Maximum Derivative of Left Ventricular Pressure Predicts Cardiac Mortality After Cardiac Resynchronization Therapy

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ABSTRACT

Background: Cardiac resynchronization therapy (CRT) has been reported to improve cardiac performance. However, CRT in patients with advanced heart failure is not always accompanied by an improvement in survival rates. We investigated the association between hemodynamic studies and long-term prognosis after CRT.

Methods: A total of 68 consecutive patients receiving CRT devices due to advanced heart failure were assessed by hemodynamic study and long-term outcome after implantation of the device. Hemodynamic parameters were measured both with the CRT on and off.

Results: Patients demonstrated significant improvement in the maximum first derivative of left ventricular (LV) pressure (LV dP/dt_{max}) and QRS duration after periods with the CRT on. During the follow-up period of 34.9 ± 17.6 months, basal LV dP/dt_{max} and isovolemic LV pressure half-time ($T_{1/2}$), but not percent change in LV dP/dt_{max}, were independent predictors of cardiac mortality or hospitalization due to heart failure after multivariate Cox regression analysis. The Kaplan-Meier survival analysis revealed that patients in the lowest basal LV dP/dt_{max} tertile or the longest basal $T_{1/2}$ tertile exhibited a significantly higher cardiac-caused mortality or heart failure hospitalization.

Conclusions: Lower LV dP/dt_{max} or longer $T_{1/2}$ independently predicts cardiac mortality or heart failure hospitalization in patients receiving CRT. The assessment of the basal LV dP/dt_{max} and $T_{1/2}$ could provide useful information in long-term prognosis after CRT.

Introduction

Cardiac resynchronization therapy (CRT) has been established as a therapeutic option in patients with advanced heart failure.[1–3] Previous studies have shown that CRT decreases mortality and hospital admission rates.[4,5] Based on current knowledge of the mechanisms involved, patients with beneficial outcomes from CRT have comprised those suffering impairment of contractility associated with electromechanical ventricular dyssynchrony and reverse remodeling.[6–8] However, it is difficult to actually identify which patients will have the best outcome after CRT from preimplant assessments. We found that approximately one-third of patients do not respond well to CRT.[2,9] A recent clinical trial[10] indicated that the echocardiographic parameters in assessing dyssynchrony did not have enough predictive value to be recommended as selection criteria for CRT beyond current guidelines. Therefore, it is clinically valuable to identify any preimplant characteristics that better predict which patients will have the best outcomes after CRT. In the present study, we investigated what kind of hemodynamic parameters could predict long-term patient prognosis after CRT.

Methods

Study Population

We retrospectively assessed 72 consecutive patients with heart failure who underwent CRT at Nagoya Daini Red Cross Hospital between June 2001 and September 2006. The patients were selected according to the established

This work was supported by grant from the Grant-in-Aid for Young Scientists, the Nakashima Foundation, and the Kowa Life Science Foundation to RS.

Hirohiko Suzuki, MD and Masayuki Shimano, MD equally contributed to the work.

Clin. Cardiol. 33, 12, E18–E23 (2010)
Published online in Wiley Online Library (wileyonlinelibrary.com)
DOI:10.1002/clc.20683 © 2010 Wiley Periodicals, Inc.

Received: August 6, 2009
Accepted with revision: September 6, 2009

CArdiac REsynchronization in Heart Failure Study (CARE-HF) selection criteria for CRT[3]: (1) severe heart failure despite optimized medical therapy; (2) left ventricular (LV) systolic dysfunction with a LV ejection fraction <35%; and (3) QRS duration >120 ms. In addition, patients with a QRS interval of 120 to 149 ms were required to meet 2 of 3 additional criteria for dyssynchrony as described previously (aortic pre-ejection delay >140 ms, interventricular mechanical delay >40 ms, delayed activation of the posterolateral left ventricular wall).[3] We excluded 4 patients with aortic valve replacements for valvular heart disease. All patients enrolled in the study provided written informed consent.

