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The Influence of a 12-Week Exercise Program on Asymmetric Dimethylarginine and Uric Acid Levels in Adults with Congenital Heart Disease–Associated Pulmonary Hypertension

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ABSTRACT: Exercise-based rehabilitation may improve functional outcomes in pulmonary hypertension, but its effects on endothelial and metabolic biomarkers in adults with congenital heart disease-associated pulmonary hypertension remain uncertain. This study evaluated the influence of a 12-week exercise program on asymmetric dimethylarginine and uric acid levels. This single-arm pre-post interventional study included 13 adults with congenital heart disease-associated pulmonary hypertension. Participants completed supervised moderate-intensity aerobic exercise twice weekly for 12 weeks, at 40%–60% of heart rate reserve for 30 minutes per session, with daily incentive spirometry. Asymmetric dimethylarginine and uric acid levels were measured at baseline and week 12 and compared using paired-samples t tests. Participants had a mean age of 32.92 ± 8.22 years, and 76.9% were female. Mean asymmetric dimethylarginine decreased from 20,933.27 ng/L at baseline to 18,518.38 ng/L at week 12; this difference was not statistically significant ($t = 0.610$, $p = 0.553$). Mean uric acid increased from 7.76 to 8.27 mg/dL, also without a statistically significant difference ($t = -2.027$, $p = 0.066$). A 12-week supervised exercise program was not associated with statistically significant changes in asymmetric dimethylarginine or uric acid levels in adults with congenital heart disease-associated pulmonary hypertension. The differing directional responses suggest that endothelial and metabolic adaptations to exercise may vary within this population.

1. INTRODUCTION

Pulmonary hypertension (PH) is a progressive cardiopulmonary disorder characterized by pulmonary vascular remodeling, increased right ventricular afterload, and a risk of right heart failure and premature death [1]. PH associated with congenital heart disease remains a clinically important condition in adults and is associated with substantial hemodynamic impairment and adverse clinical risk profiles [2]. ADMA is a relevant biomarker in pulmonary arterial hypertension because its longitudinal

change is associated with disease progression and survival [3]. Uric acid may provide complementary metabolic and prognostic information, as higher levels are associated with worse hemodynamic and clinical risk parameters in CHD-associated pulmonary arterial hypertension [2]. Exercise-based rehabilitation is an established adjunct to optimized medical therapy in selected patients with PH and may improve exercise capacity and health-related quality of life [4]. However, the effects of structured exercise on endothelial and metabolic biomarkers remain less well characterized. In patients with pulmonary arterial hypertension, endurance training has been associated with favorable changes in circulating markers of endothelial damage and repair [5]. Therefore, this study evaluated the influence of a 12-week exercise program on ADMA and uric acid levels in adults with CHD-associated PH.

2. MATERIALS AND METHODS

2.1 Study Design and Setting

This single-arm pre–post interventional study evaluated changes in ADMA and uric acid levels after a 12-week exercise program in adults with CHD-associated PH. The study was conducted at the Integrated Heart Center of Dr. Wahidin Sudirohusodo Hospital, Makassar, Indonesia, from December 2025 to February 2026.

2.2 Participants

Participants were recruited consecutively from patients with PH and CHD. Eligible participants were 18–50 years of age; had PH defined by a mean pulmonary artery pressure of at least 20 mmHg at right heart catheterization, or an equivalent echocardiographic or documented clinical diagnosis, consistent with current ESC/ERS diagnostic criteria; had CHD confirmed by echocardiography or right heart catheterization; were receiving stable sildenafil therapy; and provided written informed consent. Patients were excluded if they had cardiovascular comorbidities other than CHD-associated PH or another PH subtype, acute coronary syndrome within the preceding 40 days, or a clinical condition that precluded participation in the exercise program. Baseline comorbidities and concomitant medications, including agents that may influence asymmetric dimethylarginine or uric acid levels, such as diuretics, urate-lowering drugs, and renin–angiotensin system inhibitors, were reviewed from the medical records, and participants remained on stable background therapy throughout the study. The minimum sample size was estimated at 12 participants; 13 participants completed the intervention and were included in the analysis. Because of the small sample and the absence of a control group, the study was not powered to detect modest biomarker changes, and the analyses were considered exploratory.

