

## Original Article

**Cite this article:** Conant BJ, Becker KC, Hill GD, Hebson CL, Anderson JB, Statile CJ, Lang SM, Schneider K, Thomas C, Willis MW, and Powell AW (2025) Mechanisms of exercise-related neurocardiogenic syncope and the relationship between resting and dynamic cardiac testing. *Cardiology in the Young* 35: 399–406. doi: [10.1017/S1047951124036539](https://doi.org/10.1017/S1047951124036539)

Received: 11 October 2024

Revised: 15 November 2024

Accepted: 19 November 2024

First published online: 9 January 2025

**Keywords:**



Cardiopulmonary exercise testing; syncope; inert gas rebreathing; echocardiography

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# Mechanisms of exercise-related neurocardiogenic syncope and the relationship between resting and dynamic cardiac testing

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**Abstract**

**Objective:** Syncope is common among pediatric patients and is rarely pathologic. The mechanisms for symptoms during exercise are less well understood than the resting mechanisms. Additionally, inert gas rebreathing analysis, a non-invasive examination of haemodynamics including cardiac output, has not previously been studied in youth with neurocardiogenic syncope. **Methods:** This was a retrospective (2017–2023), single-center cohort study in pediatric patients  $\leq 21$  years with prior peri-exertional syncope evaluated with echocardiography and cardiopulmonary exercise testing with inert gas rebreathing analysis performed on the same day. Patients with and without symptoms during or immediately following exercise were noted. **Results:** Of the 101 patients ( $15.2 \pm 2.3$  years; 31% male), there were 22 patients with symptoms during exercise testing or recovery. Resting echocardiography stroke volume correlated with resting ( $r = 0.53$ ,  $p < 0.0001$ ) and peak stroke volume ( $r = 0.32$ ,  $p = 0.009$ ) by inert gas rebreathing and with peak oxygen pulse ( $r = 0.61$ ,  $p < 0.0001$ ). Patients with syncopal symptoms peri-exercise had lower left ventricular end-diastolic volume (Z-score  $-1.2 \pm 1.3$  vs.  $-0.36 \pm 1.3$ ,  $p = 0.01$ ) and end-systolic volume (Z-score  $-1.0 \pm 1.4$  vs.  $-0.1 \pm 1.1$ ,  $p = 0.001$ ) by echocardiography, lower percent predicted peak oxygen pulse during exercise ( $95.5 \pm 14.0$  vs.  $104.6 \pm 18.5\%$ ,  $p = 0.04$ ), and slower post-exercise heart rate recovery ( $31.0 \pm 12.7$  vs.  $37.8 \pm 13.2$  bpm,  $p = 0.03$ ). **Discussion:** Among youth with a history of peri-exertional syncope, those who become syncopal with exercise testing have lower left ventricular volumes at rest, decreased peak oxygen pulse, and slower heart rate recovery after exercise than those who remain asymptomatic. Peak oxygen pulse and resting stroke volume on inert gas rebreathing are associated with stroke volume on echocardiogram.

**Introduction**

Syncope is common in youth and is usually secondary to a benign, neurocardiogenic aetiology.<sup>1–4</sup> Patients typically have some degree of baseline orthostatic intolerance, which is characterised by peripheral venous pooling (especially in an underhydrated state) and decreased cardiac preload, resulting in decreased cerebral perfusion and a hyperadrenergic response.<sup>5–8</sup> Neurocardiogenic syncope occurs when a vagal reflex is activated, initiating a cascade of peripheral vasodilation (vasodepressor response) and bradycardia (cardioinhibitory response) that further decreases venous return and cardiac output. The result is a temporary but severe decrease in cerebral perfusion resulting in loss of postural tone and consciousness.<sup>4,9–11</sup>

Cardiopulmonary exercise testing is a widely utilised and established method for evaluating dynamic cardiac function; however, little research has been done using cardiopulmonary exercise testing in children with neurocardiogenic syncope.<sup>10</sup> It is unclear if the mechanism leading to symptoms at rest is the same as during exercise in these patients. Additionally, minimal research has been performed on patients with neurocardiogenic syncope and prior peri-exertional syncope to understand why some of these patients have syncope related to exercise while others do not.

Lastly, as limitation in stroke volume is felt to be a contributor to neurocardiogenic syncope,<sup>10</sup> alternative methods of determining cardiac output and stroke volume may be useful in understanding the underlying mechanisms for symptoms in these patients. Inert gas rebreathing analysis is a non-invasive method for the measurement of stroke volume and cardiac output that has previously been demonstrated to be reliable and accurate in measuring cardiac output in adults and children at rest and during cardiopulmonary exercise testing.<sup>12–15</sup>

Pairing resting cardiac imaging with cardiopulmonary exercise testing and inert gas rebreathing allows for a more comprehensive evaluation of both resting and dynamic cardiac function.

