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Research Article

Minute ventilation in cardiorespiratory exercise and its relationship with ventricular ejection fraction

Ventilación minuto en ejercicio cardiorrespiratorio y su relación con fracción de eyección ventricular

Alirio Bastidas-Goyes[1]* https://orcid.org/0000-0002-8873-9779

Eduardo Tuta-Quintero[1] https://orcid.org/0000-0002-7243-2238

Juan D. Botero[1] https://orcid.org/0000-0002-3594-9705

Daniel Botero Rosas[1] https://orcid.org/0000-0002-2590-0756

Daniel Prieto[1] https://orcid.org/0000-0002-4421-9173

Daniela Rubio[1] https://orcid.org/0000-0003-0666-4230

Cristian López[2] https://orcid.org/0000-0001-5552-5881

Gustavo A. Hincapie[2] https://orcid.org/0000-0002-3663-9995

Barbarita Mantilla[2] https://orcid.org/0000-0001-9859-0288

Abraham Brito[1] https://orcid.org/0000-0001-8462-7756

Tatiana Vargas[1] https://orcid.org/0000-0003-4415-2025

Stefania Forero[1] https://orcid.org/0009-0006-5662-6792

Laura Villarraga[1] https://orcid.org/0000-0001-8219-9874

Andrea Giraldo[1] https://orcid.org/0000-0002-4526-6377

Monica Briceño[1] https://orcid.org/0000-0002-9606-5372

Alejandra Porras[1] https://orcid.org/0000-0002-9011-8349

[1]School of Medicine. Universidad de La Sabana. Chía, Colombia.

[2]Pulmonary Medicine. Hospital Militar Central. Bogotá, Colombia.

*****Corresponding author**:** Email: alirio.bastidas@unisabana.edu.co

ABSTRACT

Introduction: Cardiorespiratory exercise testing is a non-invasive alternative in the assessment of subjects with heart failure.

Objective: To evaluate the validity of ventilatory equivalents for carbon dioxide (VE/VCO2) as a predictor of left ventricular ejection fraction (LVEF) compared to peak oxygen consumption.

Methods: Cross-sectional analytical study in patients undergoing cardiopulmonary exercise testing and transthoracic echocardiography. The study was divided into a group with reduced LVEF < 40% and preserved ≥ 40%. Bivariate analysis comparing qualitative variables with the chi-square test and quantitative variables with Student's t-test was performed. A Receiver Operating Characteristic (ROC) curve was constructed to evaluate the discriminatory capacity between ventilatory equivalent for carbon dioxide and peak oxygen pulse.

Results: The final analysis included 138 patients. In patients with reduced LVEF, peak oxygen consumption averaged 1.6 L/min (SD ± 0.68) compared to 1.7 L/min (SD ± 0.66) in the control group (p= 0.513). VE/VCO2 during ventilatory threshold and peak exercise averaged 38.4 (SD ± 7.38) and 44.6 (SD ± 8.24), respectively. The discriminatory performance of VE/VCO2 versus peak oxygen consumption was 0.737 (95% CI: 0.596-0.878; p= 0.008) in patients with reduced LVEF.

Conclusions: VE/VCO2 is a reliable predictor of normal or reduced LVEF and performs well compared to peak oxygen consumption.

Keywords: heart failure; exercise test; observational study.

RESUMEN

Introducción: La prueba de ejercicio cardiorrespiratorio es una alternativa no invasiva en la evaluación de sujetos con insuficiencia cardíaca.

Objetivo: Evaluar la validez de los equivalentes ventilatorios para dióxido de carbono (VE/VCO2) como predictor de la fracción de eyección ventricular izquierda (FEVI) en comparación con el consumo máximo de oxígeno.

Métodos: Estudio analítico transversal en pacientes con prueba de ejercicio cardiopulmonar y ecocardiografía transtorácica. Se dividió en un grupo con FEVI reducida < 40 % y conservada ≥ 40 %. Análisis bivariado comparando variables cualitativas con la prueba de *ji* cuadrado y variables cuantitativas, con la prueba t de Student. Se construyó una curva ROC (*Receiver Operating Characteristic*) para evaluar la capacidad discriminativa entre el cociente ventilatorio de dióxido de carbono y el pulso de oxígeno pico.

