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Institutional review board

This study was conducted following the Declaration of Helsinki and received approval from the Ethics Committee (CAAE: 33729120.5.0000.5253). All participants provided written informed consent before enrollment. The study maintained the confidentiality and anonymity of participant data throughout the research process.

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Abbreviations list

BF: breathing frequency

CM: cisgender men

COPD: pulmonary disease

CPET: Cardiopulmonary exercise testing

CW: cisgender women

FEV1: forced expiratory volume in one second

FVC: forced vital capacity

GAHT: Gender-affirming hormone therapy

SMM: skeletal muscle mass

TW: transgender women

OUES: oxygen uptake efficiency slope

VC: ventilatory class

$\dot{V}CO_2$: carbon dioxide production

$\dot{V}E$: minute ventilation

$\dot{V}E/\dot{V}CO_2$: carbon dioxide ventilatory equivalent

$\dot{V}O_2$: oxygen uptake

VT1 first ventilatory threshold

VT2 second ventilatory threshold

TV: tidal volume

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Abstract (limit 300 words)

Background: Ventilatory efficiency, a key parameter of cardiopulmonary function assessed through cardiopulmonary exercise testing (CPET), often demonstrates significant variability in transgender women due to the physiological changes induced by gender-affirming hormone therapy. Understanding these differences is essential for optimizing clinical management and enhancing health outcomes within this population.

Research Question: How do ventilatory efficiency, particularly the carbon dioxide ventilatory equivalent ($\dot{V}E/\dot{V}CO_2$), and other CPET variables differ between transgender women and matched cisgender controls, offering insights into the physiological impacts of gender-affirming hormone therapy?

Study Design and Methods: This case-control study included 51 participants, comprising 17 transgender women matched 1:1:1 by age, body mass index, and physical activity levels with cisgender women and cisgender men. CPET assessments were conducted between August 2018 and September 2019, before the COVID-19 pandemic.

Results: Transgender women demonstrated significantly higher $\dot{V}E/\dot{V}CO_2$ ratios at rest (31.4 ± 2.9), at the first ventilatory threshold (34.9 ± 3.9), and peak exercise (39.3 ± 5.3) compared to cisgender women (28.2 ± 2.5; 31.8 ± 3.2; 35.4 ± 4.4, respectively) and cisgender men (27.4 ± 2.1; 30.8 ± 2.6; 34.3 ± 3.5, respectively), with all comparisons reaching statistical significance ($p < 0.001$) and large effect sizes ($\eta^2 = 0.30–0.34$). The $\dot{V}E/\dot{V}CO_2$ slope was also significantly elevated in transgender women (33.9 ± 4.2) compared to cisgender women (29.5 ± 5.0) and cisgender men (28.0 ± 3.5) ($p < 0.001$; $\eta^2 = 0.29$), indicating reduced ventilatory efficiency across the effort continuum.

Interpretation: This study highlights substantial ventilatory inefficiencies in transgender women, likely associated with gender-affirming hormone therapy, underscoring the need for tailored clinical strategies to address these cardiopulmonary adaptations. These findings provide critical insights into the unique health needs of transgender individuals, contributing valuable data to support evidence-based care.

Take-home Points

Study Question: What are the differences in ventilatory efficiency, specifically the $\dot{V}E/\dot{V}CO_2$ slope, between transgender women undergoing gender-affirming hormone therapy and their cisgender counterparts?

Results: In this case-control study of 51 participants, transgender women exhibited significantly higher $\dot{V}E/\dot{V}CO_2$ ratios at all exercise intensities compared to cisgender women and men. This indicates reduced ventilatory efficiency in transgender women, likely influenced by hormonal and anatomical changes due to gender-affirming treatments.

Interpretation: The findings highlight the need for tailored clinical approaches to address the specific ventilatory inefficiencies observed in transgender women, underscoring the importance of personalized healthcare strategies to improve cardiopulmonary outcomes in this population.

Research consistently demonstrates significant knowledge gaps in transgender health among healthcare providers, resulting in barriers to care for transgender individuals[1–4]. These gaps primarily arise from inadequate medical education on transgender-specific issues[5] and are often exacerbated by transphobia, which has a greater impact on healthcare competence than educational background[6]. Addressing this requires the implementation of comprehensive transgender health curricula in medical and nursing education[1,5], alongside robust research to improve care[7].

Gender-affirming hormone therapy (GAHT) plays a vital role in alleviating gender incongruence and enhancing the well-being of transgender individuals[8]. While GAHT offers significant benefits, it also carries risks, such as venous thromboembolism and cardiovascular events[9–11]. However, evidence suggests low short-term thrombosis risks in adolescents undergoing GAHT, with ongoing investigations into its long-term cardiometabolic effects[12,13].

Cardiopulmonary exercise testing (CPET) is valuable for assessing cardiopulmonary function in different health conditions[13–15]. CPET provides comprehensive data on the cardiovascular, muscular and pulmonary systems during exercise, offering insights into the integrative responses of these systems[16]. One of the key variables is the carbon dioxide ventilatory equivalent ($\dot{V}E/\dot{V}CO_2$) slope, which represents the relationship between minute ventilation ($\dot{V}E$) and carbon dioxide production ($\dot{V}CO_2$)[17,18]. This slope reflects the efficiency of ventilation in eliminating carbon dioxide, with higher $\dot{V}E/\dot{V}CO_2$ slopes indicating poorer efficiency, often associated with worse clinical outcomes in several diseases[19–21].