The aims of the study were to (i) increase the understanding of exercise-based mechanisms in those with neurocardiogenic syncope through evaluating the relationship between resting and dynamic cardiac function and cardiopulmonary fitness; (ii) describe differences in resting and exercise performance in those with neurocardiogenic syncope who developed acute symptoms during cardiopulmonary exercise test compared to those who did not; and (iii) describe the relationship between inert gas rebreathing and resting echocardiography, body composition, and cardiopulmonary exercise test results.

## Methods

This is a retrospective single-center cohort study of patients  $\leq 21$  years old with neurocardiogenic syncope who presented with prior peri-exertional syncope to Cincinnati Children's Hospital Medical Center. All enrolled patients had a same-day echocardiogram and a cardiopulmonary exercise test between October 2017 and December 2023. Exclusion criteria included echocardiogram and cardiopulmonary exercise testing performed on different days, aetiology of syncope other than neurocardiogenic syncope, submaximal exercise test (see below), incomplete cardiopulmonary exercise testing data, treadmill exercise test, missing echocardiogram data, use of a beta-blocker, and history of congenital heart disease.

## Study measures

### Baseline data

We collected demographic and other baseline data including age, sex, height, weight, body mass index, and cardiac medication use from the electronic medical record.

### Echocardiography

All echocardiograms were performed at rest by registered cardiac sonographers and/or paediatric cardiology fellows according to American Society of Echocardiography guidelines.<sup>16,17</sup> Measurements were made in accordance with American Society of Echocardiography standards and included left ventricular volume in systole and diastole and stroke volume, as calculated by the bullet or 5/6 area-length method, and left ventricular mass measured from the parasternal short axis 2D image. These measurements were obtained by the performing sonographer and reviewed by an interpreting paediatric cardiologist specialising in echocardiography. When available, Z-scores based on the Pediatric Heart Network Echo Z-score project were determined and included.<sup>18</sup>

### Bioelectrical impedance analysis

Anthropometric measurements were obtained using bioelectrical impedance analysis (InBody370; InBody, Cerritos, CA, USA) immediately before cardiopulmonary exercise testing. Bioelectrical impedance analysis is obtained in all patients before cardiopulmonary exercise testing per the local standard of care and has been previously described.<sup>19</sup> Bioelectrical impedance analysis variables recorded included body fat mass, percent body fat, skeletal muscle mass, percent of predicted skeletal muscle mass, and total water

mass. Percent of predicted skeletal muscle mass was determined by ideal body type based on the age, sex, and size of the patient and is calculated automatically by InBody.

### Cardiopulmonary exercise testing

Exercise testing was performed on a stationary cycle ergometer (Corival; Lode; Groningen, the Netherlands) using an individualised ramp protocol selected by clinical exercise physiologists. The patient's body size and fitness level were used to determine protocols with an anticipated duration of approximately 10 min. Continuous cardiorespiratory monitoring was performed during exercise testing (Ultima CardioO2; MGC Diagnostics; Saint Paul, MN, USA). A maximal exercise test was defined as achieving a respiratory exchange ratio  $>1.10$ , a maximum heart rate of at least 85% of the age-predicted maximum (220-age), or subjective exhaustion based on a Borg scale  $\geq 18$ .<sup>20</sup> Predicted peak oxygen consumption was calculated as per Wasserman *et al.* and Cooper *et al.*<sup>21,22</sup> In adult patients with a body mass index  $<18 \text{ kg/m}^2$  or  $>25 \text{ kg/m}^2$ , the appropriate regression equation was used.<sup>22</sup> Heart rate recovery was obtained 1-min following exercise while supine. Every patient was exercised utilising our local "syncope protocol," which consists of a standard cardiopulmonary exercise testing as described above. Immediately after exercise, the patient lies on the bed for 2 min followed by standing for 10 min. Heart rate and blood pressure are recorded every 2 min and at the onset of symptoms to monitor for evidence of a vasomotor response or cardioinhibitory response. A vasodepressor response is defined as a reduction of systolic blood pressure reduction of 20 mmHg or greater from baseline measurement. The cardioinhibitory response is defined as a reduction of heart rate of 30 beats per min or more over less than 30 s.

### Inert gas rebreathing

Inert gas rebreathing utilises an oxygenated mixture of an inert, blood-soluble gas and an inert, blood-insoluble gas to determine pulmonary blood flow and, thus, calculate cardiac output. The inert gas rebreathing device (Innocor<sup>®</sup> CO, COSMED; Rome, Italy) utilises an oxygen-enriched gas mixture containing two foreign gases: nitrous oxide (blood soluble) and sulphur hexafluoride (blood insoluble). Patients rebreathe the gas mixture from a rubber rebreathing bag over approximately 20–30 s, at a rate of 20 breaths/min. During rebreathing, lung volume is determined by the concentration of the insoluble gas, and pulmonary blood flow is determined by the decrease in concentration of the soluble gas.<sup>15</sup> Measurements of heart rate, stroke volume, cardiac output, and cardiac index were taken at rest before the cardiopulmonary exercise test, during unloaded exercise, 3 min into exercise, and at exhaustion. An infrared photoacoustic gas analyser embedded within the device measured gas concentrations at the mouthpiece. Individual values were then indexed to body surface area.<sup>23</sup>

