Effects of β-Blocker Therapy on Exercise Oscillatory Ventilation in Reduced Ejection Fraction Heart Failure Patients: A Case Series Study

Juliana Fernanda Calhado Belli-Marin
Universidade de Sao Paulo Campus de Sao Paulo: Universidade de Sao Paulo
Edimar Alcides Bocchi
Universidade de Sao Paulo Campus de Sao Paulo: Universidade de Sao Paulo
Silvia Ayub-Ferreira
Universidade de Sao Paulo Campus de Sao Paulo: Universidade de Sao Paulo
Nelson Carvas Junior
Universidade de Sao Paulo Campus de Sao Paulo: Universidade de Sao Paulo
Guilherme Guimaraes (gvguima@usp.br)
Universidade de Sao Paulo Campus de Sao Paulo: Universidade de Sao Paulo https://orcid.org/0000-0003-2304-3110

Research Article

Keywords: exercise test, periodic breathing, heart failure, β-blocker

Posted Date: March 28th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1418618/v1

Effects of β-Blocker Therapy on Exercise Oscillatory Ventilation in Reduced Ejection Fraction Heart Failure Patients: A Case Series Study

Short title: β-blocker and exercise oscillatory ventilation

Juliana Fernanda Calhado Belli-Marin, PhT, PhD; Edimar Alcides Bocchi, MD, PhD; Silvia Ayub-Ferreira, MD, PhD; Nelson Carvas Junior, PhE, MsC; Guilherme Veiga Guimarães, PhE, PhD

Affiliation: Instituto do Coração, Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, Brasil

Corresponding author: Guilherme Veiga Guimarães, Instituto do Coração, Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, Brasil, Av Dr Enéas de Carvalho Aguiar, 44, São Paulo/SP, Brasil, CEP 05403-000, Tel/fax: +55 11 2661–5502, e-mail: gvguima@usp.br

ABSTRACT

PURPOSE: Exercise oscillatory ventilation (EOV) is an abnormal breathing pattern that occurs in ~20% of patients with heart failure (HF) and is associated with poor prognosis and exercise intolerance. β-blockers (βb) are prescribed for most HF patients; however, their effect on EOV remains unclear. We evaluated the effect of βb on EOV in HF patients with reduced ejection fraction (HFrEF).

METHODS: Fifteen patients diagnosed with HF, ejection fraction ≤45%, aged from 18 to 65 years, were included before starting βb therapy. Patients underwent clinical evaluation, cardiopulmonary exercise testing, echocardiography, laboratory exams (norepinephrine levels, B type natriuretic peptide) at baseline and after βb therapy optimized for six months. Presence of exercise oscillatory breathing was determined by two experienced observers who were blinded to the moment of the test (pre or post).

RESULTS: Fifteen patients (1 female), aged 49.5±2.5 years, with HFrEF, NYHA I-III enrolled in the study. The etiologies of the HFrEF were idiopathic (n=8) and hypertensive (n=7)**.** LVEF increased after βb therapy from 25.9±2.5% to 33±2.6%, *P*=0.02; peak VO_2 did not significantly change (21.8±1.7 vs 24.7±1.9, *P*=0.4); VE/VCO_2 slope changed from 32.1±10.6 to 27.5±9.1, *P*=0.03. Before βb initiation, nine patients (60%) had EOV, but only two (13%) did after optimized therapy. McNemar test was used to evaluate the significance of the association between the two moments (*P*=0.02).

CONCLUSION: In patients with HF, medical therapy with βb can reverse EOV. This may explain why these patients experience symptom improvement after βb therapy.

Key Words: exercise test; periodic breathing; heart failure; β-blocker

Abbreviations and Acronyms: βb, β-blockers; CI, cardiac index; CPET, cardiopulmonary exercise testing; EOV, exercise oscillatory ventilation; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction.

BACKGROUND

Heart failure (HF) leads to multiple organ systems dysfunction, with dyspnea and exercise intolerance being the most common.[1,2,3] The phenomenon of periodic breathing is characterized by cyclic variation of ventilation with or without interposed apnea. It has been detected at rest, during sleep, and during exercise.[4,5,6,7,8] In assessing periodic breathing, it is important to note in Cheyne-Stokes breathing and central sleep apnea that the gradual increase and decrease in minute ventilation are not separated by periods of apnea.[5,6] In contrast, periodic breathing during exercise or exercise oscillatory ventilation (EOV) in heart failure consists of cyclical fluctuations of increase and decrease in minute ventilation and is distinct during cardiopulmonary exercise testing (CPET).[4,6,7] The presence of EOV during exercise in patients with HF indicates significant impairment in hemodynamic parameters at rest and during exercise.[7,8]

The incidence of EOV among patients with HF is approximately 19-51%, which is related to adverse cardiac events, worse prognosis, and higher mortality.[8,9] The pathophysiology is complex, and the main known mechanisms of EOV include prolonged circulation time, fluctuations in pulmonary blood flow, increased pulmonary capillary pressure, and instability in ventilatory control with demodulation of the central and peripheral chemoreflex.[10,11,12,13,14] However, it is not known whether guideline-directed medical therapy for HF can affect this abnormal ventilatory pattern. Although recognition and targeting of EOV appear to be important clinical outcomes,[4,8,15,16] few reports have been related to drug treatment and normalization of this pattern. As demonstrated in a long-term study, the effects of phosphodiesterase 5 inhibition on pulmonary hemodynamics is an important accepted mechanism for EOV reversal.[13] However, it is not known whether guideline-directed medical therapy for HF can affect this abnormal ventilatory pattern.

