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Incidence and prognosis implications of long term left ventricular reverse remodeling in patients with dilated cardiomyopathy

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ABSTRACT

Background: Left ventricular reverse remodeling (LVRR) in dilated cardiomyopathy is poorly known within the context of current therapeutic approach. Our goal is to describe the present incidence of LVRR, the factors able to predict it and the long term prognosis of these patients.

Methods and results: We performed a retrospective analysis of a cohort or 387 consecutive outpatients. Mean follow-up was 50.4 ± 28.4 months. Sustained LVRR occurred in 57.6% of patients.

The number of coronary arteries with severe stenosis (HR 0.69, 95% CI 0.55–0.86; $p = 0.001$), New York Heart Association Functional Class (NYHA FC) (HR 0.39, 95% CI 0.27–0.54; $p < 0.001$) as well as the severity of mitral regurgitation (MR) at the end of follow-up (HR 0.42, 95% CI 0.30–0.58; $p < 0.001$) and the time until first event (HR 1.02, 95% CI 1.01–1.03; $p < 0.001$) were independent predictors of left ventricular ejection fraction improvement.

LVRR was tightly related to prognosis due to the fact that both improvement in cardiac function achieving normal or slightly impaired LVEF (HR 0.31, 95% CI 0.17–0.56; $p < 0.001$) and shorter time to achieve LVRR (HR 0.99, 95% CI 0.98–0.99; $p = 0.017$) formed part of the best model for predicting events in DCM.

Conclusion: More than half of the patients showed sustained LVRR associated with a significantly better prognosis.

Fewer numbers of coronary arteries with severe stenosis, milder NYHA FC and the absence of significant MR at the end of follow-up as well as longer event free period formed a simple model to prognosticate LVRR.

LVRR and the time to achieve it were strongly related to long term prognosis in patients with DCM.

1. Introduction

Reverse remodeling of the left ventricle is often observed in patients with DCM and it is known that it plays an important role in the prognosis of these patients [1–3]. Even so, there is a poor knowledge of the mechanisms implicated in this phenomenon [4–6]. Little is also known about its incidence, natural history and related factors in the current clinical scenario due to the fact that, at the best of our knowledge, the studies published up to now did not employ either current optimal medical or device therapy, included a small number of patients or had a relatively short clinical or echocardiographic follow-up [7–20].

To know which patients will develop LVRR as well as their long-term prognosis could help in the important clinical decision making process concerning the need and timing of some therapies in patients with DCM. This becomes especially important for those aggressive therapies that could involve high morbidity and a substantial increase of the costs, such as HTx and device implantation.

2. Methods

We retrospectively analyzed a series of 387 consecutive outpatients with DCM referred to a Heart Failure Care Clinic of a General Hospital from April 2005 to January 2012. An informed consent was obtained from each patient and the study protocol

Abbreviations: LVRR, Left ventricular reverse remodeling; NYHA FC, New York Heart Association Functional Class; MR, Mitral regurgitation; DCM, Dilated cardiomyopathy; HTx, Heart transplantation; HF, Heart failure; LVEF, Left ventricular ejection fraction; ESC, European Society of Cardiology; ICD, Implantable cardioverter-defibrillator; CRT, Cardiac resynchronization therapy; LV, Left ventricle; PHT, Pulmonary hypertension; PAP, Pulmonary artery pressure; HFW, Heart failure worsening; CKD, Chronic kidney disease; LBBB, Left bundle branch block; AUC, Area under the curve.

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conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

All patients with HF diagnosis, made on the basis of clinical features plus LVEF <40% measured by echocardiography, were included. Only patients with organic left valvular disease causing at least moderate stenosis or regurgitation assessed by echocardiography or with valvular prosthesis were excluded.

Patients were evaluated according to the usual clinical pathway of the Unit: an accurate clinical history was obtained and physical examination, blood test, 12-lead EKG, standard chest radiography and echocardiographic and Doppler evaluation were performed on admission.

Patients also underwent a coronary angiography – if cardiovascular risks factors or age >50 years – or coronary artery CT to determine the presence of coronary artery disease. Coronary disease was considered to be present when ≥70% stenosis in an epicardial coronary artery. Additional image, biochemical, immunological and genetic tests were performed according to clinical suspicion. All patients received adrenergic and neurohormonal blockade in accordance with the ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure [21] unless contraindicated. An ICD was implanted in patients with high risk criteria for sudden death. A CRT was associated when indicated as recommended in the ESC guidelines [21]. The etiological classification of DCM was made based on the Classification of the cardiomyopathies of the ESC [22]. CKD was defined as GFR <60mls/min/1.73m^2.

All patients were followed up for at least 18 months or until death or HTx. A standardized clinical follow-up was performed every 6 months (ranging from 1 to 9 months) in outpatient clinic or exceptionally by telephone interview.

An echocardiogram was periodically performed every 6–12 months or as clinically indicated. LVEF was measured using the apical biplane method of disks and was semi-quantitatively classified into four categories: severe (LVEF ≤30%), moderate (LVEF 31–40%) and mild LV dysfunction (LVEF 41–55%) and normal left ventricular function (LVEF ≥56%) in accordance with local clinical practice. Sustained LVRR was defined as a LVEF improvement of at least one category maintained until the last echocardiography performed during the follow-up.

MR was semi-quantitatively graded following the recommendations of the ESC Guidelines on the management of valvular heart disease [23]. MR was considered significant when it was moderate or severe. PHT was usually assessed by echocardiography and it was considered significant when estimated systolic PAP was >50 mm Hg and severe when it was >60 mm Hg.

HF symptoms were evaluated based on the NYHA classification assessed by the clinician at baseline and at the end of the follow-up [24].

