Cardiopulmonary Exercise Testing in Patients With Left Bundle Branch Block and Preserved Ejection Fraction

Milena dos Santos Barros,1,2,5 Rívia Siqueira Amorim,1 Romerito Oliveira Rocha,1 Enaldo Vieira de Melo,1,5 José Augusto Barreto-Filho PhD,1,2,5 Antônio Carlos Sobral Sousa PhD,1,2,3,5 Romeu Sérgio Meneghello PhD,4 Joselina Luzia Menezes Oliveira PhD1,2,5
Departamento da Universidade Federal de Sergipe (UFS),1 São Cristóvão, SE; Centro de ensino e pesquisa e Laboratório de ecocardiografia (0ECOLAB) da Fundação e Hospital São Lucas,2 Aracaju, SE; Fellow of the American College of Cardiology;3 Instituto Dante Pazzanese de Cardiologia,4 São Paulo, SP; Núcleo de Pós-Graduação em Medicina da UFS,5 São Cristóvão, SE – Brazil

Abstract

Background: Left bundle branch block (LBBB) has prognostic significance in patients with congestive heart failure. However, its influence is not well established in patients with preserved systolic ventricular function.

Objective: To evaluate the implications of LBBB presence in the cardiovascular performance of patients with preserved left ventricular systolic function (LVEF).

Methods: 26 LBBB patients (61.3 ± 8.2 years of age) and 23 healthy individuals (58 ± 6.8 years of age) with LVEF > 0.5 underwent cardiopulmonary exercise testing (CPET).

Results: CPET analysis revealed: peak oxygen consumption (VO2) predicted in the LBBB group was 87.2 ± 15.0% versus 105.0 ± 15.6% (p < 0.0001); peak oxygen pulse predicted in LBBB group was 98.6 ± 18.6% vs 109.9 ± 13.5% (p = 0.02); VO2 predicted anaerobic threshold in LBBB group was 67.9 ± 13.6% vs 70.2 ± 12.8% (p = 0.55); ΔVO2/Δload in the LBBB group was 15.5 ± 5.51 versus 20.7 ± 7.3 ml.min-1.watts-1 (p = 0.006); ventilation / carbon dioxide production (VE/VCO2 slope) in LBBB group was 29.8 ± 2.9 versus 26.2 ± 2.9 (p = 0.0001) and VO2 recovery time in the LBBB group was 85.2 ± 11.8 vs. 71.5 ± 11.0 seconds (p = 0.0001). LBBB was an independent marker for VE/VCO2 slope increase.

Conclusion: LBBB presence in individuals with preserved LVEF did not affect cardiovascular performance, but there was an increase of the VE/VCO2 slope in comparison to the control group. (Int J Cardiovasc Sci. 2017;30(1):11-19)

Keywords: Exercise Test; Exercise; Bundle-Branch Block; Oxygen Consumption; Heart Failure; Stroke Volume.

Introduction

The isolated presence of LBBB, regardless of cardiopathies, seems to be a slow progression marker of degenerative cardiac diseases, ischemic or not, affecting the myocardial conduction system and contractile performance.1 LBBB can induce cardiomyopathy since individuals with this condition, when submitted to cardiac resynchronization therapy, may present left ventricular reverse remodelling (LV).2,3 Thus, it should not be considered a mere electrocardiographic finding, but a “cardiac clinical entity”, as suggested by Kumar et al.4

Despite reports of LV structural alterations caused by LBBB, there is, in literature, a lack of predicting factors in the reduction of cardiovascular performance in these patients. CPET is a non-invasive method used for the diagnosis and prognostic stratification of congestive heart failure (CHF) patients, through the analysis of gases expired during stress tests. The main variables assessed with this methodology are: peak oxygen consumption (VO2 peak), VO2 at the anaerobic threshold, oxygen pulse (PO2), ΔVO2/Δload, relation between ventilation and carbon dioxide production (VE/VCO2...
slope) and VO₂ recovery kinetics. On the other hand, it has been documented that LVEF assessed through echocardiogram does not show a satisfactory relation to VO₂ and thus does not constitute a good predictor of functional capacity.

