International Journal of Transgender Health

ISSN: 2689-5269 (Print) 2689-5277 (Online) Journal homepage: www.tandfonline.com/journals/wijt21

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**To cite this article:** Fabrício Braga, Juliana Goulart Prata Oliveira Milani, Mauricio Milani, Ana Carolina Fachetti, Bruna Kalichsztein, Roberto Zagury, Karen De Marca, Rossano Fiorelli, Dominique Hansen, Gerson Cipriano Junior & Ricardo Mourilhe-Rocha (28 Aug 2025): Cardiovascular function in transgender women on hormone therapy: the role of circulatory Power, Rate-pressure product, and blood pressure responses to exercise, International Journal of Transgender Health, DOI: 10.1080/26895269.2025.2552329

**To link to this article:** https://doi.org/10.1080/26895269.2025.2552329

Published online: 28 Aug 2025.

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INTERNATIONAL JOURNAL OF TRANSGENDER HEALTH
https://doi.org/10.1080/26895269.2025.2552329

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# Cardiovascular function in transgender women on hormone therapy: the role of circulatory Power, Rate-pressure product, and blood pressure responses to exercise

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**ABSTRACT**

**Introduction:** Gender-affirming hormone therapy (GAHT) may influence cardiovascular physiology in transgender women, but its impact on hemodynamic responses to exercise remains unclear. This study investigated circulatory power (CircP), rate-pressure product (RPP), and blood pressure (BP) responses during maximal exertion in transgender women compared with cisgender women and cisgender men.

**Methods:** This cross-sectional study included 51 physically active individuals (17 transgender women on GAHT for 8.1 ± 3.7 years, 17 cisgender women, 17 cisgender men), matched by age and aerobic fitness. Participants underwent maximal cardiopulmonary exercise testing (CPET). Systolic and diastolic BP were measured at rest, at the first ventilatory threshold (VT1), and at peak. CircP was defined as peak oxygen uptake ($VO_2$) × systolic BP, and RPP as heart rate (HR) × systolic BP. Between-group differences were assessed with Analysis of Variance (ANOVA) and Bonferroni correction, and Analysis of Covariance (ANCOVA) was adjusted for hypertension.

**Results:** Transgender women exhibited significantly lower CircP than cisgender men ($\Delta = -2528.2$; $p < 0.001$; $\eta^2 = 0.287$) and similar values to cisgender women ($\Delta = -345.1$; $p = 1.000$). Peak systolic BP was lower in transgender women (180.3 ± 20.1 mmHg) versus cisgender men (200.3 ± 32.2 mmHg; $p = 0.025$), despite comparable peak $VO_2$ and HR. At VT1, transgender women resembled cisgender men in systolic BP but differed from cisgender women. RPP followed a similar gradient, with transgender women intermediate, but group differences were not significant after adjustment ($p = 0.123$; $\eta^2 = 0.089$). Diastolic BP differed at VT1 but not at peak. Hypertension did not significantly affect CircP.

**Conclusion:** transgender women under GAHT demonstrate consistently lower CircP and attenuated systolic BP responses during exercise, suggesting a distinct cardiovascular adaptation. CircP showed stronger discriminatory power than RPP, supporting its role as a sensitive marker. CPET may assist functional evaluation and cardiovascular risk stratification in gender-diverse populations.

**KEYWORDS**
Transgender persons; exercise test; blood pressure

## Background

Hemodynamic responses to exercise, especially systolic and diastolic blood pressure (SBP and DBP, respectively), vary significantly between cisgender men and women. Men typically demonstrate higher peak SBP and DBP during exertion than women, although these differences narrow after the fifth decade of life (Daida et al., 1996; Janssens et al., 2025). Conversely, older women often exhibit exaggerated BP responses during exercise relative to younger women and age-matched men (Trinity et al., 2018). Post-exercise hypotension manifests in both cisgender men and women, albeit through distinct

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physiological mechanisms: in men, it is primarily driven by a reduction in cardiac output, while in women, it results from a decrease in systemic vascular resistance (Cardozo, 2022). Notably, resistance training reduces DBP more in women whereas it induces greater arterial stiffness in men (Collier et al., 2008). Additionally, cardiorespiratory fitness (CRF) level inversely correlates with submaximal BP during exercise in both men and women, yet higher CRF has also been associated with augmented peak SBP responses (Janssens et al., 2025).

Peak oxygen uptake ($VO_2$peak) is widely recognized as the gold standard for assessing cardiorespiratory fitness, commonly measured through cardiopulmonary exercise testing (CPET). Higher $VO_2$peak values are consistently associated with lower all-cause mortality in healthy individuals and those with chronic disease (Aspenes et al., 2011; Fabricio Braga et al., 2024). However, relying solely on $VO_2$peak may fail to capture key hemodynamic determinants of functional capacity, particularly those related to blood pressure and cardiac output (Cohen-Solal et al., 1999).

Recent research has emphasized the prognostic importance of incorporating hemodynamic parameters into CPET interpretation (Moayedi et al., 2020; Pezzuto et al., 2022). Among these, peak circulatory power (CircP)—the product of $VO_2$peak and peak systolic blood pressure—has emerged as a particularly robust integrative marker. By simultaneously reflecting oxygen uptake, blood flow, and perfusion pressure, CircP provides a more comprehensive assessment of cardiovascular performance under stress than either variable alone (Cohen-Solal et al., 2002b). Clinically, CircP reflects the integrative ability of the cardiovascular system to generate forward flow under pressure, functioning as a noninvasive correlation of cardiac pumping capacity. From a physical performance perspective, it indicates how effectively central and peripheral components sustain oxygen delivery during exertion.

Introduced as a noninvasive surrogate for cardiac power, CircP has demonstrated superior predictive value compared to $VO_2$peak in patients with heart failure and pulmonary vascular disease (Giverts, 2022; Martinez et al., 2022; Tang et al., 2018). Recent normative data from large, population-based cohorts further validate CircP's clinical utility, highlighting the significant impact of demographic and anthropometric factors (Busque et al., 2022). Unlike isolated gas exchange or pressure variables, CircP captures central and peripheral cardiovascular responses and is sensitive to sex, age, and training-related physiological differences (Cohen-Solal et al., 2002a). However, the impact of gender-affirming hormone therapy (GAHT) on CircP remains unexplored. This gap is particularly relevant given that vascular compliance, cardiac structure, and metabolic demand may be profoundly affected by hormonal modulation in this population (Banks et al., 2021; Connelly et al., 2019; Deutsch et al., 2015).

