Clinical Implication of Right Bundle Branch Block in Hospitalized Patients with Acute Heart Failure: Data from the Korean Heart Failure (KorHF) Registry

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Clinical Implication of Right Bundle Branch Block in Hospitalized Patients with Acute Heart Failure: Data from the Korean Heart Failure (KorHF) Registry

Directed by Professor Seok-Min Kang

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ABSTRACT

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Background:

Conflicting data exist regarding the predictive value of bundle branch block (BBB) patterns for mortality in hospitalized patients with acute heart failure (AHF).

Methods:

Two thousand two hundred and two patients enrolled in the Korean Heart Failure (KorHF) Registry were analyzed to compare clinical outcomes among right BBB (RBBB, 5.4%), left BBB (LBBB, 4.9%), and no BBB (89.7%) on admission electrocardiogram. The primary composite endpoint was all-cause

mortality or rehospitalization. The primary composite endpoint was all-cause mortality or rehospitalization.

Results:

During the median follow-up period of 572 days, the 3-year event rate of the composite endpoint was significantly higher in the patients with RBBB compared to those with LBBB or no BBB (65.1% vs. 49.9% vs. 49.3%, log-rank, p=0.004). Multivariate analysis demonstrated an increased risk of the composite endpoint for the patients with RBBB vs. LBBB (hazard ratio (HR)=2.57, p=0.001) and the patients with RBBB vs. no BBB (HR=1.91, p<0.001). In the reduced left ventricular ejection fraction (LVEF ≤ 40%), the risk of the composite endpoint was increased in the patients with RBBB vs. LBBB (for overall from HR 1.61, p=0.002 to HR=2.28, p=0.001).

Conclusion:

RBBB but not LBBB is a significant predictor of all-cause mortality or rehospitalization in hospitalized patients with AHF, especially with reduced LV systolic function.

Key words: Bundle branch block, Acute heart failure, Clinical outcome

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I. INTRODUCTION

Prolongation of the QRS duration has been shown to be associated with increased mortality among patients with heart failure.[1-4] However, only a few studies have investigated the relationship of bundle branch block (BBB) patterns to clinical outcomes. Moreover, conflicting data exist regarding the predictive value of QRS morphology for mortality in hospitalized patients with acute heart failure (AHF).[5-10] While some studies have reported that left BBB (LBBB) is associated with higher mortality,[5-7] others have suggested that right BBB (RBBB) rather than LBBB is an independent predictor of mortality.[8-10] I hypothesized that both types of BBB would be associated with different clinical outcomes in comparison to AHF patients without this electrocardiographic finding.

Therefore, the purpose of this study was to demonstrate the relationship between the BBB patterns and clinical outcomes in hospitalized patients with AHF in Korea. In addition, we sought to identify the subgroups of patients for whom these BBB patterns have a stronger association with clinical outcomes.

II. MATERIALS AND METHODS

1. Subjects

This study specifically evaluated the prognostic utility of BBB patterns in patients with AHF enrolled in the Korean Heart Failure (KorHF) Registry.[11] The KorHF Registry is the first nationwide, prospective and observational multicenter online registry that has been investigating the etiology, clinical characteristics, treatment modalities, morbidity, mortality and prognostic markers of AHF in Korea. Between June 2004 and April 2009, 3,200 patients with AHF were enrolled following a review of the registry data from 24 hospitals in Korea. The diagnosis of heart failure was required to be confirmed at the time of a patient's discharge according to the Framingham criteria.[12]

From the initial recruits of 3,200 patients, 537 patients without available electrocardiographic data and 34 patients with permanent pacemakers including biventricular pacemakers were excluded. After this exclusion, 427 patients with a wide QRS complex that did not meet the criteria for RBBB or

LBBB were further excluded from the analysis.[13] Thus, the final analysis included 2,202 patients.

2. Data collection

The main predictor variable was the presence of RBBB or LBBB on the first 12-lead electrocardiogram, which was ascertained from the initial electrocardiogram results by investigators at each participating center using standard criteria.[13] Detailed data regarding patient characteristics, in-hospital course and discharge medications were also collected from an electronic case report form recorded on a web-based electronic data capture system retrospectively. Left ventricular ejection fraction (LVEF) was obtained using echocardiography by either M-mode or Simpson's methods and LVEF measurement was available in 1,986 (90.2%) patients. Systolic pulmonary artery pressure (PAP) was estimated from tricuspid regurgitation (TR) velocity by adding the right atrial pressure of 10 mmHg and systolic PAP measurement was available in 747 (33.9%) patients.[14]

Research coordinators guided by documented definitions used standardized report forms to collect the follow-up events until October 2009. The primary composite endpoint was all-cause mortality or rehospitalization during follow-up. If a patient was rehospitalized and then died, he was counted for just once for the primary composite endpoint. 144 non-survivors at discharge were excluded for rehospitalization analysis.