Resultados: En el análisis final se incluyeron 138 pacientes. En pacientes con FEVI reducida, el consumo máximo de oxígeno presentó un promedio de 1,6 L/min (DE ± 0,68) en comparación con 1,7 L/min (DE ± 0,66) en el grupo de control (p= 0,513). Los VE/VCO2 durante el umbral ventilatorio y máximo presentaron un promedio de 38,4 (DE ± 7,38) y 44,6 (DE ± 8,24), respectivamente. El rendimiento discriminatorio de VE/VCO2 versus el consumo máximo de oxígeno fue de 0,737 (IC95 %: 0,596-0,878; p= 0,008) en pacientes con FEVI reducida.

Conclusiones: VE/VCO2 es un predictor confiable de FEVI normal o reducida y tiene un buen desempeño en comparación con el consumo máximo de oxígeno.

Palabras clave: estudio observacional; insuficiencia cardíaca; prueba de ejercicio.

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INTRODUCTION

Cardiovascular diseases are the first cause of mortality in the world and their incidence increases due to a higher rate of longevity, comorbidities and exposure to risk factors.(1,2) Among the cardiovascular diseases with the highest burden of morbidity and mortality is heart failure (HF), affecting 23 million people worldwide and a prevalence of 2.3% to 5.8% at any age in America.(3,4) HF is a prevalent and complex disease associated with signs and symptoms due to structural and functional anomalies of the heart.[2,3] However, it is highly underdiagnosed due to the poor availability of diagnostic methods such as echocardiography and trained personnel for its performance.[4,5]

Cardiopulmonary exercise testing (CET) is a non-invasive alternative in the evaluation of subjects with HF due it comprehensively evaluates the respiratory and cardiovascular systems under conditions of physical stress.[6] In this test there are several useful parameters in evaluation of subjects with cardiac conditions, including pulse oxygen (PuO2) which is the ratio of oxygen consumption to heart rate, which may be an indirect measure of cardiac output and left ventricular ejection fraction (LVEF).[7,8] The ventilatory equivalents for oxygen (VE/VO2) and for carbon dioxide (VE/VCO2), which are indicators of respiratory efficiency and have a direct association with cardiac output, useful in the evaluation of myocardial diseases.[8,9]

Magri D et al.,[10] described the prognostic factor of CET in a cohort of patients diagnosed with HF with intermediate and reduced LVEF, showing that abnormal values of peak oxygen consumption (VO2) and VE/VCO2 were significantly associated with increased risk of cardiovascular death in the long term.[11] However, the information on the correlation between these indicators and the ejection fraction detected in echocardiography is limited.[7,8,9,10] Due to the need to better understand the usefulness of the CET in the detection of patients with cardiac pathologies, the objective of this study is to evaluate the validity of VE/VCO2 as a predictor of left ventricular ejection fraction compared to maximum oxygen consumption.

METHODS

Design

Cross-sectional analytical study in subjects with CET and transthoracic echocardiography in a tertiary care hospital at Bogotá between 2008 and 2021. The participants had a diagnosis of HF according to the American Heart Association, a group with reduced LVEF $< 40\%$ and no reduced $\geq 40\%$, this last group included patients with intermediate or normal ejection fraction.[12,13] The LVEF was obtained from echocardiographic examinations.

Subjects

Patients older than 18 years of age who underwent concomitant CET and transthoracic echocardiography during the outpatient evaluation by pulmonology and cardiology were included. Patients with uncontrolled arrhythmias, severe valvulopathies, pulmonary thromboembolism, dissecting aortic aneurysm, and mental or sensory disorders that cause inability to cooperate with the test were excluded. All subjects who met the selection criteria during the study period were entered. Data were collected by trained personnel reviewing clinical records, data review was performed by two investigators to avoid possible transcription errors.

