Exercise-Induced Left Bundle Branch Block: Prevalence and Prognosis

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Abstract

Background: **Exercise-induced left bundle branch block (EI-LBBB) is an infrequent finding. Its prevalence and prognostic significance are not clear.**

Objective: **To evaluate, in a longitudinal study, the prevalence and prognostic significance of EI-LBBB in American war veterans.**

Methods: **We evaluated 9,623 patients submitted to an exercise test (ET) in treadmill between 1987 and 2007. The outcomes were compared between those with normal TE, the ones with EI-LBBB and the ones with down-sloping ST-segment. Mortality and causes of death were identified while blinded to the ET results.**

Results: **In this prospective cohort, 6,922 individuals had normal ET results (57.2 ± 11.4 years), 1,739 had abnormal ST-segment depression (62.7 ± 9.8 years), and 38 had EI-LBBB (65.2 ± 11.9 years). The prevalence of EI-LBBB was 0.38%. After 8.8 years, there were 1,699 deaths due to all-cause mortality and 610 cardiovascular (CV) deaths; coronary artery disease and heart failure were more prevalent in patients with EI-LBBB. Patients with EI-BCRE had a hazard ratio of 2.37 (p = 0.002) for all-cause mortality, but it was not significant when adjusted for age or when the CV death was the assessed outcome.**

Conclusion: **EI-LBBB is a rare clinical finding. Individuals with BCRE-EI have higher all-cause mortality when compared to those with normal ET results. However, this fact is explained by the fact that these patients are significantly older and have more associated cardiovascular diseases. (Arq Bras Cardiol. 2011; [online].ahead print, PP.0-0)**

Keywords: **Heart block; exercise test; veterans; coronary disease; ventricular dysfunction, left.**

Introduction

Exercise-induced left bundle branch block (EI-LBBB) is a rare electrocardiographic finding that has been reported to be both associated with and without demonstrable cardiac abnormalities[1,2].

This phenomenon has been reported to occur in approximately 0.5% of all patients undergoing exercise testing[3-7].

The seminal paper by Grady et al[8], which found EI-LBBB to be an independent predictor of major cardiac events and death, utilized a case-control method based on a 4 year follow-up of only 70 cases of EI-LBBB and 70 matched controls. To validate these findings, we longitudinally evaluated EI-LBBB in a large Veteran population and compared the prognostic significance of this conduction disturbance in individuals with and without abnormal ST responses to exercise testing.

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Methods

Study population and resting electrocardiogram

Nine thousand, six hundred and twenty-three consecutive adult patients, who underwent clinically indicated treadmill testing from 1987 to 2007 at the Veteran Affairs Medical Center, were evaluated. The research database contains information collected from the physician supervising the tests, including presence of coronary artery disease (CAD) and/or heart failure. This information was obtained by questioning the patient and was also confirmed by reviewing their electronic medical records, which contains clinical and hospital admission notes and reports on previous testing performed due to clinical indications. Excluded patients were those with the following electrocardiographic (ECG) patterns that interfered with the analysis of the exercise ECG: 1) resting ST depression and/or left ventricular hypertrophy, paced rhythm and pre-excitation syndromes (n = 675, 7%), 2) atrial fibrillation (n = 109, 1.1%), resting left bundle branch block (n = 68, 0.7%) and exercise-induced right bundle branch block (n = 23, 0.24%). Three hundred and thirty-eight (3.5%) women were also excluded. The final cohort for analysis consisted of 8,410 males. The research protocol was approved by the Veteran

Affairs and Stanford Institutional Review Boards and informed consent for testing was obtained from all patients.