The institutional review board or ethics committee at Severance Hospital approved this study protocol, and the patients gave their written informed consent prior to study entry.

3. Statistical analysis

Continuous variables were compared using the analysis of variance (ANOVA) and categorical variables and frequencies were compared using the chi-square test. Survival curves were constructed using Kaplan–Meier method and compared with the log-rank test according to the BBB patterns. We estimated the hazard ratios (HR) and a 95% confidence interval (CI) computed using the Cox proportional hazards model to evaluate the effect of the BBB patterns on clinical outcomes in univariate analysis. Multivariate Cox proportional hazard analysis was also used to identify predictors of clinical outcomes after adjustment for clinical and laboratory variables identified in previous published studies as risk factors for mortality.[9-11]

Subgroup analyses stratified by selected clinical characteristics (age, gender, prior history of diabetes, hypertension and heart failure, presence of ischemic heart disease, LVEF and medication at discharge) were performed for the composite endpoint of all-cause mortality or rehospitalization among each BBB pattern. Subgroup analyses were done, each using a test for heterogeneity to assess for possible interactions between the BBB patterns and various clinical characteristics. All analyses were conducted using SPSS version 18.0 software

(SPSS Inc.). A *p*-value of less than 0.05 was considered statistically significant.

III. RESULTS

1. Baseline characteristics

RBBB was present in 118 patients (5.4%), LBBB in 107 patients (4.9%), and no BBB in 1,979 patients (89.7%). The baseline characteristics of these patients with RBBB, LBBB and no BBB are summarized in Table 1. The patients with RBBB were younger and had lower portion of women than those with LBBB. Almost one-third of the patients required intensive care and 1,708 patients (77.6%) were admitted through the emergency department. The patients with BBB patterns had a significantly higher prevalence of prior heart failure, cardiomyopathy for underlying disease, and worse New York Heart Association (NYHA) functional classes compared to no BBB patients. LVEF was relatively higher in the patients with RBBB and the proportion of reduced LVEF (LVEF ≤ 40%) was also lower in the patients with RBBB compared to LBBB patients.

There were no significant differences with respect to laboratory characteristics among each group. Medication at discharge was comparable among each group with the exception of beta-blockers, which were prescribed more often in the patients with RBBB.

Table 1. Baseline characteristics of study patients at the time of index hospitalization.

