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Clinical Determinants of Left Ventricular Ejection Fraction Deterioration in Patients Suffered From Complete Left Bundle Branch Block

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Background: Recently, the deleterious effects of left bundle branch block (LBBB) on left ventricular systolic function have been taken into consideration.
Objectives: The present study aimed to identify underlying factors that predict left ventricular ejection fraction (LVEF) deterioration in patients suffered from complete LBBB.
Patients and Methods: In a retrospective case-control study, the data of 220 consecutive patients diagnosed with LBBB on their electrocardiograms were assessed. They were referred to Isfahan Heart Center in Isfahan Province, Iran in 2013. LVEF deterioration was defined as a decrease in LVEF at least 10% between the baseline and follow-up echocardiography study. Thus, achieving the LVEF values $\leq$ 40% in patients with an initial EF of > 50% was considered LVEF deterioration.
Results: Among 220 patients, 40% of LBBB patients suffered LVEF deterioration within 3 months of initial assessment. The group with LVEF deterioration had higher male to female ratio, had higher NYHA score, and suffered more from systolic hypertension than another group. Those with coronary artery disease (CAD) had also significantly lower LVEF than non-CAD ones. Adverse associations were revealed between systolic blood pressure and LVEF measurement ($r = -0.193$, $P = 0.006$) as well as between NYHA score and LVEF ($r = -0.215$, $P = 0.002$). A multivariable logistic regression model showed that among baseline variables, male gender (OR = 3.218, $P < 0.001$), history of systolic hypertension (OR = 2.012, $P = 0.029$), higher NYHA score (OR = 1.623, $P = 0.005$), and the presence of coronary artery disease (OR = 2.475, $P = 0.028$) could effectively predict LVEF deterioration in patients with LBBB.
Conclusions: Male gender, history of hypertension, high NYHA score, and the presence of CAD predict LVEF deterioration in patients with LBBB.

Keywords: Bundle-Branch Block; Coronary Artery; Left Ventricular; Ejection Fraction

1. Background

New-onset LBBB leading to poor prognosis (even in asymptomatic patients) rises several questions concerning the importance of assessing relationship between this arrhythmic phenomenon and other functional and structural cardiac deterioration such as cardiac ischemic events (1), left ventricular hypertrophy (2), heart failure state (3), and left ventricular dysfunction (4). In this regard, the deleterious impact of LBBB on left ventricular systolic and diastolic function has been established even in patients without overt underlying heart disease (5). The poor prognosis of LBBB leading to noted cardiovascular events can be associated with an increased mortality and morbidity, whatever the control population, even in healthier individuals. In this context, Framingham heart study showed a significant increase in mortality among patients with LBBB in comparison with normal subjects (6). In other large population studies, the appearance of LBBB was associated with increased risk of progressive heart failure, acute myocardial infarction, and atrioventricular block (7). Within the last decade, the deleterious effects of LBBB on left ventricular systolic and diastolic function have been taken into consideration. Delaying left ventricular systolic and diastolic function indicated by reduced left ventricular ejection fraction (LVEF) may be explained by septal motion abnormality that has been shown by some authors (8, 9). However, the underlying factors of reduced LVEF in LBBB patients have not been clearly determined. Meanwhile, by identifying and controlling baseline triggering factors affecting LVEF decline in these patients, prevention of the progressive left ventricular dysfunction can be effectively facilitated.

2. Objectives

The present study aimed to identify underlying factors that predict LVEF deterioration in patients who suffered from complete LBBB.