## Statistics

Descriptive statistics were calculated for each variable and are presented as mean  $\pm$  standard deviation. Correlations between variables were calculated using Pearson's correlation coefficient. For between-group comparisons, a positive syncope evaluation on cardiopulmonary exercise test is considered any of the following: hypotension consistent with vasodepressor response, bradycardia consistent with cardioinhibitory response, or loss of postural tone during exercise or the recovery period.<sup>4</sup> Differences between

**Table 1.** Comparison of demographics, bioelectrical impedance, and echocardiography in patients with neurocardiogenic syncope and between those with a positive and negative syncope evaluation on cardiopulmonary exercise testing

	Total cohort	Negative syncope evaluation	Positive syncope evaluation	<i>p</i> -value
<b>Demographics</b>	<i>n</i> = 101	<i>n</i> = 79	<i>n</i> = 22	
Sex	Male = 31 Female = 70	Male = 23 Female = 56	Male = 8 Female = 14	0.5
Age (years)	15.2 ± 2.3	15.0 ± 2.3	15.6 ± 2.4	0.3
Height (cm)	165.5 ± 10.6	164.8 ± 10.8	167.8 ± 9.9	0.3
Weight (kg)	59.8 ± 13.6	58.8 ± 13.4	63.2 ± 13.9	0.2
BMI (kg/m <sup>2</sup> )	21.6 ± 3.7	21.4 ± 3.7	22.2 ± 3.9	0.3
<b>BIA</b>	<i>n</i> = 96	<i>n</i> = 74	<i>n</i> = 22	
SMM (kg)	26.0 ± 6.1	25.6 ± 6.2	27.2 ± 5.7	0.3
SMM (% predicted)	104.3 ± 13.1	104.3 ± 13.8	104.3 ± 10.7	0.9
Body fat (kg)	13.1 ± 7.1	12.7 ± 6.8	14.3 ± 7.8	0.4
Body fat (%)	21.1 ± 8.7	20.9 ± 8.7	21.8 ± 8.7	0.7
Total body water (kg)	34.2 ± 7.4	33.7 ± 7.5	35.8 ± 6.9	0.2
<b>Echocardiography</b>	<i>n</i> = 101	<i>n</i> = 79	<i>n</i> = 22	
LV EDV (mL)	122.2 ± 29.9	123.6 ± 31.0	117.0 ± 25.8	0.4
LV EDV (Z-score)	−0.54 ± 1.3	−0.36 ± 1.3	−1.2 ± 1.3	0.01
LV ESV (mL)	48.2 ± 13.2	49.1 ± 13.6	45.1 ± 10.4	0.2
LV ESV (Z-score)	−0.3 ± 1.2	−0.1 ± 1.1	−1.0 ± 1.4	0.001
LV EF (%)	60.6 ± 3.1	60.4 ± 3.2	61.5 ± 2.8	0.1
LV EF (Z-score)	−0.6 ± 0.7	−0.7 ± 0.7	−0.4 ± 0.7	0.1
Stroke volume (mL)	73.9 ± 17.7	74.5 ± 18.2	71.9 ± 15.8	0.5
LV mass (g)	103.2 ± 29.4	102.1 ± 30.4	107.4 ± 25.5	0.5
LV mass index (g/m <sup>2</sup> )	25.9 ± 6.2	25.9 ± 6.2	26.2 ± 6.0	0.8

Data are presented as mean ± SD. Differences between groups were calculated using a Student's *t*-test. A *p* < 0.05 was considered significant.

cm = centimetre; kg = kilogram; m = metres; mL = millilitres; g = grams; L = litres; min = minute; bpm = beats per minute; BMI = body mass index; SMM = skeletal muscle mass; LV = left ventricle; EDV = end-diastolic volume; ESV = end-systolic volume; EF = ejection fraction.

groups were compared using Student's *t*-tests. All *t*-tests were two-sided where applicable. A *p*-value < 0.05 was considered significant for all correlations and *t*-tests. Statistical analyses were performed using JMP®, Version 16 from SAS Institute Inc. (Cary, NC). Tables and figures were created using Microsoft Excel and Microsoft Word (Redmond, WA) and JMP®, Version 16 from SAS Institute Inc. (Cary, NC).

## Results

During the 2017–2023 study period, we identified 168 patients <21 years old with echocardiogram and cardiopulmonary exercise testing for a primary indication of peri-exertional syncope, with 101 patients (60.1%) included for data analysis. Supplemental Figure 1 details the application of exclusion criteria to arrive at the study population. Overall, none of the patients had cardiac pathology discovered during testing.