Beta-blocker therapy (βb) is an effective treatment for chronic HF that significantly changes morbidity and mortality.[17,18,19] It is well known that enhancement of sympathetic tone is among the milestone characteristics of HF. Part of the enhanced sympathetic tone is a

reflex-mediated increase in ventilation, the so-called hyperpnea. βb decreases the progression of left ventricular dysfunction, decreases sympathetic activity, and thus improves the prognosis of patients with HF.[20] The drug is well tolerated and possesses some attractive pharmacological properties that, at least in theory, might favor modulatory activity on exercise oscillatory ventilation, such as improving left ventricular function, modulating the sympathetic response in chemoreceptors, and reducing ventilation throughout the entire exercise.[20,21]

According to these premises, we hypothesized that this ventilatory pattern might reflect a marked alteration of the normal physiologic control systems important in cardiopulmonary responses and could, therefore, be normalized after medical treatment with βb. Thus, we evaluated whether βb therapy can revert EOV in patients with HF with reduce ejection fraction.

METHODS

Study Design and Population

This single-center prospective study was conducted at the Heart Institute, which is a hospital designated to treat patients with heart disease. Patients with a clinical diagnosis of HF up to three months, LVEF ≤45% and without a history of βb use were screened at the Heart Failure outpatient clinic between June 2017 and August 2019. These patients could already be using angiotensin-converting enzyme inhibitors (ACE-I), angiotensin receptor blockers (ARB), and aldosterone receptor antagonists. None of the included patients had pulmonary hypertension diagnosed by echocardiogram. Patients with neuromuscular diseases, chronic obstructive pulmonary disease, history of βb intolerance, Chagas's disease, anemia, and orthopedic impairments were excluded.

All eligible patients underwent, before introduction and after βb optimization, blood collection for brain natriuretic peptide (BNP) and plasma catecholamine measurements, echocardiography, and cardiopulmonary exercise testing (CPET). The patients received medical treatment and drug therapy according to the most recent guidelines in HF treatment and were

followed for six months through fortnightly medical consults in the outpatient clinic.[22] The βb chosen was carvedilol, which is a nonselective β-receptor antagonist that also blocks α1-receptors and, unlike other beta blockers, exerts antioxidant effects, which may contribute to its actions in heart failure.[17] The initial dose for all patients was carvedilol 3.125 mg twice a day. The optimal dose was determined according to the highest tolerated dose.[22]

Cardiopulmonary Exercise Testing

All patients were asked to refrain from both strenuous physical activity and the consumption of any stimulants (ie, coffee, tobacco, and alcohol) that could influence heart rate for 24 h before the CPET. The patients' last meal was ingested no less than 2 h before the start of the test. All subjects underwent the test on a programmable treadmill (Series 2000, Marquette Electronics, Milwaukee, WI, USA) in a temperature-controlled room (21–23◦C) between 9 and 11 A.M. with a standard 12-lead continuous ECG monitor (Max 1, Marquette Electronics). Blood pressure monitoring was obtained with the patient at rest, during effort, and during recovery. Minute ventilation, oxygen uptake, carbon dioxide output, and other cardiopulmonary variables were acquired breath-by-breath by a computerized system (Vmax 229 model, SensorMedics, Yorba Linda, CA, USA). The respiratory exchange ratios were recorded as the one-minute averaged samples obtained during each stage of a modified Naughton protocol. A satisfactory test was characterized by a peak of respiratory exchange ratio ≥1.05 and symptoms of maximum effort. The highest VO_2 uptake level was considered the peak value.[1,2]

Exercise Oscillatory Ventilation Assessment

Exercise oscillatory ventilation during exercise was established according to the criteria previously described[4]: 1) three or more regular oscillations (ie, clearly discernible from inherent data noise); 2) regularity was defined if the standard deviation of three consecutive cycle lengths was within 20% of the average; 3) minimal average amplitude of ventilatory oscillation of 5 L

(peak value minus the average of two in-between consecutive nadirs). Presence of EOV was determined by two experienced observers independently and in a blinded fashion. Graphs of VE (L/min, fixed scale) plotted against time were printed out and sent to each observer without any patient identification or test date information. Any disagreement was resolved by consensus between the observers.

Echocardiography

The patients underwent a 1-dimensional (M-mode), 2-dimensional (mode B) transthoracic echocardiographic study with pulsed, continuous, and color Doppler. Sequoia 512 equipment (Acuson, Mountain View, CA) was used, with the coupled multifrequency transducer, model 3V2c, of 2.5-4.0 MHz, according to the recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Lang cardiac morphological parameters, systolic function indexes, and diastolic function indexes were analyzed.

Serum Biomarkers

Peripheral blood samples were collected at rest, the BNP level was measured using a direct chemiluminescence test (Siemens Healthcare Diagnostics, Tarrytown, New York), and catecholamines were measured by high performance liquid chromatography.

Statistical Analysis

Initially, for the continuous variables, Shapiro-Wilk was used to verify the sample normality. Thus, the results that showed Gaussian distributions were presented using mean ± standard error, and those that did not were described using the median and its interquartile range.

