Prognostic Significance of Exercise-Induced Left Bundle-Branch Block

Thomas A. Grady, MD; Andrew C. Chiu, MD; Claire E. Snader, MA; Thomas H. Marwick, MD, PhD; James D. Thomas, MD; Fredric J. Pashkow, MD; Michael S. Lauer, MD

Context.—Approximately 0.5% of all patients who undergo exercise testing develop a transient left bundle-branch block (LBBB) during exercise, but its prognostic significance is unclear.

Objective.—To determine whether exercise-induced LBBB is an independent predictor of mortality and cardiac morbidity.

Design.—Matched control cohort study. Between September 1990 and February 10, 1994, 17,277 exercise stress tests were performed on patients.

Setting.—Tertiary care, academic medical center.

Patients.—From the cohort, 70 cases of exercise-induced LBBB were identified. The controls comprised 70 individuals without LBBB at rest or during exercise that matched the 70 cases based on age, test date, sex, prior history of coronary artery disease, hypertension, diabetes, smoking, and β-blocker use.

Main Outcome Measures.—All-cause mortality, percutaneous coronary intervention, open heart surgery, nonfatal myocardial infarction, documented asymptomatic or sustained ventricular tachydysrhythmia, or implantation of a permanent pacemaker or an implantable cardiac defibrillator.

Results.—A total of 37 events (28 events from the exercise-induced LBBB cases and 9 from the control cohort) occurred in 25 patients (17 exercise-induced LBBB patients and 8 control patients) during a mean follow-up period of 3.7 (0.9 years) (median, 3.8 years [range, 0.9-5.2 years]). There were 7 deaths, of which 5 occurred among patients with exercise-induced LBBB. Four-year Kaplan-Meier event rates were 19% among exercise-induced LBBB patients and 10% among controls (log-rank χ², 5.2; P=.02). After further adjusting for small differences in age, exercise-induced LBBB remained associated with a higher risk of primary events (adjusted relative risk, 2.78; 95% confidence interval, 1.16-6.65; P=.02).

Conclusion.—Exercise-induced LBBB independently predicts a higher risk of death and major cardiac events.

EXERCISE-INDUCED left bundle-branch block (LBBB) occurs during approximately 0.5% of exercise stress tests. Prior studies examining the prognostic significance of exercise-induced LBBB have been limited by their small size, lack of matched controls, and failure to adjust for potential confounders.¹⁻² Therefore, we performed a matched control cohort study to determine whether exercise-induced LBBB is an independent predictor for major cardiovascular morbidity and mortality in the largest series of exercise-induced LBBB reported to date.

METHODS

Study Population

Between September 4, 1990, and February 10, 1994, 17,277 patients underwent symptom-limited treadmill stress testing at the Cleveland Clinic Foundation in Cleveland, Ohio; 70 cases (0.41%) of exercise-induced LBBB were identified. Rest and exercise electrocardiograms (ECGs) were independently reviewed by 3 physicians to confirm the diagnosis of exercise-induced LBBB. The diagnosis of complete LBBB was made from the 12-lead ECG if all the following criteria were met: conduction originating above the atrioventricular node; a QRS duration of 120 milliseconds or more; predominantly upright complexes with broad-slurred R waves in leads I, V₅, and V₆; and a QS or RS pattern in V₁ with a normal intrinsicoid deflection of 35 milliseconds.⁵⁻⁷ Patients with a 6 wave or a short PR interval that suggests an accessory AV bypass tract were excluded. Patients with permanent pacemakers and/or evidence of preexcitation were also excluded. Exercise-induced LBBB was defined by LBBB that was documented only during treadmill exercise stress testing. There could be no history of LBBB and the LBBB abnormality had to resolve before the patient left the laboratory.

From the same database, a matched, controlled cohort of 70 patients was selected. This cohort comprised individuals matched to cases by the predetermined variables of sex, hypertension, diabetes, smoking, β-blocker use, and history of coronary artery disease. For each case, a pool of potential control patients was assembled. A unique control for each case was chosen by identifying the patient closest in age and test date; no maximum differences in these variables were prespecified. By definition, control patients' ECGs were without LBBB at rest and during exercise.

JAMA. 1998;279:153-156

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Clinical Cardiology section editors: Bruce Brundage, MD, University of California, Los Angeles, School of Medicine; Margaret A. Winker, MD, Senior Editor, JAMA.

This article is one of a series sponsored by the American Heart Association.
Matched variables

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†Data quantifying left ventricular function was available for 32 controls (46%) and 59 exercise-induced left bundle-branch block patients (84%).

The research protocol was approved by the Cleveland Clinic Foundation Institutional Review Board.