Exercise testing

Subjects underwent symptom-limited exercise treadmill testing (ETT) using individualized ramp protocol and exercised to maximum exertion. ECG recording and blood pressure monitoring was performed every two minutes during the test and recovery and when deemed necessary by the physician who was in charge of the exercise testing. In cases of multiple ETTs, only the first one was included for analysis. Twelve-lead ECG data were recorded during the exercise and for 6 minutes during recovery. Exercise-induced LBBB was defined as LBBB that was documented only during the exercise testing. Standard criteria were used to define left bundle branch block[9]: QRS duration > 120 milliseconds; predominately upright complexes with broad-slurred R waves in leads I, aVL, V5, V6; the QRS could be notched, but there were no Q waves in either lead I, aVL, V5 or V6; and QS or rS pattern in V1 with a normal intrinsicoid deflection of 35 milliseconds. ST-segment depression and ST slopes were measured and read by an experienced board certified cardiologist (VF). ST-segment depression was measured at the J junction and ST slope measured over the following 60 milliseconds of the ST segment, and classified as abnormal when horizontal or down-sloping[10]. Standard criteria for test interruption were used, including serious dysrhythmias, a drop in systolic blood pressure below resting levels, greater than 3.0 mm ST segment depression or ST elevation greater than 1.0 mm, severe angina pectoris, or central nervous system complaints. When the endpoint was reached, the treadmill was stopped and the patient was placed in the supine position within 1 minute. Baseline and maximal exercise variables, including exercise-induced hypotension or angina, and estimated exercise capacity in metabolic equivalents (METs) from the final treadmill speed and grade were recorded.

Outcomes

Demographic characteristics and outcomes were compared between individuals with normal ECG responses, those with ≥ 1.0 mm horizontal or down-sloping ST-segment depression and those with EI-LBBB. The primary outcome variables were all-cause and cardiovascular mortality. Social Security Death and California Death Indices (from the California Department of Health Services) were used to ascertain the vital status of each patient as of December 31, 2007. The California Death Index provided cause of death and it was confirmed by reviewing the Veteran Affairs computerized medical records.

Data analyses

Subjects with EI-LBBB, exercise-induced ST segment depression, and normal ST responses to exercise testing were grouped and compared. Analysis of variance with Bonferroni post-hoc adjustment for multiple comparisons and χ^2 tests were used for continuous and dichotomous variables, respectively. All continuous variables exhibited normal distribution and are presented as mean ± SD, while categorical variables are expressed as absolute and relative (percent) frequencies. P values < 0.05 were considered statistically significant. Age-matching was done by randomly removing patients from the normal and EI-ST depression groups until appropriately aged samples were obtained to account for age differences between the groups. The process was repeated several times.

All-cause and cardiovascular mortality were used as the primary end points for Kaplan-Meier survival analysis. Cox proportional hazards analysis was used to determine which variables were independently and significantly associated with time to death in both univariate and multivariate models. Analyses were adjusted for age in years and presence of any heart disease. The Number Cruncher Statistical System (NCSS Kaysville, Utah) was used for all statistical analysis.

Results

Of the 9,623 patients screened, 38 cases of EI-LBBB were identified, yielding a prevalence of 0.39% (Table 1). Of 8,410 subjects who met the inclusion criteria, 32 (0.38%) exhibited EI-LBBB, 1,461 (17.41%) exhibited exercise-induced ST depression, and 6,917 (82.21%) had a normal exercise ECG response. The average duration of follow-up was 8.8 years. Table 2 shows the clinical characteristics of the three groups of patients. Individuals with EI-LBBB were older and had higher prevalence of CAD, heart failure, diabetes and tobacco use. Resting heart rate and peak systolic blood pressure were similar across the three groups. The EI-LBBB patients achieved the lowest MET level and peak heart rate compared to the abnormal exercise-induced ST depression and normal ST response groups. Other demographic characteristics are shown in Table 3. Age-matched samples demonstrated that EI-LBBB patients have the same prevalence of ischemic heart disease as those with exercise-induced ST depression, but twice the prevalence as normal individuals; the EI-LBBB patients had three times the prevalence of heart failure as the normal ones (14% *vs* 5%; p < 0.001).