The paired Student *t* test was used to analyze differences between pre-introduction versus post-optimization of ßb in the variables of normal distribution, and the Wilcoxon signed rank test

was used for analysis of nonparametric variables. To evaluate the normalization of the exercise oscillatory ventilation pattern between the two moments, the McNemar test was used.

A log-rank test was performed to evaluate the effect of the medication (ACE-I, ARB, and aldosterone receptor antagonist) previously used and their adjustments during the study.

RESULTS

A total of 647 cases of HF of ischemic and nonischemic etiology were evaluated. Twenty-five patients matched the criteria for inclusion, but three patients refused to enroll in the study and one patient died before the study began. Therefore, twenty-one patients were enrolled in the study. In four patients, the exercise test was interrupted due to sustained ventricular tachycardia, one patient was lost to follow-up, and the other was hospitalized for worsening HF. Fifteen patients (14 male) with HFrEF, NYHA I-III were enrolled in the study. The baseline characteristics, determined by presence (EOV+) or absence (EOV-) of exercise oscillatory ventilation before βb introduction are shown in Table 1.

Carvedilol was well tolerated by all patients at a mean dose of 42 ± 11 mg/day. After a mean follow-up of 196 ± 30 days, 11 patients were in functional class I, 3 in functional class II, and 1 in functional class III. No adverse events occurred during the study.

After βb optimization, LVEF had a significant increase (from 25.9 ± 2.5 to 33.2 ± 2.6%, *P*=0.02), and LVEDD decreased (from 73 ± 13 to 66 ± 12 mm, *P*=0.001). Resting and maximal heart rate, VE/VCO_2 slope, and exercise tolerance significantly improved post βb optimization (Figure 1). However, βb therapy caused no significant change in peak VO_2 (from 21.8 ± 1.7 to 24.7 ± 1.9 mL/kg/min, *P*=0.46). BNP and catecholamines significantly decreased after βb therapy optimization (Figure 2).

EOV Analysis

After the initial evaluation (n=15), nine patients (60%) had EOV. After introduction and

optimization, only two patients had EOV, with a normal pattern in 13 patients. Figure 3 shows a representative example of one patient before introduction and after βb optimization, showing exercise oscillatory ventilation only during the first evaluation.

Medications

No patient had previously taken βb, although they could already be in use of ACE-I, ARB, and aldosterone receptor antagonist. When doses were compared pre-introduction and post-optimization, no statistical differences were observed. The results are presented in Table 2.

DISCUSSION

To the best of our knowledge, this is a pioneering case series study in the evaluation of the prevalence of EOV in patients with HFrEF who had never taken βb. The main findings of our study are two-fold: 1) The prevalence of EOV among HF patients with no βb therapy was elevated; and 2) Guideline-directed βb therapy was associated with a remarkable decrease in the presence of EOV in these patients.

Exercise Oscillatory Ventilation Pathophysiology

The physiologic adjustments during dynamic exercise can produce additional sources of excessive ventilatory response and, therefore, promote further instabilities. Despite the clear association between EOV and severity of HF, few studies have examined its physiological basis. The theoretical models for oscillatory breathing at rest suggest instability in feedback systems that control the ventilation.[16,23,24,25]

Ventilation is regulated through the feedback loop between the pulmonary gas exchange capillaries and chemoreceptors in the carotid bodies (peripheral) and spinal cord (central) that respond to O_2 and CO_2 levels in the blood.[26] Also, overstimulation of the ventilatory control center by pulmonary congestion has also been postulated to contribute to oscillatory breathing at rest in

HF.[26] Possible mechanisms involved in the etiology of EOV have been largely extrapolated from studies of oscillatory breathing at rest and during sleep. Studies have reported that hyperventilation and low arterial CO_2 at rest and during sleep are associated with cyclic waxing and waning of tidal volume in HF patients, a condition known as periodic breathing.[4,27]

Mechanisms stimulating EOV occurrence remain unclear, but three major pathogenetic hypotheses have been suggested. First, the hemodynamic hypothesis as suggested by several authors recognizes an increase in left atrial and pulmonary capillary pressures, pulmonary vasoconstriction, as well as a reduction in cardiac output causing fluctuations in pulmonary blood flow, as major substrates for EOV.[28,29,30]

Second, the circulatory delay hypothesis suggests that the prolonged circulation time from lungs to chemoreceptors and respiratory centers leads to disturbance of feedback systems.[31] Reduced cardiac index (CI) leads to increased circulation time, causing delay in the transfer of information to chemoreceptors, which in turn generates delayed feedback signals that result in imprecise control of respiration.[31,32]

A direct correlation was observed between lung-to-ear circulation time with cycle length and hyperpnea length, and an inverse correlation with CI in HF patients with Cheyne-Stokes respiration.[33] It was hypothesized that exercise oscillatory breathing was primarily related to the inability to augment CI during exercise.[31,34]

Lastly, the ventilatory hypothesis highlights a most important pathogenetic role for instability of central and peripheral neural control of ventilation.[12,35] HF patients with altered breathing may have increased chemosensitivity in association with an activated sympathetic nervous system.[36,37] Increased chemosensitivity enhances hyperventilation and hypocapnia along with an increase in central respiratory drive that may trigger altered breathing patterns. Thus, the pathophysiology of the abnormal ventilatory pattern during exercise seems to originate from multiple pathways.