Additionally, although the rate-pressure product (RPP)—the product of heart rate and systolic blood pressure—is a widely used marker of myocardial workload and autonomic demand (Bagali et al., 2012; Whitman & Jenkins, 2021), its behavior in transgender individuals remains unknown. Clinically, RPP serves as a noninvasive estimate of myocardial oxygen consumption and ischemic burden during exertion, allowing clinicians to gauge left ventricular stress and autonomic load. From a functional standpoint, it reflects the efficiency of the cardiovascular system to match myocardial demand to systemic workload, which is particularly relevant in populations undergoing hormonal modulation.

From a clinical perspective, relying on $VO_2$peak alone may overlook hemodynamic determinants that shape functional capacity. CircP adds information on vascular load and central-peripheral integration, while RPP captures myocardial workload and ischemic stress. For a trans person, these markers provide a clearer picture of how gender-affirming hormone therapy may influence cardiovascular performance beyond aerobic capacity alone, helping anticipate limitations during daily activities or exercise. For clinicians, they offer practical tools to distinguish whether reduced performance arises from true cardiorespiratory impairment or from altered blood pressure and cardiac workload under hormone therapy, thereby guiding safer exercise prescription and more accurate cardiovascular risk stratification.

In transgender women and transfeminine individuals (including nonbinary people receiving estrogen-based GAHT), gender-affirming hormone

therapy—typically comprising the administration of estrogens combined with antiandrogens—is known to influence cardiovascular physiology. While some studies have reported reductions in SBP following estrogen initiation (Banks et al., 2021; Deutsch et al., 2015), others have found no significant changes, suggesting that these effects may vary according to the type, dosage, and duration of antiandrogen therapy (Maraka et al., 2017). The cardiovascular implications of progestins remain even more controversial, with inconsistent associations reported concerning hypertension and thromboembolic events (Asscheman et al., 1989).

Notably, most investigations have focused on resting cardiovascular parameters, leaving a critical gap in our understanding of dynamic responses during exercise in transgender women receiving GAHT (Cortes-Puentes et al., 2024; Fabrício Braga et al., 2025). To date, no studies have evaluated this population's exercise-induced changes in blood pressure or CircP. This gap limits the characterization of their functional cardiovascular profile and hinders the development of tailored exercise prescriptions and risk stratification strategies (Streed et al., 2021). Given their distinct physiological scopes—CircP integrating central and peripheral performance, and RPP reflecting myocardial workload—examining both in the context of GAHT aligns with prior evidence and addresses a relevant gap.

This study aimed to compare CircP between transgender women undergoing GAHT, cisgender women, and cisgender men. We further evaluated exercise-induced blood pressure responses and RPP to characterize functional cardiovascular differences across groups. We hypothesized that transgender women would exhibit reduced CircP and attenuated BP responses compared to cisgender men, reflecting a distinct cardiovascular adaptation under GAHT, and that CircP would more effectively differentiate group profiles than RPP.

## Materials and methods

This retrospective cross-sectional study evaluated hemodynamic responses to maximal CPET in transgender women undergoing GAHT. All procedures strictly followed a previously published protocol from our group, which detailed the experimental design, testing environment, and data collection procedures (Fabrício Braga et al., 2025).

### Participants and study design

Seventeen transgender women aged 18 to 45 were recruited from a multidisciplinary gender clinic. All had been on uninterrupted GAHT for at least 12 months and presented documented hormonal suppression, defined as at least two serum total testosterone values below 50 ng/dL within the previous year. Eligibility also required regular follow-up with an endocrinologist and a multidisciplinary team every three to six months, ensuring consistent clinical supervision and treatment adherence. The hormonal, clinical, and eligibility protocols followed standardized procedures previously detailed by our group. Control participants (17 cisgender women and 17 cisgender men) were selected from a CPET database using 1:1:1 propensity score matching based on age, body mass index, and physical activity level. None were professional or amateur athletes. The local ethics committee approved the study (CAAE: 90047218.9.0000.5266), and all participants provided written informed consent.

### Cardiopulmonary exercise testing

CPET was conducted on an electronically braked cycle ergometer (Lode Corival, Netherlands) using individualized ramp protocols based on Wasserman's equation (Hansen et al., 1984). After a 2-min rest period followed by 3 min of unloaded pedaling, the workload was gradually increased until the participant reached volitional fatigue. Gas exchange was recorded breath-by-breath using a metabolic system (Metalyzer 3B, Cortex, Germany), and data were analyzed using MetaSoft Studio software.

### Blood pressure measurement

SBP and DBP were assessed at rest, during exercise, and at peak effort using an aneroid sphygmomanometer and auscultation following current recommendations for exercise testing (Sharman & LaGerche, 2015). The cuff was placed on the right arm at heart level and remained in position throughout the test. During the exercise phase, the same trained operator manually measured

blood pressure every two minutes. The value corresponding to the first ventilatory threshold (VT1) was the measurement closest to that metabolic point, as determined by gas exchange analysis. Peak blood pressure was defined as the last value recorded during exercise, before recovery, rather than during the first 30 s post-exercise. The resting, VT1, and peak values were compared between groups. Inflation was set at approximately 30 mmHg above the expected SBP, and deflation followed a rate of 2–3 mmHg per second. Korotkoff phases I and V were used to determine SBP and DBP; phase IV was noted when sounds persisted near zero. During recordings, care was taken to minimize muscle tension, cuff misplacement, and ambient noise.

### Circulatory power

CircP was calculated as the product of $VO_2$peak and peak SBP obtained during maximal effort.

### Rate-pressure product

RPP was calculated as the product of peak heart rate and peak systolic blood pressure obtained during maximal effort.

### Statistical analysis

The sample size was determined as previously described in our earlier publication on ventilatory efficiency in transgender women (Fabrício Braga et al., 2025). The normality of continuous variables was assessed using the Shapiro-Wilk test. Between-group comparisons were performed using one-way analysis of variance (ANOVA). Bonferroni post hoc tests were used for multiple comparisons, as appropriate. Categorical variables were analyzed using chi-square or Fisher's exact test.