There were 1,699 all-cause and 610 cardiovascular (CV) deaths in the target population. Annual death rates were 3.8% among EI-LBBB patients, 2.6% among those with abnormal exercise-induced ST depression and 1.8% in those with normal exercise tests (Log-rank $\chi 2 = 53.6$, $p < 0.0001$; Fig. 1). The rate for cardiovascular causes was 2.1% for EI-LBBB patients, 1.2% for those with exercise-induced ST depression, and 0.6% for those with a normal ECG response. Patients with EI-LBBB and those with exercise-induced ST depression had a Cox proportional hazard ratio of 2.4 (p = 0.002, 95% CI: 1.4 to 4.0) and 1.9 (p = 0.01, 95% CI: 1.1 to 2.7), respectively for all-cause mortality).Both groups did not exhibit significant predictive value when further adjusted for the presence of CAD and/or heart failure (Table 2).

Of the 32 cases of EI-LBBB, 13 deaths occurred (4 CV deaths due to acute myocardial infarction). Age, body mass index, resting heart rate, Borg rating, and METs achieved were not statistically different between the two groups (Table 4). However, the non-survivors had a significantly higher prevalence of CAD and heart failure.

Table 1 - **Demographics, clinical, baseline ECG, exercise test data and outcomes**

Variables	Total population (n = 9,623)
Age (years)	58.8 (11.3)
Height (cm)	176 (8.9)
Weight (kg)	87.7 (17.6)
Body mass index (kg/m²)	28.4 (5.3)
Women	338 (3.5%)
Medical history	
Coronary artery disease (%)	22.3
Ischemic heart failure (%)	3.7
Non-ischemic heart failure (%)	3.4
Hypertension (%)	50.6
Tobacco use (%)	58.2
Diabetes (%)	13.5
Obesity (%)	32.1
Pulmonary	6.0
Baseline ECG	
Rest left bundle branch block (%)	0.7
Rest right bundle branch block (%)	3.2
Atrial fibrillation (%)	1.1
Rest ST segment depression ≥ 1 mm (%)	7.0
Any diagnostic ECG Q wave (%)	15.9
Exercise test	
Resting heart rate (bpm)	77 (21)
Maximum heart rate (bpm)	138 (24)
Peak systolic blood pressure (mmHg)	177 (29)
METS	8 (3)
BORG scale	17 (3)
Exercise-induced ST depression (%)	8.0
Exercise-induced left bundle branch block (%)	0.39
Exercise-induced right bundle branch block (%)	0.27
Outcomes	
Annual all-cause mortality (%)	1.8
Annual cardiovascular mortality (%)	0.6
Died	1,694 (17.6)

Data presented as mean (+SD). Coronary artery disease was defined as a history of previous myocardial infarction, percutaneous coronary intervention, coronary artery by-pass grafting surgery or a positive cardiac angiogram. Obesity was defined as body mass index > 30 kg/m².

Table 2 - **Male study cohort characteristics (after exclusions)**

	Normal ETT	EI-ST dep	EI-LBBB	ANOVA p-value
Sample size (n)	6917	1461	32	
Age (years)	57.2 (11.4)	62.7 (9.8)	65.2 (11.9)*	<0.0001
Height (cm)	176 (29.2)	176.3 (40.4)	174.8 (8.6)	0.250
Weight (kg)	88.3 (19.1)	85.3 (16.3)	82.7 (22.9) *	<0.0001
Body mass index (kg/m²)	28.5 (5)	27.7 (4.9)	27 (6.7) *	0.01
Resting heart rate (bpm)	77 (23)	76 (15)	74.5 (14)	0.068
Peak heart rate (bpm)	140 (26)	137 (24)	134 (29) *	0.001
Peak systolic blood pressure (mmHg)	177 (28)	177(29)	169 (3)	0.209
METs	8.6 (3.5)	7.6 (3.3)	6.6 (3.1) *	<0.0001
Coronary artery disease (%)	18.2	31.9	34.2*	<0.0001
Any diagnostic ECG Q wave (%)	13.2	17.4	8.1*	<0.0001
Heart failure (%)	2.6	6.8	15.8*	<0.0001
Ischemic heart failure (%)	2.4	4.4	18.4*	<0.0001
Diabetes (%)	12.7	15.5	15.8*	0.007
Tobacco use (%)	59.8	53.7	63.2*	<0.0001
Annual all-cause mortality (%)	1.8	2.64	3.76*	<0.0001
Annual CV mortality (%)	0.6	1.2	2.1	0.112