The normalization of exercise oscillatory breathing after treatment with βb in HFrEF

appears to be associated with the improvement of other prognostic determinants assessed in our study, besides the decrease in cardiac frequency, such as improvement in LVEF and decrease in BNP and VE/VCO_2 slope.

Possible Mechanisms of Action of βb in EOV

Because the pathophysiology of the abnormal ventilatory pattern during exercise seems to originate from multiple pathways, we hypothesized why βb might affect this pattern. There were no statistical differences between other medications in use, so we did not attribute the pattern change to other conditions that might be affected by any other drugs. Regarding the hemodynamic hypothesis of EOV, cardiac output oscillations can be achieved through heart rate, stroke volume oscillations, or both. Although βb works mainly by decreasing the heart rate, the reserve heart rate remains the same. In this study, as in several previous reports, treatment of HF with carvedilol improves clinical status and reduces left ventricle dimensions without affecting exercise performance.[17,38,39] Indeed, peak VO_2 was unaffected by carvedilol. Our results, in agreement with those observed, sought to refine the prediction of cardiac events by performing a combined analysis of NT-proBNP with markers of exercise ventilatory efficiency in HF patients.[13,21] The results revealed that NT-proBNP levels together with exercise oscillatory ventilation led to the most powerful definition. Our results showed a great decrease in BNP levels and agree with those findings because NT-proBNP and BNP are directly related.[13,21,38]

Moreover, the study seems to show some influence of βb on the ventilatory hypothesis. Regarding catecholamines, the reduction shows a decrease in sympathetic activity. At this point, we attribute the improvement in the pattern observed due to decreased arousal of the central and peripheral chemoreflexes, which are also mediated by the sympathetic nervous system observed in chronic HF at sea level, carvedilol reduced exercise-induced hyperventilation without affecting exercise performance.[13,40] Lowering of hyperventilation is a positive event because hyperventilation is related to an increase in the work of breathing, HF symptoms like dyspnea,

and poor prognosis.[41,42]

Also, after the optimized therapy with βb, we observed improvement in exercise time, during the cardiopulmonary test without changes in VO_2.[43,44] βb reduces maximal heart rate to exercise and would perhaps be expected to even reduce maximal exercise capacity.[43,44,45,46] On the other hand, finding a positive effect on exercise time shows that this variable was sensitive in detecting changes in effort tolerance. The increase in exercise tolerance agrees with the improvement in functional class (NYHA), less hyperventilation, and can be translated into less dyspnea.[47]

Clinical Implications

The present case series study guided us to new thoughts about the genesis of EOV. Because βb seems to play a role in its normalization, it sheds light on some pathophysiologic determinants of EOV, such as the sympathetic nervous system and central hemodynamic improvements.

By indicating an inadequate hemodynamic response to exercise and the ability of a pharmacological intervention, our study also makes EOV a potential endpoint of interest for interventions expected to decrease dyspnea and improve effort tolerance shown by the functional capacity's improvement in HFrEF. Further work is needed to determine if interventions like cardiac resynchronization, intensification of neurohormonal blockade, or emerging HFrEF therapies will successfully attenuate EOV.

Study Limitations

Important limitations for this case series must be considered. We did not assess sleep apnea. However, periodic breathing has been characterized in different physiological states, including during sleep and during exercise. We only used the βb carvedilol, as it is the only βb available at our institution for patients with heart failure. This study appears to be the first to elucidate the influence of βb on one or more mechanisms in the genesis of EOV.[14,16,48] It is already

known that βb improves the prognosis in patients with HF, being widely used for the treatment of this disease since the 1990s; however, in the absence of a control group, our results may be influenced by secular effects. Furthermore, a placebo-controlled study would be unethical in this setting, as βb therapy is a class I recommendation, level A of evidence in patients with HFrEF. We also approached the presence of EOV blindly and with two independent reviewers to mitigate any misclassification bias.

CONCLUSION

We report a case series of likely evidence that βb therapy can reverse EOV in patients with HFrEF. Although the true incidence of this adverse event remains incompletely understood at this time, the pattern of presentation and the clinical course suggest distinct pathophysiologic mechanisms during sleep, and during exertion. Our results indicate that this respiratory abnormality, which occurs in patients with chronic HFrEF, can be reversed with guideline-based treatment and provides mechanistic insights into the development of EOV.

