

Prognostic effects of pulmonary hypertension in patients undergoing cardiac resynchronization therapy

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ABSTRACT

Background Aim of this study is to investigate the impact of elevated pulmonary artery systolic pressure (PASP) on mortality and the clinical outcome after cardiac resynchronization therapy (CRT).

Methods Ninety-three patients with heart failure were enrolled into this study, and all of them have been treated by CRT for more than 6 months. Based on the level of preoperative PASP, they were divided into three groups (Group I: PASP>50mmHg, n=29; Group II: 30mmHg<PASP≤50mmHg, n=17; Group III: PASP≤30mmHg, n=47). Mortality and the clinical outcome were compared among three groups in a mean follow-up period of 32.01±20.05 months.

Results ①Eight (28%), one (6%) and eight (17%) patients died in-group I, II and III respectively. Among those patients, 5 in group I and 1 in group III died of heart failure, while the patient in group II died of sudden death. ②In all three groups, CRT significantly improved heart function evaluated by NYHA heart function class and 6 minutes walking distance (6-MWT) (P<0.01). The improvement was more significant in group III than group I (P<0.01). ③At 3 months after CRT, Left ventricular ejection fraction (LVEF) increased significantly in Group III (P<0.01), but not in Group I or II (all P>0.05). At 6 months after CRT, LVEF increased significantly in all three groups (all P<0.05).

Conclusions Elevated PASP has no prognostic effects on heart function improvement in patients undergone CRT. However, it was associated with worse LV remodeling and increased death due to aggravation of heart failure.

Key Words:

heart failure; cardiac resynchronization therapy; pulmonary artery systolic pressure; prognosis

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Introduction

The cardiac resynchronization therapy (CRT) has been used in treating congestive heart failure for 15 years. Reported clinical trials have shown that CRT is beneficial for the severe heart failure. The CRT alone or combined with the medical management has shown evidence in improving the heart failure symptoms, quality of life, exercise capacity, and left ventricular (LV) systolic performance and overall survival time (1-5). CRT has become a standard therapy in cases of heart failure and inter-and intra-ventricular conduction disturbances. Unfortunately, 20~30% of patients do not respond to CRT (6). The reason for this failure of CRT may be the poor positioning of LV leads, poor resynchronization

of LV and scar, ischemia/hibernation of myocardium. (7,8,9). Pulmonary hypertension is a frequently found in patients with congestive heart failure, which is associated with a worse prognosis in these patients. Adjunctive measurements, for this group of patients with refractory symptomatic pulmonary hypertension are needed. This study aims on efficacy of CRT in patients with cardiac failure along with pulmonary hypertension.

Methods

Patient characteristics

Between March 2003 and June 2008, a total 93 consecutive patients with cardiac failure underwent CRT after failed conventional medical management. There were 76 men and 17 women; with mean age of cohort were 59.4 (range, xx-xx). Twenty-five of these patients had ischemic heart disease (CAD) and 68 patients presented with idiopathic dilated cardiomyopathy (DCM). All patients met the criteria of I or IIa indication for CRT (10), including New York Heart Association (NYHA) Class III to IV, left ventricular end-diastole diameter (LVEDD) >55mm, left ventricular ejection fraction (LVEF) <35%, mitral regurgitation and underwent CRT-P/CRT-D implantation.

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Table 1: the comparison of basis status in 3 groups

Parameters	PASP >50mmHg	30 <PASP ≤50mmHg	PASP ≤30mmHg
Patient number	29	17	47
Gender		15/2	38/9
Male	23	15	38
Female	6	2	9
Age (year)	57.27±9.47*	57.87±10.22	62.95±11.17
QRS width(ms)	157.66±35.34	144±33.99	155.67±32.78
Underlying cardiac disease			
Ischemic cardiomyopathy	4	5	16
Non-ischemic cardiomyopathy	26	10	32
NYHA cardiac function(class)	3.5±0.51	3.44±0.51	3.36±0.51
6-MWT(m)	271.8±94.61	295.8±113.7	277.1±96.8
LVEDD(mm)	70.7±7.46	69.2±8.22	71.1±6.99
LVEF (%)	31.32±6.84	31.31±5.27	31.54±5.85
Drug treatment (%)			
diuretics	100	100	100
B-blockers	92	93	91
ACEI	97	95	94
digitalis	90	91	89

Values are presented as mean ± standard deviation where appropriate. 6-MWT: 6 minutes walking distance
ACEI: vascular angiotensin-converting enzyme inhibitor, The comparison between Group III and Group I,
Group III and Group II * P<0.05

Based on echocardiographic estimation of pulmonary artery pressure (PASP), patients were retrospectively divided into 3 groups. There were 29 patients in group I with PASP greater than 50mmHg, 17 patients in group II with PASP greater than 30mmHg but equal or less 50mmHg, and 47 patients in group III with PASP less than 30mmHg (table 1). After the CRT, patients continued their conventional therapies, including diuretics, angiotensin-converting enzyme inhibitors, digitalis and b-blockers.