Echocardiography

Both 2-dimensional and Doppler echocardiography were performed by an experienced sonographer using the Sonos 5500 System (Philips Electronics, Amersterdam, The Netherlands) before the hemodynamic study. The images were recorded on videotape and analyzed off-line. Left ventricular end-diastolic diameter (LVEDD) and left atrial dimension (LAD) were measured from standard M-mode measurements as recommended by the American Society of Echocardiography. Left ventricular ejection fraction (EF) was calculated using a modified Simpson's rule.

Cardiac Hemodynamic Analysis

Invasive hemodynamic study using a micro-manometer-tipped catheter (Millar Instruments, Houston, Texas) was performed immediately after CRT device implantation with a standard pacing protocol described previously.[11,12] Hemodynamic and electrical signals were digitized at a sampling rate of 12 kHz and stored on a PC. Left ventricular end-diastolic pressure (LVEDP), the maximum first derivative of LV pressure (LV dP/dt_{max}) as an index of contractility, and the pressure half-time ($T_{1/2}$) to evaluate LV isovolumic relaxation according to Mirsky's method were measured both with CRT on (CRT basal) and off.[13] Hemodynamic data were analyzed by 2 independent observers who were unaware of the clinical and echocardiographic data.

Follow-Up and Assessment of Cardiac Events

All patients underwent regular follow-ups (typically every 2 mo) by means of outpatient clinical visits or telephone interviews. Hospitalizations for worsening of heart failure were adjudicated by Nagoya Daini Red Cross Hospital staff cardiologists. Causes of death were ascertained by reviewing the clinical records.

Statistical Analysis

All data are expressed as mean ± standard deviation (SD). Univariate and multivariate Cox regression analysis were performed to control for potentially confounding hemodynamic, demographic, and clinical variables. Freedom from all causes of death, cardiac death, or hospitalization for heart failure was determined by Kaplan-Meier analysis with the log-rank test. A level of $P < 0.05$ indicated statistical significance. All analyses were performed using SPSS 16.0 (SAS Institute Inc., Cary, NC).

Results

Baseline Characteristics

Baseline characteristics are shown in Table 1. A total of 68 patients who received CRT were 66.2 ± 9.2 years of age, 58.8% male, and predominantly classified as New York Heart Association (NYHA) functional class III and IV with QRS prolongation (169.4 ± 29.5 ms). Patients had

Table 1. Patients Characteristics (n = 68)

Age (yrs)	66.2 ± 9.2
Male (%)	40 (58.8%)
NYHA class III/IV (%)	54(79.4%)/14 (20.6%)
QRS width (ms)	169.4 ± 29.5
Echocardiography	
Left ventricular end diastolic diameter (mm)	67.6 ± 9.0
Left ventricular ejection fraction (%)	27.1 ± 9.5
Mitral regurgitation (grade)	1.6 ± 0.7
Left atrial dimension (mm)	45.2 ± 7.9
Ischemic heart disease (%)	7 (10.3%)
History of atrial fibrillation (%)	13 (19.1%)
Upgrading of existing device	23 (33.8%)
Hemodynamic data	
Positive LV dP/dt_{max} (mm Hg/sec)	748.1 ± 246.4
Peak LV pressure (mm Hg)	102.2 ± 22.2
Negative LV dP/dt_{min} (mm Hg/sec)	758.2 ± 222.4
LVEDP (mm Hg)	14.2 ± 8.1
$T_{1/2}$ (ms)	47.7 ± 7.6
eGFR (mL/min)	51.2 ± 16.3
BNP (pg/mL)	576.6 ± 414.3
Preferable LV lead position	63 (92.6%)
Follow-up (mo)	34.9 ± 17.6

Abbreviations: BNP, brain natriuretic peptide; eGFR, estimated glomerular filtration rate; LV, left ventricle; LVEDP, left ventricular end-diastolic pressure; NYHA, New York Heart Association; $T_{1/2}$, isovolemic pressure half-time.
Values are mean ± standard deviation.