Regarding differences between genders, studies have indicated that cisgender women (CW) typically exhibit lower ventilatory efficiency compared to cisgender men (CM), partly due to physiological differences such as lung volumes and airway sizes[22]. In

transgender women (TW) undergoing GAHT, these variables may be altered, necessitating a tailored approach[23]. Research suggests long-term GAHT influences TW's cardiopulmonary capacity and muscle strength, often placing their exercise response between CW and CM[24]. Specifically, while the absolute oxygen uptake ($\dot{V}O_2$) at peak tends to be lower in TW than in CM, it remains higher than in CW[25]. However, although transgender women have greater absolute fat-free mass than cisgender women, this appears largely related to height differences—around 10 cm on average. When adjusted for body size, relative fat-free mass differences diminish, indicating muscle mass as the primary factor[24]**.** Although no specific studies have directly compared the $\dot{V}E/\dot{V}CO_2$ slope in TW versus CW or CM, the existing data underscores the need for personalized approaches in CPET interpretation for TW, considering the complex interactions between GAHT, body composition, and cardiopulmonary responses[26].

The inclusion of transgender women in competitive sports has generated disproportionate debate given their limited numbers. Much of the controversy centers on whether physiological advantages in strength and endurance persist despite hormonal suppression.[27]. Yet, empirical data on cardiopulmonary adaptations in this population remain scarce, hindering evidence-based sports policy and clinical guidance.

Our study aims to provide detailed comparisons of ventilatory efficiency and other CPET variables across these populations, contributing with valuable insights to the field of transgender health.

MATERIALS AND METHODS

Study design and sample

This cross-sectional study included TW undergoing GAHT, who underwent CPET between August 2018 and September 2019. This study was approved by the Research Ethics Committee of the Instituto Estadual de Diabetes e Endocrinologia Luiz Capriglione, under protocol number CAAE: 90047218.9.0000.5266. All participants provided written informed consent before enrollment.

Eligible participants were TW aged 18 to 45 years who had expressed a desire to transition from male to female and had been diagnosed with gender identity disorder by the multidisciplinary team at the Gender Dysphoria Clinic. Participants had to be in regular follow-up every 3 to 6 months at the specific clinic and other multidisciplinary clinics. They must have begun GAHT after puberty and maintained regular GAHT for at least one year, with at least two total testosterone measurements below 50 ng/dL in the past year. Adequate control of hormone therapy was required, demonstrated by attendance at endocrinological consultations every 3 to 6 months over the last year and regular consultations with the multidisciplinary team.

Exclusion criteria included conditions that could compromise hormonal measurement, such as hypogonadism, untreated thyroid diseases, and other chronic diseases without clinical control. Additional exclusions were made for individuals with malabsorptive, eating, or metabolic disorders, those on prolonged glucocorticosteroid use, and those with osteoarticular injuries.

Cisgender Control Group

The study reviewed 5,078 CPETs conducted between May 2018 and June 2023, which included 4,419 unique cisgender patients. Of these, 659 individuals were excluded due to repeated tests and 1,830 patients were excluded based on comorbidities, such as cardiac diseases, chronic obstructive pulmonary disease (COPD), interstitial lung disease,

chronic kidney disease, stroke, active cancer, diabetes, neuromuscular and neurological diseases. Furthermore, 772 individuals were excluded due to their participation in competitive professional or amateur sports, 712 were excluded for undergoing CPETs due to COVID-19 complications, and 701 were excluded for being outside the age range of 18 to 45 years. After these exclusions, 468 individuals were considered for propensity score matching.

Propensity score matching was performed to ensure comparability across the groups based on age, body mass index, and physical activity level. The propensity scores were calculated using logistic regression, with transgender status as the dependent variable. The nearest neighbor method matched each TW with one CW and one CM, resulting in a 1:1:1 ratio. This method ensured that the control groups were similar to TW in critical characteristics, thereby enhancing the validity of the comparisons. A flowchart of the inclusion process is provided in Figure 1.

Body Composition

At baseline, data on age, gender, weight, height, percentage of body fat, skeletal muscle mass (SMM), SMM/m², and body fat mass per square meter were collected. Weight, percentage of body fat, SMM, SMM/m², and body fat mass per square meter were assessed using bioimpedance analysis (Inbody® 770; Inbody Co., LTD, Seoul, Korea) immediately before the CPET, following published technical recommendations.

Pulmonary Function Test

All participants underwent standardized resting spirometry before cardiopulmonary exercise testing, following international guidelines. Tests were performed using an automated system (Metalyzer 3B®, Cortex®, Leipzig, Germany) by trained professionals under controlled conditions. Analyzed parameters included forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), and the FEV_1/FVC ratio. Each was expressed as both percent predicted and Z-scores. Race-neutral Global Lung Function Initiative (GLI) reference equations were applied using sex assigned at birth as the biological reference. Z-scores enabled interpretation relative to normative population distributions, enhancing detection of potential impairments. These values were then compared across the three study groups: transgender women, cisgender women, and cisgender men.

Physical Activity Assessment

Participants self-reported their weekly physical activity level over the previous 12 months using the Saltin–Grimby Scale, categorizing their activity as sedentary, some physical activity, or regular physical activity[28].