Variables

- Age: years.
- Sex: men, women.
- Height: centimeters.
- Weight: kilograms.
- Body mass index (BMI): kilograms/meters^2.
- BMI: > 24.9 kilograms/meters^2, > 29.9 kilograms/meters^2.
- pH: -log[H+].
- Partial pressure of carbon dioxide (pCO_2): mmHg.
- Partial pressure of oxygen (pO_2): mmHg.
- Bicarbonate ($HCO3^-$): mEq/liters.
- Arterial oxygen saturation of arterial blood gasses (SaO_2): percentage.
- Hemoglobin; grames/deciliters.
- Oxygen consumption (VO_2): liters/minutes.
- Heart rate (HR): beats per minute (bpm).
- Oxygen pulse (O2): percentage.
- Forced vital capacity (FVC): liters.
- Forced expiratory volume in the first second (FEV1): liters.

- Maximum voluntary ventilation (MVV): liters/minutes.

CET and spirometry were performed according to the recommendations of the American Thoracic Society, American College of Chest Physicians, and European Respiratory Society.[12]

Statistical analysis

Data from the exercise tests and transthoracic echocardiogram were transcribed to an Excel spreadsheet and subsequently analyzed in the SPSS 25 licensed program. Qualitative variables were summarized as frequencies and percentages; quantitative variables were summarized as mean and standard deviation (SD) if their distribution was normal, and median and interquartile range if their distribution was non-normal. A bivariate analysis will be performed comparing qualitative variables with the chi-square test and quantitative variables with Student's *t* test or Mann Whitney U test, considering a significant $p < 0.05$. A ROC (Receiver Operating Characteristic) curve was constructed to evaluate the discriminatory capacity between the ventilation equivalent for carbon dioxide and the peak oxygen pulse.

Bioethical aspects

This study adheres to the international ethical guidelines, such as the Helsinki Declaration, as well as the national standards of Resolution 8430 of 1993 of the Colombian Ministry of Health. No biological or psychological interventions were performed on the participants, so it is considered a "no risk" investigation. All patient data was handled confidentially, in compliance with the habeas data law 1266 of 2008, and no identifying data of any of the participants was revealed.

The research protocol was previously approved by the Ethics and Research Committee of the Hospital Militar Central (code project: 2023029). The Ethics and Research Committee of the Hospital Militar Central has granted an authorization to exempt the requirement of obtaining the informed consent signature from each patient in the study population.

RESULTS

In the final analysis, 138 patients were included, of whom 88% (122/138) had reduced LVEF and 12% (16/138) not reduce LVEF (Fig. 1).

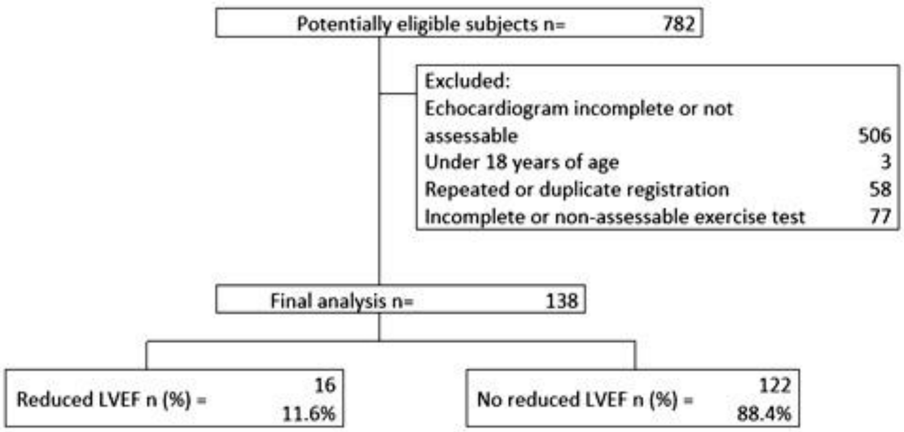

Fig. 1 - Flow chart. LVEF: left ventricular ejection fraction.

Table 1 shows the general characteristics of the study population. In the general population, the mean age was 58.9 years (SD ± 16.37), 65% were men, and the BMI was 27.6 (SD ± 4.56). In the population with reduced LVEF, pre-bronchodilator FVC and FEV1 were 3.6 L (SD ± 1.02) and 2.7 L (SD ± 0.85), respectively.