References

1. Guimaraes GV, d'Avila VM, Silva MS, et al. A cutoff point for peak oxygen consumption in the prognosis of heart failure patients with beta-blocker therapy. *Int J Cardiol.* 2010;145(1):75–7.
2. Guimarães GV, Silva MS, d'Avila VM, Ferreira SMA, Silva CP, Bocchi EA. VO2 pico e inclinação VE/VCO2 na era dos betabloqueadores na insuficiência cardíaca: uma experiência brasileira. *Arq Brasil Cardiol*. 2008;91(1):39–48.
3. Forman DE, Guazzi M, Myers J, et al. Ventilatory power: a novel index that enhances prognostic assessment of patients with heart failure. *Circ Heart Fail.* 2012;5(5):621–6.
4. Leite JJ, Mansur AJ, de Freitas HFG, et al. Periodic breathing during incremental exercise predicts mortality in patients with chronic heart failure evaluated for cardiac transplantation. *J Am Coll Cardiol*. 2003;41(12):2175–81.
5. Guazzi M, Raimondo R, Vicenzi M, et al. Exercise oscillatory ventilation may predict sudden cardiac death in heart failure patients. *J Am Coll Cardiol.* 2007;50(4):299–308.
6. Guazzi M, Boracchi P, Arena R, et al. Development of a cardiopulmonary exercise prognostic score for optimizing risk stratification in heart failure: The (P)e(R)i(O)dic (B)reathing During (E)xercise (PROBE) Study. *J Cardiac Fail.* 2010;16(10):799–805.
7. Balady GJ, Arena R, Sietsema K, et al. Clinician's Guide to Cardiopulmonary Exercise Testing in Adults. *Circulation.* 2010;122(2):191–225.
8. Sun X-G, Hansen JE, Beshai JF, Wasserman K. Oscillatory breathing and exercise gas exchange abnormalities prognosticate early mortality and morbidity in heart failure. *J Am Coll Cardiol.* 2010;55(17):1814–23.
9. Makita S. Significance of oscillatory breathing on cardiopulmonary exercise testing in chronic heart failure. *Circ J.* 2013;77(3):598–9.
10. Tkacova R, Niroumand M, Lorenzi-Filho G, Bradley TD. Overnight shift from obstructive to central apneas in patients with heart failure. *Circulation*. 2001;103(2):238–43.
11. Olson TP, Frantz RP, Snyder EM, O'Malley KA, Beck KC, Johnson BD. Effects of acute changes in pulmonary wedge pressure on periodic breathing at rest in heart failure patients. *Am Heart J.* 2007;153(1):104.e1-104.e7.
12. Francis DP, Willson K, Davies LC, Coats AJS, Piepoli M. Quantitative general theory for periodic breathing in chronic heart failure and its clinical implications. *Circulation.* 2000;102(18):2214–21.
13. Guazzi M, Vicenzi M, Arena R. Phosphodiesterase 5 inhibition with sildenafil reverses exercise oscillatory breathing in chronic heart failure: a long-term cardiopulmonary exercise testing placebo-controlled study. *Eur J Heart Fail.* 2012;14(1):82–90.
14. Kato J, Koike A, Hashimoto-Iwamoto M, et al. Relation between oscillatory breathing and cardiopulmonary function during exercise in cardiac patients. *Circ J.* 2013;77(3):661–6.
15. Corrà U, Giordano A, Bosimini E, et al. Oscillatory ventilation during exercise in patients with chronic heart failure. *Chest.* 2002;121(5):1572–80.
16. Dhakal BP, Lewis GD. Exercise oscillatory ventilation: Mechanisms and prognostic significance. *World J Cardiol.* 2016;8(3):258.
17. Packer M, Fowler MB, Roecker EB, et al. Effect of carvedilol on the morbidity of patients with severe chronic heart failure: Results of the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) Study. *Circulation*. 2002;106(17):2194–9.
18. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): A randomised trial. *Lancet*. 1999;353(9146):9–13.
19. Agostoni P, Contini M, Magini A, et al. Carvedilol reduces exercise-induced hyperventilation: A benefit in normoxia and a problem with hypoxia. *Eur J Heart Fail.* 2006;8(7):729–35.
21. Agostoni P, Palermo P, Contini M. Respiratory effects of β-blocker therapy in heart failure. *Cardiovasc Drugs Ther*. 2009;23:377–384.

22. Bocchi EA, Marcondes-Braga FG, Bacal F, et al. Sociedade Brasileira de Cardiologia. Atualização da Diretriz Brasileira de Insuficiência Cardíaca Crônica. *Arq Bras Cardiol.* 2012;98 (Suppl. 1):S1-33.
23. Cherniack NS, Longobardo GS. Cheyne-Stokes breathing. An instability in physiologic control. *N Engl J Med*. 1973;288(18):952-957.
24. Millar TW, Hardy PJ, Hunt B, Frais M, Kryger MH. The entrainment of low frequency breathing periodicity. *Chest*. 1990;98(5):1143–8.
25. Ponikowski P, Anker SD, Chua TP, et al. Oscillatory breathing patterns during wakefulness in patients with chronic heart failure: clinical implications and role of augmented peripheral chemosensitivity. *Circulation*. 1999;100(24):2418–24.
26. Lorenzi-Filho G, Azevedo ER, Parker JD, Bradley TD. Relationship of carbon dioxide tension in arterial blood to pulmonary wedge pressure in heart failure. *Eur Respir J.* 2002;19(1):37–40.
27. Naughton M, Benard D, Tam A, Rutherford R, Bradley TD. Role of hyperventilation in the pathogenesis of central sleep apneas in patients with congestive heart failure. *Am Rev Respir Dis.* 1993;148(2):330–8.
28. Ben-Dov I, Sietsema KE, Casaburi R, Wasserman K. Evidence that circulatory oscillations accompany ventilatory oscillations during exercise in patients with heart failure. *Am Rev Respir Dis.* 1992;145(4_pt_1):776–81.
29. Olson TP, Frantz RP, Snyder EM, O'Malley KA, Beck KC, Johnson BD. Effects of acute changes in pulmonary wedge pressure on periodic breathing at rest in heart failure patients. *Am Heart J.* 2007;153(1):104.e1-104.e7.
30. Murphy RM, Shah RV, Malhotra R, et al. Exercise oscillatory ventilation in systolic heart failure. *Circulation.* 2011;124(13):1442–51.
31. Dhakal BP, Murphy RM, Lewis GD. Exercise oscillatory ventilation in heart failure. *Trends Cardiovasc Med.* 2012;22(7):185–91.
32. Mortara A, Sleight P, Pinna GD, et al. Association between hemodynamic impairment and Cheyne-Stokes respiration and periodic breathing in chronic stable congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. *Am J Cardiol.* 1999;84(8):900–4.
33. Hall MJ, Xie A, Rutherford R, Ando S, Floras JS, Bradley TD. Cycle length of periodic breathing in patients with and without heart failure. *Am J Respir Crit Care Med.* 1996;154(2):376–81.
34. Corrà U. Exercise oscillatory ventilation in heart failure. *Int J Cardiol.* 2016;206:S13–5.
35. Francis DP, Davies LC, Piepoli M, Rauchhaus M, Ponikowski P, Coats AJS. Origin of oscillatory kinetics of respiratory gas exchange in chronic heart failure. *Circulation.* 1999;100(10):1065–70.
36. Guimarães GV, Belli JF, Bacal F, Bocchi EA. Behavior of central and peripheral chemoreflexes in heart failure. *Arq Bras Cardiol.* 2011;96:161-167.
37. Yamada K, Asanoi H, Ueno H, et al. Role of central sympathoexcitation in enhanced hypercapnic chemosensitivity in patients with heart failure. *Am Heart J.* 2004;148(6):964–70.
38. Colucci WS, Packer M, Bristow MR, et al. Carvedilol inhibits clinical progression in patients with mild symptoms of heart failure. *Circulation.* 1996;94(11):2800–6.
39. Agostoni P, Guazzi M, Bussotti M, De Vita S, Palermo P. Carvedilol reduces the inappropriate increase of ventilation during exercise in heart failure patients. *Chest*. 2002;122(6):2062–7.
40. Soares Barreto-Filho JA, Consolim-Colombo FM, Ferreira Lopes H, et al. Dysregulation of peripheral and central chemoreflex responses in Chagas' heart disease patients without heart failure. *Circulation*. 2001;104(15):1792–8.
41. Johnson BD, Beck KC, Olson LJ, et al. Ventilatory constraints during exercise in patients with chronic heart failure. *Chest*. 2000;117(2):321–32.