Cardiopulmonary Exercise Testing

CPET was performed using a cycle ergometer (Lode Corival®, Groningen, Netherlands) following an individualized ramp protocol based on Wasserman's equation[29]. After 2 minutes of rest, participants pedaled unloaded for 3 minutes before starting the incremental phase. Cadence was maintained between 60–80 rpm, with the test terminated if it dropped below 50 rpm for over 5 seconds despite encouragement.

During exercise, tidal volume ($\dot{V}T$), breathing frequency (BF), oxygen uptake ($\dot{V}O_2$), and carbon dioxide output ($\dot{V}CO_2$) were measured breath-by-breath using a

metabolic cart (Metalyzer 3B®; Cortex®, Leipzig, Germany), with data smoothed via a 15-point moving average and analyzed using MetaSoft Studio®. Oxygen saturation was continuously monitored with a Nonin® 3150 WristOx-2.

Peak values were defined as the highest 30-second average. Percentage of predicted $\dot{V}O_2$ peak was calculated using the Wasserman equation, based on sex assigned at birth for TW. $\dot{V}O_2$ peak was also normalized by body weight, skeletal muscle mass, and lean mass for group comparisons The first and second ventilatory thresholds (VT1 and VT2) were determined using standard methodologies[30]. The $\dot{V}E/\dot{V}CO_2$ slope was calculated by linear regression from rest to VT2. The oxygen uptake efficiency slope (OUES) was determined by linear regression of $\dot{V}O_2$ and $\log\dot{V}E$[31].

Statistical Analysis

Data analysis was conducted using Prism 10.0 (GraphPad Software, San Diego, CA, USA) and SPSS version 27 (IBM Corp., Armonk, NY, USA). Descriptive statistics summarized the data, with continuous variables expressed as mean (standard deviation) or median (interquartile range), and categorical variables as counts and percentages. Between-group comparisons used one-way ANOVA with Bonferroni correction for parametric data, and Kruskal-Wallis with Dunn's post hoc test for non-parametric data. Effect sizes were calculated using eta-squared (η^2) and epsilon-squared (ε^2), respectively. Chi-square or Fisher's exact tests were used as appropriate for categorical variables. The $\dot{V}E/\dot{V}CO_2$ slope was compared among groups at different exercise stages (rest, VT1 and peak) using two-way ANOVA. Statistical significance was set at $p < 0.05$.

A sample size calculation was performed using a one-way ANOVA model with three groups, 80% power, and a two-tailed alpha of 0.05, based on estimated $\dot{V}E/\dot{V}CO_2$ slope

means at VT1 (30.0 for TW, 28.0 for CW, and 25.0 for CM) and a pooled standard deviation of 4.5. Although not derived from a formal dataset, these values reflect plausible group differences, supporting the study hypothesis and estimating a medium to large effect size. The minimum sample size required was 15 participants per group.

RESULTS

Participant Characteristics

Seventeen TW volunteered for the study. Propensity score matching was used to ensure comparability between groups for age, body mass index, and physical activity. Mean propensity scores were 0.075 ± 0.050 (TW), 0.072 ± 0.040 (CM), and 0.098 ± 0.023 (CW), with no significant differences among groups ($p = 0.123$), confirming adequate matching. The final sample included 51 participants, equally distributed across groups. Table 1 summarizes demographic data, comorbidities, and physical activity profiles, including GAHT details for TW.

Body Composition

TW exhibited distinct body composition metrics compared to CW and CM. TW had significantly higher weight and height than CW, with values comparable to CM. SMM and SMM/m^2 were lower in TW than in CM but higher than in CW. The percentage of body fat in TW was higher than in CM but similar to CW. However, body fat mass per square meter was significantly higher in TW compared to both CW and CM (Table 2).

Lung Function

Regarding lung function, no statistically significant differences were observed among groups for percent-predicted or Z-score values of FVC, FEV_1, or the FEV_1/FVC ratio (Table 2).

Cardiopulmonary Exercise Testing (CPET)

During CPET, differences emerged between TW, CW, and CM at various exercise intensities (Table 3).

***At Rest*:** No significant differences in $\dot{V}O_2$ and heart rate (HR) were observed among the groups. However, TW had higher TV and $\dot{V}E$ than CW, with no differences from CM. The partial pressure of end-tidal carbon dioxide ($PETCO_2$) at rest was lower in TW than in both cisgender groups.

***At VT1*:** TW exhibited higher TV and $\dot{V}E$ than CW, with no differences from CM. The $\dot{V}E/\dot{V}CO_2$ ratio was higher in TW than in both CW and CM, and $PETCO_2$ was lower in TW than in both cisgender groups. However, no significant differences were found among the groups for $\dot{V}O_2$, workload per kilogram, and HR.

***At Peak*:** TW exhibited lower peak $\dot{V}O_2$ compared to CM, with no significant difference when compared to CW. $\dot{V}E$ and TV at peak exercise were significantly lower in CW than in both TW and CM, while no differences were found between TW and CM. The $\dot{V}E/\dot{V}CO_2$ slope was significantly higher in TW than in both CW and CM, and OUES was significantly lower in TW compared to CM. Peak respiratory exchange ratio was similar across all groups.

