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# Right ventricular dysfunction, late gadolinium enhancement, and female gender predict poor outcome in patients with dilated cardiomyopathy

Christina Doesch [a,c,*], Désirée-Marie Dierks [a], Dariusch Haghi [a,c], Rainer Schimpf [a,c], Jürgen Kuschyk [a,c], Tim Suselbeck [a,c], Stefan O. Schoenberg [b,c], Martin Borggrefe [a,c], Theano Papavassiliu [a,c]

[a] 1st Department of Medicine, Cardiology, University Medical Centre Mannheim, Medical Faculty Mannheim, University of Heidelberg, Germany
[b] Institute of Clinical Radiology and Nuclear Medicine, University Medical Center Mannheim, Medical Faculty Mannheim, University of Heidelberg, Germany
[c] DZHK (German Centre for Cardiovascular Research) partner site, Mannheim, Germany

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ABSTRACT

*Aims:* Dilated cardiomyopathy (DCM) shows a variable disease course and is associated with significant morbidity and mortality. So far, left ventricular function (LVF) is the major determinant for risk stratification. However, since it has shown to be a poor guide to individual outcome, we studied the prognostic value of cardiovascular magnetic resonance imaging (CMR) parameters, late gadolinium enhancement (LGE) and epicardial adipose tissue (EAT).

*Methods and results:* 140 patients with DCM underwent late gadolinium enhancement (LGE) CMR. During a median follow-up of 3 years, 22 patients (16%) died and another 51 (36%) were hospitalized due to congestive heart failure (CHF). Female gender and right ventricular ejection fraction (RV-EF) below the median of 38% were independent predictors of all-cause mortality in multivariable analysis. In patients who were hospitalized due to CHF, RV-EF below the median of 38% was the only independent predictor in multivariable analysis. When patients where further stratified according to systolic LV-EF, the prognostic value of RV-EF to predict mortality and cardiac morbidity remained unchanged. Looking at DCM patients who died during follow-up compared to those who were hospitalized due to CHF, the former presented with a higher prevalence of LGE as well as reduced indexed EAT.

*Conclusion:* Female gender, RV-EF and the presence of LGE are of prognostic importance in patients with DCM. Therefore, the present study underlines the role of CMR as an important tool for risk stratification in patients with DCM.



## 1. Introduction

Dilated cardiomyopathy (DCM) shows a variable disease course and is associated with significant morbidity and mortality [1–3]. So far, left ventricular ejection fraction (LV-EF) is the major determinant for risk stratification and the current guidelines recommend implantation of a defibrillator for primary prevention in symptomatic patients (New York Heart Association functional class II/III) with a LV-EF less than 35% [4,5]. However, LV-EF alone has shown to be a poor guide to outcome.

Cardiovascular magnetic resonance imaging (CMR) is the gold standard for non-invasive, accurate, and reproducible assessment of left and right ventricular function, cardiac mass and morphology [6]. Due to the use of late gadolinium enhancement (LGE) technique, CMR allows in vivo quantification of regions of replacement fibrosis in patients with DCM that has shown a good correlation with histological data [7]. In prior studies [7–10], the presence of LGE in patients with DCM was also associated with an unfavorable prognosis. Additionally, CMR allows the quantification of epicardial adipose tissue (EAT) that has been shown to be reduced in patients with DCM [11–13] and became also suspect to be associated with a poor prognosis [13].

Since one single parameter does not seem to be sufficient to predict the clinical outcome of patients with NICM, we studied the prognostic value of CMR parameters, LGE and EAT.

## 2. Methods

### 2.1. Study population

Between February 2003 and February 2011, 150 consecutive patients with DCM that underwent late gadolinium enhancement CMR to quantify left ventricular (LV) function and myocardial scarring as part of their routine clinical work-up were enrolled at our tertiary referral hospital.

* Corresponding author at: 1st Department of Medicine, Cardiology affiliated at the DZHK (German Centre for Cardiovascular Resarch) partner site Mannheim, University Medical Center Mannheim, Medical Faculty Mannheim, University of Heidelberg, Theodor-Kutzer-Ufer 1-3, 68167 Mannheim, Germany. Tel.: +49 621 383 2204; fax: +49 621 383 3821.
*E-mail address:* Christina.Doesch@umm.de (C. Doesch).