We can then hypothesize that CPET could show, in asymptomatic LBBB patients, cardiovascular behavior alterations that precede LVEF compromise. The present research investigated if isolated LBBB in patients with normal LVEF interferes in the cardiovascular performance evaluated through CPET.

**Methods**

**Design and study population**

This is an observational cross-section analytical study, in which we evaluated 26 LBBB patients (LBBB group) and 23 individuals without LBBB (control group). LBBB was defined according to the following electrocardiographic criteria: enlarged QRS (with duration ≥ 120 ms); wide S waves in V1 and V2 with the absence of R waves, or its occurrence in an embryonic form; and R waves predominant in leads D1, AVL, V5, and V6. All volunteers presented LVEF, obtained through transthoracic echocardiogram, superior to 0.50 and underwent CPET. Myocardial ischemia was excluded through stress echocardiogram. All exams were performed in the sector of graphic methods of a hospital specialized in cardiology, which has a level 3 accreditation (IQG – Health Accreditation Services).

**Exclusion criteria**

Exclusion criteria included patients with: LVEF < 0.50 calculated by the Simpson method, previous coronary artery disease (CAD), moderate to severe valvulopathy, cardiac arrhythmia that hindered PO₂ analysis, pulmonary disease, and anemia (hemoglobin < 10 mg/dl).

**Cardiopulmonary exercise test protocol**

Analysis of minute ventilation (VE), VO₂′ and production of carbon dioxide (VCO₂) was performed every 10 seconds through the gas analyser Cortex Metalyser 3B (Micromed) connected to the computer, equipped with the software Elite. We used: Micromed digital electrocardiograph to register and analyse the electrocardiogram during effort and an Inbrasport treadmill, model Super ATL. Negative chronotropic medications were suspended three days before CPET.

Participants were encouraged to exercise to exhaustion, according to the ramp protocol, which is characterized by a duration between 8 and 12 minutes, with constant gradual increase in speed and inclination. The test was considered maximum when RER > 1.05 was reached. The test was interrupted according to criteria established by the III Brazilian Society of Cardiology Guidelines on Exercise Tests. The following CPET variables were evaluated:

- a. Peak VO₂ is the highest VO₂ value, reached in the last 30 seconds of effort and expressed in ml.kg⁻¹.min⁻¹. The predicted peak VO₂ was calculated with base on age, gender, weight, and level of physical activity using the Wasserman equation. We evaluated the percentage reached by the patient of the predicted VO₂.
- b. VO₂ at anaerobic threshold was determined by the “V slope method”. If that was not possible, it was performed through the analysis of the plot graph of ventilator equivalents. We also assessed the percentage of VO₂ predicted at anaerobic threshold.
- c. Peak VO₂ was the highest value reached in the last 30 seconds and was expressed in ml/beats. We analysed the percentage of the predicted peak PO₂ max by the maximum heart rate predicted by age.
- d. The relation ΔVO₂/Δload was calculated by the difference between VO₂ max and at rest, divided by the maximum load and expressed in ml.min⁻¹.watts⁻¹. For practical purposes, we considered VO₂ at rest as 3.5 ml.kg⁻¹.min⁻¹. Since the exam was performed on a treadmill, we adapted the load to Watts. Power calculation for the treadmill was: W (kgm/minute) = mass (patient weight – Kg) x speed (meters/minute) x sine of the alpha angle (which is the angle between the treadmill and the ground). The relation between kilogram-metres and watts is: 1 watt corresponds to 6.1 kilogram-metres/minute, and the transformation of the load from Kgm/min to Watts is done.
- e. VE/VCO₂ slope corresponds to the inclination of the representative regression line between VE and VCO₂.
- f. T₁/₂ VO₂ the necessary time for a 50% drop of peak VO₂ in the recovery period, was quantified in seconds.
Statistical analysis

Statistical analyses were processed through the software SPSS Statistic 19.0 (IBM Corporation, 2010). Quantitative variables were described as mean ± standard deviation, fulfilled the assumption of normality, and the comparison between the groups was done through unpaired Student’s t test. Categorical variables were summarized as percentages and compared between the groups through chi-square test (X²) or Fisher’s exact test, when appropriate. Significance level was set at 5% for α error and tests were two-tailed. Relative risks with confidence intervals (CI) of 95% were estimated. For the multivariate analysis of covariance (MANCOVA), we used the Trace of Pillai, power (≥ 0.8) and partial ETA² (effect dimension) as statistical tests. Partial ETA² was applied to infer clinical significance, considering the greatly elevated effect dimension if values are > 0.5, and small effect dimension if values are ≤ 0.05.