Although participants were matched by age, body mass index, and physical activity level, the prevalence of hypertension was not balanced across groups due to the observational nature of the design. Therefore, for outcomes in which hypertension could plausibly confound group comparisons, we conducted additional analyses using univariate analysis of covariance (ANCOVA), with hypertension status included as a covariate. Group (transgender women, cisgender women, and cisgender men) was modeled as a between-subject factor.

To address the potential for unequal error variances and violations of ANCOVA assumptions, all models were estimated using robust standard errors based on the HC3 heteroskedasticity-consistent estimator. This method provides reliable standard error estimates even in non-constant residual variance and is particularly recommended for small samples (MacKinnon & White, 1985).

Adjusted group means and 95% confidence intervals were calculated. Effect sizes were reported as partial eta squared ($\eta^2$) and interpreted according to conventional thresholds: negligible (<0.01), small (0.01–0.059), medium (0.06–0.139), and large (≥0.14). All analyses were conducted using Prism version 10.0 (GraphPad Software) and SPSS version 27.0 (IBM Corp.). Statistical significance was defined as $p < 0.05$.

## Results

Group characteristics are summarized in Table 1. No significant differences were observed in age distribution, prevalence of hypertension and asthma, smoking status, or physical activity patterns. Although not statistically significant, hypertension was more frequent in cisgender men, while thyroid disease appeared exclusively among cisgender women, reaching significance. Transgender women had a well-established GAHT history, with prolonged treatment duration and consistent hormonal suppression. Cyproterone was the most common antiandrogen, followed by spironolactone and finasteride, reflecting typical prescribing patterns in feminizing therapy. Most transgender women used transdermal or oral estradiol, with a smaller subset receiving injectable formulations.

Body composition and CPET data are presented in Table 2. Cisgender men had the highest skeletal muscle mass (absolute and relative to body surface area), while cisgender women had the lowest. Transgender women resembled cisgender men in weight and height but showed significantly lower lean mass (SMM and SMM/kg$^2$) compared to cisgender men ($p < 0.01$). Although predicted $VO_2$peak percentages were similar,

**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) | 0.925 |
| Irregular (%) | 5 (29.4) | 4 (23.5) | 5 (29.4) | |
| 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 are 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.

cisgender men reached higher absolute and relative $VO_2$ peak, oxygen pulse, and ventilatory volumes. Transgender women exhibited elevated ventilatory equivalents for oxygen and carbon dioxide across all stages. No significant differences were observed in resting or peak HR, chronotropic index, or HRR at 1 min, suggesting comparable autonomic recovery patterns across groups.

### Blood pressure responses

SBP and DBP values across groups are summarized in Table 3. At rest, systolic blood pressure differed significantly between groups ($p$ = 0.037; $\eta^2$ = 0.13, medium effect), while DBP did not ($p$ = 0.340; $\eta^2$ = 0.04, small effect). At $VT_1$, both SBP and DBP differences reached statistical significance ($p$ = 0.002 and $p$ = 0.009, respectively), with large effect sizes ($\eta^2$ = 0.23 and 0.18). At peak effort, SBP remained significantly different between groups ($p$ = 0.007; $\eta^2$ = 0.19, large effect), whereas DBP did not reach significance ($p$ = 0.113; $\eta^2$ = 0.09, small to medium effect).

ANCOVA models adjusted for hypertension status were conducted for BP variables that showed significant differences in the initial ANOVA (Table 4). Effect sizes ranged from medium to large, depending on the parameter and stage of exercise. At rest, SBP was significantly higher in cisgender men compared to cisgender women (Δ = +10.9 mmHg, $p$ = 0.035; $\eta^2$ = 0.13). At VT, cisgender men had higher SBP than both transgender women (Δ = +24.1 mmHg, $p$ = 0.017; $\eta^2$ = 0.23) and cisgender women (Δ = +24.1 mmHg, $p$ = 0.008; $\eta^2$ = 0.23). DBP also differed, with higher values in cisgender men compared to cisgender women (Δ = +11.2 mmHg, $p$ = 0.043; $\eta^2$ = 0.18). At peak effort, SBP remained higher in cisgender men than in transgender women (Δ = +24.1 mmHg, $p$ = 0.025; $\eta^2$ = 0.19) and cisgender women (Δ = +25.0 mmHg, $p$ = 0.020; $\eta^2$ = 0.19).

### Circulatory power

CircP differed significantly between groups (ANOVA $p < 0.001$; Table 3), with cisgender men showing the highest mean values, followed by cisgender women and transgender women. The overall effect size was large ($\eta^2$ = 0.29).

After adjusting for hypertension, the group effect on CircP remained significant ($p < 0.001$; $\eta^2$ = 0.29, large effect), while hypertension was not associated with CircP ($p$ = 0.718; $\eta^2$ = 0.003). Pairwise comparisons showed significantly lower CircP in transgender women compared to cisgender men (Δ = −2528.2, $p < 0.001$), with no difference between transgender women and cisgender women.

### Rate-pressure product

RPP differed significantly between groups in the initial analysis (ANOVA $p$ = 0.022), with cisgender men showing the highest mean values, followed by transgender women and cisgender women. The overall effect size was moderate ($\eta^2$ = 0.15) (Table 3).

All pairwise comparisons remained non-significant ($p > 0.30$) (Table 4).

