Prognostic Significance of Electrocardiogram and Cine Magnetic Resonance Imaging Parameters in Patients with Idopathic Dilated Cardiomyopathy

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Abstract

Patients with idopathic dilated cardimyopathy (IDC) and reduced left ventricular function have a limited prognosis. Aim of this study was the evaluation of parameters of cardiac magnetic resonance imaging (CMRI) and ECG for prognosis.

149 patients with IDC were studied by CMRI for hemodynamic and late enhancement (LE) analysis and followed for a mean of 986 ± 588 days. QRS and QTc intervals were measured. In total we recorded 16 parameters including NYHA status, age and diabetes mellitus. Combined endpoint was cardiac death, sudden death (SCD) or rehospitalization for pump failure.

We used a bootstrap approach over the cases combined with a stepwise parameter selection method to find the most relevant variables in a Cox proportional hazard model. We found that 3 parameters, namely QRS duration > 110ms, left ventricular enddiastolic volume index, and left ventricular cardiac index were most predictive.

1. Introduction

The natural history of patients with idiopathic dilated cardiomyopathy (IDC) is variable. Some patients may have minimal or no symptoms and the progression of the disease is unclear. On the other hand symptomatic patients seem to experience progressive deterioration, and 10 to 50 percent with heart failure may succumb within one year [1]. The annual mortality rate for a typical patient with heart failure has been estimated to be 10 to 13 percent [2]. Clinical predictors such as advanced age, protodiastolic gallop, failure of the myopathic ventricle to respond to inotropic stimulation and ventricular arrhythmias have been identified as risk factors of dying from IDC [3]. However, the predictive value of any single parameter is not strong enough to assess the clinical course and outcome in an individual patient with reasonable accuracy.

Cardiac magnetic resonance imaging (CMRI) is a powerful tool to assess morphology and myocardial function as well as changes in tissue structure. Myocardial damage, viability and scarring has been frequently studied in patients with coronary artery disease (CAD) post myocardial infarction using pathological late uptake of extracellular MR contrast media by the ventricular myocardium, i.e. the detection of delayed contrast enhancement (LE) [4-7]. The aim of this study was to assess the prognostic value of parameters, that are most precisely determined by MRI (e.g. RV dysfunction, LE, etc) and those that are regularly determined, such as QRS duration, NYHA status, diabetes mellitus.

2. Methods

Patients

One hundred forty nine consecutive patients with idiopathic dilated cardiomyopathy (IDC) according to the definitions of the Word Health Organization [8], 35 females and 114 males, aged 54.7 ± 13.4 (17 - 75) years were enrolled and prospectively followed for a mean of 986 ± 588 (17 – 2311) days. Patient characteristics are summarized in Table 1. Diagnosis was established by clinical examination, echocardiography and by normal coronary angiograms. MRI was performed for additional evaluation of right and left ventricular function, LE and myocardial edema. All patients had chronic heart failure of at least 12 months duration and had presented with typical onset and clinical signs of heart failure. None of the patients had clinical symptoms or signs of ongoing myocarditis. Any patients with clinical evidence of left ventricular damage caused by CAD were excluded. Patients with atrial fibrillation 54 (36%) or flutter 2 (1%) were not excluded from the study in order to enroll an unselected patient population with IDC. In this study all obese patients with IDC planned for MRI could be investigated and no patient was excluded because of claustrophobia. The study was approved by the local

Ethics Committee and all patients gave their written informed consent.

Table1. Patient characteristics

Number	149
Male, No. / Female No.	35 / 114
Age, y	54.7 ± 13.4
Cardiovascular risk factors:	
Diabetes mellitus, No.	26 (17%)
Arterial hypertension, No.	59 (40%)
Hypercholesterolemia, No.	57 (38%)
Smoking, No.	41 (28%)
Familial disposition, No.	22 (15%)
ICD (intra cardiac defibrilator)	35 (23%)
BMI, kg/m^2	26.8 ± 4.8
NYHA class I, No.	19 (13%)
NYHA class II, No.	19 (13%)
NYHA class III, No.	66 (44%)
NYHA class IV, No.	45 (30%)
ACE inhibitor, No.	131 (88%)
Drug therapy	
Betablocker, No.	135 (91%)
Spironolactone, No.	114 (77%)
Diuretic, No.	135 (91%)
QRS duration, ms	140.7 ± 40.3
QTc, ms	422.4 ± 65.6
Late enhancement, No.	40 (27%)
Total number of events	69 (46%)
Cardiac death	17 (11%)
Sudden cardiac death	10 (7%)
Rehospitalization for pump failure	43 (29%)