Table 1 - General Characteristic of the population

Variables	Total population n=138	Reduced LVEF n=16	No reduced LVEF n=122	p
Age years, media (SD)	58.9 (16.37)	49.3 (19.7)	60.2 (15.54)	0.012
Men, n (%)	90 (65.22)	14 (87.5)	76 (62.3)	0.047
Size cm, media (SD)	162.5 (9.21)	165.8 (9.56)	162 (9.12)	0.123
Weight kg, media (SD)	72.7 (13.38)	76.1 (19.56)	72.3 (12.39)	0.481
BMI kg/m^2, media (SD)	27.6 (4.56)	27.7 (6.96)	27.5 (4.19)	0.936
BMI >24.9, n (%)	101 (0.71)	11 (0.52)	90 (0.73)	0.030
BMI >29.9, n (%)	31 (0.23)	3 (0.18)	28 (0.24)	0.705

LVEF: left ventricular ejection fraction; SD: standard deviation; cm: centimeters;
BMI: body mass index; kg/m^2: kilogram/square meters.

Patients with reduced LVEF show a hemoglobin of 14.1 g/dL (SD ± 2.87) and patients with no reduced LVEF show 15.1 g/dL (SD ± 0.77). Peripheral arterial saturation did not show differences before or after the exercise test in both groups. Table 2 shows the laboratory exams of population.

Table 2 - Laboratory exams

Variables	Total population n=138	Reduced LVEF n=16	No reduced LVEF n=122	p
pH before CET, media (SD)	7.4 (0.03)	7.4 (0.04)	7.4 (0.03)	0.065
pH after CET, media (SD)	7.3 (0.06)	7.3 (0.07)	7.3 (0.05)	0.633
pCO_2 (mmHg) before CET, media (SD)	32.6 (3.74)	30.1 (3.1)	32.9 (3.7)	0.004
pCO_2 (mmHg) after CET, media (SD)	30.3 (5.58)	28.9 (3.48)	30.4 (5.78)	0.121
pO_2 (mmHg) before CET, media (SD)	61.9 (8.89)	66.7 (9.22)	61.3 (8.69)	0.021
pO_2 (mmHg) after CET, media (SD)	69.9 (13.36)	66.8 (18.57)	70.3 (12.6)	0.460
$HCO3^-$ (meq/L) before CET, media (SD)	20.4 (2.18)	19.5 (2.53)	20.5 (2.11)	0.085
$HCO3^-$ (meq/L) after CET, media (SD)	15.6 (3.04)	14.7 (2.78)	15.7 (3.06)	0.236
SaO_2 (%) before CET, media (SD)	91.2 (4.45)	92.3 (5.77)	91.1 (4.24)	0.391
SaO_2 (%) after CET, media (SD)	91.2 (6.51)	91.2 (5.83)	91.1 (6.62)	0.972
Hb gr/dL, media (SD)	15 (1.28)	14.1 (2.87)	15.1 (0.77)	0.155

LVEF: left ventricular ejection fraction; CET: Cardiopulmonary Exercise Testing; SD: standard deviation; pO2: partial pressure of oxygen; pCO2: partial pressure of carbon dioxide; HCO3: bicarbonate; SaO2: arterial oxygen saturation of arterial blood gasses; Hb: hemoglobin; g/dL: grams per deciliter.

Table 3 shows the cardiopulmonary exercise testing of the study population. In patients with reduced LVEF, maximum VO2 presented an average of 1.6 L/min (SD ± 0.68) compared to 1.7 L/min (SD ± 0.66) in the control group (p= 0.513). HR during the ventilatory threshold was 13 bpm higher in patients with non-reduced LVEF (107.1 vs. 96.1; p= 0.008). The VE/CO2 during the ventilatory and maximum threshold presented an average of 38.4 (SD ± 7.38) and 44.6 (SD ± 8.24), respectively.