3. Patients and Methods

3.1. Study Population

In this retrospective case-control study, the data of 220 consecutive patients diagnosed with LBBB on their electrocardiograms were assessed. They were referred to Isfahan Heart center, as a general referral hospital in Isfahan Province, Iran from July to September 2013. LBBB was diagnosed according to the definition criteria of the New York Heart Association as "QRS interval ≥ 120 ms, notched, wide and predominant R waves in leads I, aVL, V5, and V6, notched and broad S waves in V1 and V2 with absent or small R waves, notching or a plateau in the mid-QRS wave, ventricular activation time > 50 ms at the onset of the QRS interval, M-shaped QRS variants with occasionally wide R waves in V5 and V6, no initial Q wave over the left precordium and absence of pre-excitation" (10). The diagnosis of LBBB was performed by a cardiologist blinded to the study design. The main inclusion criteria included the presence of LBBB, the existence of at least two consecutive echocardiography studies with a minimum follow-up of 3 months and a reliable left ventricular ejection fraction (LVEF), and a LVEF > 50% at initial assessment. All patients who suffered ischemic events or underwent any cardiac interventions between the two echocardiography assessments were excluded from the study. Because none of the patients experienced these events, 220 initially included patients were finally assessed. The study met the requirements for a waiver of informed consent from the institutional review board at Isfahan University of Medical Sciences. In this study, LVEF deterioration was defined as a decrease in LVEF at least 10% between the baseline and follow-up echocardiography study. Thus, achieving the LVEF values ≤ 40% in patients with an initial EF of > 50% was considered as LVEF deterioration. LVEF was visually estimated in the apical 4- and 2-chamber views (11).

3.2. Data Collection

Data were collected by reviewing hospital recorded files, including demographic characteristics and clinical data on cardiovascular risk factors such as current smoking history (patients regularly smoke a tobacco products one or more times per day or have smoked in the last 30 days prior to admission) (12), hypercholesterolemia (total cholesterol ≥ 5.0 mmol/L, HDL-cholesterol ≥ 1.0 mmol/L in men, or ≥ 1.1 mmol/L in women, and triglycerides ≥ 2.0 mmol/L) (13), hypertension (systolic blood pressure ≥ 140 mmHg and/or diastolic ≥ 90 mmHg and/or on antihypertensive treatment), diabetes mellitus (symptoms of diabetes plus at least one of the following parameters: plasma glucose concentration ≥ 11.1 mmol/L, fasting plasma glucose ≥ 7.0 mmol/L, and 2-hpp ≥ 11.1 mmol/L) (14), and the New York Heart Association (NYHA) functional classification for assessing heart failure state (15). Also, the angiography reports were assessed for determining the presence of CAD that was defined as ≥ 70% luminal diameter narrowing of a major epicardial artery or ≥ 50% narrowing of the left main coronary artery. Also, the number of involved coronary vessels and left main lesion were also assessed.

3.3. Study Endpoints

The study endpoint determined main baseline indicators, which associated with LVEF deterioration and could predict this phenomenon in complete LBBB patients.

3.4. Statistical Analysis

Sample size was determined at 95% confidence interval, and 20% precision. The expected prevalence of LV systolic function is 40.0% and 20.0% in those with and without LBBB, respectively from previous study (16), which eventually determined to be at least 220 patients. In this regard, the study power was also determined at 95.6%. Results were reported as mean ± standard deviation (SD) for the quantitative variables and percentages for the categorical variables. The groups were compared using the Student t test or Mann-Whitney U test regarding the continuous variables and the chi-square test (or Fisher exact test if required) for the categorical variables. The normality distribution of variables was assessed using the Kolmogorov-Smirnov test. Predictors exhibiting a statistically significant relation with LVEF deterioration in two groups were taken for a multivariable logistic regression analysis to investigate their independence as predictors. P values of 0.05 or less were considered statistically significant. All the statistical analyses were performed using SPSS version 19.0 (SPSS Inc., Chicago, IL, USA) for Windows.