*Data presented as mean (+SD). Normal ETT - normal exercise treadmill testing; EI-ST dep - exercise-induced ST depression; EI-LBBB - exercise-induced left bundle branch block; MET - metabolic equivalent. * Denotes p < 0.01 EI-LBBB vs normal ETT.*

Discussion

In this large cohort of men, we confirmed that EI-LBBB is an unusual response in individuals who undergo routine, clinical exercise testing (0.38%). The rarity of this finding is consistent with that reported in previous studies (Table 5). In addition, we have confirmed previous studies that have documented a strong association with CAD and/or heart failure in patients with EI-LBBB. We also observed that individuals who develop EI-LBBB during treadmill testing have a significantly higher all-cause mortality rate compared to both individuals with normal and those with abnormal ST-segment depression. However, it loses it predictive ability when adjusted for the presence of CAD and/or heart failure. This latter finding is consistent with authors who have attributed EI-LBBB to functional alterations of the conduction system mediated by autonomic influences[2,4,6,7,11,12], while our prevalence findings are consistent with those who have proposed an association with CAD[3,5,13-16].

A lower heart rate at peak exercise and poor functional capacity are variables that identify a higher risk group for subsequent all-cause and cardiovascular mortality[17,18]. An interesting finding in the present study was that the presence of EI-LBBB was associated with a lower maximal heart rate and lower exercise capacity compared to those with exercise-induced abnormal ST depression and normal subsets of patients.

Table 3 - Age matched male study cohort characteristics (after exclusions)

	Normal ETT	EI-ST dep	EI-LBBB	ANOVA p-value
Sample size (n)	128	64	32	
Age (years)	63 (9.4)	62.9 (10)	64.2 (11.9)	0.24
Height (cm)	175.8 (29)	174.5 (39.4)	174.8 (8.6)	0.27
Weight (kg)	87.4 (19.1)	92.5 (16)	82.7 (22.7) *	<0.0001
Body mass index (kg/m^2)	28.2 (5)	30.4 (4.3)	27 (6.7) *	0.01
Resting heart rate (bpm)	76 (22)	77 (14)	74.5 (14)	0.068
Peak heart rate (bpm)	142 (25)	139 (22)	134 (29) *	0.001
Peak systolic blood pressure (mmHg)	177 (28)	172 (30)	169 (30)	0.21
METs	8.7 (3.3)	7.7 (3.1)	6.6 (3.1) *	<0.0001
Coronary artery disease (%)	16.3	18.6	34.2*	<0.0001
Any diagnostic ECG Q wave (%)	12.8	17.6	8.0*	<0.0001
Heart failure (%)	5.0	10.2	15.8*	<0.0001
Ischemic heart failure (%)	2.5	6.8	18.4*	<0.0001
Diabetes (%)	12.5	11.9	15.8*	0.006
Tobacco use (%)	58.8	52.5	63.2*	<0.0001
Annual all-cause mortality (%)	1.8	2.2	3.76*	<0.0001
Annual CV mortality (%)	0.7	1.0	2.1	0.12

*Data presented as mean (+SD). Normal ETT - normal exercise treadmill testing; EI-ST dep - exercise-induced ST depression; EI-LBBB - exercise-induced left bundle branch block; MET - metabolic equivalent. * Denotes p < 0.01 EI-LBBB vs normal ETT.*