Table 3 - Cardiopulmonary exercise testing

Variables	Total population n=138	Reduced LVEF n=16	No reduced LVEF n=122	P
Time (min) Base measurement, media (SD)	0.61 (0.73)	0.51 (0.35)	0.62 (0.77)	0.154
Time (min) AU measurement, media (SD)	4.2 (2.13)	5 (2.79)	4.1 (2.06)	0.131
Time (min) VO_2 Peak Measurement, media (SD)	8.7 (3.19)	10.5 (3.81)	8.5 (3.05)	0.021
VO_2 (L/Min) Base Measurement, media (SD)	0.4 (0.17)	0.5 (0.28)	0.4 (0.15)	0.387
VO_2 (L/Min) AU Measurement, media (SD)	1.1 (0.46)	1.0 (0.53)	1.2 (0.45)	0.195
VO_2 (L/Min) VO_2 Peak Measurement, media (SD)	1.7 (0.66)	1.6 (0.68)	1.7 (0.66)	0.513
VO_2/kg (ml/kg/min) Base measurement, media (SD)	5.8 (2.18)	6.0 (2.68)	5.7 (2.12)	0.701
VO_2/kg (ml/kg/min) AU measurement, media (SD)	15.5 (6.17)	12.9 (6.56)	15.8 (6.08)	0.077
VO_2/kg (ml/kg/min) Peak VO_2 measurement, media (SD)	23.4 (8.06)	21.4 (7.88)	23.7 (8.07)	0.273
HR (bpm) Base measurement, media (SD)	82.5 (17.04)	80.5 (15.09)	82.8 (17.33)	0.616
HR (bpm) AU measurement, media (SD)	106.1 (15.54)	96.1 (13.75)	107.1 (15.43)	0.008
HR (bpm) VO_2 peak measurement, media (SD)	137.1 (23.38)	128.6 (22.58)	138.2 (23.34)	0.120
O_2 Pulse (ml/beat) Peak VO_2 measurement, media (SD)	12.5 (4.45)	12.5 (4.63)	12.5 (4.45)	0.990
O_2 Pulse (ml/beat) Base Measurement, media (SD)	5.2 (2.08)	5.3 (2.24)	5.2 (2.07)	0.867
O_2 Pulse (ml/beat) AU measurement, media (SD)	11.4 (3.81)	11.1 (3.83)	11.4 (3.83)	0.796
RER Base Measurement, media (SD)	0.9 (0.12)	0.9 (0.09)	0.9 (0.12)	0.846
RER AU measurement, media (SD)	0.9 (0.1)	0.8 (0.13)	0.9 (0.1)	0.024
RER/VO_2 peak measurement, media (SD)	1.1 (0.14)	0.8 (0.13)	0.9 (0.1)	0.028
VEO_2 Base Measurement, media (SD)	43.2 (10.94)	46.6 (7.61)	42.8 (11.25)	0.081
VEO2 AU measurement, media (SD)	33.6 (6.35)	35.4 (7.07)	33.4 (6.29)	0.242
VEO_2/VO_2 peak measurement, media (SD)	44.6 (10.72)	48.5 (12.15)	44.1 (10.5)	0.125
$VECO_2$ Base Measurement, media (SD)	48.9 (9.51)	53.4 (11.05)	48.3 (9.21)	0.045
$VECO_2$ AU Measurement, media (SD)	37.2 (8.5)	38.8 (13.19)	37 (7.83)	0.605
$VECO_2$/VO_2 peak measurement, media (SD)	39.1 (7.7)	44.6 (8.24)	38.4 (7.38)	0.002

VO_2: oxygen consumption; SD: standard deviation; L: liter; min. minute; AU: ventilatory threshold; max: maximum; ml: milliliter; kg: kilogram; HR: heart rate; bpm: beats per minute; O_2: oxygen pulse; VEO_2: ventilation equivalent for oxygen; $VECO_2$: ventilation equivalent for carbon dioxide; RER: respiratory quotient.

The discriminatory performance of VE/VCO_2 versus peak VO_2 was 0.737 (95% CI95%: 0.596-0.878; p= 0.008) in patients with LVEF < 40% (Fig. 2).