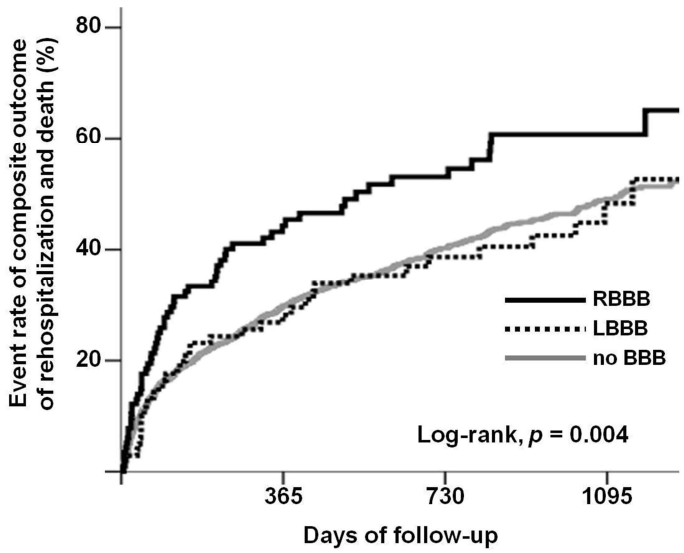
	RBBB (n=118)	LBBB (n=107)	No BBB (n=1977)	*p*-value
Age (years)	68 ± 15	71 ± 12	67 ± 15	0.018
Women	49 (41.5%)	63 (58.9%)	992 (50.2%)	0.034
BMI (Kg/m^2)	23.2 ± 3.6	22.8 ± 3.6	23.3 ± 4.1	0.543
Emergency department admission	96 (81.4%)	90 (84.9%)	1522 (79.9%)	0.455
Intensive care unit admission	38 (32.2%)	38 (35.5%)	601 (30.4%)	0.506
Previous medical history				
Heart failure	47 (39.8%)	38 (35.3%)	499 (25.3%)	<0.001
Hypertension	50 (42.4%)	48 (44.9%)	943 (47.7%)	0.462
Diabetes mellitus	36 (30.5%)	31 (29.0%)	631 (31.9%)	0.781
Chronic renal disease	11 (9.3%)	4 (3.7%)	176 (8.9%)	0.175
Chronic pulmonary disease	8 (6.8%)	6 (5.6%)	70 (3.5%)	0.125
Underlying disease				
Ischemic heart disease	54 (47.4%)	43 (42.6%)	850 (44.4%)	0.764
Hypertension	20(16.9%)	21(19.6%)	443(22.4%)	0.317
Cardiomyopathy	29 (25.4%)	32 (31.7%)	270 (14.1%)	<0.001
Valvular heart disease	15 (13.2%)	12 (11.9%)	229 (12.0%)	0.929
Myocarditis	4(3.5%)	1 (1.0%)	15(0.8%)	0.014
Infiltrative disease	1 (0.9%)	0 (0%)	10 (0.5%)	0.666
NYHA functional class III or IV	84 (80.0%)	76 (75.2%)	1145 (69.1%)	0.031
Clinical finding				
SBP (mmHg)	129 ± 33	127 ± 25	133 ± 31	0.073
DBP (mmHg)	77 ± 19	77 ± 15	79 ± 18	0.074
Hypotension (SBP <90 mmHg)	5 (4.2%)	7 (6.5%)	67 (3.4%)	0.215
Heart rate (per min)	87 ± 27	94 ± 29	92 ± 25	0.098
Laboratory finding				
Sodium (mM)	138.0 ± 5.4	138.4 ± 4.9	138.2 ± 5.2	0.812
Hemoglobin (g/dL)	12.3 ± 2.2	12.3 ± 2.2	12.4 ± 2.4	0.774
Creatinine (mg/dL)	1.52 ± 1.21	1.34 ± 0.91	1.47 ± 1.15	0.470
NT-proBNP (ng/L)	9067 ± 11236	7647 ± 7987	8626 ± 10045	0.653
Echocardiographic finding				
LVEF (%)	39.3 ± 13.6	29.3 ± 12.1	40.0 ± 15.7	<0.001
LVEF ≤ 40%	61 (57.0%)	83 (87.4%)	1008 (56.5%)	<0.001
Medication at discharge				
Beta-blocker	43 (36.4%)	29 (27.4%)	785 (40.3%)	0.023
ACE inhibitor or ARB	68 (57.6%)	66 (61.7%)	1177 (59.6%)	0.826
Aldosterone antagonist	38 (32.2%)	36 (34.0%)	580 (29.6%)	0.549

Values are meant ± SD or number (%). BBB = bundle branch block, RBBB = right bundle branch block, LBBB = left bundle branch block, BMI = body mass index, NYHA = New York Heart Association, SBP = systolic blood pressure, DBP = diastolic blood pressure, LVEF = left ventricular ejection fraction, ACE = Angiotensin converting enzyme, ARB = angiotensin II receptor blocker

2. Clinical outcomes according to BBB patterns

With regard to composite endpoint of all-cause mortality or rehospitalization, 61 patients (51.7%) with RBBB, 38 patients (35.5%) with LBBB and 722 patients (36.5%) with no BBB were rehospitalized or died during a median follow-up period of 572 days. Kaplan-Meier analysis revealed that the composite endpoint at 3 years was significantly higher in the RBBB patients (65.1%), mainly driven by increase rate of rehospitalization when compared with the LBBB patients (49.9%) and no BBB patients (49.3%) (log-rank, p=0.004, Figure 1).

Figure 1. Kaplan-Meier analysis of event rate of the composite endpoint according to BBB patterns.



During the median follow-up period of 572 days, the 3-year event rate of the composite endpoint of all-cause mortality or rehospitalization was significantly higher in the patients with RBBB than those with LBBB or no BBB (65.1% vs. 49.9% vs. 49.3%, log-rank, p = 0.004). BBB = bundle branch block, RBBB = right bundle branch block, LBBB = left bundle branch block.