Patient demographics, body composition, and echocardiogram data are presented in Table 1, and inert gas rebreathing and cardiopulmonary exercise testing data are presented in Table 2. The mean age was 15.2 ± 2.3 years (31% male), and the average body mass index was normal (21.6 ± 3.7 kg/m<sup>2</sup>). Data for the full cohort were used to evaluate correlations, which are displayed in

Figures 1 and 2 and Supplemental Figure 2. Stroke volume on echocardiogram demonstrated a significant correlation with resting stroke volume ( $r = 0.53$ ,  $p < 0.0001$ ) and peak stroke volume ( $r = 0.32$ ,  $p = 0.009$ ) measured via inert gas rebreathing (Figure 1). Resting stroke volume on echocardiogram also correlated with peak oxygen pulse during cardiopulmonary exercise testing ( $r = 0.61$ ,  $p < 0.0001$ ) and bioelectrical impedance analysis measurement of total body water ( $r = 0.67$ ,  $p < 0.0001$ ), total body fat ( $r = 0.2$ ,  $p = 0.04$ ), and total skeletal muscle mass ( $r = 0.67$ ,  $p < 0.0001$ ) (Figure 1). Peak stroke volume measured via inert gas rebreathing was also correlated with peak oxygen pulse ( $r = 0.49$ ,  $p < 0.0001$ ), total body water ( $r = 0.46$ ,  $p = 0.0002$ ), and total skeletal muscle mass ( $r = 0.49$ ,  $p < 0.0001$ ) (Supplemental Figure 2). Peak cardiac output on inert gas rebreathing correlated with oxygen pulse on exercise testing ( $r = 0.54$ ,  $p < 0.0001$ ).

Left ventricular mass was correlated with cardiac output both at rest ( $r = 0.44$ ,  $p < 0.0001$ ) and at peak exercise ( $r = 0.5$ ,  $p < 0.0001$ ) measured by inert gas rebreathing and with absolute peak oxygen consumption ( $r = 0.7$ ,  $p < 0.0001$ ) and peak oxygen pulse ( $r = 0.74$ ,  $p < 0.0001$ ) measured during cardiopulmonary exercise testing. Left ventricular mass was not significantly correlated with the percent predicted peak oxygen consumption (Supplemental Figure 2). On inert gas rebreathing, resting cardiac output correlated with

**Table 2.** Comparison of inert gas rebreathing and cardiopulmonary exercise testing in patients with neurocardiogenic syncope and between those with a positive and negative syncope evaluation on cardiopulmonary exercise testing

	Total cohort	Negative syncope evaluation	Positive syncope evaluation	<i>p</i> -value
<b>Resting Inert Gas Rebreathing</b>	<i>n</i> = 89	<i>n</i> = 70	<i>n</i> = 19	
Cardiac output (L/min)	5.1 ± 1.4	5.1 ± 1.4	5.1 ± 1.4	0.9
Cardiac index (L/m <sup>2</sup> /min)	3.1 ± 0.7	3.1 ± 0.7	3.0 ± 0.7	0.1
Stroke volume (mL)	67.4 ± 19.9	67.3 ± 19.4	67.7 ± 20.2	0.9
<b>Peak Inert Gas Rebreathing</b>	<i>n</i> = 64	<i>n</i> = 53	<i>n</i> = 11	
Cardiac output (L/min)	10.7 ± 3.0	10.6 ± 3.0	11.3 ± 3.4	0.5
Cardiac index (L/m <sup>2</sup> /min)	6.5 ± 1.5	6.5 ± 1.5	6.7 ± 1.9	0.7
Stroke volume (mL)	59.2 ± 17.2	58.7 ± 17.1	61.6 ± 18.5	0.6
<b>CPET</b>	<i>n</i> = 101	<i>n</i> = 79	<i>n</i> = 22	
Resting HR (bpm)	65.1 ± 11.2	64.7 ± 11.4	66.5 ± 10.5	0.7
Peak HR (bpm)	182.5 ± 10.9	181.7 ± 10.8	185.6 ± 10.9	0.1
RER	1.2 ± 0.1	1.2 ± 0.09	1.3 ± 0.1	0.04
VO <sub>2</sub> peak (mL/min)	2104 ± 612.0	2098.1 ± 637.2	2125.3 ± 524.3	0.9
VO <sub>2</sub> peak (mL/kg/min)	35.5 ± 6.6	35.5 ± 6.5	34.0 ± 6.9	0.4
VO <sub>2</sub> peak (%)	93.8 ± 16.8	95.1 ± 17.3	88.9 ± 14.4	0.1
Peak O <sub>2</sub> pulse (mL/beat)	11.5 ± 3.3	11.5 ± 3.3	11.6 ± 3.0	0.9
Peak O <sub>2</sub> pulse (%)	102.6 ± 18.0	104.6 ± 18.5	95.5 ± 14.0	0.04
Peak SBP (mmHg)	170.3 ± 18.3	170.5 ± 17.1	169.5 ± 22.5	0.8
1 min HR recovery (bpm)	36.3 ± 13.4	37.8 ± 13.2	31.0 ± 12.7	0.03