Ethical aspects

The project was submitted to the Research Ethics Committee and approved under protocol number 0770.0.000.107-11. All patients who participated in the research signed a free consent form.

Results

The sample was composed by 49 consecutive individuals (18 men and 31 women; mean age of 59.8 ± 7.7 years) who underwent CPET, distributed into: LBBB group (26 patients) and control group (23 patients).

Those with LBBB presented a higher frequency of systemic arterial hypertension (SAH), when compared to the control group (73.1% vs. 30.4%; p = 0.007). No substantial difference was observed between the groups in relation to age (p = 0.13), gender (p = 0.36), body mass index (BMI) (p = 0.79), sedentary life-style (p = 0.13), smoking (p = 0.93), diabetes mellitus (p = 0.1), and dyslipidemia (p = 0.72), as depicted in Table 1.

LBBB group present significantly higher values of LV systolic and diastolic diameter in comparison to the control group, with a mean difference of 0.34 ± 0.11 cm and 0.39 ± 0.13 cm, respectively. Left ventricular mass index (LVMI) was also significantly higher in the LBBB group, with a mean difference of 13.19 ± 6.18 g/m² (p = 0.039). LVEF was lower in the LBBB group, with a significant mean difference of 0.12 ± 0.02% (p < 0.0001) (Table 2). No significant difference was found between the groups regarding the occurrence of diastolic dysfunction (Table 3).

Table 4 shows the hemodynamic and ventilatory variables of the CPET between LBBB and the control group. Through MANCOVA, we verified a significant association between LBBB and the six-variable set of the cardiopulmonary test, with an elevated effect dimension (η² = 0.578), and power above recommended (β = 0.997). Adjustment was done for sedentary life style and the following covariables: age, gender, BMI, arterial hypertension, LVMI, and LVEF (Table 5).
Table 2 – Echocardiographic variables of LBBB patients and control group

| Variables                           | LBBB group n = 26 | Control n = 23 | p       |
|-------------------------------------|-------------------|---------------|---------|
| Left atrium (cm)                    | 3.76 ± 0.37       | 3.58 ± 0.40   | 0.11    |
| Septum thickness (cm)               | 0.84 ± 0.11       | 0.89 ± 0.15   | 0.21    |
| Posterior wall (cm)                 | 0.85 ± 0.11       | 0.81 ± 0.10   | 0.19    |
| Relative thickness of the LV (%)    | 33.07 ± 5.15      | 33.24 ± 4.09  | 0.91    |
| LV diastolic diameter (cm)          | 5.26 ± 0.51       | 4.87 ± 0.41   | 0.005   |
| LV systolic diameter (cm)           | 3.22 ± 0.41       | 2.89 ± 0.37   | 0.004   |
| Ejection fraction (%)               | 59.00 ± 7.00      | 71.00 ± 6.00  | < 0.0001|
| LV mass index (g/m²)                | 96.10 ± 22.9      | 82.9 ± 17.90  | 0.039   |

Continuous variables expressed as mean ± SD. Student's t test; significance level p ≤ 0.05. SD: standard deviation; LBBB: left bundle branch block; LV: left ventricle.

Table 3 – Diastolic function between LBBB patients and the control group (p = 0.47)

| Diastolic Function            | LBBB Group n = 26 | Control n = 23 |
|-------------------------------|-------------------|---------------|
| Normal                        | 18(69.2%)         | 18(78.3%)     |
| Mild dysfunction              | 6(23.1%)          | 5(21.7%)      |
| Moderate dysfunction          | 2(7.7%)           | 0             |

Categorical variables expressed as absolute frequency = n (relative frequency = %). Chi-square test; significance level p ≤ 0.05. LBBB: left bundle branch block.

There was a second multivariate analysis to identify if LBBB had an effect on one or more of the six outcome variables of CPET (Table 6). It was observed that LBBB interfered only in the analysis of VE/VCO₂ slope, with elevated effect dimension (η² = 0.504) and elevated power (β > 0.80).