## Discussion

This is the first study to investigate CircP and RPP in transgender women using maximal CPET. CircP was significantly lower in transgender women compared to cisgender men and closely

**Table 2.** Body composition and cardiopulmonary exercise responses in transgender women, cisgender women, and cisgender men.

| | | | | P-value | | | |
|---|---|---|---|---|---|---|---|
| | TW ($N=17$) | CW ($N=17$) | CM ($N=17$) | Between-group | Pairwise comparisons | | |
| Body composition | | | | | *TW vs. CW* | *TW vs. CM* | *CW vs. CM* |
| Weight (kg) | 76.7 ± 14.5 | 61.0 ± 13.4 | 81.9 ± 12.7 | <0.01 | 0.04 | 0.81 | <0.01 |
| Height (cm) | 174.9 ± 5.4 | 162.3 ± 5.4 | 177.1 ± 6.4 | <0.01 | <0.01 | 0.83 | <0.01 |
| SMM (kg) | 29.6 ± 3 | 22.0 ± 3.1 | 35.9 ± 5.1 | <0.01 | <0.01 | <0.01 | <0.01 |
| SMM/$m^2$ | 15.4 ± 0.8 | 13.3 ± 1.3 | 17.9 ± 1.7 | <0.01 | <0.01 | <0.01 | <0.01 |
| PBF (%) | 29.3 ± 8 | 32.0 ± 10.3 | 22.4 ± 8.8 | 0.01 | 1.00 | 0.09 | 0.01 |
| BFM/$m^2$ | 27.7 ± 1.3 | 24.6 ± 2.2 | 31.4 ± 2.9 | <0.01 | <0.01 | <0.01 | <0.01 |
| **CPET** | | | | | | | |
| ***Rest*** | | | | | | | |
| $VO_2$ (ml/kg/min) | 4.4 ± 0.9 | 4.8 ± 1.1 | 5.2 ± 2.1 | 0.36 | — | — | — |
| HR (bpm) | 84.3 ± 14.8 | 81.7 ± 10.2 | 78.2 ± 15.4 | 0.42 | — | — | — |
| TV (L) | 0.77 (0.28) | 0.54 (0.13) | 0.87 (0.2) | <0.01 | <0.01 | 0.22 | <0.01 |
| VE (L/min) | 14 (3.5) | 10.1 (2.4) | 13.6 (2.7) | <0.01 | <0.01 | 0.71 | <0.01 |
| $VE/VCO_2$ | 40.4 ± 5.2 | 32.9 ± 5 | 33.7 ± 4.6 | <0.01 | <0.01 | <0.01 | 1.00 |
| $VE/VO_2$ | 33.7 ± 6.0 | 26.5 ± 5.0 | 26.3 ± 5.4 | <0.001 | 0.001 | <0.001 | 1.000 |
| ***$VT_1$*** | | | | | | | |
| $VO_2$ (ml/kg/min) | 15.2 (7.0) | 13.9 (6.8) | 17.1 (13.2) | 0.14 | — | — | — |
| Workload (Watts/kg) | 0.9 (0.5) | 1 (0.5) | 1.2 (0.6) | 0.23 | — | — | — |
| HR (bpm) | 130.6 ± 19 | 120.3 ± 21.4 | 121.4 ± 21.1 | 0.27 | — | — | — |
| TV (L) | 1.6 ± 0.5 | 1.2 ± 0.3 | 1.7 ± 0.4 | <0.01 | 0.01 | 1.00 | 0.01 |
| VE (L/min) | 39.7 ± 10.9 | 26.9 ± 9.1 | 42.4 ± 17.3 | <0.01 | 1.00 | 0.01 | 0.03 |
| $VE/VCO_2$ | 34 (4.7) | 26.1 (5.6) | 28 (5.6) | <0.01 | <0.01 | <0.01 | 0.61 |
| $VE/VO_2$ | 30.6 ± 3.9 | 25.2 ± 3.9 | 23.0 ± 2.9 | <0.001 | <0.001 | <0.001 | 0.230 |
| ***Peak*** | | | | | | | |
| $VO_2$ (L/min) | 1.95 ± 0.40 | 1.65 ± 0.49 | 2.84 ± 0.85 | <0.01 | 0.49 | <0.01 | <0.01 |
| $VO_2$ (ml/Kg/min) | 25.8 ± 5.6 | 28 ± 9.9 | 34.6 ± 9.7 | <0.01 | 1.0 | 0.014 | 0.09 |
| $VO_2$ (% predicted) | 98.6 ± 21.3 | 93.5 ± 24.2 | 91.4 ± 23.9 | 0.64 | ----- | ----- | ----- |
| Workload (Watts/kg) | 2 (0.7) | 2.3 (1.3) | 2.6 (2) | 0.13 | ----- | ----- | ----- |
| HR (bpm) | 176 (13) | 172 (21) | 175 (19) | 0.39 | ----- | ----- | ----- |
| $O_2$pulse (ml/beat) | 11.4 (2.4) | 9 (4.2) | 16 (8.3) | <0.01 | 0.20 | 0.92 | <0.01 |
| TV (L) | 2.2 ± 0.6 | 1.7 ± 0.3 | 2.4 ± 0.6 | <0.01 | 0.03 | 0.42 | <0.01 |
| VE (L/min) | 97.5 ± 25.3 | 72.3 ± 16.5 | 111 ± 31.6 | <0.01 | 0.01 | 0.38 | <0.01 |
| $VE/VCO_2$ | 35.8 ± 4.7 | 31.2 ± 5 | 28.9 ± 3.5 | <0.01 | 0.01 | <0.01 | 0.40 |
| $VE/VCO_2$ slope | 33.9 ± 4.2 | 29.5 ± 5 | 28 ± 3.5 | <0.01 | 0.01 | <0.01 | 0.98 |
| $VE/VO_2$ | 46.6 ± 8.1 | 41.3 ± 7.0 | 36.9 ± 5.5 | <0.001 | 0.096 | <0.001 | 0.212 |
| Chronotropic Response (%) | 91 ± 13 | 87 ± 13 | 87 ± 14 | 0.516 | ----- | ----- | ----- |
| HRR (bpm) | 30.12 ± 12.71 | 31.18 ± 13.69 | 33.00 ± 14.61 | 0.825 | ----- | ----- | ----- |
| RER | 1.2 ± 0.1 | 1.2 ± 0.1 | 1.1 ± 0.1 | 0.06 | 0.42 | 1.00 | 0.06 |
| OUES | 2.1 (0.6) | 1.7 (0.7) | 2.9 (0.9) | <0.01 | 0.48 | 0.01 | <0.01 |

Data are expressed as mean and standard deviation. Statistical analysis: one-way ANOVA for between-group comparisons (first column), with Bonferroni-corrected post hoc tests for pairwise analyses.

