LV dysfunction caused by CAD could have lead to an incorrect assignment of DCM cause in 13% of patients, possibly because of coronary recanalization after infarction. The midwall myocardial enhancement in patients with DCM is similar to the fibrosis found at autopsy; it has not previously been visualized in vivo and warrants further investigation. CMR may become a useful alternative to routine coronary angiography in the diagnostic workup of DCM. **(*Circulation*. 2003;108:54-59.)**

Key Words: magnetic resonance imaging ■ cardiomyopathy ■ heart failure

The treatment of patients with left ventricular (LV) systolic dysfunction is determined in part by the identification of the underlying disease process. The primary diagnostic issue centers on differentiating an underlying cause for the LV dysfunction that is related to dilated cardiomyopathy (DCM) or coronary artery disease (CAD). In many centers, coronary angiography is routinely performed for this task. In those patients with unobstructed coronary arteries and no other etiological factor, the diagnosis of DCM is usually made. This differentiation is important clinically for several reasons in patients with CAD: They have a worse prognosis,[1,2] they may benefit from revascularization and/or aneurysmectomy, and secondary preventive pharmacotherapy with statins and aspirin are typically used. Conversely, in patients with DCM, secondary causes such as excess ethanol ingestion or myocardial iron overload[3] need to be excluded, and as genetic studies of DCM begin to identify inherited abnormalities,[4,5] accurate phenotyping and family screening will become more important for early diagnosis.

The value of cardiovascular magnetic resonance (CMR) in the treatment of heart failure is becoming established in initial functional assessment[6,7] and in the determination of secondary causes.[3] In serial follow-up of ventricular function, CMR offers excellent interstudy reproducibility[8] that allows the technique to be used to determine treatment responses.[9] Gadolinium-enhanced CMR can also characterize areas of myocardial infarction,[10,11] and limited results suggest that gadolinium enhancement is absent in nonischemic LV dysfunction.[10] We therefore evaluated whether gadolinium enhancement might be a useful clinical tool in distinguishing LV dysfunction related to DCM or CAD and whether it may also offer new insights in DCM.

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TABLE 1. Baseline Characteristics of Subjects

	DCM	Ischemic LV	Control Subjects
No. of subjects	63	27	15
		1-VD: 7	
		2-VD: 8	
		3-VD: 12	
Age, y*	54±14	67±10	57±10
Gender, M:F, %*	65:35	93:7	47:53
Weight, kg	82±16	81±17	80±11
Height, m	1.74±0.13	1.75±0.12	1.74±0.10
ECG characteristics, n (%)			
AF	10 (16)	4 (14)	†
LBBB	15 (23)	8 (29)	†
Q waves*	5 (8)	11 (41)	†
Poor RWP*	21 (32)	5 (18)	†
Minor T-wave changes	9 (14)	2 (7)	†
No. of risk factors*	0.5±0.9	1.8±0.6	0
Interval angiography to CMR, y	2.2±2.2	3.4±3.5	1.0±0.65

VD indicates vessel disease; AF, atrial fibrillation; LBBB, left bundle-branch block; and RWP, R-wave progression.

*$P<0.05$ between DCM and ischemic LV groups.

†Control subjects had no ECG abnormalities.