CRT device implantation

A permanent biventricular intravenous pacing systems were implanted, consistent of 17 patients model 8040, 38 patients with model 8042, 2 patients with model 7272, 4 patients with model 7279, 3 patients with model 7285, 4 patients with Sentry; 2 patients with Medtronic Inc. model 5510, 21 patients with model V350, ST. Jude Medical). All implant devices were programmed to maximize biventricular pacing throughout the ranges of expected patient's activity, and to minimize the power output to prolong the battery life. Further optimization of atrio-ventricular (AV) delay was adjusted by using Doppler trans-mitral flow to provide the maximum left ventricular filling time without compromising cardiac resynchronization. The AV delay was set at a value that provided maximum separation of the E and A waves to

select the shortest AV delay without compromising the left atrial contribution to the left ventricular filling. The VV delay was set at the maximal value of velocity time integral (VTI).

Echocardiography

Transthoracic 2-dimensional (2D) echocardiography was performed the day before CRT implantation, 3 months and 6 months after CRT. Patients were imaged in the left lateral decubitus position. Images were obtained using a 3.5-MHz transducer, at a depth of 16 cm in the parasternal and apical views (standard long-axis, 2- and 4-chamber images). Standard 2D and color Doppler data, triggered to the QRS complex, were saved in dincine loop format. The LV volume (from the end-diastolic to the end-systolic volume) and LVEF were calculated from the conventional apical 2- and 4-chamber images, using the biplane Simpson's technique (11).

Follow up

Patients were followed 1, 3 and 6 months after the procedure and every 6 months thereafter at our outpatient heart failure clinic. All patients were re-evaluated at 3 months and 6 months after a CRT implantation, which included the NYHA heart function class, 6-MWT and echocardiographic parameters (LVEDD, LVEF). A median

follow-up in this study was 32.0 months (range, 6-60 months). The mortalities were assessed up to 5 years.

Statistical analysis

Data are expressed as mean SD. Comparisons between mean values of continuous variables were performed by a two-sided paired t-test, or an unpaired t-test when necessary; chi-square test with continuity correction was used for dichotomous variables. Kaplan-Meier curves for evaluation of survival rate were established using the log-rank test. For all analyses, $p < 0.05$ was considered to be statistical significant.

Results

Mortality

Eight patients (28%) in group I have died. Five of these patients died of aggressive heart failure, 1 patient died of AMI, and 2 patients died of sudden death unknown reason. One patient (6%) died in Group II, and cause of death was a sudden death. Eight patients (17%) have died group III, including that 1 died of advanced heart failure, 4 died of sudden death, and 3 others died of non-cardiac diseases. There was no statistical difference among group I, II, and III in terms of total mortality ($P > 0.05$), while mortality from decomposition of heart failure was significantly higher in Group I ($p < 0.01$). Figure 1 shows the mortalities in all three groups.

NYHA heart function

After CRT implantation, all group patients' NYHA heart function grades showed significant improvements ($P < 0.01$), among which patients in Group III demonstrated more

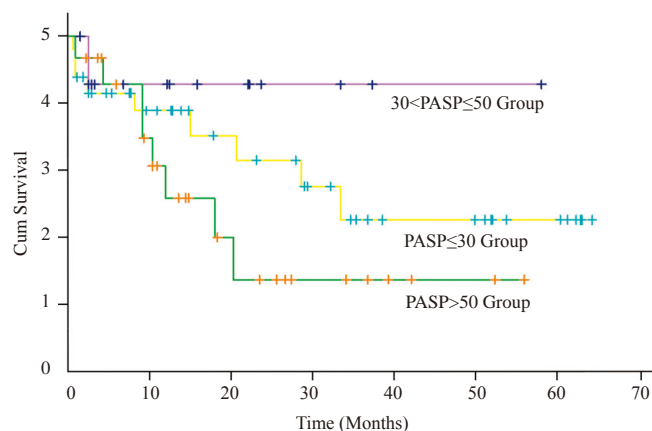


Fig 1. Kaplan-Meier cumulative survival curve among three groups according to PASP. There was no statistical significance among curves ($p = 0.33$).

significant improvement than those in Group I (Figure 2. A, $P < 0.01$).