Data are presented as mean ± SD. Differences between groups were calculated using a Student's *t*-test. A *p* < 0.05 was considered significant.

cm = centimetre; kg = kilogram; m = metres; mL = millilitres; g = grams; L = litres; min = minute; bpm = beats per minute; HR = heart rate; RER = respiratory exchange ratio; VO<sub>2</sub> peak = peak oxygen consumption; O<sub>2</sub> pulse = oxygen pulse; SBP = systolic blood pressure; mmHg = millimetres mercury.

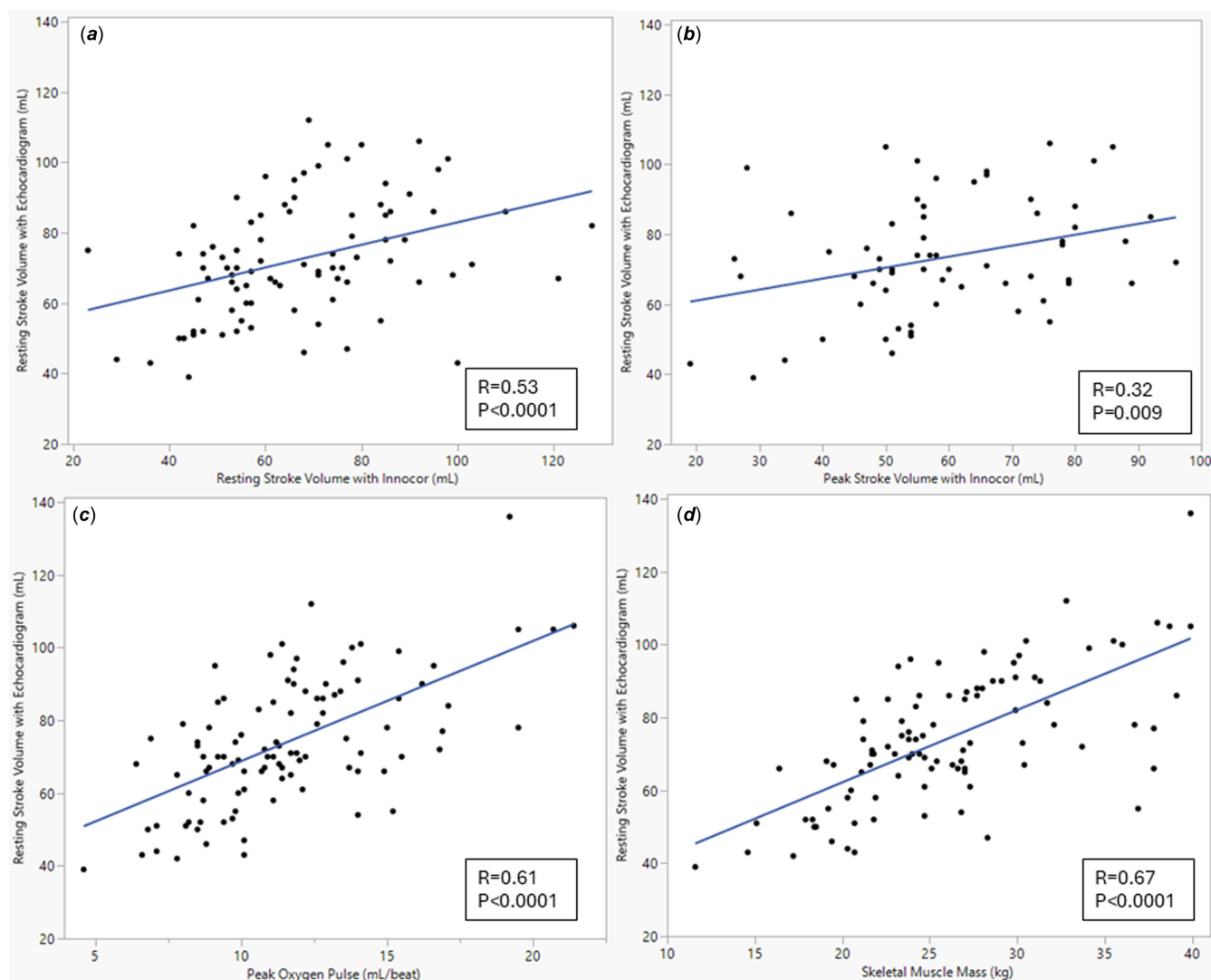
peak cardiac output ( $r = 0.43$ ,  $p = 0.0004$ ), and resting stroke volume correlated with peak stroke volume ( $r = 0.38$ ,  $p = 0.002$ ). The change in resting to peak cardiac output on inert gas rebreathing correlated with oxygen pulse ( $r = 0.41$ ,  $p = 0.0008$ ).