Methods

Patient Population

We prospectively acquired 105 gadolinium-enhanced CMR studies in 90 patients with chronic stable heart failure with dilated heart and LV systolic dysfunction and 15 control subjects (normal ventricular function and ECG and no cardiac risk factors). All patients were recruited from a specialist heart failure clinic. The patients with idiopathic DCM were a consecutive series who consented to participate during their routine outpatient appointment from ≈300 potentially suitable patients with this diagnosis. The study patients had a clinical diagnosis of heart failure made on the basis of compatible clinical presentation and history combined with documented systolic LV dysfunction and dilation by echocardiography or radionuclide imaging. All 90 patients had undergone coronary angiography and 63 had unobstructed coronary arteries and no identifiable secondary cause (including no documented infarction by history or the presence of Q waves satisfying standard ECG criteria of infarction[12]) and were being treated with a clinical diagnosis of DCM; 27 subjects had angiographically documented CAD (>50% stenosis in ≥1 coronary arteries) and had a history of myocardial infarction. All 15 control subjects had normal systolic function and a low (<10%) 10-year risk for coronary events[13]; 9 had unobstructed coronary arteries, with angiography having been performed for atypical chest pain. The patient characteristics are detailed in Table 1. Exclusion criteria were the presence of contraindications to CMR, suspected infiltrative heart disease (no evidence of hilar lymphadenopathy or suggestive skin, eye, joint, neurological, or gastrointestinal disorder in the included patients in 1.5 to 11 years of follow-up), hypertrophic cardiomyopathy, previous revascularization, significant valve disease, or a history of myocarditis. All participants gave written informed consent. The project was approved by the institutional ethics committee.

Cardiovascular Magnetic Resonance

A Siemens Sonata 1.5-T scanner was used (Erlangen, Germany). Steady-state, free precession cines were acquired during 8-second breath-holds (TE/TR 1.6/3.2 ms, flip angle 60°) in long-axis planes and sequential 8-mm short-axis slices (2-mm gap between slices) from the atrioventricular ring to the apex. Intravenous gadolinium-DTPA was given (0.1 mmol/kg) and contrast-enhanced images were acquired after 10 to 15 minutes in 6 identical short-axis planes by using an inversion-recovery segmented gradient echo sequence, starting with a basal slice 1 cm below the aortic outflow tract and stopping before the apical slices, which can be affected by partial volume effects.[10] Inversion times were adjusted to null normal myocardium (260 to 400 ms) with voxel sizes of 1.7×1.4×8.0 mm.

Data Analysis

Ventricular function parameters were assessed in a standard way,[14] using in-house software (CMRtools, Imperial College). CMR has excellent reproducibility,[8] and normal ranges are published.[15] Wall motion and gadolinium enhancement were assessed blindly by using 12 segments in each of 6 short-axis slices.[11] Segmental wall motion was visually assessed as 0=normal, 1=moderate hypokinesis, 2=severe hypokinesis, 3=akinesis, and 4=dyskinesis. The average segmental transmural extent of enhancement in each segment was assessed visually by using the following scale: 0=none, 1=1% to 25%, 2=26% to 50%, 3=51% to 75%, and 4=76% to 100% enhancement. The segments scores were summed, yielding a range per patient of 0 (no enhancement in any slice) to 288. Coronary angiography was read blindly by a single cardiologist.

Statistical Analysis

All continuous variables are expressed as mean±SD; comparison between groups were made by means of unpaired *t* tests. ANOVA was used to assess differences between more than 2 groups. χ^2 testing or Fisher's exact test were performed for noncontinuous variables where appropriate. A 2-tailed probability value of <0.05 was considered statistically significant.

Results

The DCM group was younger, with fewer men and fewer risk factors than in the ischemic group (Table 1). Q waves on the ECG were more common in the ischemic group, with poor R-wave progression being the most common ECG finding in the DCM group. The LV parameters were similar between groups, but the ischemic group had a higher New York Heart

TABLE 2. Functional Parameters Determined by CMR

	Normal CMR Range	DCM	Ischemic LV	*P*
LV wall motion score	0	94±64	114±57	0.2
LVEDV, mL	136±30	246±79	261±62	0.4
LVEDVI, mL/m^2	69±11	127±37	140±43	0.2
LVESV, mL	45±14	155±78	177±66	0.2
LVESVI, mL/m^2	23±5	80±37	95±42	0.1
LVEF, %	67±5	39±13	33±11	0.1
LVM, g	178±31	187±57	185±41	0.9
LVMI, g/m^2	91±11	97±25	94±15	0.6
RVEDV, mL	157±35	177±45	148±50	0.01
RVEDVI, mL/m^2	80±13	91±21	77±24	0.01
RVESV, mL	63±20	99±36	79±36	0.02
RVESVI, mL/m^2	32±8	51±19	41±17	0.02
RVEF, %	60±7	45±11	48±10	0.3
NYHA score	NA	1.6±0.8	2.1±0.5	0.005

EDV indicates end-diastolic volume; ESV, end-systolic volume; EF, ejection fraction; I, indexation to body surface area; M, mass; and NYHA, New York Heart Association.