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DOI:10.1002/clc.20683 © 2010 Wiley Periodicals, Inc.

severe LV dysfunction (mean LVEF 27.1% ±9.5%), with extensive dilatation (LVEDD 67.6 ± 9.0 mm). The etiology of heart failure in 10.3% of patients was ischemic heart disease. Hemodynamic data immediately after CRT device implantation demonstrated significant improvement in LV dP/dt_{max} (24.4%), LVEDP (−17.9%), and $T_{1/2}$ (−6.8%) as compared with basal conditions. CRT also made QRS width shortened (26.0%) as compared with basal conditions.

Clinical Outcome of Patients During Follow-Up

The mean duration of follow-up was 34.9 ± 17.6 months. There were 13 (19.1%) deaths. Causes of death included sudden cardiac death in 5 patients, heart failure in 3 patients, and noncardiac-related deaths in 5 patients (2 deaths from cancer, 1 of infection, 1 traumatic accident, and 1 renal failure). A total of 6 patients were hospitalized due to exacerbation of heart failure after CRT device implantation.

Prediction of Prognosis After CRT

We first performed univariate Cox regression analysis to examine the relationship between long-term prognosis (cardiac mortality and heart failure hospitalization) after CRT and cardiac parameters including conventional risk factors. We found the statistical significance in NYHA functional class ($P < 0.01$), plasma brain natriuretic peptide (BNP) levels ($P < 0.05$), estimated glomerular filtration rate (eGFR; $P < 0.05$), LV dP/dt_{max} during CRT ($P < 0.001$) and $T_{1/2}$ during CRT ($P < 0.01$; Table 2). There were no significant differences in age, LVEDD, LVEF, QRS duration, percent change in QRS duration, percent change in LV dP/dt_{max}, LVEDP, preexisting atrial fibrillation (AF), etiology of cardiomyopathy, and preferable LV lead position (posterolateral or lateral tributary of coronary sinus).

Basal LV dP/dt_{max} ($P < 0.05$) and $T_{1/2}$ ($P < 0.05$) during CRT are independent predictors of cardiac death or heart failure hospitalization in multivariate Cox regression models, after controlling for NYHA functional class, plasma BNP levels, eGFR, basal LV dP/dt_{max}, and basal $T_{1/2}$ (Table 2).

The Kaplan-Meier survival analysis demonstrated that patients in the lowest tertile of basal LV dP/dt_{max} during CRT (<750 mm Hg/s) had a significantly higher cardiac-caused mortality and hospitalization for heart failure compared with those in the upper tertile (>750 mm Hg/s; Figure 1A,B). In addition, patients in the lowest tertile

Table 2. Predictors of Cardiac Mortality and Heart Failure Hospitalization

	Univariate			Multivariate		
	OR	CI (OR)	*P* value	OR	CI (OR)	*P* value
Age	0.956	0.909–1.006	0.081			
NYHA	4.097	1.497–11.213	0.008	2.217	0.772–6.366	0.139
Atrial fibrillation	1.201	0.335–4.307	0.779			
Ischemic etiology	3.453	0.956–12.469	0.059			
LVEDD	1.054	0.993–1.119	0.085			
LVEF	0.986	0.931–1.044	0.619			
BNP	1.001	1.000–1.002	0.026	1.001	0.999–1.002	0.213
eGFR	0.965	0.933–0.997	0.033	0.971	0.939–1.005	0.095
LV dP/dt_{max}	0.994	0.990–0.998	0.001	0.996	0.992–0.995	0.018
% change in LV dP/dt_{max}	0.993	0.956–1.030	0.693			
LVEDP	1.018	0.955–1.085	0.587			
$T_{1/2}$	1.092	1.028–1.159	0.004	1.076	1.011–1.145	0.021
QRS width	1.007	0.990–1.025	0.417			
% change in QRS width	0.983	0.960–1.006	0.135			
LV lead position	2.323	0.516–10.451	0.272			

Abbreviations: BNP, brain natriuretic peptide; CI, 95% confidence interval; eGFR, estimated glomerular filtration rate; LV, left ventricle; LVEDD, left ventricular end-diastolic diameter; LVEDP, left ventricular end-diastolic pressure; NYHA, New York Heart Association; OR, odds ratio; $T_{1/2}$, isovolemic pressure half-time.