BFM/$m^2$: body fat mass indexed to body surface area; CM: cisgender men; CPET: cardiopulmonary exercise testing; CW: cisgender women; DBP: diastolic blood pressure; HR: heart rate; HRR: heart rate recovery; OUES: oxygen uptake efficiency slope; $O_2$pulse: oxygen pulse; PBF: percent body fat; VE: minute ventilation; RER: respiratory exchange ratio; SBP: systolic blood pressure; SMM: skeletal muscle mass; SMM/$m^2$: skeletal muscle mass indexed to body surface area; TV: tidal volume; TW: transgender women; $VE/VCO_2$: ventilatory equivalent for carbon dioxide; $VE/VO_2$: ventilatory equivalent for oxygen; $VO_2$: oxygen uptake; $VT_1$: first ventilatory threshold.

resembled values observed in cisgender women, supporting the existence of a hormonally modulated cardiovascular phenotype. Despite our sample's low prevalence of hypertension, we accounted for its potential influence through statistical adjustment. The persistence of group differences after this correction reinforces the interpretation that these hemodynamic patterns are more likely related to intrinsic physiological and hormonal factors than differences in comorbidity burden.

Previous research employing cardiopulmonary exercise testing in transgender women has consistently demonstrated reductions in aerobic capacity and muscle strength after gender-affirming hormone therapy, although findings vary according to study design and athletic status (Alvares et al., 2022; Hamilton et al., 2024). More recently, large cohort and interventional studies have further characterized the impact of feminizing therapy on physical performance and exercise physiology, reinforcing that changes in aerobic and anaerobic profiles are multifactorial and extend beyond body composition alone (Alvares et al., 2025; Cheung et al., 2024). However, none of these studies have examined hemodynamic responses such as blood pressure regulation or circulatory power, which are key determinants of exercise capacity and cardiovascular risk. This highlights the novelty and clinical relevance of our findings.

**Table 3.** Blood pressure responses, circulatory power and rate-pressure response at rest, first ventilatory threshold, and peak exercise in transgender women, cisgender women, and cisgender men.

| Variable | TW ($N=17$) | CW ($N=17$) | CM ($N=17$) | $P$-value | $F$ (ANOVA) | $\eta^2$ (95% CI) | TW vs. CW MD (95% CI) | TW vs. CM MD (95% CI) | CW vs. CM MD (95% CI) |
|---|---|---|---|---|---|---|---|---|---|
| **Rest** | | | | | | | | | |
| SBP (mmHg) | 121.76 ± 12.37 | 117.35 ± 9.70 | 128.24 ± 13.80 | 0.037 | 3.492 | 0.13 (0.00–0.15) | 4.41 [−5.86 to 14.69] ($p=0.876$) | −6.47 [−16.75 to 5.56] ($p=0.374$) | −10.88 [−21.16 to −0.61] ($p=0.035$) |
| DBP (mmHg) | 76.47 ± 8.61 | 75.29 ± 6.24 | 78.82 ± 6.00 | 0.340 | 0.923 | 0.04 (0.00–0.16) | — | — | — |
| **$VT_1$** | | | | | | | | | |
| SBP (mmHg) | 159.41 ± 26.33 | 139.41 ± 16.00 | 163.53 ± 16.18 | 0.002 | 7.009 | 0.23 (0.04–0.39) | 20.0 [2.90 to 37.10] ($p=0.017$) | −4.11 [−21.21 to 12.98] ($p=1.0$) | −24.12 [−41.21 to −7.02] ($p=0.003$) |
| DBP (mmHg) | 88.24 ± 12.37 | 77.06 ± 6.86 | 86.47 ± 12.22 | 0.009 | 5.272 | 0.18 (0.01–0.34) | 11.17 [2.0 to 20.36] ($p=0.012$) | 1.76 [−7.42 to 10.95] ($p=1.0$) | −9.41 [−18.49 to −0.32] ($p=0.043$) |
| **Peak** | | | | | | | | | |
| SBP (mmHg) | 179.41 ± 20.15 | 178.53 ± 19.83 | 203.53 ± 32.20 | 0.007 | 5.591 | 0.19 (0.02–0.35) | 0.88 [−20.17 to 21.93] ($p=1.0$) | −24.12 [−45.08 to −3.07] ($p=0.02$) | −25.00 [−46.05 to −3.95] ($p=0.015$) |
| DBP (mmHg) | 85.88 ± 14.60 | 77.65 ± 12.52 | 86.47 ± 13.20 | 0.113 | 2.281 | 0.09 (0.00–0.24) | — | — | — |
| CircP (ml/kg/min*mmHg) | 4604.53 ± 972.25 | 4964.83 ± 1730.02 | 7087.12 ± 2317.38 | <0.001 | 9.859 | 0.29 (0.08–0.45) | −360.30 [−1859.15 to 1138.39] ($p=1.0$) | −2482.58 [−3981.43 to −983.73] ($p=0.001$) | −2122.28 [−3711.02 to −533.74] ($p=0.003$) |
| RPP (mmHg*bpm) | 31504.12 ± 3429.64 | 30290.00 ± 4294.58 | 34851.18 ± 6239.83 | 0.022 | 4.12 | 0.15 (0.00–0.31) | 1214.1 [−2870.8 to 5299.1] $p=1.000$ | −3347.1 [−7432.0 to 737.9] $p=0.143$ | −4561.2 [−8646.1 to −476.2] $p=0.024$ |

Data are expressed as mean and standard deviation. Statistical analysis: P-values and effect sizes ($\eta^2$ with 95% confidence intervals) were obtained from one-way ANOVA. Pairwise comparisons (TW vs. CW, TW vs. CM, CW vs. CM) are reported as mean differences (MD) with 95% confidence intervals and Bonferroni-adjusted P-values.

ANOVA: analysis of variance; CI: confidence interval; CircP: circulatory power; CM: cisgender men; CW: cisgender women; DBP: diastolic blood pressure; MD: mean difference; RPP: rate-pressure product; SBP: systolic blood pressure; TW: transgender women; $VT_1$: first ventilatory threshold; $\eta^2$: Eta-squared.

SBP responses during exercise exhibited a similar trajectory: at submaximal intensity, transgender women presented values comparable to cisgender men, whereas at peak exertion, their responses aligned more closely with cisgender women. These patterns were consistent across intensities and do not suggest an intermediate profile but a distinct physiological configuration. CircP proved sensitive in capturing these nuances, reinforcing its value as an integrative marker of cardiovascular function in gender-diverse populations. RPP revealed similar directional trends but failed to reach statistical significance after adjustment, displaying smaller effect sizes. This contrast highlights the clearer separation between groups observed with CircP and underscores its stronger capacity to capture physiologically meaningful differences in this context (Figure 1).