Exercise Testing

All patients underwent symptom-limited treadmill stress testing usually according to the Bruce or modified Bruce protocol. During each stage of exercise and recovery, data on symptoms, rhythm, heart rate, blood pressure, workload in metabolic equivalents (METs), and ST segment changes were prospectively collected and recorded online until recovery was complete. Participants were encouraged to achieve at least 85% of their maximum age-predicted exercise heart rate (calculated as 220-age of the participant). Participants were not allowed to lean on handrails during exercise testing. Among controls, an ischemic ST-segment response was considered present if there was 1 mm of horizontal or down-sloping ST-segment depression 80 milliseconds after the J-point.6

Baseline Characteristics

By both chart review and structured interview, the following characteristics were identified: age, sex, a history of diabetes, a history of hypertension (defined as resting systolic blood pressure of >140 mm Hg, and/or a resting diastolic blood pressure of >90 mm Hg, and/or taking antihypertensive medication), use of a β-blocker, a history of coronary artery disease, and current or past smoking.21

Cholesterol values predating the exercise test or occurring within 90 days following the stress test were identified for 63 (90%) of the case patients and 59 (84%) of the control patients. Hypercholesterolemia was defined as having a total cholesterol value of 6.21 mmol/L (240 mg/dL) and/or taking cholesterol-lowering medication.21

The presence of a Q or QS wave was defined as having an amplitude of 0.25 mm or more and a duration exceeding 20 milliseconds in the majority of beats in any 1 lead except aVR.6,7

Left ventricular function and ejection fraction were determined by echocardiography, ventriculography, and/or nuclear multigated acquisition scintigraphy. Left ventricular function was quantified in 59 patients (84%) with exercise-induced LBBB and 32 controls (46%). Information regarding degree of coronary artery disease was obtained by reviewing coronary angiograms. Narrowing of 50% or more was considered significant (Table 2).

End Points and Follow-up

The prospectively defined primary end point in this study was a composite of all-cause mortality, percutaneous and/or surgical revascularization, nonfatal myocardial infarction, and need for a permanent pacemaker and/or an implantable cardiac defibrillator with documented symptomatic or sustained ventricular tachycardia or ventricular fibrillation by either telemetry and/or Holter monitor. Follow-up was obtained by a structured chart review and telephone interview. If a patient had died, the next of kin was interviewed and the death certificate was reviewed. Follow-up was performed by 2 physicians who were blinded to results of the stress test. Follow-up was obtained for 100% of patients. The duration of follow-up was a mean (SD) of 3.7 (0.9) years with a median of 3.8 years (range, 0.9-5.2 years).

Statistical Analyses

Continuous variables are described as mean (SD). Differences in unmatched baseline characteristics were compared between the 2 groups using the Student t, Wilcoxon rank sum, χ², and Fisher exact tests as appropriate.

Cumulative incidence rates of primary events according to presence or absence of exercise-induced LBBB were calculated using the Kaplan-Meier product limit method. Differences between event-free survival curves were compared using the log-rank test. The Cox proportional hazards model was used to further adjust for age and extent of coronary artery disease at the time of exercise testing.22 The validity of the proportional hazards assumption was confirmed by examination of weighted residuals.23 Analyses were not specifically performed for matched pairs. All statistical analyses were performed using SAS 6.12 statistical package (SAS Inc, Cary, NC).

Before performing the analyses, a power calculation was performed that assumed 36% as being the lowest rate of developing a cardiovascular event for cases; this event rate was obtained from the literature reporting outcomes for similar populations.15 It was assumed that cardiovascular events among all patients undergoing exercise stress testing occurs at a 3% rate over a similar period based on the results of the follow-up period in this study, which found a 1% rate per year or 3% to 4% over 3.7 years. A matched control cohort study with a study population of 70 subjects and 70 controls was confirmed to have more than 90% statistical power to detect this difference.

Table 1.—Baseline Characteristics at Time of Stress Testing

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RESULTS

Baseline Exercise Characteristics

The cases and controls had similar baseline characteristics except for age (Table 1). For both the case and control groups, for those who had coronary angiography prior to exercise testing, the mean time between coronary angiography and exercise stress testing was 3.5 (3.5) years with a median of 2.3 years (range, 0.01-13.1 years). There were no marked differences in the distribution of severity of coronary disease between the 2 groups (Table 2).
Indications for stress testing among patients with exercise-induced LBBB were follow-up for known coronary disease in 23 (33%), evaluation for possible coronary disease in 23 (33%), and arrhythmia evaluation in 4 (6%). The corresponding values for indications for stress testing among controls were 43 (61%), 22 (31%), and 3 (4%), along with 2 (4%) who were referred for other reasons ($P=.98$ for differences in indications for stress testing between the 2 groups). No marked difference in exercise characteristics were noted (Table 3).

End Points

The mean length of follow-up for all patients was 3.7 (0.9) years with a median of 3.8 years (range, 0.9-5.2 years). Primary end points were more common among exercise-induced LBBB cases than controls (Table 4). The Figure illustrates the event-free survival of the 2 groups over the period of follow-up. Four-year cumulative event rates were 10% (8 patients) in the control cohort and 19% (17 patients) in the case cohort (log-rank $x^2=5.2; P=.02$). After adjusting for the small differences in age in the 2 groups, the relative risk was 2.78 (95% confidence interval [CI], 1.16-6.65; $P=.02$).