4. Results

The echocardiography reports of 220 patients were reviewed for assessing LVEF deterioration. In this regard, 90 patients experienced deterioration (LVEF ≤ 40%) compared to 130 patients without this event (LVEF > 40%). As shown in Table 1, the former group had higher male to female ratio, had higher NYHA score, and also suffered more from systolic hypertension than those without LVEF deterioration (mean systolic blood pressure, 134.80 ± 23.48 mmHg versus 127.53 ± 20.41 mmHg, P = 0.021). The mean LVEF after follow-up period in men was 39.12 ± 15.29% and in women was 47.98 ± 14.53 that was considerably lower in men. Also, mean LVEF in patients with and without systolic hypertension was 41.49 ± 16.30% and 47.92 ± 13.40% with a significant discrepancy (P = 0.002). Those with CAD was also significantly lower LVEF than non-CAD ones (40.65 ± 15.14% versus 46.66 ± 12.26%, P = 0.004). In this regard, the patients

with 3-vessel coronary involvement had considerably lower mean LVEF than the group with normal coronary vessels (34.49 ± 15.30% versus 46.66 ± 15.26%, P = 0.004) (Figure 1). However, no significant differences were observed between two groups in other variables such as average age, history of diabetes mellitus, hyperlipidemia, and smoking. The Pearson correlation coefficient analysis showed adverse associations between systolic blood pressure and LVEF measurement (r = -0.193, P = 0.006) as well as between NYHA score and LVEF (r = 0.215, P = 0.002) at follow-up time. A multivariable logistic regression model showed (Table 2) that among baseline variables, male gender (OR = 3.218, P < 0.001), history of systolic hypertension (OR = 2.012, P = 0.029), and higher NYHA score (OR = 1.623, P = 0.005), and the presence of coronary artery disease (OR = 2.475, P = 0.028) could effectively predict LVEF deterioration in LBBB patients.

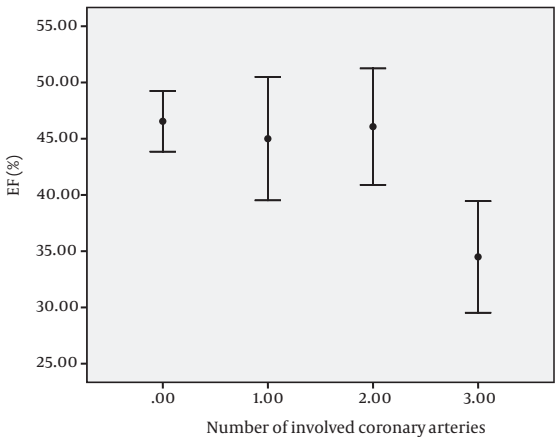

Figure 1. Association Between the Number of Involved Coronary Arteries and Left Ventricular Ejection Fraction in Patients With LBBB

Table 1. Baseline Characteristics and Clinical Data of Study Subjects [a]

Characteristics	Group with LVEF ≤ 40%	Group with LVEF > 40%	P Value
Male gender	53 (58.9)	42 (32.3)	< 0.001
Age, y	66.70 ± 9.79	65.62 ± 10.41	0.437
NYHA score			0.011
I	33 (36.7)	63 (48.5)	
II	27 (30.0)	42 (32.3)	
III	24 (26.7)	23 (17.7)	
IV	6 (6.7)	2 (1.5)	
History of hypertension	43 (47.8)	40 (30.8)	0.010
History of diabetes mellitus	24 (26.7)	27 (20.8)	0.308
History of hyperlipidemia	56 (62.2)	84 (64.6)	0.716
Current smoking	16 (17.8)	24 (18.5)	0.895
Coronary artery disease	46 (51.1)	46 (35.4)	0.020
Number of coronary involvement			0.003
0	43 (47.8)	82 (63.1)	
1	12 (13.3)	16 (12.3)	
2	9 (10.0)	19 (14.6)	
3	26 (28.9)	13 (10.0)	
Left main lesion	1 (1.1)	1 (0.8)	0.999

[a] Data are presented as No. (%) and mean ± SD.