Figure 1 shows the study sensitivity analysis, considering the sample dimension (n), α = 0.05, and power of 0.80 (1 - β). With the sample size (we considered a n = 48, value multiple of 4, corresponding to the number of groups to be compared: LBBB and SAH) and the assumed power and statistical significance, it was verified that the study was able to detect effect dimensions above 0.18 through MANOVA.

Discussion

In the studied population, VE/VCO₂ significantly increased in the LBBB group in relation to the control group. The ventilatory equivalent of carbon dioxide represents how much it is necessary to ventilate to eliminate a certain amount of produced carbon dioxide. This relation is analysed by linear regression, which reflects the slope of the line. VE/VCO₂ slope is already established in literature as a marker of poor prognosis in CHF patients, when it reaches a value > 3.4.13 There is a relation between VE/VCO₂ slope increase and the presence of LBBB in dilated cardiomyopathy patients, regardless of CAD.14 However, the literature is still scarce in the analysis of this variable for those without ventricular dysfunction.
### Table 4 – Hemodynamic and ventilatory variables of CPET between LBBB patients and the control group

| Variables                                      | LBBB group (n = 26) | Control group (n = 23) | p   |
|------------------------------------------------|---------------------|------------------------|-----|
| Peak heart rate. % of the predicted            | 94.8 ± 9.0          | 98.6 ± 6.3             | 0.10|
| Maximum ventilation. % of the predicted         | 59.0 ± 13.0         | 63.2 ± 11.0            | 0.23|
| Respiratory quotient                           | 1.08 ± 0.07         | 1.10 ± 0.08            | 0.30|
| Peak VO$_2$ (ml.kg$^{-1}$.min$^{-1}$)           | 21.7 ± 5.4          | 29.07 ± 6.7            | < 0.0001|
| Peak VO$_2$. % of the predicted                 | 87.2 ± 15.0         | 105.0 ± 15.6           | < 0.0001|
| VO$_2$ at the anaerobic threshold (ml.kg$^{-1}$.min$^{-1}$) | 15.5 ± 2.1          | 18.7 ± 4.4             | 0.002|
| Anaerobic threshold. % of the predicted VO$_2$  | 67.9 ± 13.6         | 70.2 ± 12.8            | 0.55|
| Peak O$_2$ pulse (ml/beat)                      | 10.3 ± 2.6          | 13.54 ± 4.6            | 0.003|
| Peak O$_2$ pulse. % of the predicted            | 98.6 ± 18.6         | 109.9 ± 13.5           | 0.02|
| Δ VO$_2$ / Δ load (ml.min$^{-1}$.watts$^{-1}$)  | 15.5 ± 5.5          | 20.7 ± 7.3             | 0.006|
| T$_{1/2}$ VO$_2$ (seconds)                      | 85.2 ± 11.8         | 71.5 ± 11.0            | 0.0001|
| VE/VECO$_2$ slope                               | 29.8 ± 2.9          | 26.2 ± 2.9             | 0.0001|

Continuous variables expressed as mean ± SD; Student’s t test; significance level p ≤ 0.05; SD: standard deviation; VO$_2$: oxygen consumption; O$_2$: oxygen; VE: ventilation; VCO$_2$: carbon dioxide production.

### Table 5
Multivariate analysis to assess LBBB and sedentary life style influence in CPET variables, adjusted for covariables

| Variables                                      | Trace of Pillai | p       | Partial ETA$^2$ | Power |
|------------------------------------------------|-----------------|---------|-----------------|-------|
| LBBB                                          | 0.578           | 0.0001  | 0.578           | 0.997 |
| Sedentary life style                          | 0.324           | 0.052   | 0.324           | 0.727 |
| LBBB x sedentary life style                   | 0.318           | 0.058   | 0.318           | 0.713 |