TW exhibited significantly higher $\dot{V}E/\dot{V}CO_2$ ratios at all stages of exercise compared to CW and CM, indicating reduced ventilatory efficiency. The 95% confidence intervals for these comparisons, already provided in Table 2, demonstrate that the differences were not only statistically significant but also clinically meaningful, supporting the presence of a consistent and relevant ventilatory inefficiency in TW across different exercise intensities. Similarly, $\dot{V}E/\dot{V}O_2$ ratios were elevated in TW, with confidence intervals reflecting comparable effect sizes, reinforcing the robustness of the findings

Ventilatory Efficiency

TW exhibited significantly higher $\dot{V}E/\dot{V}CO_2$ ratios at all exercise stages compared to CW and CM, indicating reduced ventilatory efficiency. At rest, the mean difference between TW and CM was 7.00 (95% CI: 2.74 to 12.07; $p < 0.001$), and between TW and CW was 7.24 (95% CI: 2.57 to 11.90; $p = 0.001$). Similar significant differences were observed at VT1 and peak effort. Additionally, $\dot{V}E/\dot{V}O_2$ ratios were also significantly higher in TW compared to CW and CM at the same stages, further reinforcing ventilatory inefficiency. Figure 3 displays the $\dot{V}E/\dot{V}CO_2$ and $\dot{V}E/\dot{V}O_2$ ratios at rest, VT1, and peak exercise across the three groups.

DISCUSSION

In this case-control study, the first of its kind, TW demonstrated significantly lower ventilatory efficiency across all stages of exercise compared to CW and CM. Notably, TW exhibited higher $\dot{V}E/\dot{V}CO_2$ ratios at rest, VT1, and peak, alongside an increased $\dot{V}E/\dot{V}CO_2$ slope, clearly illustrating impaired ventilatory efficiency. This pattern of reduced efficiency was further corroborated by elevated $\dot{V}E/\dot{V}O_2$ ratios observed throughout the exercise protocol in TW. These findings suggest that TW experience unique physiological challenges in ventilatory regulation, which are likely influenced by both hormonal and anatomical changes associated with gender-affirming treatments.

Ventilatory inefficiency observed in TW may stem from multiple physiological mechanisms. One potential contributor is altered pulmonary gas exchange, as seen in cardiopulmonary diseases. This condition often involves increased dead space ventilation and ventilation-perfusion mismatch, leading to elevated ventilatory responses—phenomena well documented in disorders such as chronic heart failure and pulmonary hypertension.[32]. These abnormalities increase ventilatory demand for a given metabolic

load, exacerbating dyspnea and reducing exercise tolerance[33]. However, in our sample of TW, the %$\dot{V}O_2$peak is within average values and not different from the cisgender groups, moving away from this pathological mechanism.

Another possibility is GAHT, which may influence respiratory muscle function, impacting breathing mechanics. Research indicates that hormonal treatments can lead to changes in muscle mass and distribution, which could contribute to the observed ventilatory inefficiency in TW. Factors such as skeletal muscle ergoreceptor activity, chemoreceptor sensitivity, and baroreceptor feedback could also play significant roles in the heightened ventilatory response during exercise[34,35].

Another potential mechanism contributing to the ventilatory inefficiency in TW is central hyperventilation. Central hyperventilation refers to an abnormal increase in ventilation driven by central neural mechanisms rather than the body's metabolic demands[36]. This phenomenon can occur due to altered central chemoreceptor sensitivity, leading to a disproportionate increase in ventilation relative to carbon dioxide production. Studies have shown that individuals undergoing significant physiological changes, such as those on GAHT[37], may experience modifications in central respiratory control[38]. This altered control can lead to an inappropriate ventilatory response during exercise, exacerbating ventilatory inefficiency and increasing the work of breathing.

The observation of other CPET findings helps interpret the observed ventilatory inefficiency. TW had higher $\dot{V}E$ than CW at all exercise intensities, with no difference from CM. However, an opposite response in $\dot{V}O_2$ was observed at peak, as values were lower in TW than in CM, but without differences from CW. Therefore, the ventilatory inefficiency observed in TW may reflect hyperventilation relative to CW and reduced metabolic activity compared to CM. This suggests that the ventilatory response remains aligned with the sex assigned at birth, not adapting to the metabolic response driven by

reduced muscle mass (SMM/m^2 was 13% lower in TW compared to CM and 11% higher than CW), consequently reducing metabolic activity.

Analysis of $PETCO_2$ values during exercise indicates that the ventilatory inefficiency observed in TW is related to ventilatory control mechanisms rather than a primary ventilation/perfusion (V/Q) mismatch[39,40]. Similar to dysfunctional breathing, TW had markedly lower resting $PETCO_2$ than CW and CM, with this trend persisting at VT1. However, examining the $PETCO_2$ curve during exercise reveals no differences in the rise of values among the groups[41]. Hansen et al.[42] demonstrate minimal elevation or even reduction in $PETCO_2$ values from rest to VT1 in clinical conditions associated with V/Q mismatch, such as heart failure, COPD, and pulmonary hypertension. This finding can also be seen in patients with hyperventilation syndrome, a condition characterized by episodic dyspnea and disproportionately high alveolar ventilation, highly prevalent in psychological conditions, as observed by Brat et al.[36]. We hypothesize that the observed ventilatory inefficiency in TW compared to cisgender controls is a maintenance of the ventilatory drive of the sex assigned at birth, not aligning with the reduced metabolic activity associated with reduced muscle mass from GAHT.