All *P* values compare DCM and ischemic LV groups. Normal CMR ranges from reference is for a mixed-gender population.

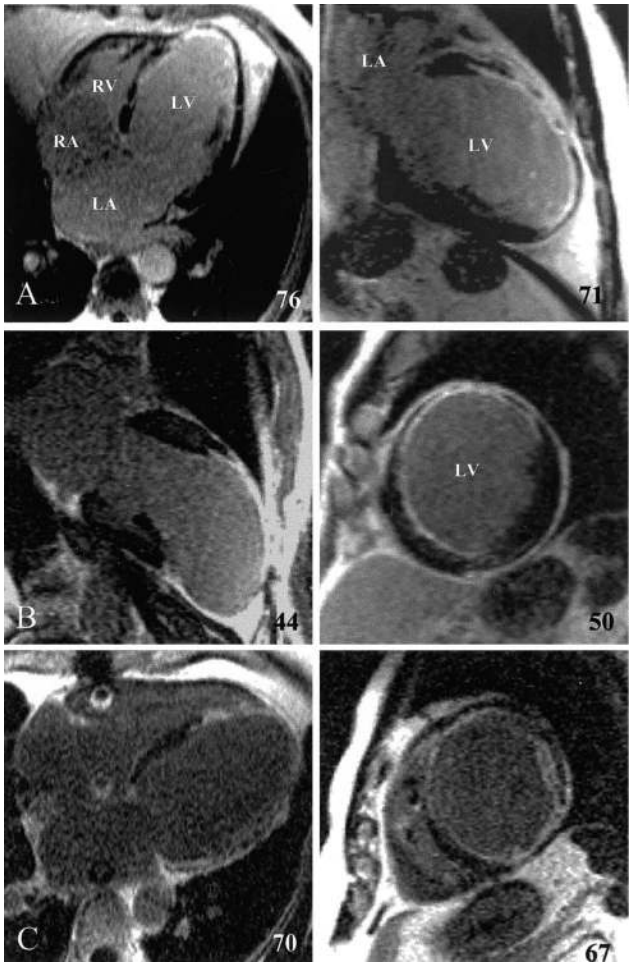

Figure 1. Three patients with heart failure related to CAD with subendocardial and/or transmural infarction. A, Late gadolinium enhancement CMR (HLA and VLA) of single-vessel infarction of the territory of the LAD. B, Two-vessel infarction in the territory of the LAD and RCA (VLA and SA). Thinning is clearly seen where gadolinium enhancement is near transmural, especially in the anterior wall. C, Three-vessel infarction in the LAD, RCA, and LCx territories (HLA and SA). Gadolinium enhancement is bright in the subendocardium and distinct from viable myocardium (black) and blood pool (mid-gray). Note distribution of enhancement occurs in coronary territories. CAD indicates coronary artery disease; LAD, left anterior descending; RCA, right coronary artery; LCx, left circumflex; HLA, horizontal long axis; VLA, vertical long axis; and SA, short axis. Chamber markings for the 3 cardiac axes are LV, left ventricle; RV, right ventricle; LA, left atrium; and RA, right atrium. Numbers quoted are the ventricular diameter halfway from base to apex in the long axis and maximum vertical diameter in the short axis.

Association grade and lower right ventricular (RV) volumes (Table 2). None (0%) of the control subjects had late enhancement. All patients (100%) in the ischemic group had subendocardial or transmural enhancement (Figure 1 and Table 3). The proportion of subjects with enhancement was higher in the ischemic group (100% versus 41%, $P<0.001$), as was the gadolinium score (66 versus 15, $P<0.001$).