Echocardiography, cardiopulmonary exercise testing, bioelectrical impedance analysis, and inert gas rebreathing data for 22 patients with symptoms or vital sign changes following cardiopulmonary exercise testing were compared to 79 patients without symptoms (Tables 1 and 2). There were no significant differences in size, age, or sex between groups, and the groups had similar skeletal muscle mass and total body water by bioelectrical impedance analysis measurements. Patients with symptoms following cardiopulmonary exercise testing had relatively lower left ventricular end-diastolic volumes ( $Z$ -score  $-1.2 \pm 1.3$  vs.  $-0.36 \pm 1.3$ ,  $p = 0.01$ ) and left ventricular end-systolic volumes ( $Z$ -score  $-1.0 \pm 1.4$  vs.  $-0.1 \pm 1.1$ ,  $p = 0.001$ ) on echocardiogram compared to those without symptoms (Figure 2). Patients with symptoms or vital sign changes following cardiopulmonary exercise testing also reached a lower percentage of predicted peak oxygen pulse ( $95.5 \pm 14.0\%$  vs.  $104.6 \pm 18.5\%$ ,  $p = 0.04$ ) despite demonstrating a higher level of exertion based on respiratory exchange ratio ( $1.3 \pm 0.1$  vs.  $1.2 \pm 0.09$ ,  $p = 0.04$ ). Heart rate recovery in the first min after exercise was slower in those with symptoms or vital sign changes compared to those without ( $31.0 \pm 12.7$  bpm vs.  $37.8 \pm 13.2$  bpm,  $p = 0.03$ ) (Figure 2). There was no significant difference in minute ventilation, the slope between minute ventilation and expired carbon dioxide, or the

breathing reserve between those with and without vital sign changes following exercise testing.

## Discussion

Our primary aim of this study was to further the understanding of exercise physiology in youth with neurocardiogenic syncope. Previous research has extensively described their resting cardiac performance, including high resting heart rates, chronically low intravascular volume leading to cardiac remodelling, and impaired stroke volume,<sup>5,10,24</sup> which is supported by our resting echocardiogram findings. This study differs from many of these studies in that all patients in our study had prior peri-exertional syncope and were further divided based on whether they developed symptoms on their upcoming cardiopulmonary exercise testing. Interestingly, in those with prior exertional syncope, the only resting findings that differed between those who were going to have symptoms during cardiopulmonary exercise test were smaller left ventricular dimensions. This is supported by Fu *et al.* on the importance of intravascular volume, its relationship to stroke volume, and the development of symptoms in this population.<sup>10</sup> Additionally, there were no differences in body composition or cardiac mass in those who did or did not have symptoms during their upcoming cardiopulmonary exercise testing. These findings show that in those with prior peri-exertional syncope, resting cardiac volume may be a more prominent driver of upcoming