Since the first case report on EI-LBBB[7], a number of studies have been published with small samples of subjects, which have suggested an association between this finding and CAD or left ventricular dysfunction[1,3,6,16]. Other investigators[19-21] have proposed that in patients without evidence of heart disease, EI-LBBB could be due to a primary defect of the conduction system, with a good prognosis. In the seminal prognostic publication regarding EI-LBBB, a Cleveland Clinic study by Grady et al[8], EI-LBBB was investigated in seventy cases and seventy matched controls. The primary endpoint was a composite of all-cause mortality, percutaneous coronary intervention[22], open heart surgery, non-fatal myocardial infarction, documented symptomatic or sustained ventricular tachycardia, and the need to implant a pacemaker or internal cardiac defibrillator. The median follow-up was 3.8 years. After adjustment for age, EI-LBBB was associated with increased risk of primary endpoints including death and major cardiac events. One significant limitation of the study, however, was the sample size. Hence, aiming to overcome the limitation of the Cleveland Clinic study and better define the long-term outcomes associated with EI-LBBB in a larger population, we performed the current study. The 8.8 year follow-up of our patient database is the longest follow up available to date.

Isolated exercise-induced ST-segment depression is the most common manifestation of myocardial ischemia and its risk has been well established[10,23]. To date, this is the first study comparing mortality in patients with abnormal exercise-induced ST depression and those with EI-LBBB (Fig. 1). We observed higher mortality rates from all-causes in patients with EI-LBBB, compared to subjects with a normal exercise test and those with ST-segment depression suggestive of myocardial ischemia. Interestingly, patients with EI-LBBB had a significant Cox hazard ratio of 2.37 ($p = 0.002$) for all-cause mortality, but not when adjusted for the presence of CAD and/or heart failure.

The value of exercise testing for prognostic assessment in older subjects has been described by Goraya et al[24]. As expected, these individuals had more comorbidities and a lower exercise capacity than their younger counterparts. They also had a significantly worse unadjusted survival. Meanwhile, a positive ST response was not prognostic in these patients when tested as a dichotomous variable[24]. Of clinical importance is the fact that after adjustment for age and presence of CAD and/or heart failure, abnormal exercise-induced ST segment depression lost its independent predictability for all-cause mortality in the 1,461 patients in our cohort (mean age 62.7 ± 9.8 years - Table 2).

Study limitations

Predictably, several limitations can be seen in our study. First, the sample was composed exclusively of male veterans and thus our results may not be reflective of the general population who are undergoing exercise testing. Second, women have been excluded due to a low number of them undergoing exercise testing (3.5% in our exercise laboratory). Third, low incidence rates of EI-LBBB were identified in our cohort, 19 survivors and 13 non-survivors, thereby reducing the power of the study to detect other associations in the multivariate analysis. However, it seems reasonable from the observation that 61.5% of the EI-LBBB non-survivors had CAD and 38% had heart failure that these morbid states are involved in the mechanisms associated with poorer prognosis. Fourth, heart rate-dependence association deserves some merit; unfortunately this information was not collected in our study. The limited available information regarding this issue suggests that when the exercise-induced block occurs under 132 beats per minute, the possibility of obstructive CAD increases[3,6,7,16]. Fifth, data on pacemaker implantation and follow up in the EI-LBBB patients were either missing or not collected for this study.

Clinical implications

Altogether, the findings of this study and previous publications demonstrate that patients who exhibit EI-LBBB should be further investigated for the presence of CAD and/or left ventricular dysfunction, following the same principles that guide the investigation of a patient with abnormal