RBBB was also an independent predictor of the composite endpoint when compared with LBBB (adjusted HR=2.57, 95% CI=1.46–4.50, p=0.001) and no BBB (adjusted HR=1.91, 95% CI=1.37–2.67, p<0.001) even after adjustment for clinical and laboratory variables (Table 2). In contrast to RBBB, LBBB did not have any prognostic value in univariate and multivariate analysis when compared with no BBB (Table 2). With regard to rehospitalization, the unadjusted HR for RBBB vs. LBBB was 1.64 (95% CI=1.00–2.69, p=0.052) and 1.60 for RBBB vs. no BBB (95% CI=1.16–2.20, p=0.002). On multivariate analysis, RBBB was also an independent predictor of rehospitalization when compared with LBBB (adjusted HR=3.09, 95% CI=1.59–6.01, p=0.001) and no BBB (adjusted HR=2.21, 95% CI=1.51–3.25, p<0.001) (Table 2).

In-hospital mortality was not different among groups with 6.8% (8/118) of RBBB, 7.5% (8/107) of LBBB, and 6.5% (128/1977) of no BBB patients (p=0.918).

A total of 390 patients died during follow-up, with 31 RBBB patients (26.3%), 19 LBBB patients (17.8%), and 340 no BBB patients (17.2%). In terms of all-cause mortality, the unadjusted HR for RBBB vs. LBBB was 1.51 without significance (95% CI=0.85–2.67, p=0.158). However, there was a significant difference between RBBB and no BBB (unadjusted HR=1.56, 95% CI= 1.08-2.25, p=0.019). Multivariate analysis showed a marginal significance for increased risk of all-cause mortality in the RBBB patients compared with no BBB patients (adjusted HR=1.63, 95% CI=1.00–2.65, p=0.049) (Table 2).

Table 2. Clinical outcomes according to bundle branch block patterns.

	Number of events/ Number of patients	Univariate analysis			Multivariate analysis		
		HR	95% CI	*p*-value	HR	95% CI	*p*-value
All-cause mortality or rehospitalization							
RBBB vs. LBBB	61/118 vs. 38/107	1.61	1.07 – 2.41	0.022	2.57	1.46 – 4.50	0.001
RBBB vs. no BBB	61/118 vs. 722/1977	1.54	1.19 – 2.00	0.001	1.91	1.37 – 2.67	<0.001
LBBB vs. no BBB	38/107 vs. 722/1977	0.96	0.69 – 1.33	0.811	0.75	0.46 – 1.20	0.223
Rehospitalization							
RBBB vs. LBBB	41/110 vs. 25/99	1.64	1.00 – 2.69	0.052	3.09	1.59 – 6.01	0.001
RBBB vs. no BBB	41/110 vs. 470/1849	1.60	1.16 – 2.20	0.004	2.21	1.51 – 3.25	<0.001
LBBB vs. no BBB	25/99 vs. 470/1849	0.98	0.65 – 1.46	0.912	0.72	0.41 – 1.27	0.253
All-cause mortality							
RBBB vs. LBBB	31/118 vs. 19/107	1.51	0.85 – 2.67	0.158	2.19	0.96 – 5.00	0.062
RBBB vs. no BBB	31/118 vs. 340/1977	1.56	1.08 – 2.25	0.019	1.63	1.00 – 2.65	0.049
LBBB vs. no BBB	19/107 vs. 340/1977	1.03	0.65 – 1.64	0.899	0.75	0.37 – 1.49	0.406

Adjusted for age, sex, history of heart failure, myocardial infarction, diabetes, chronic pulmonary disease, New York Heart Association functional class III or IV vs. I or II, systolic blood pressure, admission creatinine level <2 vs. ≥2 mg/dL, hemoglobin <10 vs. ≥10 g/dL, sodium <135 vs. ≥135 mM, NT-proBNP <1000 vs. ≥1000 ng/L, left ventricular ejection fraction (LVEF) ≤40 vs. >40%, beta-blocker, angiotensin converting enzyme inhibitor and angiotensin II receptor blocker medication at discharge. HR = hazard ratio, CI = confidence interval, RBBB = right bundle branch block, LBBB = left bundle branch block, BBB = bundle branch block.