In the DCM group, 37 (59%) had no gadolinium enhancement (subgroup 1, Figure 2). In the remaining 26 (41%), however, gadolinium enhancement occurred in 2 distinct patterns: subendocardial enhancement, which was indistinguishable (subendocardial extending toward the epicardium) from the ischemic group (subgroup 2, 13%, Figure 3), or midwall striae or patches of enhancement (subgroup 3, 28%, Figures 4 and 5). In DCM subgroup 2, there was marked wall thinning in the enhanced regions with more pronounced wall motion abnormalities in the enhancing versus the nonenhancing segments (6.3 ± 2.3 mm versus 10.7 ± 1.9 mm, $P<0.0001$). In 50% of these 8 patients, the enhancement was extensive (Figure 3A). The remaining 4 patients had more limited subendocardial infarction and wall thinning (Figure 3B). In all cases, there was no event suggestive of infarction and no Q waves were present, but all had undergone hospitalization for heart failure decompensation of unknown cause.

TABLE 3. Findings of Contrast-Enhanced CMR

	DCM	Ischemic LV	*P*
Enhancement, n (%)	26 (41)	27 (100)	<0.001
Average gadolinium score	15±33	66±46	<0.001
Gadolinium score, % of patients			
0	59	0	
1–50	31	37	
50–100	8	39	
>100	2	24	
Enhancement location, n (%)			
Absent	37/63 (59)	0	
Endocardial	8/26 (13)	27/27 (100)	
Midwall	18/26 (28)	0	

In DCM subgroup 3, the enhancement was in the midwall of the myocardium, clearly distinct from the subendocardium and subepicardium. There were 2 distributions of enhancement: longitudinal striae, following the fiber orientation of

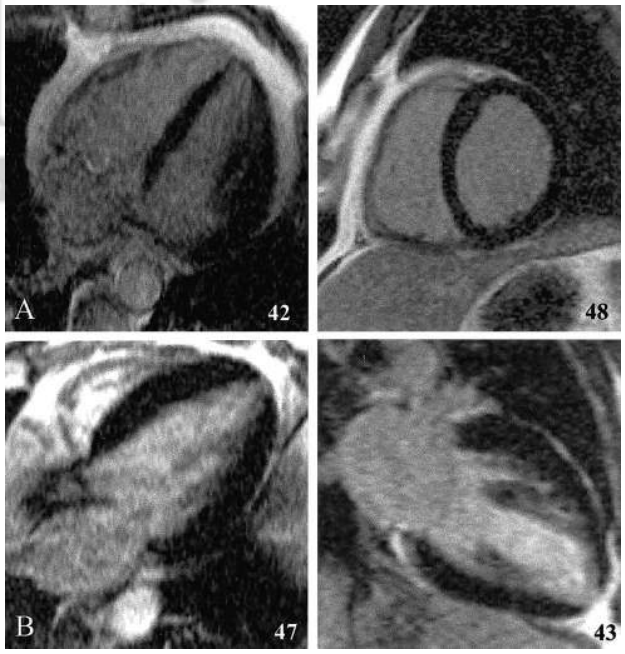

Figure 2. Two patients (A, HLA and SA; B, HLA and VLA) with DCM and no late gadolinium enhancement (subgroup 1) despite dilation and LV systolic dysfunction. Abbreviations and numbers as in Figure 1.