**Covariables**

| Variables | Trace of Pillai | p       | Partial ETA$^2$ | Power |
|-----------|-----------------|---------|-----------------|-------|
| Age       | 0.365           | 0.079   | 0.298           | 0.666 |
| Gender    | 0.174           | 0.413   | 0.174           | 0.348 |
| BMI       | 0.281           | 0.104   | 0.281           | 0.622 |
| SAH       | 0.143           | 0.554   | 0.143           | 0.277 |
| LVMI      | 0.163           | 0.460   | 0.163           | 0.322 |
| LVEF      | 0.472           | 0.002   | 0.472           | 0.959 |

MANCOVA: multivariate analysis of covariance. Fixed factors: LBBB and sedentary life style. Covariables: age, gender, BMI, SAH, LVMI, and LVEF. Significance level p ≤ 0.05; power ≥ 0.80. LBBB: left bundle branch block; SAH: systemic arterial hypertension; BMI: body mass index; LVMI: left ventricular mass index; LVEF: left ventricle ejection fraction.
Table 6 – Multivariate analysis to identify outcome variables, influenced by fixed factors and covariables, on significance, effect dimension and power

| Variables                        | p       | Partial ETA² | Power  |
|----------------------------------|---------|--------------|--------|
| LBBB                             |         |              |        |
| % peak \( \text{VO}_2 \) predicted | 0.37    | 0.024        | 0.145  |
| % \( \text{VO}_2 \) predicted at anaerobic threshold | 0.13    | 0.063        | 0.320  |
| % peak \( \text{O}_2 \) pulse predicted | 0.94    | < 0.0001     | 0.051  |
| \( \Delta \text{VO}_2 / \Delta \text{load} \) | 0.39    | 0.021        | 0.136  |
| \( T_{1/2} \text{VO}_2 \) | 0.21    | 0.045        | 0.237  |
| VE/\( \text{VO}_2 \) slope | < 0.0001 | 0.504        | 1.000  |

MANCOVA: multivariate analysis of covariance. Fixed factors: LBBB and sedentary life style. Covariables: age, gender, BMI, SAH, LVMI, and LVEF. Significance level p ≤ 0.05; power ≥ 0.80. LBBB: left bundle branch block; SAH: systemic arterial hypertension; BMI: body mass index; LVMI: left ventricular mass index. LVEF: left ventricle ejection fraction. \( \text{VO}_2 \): oxygen consumption; \( \text{O}_2 \): oxygen; VE: ventilation; \( \text{CO}_2 \): carbon dioxide production.

In patients with CHF, the VE/\( \text{VCO}_2 \) slope increase generally occurs by hemodynamic compromise, caused by cardiac debit reduction and consequent pulmonary hypoperfusion, demonstrating an advanced stage of CHF and poorer prognosis.\(^{15}\) However, there is evidence that VE/\( \text{VCO}_2 \) slope increase may occur since the initial stage of CHF through autonomic imbalance. The autonomic nervous system allows the body to adjust circulation and ventilation to keep oxygen supply to the tissues. The autonomic balance is kept through the complex interaction of the arterial baroreflex, peripheral and central chemoreflex, ergoreflex, and pulmonary stretch reflex.\(^{16}\)
Chemoreflexes are the main control and regulation mechanisms of ventilatory responses to changes in oxygen and carbon dioxide concentrations. Peripheral chemoreceptors located in the carotid bodies respond primarily to hypoxia, and central chemoreceptors, located in the ventral surface of the spinal cord, respond primarily to hypercapnia. It has been proven that there is a potential selection of central chemosensitivity in CHF patients functional class I and II.17

Ponikowski et al.18 studied CHF patients with preserved tolerance to exercise and observed that the normal increase of ventilatory response to exercise occurred due to the high sensitivity of the cardiorespiratory system control reflex. They showed the increase of central and peripheral chemosensitivity, compromise of the sympathovagal system with sympathetic predominance, hyperactivity of peripheral muscles ergoreceptors, and reduction of circulation baroreflex control.

The present work showed a VE/VCO₂ slope increase in the LBBB group with preserved LVEF. It is more likely that the mechanism responsible for this alteration is the initial imbalance of the autonomic system, because this population does not present hemodynamic compromise.