6-MWT

6-MWT increased significantly at postoperative 3 to 6 months in all groups ($P < 0.05$ in Group I, $P < 0.05 \sim 0.01$ in Group II, and $P < 0.01$ in Group III), particularly, which in Group III increased by 130m compared to ones in pre-operative evaluation ($P < 0.01$). 6-MWT measurements showed a significant improvement in Group III than in Group I at 3 and 6 months post-implantation (Figure 2. B).

LVEDD

The LVEDD diminished significantly from 71mm to 66mm at 3-6 months in Group III ($P < 0.05$), but not significantly different in Group I (from 71mm to 68mm, $P > 0.05$) and Group II (from 69mm to 66mm, $P > 0.05$). Figure 2 (C) shows LVEDD changes in all groups.

LVEF

The LVEF improved at 3-6 months in all groups. LVEF increased from 31 to 39% at 6 months in Group II ($P < 0.01$), and group III showed a significant increase at 3-6 months, consisting of from 31 to 39% at 3 months, and from 31 to 44% at 6 months (all $P < 0.01$). The LVEF in Group III increased more significant than ones in Group I and Group II at postoperative 6 months. Figure 2 (D) shows LVEF changes in all groups.

Discussion

The systolic function of the heart depends on the concordant contraction of each compartment of the heart. The poor concordant contraction can reflect the disorder of myocardial movement and function from the change of myocardial construction (12). Pulmonary hypertension is the pathologic status of pulmonary artery pressure over normal from all reasons. Continuation of elevating pulmonary artery pressure can lead to increase of right ventricular filling pressure resulting in the thickening, degenerating, and fibrosis of the myocardium, further causing the right ventricular (RV) dysfunction and right heart failure (13). Pulmonary hypertension (a mean PASP of 49 ± 7 mmHg vs PASP of 27 ± 5 mmHg) results in lower peak longitudinal RV free wall (RVF) strain (-27.3 ± 7.1 % vs. -31.9 ± 8.7 %, $P < 0.04$), longer time to peak RVF strain (448 ± 57 ms vs. 411 ± 43 ms; $P < 0.03$) and evidence of significant RV dyssynchrony (-83 ± 55 ms vs. 1 ± 17 ms, $P < 0.00001$) (14). RV mechanical delay can increase in proportion to pulmonary pressure (15). RV and left ventricular dyssynchrony were detected by Tissue Doppler Imaging in HF patients, but behaviors of the ventricular