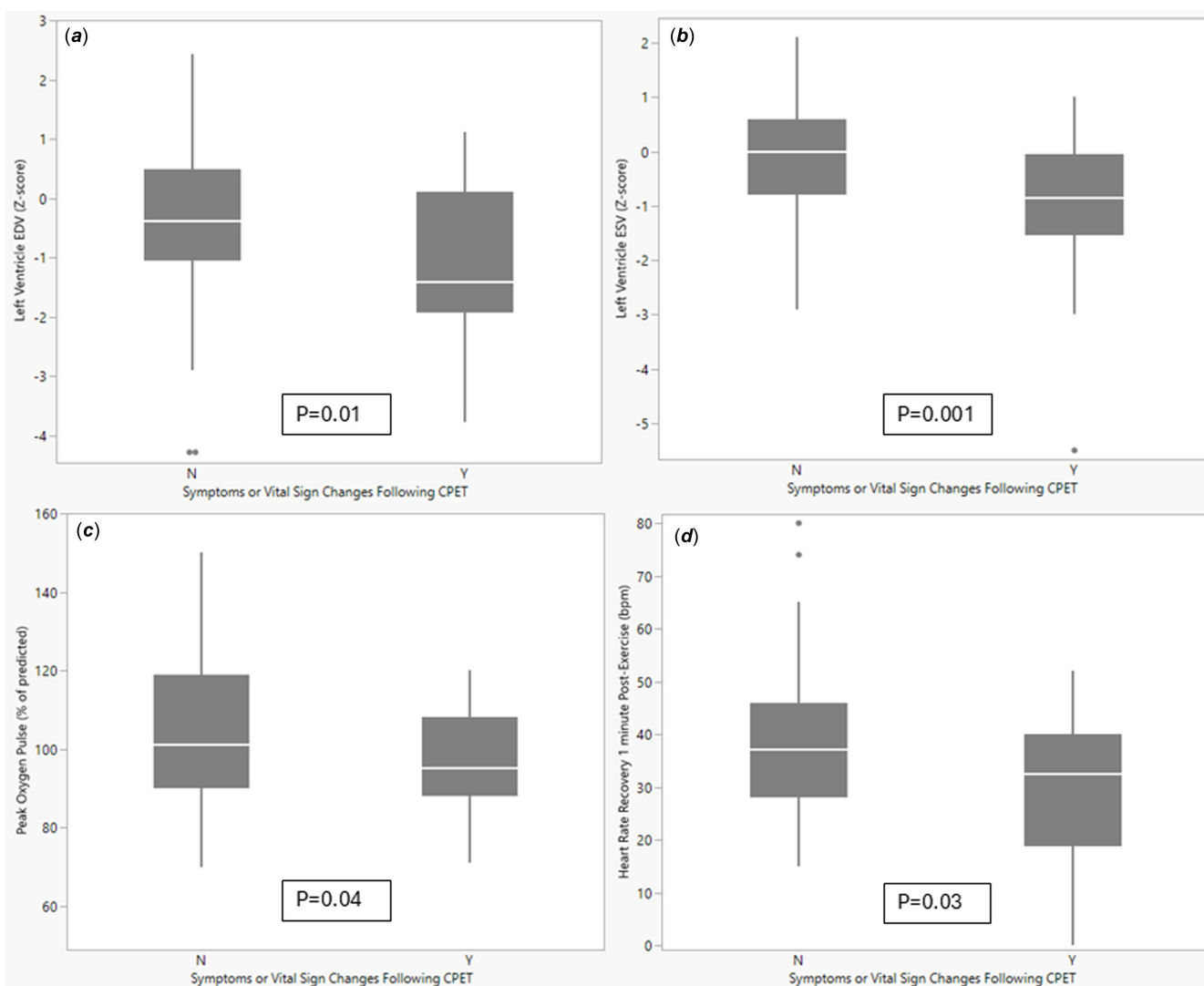
**Figure 1.** The relationship between stroke volume on echocardiogram and resting stroke volume on inert gas rebreathing (1A), peak stroke volume on inert gas rebreathing (1B), peak oxygen pulse on cardiopulmonary exercise testing (1C), and total skeletal muscle mass on bioelectrical impedance analysis (1D). Correlations were performed using Pearson's correlation coefficient.  $p < 0.05$  was considered significant.

symptoms than either cardiac function, cardiac mass, or body composition.

In addition to the resting findings, our study is unique in that it examined the dynamic cardiac performance in those with prior peri-exertional syncope. We found significant differences in oxygen pulse, a cardiopulmonary exercise testing indicator of dynamic cardiac stroke volume and tissue oxygen extraction in those who did and did not develop symptoms during their upcoming cardiopulmonary exercise testing. These were not secondary to age, size, and sex as there were no differences in these two groups. Additionally, the peak oxygen consumption and peak heart rate were similar between the groups, so the development of symptoms during exercise was not secondary to differences in fitness or peak heart rates. This demonstrates a potential mechanism for the development of peri-exertional syncope. Resting stroke volume is similar in those with and without symptoms. During progressive exercise, however, stroke volume limitations occur demonstrated by the oxygen pulse differences. This is a logical and expectant finding based on previous research stressing the importance of how fitness, hydration, and salt intake

dynamically change ventricular preload and thus cardiac stroke volume.<sup>5,10,24,25</sup> This has clinical implications in that it further enforces the importance of pre-exercise hydration and dietary salt intake to optimise intravascular volume. The major limitation of this observation is that the oxygen pulse on cardiopulmonary exercise testing is a surrogate, but not synonymous with stroke volume, and further study with stress echocardiography should be performed to reproduce this finding.

Another interesting post-exercise finding was the difference in heart rate recovery after exercise, with the heart rate recovery being slower 1 min after exercise in those with symptoms compared to those without. Heart rate recovery is a marker of autonomic health, and it relates to clinical outcomes in multiple populations.<sup>26,27</sup> Of note, this contrasts with prior studies demonstrating more rapid heart rate recovery in individuals with vasovagal syncope compared with healthy controls; however, these studies were conducted on adult patients and did not include orthostatic changes.<sup>28,29</sup> Additionally, heart rate recovery is a marker of fatigue and physiologic stress and is often monitored by athletes for potential alterations in training load.<sup>30,31</sup> The longer time frame for



**Figure 2.** Box and whisker plots comparing patients with and without either vital sign changes or symptoms following cardiopulmonary exercise testing and left ventricular end-diastolic volume (3A), left ventricular end-systolic volume (3B), peak oxygen pulse (3C), and heart rate recovery 1 min after exercise (3D). The white line represents the median with boxes representing the 25–75<sup>th</sup> percentile, and whiskers represent the range. Comparison between groups performed with a Student's *t*-test.  $p < 0.05$  was considered significant. EDV = end-diastolic volume; ESV = end-systolic volume; bpm = beats per minute; CPET = cardiopulmonary exercise test.

the heart rate to recover from exercise in those with peri-exertional symptoms is in keeping with previously proposed mechanisms on the autonomic instability in these patients.<sup>32,33</sup> This finding should be confirmed in a larger cohort. If reproducible, slow heart rate recovery may be a clinical measure that the patient could monitor, as it is monitored in athletes. If their heart rate recovery is at their baseline, that could provide further reassurance for continued exercise therapy.