3. Subgroup analyses for composite endpoint

Interactions between the BBB patterns and clinical parameters were estimated and were shown in Figure 2. The HRs of the composite endpoint for RBBB vs. LBBB were significantly higher in the subgroups of younger than 65 years, men, no prior diabetes, no prior hypertension, ischemic heart disease, and angiotensin converting enzyme inhibitor or angiotensin II receptor blocker use, though the test for interaction was not significant (Figure 2).

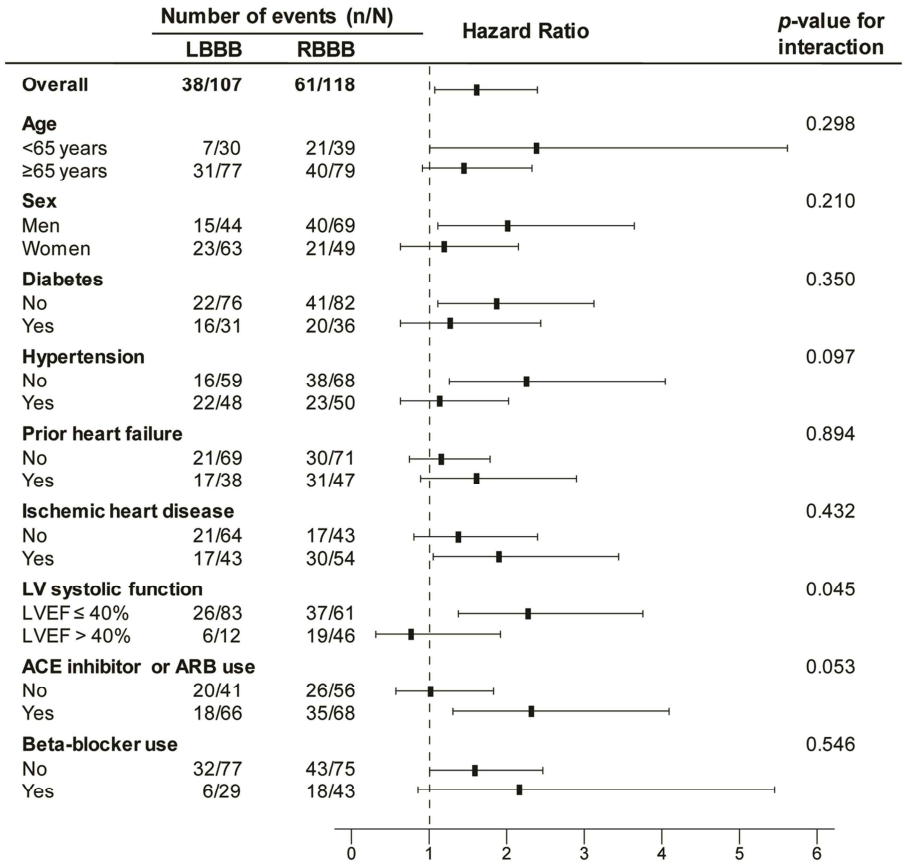
However, we observed a significant interaction between the BBB patterns and LVEF for predicting the composite endpoint (p=0.045 for interaction, Figure 2). For an LVEF of 40% or less, HR for RBBB vs. LBBB was 2.28 (95% CI, 1.38–3.76, p=0.001). By contrast, for LVEF more than 40%, HR was 0.77 (95% CI, 0.31–1.93, p=0.578).

4. Comparison systolic PAP according to the BBB patterns and LVEF

The prevalence of moderate to severe TR was significantly higher in RBBB patients compared with LBBB or no BBB patients (p=0.029, Table 3). Systolic PAP was not significantly different among group with 47.5 ± 16.6 mmHg for RBBB, 46.2 ± 16.2 mmHg for LBBB, and 44.1 ± 16.0 mmHg for no BBB (p=0.356, Figure 3). However, in the patients with RBBB, significantly elevated systolic PAP was noted in the subgroup of reduced LVEF vs. preserved LVEF (52.5 ± 17.5 mmHg vs. 40.0 ± 12.4 mmHg, p=0.014, Figure 3). In contrast to RBBB, in the patients with LBBB and no BBB, systolic PAP was