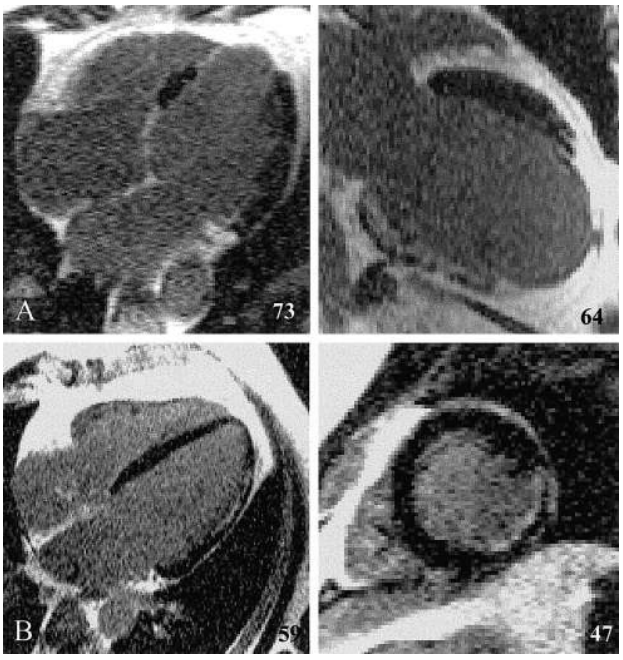

Figure 3. Two patients with DCM and subendocardial or transmural enhancement (subgroup 2; A, HLA and VLA; B, HLA and SA). Pattern of enhancement was indistinguishable from patients with heart failure related to CAD. Degree of enhancement ranged from extensive LV involvement (A, anterior, septal, apical and inferior) to focal enhancement in one region only (B, inferolateral). Abbreviations and numbers as in Figure 1.

the ventricular muscle bundles (Figure 4), and basal to midventricular patchy foci (Figure 5). Finally, 1 patient was diagnosed with arrhythmogenic RV dysplasia.[16]

Discussion

We investigated CMR for differentiating between DCM and CAD as the underlying cause of LV systolic dysfunction in patients with chronic stable heart failure. The differentiation between control subjects and patients with dysfunction caused by CAD was complete (0% versus 100% enhancement). The patients with DCM could be divided into 3 types: subgroup 1 (59%) showed no enhancement; subgroup 2 (13%) had subendocardial or transmural enhancement that was indistinguishable from the ischemic patients; and subgroup 3 (28%) had longitudinal or patchy midwall enhancement not in the territory of a coronary artery and not subendocardial or otherwise similar to the enhancement in the patients with CAD. The findings in DCM subgroups 1 and 3 are consistent with the clinical diagnosis of dilated cardiomyopathy. The most common pattern of no gadolinium enhancement (subgroup 1) clearly distinguishes these patients from those with CAD. The finding of no gadolinium enhancement in 20 patients with DCM has also been reported by Wu et al[10]; however, our report differs in that in a minority we have also found enhancement of the midwall or subendocardium. This may have resulted from our larger sample size of 63. The midwall enhancement seen in DCM subgroup 3 probably reflects the focal segmental fibrosis at autopsy.[17,18] Myocardial fibrosis in DCM can be divided into 3 groups: mild diffuse fibrosis, severe diffuse fibrosis, and segmental