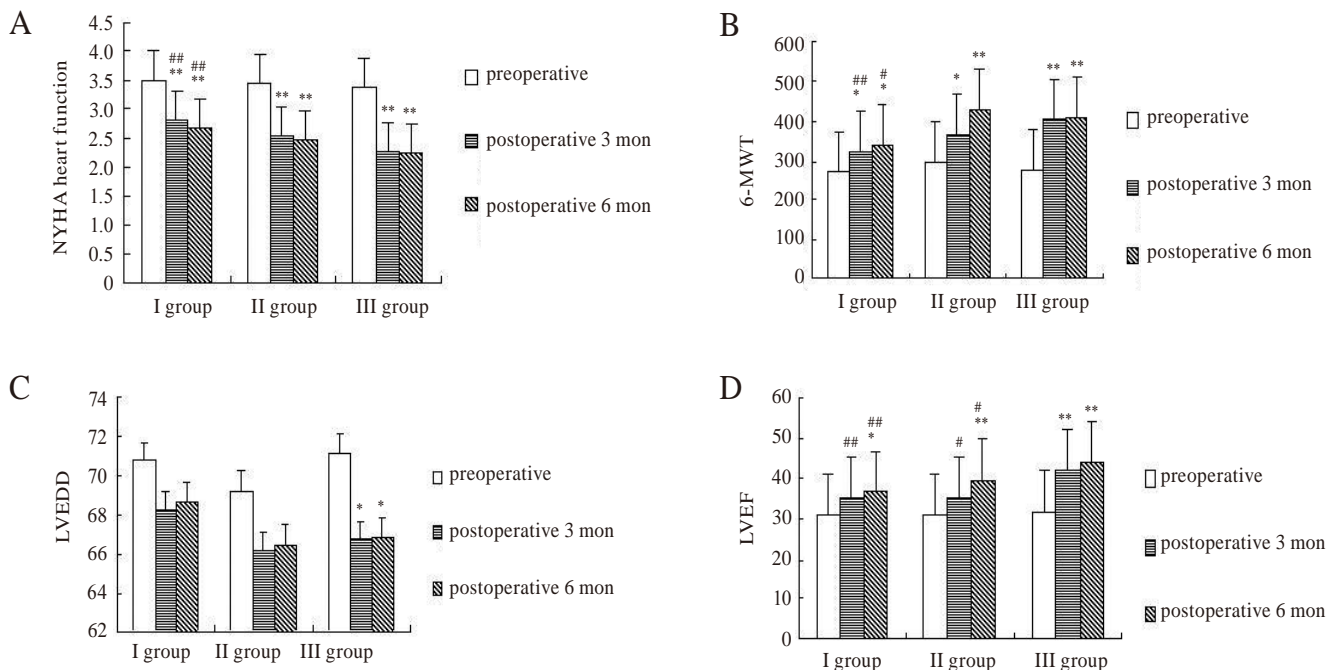


Fig 2. Panel A: The improvement of NYHA class among groups. Panel B: The difference of 6-MWT among groups. Panel C: The diminution of LVEDD among groups. Panel D: The increase of LVEF among groups. * $P < 0.05$, ** $P < 0.01$ the postoperative compared with the preoperative in the group. # $P < 0.05$, ## $P < 0.01$ vs. same time among groups.

dyssynchron were different in the two ventricles. Mean time of right ventricular dyssynchrony was 59 ± 45 ms, while the mean time of the left ventricular dyssynchrony was 80 ± 62 ms. There was a strong correlation between right ventricular dyssynchrony and pulmonary artery systolic pressure ($r = 0.73$; $P < 0.001$) and a negative correlation between right ventricular dyssynchrony and right ventricular fractional area change ($r = -0.43$; $P < 0.02$) (16). The increase of right ventricular systolic pressure (RVSP) would lead to right heart insufficiency. The baseline $RVSP > 35$ mmHg was associated with worse clinical outcome after CRT (17). Progressive RV dysfunction and RV failure causes increased morbidity and mortality in patients with chronic heart failure and elevation of pulmonary arterial pressure (18,19,20).

Pulmonary hypertension is associated with an increased left atrial pressure. Congestive heart failure leads pulmonary hypertension by an increased left atrium pressure. Pulmonary hypertension either due to increased left atrial pressure or high pulmonary vascular resistance can lead to the worse clinic outcome in these patients (21). The past studies have provided evidence that PASP greater than 50 mmHg is associated with poor clinical outcomes. (22,22,23). Stern et al found that compare when compared to PASP < 50 mmHg the patients with $PASP \geq 50$ mmHg had a significantly worse survival ($p = 0.02$), clinical outcome and poor LV reverse remodeling after CRT ($p = 0.045$) (21).

Our results showed though the total mortality was higher in patients with $PASP > 50$ mmHg, but there were no statistical different in all 3 groups of patients with PASP either greater or less 50 mmHg. The main cause of death was sudden cardiac death and non-cardiac diseases in patients with $PASP \leq 50$ mmHg, and decompression of heart failure in patients with $PASP > 50$ mmHg. In patients with $PASP > 50$ mmHg, the risk of death from decompression of heart failure was higher than in patients with $PASP \leq 50$ mmHg ($P < 0.01$). Based on our experience, CRT has improved the left ventricular function and locomotivity, and the most noted improvements of left ventricular function and locomotivity were seen in patients with $PASP \leq 30$ mmHg. Reverse remodeling was a measurement of LV response to CRT, while the elevated PASP did not predict the presence of LV reverse remodeling, and patients with $PASP \leq 30$ mmHg LV reverse remodeling had a better prognosis in terms of improvement in cardiac function and survival benefit after CRT implantation. The LVEF was still an important conventional marker of response of CRT, which may be less relevant in patients with elevated PASP, but our finding improvement of LVEF in patients with normal PASP was very significant compared to elevated PASP ($p < 0.01$). To further investigate the efficacy and clinical outcomes, large size prospective studies with longer follow-up should be conducted.

In conclusion, elevated PASP has no prognostic effect on

improvement in heart functioning in patients undergoing CRT. However, it is associated with worse LV remodeling and increased mortality due to decompensated heart failure.

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