Regardless of the underlying mechanisms, the reduced ventilatory efficiency observed in TW potentially promotes limitations in their exercise capacity. Increased $\dot{V}E/\dot{V}CO_2$ ratios, indicative of ventilatory inefficiency, are known to correlate with reduced exercise performance, greater dyspnea, and overall poorer prognosis, as seen in conditions like COPD and heart failure[43,44]. While TW and the control groups in this study do not have COPD or heart failure, the elevated ventilatory demand relative to carbon dioxide production may still lead to comparable constraints in exercise capacity. Notably, none of the TW participants reported respiratory symptoms. However, the increased work of breathing associated with inefficient ventilatory responses may compromise exercise

performance by heightening muscle sympathetic nerve activity and reducing endurance during exertion.[45,46]. Thus, the heightened ventilatory inefficiency in TW, regardless of the exact physiological or biochemical cause, could potentially manifests in diminished exercise capacity, underscoring the critical need for tailored interventions to mitigate these respiratory challenges.

In an era of growing debate over the inclusion of transgender women in competitive sports, our findings contribute a critical physiological dimension. Although the study sample did not include athletes, the ventilatory inefficiency observed in transgender women may extend to athletic populations. Existing research suggests that some physiological advantages may persist following testosterone suppression, with the extent varying by sport.[47–49]. Since ventilatory efficiency is a key determinant of endurance and performance, such inefficiency could affect competitive outcomes. These findings underscore the need for further investigation into how gender-affirming treatment influences exercise physiology and the implications for sports policy and inclusion.

Beyond the physiological effects of GAHT, lifelong social and behavioral factors may influence ventilatory responses. Transgender individuals often face barriers to physical activity, especially in childhood and adolescence, due to gender dysphoria and social exclusion. This reduced engagement is linked to lower cardiorespiratory fitness and ventilatory inefficiency in adulthood. Thus, the observed inefficiency may reflect both hormonal factors and the cumulative impact of limited physical activity across the lifespan[50].

This study has important limitations. Firstly, our study's cross-sectional design limits the ability to establish causal relationships between GAHT and ventilatory efficiency. While this design provides valuable insights, longitudinal studies are needed

to understand the long-term effects of GAHT on respiratory function. Secondly, the sample size was small and specific to a single clinic, which may not fully represent TW's broader population. Larger, multicenter studies would enhance the generalizability of our findings. Thirdly, our study did not include elite athletes, limiting our findings' applicability to high-performance sports contexts.

Finally, while we observed differences in ventilatory efficiency, the underlying mechanisms remain unclear. Future studies should explore the roles of hormone-related chemoreceptor sensitivity, respiratory mechanics, and oxidative muscle capacity. Integrating CPET with measures like inspiratory muscle strength, blood gases, and pulmonary hemodynamics may help clarify the pathophysiology in transgender women

INTERPRETATION

In conclusion, our study provides crucial insights into the unique ventilatory challenges faced by TW undergoing GAHT. The findings reveal a marked reduction in ventilatory efficiency in TW compared to their cisgender counterparts, highlighting the necessity for specialized clinical approaches to address these disparities. This research not only advances our understanding of the physiological impacts of GAHT but also underscores the importance of personalized healthcare strategies for transgender individuals.

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Figure 1: Flowchart illustrating the participant selection process for the case-control study.

Abbreviations: CPET, cardiopulmonary exercise test; HF, heart failure; CABG, coronary artery bypass grafting; ICD, implantable cardioverter-defibrillator; VHD, valvular heart disease; COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; CKD, chronic kidney disease

Figure 2. Comparative analysis of peak oxygen uptake normalized by body mass, skeletal muscle mass, and lean mass among study groups.

Data expressed as median and interquartile range.

Abbreviations: TW, transgender women; CW, cisgender women; CM, cisgender men; $\dot{V}O_2$, oxygen uptake.

Statistics: *$P < 0.05$.

Figure 3: Comparative analysis of ventilatory efficiency using $\dot{V}E/\dot{V}CO_2$ and $\dot{V}E/\dot{V}O_2$ ratios across various exercise stages in study groups.

Data expressed as median and interquartile range.

Abbreviations: $\dot{V}E/\dot{V}CO_2$, ventilatory efficiency as a ratio of minute ventilation to carbon dioxide production; $\dot{V}E/\dot{V}O_2$, ventilatory efficiency as a ratio of minute ventilation to oxygen consumption; VT1, first ventilatory threshold.

Statistics: *$P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$

Table 1. Participant Demographics, Comorbidities, Physical Activity Levels, and Gender-Affirming Hormone Therapy Details in a Case-Control Study of Ventilatory Efficiency.