MRI protocol and data analysis

MRI was performed on a 1.5T whole body scanner (Intera CV, Philips Medical Systems, Best, The Netherlands). To define the position and axis of the left ventricle, three survey scans were performed along right-left (RL), anterior-posterior (AP) and foot-head (FH) orientation. Resting left (LV) and right ventricular (RV) function was determined with cine images applying a multiple breath hold segmented k-space balanced FFE sequence (steady-state-free-precession = SSFP) in short and long axis views aligned with the true heart axis. Parallel imaging was employed for all scans to minimize acquisition time. Depending on the field of view (FOV) in-plane resolution was between 1.5x1.8mm to 2.3x1.8mm with a slice thickness of 10mm for the functional scans. The short axis scans covered the whole LV and RV with 10-14 contiguous slices with a temporal resolution of 34 cardiac phases. 10-15 minutes after infusion of 0.2 mmol/kg body weight gadolinium-diethylenetriaminepentaacetate (Gd-DTPA, Magnevist, Schering, Germany) a late enhancement (LE) analysis using a 3D spoiled turbo Gradient Echo sequence (Turbo-FLASH) with a selective 180° inversion recovery prepulse was acquired in the short axis covering the whole left ventricle (20-22 5mm-slices). Two to three additional long axis views with a similar 2D-sequence were additionally performed. The pre-pulse delay (range 200 to 250 ms) was adjusted individually using a Look-Locker sequence [9]. The LE was assessed visually and was defined as a region with signal intensity >2 SD the mean intensity of remote myocardium in the same slice. MRI protocols used were identical during the whole series of patient investigations, and image quality was good to excellent in all patients studied.

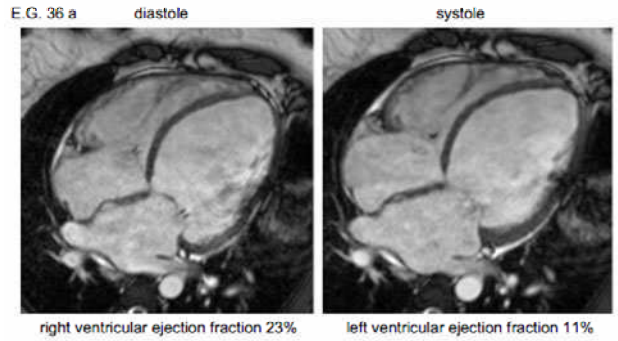

Figure 1. MRI of a patient with severe IDC and poor left and right ventricular function. This young female patient died from cardiac death (pump failure) after a follow-up of 59 months.

Wall motion abnormalities were visually classified as hypo-, dys- or akinesia and documented on the usual 17-segment model [10]. LV and RV volumes and functional parameters (LV-EF, RV-EF, cardiac index = CI) were analyzed off-line on a ViewForumTM Workstation (Philips, Best, The Netherlands) using short axis volumetry. Papillary muscles were assigned to the myocardium.

QRS and QTc interval measurement

At patient's time of entry into the study a 12 lead electrocardiogram (ECG) was recorded at a paper speed of 50mm/s on a digital ECG recorder (GE Medical Systems, Information Technologies, Freiburg, Germany) and the relevant intervals were automatically analyzed (CardioSoft Version 4.2). Heart rate correction was done by the Bazett formula, prolonged QRS was defined as QRS width >110ms, and prolonged QTc as a QTc interval >440ms.

Follow-up and endpoints

Patients were followed by a questionnaire or telephone call to either patients or physicians for NYHA functional status, actual medication, new cardiac events, worsening of disease state, and one of the endpoints. The combined endpoint was defined as cardiac death from pump failure, sudden cardiac death from lethal ventricular tachyarrhythmias (ventricular flutter or fibrillation) or rehospitalization for decompensated heart failure. In case of multiple events occurring during follow-up the first event was used as endpoint for statistical evaluation.

Resampling procedure and Cox model

Stepwise parameter selection methods are often used for finding the most important variables in regression models, such as Cox proportional hazards regression [11]. This model forces the hazard ratio between two individuals to be constant over time and can be written as

$$h(t) = h_0(t)\ \exp(\beta_1 x_1 + \mathsf{K} + \beta_q x_q),$$

with $h_0(t)$ being the baseline hazard function, i.e. the hazard function for individuals with all explanatory variables equal to zero. The hazard function $h(t)$ characterizes the probability of an event among those not having experienced the event in a small time interval, s and T being the survival time of the individual:

$$h(t) = \lim_{s \to 0} P(t \le T \le t + s \mid T \ge t) \cdot$$

In this model the relative risk $\exp(\beta^T \mathbf{x})$, gives the level of each individual's hazard. Unfortunately this method is instable in their selected parameters as they do not take variations in the data used for model building into account and the selection of the variables that influence the outcome is difficult. We have therefore used a bootstrap approach, see Figure 2, over the cases, that has a nested sequential backward selection procedure (Akaike information criterion) to determine the most relevant features in each resampling step, i.e. only the most frequent variables from all runs are used and collinearity is accounted for [12]. The basic algorithm is:

```
Loop over
     1. Generate a bootstrap sample from
        the cases
     2. Perform a stepwise model selection
     3. Store best model
Select variables most frequent in best
models
```

A detailed version is given in Figure 2. All simulations including algorithm implementation were performed in the statistical framework R (www.r-project.org).