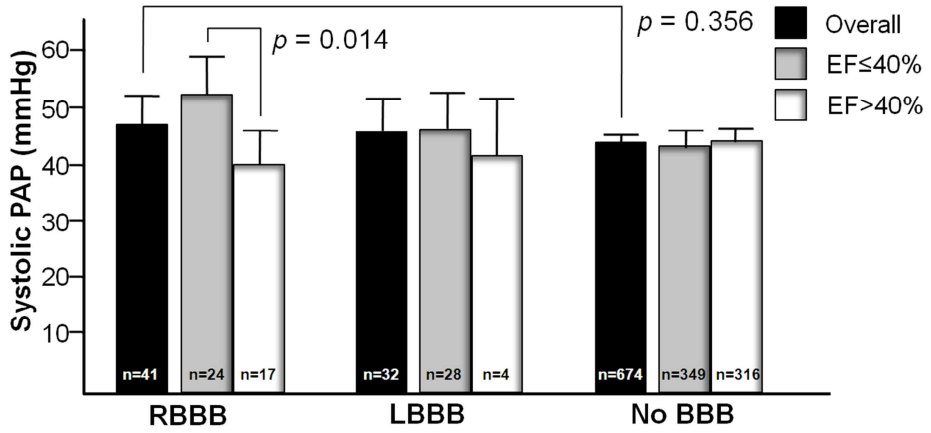
not significantly different between the subgroup of reduced LVEF and preserved LVEF.

Figure 2. Forest plot of subgroup analyses of the composite endpoint comparing RBBB with LBBB.



The hazard ratios of RBBB were significantly higher in subgroups of younger than 65 years, men, no prior diabetes, no prior hypertension, ischemic heart disease, reduced LVEF, and ACE inhibitor or ARB use. The test for interaction was significant only within strata formed by LVEF. LBBB = left bundle branch block, RBBB = right bundle branch block, LV = left ventricular, LVEF = LV ejection fraction, ACE = angiotensin converting enzyme, ARB = angiotensin II receptor blocker.

Figure 3. Comparison systolic PAP according to the BBB patterns and LVEF.



In each box plot, the mean value is indicated and the error bars represent the 95% confidence interval. Systolic PAP was not different among three groups with 47.5 ± 16.6 mmHg for RBBB, 46.2 ± 16.2 mmHg for LBBB, and 44.1 ± 16.0 mmHg for no BBB (p=0.356). Only in the patients with RBBB, significantly elevated systolic PAP was noted in the subgroup of reduced LVEF vs. preserved LVEF. PAP = pulmonary artery pressure, BBB = bundle branch block, LVEF = left ventricular ejection fraction, RBBB = right BBB, LBBB = left BBB.

IV. DISCUSSION

The principal finding of this study is that (1) RBBB but not LBBB is an independent predictor of all-cause mortality or rehospitalization in hospitalized patients with AHF. (2) This finding is pronounced in patients with reduced left ventricular (LV) systolic function. (3) In the patients with RBBB, elevated systolic PAP was noted in the reduced LVEF vs. preserved LVEF.

Recent studies have highlighted the prognostic value of QRS morphology on mortality especially in the setting of AHF. However, these

studies did not show consistent result of mortality regarding the BBB patterns. McCullough et al. found higher 2-year mortality rates for RBBB (57%) and LBBB (58%) compared with the patients with QRS intervals <120 ms (46%) with the patients admitted to intensive care units, but RBBB was not as powerful a predictor of mortality as LBBB on multivariate analysis.[5] Huvelle et al. investigated patients discharged after a de novo episode of AHF or AHF complicating a mild or chronic heart failure and LBBB was an independent predictor of one-year mortality in the four-week survivors.[6] In contrast to these reports, Tabrizi et al. found that LBBB did not have any independent influence on five-year mortality in the patients with symptomatic heart failure requiring hospitalization to coronary care units.[15] Consistent with my findings, Mueller et al. reported that RBBB but not LBBB was a powerful predictor of long-term mortality during 720-day follow-up, and more recently Barsheshet et al. found that the presence of RBBB increased four-year mortality in the hospitalized patients with systolic heart failure.[8, 10]

These conflicting results may be attributed to the heterogeneous nature of AHF and the patients' characteristics enrolled in each study.[16] The subjects enrolled in this study were relatively younger, had a lower proportion of male, ischemic heart disease, and had a higher proportion of prior heart failure and admission history through emergency department.[7-10] However, the clinical characteristics of RBBB patients were similar to several previous studies.[7-10]