**Table 4.** ANCOVA results for blood pressure responses, circulatory power and rate-pressure response at rest, first ventilatory threshold, and peak exercise adjusted for hypertension.

| Variable | *p*-value | $\eta^2$ | Effect size | Adjusted pairwise differences |
|---|---|---|---|---|
| Rest SBP | 0.038 | 0.13 | Medium | CM > CW (Δ = +10.9 mmHg, $p = 0.035$) |
| $VT_1$ SBP | 0.002 | 0.23 | Large | CM > TW (Δ = +24.1 mmHg, $p = 0.017$); CM > CW (Δ = +24.1 mmHg, $p = 0.008$) |
| $VT_1$ DBP | 0.009 | 0.18 | Large | CM > CW (Δ = +11.2 mmHg, $p = 0.043$) |
| Peak SBP | 0.005 | 0.19 | Large | CM > TW (Δ = +24.1 mmHg, $p = 0.025$); CM > CW (Δ = +25.0 mmHg, $p = 0.020$) |
| CircP | <0.001 | 0.29 | Large | TW < CM (Δ = −2528.2 mmHg·mL·min$^{-1}$, $p < 0.001$); TW < CW (Δ = −345.1, $p = 1.000$) |
| RPP | 0.077 | 0.10 | Medium | All pairwise comparisons: $p > 0.30$ |

Statistical analysis: ANCOVA models adjusted for hypertension status. Only variables with significant ANOVA results included. Effect size interpretation: negligible (<0.01), small (0.01–0.059), medium (0.06–0.139), large (≥0.14).
CircP: circulatory power; CM: cisgender men; CW: cisgender women; DBP: diastolic blood pressure; RPP: rate-pressure product; SBP: systolic blood pressure; TW: transgender women; $VT_1$: first ventilatory threshold; $\eta^2$: partial eta squared.

## *Blood pressure responses*

Exercise-induced BP responses observed in transgender women may reflect hormonal influences on vascular tone and autonomic control. Estrogen has been shown to enhance nitric oxide-mediated

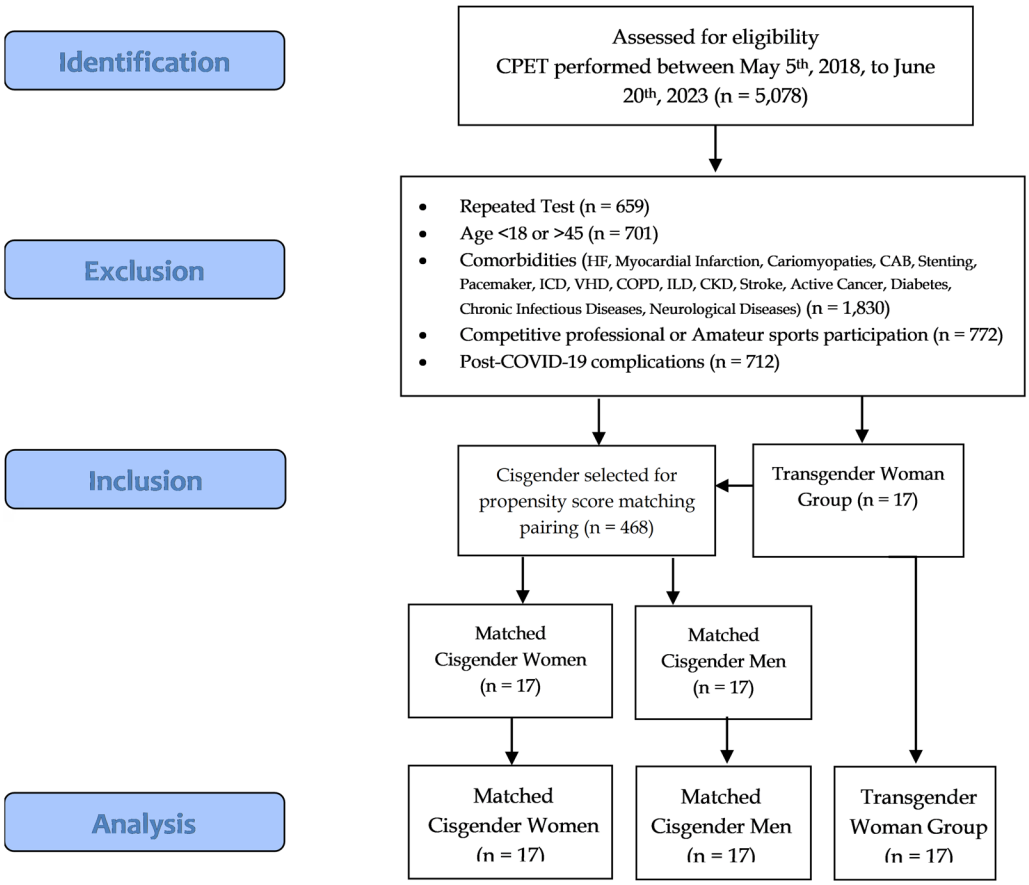


**Figure 1.** Flowchart of participant selection. CPET: Cardiopulmonary Exercise Testing; TW: transgender women; CW: cisgender women; CM: cisgender men; COPD: Chronic Obstructive Pulmonary Disease; ILD: Interstitial Lung Disease; CKD: chronic kidney disease; CVD: cardiovascular disease; VT1: First Ventilatory Threshold; GAHT: Gender-Affirming Hormone Therapy.

vasodilation and reduce systemic vascular resistance, contributing to lower systolic responses during peak exertion (Coylewright et al., 2008; Sudhir et al., 1997). In contrast, testosterone is associated with heightened sympathetic activity and increased vascular reactivity (Reckelhoff, 2001), which may partially explain the elevated SBP responses typically observed in cisgender men. The intermediate profile of transgender women—resembling cisgender men at submaximal intensities and cisgender women at peak—suggests that GAHT may blunt the pressor response during high exertion while preserving sympathetic tone at lower workloads. This pattern has also been described in cisgender women, where SBP rises more slowly with incremental effort and plateaus earlier compared to cisgender men (Gleim et al., 1991).