Algorithm 1 CoxBoot

INPUT: DATA = matrix of cases vs. covariates,
k = number of bootstrap samples,
r1 = minimum covariate inclusion frequency,
r2 = minimum paired covariate inclusion frequency

Get k sample sets by k-times bootstrap resampling cases from DATA
FOR (all sample sets) **DO**
  Fit a Cox proportional hazards regression model
  Compute Akaike's AIC
  Perform stepwise model selection
  Add resulting model to list of best models L
END FOR
FOR all covariates C in DATA **DO**
  Compute $cf(C)$ = covariate frequency of occurance in L
  IF $cf(C) < r1$ **THEN**
    Add C to list of rejected covariates R
  END IF
END FOR
FOR all pairs of covariates (C_i, C_j) in R **DO**
  Compute $pf(C_i, C_j)$ = pairwise frequency of occurance in L
  IF $pf(C_i, C_j) > r2$ **THEN**
    Remove C_k with $k = argmax(cf(C_i), cf(C_j))$ from R
  END IF
END FOR
Return output model O = full model without covariates still in list of rejected covariates R

Figure 2. Algorithm for determining the most relevant variables in the Cox proportional hazard model, following the method of Sauerbrei & Schumacher [12].

3. Results

For the simulations described here we used 1000 bootstrap samples (k= 1000) and values of, r_1=0.7, r_2=0.9 for the algorithm depicted in Figure 2.

Table 2. Hazard ratio (95% confidence intervals) in univariate and multivariate analysis (resampling procedure) for predictors of the combined endpoint. The frequency of the predictors within the 1000 bootstrap samples after stepwise model selection is given by freq.

	Univariate Analysis		Resampling Procedure		
Variable	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**	**freq**
Age	1.02 (0.99-1.04)	0.13	-	-	0.513
BMI	1.00 (0.95-1.06)	0.90			0.260
NYHA class	1.19 (0.91-1.54)	0.21	-	-	0.298
Diabetes mellitus	1.94 (1.12-3.38)	0.019	-	-	0.498
CRVF_aHT	0.99 (0.59-1.66)	0.99			0.343
CRVF_HLP	1.17 (0.70-1.96)	0.54			0.285
QRS > 110	3.16 (1.55-6.42)	0.0015	2.75 (1.30-5.82)	0.0080	0.839
QTc > 440	1.59 (0.95-2.65)	0.074			0.631
LVEDVI	1.01 (1.0–1.01)	0.0011	1.01 (1.002-1.013)	0.0053	0.833
RVEDVI	1.01 (0.99–1.01)	0.21			0.306
LV Cardiac Index	0.68 (0.43–1.07)	0.096	0.60 (0.42-0.85)	0.0050	0.894
Edema	0.92 (0.487-1.75)	0.80			0.259
Asynchrony	1.00 (1.00-1.01)	0.071			0.416
LVEF < 30%	0.46 (0.26–0.80)	0.0066			0.280
RVEF < 30%	0.64 (0.34–1.19)	0.16			0.360
Late Enhancement (presence)	1.04 (0.95–1.13)	0.36			0.296

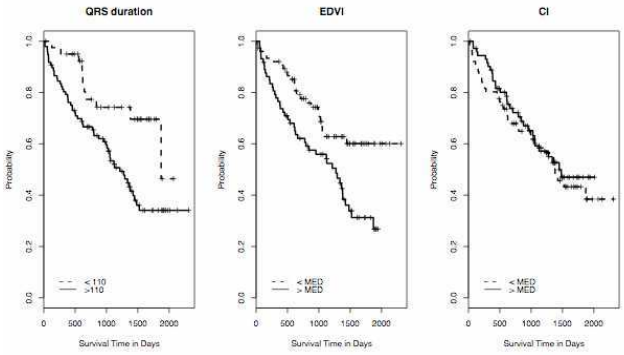

Figure 3. Kaplan-Meier curves for the predictors given in Table 2 (right half): QRS duration > 110ms (p= 0.005, log-rank test), left ventricular enddiastolic volume index (p= 0.003) and left ventricular cardiac index (p= 0.5, from left to right).

The proportional hazards assumption was verified for all predictors.

4. Discussion and conclusions

In our investigation, which in addition to the study of Assomul et al.[13] is a prospective MRI study on a large cohort of patients with exclusively idiopathic dilated cardiomyopathy. We assessed and combined specific MRI and ECG parameters in a Cox proportional hazard model for the prediction of cardiac death, SCD, or rehospitalization from pump failure. We found that significant predictors derived from one study modality only, may not always be the best predictors including singularly significant predictors. We were able to demonstrate that after the resampling procedure both, ECG and MRI parameters remained predictive.

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