Original article

Early vs. late reverse ventricular remodeling in patients with cardiomyopathy

Aya Banno (MD)[a], Shun Kohsaka (MD, PhD)[a,*], Taku Inohara (MD)[a], Kimi Koide (MD)[a], Yasuyuki Shiraishi (MD)[a], Takashi Kohno (MD, PhD)[a], Motoaki Sano (MD, PhD, FJCC)[a], Tsutomu Yoshikawa (MD, PhD, FJCC)[b], Keiichi Fukuda (MD, PhD, FJCC)[a]

[a] Division of Cardiology, Keio University School of Medicine, Tokyo, Japan
[b] Division of Cardiology, Sakakibara Heart Institute, Tokyo, Japan

ABSTRACT

Background: Predictors of left ventricular reverse remodeling (LVRR) and differences in the time taken to achieve LVRR remain unclear.
Methods: We consecutively registered 129 patients with severe cardiomyopathy admitted with heart failure (HF). Patients were followed for a median of 778.0 days (IQ: 457.0, 1078.0). LVRR was defined as a decrease in indexed left ventricular systolic dimension of at least 15% additional to a 25% improvement in left ventricular ejection fraction at outpatient check-up compared with discharge. LVRR accomplishment within 400 days was defined as early-LVRR opposing the remaining late-LVRR patients. Primary endpoint was a composite of all-cause mortality and HF re-hospitalization.
Results: LVRR was observed in 51 patients (39.5%). Baseline predictors for LVRR were age younger than 60 years (OR, 3.27; 95% CI 1.04–10.37, $p = 0.043$), no history of previous HF hospitalization (OR, 0.32; 95% CI 0.12–0.86, $p = 0.025$), and systolic blood pressure (sBP) >100 mmHg at discharge (OR, 4.39; 95% CI 1.39–13.81, $p = 0.011$). Overall, there were 51 endpoint events [LVRR 11 (21.6%) vs. non-LVRR 40 (49.4%), $p < 0.001$]. LVRR was a significant predictor of favorable prognosis (HR, 3.77; 95% CI 1.68–8.47, $p < 0.001$). Notably, 41 (80.4%) patients qualified for early-LVRR. Early-LVRR was associated with better prognosis compared with late-LVRR [early-LVRR 6 (14.6%) vs. late-LVRR 5 (50.0%), $p = 0.066$]. Among assessed variables, sBP >100 mmHg at discharge was a significant predictor of early-LVRR (OR, 10.87; 95% CI 1.19–100.0, $p = 0.034$).
Conclusion: Prognosis was improved in patients who achieved LVRR. Early-LVRR tended to be an advantage in terms of long-term prognosis. Higher sBP was a predictor not only for all-LVRR but also early-LVRR.

© 2015 Japanese College of Cardiology. Published by Elsevier Ltd. All rights reserved.

Introduction

Prognosis of heart failure (HF) has drastically improved over the past decade, yet its prognosis, particularly in patients with advanced cardiomyopathy remains limited. The majority of HF patients undergo left ventricular remodeling; a process by which mechanical, neurohormonal, and possibly genetic factors alter ventricular size, shape and function [1]. The eventual change in the ventricle becomes a threat to overall hemodynamics [2]. Recently, left ventricular reverse remodeling (LVRR) defined as a decrease in

dimensions and modification of the shape of the heart resulting in a significant improvement in pump function, has been defined as a clinical entity and is observed in about one third of cardiomyopathy patients [3–8]. In several of the studies, prognosis has been proved to be better among patients who have achieved LVRR.

However, LVRR is a heterogeneous process, and its clinical implications may vary over time. Previous studies have suggested that higher systolic blood pressure (sBP) is a predictor of LVRR [6], but not many have used multivariate analysis for further investigation. Furthermore, given that left ventricular remodeling continues for months after the initial insult [9], LVRR at the early phase may play a more important role compared to remodeling occurring at the later phase. Despite the timing of remodeling being a major objective in this field, previous studies have not examined chronological relationships between LVRR and HF prognosis. In addition, little is known about LVRR in the modern

Asian HF population. Nevertheless, it is known that beta-blockers and other HF-related medications in Japan are administered at lower doses than in Western facilities, and therefore it is essential to analyze a study population in Japan because these medical agents play an important role in LVRR [10,11].

The objective of this study was to determine early clinical characteristics that predict LVRR. We also sought to identify differences in time to LVRR achievement in a long-term follow-up study. LVRR is an important predictor of long-term prognosis in patients with advanced cardiomyopathy, and further delineation of its process will aid their risk stratification. We also suggest defining the appropriate interval for LVRR after acute decompensation, as it may be essential for predicting prognosis.