RBBB may result from various disorders affecting the right heart,

which indicates structural changes in the right ventricle with pulmonary hypertension or right ventricular dysfunction, which complicate the clinical course of the primarily left heart disease resulting in AHF.[17-19] Right ventricular dysfunction had an additive predictive value in patients with LV systolic dysfunction.[20, 21] Generally, the patients with AHF do have advanced cardiac diseases involving the left ventricle that is severe enough to cause AHF. Therefore, LBBB itself may not provide incremental prognostic information in the patients with severe LV dysfunction. Accordingly, the presence of right ventricular dysfunction or structural change rather than the severity of LV dysfunction can give more important prognostic implications.[22, 23] Therefore, it is conceivable that RBBB had a significant prognostic role in this setting. In the line of these perspectives, my results that RBBB had a more marked prognostic impact especially in severe reduced LV systolic function support these explanations. Also, I found that systolic PAP was significantly elevated in the reduced LVEF patients with RBBB compared to preserved LVEF patients with RBBB. One more possible reason is that most of these patients had admission history through emergency department which means acute exacerbation of heart failure, resulting in transiently RBBB with acute distention of right heart and increase in right-side pressure.

Several potential limitations of the present study need consideration. Firstly, the analysis of BBB patterns was performed with only admission electrocardiograms, so it was unknown when new BBB had appeared or

potentially disappeared. Secondly, an evaluation of right ventricular function or structural disease by echocardiogram or other modalities, which provides additional prognostic information to RBBB on electrocardiogram, was not performed. However, SPAP was measured, which could suggest one possible reason for a worse prognosis in patients with RBBB combined with reduced LV systolic function. Thirdly, details about long-term complications including ventricular arrhythmias, stroke, and competing causes of rehospitalization and death were unavailable.

Ⅴ. CONCLUSION

RBBB on admission electrocardiogram is associated with poor clinical outcomes in hospitalized patients with AHF and its significance is pronounced with reduced LV systolic function.

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ABSTRACT (IN KOREAN)

한국 심부전 등록 사업 자료를 이용한 급성 심부전으로 입원한 환자에서 우각차단이 갖는 임상적 의의

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배 경:
급성 심부전으로 입원한 환자에서 각차단에 따른 예후에 대해 상반된 결과가 보고 되고 있다. 따라서 본 연구에서는 한국 심부전 등록 사업 자료를 이용하여 급성 심부전으로 입원한 환자에서 각차단에 대한 예후를 알아보고, 소집단 분석을 통해 우각차단 혹은 좌각차단이 더 예후에 의의를 가지는 임상적 집단을 찾고자 하였다.

방 법:
한국 심부전 등록 사업에 급성 심부전으로 입원하여 등록된 총 2,202 명에 대해 입원 당시에 시행한 심전도 상에서 우각차단이 있는 환자 군 (5.4%), 좌각차단이 있는 환자 군 (4.9%), 각차단이 없는 환자 군 (89.7%)에 대해 임상적 결과를 비교하였다. 일차 평가 기준으로 전체 사망 및 재입원 사건 발생을 세 군에 대해 비교하였다.

결 과:
추적관찰 기간 동안 우각차단이 있는 환자 군에서 좌각차단이나 각차단이 없는 환자 군에 비해 3 년 전체 사망 및 재입원 사건 발생률이 유의 있게 가장 높았다 (우각차단이 있는 환자 군 65.1%, 좌각차단이 있는 환자 군 49.9%, 각차단 없는 환자 군 49.3%, log-rank, p=0.004). 다변량 분석에서도 역시 우각차단이 있는 환자 군은 좌각차단이 있는 환자 군과 각차단이 없는 환자 군에 비해 전체 사건 발생의 위험이 높았다 (좌각차단이 있는 환자 군과 비교 시 위험률 2.57 배, p=0.001, 각차단이 없는 환자 군 과 비교 시 위험률 1.91 배, p<0.001). 소집단 분석에서는 좌심실 박출율이 40% 이하로 감소되어 있는 환자 군에서 우각차단의 전체 사망 및 재입원 사건 발생률 위험 증가가 더욱 심화되었다 (전체 환자 분석에서는 좌각차단이 있는 환자 군과 비교 시 위험률 1.61 배, p=0.002, 좌심실 박출율이 40% 이하로 감소되어 있는 소집단에서는 위험률 2.28 배, p=0.001).

결 론:
좌각차단이 아닌 우각차단이 급성 심부전으로 입원한 환자에서 전체 사망 및 재입원을 유의하게 예측하였으며, 특히 좌심실 수축 기능이 감소해 있는 환자에서 보다 더 의미가 있었다.

핵심되는 말 : 각차단, 급성심부전, 임상적 결과