	Transgender women (N=17)	Cisgender women (N=17)	Cisgender men (N=17)	*P* value
Age (years)	35.1 ± 8.5	36.4 ± 7.1	34.6 ± 8.3	0.782
Comorbidities				
Hypertension (%)	2 (11.8)	1 (5.9)	5 (29.4)	0.146
Ever Smoke (%)	2 (11.8)	1 (5.9)	2 (11.8)	0.801
Asthma (%)	3 (17.6)	5 (29.4)	3 (17.6)	0.629
Thyroid disease (%)	0 (0)	4 (23.5)	0 (0)	0.013
Physical Activity				
Sedentary (%)	5 (29.4)	6 (35.3)	7 (41.2)	
Irregular (%)	5 (29.4)	4 (23.5)	5 (29.4)	0.925
Regular (%)	7 (41.2)	7 (41.2)	5 (29.4)	
GAHT				
Mean age at initiation (years)	29.8 ± 7.6			
Duration (years)	8.1 ± 3.7			
GAS (%)	4 (23.5)			
OE (%)	6 (35.3)			
TE (%)	11 (64.7)			
IME (%)	2 (11.8)			

Cyproterone (%)	13 (76.4)
Finasteride (%)	3 (17.6)
Spironolactone (%)	7 (41.2)

Data is expressed as mean and standard deviation or absolute and relative frequency.

GAHT, gender-affirming hormone therapy; GAS, gender-affirming surgery; OE, oral estrogen; TE, transdermal estrogen; IME, intra-muscular estrogen.

Table 2. Comparative Analysis of Body Composition and Lung Function Variables Across Transgender Women, Cisgender Women, and Cisgender Men in a Case-Control Study

	TW (N=17)	CW (N=17)	CM (N=17)	η^2 *or* ε^2	*F*	ANOVA or KW p-value	Multiple comparisons								
							TW vs. CW			TW vs. CM			CW vs. CM		
Body composition	**M±SD**	**M±SD**	**M±SD**				**MD**	**(95% CI)**	**p-value**	**MD**	**(95% CI)**	**p-value**	**MD**	**(95% CI)**	**p-value**
Weight (kg)	76.7 ± 14.5	61.0 ± 13.4	81.9 ± 12.7	0.31	10.89	<0.01	15.72	(4.15 to 27.30)	0.04	-5.18	(-16.76 to 6.39)	0.81	-20.91	(-9.33 to -32.49)	<0.01
Height (cm)	174.9 ± 5.4	162.3 ± 5.4	177.1 ± 6.4	0.57	32.47	<0.01	12.58	(7.68 to 17.50)	<0.01	-2.17	(-7.08 to 2.73)	0.83	-14.76	(-9.86 to -19.67)	<0.01
SMM (kg)	29.6 ± 3	22.0 ± 3.1	35.9 ± 5.1	0.69	54.07	<0.01	7.57	(-2.96 to 10.87)	<0.01	-6.27	(-9.57 to -2.96)	<0.01	-13.84	(-17.148 to -10.53)	<0.01
SMM/m^2	15.4 ± 0.8	13.3 ± 1.3	17.9 ± 1.7	0.67	49.09	<0.01	2.05	(0.91 to 3.18)	<0.01	-2.47	(-1.34 to -3.61)	<0.01	-4.52	(-3.39 to -5.66)	<0.01
PBF (%)	29.3 ± 8	32.0 ± 10.3	22.4 ± 8.8	0.69	5.10	0.01	-2.77	(-10.49 to 4.94)	1.00	6.88	(-0.84 to 14.60)	0.09	9.65	(1.93 to 17.38)	0.01
BFM/m^2	27.7 ± 1.3	24.6 ± 2.2	31.4 ± 2.9	0.62	40.40	<0.01	3.15	(1.26 to 5.04)	<0.01	-3.68	(-1.79 to -5.57)	<0.01	-6.84	(-4.95 to -8.73)	<0.01
Lung Function															
FVC Z-Score	-0.79 (0.78)	-0.27 (0.90)	-0.85 (0.66)	0.03		0.191	-0.27	(–0.89 to 0.34)		0.18	(–0.43 to 0.80)		-0.45	(–1.07 to 0.16)	
FVC % predicted	0.87 ± 0.15	0.92 ± 0.11	0.84 ± 0.15	0.058	1.47	0.236	–0.05	(–0.14 to 0.03)		0.03	(–0.07 to 0.12)		–0.08	(–0.18 to 0.01)	
FEV_1 Z-Score	-0.75 (1.03)	-0.38 (0.57)	-0.56 (0.70)	0.00		0.505	-0.27	(–0.94 to 0.40)		0.03	(–0.64 to 0.70)		-0.30	(–0.98 to 0.37)	
FEV_1 % predicted	0.87 ± 0.17	0.91 ± 0.11	0.87 ± 0.17	0.024	0.58	0.560	–0.05	(–0.14 to 0.05)		0.01	(–0.10 to 0.09)		–0.05	(–0.15 to 0.05)	

FEV_1/FVC Z-Score	0.05 (2.36)	-0.05 (3.06)	1.09 (2.19)	0.00		0.373	-0.05	(–2.02 to 1.91)	-0.81	(–2.78 to 1.16)	0.76	(–1.21 to 2.73)
FEV_1/FVC % pred.	0.99 ± 0.08	1.00 ± 0.11	1.03 ± 0.08	0.024	0.61	0.552	–0.01	(–0.07 to 0.06)	–0.03	(–0.09 to 0.04)	–0.02	(–0.08 to 0.04)

Data are presented as mean ± standard deviation (M ± SD), median and interquartile range (Mdn [IQR]), or mean difference and 95% confidence interval (MD [95% CI]). Effect sizes are reported as eta squared (η^2) for parametric variables and epsilon squared (ε^2) for non-parametric variables. Abbreviations: TW, transgender women; CW, cisgender women; CM, cisgender men; SMM, skeletal muscle mass; PBF, percent body fat; BFM, body fat mass; FVC, forced vital capacity; FEV_1, forced expiratory volume in one second.