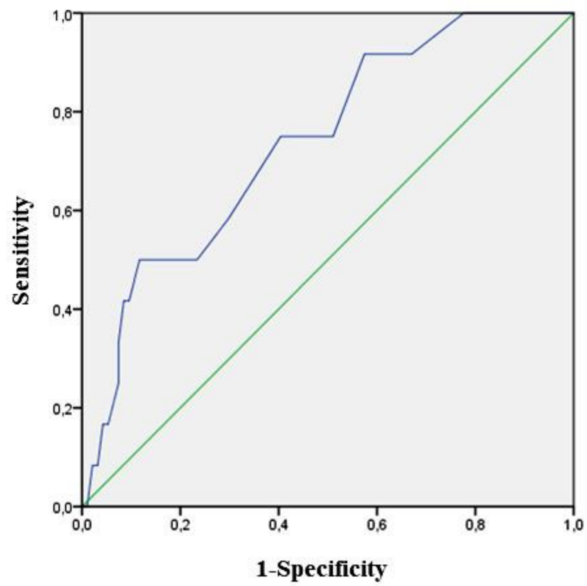

Fig. 2 - Discriminatory performance of ventilation equivalent for carbon dioxide versus peak oxygen pulse.

DISCUSSION

This study analyzes the relationship between the variables described in CET and LVEF in subjects with HF, showing a relationship between peak VE/VCO_2, HR during the ventilatory threshold, and respiratory quotient during the ventilatory threshold with a reduced ejection fraction detected by echocardiography. On the contrary, few consistent data are described by the values of VE/VO_2, VO_2 and O_2 pulse. Age and sex were additional variables related to a decrease in ejection fraction.

The relationship found between peak VE/VCO_2 with a reduced ejection fraction agrees with other studies where subjects with impaired LVEF are compared with a normal ejection fraction.[13,14,15] In addition, increased VE/VCO_2 was associated with a greater number of ventricular assist device implantations, cardiac transplantation, and all-cause mortality.[10,14,16] Data reported higher peak VE/VCO_2 levels in subjects with reduced ejection fraction compared to controls, since 9.3% of subjects with $VE/VCO_2 \geq 36$ had ventricular failure compared to 0% of subjects with $VE/VCO_2 < 36$ ($p= 0.003$).[15] In addition, the greater deterioration of cardiac contractility would be reflected with the inability to transport carbon dioxide as the final product of cellular metabolic processes to the lung, which would increase this relationship.[17,18,19,20]

Imai K et al.,[21] described in subjects with HF and reduced LVEF an average of 7 bpm at HR/anaerobic threshold ratio lower than subjects with normal LVEF, related to lack of compensation for low stroke volume, chronotropic incompetence, and β-blocker therapy.[22] *Gitt AK* et al.,[23] in an analysis of 223 subjects, found no differences in survival at 644 days of follow-up when comparing HR at rest or maximum exercise; however, the HR/anaerobic threshold ratio has not been studied in relation to this outcome.

Regarding the respiratory quotient/anaerobic threshold ratio and the diagnosis of reduced ejection fraction, there are contradictory results. Our data show that there is a difference of 0.1 points less in subjects with heart failure with reduced LVEF ($p= 0.024$). *Kakutani N* et al.,[24] retrospectively analyzed 295 patients with HF, without finding a relationship between the respiratory ratio/anaerobic threshold and the ejection fraction. However, this measurement is related to older age, low body mass index, anemia, and advanced New York Heart Association functional class.[24] In the face of a deficient stroke volume in anaerobic or lactic conditions, this ratio remains high and, therefore, may be directly related to the decrease in cardiac output.[25] The respiratory/anaerobic threshold ratio seems to have a prognostic value, in the *Kakutani N* et al. cohort it is described that a respiratory/anaerobic threshold ratio greater than or equal to 0.97 is related to a higher rate of hospital readmission and higher mortality from all causes at three years (29% vs. 15%; $p= 0.001$).[24]

Advanced age and female sex are variables related to a decrease in ejection fraction.[26,27] The changes in the ejection fraction related to age are attributed to two main causes, the first to an alteration in peripheral oxygen extraction due to the decrease in lean body mass in senescence and to skeletal muscle cell aging with alterations in the ejection fraction blood flow during exercise with maximum effort.[26,27] The second is due to the decrease in maximum cardiac output due to the inability to increase stroke volume at an older age.[28,29] Regarding the female sex, the lower ventricular mass and the effect of estrogens can affect the values of ventricular EF in relation to men.[30]