Furthermore, using antiandrogens such as cyproterone acetate has been associated with altered adrenergic receptor sensitivity and reduced vascular contractility (Campos et al., 2003), possibly contributing to the attenuated peak SBP observed in transgender women. The dissociation between systolic and diastolic responses, particularly at $VT_1$, may reflect differential modulation of cardiac output versus peripheral resistance, a distinction not uncommon in populations with hormonal variation (Connelly et al., 2019; Dubey et al., 2002; Cottin et al., 2010). Collectively, these findings support the hypothesis that GAHT influences vascular and autonomic responses during exercise in a phase-dependent manner (Figure 2).

The dissociation between SBP and DBP responses observed in transgender women at $VT_1$ may be partly explained by their intermediate skeletal muscle mass and the vascular effects of GAHT (McGinley et al., 2024; Sugie et al., 2017). Transgender women are aerobically comparable to cisgender men in terms of predicted $VO_2$; however, they have significantly lower skeletal muscle mass, which likely limits stroke volume and the capacity to augment cardiac output during incremental exercise. This is supported by evidence that peak $VO_2$/HR—an index of stroke volume—correlates strongly with skeletal muscle mass (Sugie et al., 2017). At the same time, the hormonal milieu induced by prolonged use of antiandrogens and estrogens may promote enhanced vascular compliance and reduced sympathetic-mediated vasoconstriction (Orshal & Khalil, 2004). Although transgender women have greater muscle mass and height than cisgender women, their SBP response remains similarly attenuated, suggesting that hormonal modulation may exert a more substantial influence than body composition alone. These central and peripheral mechanisms may contribute to the blunted SBP and preserved DBP responses observed in transgender women, reflecting a distinct, hormonally mediated hemodynamic profile.

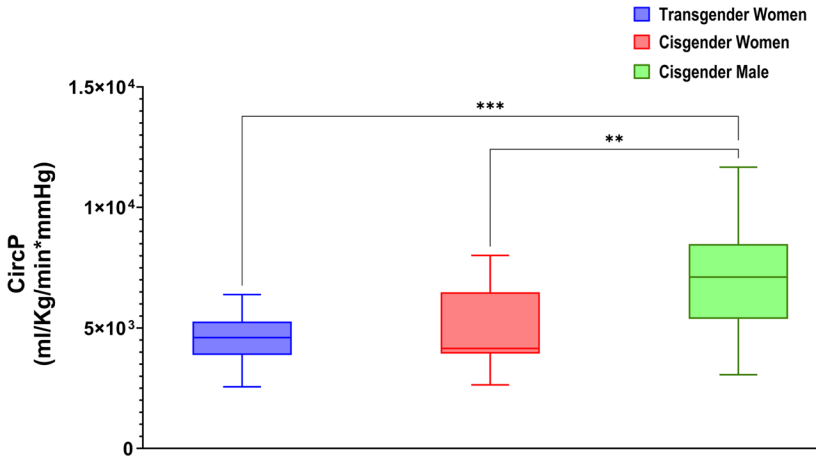


**Figure 2.** Circulatory power in transgender women, cisgender women, and cisgender men. Boxplot comparing circulatory power among transgender women, cisgender women, and cisgender men. Asterisks indicate statistically significant differences between groups based on post hoc Bonferroni-adjusted comparisons following one-way ANOVA (**$p < 0.01$; ***$p < 0.001$). CircP: circulatory power.

### *Circulatory power and rate-pressure product*

CircP reflects the interaction between cardiac output and peripheral perfusion pressure, integrating central and peripheral cardiovascular performance. Despite matched CRF, the reduced CircP observed in transgender women compared to cisgender men suggests a physiologic divergence that cannot be explained by conditioning alone. Given that CircP is directly influenced by stroke volume and peak SBP, the lower values in transgender women likely reflect reduced pressure generation and/or central hemodynamic output. Previous studies have shown that estrogen therapy is associated with lower systemic vascular resistance and attenuated systolic responses to physical stress, which may contribute to this pattern (Connelly et al., 2019; Deutsch et al., 2015). Moreover, feminizing regimens often include antiandrogens such as cyproterone acetate, which have been implicated in adverse inotropic effects and blunted adrenergic responsiveness (Burinkul et al., 2021; Glintborg et al., 2021; Wilson et al., 2019)

The absence of difference between transgender women and cisgender women in CircP reinforces the concept of a hormonally modulated convergence toward a female cardiovascular phenotype. This alignment is not simply a consequence of reduced muscle mass or body size, as the groups were matched by aerobic performance, and differences persisted after adjustment for hypertension. Prior population-based data have demonstrated that cisgender women exhibit lower CircP values than cisgender men, even after accounting for fitness and anthropometrics (Hulkkonen et al., 2014). These findings suggest that GAHT may influence cardiovascular integration under exercise conditions through structural and neurohumoral pathways, potentially altering preload, myocardial contractility, or baroreflex function.

Moreover, these findings expand on our previous work, which identified impaired ventilatory efficiency in transgender women across all exercise intensities (Fabrício Braga et al., 2025). Transgender women consistently presented elevated $\dot{V}E/\dot{V}CO_2$ ratios and steeper $\dot{V}E/\dot{V}CO_2$ slopes, pointing to increased ventilatory demand despite matched aerobic capacity. The current demonstration of reduced CircP in the same population adds a central hemodynamic dimension to this physiological profile. These two studies reveal that transgender women under GAHT displays coordinated alterations in circulatory performance and ventilatory control during exercise. This integrative pattern suggests that hormonal therapy may modulate multiple components of cardiopulmonary function, reinforcing the importance of population-specific reference values and interpretative frameworks in exercise testing.

Importantly, the reduced CirP observed in transgender women does not indicate an inability to elevate SBP during exercise. In our cohort, pressor responses were preserved across intensities, but peak systolic values were lower compared with cisgender men. This distinction underscores that the limitation reflects the magnitude of pressure generation at maximal effort rather than an absent pressor response.