42. Agostoni P, Pellegrino R, Conca C, Rodarte JR, Brusasco V. Exercise hyperpnea in chronic heart failure: relationships to lung stiffness and expiratory flow limitation. *J Appl Physiol.* 2002;92(4):1409–16.
43. Carvalho VO, Guimarães GV, Ciolac EG, Bocchi EA. Heart rate dynamics during a treadmill cardiopulmonary exercise test in optimized beta-blocked heart failure patients. *Clinics*. 2008;63(4).
44. Carvalho VO, Rodrigues Alves RX, Bocchi EA, Guimarães GV. Heart rate dynamic during an exercise test in heart failure patients with different sensibilities of the carvedilol therapy. *Int J Cardiol.* 2010;142(1):101–4.
45. Abdulla J, Køber L, Christensen E, Torp-Pedersen C. Effect of beta-blocker therapy on functional status in patients with heart failure - A meta-analysis. *Eur J Heart Fail.* 2006;8(5):522–31.
46. Ismail H, McFarlane J, Smart NA. Is exercise training beneficial for heart failure patients taking β-adrenergic blockers? A systematic review and meta-analysis. *Congest Heart Fail.* 2012;19(2):61–9.
47. Guimarães GV, Carvalho VO, Bocchi EA, d'Avila VM. Pilates in heart failure patients: a randomized controlled pilot trial. *Cardiovasc Ther*. 2012;30(6):351-6.
48. Corrà U, Giordano A, Bosimini E, et al. Oscillatory ventilation during exercise in patients with chronic heart failure: clinical correlates and prognostic implications. *Chest*. 2002;121(5):1572–80.

Sources of Funding

This work was supported by *Fundação de Amparo à Pesquisa do Estado de São Paulo* (FAPESP # 2009/17457-8) as part of Juliana F.C. Belli-Marin's doctoral thesis under the guidance of Guilherme V. Guimarães. Guilherme Veiga Guimarães was supported by *Conselho Nacional de Desenvolvimento Cientıfico e Tecnológico* (CNPq # 301957/2017-7) during this project. Neither of these funding sources had any involvement in the conducting of this research or preparation of this article.

Competing Interests

The authors report that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

Author contribution

JFCBM, EAB, SAF, NCJ, and GVG contributed to the study design, data analysis and interpretation, and manuscript writing. All authors gave final approval and agreed to all aspects of the work ensuring integrity and accuracy. The current study is presented honestly without fabrication, falsification, or inappropriate data manipulation. The authors declare no potential conflicts of interest concerning the research, authorship, and/or publication of this article.

Ethics approval

The study complied with the Declaration of Helsinki and the Research Ethics Board of the Heart Institute (SDC: 3324/09/075), and the Human Subject Protection Committee at the Clinics Hospital of the University of São Paulo Medical School (CAPPesq 0856/09).

Consent to participate

Informed consent was obtained from all individual participants included in the study.

Consent to publish

No apply.

Data availability statements

The data emerging from this research may be shared and used in research projects or other scientific documents, after publication of their results in indexed scientific journals. Prior request for use of this data must be granted, provided that the source is cited. The names of the participants will be kept confidential and the study will be available in the University's database (pdf format) with thanks to possible funding agencies.