Finally, this study aimed to describe our experience with inert gas rebreathing in the exercise evaluation of those with neurocardiogenic syncope. While not a new technology, inert gas rebreathing has minimally been used for clinical purposes; thus, data on expected findings are limited. To the best of our knowledge, no studies on inert gas rebreathing have been published before in those with neurocardiogenic syncope.<sup>14,34–36</sup> There was a reasonable correlation between resting stroke volume on inert gas rebreathing compared to an echocardiogram, in keeping with other populations. Cardiac stroke volume on echocardiogram and inert gas rebreathing were both correlated

with skeletal muscle mass. Additionally, stroke volume measured with inert gas rebreathing fell to lower values during exercise, in keeping with published data on the fall of cardiac output and stroke volume in patients with neurocardiogenic syncope.<sup>37</sup> The clinical implication of these findings further supports the importance of exercise therapy in this population as cardiac stroke volume represents a modifiable risk factor.<sup>10,24,38</sup> Exercise therapy has been shown to improve stroke volume, skeletal muscle mass, and symptoms in these patients.<sup>39–44</sup> Despite this, there is a lack of clinical exercise programmes for youth with this condition<sup>45</sup>. On the other hand, there was not an extremely strong correlation between resting and peak stroke volume on inert gas rebreathing, possibly secondary to limitations in technique.

While the main purposes of our paper were to further describe the exercise phenotype in those with syncope and to describe our experience with inert gas rebreathing during exercise in this population, there are several other important clinical implications from this study. Importantly, none of the patients in our cohort had significant cardiac pathology discovered as the cause of their

symptoms, which is consistent with the expected low yield of cardiopulmonary exercise testing in paediatric patients with syncope.<sup>46,47</sup> While there was no cardiac pathology discovered, ~20% of patients with prior peri-exertional syncope showed reproducibility of their symptoms. While this may provide reassurance, as neurocardiogenic syncope often causes significant distress for the patient and families,<sup>48</sup> the widespread use of cardiopulmonary exercise testing to solely provide reassurance when there is no concern for cardiac pathology is not advised as it can be costly and labour-intensive for the overall low diagnostic yield. The diagnosis of non-cardiac syncope can typically be made with history, physical, and electrocardiography, while additional testing should be reserved for patients with significant concern for cardiac pathology. Additionally, the resources spent on testing may be better utilised for additional treatment strategies for these patients, including improved access to mental health professionals and exercise therapy programmes.

There are several limitations of this study that must be considered. First, as a single-center study, our findings may not be generalisable to other contexts. Second, a relatively small sample of 22 patients with positive syncope evaluation may have left the study underpowered to detect differences in some variables at the predetermined significance level. Third, important changes in body position could not be fully accounted for in this study. There may be important differences in resting cardiac measurements obtained in the supine position via echocardiogram and those obtained in an upright, seated position via inert gas rebreathing. Additionally, there may be differences between seated exercise on a cycle ergometer and standing exercise, such as running, that were not captured. Fourth, the study was not controlled for relatively common comorbid diagnoses such as anaemia and mental health conditions, which may have influenced some measured variables. Finally, our data collection was limited to discrete time points rather than continuous monitoring, and haemodynamic data immediately preceding the onset of symptoms are, therefore, unavailable.

## Conclusion

Among youth with a history of peri-exertional syncope, those who become syncopal following cardiopulmonary exercise testing have lower left ventricular volumes at rest, decreased oxygen pulse at peak exercise, and slower heart rate recovery after exercise than those who remain asymptomatic. Peak oxygen pulse on cardiopulmonary exercise testing and resting stroke volume on inert gas rebreathing are associated with stroke volume on resting echocardiogram.

**Supplementary material.** The supplementary material for this article can be found at <https://doi.org/10.1017/S1047951124036539>.

**Acknowledgements.** We would like to thank the Cardiopulmonary Exercise Laboratory and the Syncope Clinic at Cincinnati Children's Hospital for all their fantastic service in caring for our patients with syncope.

All authors contributed to the study's conception and design. Material preparation, data collection, and analysis were performed by Bradley Conant and Adam Powell. The first draft of the manuscript was written by Bradley Conant and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

**Financial support.** The authors have no financial or non-financial interests to declare that are relevant to the content of this article.

**Competing interests.** None

**Ethical standard.** This study was designated exempt by the Cincinnati Children's Hospital Institutional Review Board.

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