Among the limitations of our study is the sample size that limits the comparative study with other important variables in the CET such as VO_2 and VE/VO_2 peak and oxygen pulse, which did not show significant differences, possibly due to the number of subjects admitted to this analysis.[31,32] Being a single-center, high-altitude study limits extrapolation of results, but authors consider that the findings are relevant for the cardiovascular evaluation of patients taken to CET. Studies are required to corroborate these results at similar altitudes and to evaluate VE/VCO_2, HR/anaerobic threshold ratio, and respiratory quotient/anaerobic threshold ratio as therapeutic targets in cardiopulmonary rehabilitation and whether their favorable change would have a positive impact on long-term survival.

VE/VCO2 was a reliable predictor of normal or reduced LVEF and performs well against peak oxygen consumption. HR during the ventilatory threshold, and respiratory quotient during the ventilatory threshold were associated with LVEF changes. However, larger trials are needed to confirm the results.

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Conflicts of interest

The authors declare that they have no conflict of interest or funding.

Author contributions

Conceptualization: *Alirio Bastidas-Goyes, Eduardo Tuta-Quintero, Juan D. Botero, Daniel Botero Rosas.*

Data curation: *Alirio Bastidas-Goyes, Eduardo Tuta-Quintero, Juan D. Botero, Daniel Botero Rosas.*

Formal analysis: *Alirio Bastidas-Goyes, Eduardo Tuta-Quintero, Juan D. Botero.*

Investigation: *Alirio Bastidas-Goyes, Eduardo Tuta-Quintero.*

Metodology: *Alirio Bastidas-Goyes, Eduardo Tuta-Quintero, Juan D. Botero, Daniel Botero Rosas, Daniel Prieto, Daniela Rubio, Cristian López, Gustavo A. Hincapie, Barbarita Mantilla.*

Project management: *Alirio Bastidas-Goyes, Eduardo Tuta-Quintero, Juan D. Botero, Daniel Botero Rosas, Daniel Prieto, Daniela Rubio, Cristian López, Gustavo A. Hincapie, Barbarita Mantilla.*

Resources: *Daniel Prieto, Daniela Rubio, Cristian López, Gustavo A. Hincapie, Barbarita Mantilla, Abraham Brito, Tatiana Vargas, Stefania Forero, Laura Villarraga, Andrea Giraldo, Monica Briceño, Alejandra Porras.*

Supervision: *Alirio Bastidas-Goyes, Eduardo Tuta-Quintero, Juan D. Botero, Daniel Botero Rosas, Daniel Prieto, Daniela Rubio, Cristian López, Gustavo A. Hincapie, Barbarita Mantilla.*

Validation: *Alirio Bastidas-Goyes, Eduardo Tuta-Quintero, Juan D. Botero, Daniel Botero Rosas, Daniel Prieto, Daniela Rubio, Cristian López, Gustavo A. Hincapie, Barbarita Mantilla, Abraham Brito, Tatiana Vargas, Stefania Forero, Laura Villarraga, Andrea Giraldo, Monica Briceño, Alejandra Porras.*
Visualization: *Abraham Brito, Tatiana Vargas, Stefania Forero, Laura Villarraga, Andrea Giraldo, Monica Briceño, Alejandra Porras.*
Writing – original draft: *Alirio Bastidas-Goyes, Eduardo Tuta-Quintero, Juan D. Botero, Daniel Botero Rosas, Daniel Prieto, Daniela Rubio, Cristian López, Gustavo A. Hincapie, Barbarita Mantilla, Abraham Brito, Tatiana Vargas, Stefania Forero, Laura Villarraga, Andrea Giraldo, Monica Briceño, Alejandra Porras.*
Writing – review and editing: *Alirio Bastidas-Goyes, Eduardo Tuta-Quintero, Juan D. Botero.*

Data Availability Statement

The study data is confidential according to the authors; therefore, they cannot be publicly disclosed or shared. They are stored in a private repository of the authors, and authorization from them is required to access them.