Figure 1. Resting heart rate, resting left ventricular ejection fraction, VE/VCO_2 slope and peak VO_2 pre- and post-β-blocker introduction.

Figure 2. Brain natriuretic peptide and catecholamine pre- and post-β-blocker introduction.

Figure 3. Representative example of a patient's oscillatory exercise breathing before and after β-blocker introduction.

Figures

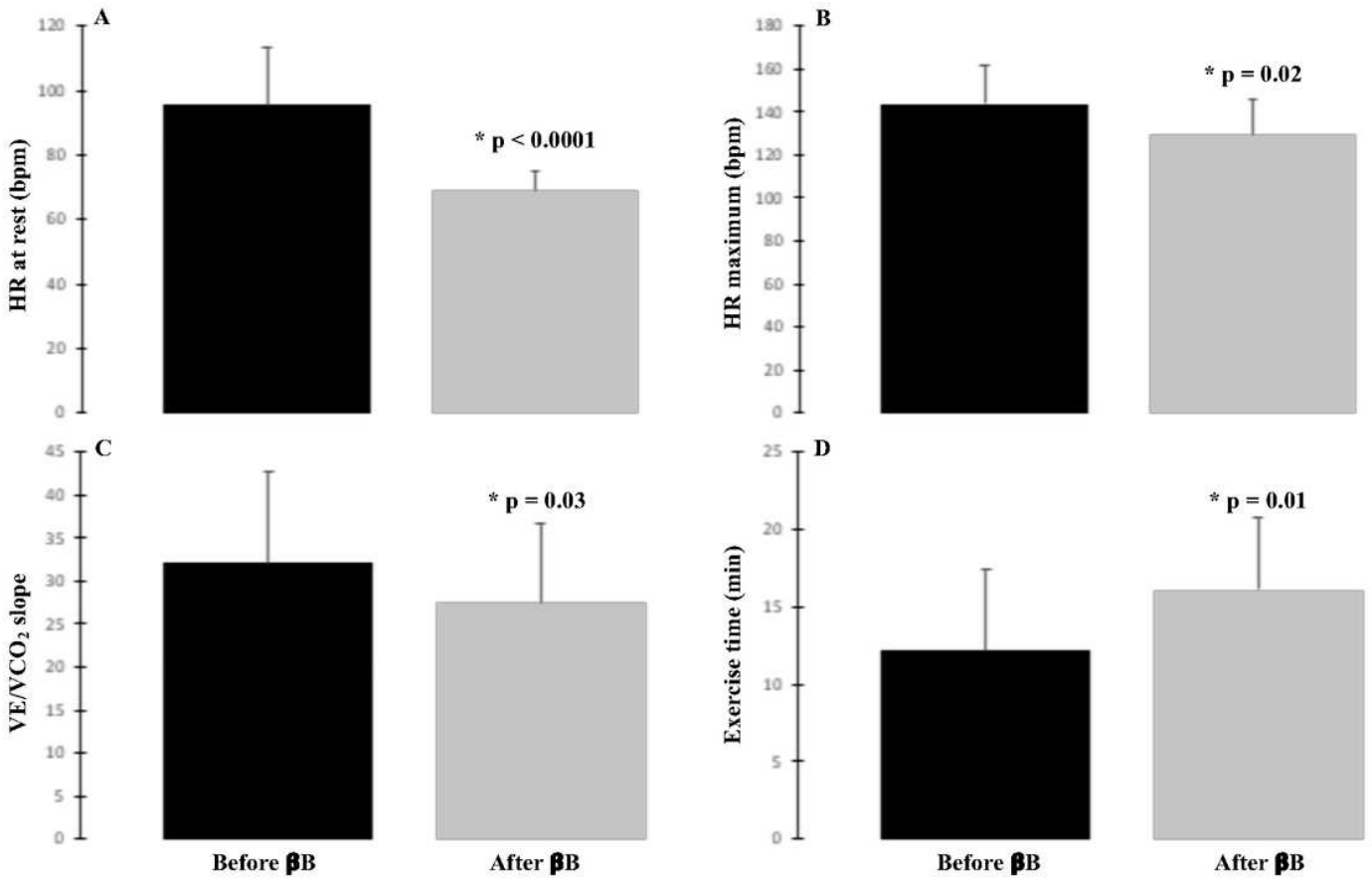

Figure 1

Resting heart rate, resting left ventricular ejection fraction, VE/VCO2 slope and peak VO2 pre- and post-β-blocker introduction.