Echocardiographic results suggest that LBBB presence may trigger LV remodelling. These data were also presented in studies, such as the one by Melek et al.,19 who evaluated LBBB patients without cardiomyopathy though echocardiography and observed that the end systolic diameter was larger and LVEF was smaller in the LBBB group (54 ± 7%) in relation to the control group (61 ± 6%, p < 0.001). Valenti et al.20 studied LV and LVEF through cardiac MRI, and demonstrated that LBBB patients presented higher LV and LVMI volumes and lower LVEF in comparison to control individuals.

It is established in the literature that there is no good correlation between peak VO₂ and ventricular function.56 VO₂ during exercise provides an objective parameter of functional capacity, and indirectly reflects cardiovascular function. Impairment of exercise capacity is an independent predictor of adverse prognosis. In our work, we evaluated the main CPET variables related to cardiovascular performance. LBBB patients reached lower percentage of the predicted peak VO₂ but in the multivariate analysis, it was shown that the predicting factor for the referred reduction was sedentary life style, and not LBBB. Duncan et al.14 studied functional capacity predictors in dilated cardiomyopathy patients, and LBBB was also not an independent predictor of the percentage of the peak VO₂ predicted in the multivariate analysis.

PO₂ is representative of LV systolic volume and of the arteriovenous difference of O₂ during effort, and it reflects O₂ supply to the myocardial and the cardiac functional reserve under physiological stress. Generally, it increases gradually and linearly with the load increase until it reaches its highest value. In ventricular dysfunction patients, PO₂ may be reduced, despite the increase in load, or reach an early plateau even before reaching effort exhaustion.11,12 In LBBB patients, LV shape is distorted during pre-ejection, as a result of the flattening of the septal curvature and simultaneous stretching of the lateral wall activated late.21 The present work showed that the LBBB group reached peak PO₂ > 85% of the predicted value, and presented ascending behavior of the PO₂ curve during effort. Even though there are structural alterations in the LV, LVEF was preserved, without cardiovascular performance deficit.

It was demonstrated that isolated LBBB did not interfere in the ΔVO₂/Δload – VO₂ was adequate for the applied workload. There was also no LBBB interference in T₁/₂ VO₂. T₁/₂ of VO₂ is a prognostic marker, and its value increases according to the severity of CHF. It was demonstrated that the association of T₁/₂ VO₂ with peak VO₂ improves the prognosis evaluation and identifies higher risk groups.22 The groups had T₁/₂ VO₂ lower than 90 seconds, a time considered to be within normality.

Our results show that CPET is a non-invasive, physiological, low cost method that could contribute in the follow-up of LBBB patients. We have demonstrated that, even though the LBBB group with preserved LVEF presented LV structural alterations within thresholds considered normal, cardiovascular performance was not impaired in the analysis of CPET metabolic variables, but there was an increase in the VE/VCO₂ slope in relation to the control group. It is not yet possible to identify which individual with isolated LBBB will develop ventricular dysfunction. Further studies should evaluate the impact of VE/VCO₂ slope increase by following up this sample of the population.

During this research, there were difficulties in the selection of LBBB patients, due to this pathology’s comonitance with SAH, ventricular dysfunction and/or myocardial ischemia. SAH was not considered an exclusion criterion due to its high prevalence in this population, making it necessary to adjust its influence through statistical analysis. Another limitation was the exclusion of myocardial ischemia through echocardiography during physical stress, for which the ideal exam would be coronary angiotomography or coronary cineangiography.
due to the asynchrony between the intraventricular septum and LV contraction caused by LBBB.

Conclusions

The presence of LBBB with preserved LVEF did not compromise cardiovascular performance. LBBB did not interfere in the percentage of the predicted peak VO$_2$, percentage of the predicted VO$_2$ at the anaerobic threshold, oxygen pulse, $\Delta$VO$_2$/Δload and $T_{1/2}$ VO$_2$.

LBBB was an independent marker for VE/VCO$_2$ slope increase, possible representing an early marker in the course of ventricular dysfunction.

Author contributions

Conception and design of the research: Barros MS, Amorim RS, Rocha RO, Melo EV, Barreto-Filho JA, Sousa ACS, Oliveira JLM. Acquisition of data: Barros MS, Amorim RS, Rocha RO. Analysis and interpretation of the data: Barros MS, Amorim RS, Rocha RO, Melo EV, Barreto-Filho JA, Sousa ACS, Meneghelo RS, Oliveira JLM.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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