Including RPP in this study offers an opportunity to contextualize the observed hemodynamic responses using a more traditional index of cardiac workload. Although RPP followed a similar distribution pattern to CircP—being higher in cisgender men, intermediate in transgender women, and lower in cisgender women—it did not reach statistical significance after adjustment for hypertension, and effect sizes were smaller. This contrast is physiologically coherent: while RPP reflects the product of HR and SBP, broadly capturing autonomic drive and myocardial oxygen demand (Chaikijurajai et al., 2025; Gobel et al., 1978), CircP integrates both pressure generation and $\dot{V}O_2$, offering a more comprehensive view of cardiopulmonary performance (Cohen-Solal et al., 2002c). The stronger group effect and larger effect size observed for CircP, compared to RPP, suggest that it is more sensitive to hormonal modulation and central-peripheral integration under stress. While both indices followed similar directional patterns, only CircP significantly differentiated transgender women from cisgender men after adjustment. This reinforces its clinical relevance as a more suitable functional marker to capture cardiovascular adaptations in gender-diverse individuals with preserved CRF.

A recent study (Adel et al., 2024) also evaluated RPP in transgender women undergoing estrogen-

based gender-affirming hormone therapy, compared with cisgender women and men. Consistent with our findings, they reported attenuated exercise-induced increases in RPP among transgender women relative to cisgender men, suggesting a blunted ability to raise myocardial workload under stress. However, while Adel et al. emphasized the clinical implications of reduced cardiac workload as a potential cardioprotective adaptation, our results highlight that such attenuation may also contribute to lower CirP and diminished integrative cardiovascular performance. Together, these studies underscore that differences in RPP extend beyond isolated hemodynamic markers and interact with aerobic and muscular determinants to shape exercise capacity in transgender women.

### Clinical implications

The findings of our study gain additional relevance in light of growing evidence that transgender women face an increased risk of cardiovascular disease (CVD) compared to cisgender individuals (Masumori & Nakatsuka, 2023; Moreira Allgayer et al., 2023; Seal, 2019). According to a recent systematic review and meta-analysis (van Zijverden et al., 2024), transgender women have a 30% higher risk of stroke and more than double the risk of venous thromboembolism compared to cisgender men. Although the risk of myocardial infarction appears comparable, the overall CVD burden in transgender populations is approximately 40% higher relative to their cisgender counterparts (Seal, 2019).

This elevated risk is multifactorial, encompassing not only the vascular effects of GAHT—particularly estrogen-associated thrombotic potential—but also social determinants of health (Poteat et al., 2021). Discrimination, psychological distress, adverse childhood experiences, and a higher prevalence of untreated comorbidities contribute significantly to cardiovascular vulnerability (Howerton & Harris, 2022; Martinez et al., 2020). Moreover, higher rates of mental health disorders and substance use in transgender individuals compound the risk profile (Denby et al., 2021; Streed et al., 2021).

In this context, the hemodynamic alterations observed in our study, such as attenuated SBP responses and reduced CircP, may represent early, subclinical indicators of cardiovascular dysregulation. These markers, particularly when captured during submaximal exercise, can provide valuable insight into autonomic and vascular health. Therefore, CPET may serve as a crucial tool not only for exercise prescription but also for risk stratification and ongoing cardiovascular monitoring in transgender women receiving GAHT. Tailored approaches to exercise, preventive care, and long-term cardiovascular follow-up are essential to mitigate the disproportionate burden of CVD in this population.

### Limitations and future directions

This study has several limitations that should be acknowledged. First, the relatively small sample size may limit the generalizability of the findings; however, strict matching by age and CRF and the use of effect size estimates help mitigate this issue. Second, the cross-sectional design precludes causal inferences but provides an essential snapshot of hemodynamic differences under standardized conditions. Third, although all participants were physically active, the group was heterogeneous regarding training modality, which may influence cardiovascular adaptations; this was partially addressed by matching aerobic capacity across groups. Fourth, the distribution of comorbidities such as hypertension and thyroid disorders was not balanced across groups, potentially introducing confounding; nonetheless, statistical adjustment and sensitivity analyses were employed to control for these variables. Fifth, the absence of contemporaneous hormonal laboratory data limits the ability to correlate hemodynamic patterns with specific endocrine profiles; future studies with longitudinal hormone monitoring could address this. Sixthly, our analysis was restricted to transgender women; therefore, the findings cannot be generalized to transgender men, underscoring the need for future studies addressing this population. Finally, although practical and widely used, indirect blood pressure measurements during exercise may introduce some variability; still, the protocol employed was validated and consistently applied across participants.

Future studies should aim to include larger, more diverse samples and adopt longitudinal

designs to track the evolution of hemodynamic responses over time. Integrating serial hormonal measurements and direct, beat-by-beat BP monitoring could enhance mechanistic understanding. Expanding this line of research is essential to refining cardiovascular risk assessment and improving care strategies tailored to the needs of transgender populations.

## Conclusion

This study is the first to characterize the hemodynamic responses of transgender women under GAHT during CPET, demonstrating consistently reduced CircP and attenuated SBP responses across exercise intensities, despite matched CRF. RPP followed a similar distribution but showed weaker group differentiation, reinforcing the added value of CircP as an integrative functional index. These findings provide new insight into how hormonal modulation shapes cardiovascular adaptation in transgender women, highlighting that their physiological responses do not represent a midpoint between cisgender men and cisgender women but a distinct profile. By linking reduced CircP to exercise performance, our results contribute to the understanding of physical capacity and potential sport participation in transgender women. In this context, CPET emerges as a valuable tool not only for tailoring exercise prescription and monitoring safety but also for informing fair and evidence-based approaches to athletic participation, while helping to identify early signs of cardiovascular vulnerability and promoting equitable care for gender-diverse populations.

## Author contributions

FB: guarantor of the study, data collection, analysis and interpretation, writing of the first draft. MM, JGPM, GCJ: data analysis and interpretation, critical review of the text. DH: data analysis and interpretation, critical review of the text. ACF, BK, RZ, KDM, RF: data collection and interpretation. RMR: data analysis and interpretation, review of the text, supervision.

## Guarantor statement

FB takes responsibility for the content of the manuscript, including the data and analysis.

## Role of the sponsors

None.

## Use of AI tools

During the preparation of this manuscript, no generative artificial intelligence (AI) tools were used to generate, compose, or modify scientific content. AI-assisted tools were used solely for language editing purposes under the full supervision of the corresponding author (FB). All content remains the responsibility of the authors.

## Disclosure statement

All authors declare no conflicts of interest.

## Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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## Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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