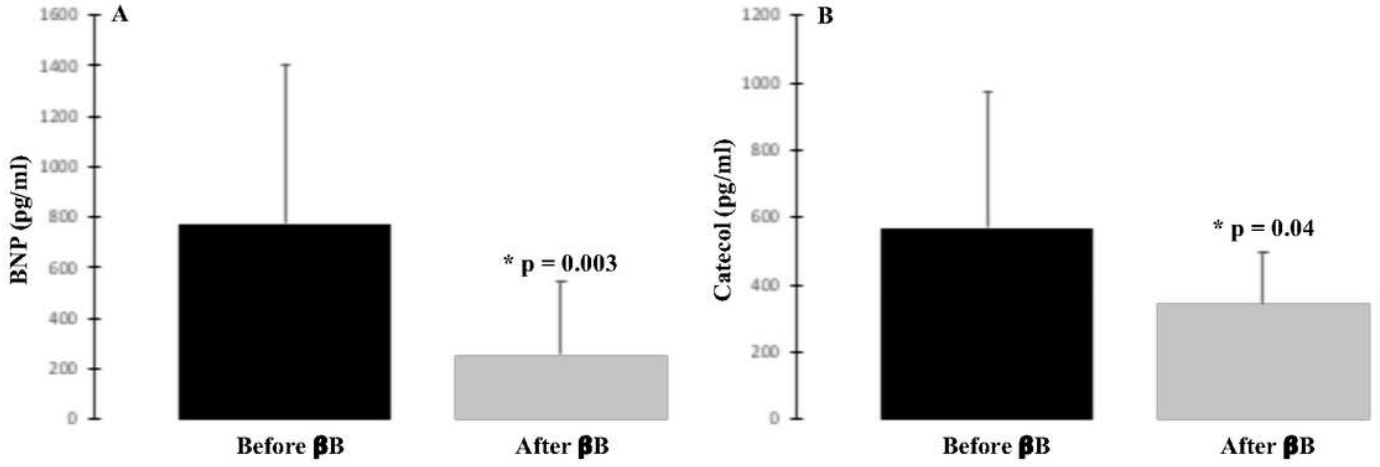

Figure 2

Brain natriuretic peptide and catecholamine pre- and post-β-blocker introduction.

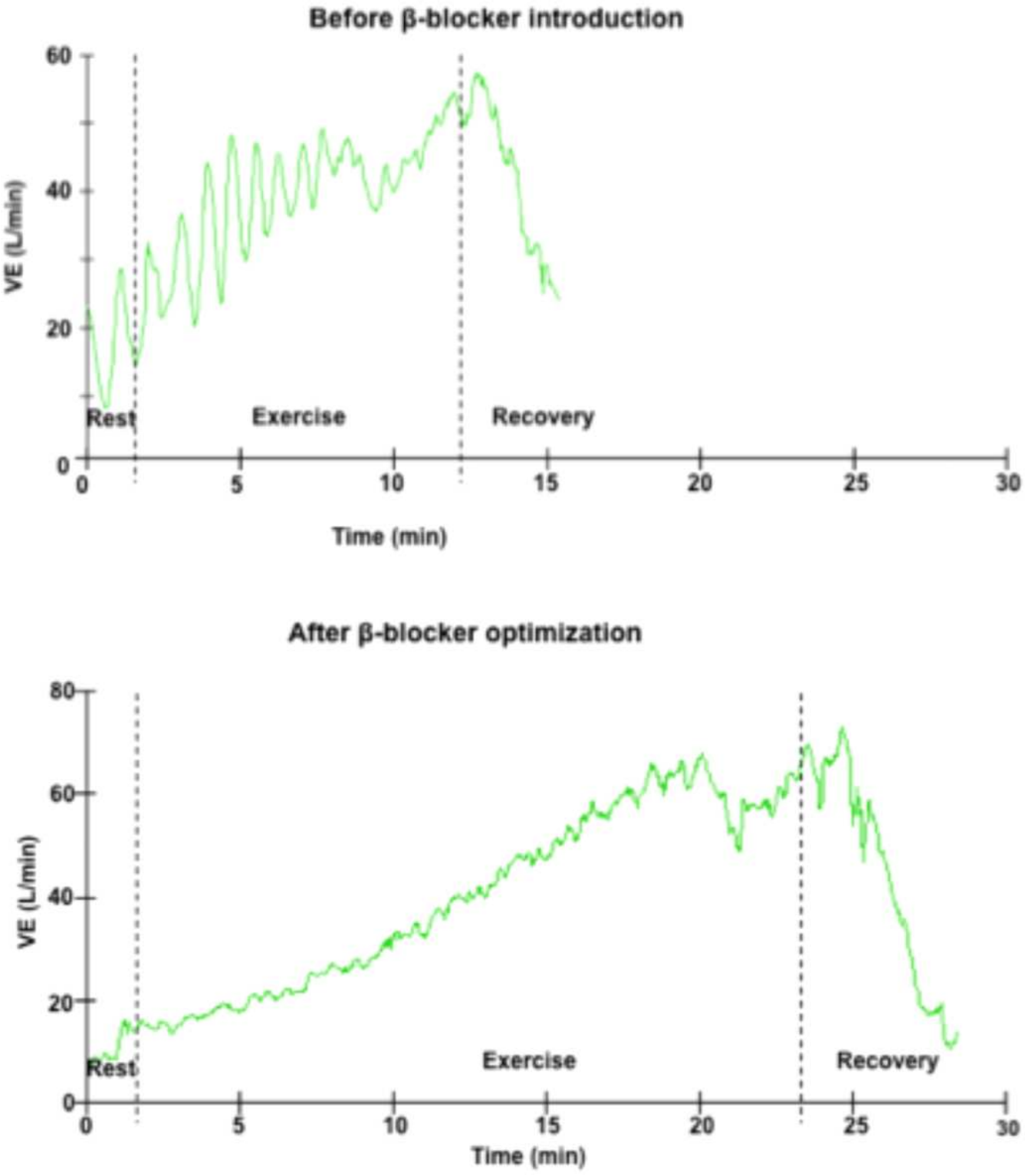

Figure 3

Representative example of a patient's oscillatory exercise breathing before and after β-blocker introduction.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table1EOB.pdf
- Table2EOB.pdf