Table 2. Multivariate Logistic Regression Modeling to Determine Main Determinants of LVEF Deterioration in Patients With LBBB [a]

Characteristics	P Value	Odds Ratio	95% CI
Male gender	< 0.001	3.218	1.722-6.014
Advanced age, y	0.507	0.990	0.960-1.020
Higher NYHA score	0.005	1.623	1.155-2.278
History of hypertension	0.029	2.012	1.075-3.759
History of diabetes mellitus	0.080	1.910	0.926-3.940
History of hyperlipidemia	0.625	0.884	0.521-1.161
Smoking	0.124	0.324	0.202-1.654
Coronary artery disease	0.028	2.475	1.103-5.556

[a] Abbreviation: LBBB; left bundle branch block.

5. Discussion

The present study aimed to assess LVEF deterioration in patients with LBBB and also tried to determine its main determinants helping prediction of this decline in patients with LBBB. The results showed that about 40% of LBBB patients would suffer LVEF deterioration within 3 months of initial assessment. Also, among all baseline parameters, hypertension status, male gender, high HYHA score, and presence of CAD could effectively predict LVEF deterioration in these patients. In fact, a significant link was revealed between interventricular dyssynchrony and LV dysfunction consistently with previous studies (4, 10, 17).

Xiao et al. (16) reported a similar association of LBBB with deterioration of LV systolic function in patients with cardiomyopathy. Also, this association has been quantified by Zhou et al. (18) who showed that the LBBB-dependent activation abnormalities had a dominant effect on the deterioration of LV function. Moreover, Brunekreeft et al. confirmed a significant difference in left ventricular volumes, and LVEF between two groups with and without LBBB (19). Regarding deterioration of LVEF and similar to our study, Framingham study showed that the appearance of complete LBBB on a routine ECG was frequently associated with underlying hypertension and CAD. In Angheloiu study, history of congestive heart failure prior to baseline echocardiogram and high LV mass were associated with this phenomenon. According to these findings, it can be concluded that some underlying risk profile such as systolic hypertension, heart failure (assessed by NYHA classification), and cardiac ischemic event can predispose LBBB patients to LV dysfunction indicated by decline LVEF. In fact, as confirmed by some previous studies, some cardiovascular risk profile leading to elevated LV mass, shortening LV filling time, prolongation of relaxation times, increase in wall thickness, reduction of LV stroke index, and LV hypertrophy potentially result in lowering LVEF and consequently LV dysfunction in LBBB patients (20-22).

Regarding association between systolic hypertension and LVEF deterioration, this deteriorating effect can be mediated by the worsening effects of elevated systolic blood pressure on loading conditions of the ventricle, and also increase in afterload that produce a large decrease in stroke volume (23). Also, elevated blood pressure can increase cardiac workload, which leads to the development of left ventricular hypertrophy, LV mass, as well as relatively increased wall thickness. These abnormalities cause reduced LVEF. Also, decrease in LVEF may be due to systolic hypertension developing CAD that was also shown in our study as another main determinant (24).

With regard to the gender difference in left ventricular systolic function and reduced LVEF, the studies on a population-based sample aged 45 to 74 years showed that LVEF was less than the predefined partition value in 4.7% of women and in 16.7% of men in normal population, leading greater LV myocardial and chamber function in men than in women (25). Echocardiography assessments indicated higher velocity of mitral inflow early wave and the systolic velocity of the pulmonary vein flow as well as lower velocities of mitral annulus motion in the atrial and systolic phases in women, especially in postmenopausal state compared with men (26). This superiority has been also detected independent of hypertension condition as Celentano and colleagues indicated that clinically healthy hypertensive and normotensive women had higher LV chamber and midwall systolic function than men, independent of left ventricular geometry, body size, age and heart rate (27). These findings may also explain lower deterioration of LVEF in LBBB patients likely to healthy subjects.

The present study could effectively assess the left ventricular function status in those patients with LBBB and in this line, determined main determinants of LVEF deterioration in LBBB patients, especially in our population with a high prevalence of cardiovascular ischemic events. However, because of small available cases of LBBB in our center, further studies considering population-based survey, including cases from other referral centers is recommended.

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