Table 3. Comparative Analysis of Cardiopulmonary Exercise Test Parameters Across Transgender Women, Cisgender Women, and Cisgender Men

	TW (N=17)	CW (N=17)	CM (N=17)				Multiple Comparisons								
							TW vs. CW			TW vs. CM			CW vs. CM		
Rest	**M±SD or Mdn (IQR)**	**M±SD or Mdn (IQR)**	**M±SD or Mdn (IQR)**	**η^2 *or* ε^2**	***F***	**ANOVA or KW p-value**	**MD**	**(95% CI)**	**p-value**	**MD**	**(95% CI)**	**p-value**	**MD**	**(95% CI)**	**p-value**
$\dot{V}O_2$ (ml/kg/min)	4.4 ± 0.9	4.8 ± 1.1	5.2 ± 2.1	1.02	0.04	0.36	-0.71	(-1.95 to 0.53)	-----	-0.38	(-1.62 to 0.86)	-----	-0.33	(-1.57 to 0.91)	-----
HR (bpm)	84.3 ± 14.8	81.7 ± 10.2	78.2 ± 15.4	0.86	0.04	0.42	6.12	(-5.50 to 17.73)	-----	2.59	(-9.03 to 14.20)	-----	3.53	(-8.08 to 15.14)	-----
TV (L)	0.77 (0.28)	0.54 (0.13)	0.87 (0.2)	0.29	-----	<0.01	-0.02	(-0.26 to 0.21)	<0.01	0.26	(0.03 to 0.50)	0.22	-0.29	(-0.52 to -0.05)	<0.01
$\dot{V}E$ (L/min)	14 (3.5)	10.1 (2.4)	13.6 (2.7)	0.28	-----	<0.01	-0.25	(-3.11 to 2.60)	<0.01	3.75	(0.89 to 6.60)	0.71	-4.00	(-6.85 to -1.15)	<0.01
$\dot{V}E/\dot{V}CO_2$	40.4±5.2	32.9±5	33.7±4.6	11.51	0.32	<0.01	6.68	(2.46 to 10.91)	<0.01	7.42	(3.19 to 11.64)	<0.01	-0.74	(-4.96 to 3.49)	1.00
$\dot{V}E/\dot{V}O_2$	33.7 ± 6.0	26.5 ± 5.0	26.3 ± 5.4	0.30	10.10	<0.001	7.24	(2.57 to 11.90)	0.001	7.40	(2.74 to 12.07)	<0.001	0.16	(–4.83 to 5.15)	1.000
$PETCO_2$ (mmHg)	27.2 ± 2.6	30.4 ± 3.4	32.2 ± 3.7	10.01	0.29	<0.01	-5.00	(-7.80 to -2.20)	<0.01	-3.12	(-5.92 to -0.32)	0.02	-1.88	(-4.68 to 0.92)	0.30
VT1															
$\dot{V}O_2$ (ml/kg/min)	15.2 (7.0)	13.9 (6.8)	17.1 (13.2)	0.02	-----	0.14	-5.16	(-11.44 to 1.12)	-----	-1.11	(-7.39 to 5.17)	-----	-4.04	(-10.32 to 2.24)	-----
Workload (Watts/kg)	0.9 (0.5)	1 (0.5)	1.2 (0.6)	0.04	-----	0.23	-0.36	(-0.92 to 0.20)	-----	-0.13	(-0.68 to 0.43)	-----	-0.23	(-0.80 to 0.33)	-----
HR (bpm)	130.6 ± 19	120.3 ± 21.4	121.4 ± 21.1	1.31	0.05	0.27	9.29	(-8.15 to 26.74)	-----	10.35	(-7.09 to 27.80)	-----	-1.06	(-18.51 to 16.39)	-----
TV (L)	1.6 ± 0.5	1.2 ± 0.3	1.7 ± 0.4	7.85	0.25	<0.01	0.40	(0.06 to 0.75)	0.01	-0.13	(-0.47 to 0.22)	1.00	-0.53	(-0.88 to -0.18)	0.01
$\dot{V}E$ (L/min)	39.7 ± 10.9	26.9 ± 9.1	42.4 ± 17.3	6.91	0.22	<0.01	-2.67	(-13.70 to 8.36)	1.00	12.79	(1.76 to 23.82)	0.01	-15.46	(-26.48 to -4.43)	0.03
$\dot{V}E/\dot{V}CO_2$	34 (4.7)	26.1 (5.6)	28 (5.6)	0.26	-----	<0.01	5.98	(2.28 to 9.68)	<0.01	4.98	(1.28 to 8.68)	<0.01	1.00	(-2.70 to 4.70)	0.61
$\dot{V}E/\dot{V}O_2$	30.6 ± 3.9	25.2 ± 3.9	23.0 ± 2.9	0.46	20.74	<0.001	5.46	(2.42 to 8.51)	<0.001	7.69	(4.64 to 10.74)	<0.001	2.22	(–0.82 to 5.27)	0.230
$PETCO_2$ (mmHg)	33.6 ± 3.8	37.6 ± 4.8	39.2 ± 3.4	8.60	0.26	<0.01	-5.59	(-9.03 to -2.14)	<0.01	-4.00	(-7.45 to -0.55)	0.01	-1.59	(-5.03 to 1.86)	0.7
Peak															
$\dot{V}O_2$ (L/min)	1.95 ± 0.40	1.65 ± 0.49	2.84 ± 0.85	0.42	17.41	<0.01	0.29	(-2.2 to 0.8)	0.49	-0.89	(-1.14 to -0.37)	<0.01	-1.19	(-1.71 to -0.67)	<0.01
$\dot{V}O_2$ (ml/Kg/min)	25.8 ± 5.6	28 ± 9.9	34.6 ± 9.7	4.78	0.17	0.01	-2.19	(-9.56 to 5.18)	1.0	-8.82	(-16.20 to 1.45)	0.014	-6.64	(-0.73 to 14.01)	0.09