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DOI:10.1002/clc.20683

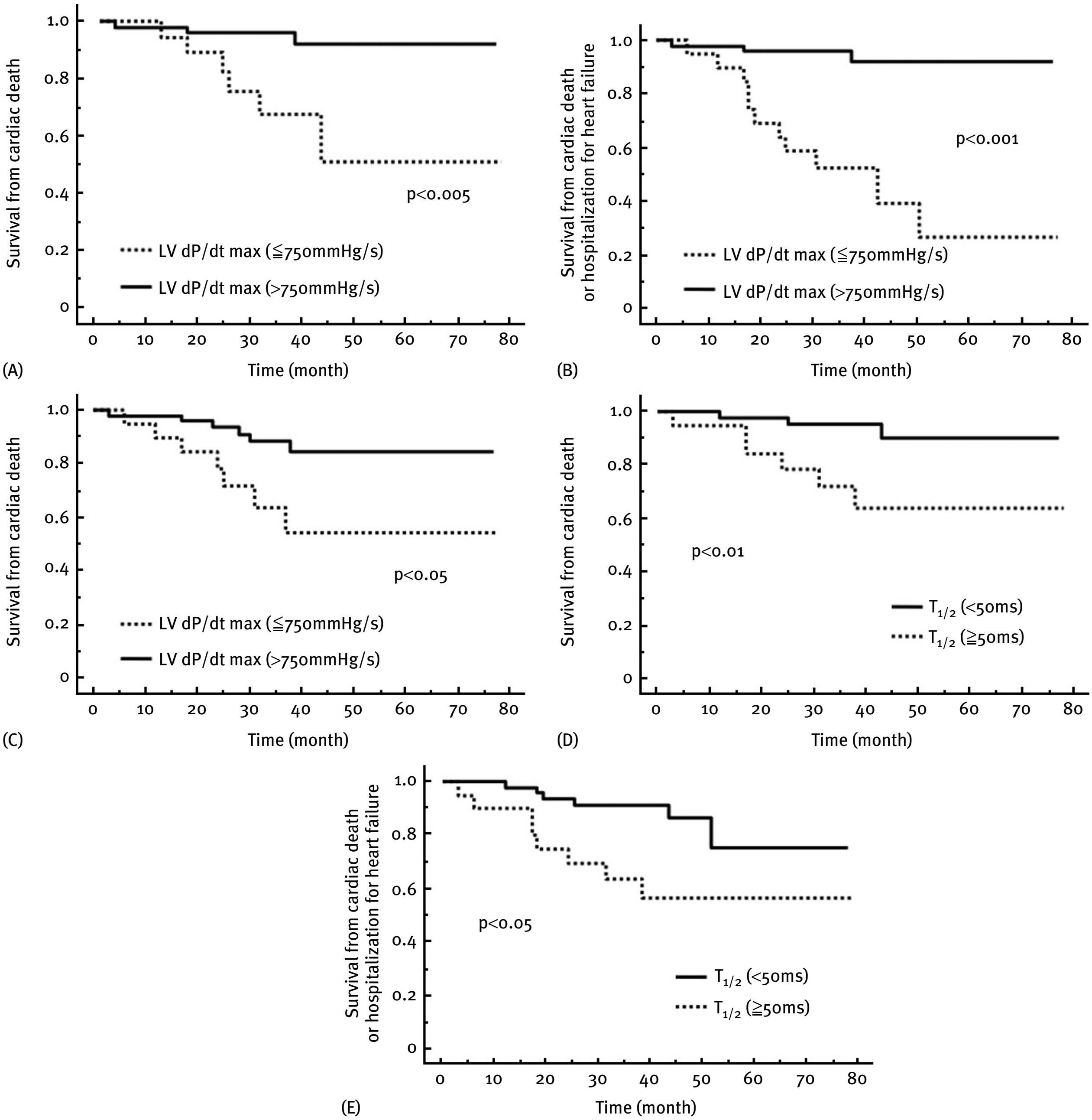

Figure 1. Kaplan-Meier estimates of the time to various clinical end points; (A,D) cardiac death, (B,E) cardiac death or hospitalization for heart failure, (C) all-cause death. Patients were stratified according to (A,B,C) peak positive LV dP/dt and (D,E) isovolemic LV pressure half-time ($T_{1/2}$).