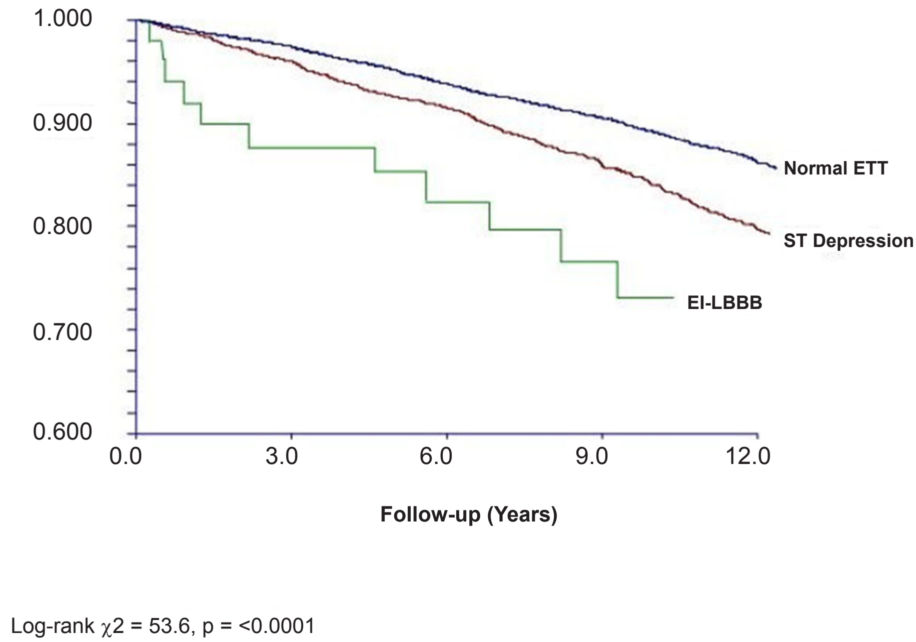

Figure 1 - *Kaplan Meier survival curves for all-cause mortality.*

Table 4 - **Characteristics of patients with exercise-induced left bundle branch block classified by vital status at the end of follow-up (after exclusions)**

	EI-LBBB survivors	EI-LBBB non-survivors	p-value
Sample size (n)	19	13	0.186
Age (years)	64.0	67.5	0.404
Height (cm)	175.8	173.2	0.380
Weight (kg)	86.1	76.2*	0.02
Body mass index (kg/m^2)	27.7	25.5	0.340
Rest heart rate (bpm)	74	76	0.746
Peak systolic blood pressure (mmHg)	172	163	0.405
Peak heart rate (bpm)	134	135	0.905
METS	6.9	6.0	0.434
BORG	17	17	-
Coronary artery disease (%)	20	61.5*	0.001
Ischemic heart failure (%)	8	38 *	<0.0001
Non-ischemic heart failure (%)	12	23 *	<0.0001
Hypertension (%)	68	61.5	0.690
Diabetes (%)	12	23.1	0.374
Tobacco use (%)	64	61.5	0.881

EI-LBBB - exercise-induced left bundle branch block; MET - metabolic equivalent.
**Denotes p < 0.01 between EI-LBBB survivors vs EI-LBBB non-survivors.*

exercise-induced ST segment depression. It is noteworthy that the occurrence of EI-LBBB itself, without evidence of CAD and/or heart failure, may be due to conduction disease and can be associated with a good prognosis. This is in agreement with our recently published paper on exercise-induced right bundle branch block, which demonstrated that EI-RBBB is also an uncommon finding during routine clinical exercise testing and was mainly associated with aging, without independent prognostic value[25]. Therefore, these two analyses indicate that exercise-induced conduction disturbances alone do not carry an increased risk, but they may represent markers of cardiovascular abnormalities which should prompt further investigation.

Conclusions

EI-LBBB is a rare occurrence during routine clinical exercise testing and patients with this finding have significantly higher all-cause mortality rates compared to those with normal ETT results. The higher mortality with EI-LBBB is largely explained by age and association with CAD and/or heart failure.

Table 5 - Comparison of studies regarding exercise-induced left bundle branch block

Author	Present Study	Moran et al[19]	Williams et al[11]	Wayne et al[1]	Bounhoure et al[22]	Boran et al[5]
Number of patients	8,410	5,990	10,176	4,100	16,500	2,200
Mean age (years)	59	63	61	59	60	51
EI-LBBB	32	37	37	11	25	1
EI-LBBB (%)	0.38	0.48	0.36	0.27	0.15	0.04

EI-LBBB - exercise-induced left bundle branch block.

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