The primary end point was all-cause mortality or HTx. The secondary end point was determined as the combination of HFW, death or HTx. We considered that there was a HFW when a patient consulted with HF symptoms and required intravenous diuretic therapy.

Our goal was to determine the current incidence of sustained LVRR in patients with DCM receiving optimal treatment, the factors able to predict it as well as to identify its role in the long term prognosis of these patients.

2.1. Statistical analysis

Continuous data were presented as mean and SD and categorical data as numbers and percentages (%). Differences between groups were tested using Student's t-test for continuous data and chi-square test (or Fisher's exact test where appropriate) for categorical variables. Paired t-tests were used to compare the values between the baseline and long-term follow-up. In order to evaluate the predictors of LVRR, univariate analysis included all relevant clinical or laboratory parameters of the patients at baseline and during follow-up. In the multivariate logistic regression analysis, a backward stepwise algorithm was applied to the list of selected parameters with a p value <0.05 from the univariate analysis. Survival data were analyzed using the Kaplan–Meier method and compared using the log-rank test. Multivariate Cox regression analysis was used to identify independent predictors for clinical events from the data obtained from clinical, electrocardiographic and imaging test. When the final model was acquired its calibration was tested using the Hosmer–Lemershow χ^2 test and capacity of discrimination was checked using the area under the receiver operating characteristic curve (COR curve). Significance was defined as $p < 0.05$.

3. Results

A cohort of 387 consecutive outpatients with diagnosis of DCM was included in the analysis.

Mean age at diagnosis was 64.5 ± 12.1 and patients were predominantly males (74.4%). All patients had LVEF <40% at baseline.

Idiopathic dilated cardiomyopathy was the most prevalent etiology (34.1%, including 9.6% with familial pattern of inheritance) followed by ischemic (31.0%), alcoholic (13.7%), myocarditis (8.0%), hypertensive (7.5%), chemotherapy induced cardiomyopathy (1.8%), restrictive (1.6%), muscular dystrophy cardiomyopathy (1.0%), toxic (0.5%) and lastly hypertrophic (0.3%), thyrotoxic (0.3%) and peripartum cardiomyopathy (0.3%).

Patients with NYHA FC I, II, III and IV at baseline were 84 (21.7%), 188 (48.6%), 114 (29.5%) and 1 (0.3%) respectively.

374 patients (96.6%) were receiving beta-blockers at the end of the follow-up period; 370 (95.6%), angiotensin-converter enzyme (ACEI) or angiotensin receptor blocker (ARB); 235 (60.7%), antagonists of aldosterone and 24 (6.2%) were taking ivabradin. 212 patients (54.8%) had an implanted device: 99 (25.6%) received an implantable cardioverter defibrillator (ICD) and 113 (29.2%) had a device with cardiac resynchronization therapy combined with ICD (CRT-ICD).

Regarding ischemic DCM, most of these patients had three-vessel disease (41.7%, 50p). Almost a third of ischemic population (29.2%, 35p) was treated medically; more than a half (54.2%, 65p) had percutaneous treatment and a minority had surgical (13.3%, 16p) or mixed revascularization (3.3%, 4p). Complete revascularization was achieved in little over a third of ischemic patients (34.2%, 41p).

Clinical, laboratory, electrocardiographic and echocardiographic findings of these patients at baseline are summarized in Table 1.

Mean follow-up was 50.4 ± 28.4 months, with an expected follow-up period of at least 18 months. Only 2.1% (8p) of patients were lost to follow-up during this period, with no significant differences in basal characteristic or prognosis between these patients and the rest of the series.

3.1. Current incidence of left ventricular reverse remodeling

Sustained LVRR occurred in 223 patients (57.6%) during the follow-up period. Mean time for the latest observed improvement in LVEF was 27.75 ± 25.91 months, ranging from 1 to 109 months. Complete normalization of LVEF was shown in 79 patients (20.2%). Changes in LVEF during the follow-up are shown in Fig. 1.

3.2. Predictors of sustained left ventricular reverse remodeling

Non-adjusted analysis demonstrated a significant association between lack of LVRR and ischemic, myocarditis and hypertensive etiology; familial inheritance pattern; CKD; atrial fibrillation; severe NYHA FC at the end of the follow-up; LBBB; significant MR both at the beginning and the end of the follow-up; severe pulmonary hypertension; ICD alone (not with CRT combined); absence of treatment with betablockers and statines; treatment with oral anticoagulants, antagonist of mineralocorticoid receptors and diuretics and clinical events (death, HTx and HFW) (Table 1).

In adjusted analysis the number of coronary arteries with severe stenosis (HR 0.69, 95% CI 0.55–0.86; $p = 0.001$), the NYHA FC (HR 0.39, 95% CI 0.27–0.54; $p < 0.001$) and the degree of MR at the end of the follow-up (HR 0.42, 95% CI 0.30–0.58; $p < 0.001$) as well as the time until first event (including death, HTx and HFW) (HR 1.02, 95% CI 1.01–1.03; $p < 0.001$) were independent predictors for sustained LVRR (Table 2).

According to these findings, the equation for the best predictive model for LVRR expressed as the logit (linear exponential term of the logistic model) was:

$$\begin{aligned} logit\, P = {} & 3.20 - 0.87 \times final\ MR - 0.37 \times number\ of\ arteries\ with\ severe\ stenosis \\ & - 0.97 \times NYHA - FC\ at\ the\ end\ of\ follow - up + 0.02 \\ & \times follow - up\ until\ first\ event\ (months). \end{aligned}$$

The Hosmer–Lemeshow test, which assesses if observed event rates match expected event rates of the model population, provided a χ^2 p value of 0.098 indicating a good calibration. The c statistic or AUC was 0.83 (95% CI 0.79–0.87; $p < 0.001$) indicating a fine discriminatory capacity of the model (Fig. 2).