of basal LV dP/dt$_{max}$ during CRT (<750 mm Hg/s) had exhibited higher all-cause death (Figure 1C). Kaplan-Meier survival analysis also presented that patients in the longest tertile of basal $T_{1/2}$ during CRT (>50 ms) had significantly higher cardiac-based mortality and hospitalization for heart failure (Figure 1D,E).

Discussion

This study has demonstrated for the first time that LV dP/dt$_{max}$ and $T_{1/2}$ during CRT just after implantation estimated by invasive hemodynamic study independently predicts cardiac mortality and morbidity in patients receiving CRT.

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DOI:10.1002/clc.20683

The reason that LV dP/dtmax is such a sensitive index[14–17] for response to CRT is thought to involve the manner in which mechanical dyssynchrony rises during early isovolumic contraction and peaks at end systole or early relaxation.[18] Myocardial dyssynchrony as assessed by magnetic resonance imaging was an independent predictor of mortality after CRT.[19] Doppler-derived LV dP/dt_{max} also predicts survival in patients with heart failure in the settings without CRT.[20] In addition, it has been noted that CRT provides long-term beneficial effects to patients in early stages of heart failure,[21] thus indicating those who do not have low basal LV dP/dt_{max}. Left ventricular dyssynchrony caused the prolongation of isovolemic relaxation through asynchronous relaxation time.[22] Consistent with these findings, the present study demonstrates that lower peak positive LV dP/dt and longer $T_{1/2}$ at baseline independently predicts cardiac death or hospitalization for heart failure in patients receiving CRT. These data suggest that measurements of hemodynamics before CRT implantation could provide useful clinical information regarding cardiac mortality and morbidity after CRT.

It was recently reported that echocardiographic assessments of the acute hemodynamic response to CRT such as percent change in LV dP/dt_{max} predict long-term clinical outcomes.[23–26] However, the association between the acute hemodynamic response to CRT and long-term outcome is controversial. In contrast, conclusions from the Predictors of Response to CRT (PROSPECT) trial[10] and contemporary review[27] suggested that single echocardiographic measure of dyssynchrony might not be recommended to improve patient selection for CRT. The differences between the results of the various studies may be due to underlying differences in the severity of heart failure or frequency of ischemic cardiomyopathy. Our findings also showed that percent change in LV dP/dt_{max} by invasive hemodynamic study did not predict cardiac mortality in patients receiving CRT. Therefore, it appears that the acute hemodynamic response to CRT is not an independent predictor of long-term outcome after CRT.

The present study has several limitations. First, the sample size is relatively small. Second, because we excluded patients with aortic valve replacements, there were no heart failure patients with valvular heart diseases in this study. Finally, the frequency of ischemic etiology was relatively low in this population. This probably reflects the lower cardiac mortality compared with the various CRT-related studies. Accordingly, inconsistent with previous studies,[28–30] ischemic etiology was not a major predictor of cardiac mortality.

In conclusion, our findings suggest that basal LV dP/dt_{max} and $T_{1/2}$ during CRT—but not percent change in LV dP/dt_{max}—predict cardiac mortality in patients receiving CRT. Measurements of hemodynamics just after CRT implantation could provide useful information in long-term prognosis after CRT. More aggressive utilization of CRT should be considered in early stages of heart failure characterized by relatively intermediate LV dP/dt_{max} values.

Acknowledgments

The authors gratefully acknowledge the assistance of Yutaka Kose and Toru Kaneko.

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DOI:10.1002/clc.20683