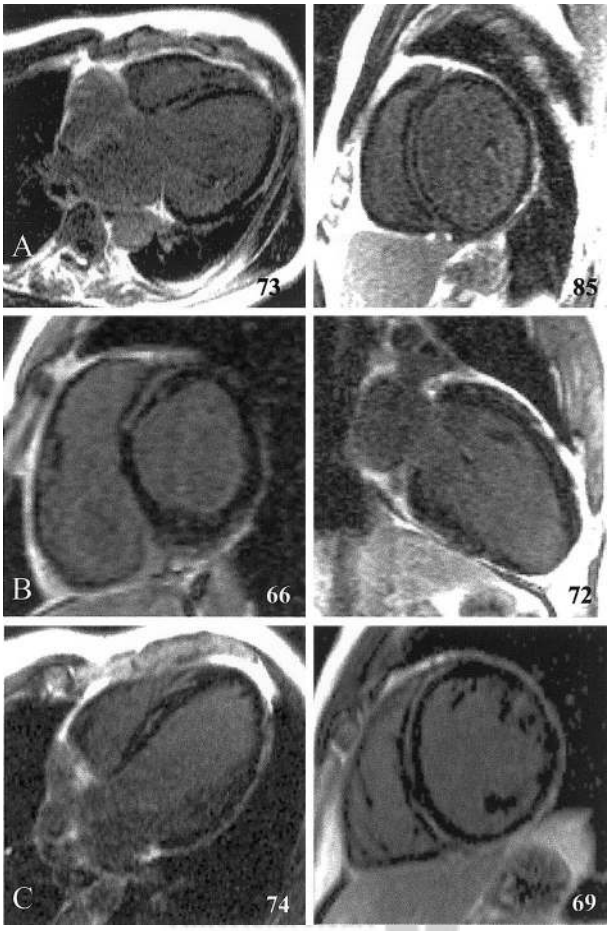

Figure 4. Three patients with DCM with midwall striae of enhancement (subgroup 3). Gadolinium enhancement followed ventricular longitudinal muscle fibers, particularly involving the septum and basal to mid-LV regions. Pattern is clearly different from patients with heart failure related to CAD. Abbreviations and numbers as in Figure 1.

fibrosis. Current CMR techniques are unlikely to detect diffuse microscopic fibrosis and hence most patients with DCM will have absent enhancement. However, our data suggest that CMR does have sufficient resolution to image foci of fibrosis for the first time in vivo. The overall extent of fibrosis in DCM is lower than that seen in CAD,[19] and our results are consistent with this.

DCM subgroup 2 patients have normal luminal appearances by coronary angiography, but the pattern of subendocardial to transmural enhancement strongly suggests the presence of prior infarction. The occurrence of recanalization after an occlusive coronary event or embolization from minimally stenotic but unstable plaque is well documented.[20,21] Autopsy studies in DCM have also described patients with endocardial and transmural fibrosis indistinguishable from myocardial infarction,[22] which have been grouped as DCM variants or excluded as myocardial infarction.[22] Half of the subgroup 2 patients had extensive gadolinium enhancement, and all had significant risk factors for CAD. This would be most consistent with the assertion that the correct clinical diagnosis should be LV dysfunction related to CAD. The more limited endocardial enhancement in the remaining

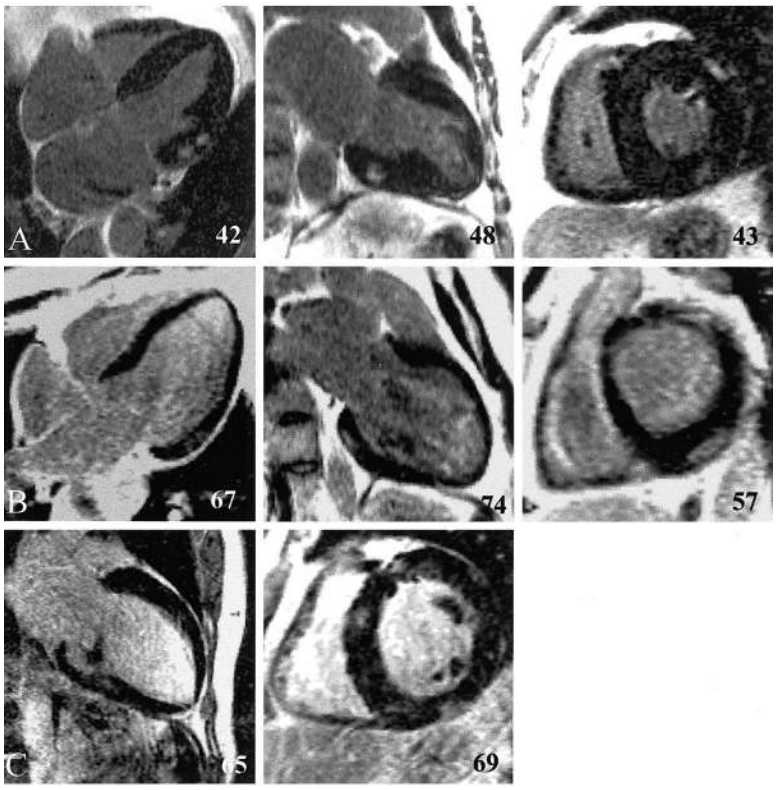

Figure 5. DCM with patchy foci of midwall enhancement in 3 patients (subgroup 3). Patchy gadolinium enhancement involved basal to mid-LV regions. Abbreviations and numbers as in Figure 1.

