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Original article

Significance of change in serum bilirubin in predicting left ventricular reverse remodeling and outcomes in heart failure patients with cardiac resynchronization therapy

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ABSTRACT

Background: Research on the correlation of serum bilirubin level with cardiac function as well as outcomes in heart failure patients with cardiac resynchronization therapy (CRT) has not yet been reported. The aim of this study was to analyze the relationship between change in serum bilirubin level and left ventricular reverse remodeling, and also to clarify the impact of bilirubin change on clinical outcomes in CRT patients.

Methods: We evaluated 105 consecutive patients who underwent CRT. Patients who had no serum total-bilirubin data at both baseline and 3–9 months' follow-up or had died less than 3 months after CRT implantation were excluded. Accordingly, a total of 69 patients were included in the present analysis. The patients were divided into two groups: decreased bilirubin group (serum total-bilirubin level at follow-up $\leq$ that at baseline; $n = 48$) and increased bilirubin group (serum total-bilirubin level at follow-up $>$ that at baseline; $n = 21$).

Results: Mean follow-up period was 39.3 months. In the decreased bilirubin group, mean left ventricular end-systolic diameter decreased from 54.5 mm to 50.2 mm ($p = 0.001$) and mean left ventricular ejection fraction increased significantly from 29.8% to 37.0% ($p = 0.001$). In the increased bilirubin group, there was no significant change in echocardiographic parameters from baseline to follow-up. In Kaplan–Meyer analysis, cardiac mortality combined with heart failure hospitalization in the increased bilirubin group was significantly higher than that in the decreased bilirubin group (log-rank $p = 0.018$). Multivariate Cox regression analysis revealed that increased bilirubin was an independent predictor of cardiac mortality combined with heart failure hospitalization (OR = 2.66, $p = 0.023$).

Conclusions: The change in serum bilirubin is useful for assessment of left ventricular reverse remodeling and prediction of outcomes in heart failure patients with CRT.

Introduction

Liver function abnormalities are frequently observed in patients with heart failure [1–5]. The mechanism is considered to be derived from two hemodynamic alterations: low hepatic blood flow due to decreased cardiac output and high central venous pressure with atrophy of liver cells and edema of the peripheral area, both leading to hypoxic liver injury [5–10]. In particular, serum bilirubin level is likely to correlate with hemodynamic status, and, in fact, an elevation of bilirubin was recognized in some studies as a predictor of mortality and adverse outcome in heart failure patients [5,11–14]. Recently, cardiovascular implantable electronic devices were rapidly developed, and in particular, cardiac resynchronization therapy (CRT) improves left ventricular function, symptoms, and exercise capacity and reduces both morbidity and mortality in patients with advanced heart failure [15–18]. To our knowledge, however, research on the correlation of serum bilirubin level with cardiac function as well as outcomes in

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CRT patients has not yet been reported. The aim of this study was to analyze the relationship between change in serum bilirubin level and left ventricular reverse remodeling, and also to clarify the impact of bilirubin change on clinical outcomes in heart failure patients with CRT.

Methods

We evaluated 105 consecutive patients who underwent CRT at Yokohama City University Hospital. The selection criteria for CRT included advanced symptomatic heart failure despite optimal medical therapy, which was applied to the patients according to the current guidelines and clinical standards. A CRT-P (pacemaker) or CRT-D (defibrillator) was implanted transvenously, and a left ventricular (LV) pacing lead was inserted through the coronary sinus and positioned as far as possible in the venous system, preferably in a posterolateral vein. Optimization of the devices, such as atrioventricular delay, was performed by echocardiography. Laboratory variables including serum total-bilirubin were determined just before (baseline) and 3–9 months after CRT implantation (follow-up). Measured values closest to 6 months after implantation were used as laboratory variables at follow-up. If patients had earlier adverse events than follow-up period, the variables just before the events were collected. Patients who had no serum total-bilirubin data at both baseline and follow-up or had died less than 3 months after CRT implantation were excluded. Accordingly, a total of 69 patients were included in the present analysis. The patients were divided into two groups: decreased bilirubin group (serum total-bilirubin level at follow-up $\leq$ that at baseline; $n = 48$) and increased bilirubin group (serum total-bilirubin level at follow-up $>$ that at baseline; $n = 21$). The mean duration from baseline to follow-up serum bilirubin assessment in the decreased bilirubin group was 5.2 ± 1.9 months, and that in the increased bilirubin group was 4.9 ± 2.0 months. Echocardiographic evaluation was performed before CRT implantation and at 3–9 months' follow-up. The primary endpoint of this study was hospitalization due to heart failure or cardiac death during long-term follow up after implantation. This study was approved by the Yokohama City University Hospital Ethics Committee (approval number B080703013).

Statistical analysis

Comparisons of quantitative and categorical variables between groups were performed using Pearson Chi-squared test or Student's *t*-test. All continuous data were expressed as mean $\pm$ standard deviation (SD). Univariate or multivariate Cox regression models with a forward stepwise approach were run to assess crude and multivariate adjusted odds ratios (ORs), which were presented with 95% confidence intervals (CIs). For all tests, $p < 0.05$ was considered statistically significant. All statistical analysis was carried out using SPSS (Chicago, IL, USA).