Methods

Study population

We enrolled 325 consecutive HF patients with post-acute decompensation who were admitted to Keio University Hospital from June 2005 to February 2011. Patients were followed up at the outpatient clinic of our institute after discharge. Informed consent was obtained from all subjects in accordance with the Keio Hospital admission policies. Of the 325 patients, 69 were excluded on the basis of etiology: valvular disease, sarcoidosis, tachycardia, takotsubo cardiomyopathy, pericarditis, myocarditis, congenital heart disease, right ventricular failure, and miscellaneous infiltrative etiologies.

The remaining 256 patients with idiopathic dilated cardiomyopathy, hypertrophic cardiomyopathy, hypertensive cardiomyopathy, and ischemic cardiomyopathy were assessed. We subsequently excluded 30 patients whose left ventricular ejection fraction (LVEF) was preserved at admission and 2 patients who received cardiac resynchronization therapy. In total, follow-up echocardiogram was not obtained in 196 patients of the 325 patients within 400 days of discharge. Clinical and echocardiographic data were available for 129 patients at mid-term follow-up. A flowchart of the inclusion criteria is shown in Supplementary Figure 1.

Clinical evaluation and biomarker measurements

Clinical data including New York Heart Association functional class, heart rate, sBP, body mass index (BMI), and serum hemoglobin concentration and creatinine level were determined by standard laboratory methods. The estimated glomerular filtration rate (eGFR) was calculated using the Cockcroft–Gault formula.

The plasma brain natriuretic peptide (BNP) level and other biomarkers were measured before discharge and 6 months after initial admission for HF. Commercially available kits were used to measure BNP (Shionogi, Tokyo, Japan) and cardiac troponin T (cTnT; Roche Diagnostics, Tokyo, Japan). The lower limit of detection for cTnT was 0.01 ng/ml.

In the evaluation of prescribed medication, the dosage of each beta-blocker was converted to carvedilol equivalent dose (Supplementary Table 2) (e.g. titer of bisoprolol against carvedilol is 5:1).

Echocardiographic study

Conventional M-mode, two-dimensional, and Doppler variables were measured in all patients at discharge and at the outpatient clinic during follow-up in accordance with guidelines of the American Society of Echocardiography [12]. Left atrial and ventricular diameters, along with wall thicknesses were measured using M-mode echocardiography at the parasternal long-axis acoustic window. LVEF was graded by two dedicated echocardiographers, using the Teicholz method and the biplane method of disks. Referencing these calculations, the LVEF was determined in accordance with the American Society of Echocardiography recommendations [12]. Mitral regurgitation was semi-quantitatively graded considering the regurgitant jet area on color Doppler imaging. Mitral regurgitation with a jet area >4 cm^2 was considered significant. All measurements were obtained from the mean of 3 beats for patients with sinus rhythm. The standard measurement for heart failure patients with atrial fibrillation was to average the measurement of five cardiac cycles or to measure the representative cardiac cycle. All echocardiograms at our facility were recorded according to the recommended protocol of the American Society of Echocardiography. The quality check was performed by the two board-certified echocardiologists assigned to the laboratory.

Criteria of reverse remodeling

LVRR was defined as the presence of a decrease in indexed left ventricular systolic dimension of at least 15% with addition to 25% improvement in LVEF at outpatient check-up compared with measurements at discharge. Algorithm for LVRR classification is shown in Fig. 1. Patients who completed LVRR by the first
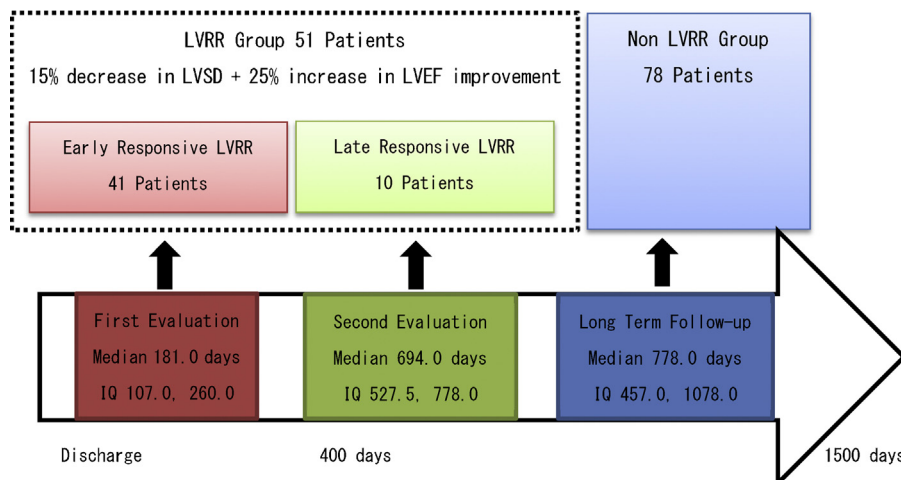

Fig. 1. Classification according to timing of LVRR accomplishment. LVRR, left ventricular reverse remodeling; LVSD, left ventricular systolic dimension; LVEF, left ventricular ejection fraction.