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The diagnosis of DCM was based on the 1995 WHO/International Society and Federation of Cardiology criteria [14]. All patients had undergone coronary angiography and were classified as non-ischemic if they had no history of myocardial infarction or revascularization and no evidence of coronary artery stenoses >50% of 2 or more epicardial vessels or left main or proximal anterior descending coronary artery >50% [15]. Patients with a normal CMR-derived left ventricular ejection fraction (LV-EF > 55%) were not included in the study. Other exclusion criteria were standard contraindications to CMR examination.

CMR examination was not possible in 5 (3.3%) patients due to claustrophobia and in 3 (2.0%) patients due to severe obesity. 2 (1.3%) patients were lost during follow-up so that the final study population consisted of 140 patients. Of these 140 patients, 19 patients were included in an earlier study [13] and are now reported with an extended follow-up.

The study was approved by the local ethics committee and informed consent was obtained from all patients.

### 2.2. Image acquisition

All studies were performed using 1.5 Tesla whole-body imaging systems (Magnetom Sonata and Avanto, Siemens Healthcare Sector, Erlangen, Germany). To evaluate functional parameters, electrocardiogram-gated cine images were acquired using a segmented steady-state free precession [fast imaging with steady-state precession (true-FISP)] sequence (time to echo/time of repetition 1.6/3.2 ms, temporal resolution 35 ms, in-plane spatial resolution 1.4 × 1.8 mm, slice thickness 8 mm, interslice gap 2 mm). For the assessment of the epicardial adipose tissue, we used a dark blood prepared T1-weighted multislice turbo spin-echo pulse sequence with a water suppression prepulse (time of repetition = 800 ms, time to echo = 24 ms, slice thickness = 6 mm, interslice gap = 2 mm, and field of view = 30 to 34 cm) in the same orientations as the short-axis images.

### 2.3. LGE

Ten minutes after contrast agent injection (BW gadoterate meglumine, Dotarem, Guerbet, France), late gadolinium enhancement (LGE) images were acquired. An inversion time (TI) scout was performed to choose the optimal TIs between 200 and 360 ms. LGE images were assessed using either an inversion recovery Turbo FLASH 2D sequence: field of view 300–340 mm, TR 9.56 ms, TE 4.38 ms, flip angle 25°; matrix 166 × 256 and slice thickness 6 mm or a phase-sensitive inversion recovery TrueFISP sequence [16]: field of view 290 mm × 260 mm, TR 2.2 ms, TE 1.1 ms, flip angle 50°; matrix, 140 × 192 and slice thickness 6 mm, in-plane resolution 1.4 × 1.9 × 6 mm. LGE was only considered to be present if it was also present in the same slice after swapping phase encoding, thus excluding artifacts.

### 2.4. Image analysis

Image analysis and quantitative analysis were performed off-line using dedicated software (ARGUS, Siemens, Germany). The readers were blinded to patient data and outcome. On the four-chamber view, the tricuspid annular plane systolic excursion (TAPSE) was calculated as previously described [17]. The amount of EAT was determined according to the method described by Fluechter S et al. [18].

### 2.5. Extent of LGE

The extent of LGE was assessed visually by two independent experienced readers. LGE was only considered to be present if it was also present in the same slice after swapping phase encoding, thus excluding artifacts. The pattern of LGE was characterized as midwall, patchy foci, epicardial, or diffuse [9,10]. For quantification of fibrosis, LGE was defined as areas with a signal intensity > 2 standard deviation (SD) above mean signal intensity of remote myocardium in the same short-axis slice [8]. Areas were measured by planimetry and expressed as percentage of the myocardial area using the VPT tool (Siemens Healthcare Systems Erlangen, Germany).

### 2.6. Follow-up data and definition of study endpoints

The long-term follow-up was performed by patient interview at our outpatient clinic and by telephone contact. The observers were unaware of the CMR results and collected data with a standardized questionnaire. Reported clinical events were confirmed by review of the corresponding medical records in our electronic Hospital Information System, contact with the general practitioner, referring cardiologist, or the treating hospital. The definition of cardiac event required the documentation of significant ventricular arrhythmia or cardiac arrest or death attributable to congestive heart failure or myocardial infarction in the absence of any other precipitating factor. In case of out-of-hospital death not followed by autopsy, sudden unexpected death was classified as cardiac death. The primary study endpoint was a combined endpoint of all-cause mortality including non cardiac and cardiac death as well as heart transplantation (HTX). The secondary endpoint was hospitalization due to worsening of CHF. Patients who were hospitalized and died over the course of follow-up were only counted regarding the primary endpoint and not the secondary endpoint.