$\dot{V}O_2$ (% predicted)	98.6 ± 21.3	93.5 ± 24.2	91.4 ± 23.9	0.01	0.43	0.64	5.13	(-14.57 to 24.84)	-----	7..21	(-12.48 to 26.92)	-----	-2.08	(-21.78 to 17.62)	-----
Workload (Watts/kg)	2 (0.7)	2.3 (1.3)	2.6 (2)	0.04	-----	0.13	-0.79	(-1.66 to 0.08)	-----	-0.64	(-1.47 to 0.20)	-----	-0.16	(-1.02 to 0.71)	-----
HR (bpm)	176 (13)	172 (21)	175 (19)	0.00	-----	0.39	4.71	(-6.20 to 15.61)	-----	6.41	(-4.49 to 17.32)	-----	-1.71	(-12.61 to 9.20)	-----
O_2 pulse (ml/beat)	11.4 (2.4)	9 (4.2)	16 (8.3)	0.31	-----	<0.01	-5.29	(-8.35 to -2.24)	0.20	1.27	(-1.78 to 4.33)	0.92	-6.56	(-9.62 to -3.51)	<0.01
TV (L)	2.2 ± 0.6	1.7 ± 0.3	2.4 ± 0.6	0.26	8.64	<0.01	0.47	(0.02 to 0.92)	0.03	-0.27	(-0.72 to 0.18)	0.42	-0.75	(-1.20 to -0.30)	<0.01
$\dot{V}E$ (L/min)	97.5 ± 25.3	72.3 ± 16.5	111 ± 31.6	0.30	10.26	<0.01	25.18	(3.70 to 46.65)	0.01	-13.45	(-34.92 to 8.03)	0.38	-38.62	(-60.10 to -17.15)	<0.01
$\dot{V}E/\dot{V}CO_2$	35.8±4.7	31.2±5	28.9±3.5	0.30	10.44	<0.01	4.55	(1.31 to 7.79)	0.01	5.94	(2.65 to 9.23)	<0.01	2.30	(-6.07 to 1.47)	0.40
$\dot{V}E/\dot{V}CO_2$ slope	33.9 ± 4.2	29.5 ± 5	28 ± 3.5	0.26	8.41	<0.01	4.36	(0.70 to 8.02)	0.01	5.82	(2.15 to 9.48)	<0.01	1.45	(-2.20 to 5.12)	0.98
$\dot{V}E/\dot{V}O_2$	46.6 ± 8.1	41.3 ± 7.0	36.9 ± 5.5	0.26	8.26	<0.001	5.26	(–0.65 to 11.18)	0.096	9.67	(3.76 to 15.58)	<0.001	4.41	(–1.50 to 10.32)	0.212
$PETCO_2$ (mmHg)	28.5±4.2	31.5±4.3	33.4±3.8	0.20	6.12	0.04	-3.06	(-6.56 to 0.44)	0.10	-4.88	(-8.38 to -1.39)	0.03	-1.82	(-5.32 to 1.67)	0.60
RER	1.2 ± 0.1	1.2 ± 0.1	1.1 ± 0.1	0.10	2.86	0.06	-0.04	(-0.11 to 0.02)	0.42	0.02	(-0.04 to 0.93)	1.00	-0.06	(-0.13 to 0.03)	0.06
OUES	2.1 (0.6)	1.7 (0.7)	2.9 (0.9)	0.30	10.69	<0.01	0.38	(-0.28 to 1.05)	0.48	-0.83	(-1.50 to -0.16)	0.01	1.21	(0.55 to 1.88)	<0.01

Data are presented as mean ± standard deviation (M ± SD), median and interquartile range (Mdn [IQR]), or mean difference and 95% confidence interval (MD [95% CI]). Effect sizes are reported as eta squared (η^2) for parametric variables and epsilon squared (ε^2) for non-parametric variables, as appropriate for each comparison. ANOVA was used for parametric comparisons, while Kruskal-Wallis tests were applied to non-parametric data.

Abbreviations: TW, transgender women; CW, cisgender women; CM, cisgender men; SMM, skeletal muscle mass; PBF, percent body fat; BFM, body fat mass; FVC, forced vital capacity; FEV_1, forced expiratory volume in one second; VE, minute ventilation; TV, tidal volume; VO_2, oxygen uptake; VCO_2, carbon dioxide output; $PETCO_2$, end-tidal carbon dioxide pressure; RER, respiratory exchange ratio; OUES, oxygen uptake efficiency slope.