In additional analyses, we considered the impact of a history of coronary artery disease on outcome, a variable for which controls had been matched to cases. Of the 86 patients with known coronary artery disease, 19 (22%) went on to develop a specified end point while 6 (13%) without a known history of coronary artery disease went on to develop a specified end point. In a Cox model that included exercise-induced LBBB, age, and documented coronary disease, the association of exercise-induced LBBB with the outcome measures was unchanged with an adjusted relative risk of 2.73 (95% CI, 1.14-6.56; $P=.02$). Thus, the association of exercise-induced LBBB with predefined end points was independent of documented coronary disease.

Among patients with a history of coronary artery disease, the 7 patients who went on to coronary artery bypass surgery, 5 were in the exercise-induced LBBB group and 2 were in the control group; there were no deaths among these patients. Of the 15 patients who went on to percutaneous intervention, 10 patients were in the exercise-induced LBBB group and 5 were in the control group; there was 1 death in each group.

When left ventricular function was analyzed as ejection fraction, defined as less than 40%, did not influence the association of exercise-induced LBBB with predefined end points. In a Cox model that included exercise-induced LBBB, age, and known low ejection fraction, the association of exercise-induced LBBB with adverse events was unchanged with an adjusted relative risk of 2.77 (95% CI, 1.15-6.67; $P=.02$).

The median heart rate when exercise-induced LBBB developed among the cases was 121 beats per minute (25th to 75th percentiles; range, 105-140 beats per minute). At the time of exercise-induced LBBB, the median blood pressure was 168/88 mm Hg (25th to 75th percentiles; range, 164-172/84-98 mm Hg). Blood pressure and heart rate did not fluctuate at the time when exercise-induced LBBB developed. The mean metabolic equivalents achieved at the onset of exercise-induced LBBB was 7.2 (2.5) with a median of 7.1 (range, 3.2-12.8) while the mean rate pressure product was 26,508 (4915) with a median of 26,494 (range, 18,702-29,975). There was no association between the heart rate at which LBBB occurred and the risk of developing adverse events.

COMMENT

The prognostic significance of exercise-induced LBBB has been variably reported in the literature. Interpretation of prior studies is limited by lack of control groups, the wide spectrum of patients referred for exercise testing, crossover to coronary revascularization, and small sample sizes. Our investigation represents the largest published series to date and is the first to our knowledge to utilize a matched control cohort method. Despite the achievement of a comparable work capacity, heart rate, and rate-pressure product, our study population demonstrated a significantly lower event-free survival compared with the matched control sample.

Wayne et al observed that exercise-induced LBBB occurs most commonly in the presence of underlying heart disease, particularly coronary artery disease. However, a smaller series reported that this phenomenon was associated with normal coronary arteries. Two larger series by Bouhoure et al and Williams et al reported a high prevalence of coronary artery disease (64% to 75%) but a variable incidence of cardiac events (36% to 50%). However, without considering a control group, the independent prognostic impact of exercise-induced LBBB is difficult to gauge.

Our series complements the findings of Schneider et al from the Framingham Heart Study regarding the significance of newly acquired LBBB. During an 18-year period of observation, of 5209 subjects followed, 56 patients (1.1%) developed LBBB. Fifty percent of these patients died within 10 years after the development of the abnormality and only 11% remained free of clinically ap-
parent cardiovascular events. Because the left bundle-branch of the cardiac conduction system has a dual blood supply involving both the left anterior descending coronary artery and posterior descending coronary artery (a branch of a dominant right coronary artery and/or a dominant left circumflex coronary artery), exercise-induced LBBB may be a clinical marker for a greater degree of underlying coronary artery disease and/or ischemic burden.26

Some important limitations in our study need to be noted. Outcomes measured in this study may reflect some degree of bias since patients with an exercise stress test abnormality, such as exercise-induced LBBB, may have had closer follow-up. Hence, earlier detection and treatment of these patients may have had some role in their higher frequency of primary events. Markedly more deaths occurred among the case patients, though, arguing against clinician bias being the major reason for the difference in event rates. Another limitation is that angiography was not performed in all patients and often preceded the exercise test by more than 2 years, precluding complete adjustment of the analysis for baseline coronary artery disease. However, the data available indicate a similar degree of severity between the groups.

Because exercise-induced LBBB is a comparatively infrequent finding during exercise testing, our case and control populations are small. Thus, any conclusion about lack of difference regarding certain parameters, for example, ejection fraction, may be due to insufficient sample size. Nonetheless, to our knowledge, this analysis is the largest study to date examining the prognostic significance of exercise-induced LBBB. We did not systematically record the length of time the LBBB persisted after exercise and what impact this might have on prognosis. As our hospital is a major tertiary referral center, our patient population may not reflect the population at large who are undergoing exercise stress testing, but the frequency of exercise-induced LBBB in our population was 0.41%, a value which closely parallels that reported in the literature.5,10,12,15,19

Though exercise-induced LBBB is comparatively infrequent, approximately 10 000 new cases will be observed annually in the United States, where more than 2 million exercise stress tests are currently performed each year.24 Thus, the independent contribution of exercise-induced LBBB to prognosis warrants attention among clinicians whose patients undergo stress testing.

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