### 2.7. Statistical analysis

Since we aimed to study to what extent CMR results, age and gender were associated with events, Cox proportional hazard regression models were constructed for age, gender and CMR parameters. To check the proportional hazard assumption for different categories, they were plotted against time to ensure that the curves were reasonably parallel. Those variables which appeared to be associated with events at a value of $p \leq 0.1$ level in univariable analysis were eligible for multivariable analysis to predict hospitalization for CHF. Forward stepwise logrank regression ($p < 0.2$ for entry, $p > 0.1$ for removal) was used. Due to the limited number of all-cause mortality events, the number of candidate parameters for multivariable analysis was limited to two (the clinical and CMR parameter with the best performance in univariable analysis) to avoid model overfitting. Results are presented as hazard ratios with 95% confidence intervals (CIs). The follow-up duration was measured from the CMR study date.

The performance of the final models was assessed with respect to discrimination. Discrimination is the model's ability to separate patients with different outcomes. To quantify the discrimination, we used the c-statistic (Harrell's C) [19]. The maximum value of the c-statistic is 1.0; indicating a perfect prediction model. A value of 0.5 indicates that patients are correctly classified in 50% of the cases, e.g. as good as chance. The performance of a prediction model is generally worse in new patients than initially expected. This "optimism" can be studied with internal validation techniques [20]. Internal validity of our models was assessed with standard bootstrapping techniques [20]. The c-statistic of the final multivariable model, corrected for optimism, was reported.

Kaplan–Meier analysis was performed for the independent predictors of all-cause-mortality. For this analysis the study population was divided into two groups according to the median value of the entire study population. Difference in survival over time was evaluated by a log-rank test.

Analysis was performed using SPSS statistical software (version 14.0, SPSS Inc., Chicago, Illinois), Stata version 11 (StataCorp), and R software (version 2.8.1, R foundation for statistical computing, Vienna, Austria).

## 3. Results

140 patients with DCM (77% men, mean age 59.2 ± 13.9) were included in the study. The baseline clinical characteristics are presented in Table 1. Most patients presented with symptomatic heart failure (NYHA > I). Median follow-up was 3 years (interquartile range 0.5–5.0 years).

### 3.1. Outcome

During the follow-up, 22 (16%) patients died. Thereof 15 (11%) patients suffered cardiac death, 1 (0.7%) patient underwent HTX and non cardiac death was reported in 6 (4%) patients. 51 (36%) were hospitalized due to congestive heart failure (CHF). 67 (48%) showed an event-free survival.

**Table 1**
Baseline demographic and clinical characteristics.

| | All DCM patients $n = 140$ |
|---|---|
| Male *n* (%) | 108 (77.1) |
| Age (yrs) | 59.3 ± 13.8 |
| NYHA functional class | |
| • I | 7 (5.0) |
| • II | 26 (18.6) |
| • II | 64 (45.7) |
| • IV | 43 (30.7) |
| Atrial fibrillation *n* (%) | 54 (38.6) |
| Family history of DCM *n* (%) | 8 (5.7) |
| Hypertension *n* (%) | 46 (32.9) |
| Smoking *n* (%) | 20 (14.3) |
| Hyperlipidemia *n* (%) | 41 (29.3) |
| Diabetes *n* (%) | 31 (22.1) |
| Medication *n* (%) | |
| • Beta-blocker | 118 (84.3) |
| • ACEI | 113 (80.7) |
| • ARB | 21 (15.0) |
| • Spironolactone | 34 (24.3) |
| • Diuretics | 100 (71.4) |
| • Digoxin | 38 (27.1) |
| • Amiodarone | 12 (8.6) |

Abbreviations: ACEI: angiotensin-converting-enzyme inhibitor, ARB: angiotensin II receptor blockers, CHF: congestive heart failure, *n*: number, DCM: dilated cardiomyopathy, NYHA: New York Heart association functional class, yrs: years