subjects suggests infarction of lesser degree. However, LV remodeling occurs with nonextensive infarctions,[23] especially in the absence of suitable modern therapy,[24] and it is noteworthy that none of these patients had a history of acute infarction, having presented directly with heart failure as their first cardiovascular symptom. This is consistent with untreated LV remodeling after ischemic damage as the cause, although the coexistence of LV dysfunction from DCM combined with CAD cannot be excluded. There was no clinical evidence for other potential pathologies such as viral myocarditis[25] or sarcoidosis.[26]

These data suggest therefore that the clinical diagnosis in 13% of our DCM population was either partly or wholly incorrect, which has important therapeutic implications. In addition, as genotyping of DCM matures,[4,5] accurate phenotyping is important to prevent the unnecessary adverse psychological effects of investigating relatives. Accurate phenotyping also improves the power of gene studies, allowing smaller sample sizes in the investigation of genotypes and gene environment interactions.[27,28]

Clinical Implications

Noninvasive tests are not reliable in distinguishing dysfunction related to DCM or CAD because segmental wall motion abnormalities are common in DCM,[29] and scintigraphic perfusion techniques are complicated by attenuation artifacts and denervation in large DCM hearts, leading to false-positive results.[30] Our data show that the coronary disease risk score and RV volumes are different between the DCM and ischemic groups, but substantial overlap occurs. Thus, coronary angiography is usually performed in all cases so that LV dysfunction will not be missed. However, coronary angiography is flawed in identifying the myocardial substrate for heart failure because significant CAD may exist without infarction, and "normal" coronaries may exist in the presence of myocardial damage. This was graphically illustrated in the Assessment of Treatment with Lisinopril And Survival (ATLAS) study, which identified the incorrect assignment at autopsy of an ischemic/nonischemic cause in 17% of patients with an established clinical label of LV dysfunction caused by CAD and 28% of patients with an established clinical label of DCM.[31] It is also implicit in reports attempting to deal with the contingent relation of coronary artery appearance and myocardial damage, which classify patients with heart failure as nonischemic who have single-vessel disease without prior history of infarction or revascularization.[32] Our study suggests that CMR distinguishes LV dysfunction related to DCM or CAD on the basis of identifying gadolinium enhancement and patterns within the myocardium, which is the target tissue in question. This also suggests the potential to reduce the costs and inherent risks associated with invasive cardiac catheterization on which the diagnosis of DCM has until now depended. Although the newer noninvasive techniques of coronary angiography by magnetic resonance and computed tomography are likely to be cheaper and lower risk, the same limitations would apply.

Limitations

We used a dose of gadolinium of 0.1 mmol/kg, but higher doses up to 0.2 mmol/kg have been used for late gadolinium enhancement.[10,11] An optimal dose has not been defined, although doses in the range of 0.1 to 0.2 mmol/kg are suitable, but higher dosing is more expensive and usually requires a longer delay after injection before imaging to allow

blood pool signal to fall. A confounding possibility of the use of late gadolinium enhancement to identify DCM would be balanced severe ostial stenoses of left and right coronary arteries in the absence of any infarction potentially leading to a clinical picture of DCM with global dysfunction on the basis of pan–myocardial hibernation. This is very rare, and it is likely that such a patient would have severe unresponsive symptoms. Further studies will clarify this issue. Other conditions cause gadolinium uptake in the myocardium, and this must be considered in interpretation of results in patients with DCM.[33,34]

Conclusions

Our data suggest that gadolinium CMR can exclude the presence of LV dysfunction related to CAD in heart failure. Furthermore, CMR can identify 2 substantial subgroups of patients with DCM who have either midwall fibrosis or who have an infarction pattern of enhancement and require further evaluation for CAD. Further studies are needed to establish the relation of these new findings to prognosis in heart failure and to confirm whether gadolinium CMR could be used to avoid invasive coronary angiography in patients with DCM.

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