Results

Baseline characteristics

The mean age of the study population was 65.6 ± 13.7 years, and 69.6% were male. The etiology of heart failure was ischemia in 23.2%, dilated cardiomyopathy in 58.0%, and other causes in 18.8%. These patients had advanced heart failure with mean New York Heart Association of 2.80 ± 0.70, LVEF of 29.7 ± 11.0%, and QRS duration of 149.1 ± 35.8 ms. The proportion of patients receiving an angiotensin-converting enzyme inhibitor (ACE-I) or angiotensin receptor blocker (ARB) was 66.7%, and a β-blocker was 52.2%. Baseline clinical characteristics of the decreased bilirubin group and increased bilirubin group are listed in Table 1. There were no statistically significant differences between the two groups. Mean baseline serum total-bilirubin also did not differ between the two groups (0.87 ± 0.44 mg/dl in decreased bilirubin group, 0.71 ± 0.36 mg/dl in increased bilirubin group, p = ns). On the other hand, mean baseline total-bilirubin in seven patients who died less than 3 months after CRT implantation was significantly higher than that of the study population (1.45 ± 0.79 mg/dl vs. 0.82 ± 0.42 mg/dl, $p = 0.002$).

Table 1
Baseline clinical characteristics according to change in serum bilirubin.

	Decreased bilirubin group ($n = 48$)	Increased bilirubin group ($n = 21$)	*p*-Value
Age (years)	64.0 ± 15.2	69.1 ± 8.4	0.154
Male	32 (67%)	16 (76%)	0.436
NYHA	2.83 ± 0.78	2.74 ± 0.51	0.163
Ischemic HF	10 (21%)	6 (29%)	0.491
Hypertension	11 (23%)	6 (29%)	0.622
Diabetes mellitus	14 (29%)	5 (24%)	0.652
Atrial fibrillation	27 (35%)	6 (29%)	0.585
Ventricular arrhythmia	14 (29%)	11 (52%)	0.066
e-GFR <50 ml/min	24 (50%)	13 (62%)	0.369
BNP (pg/ml)	776 ± 1077	531 ± 485	0.323
Total-bilirubin (mg/dl)	0.87 ± 0.44	0.71 ± 0.36	0.125
LBBB	20 (42%)	10 (48%)	0.652
LVEDd (mm)	64.7 ± 10.0	67.9 ± 12.3	0.361
LVESd (mm)	54.5 ± 10.9	57.3 ± 13.8	0.412
LVEF (%)	29.8 ± 10.4	29.6 ± 14.3	0.903
ACE-I or ARB	29 (61%)	17 (81%)	0.099
B-blocker	26 (54%)	10 (48%)	0.623
Spironolactone	26 (54%)	15 (71%)	0.184
Inotropic agent	8 (17%)	1 (5%)	0.182
CRT-D implantation	34 (71%)	17 (81%)	0.386

NYHA, New York Heart Association; HF, heart failure; e-GFR, estimated glomerular filtration rate; BNP, B-type natriuretic peptide; LBBB, left branch bundle block; LVEDd, left ventricular end-diastolic diameter; LVESd, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction; ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CRT-D, cardiac resynchronization therapy defibrillator.

Relationship between change in bilirubin level and echocardiographic parameters

The echocardiographic parameters at baseline and follow up were compared between the decreased bilirubin group and increased bilirubin group, and the relationship between the change in bilirubin level and CRT response was examined. In the decreased bilirubin group, mean left ventricular (LV) end-diastolic diameter (LVEDd) decreased from 64.7 ± 10.0 mm to 61.9 ± 10.6 mm ($p = 0.002$), mean LV end-systolic diameter (LVESd) decreased from 54.5 ± 10.9 mm to 50.2 ± 12.5 mm ($p = 0.001$), and mean LV ejection fraction (LVEF) increased from 29.8 ± 10.4% to 37.0 ± 13.2% ($p = 0.001$). In the increased bilirubin group, there was no significant change in echocardiographic parameters from baseline to follow-up (Table 2).

Impact of change in bilirubin on clinical outcomes

During a mean follow-up period of 39.3 ± 29.6 months, 30 (43.5%) of 69 patients died of any cause, including 19 (27.5%) cardiac deaths, and 23 (33.3%) patients were hospitalized for heart failure. In Kaplan–Meyer analysis, survival free from cardiac death combined with heart failure hospitalization in the decreased bilirubin group was significantly higher than that in the increased bilirubin group (72.7% vs. 45.7% at 2 years, log-rank $p = 0.018$) (Fig. 1).

In univariate Cox regression analysis, increased bilirubin was associated with a higher risk of cardiac mortality combined with heart failure hospitalization (OR = 2.28, 95% CI 1.13–4.60, $p = 0.022$). Delta (Δ) of variables indicated the change in laboratory

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