2.3 Exercise Intervention

All participants received a standardized cardiac rehabilitation program. Before commencing the intervention, participants received education on medication adherence, stress management, cardiovascular risk-factor control, and safe exercise practice. Each participant received an exercise kit containing 0.5-kg dumbbells, an incentive spirometer, a pulse oximeter, a water bottle, exercise clothing, and an activity logbook. The supervised exercise program consisted of moderate-intensity aerobic exercise performed twice weekly for 12 weeks. Each session lasted 30 minutes and was prescribed at 40%–60% of heart rate reserve, with the target heart rate calculated for each participant using the Karvonen method. Heart rate and peripheral oxygen saturation were monitored throughout every session using the pulse oximeter provided in the exercise kit, and the workload was adjusted to maintain the prescribed target range. All sessions were supervised in person by the cardiac rehabilitation team at the Integrated Heart Center under physician oversight, with predefined criteria for pausing or terminating exercise in the event of symptoms, oxygen desaturation, or hemodynamic instability. Participants were also instructed to perform breathing exercises using a triflow incentive spirometer three times daily throughout the intervention period, and these daily sessions formed an integral component of the overall intervention alongside the supervised aerobic training. Adherence to both the supervised sessions and the daily incentive spirometry was recorded in the activity logbook and reviewed at each visit. All 13 participants completed the full 12-week program (100% completion), and no adverse events were observed during the supervised exercise sessions.

2.4 Outcome Measurements

The primary outcomes were changes in ADMA and uric acid levels from baseline to week 12. Clinical and laboratory data were obtained from medical records and laboratory reports and recorded using standardized data-collection forms. Demographic characteristics, including age and sex, and the underlying CHD diagnosis were also collected.

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2.5 Statistical Analysis

Data were analyzed using IBM SPSS Statistics version 26.0. Continuous variables were summarized as mean ± standard deviation or median, as appropriate, whereas categorical variables were presented as frequencies and percentages. Normality of paired differences was assessed using the Shapiro–Wilk test. Baseline and post-intervention ADMA and uric acid levels were compared using the paired-samples t test for normally distributed data or the Wilcoxon signed-rank test for non-normally distributed data. For each outcome, mean values at baseline and week 12 and the mean paired difference are reported. A two-sided p value of ≤0.05 was considered statistically significant. Given the single-arm design and limited sample size, a nonsignificant result was interpreted as the absence of a statistically detectable change rather than as evidence that no effect exists.

3. RESULTS AND DISCUSSION

3.1 Participant Characteristics

All 13 enrolled participants completed the 12-week exercise program and were included in the final analysis; no outcome data were missing. Participants had a mean age of 32.92 ± 8.22 years, and 10 participants (76.9%) were female. Atrial septal defect was the predominant congenital heart disease diagnosis, affecting 10 participants (76.9%). At baseline, mean pulmonary artery pressure was 61.00 ± 22.51 mmHg. Additional demographic, anthropometric, diagnostic, and selected hemodynamic characteristics are presented in Table 1. Detailed baseline right heart catheterization and oximetry findings are presented in Supplementary Table S1.

Table 1. Baseline characteristics of participants

Characteristic	Value
Age, years	32.92 ± 8.22
Female sex, *n* (%)	10 (76.9)
Weight, kg	46.92 ± 7.18
Height, cm	153.15 ± 6.20
Body mass index, kg/m²	19.97 ± 2.73
Atrial septal defect, *n* (%)	10 (76.9)
Ventricular septal defect, *n* (%)	2 (15.4)
Patent ductus arteriosus, *n* (%)	1 (7.7)
Mean right atrial pressure, mmHg	8.23 ± 4.21
Mean pulmonary artery pressure, mmHg	61.00 ± 22.51

Values are mean ± standard deviation unless otherwise indicated.

3.2 Changes in ADMA and Uric Acid After the Exercise Program

The paired differences for ADMA and uric acid were normally distributed (Shapiro-Wilk p = 0.730 and p = 0.321, respectively). Mean ADMA decreased from 20,933.27 ng/L at baseline to 18,518.38 ng/L after 12 weeks; however, this change was not statistically significant (mean paired difference, 2,414.89 ng/L; t = 0.610; p = 0.553). Mean uric acid increased from 7.76 mg/dL at baseline to 8.27 mg/dL at week 12, without a statistically significant difference (mean paired difference, -0.51 mg/dL; t = -2.027; p = 0.066). The paired comparisons are summarized in Table 2.

Table 2. Changes in ADMA and uric acid after the 12-week exercise program

Outcome	Baseline mean	Week 12 mean	Mean paired difference	*t*	*p* value
ADMA, ng/L	20,933.27	18,518.38	2,414.89	0.610	0.553
Uric acid, mg/dL	7.76	8.27	-0.51	-2.027	0.066

Values were compared using paired-samples t-tests. Mean paired difference was calculated as baseline minus week 12.

3.3 Discussion

This study found no statistically significant change in ADMA or uric acid after the 12-week exercise program in adults with CHD-associated PH. Although the two biomarkers did not show a uniform response, their contrasting directional changes may reflect their distinct biological roles. PH is characterized by endothelial dysfunction, vascular remodeling, inflammation, oxidative stress, and metabolic dysregulation; therefore, a single intervention may influence individual biological pathways differently [1,6].

The observed direction of change in ADMA may warrant further investigation because this biomarker reflects endothelial nitric oxide-related dysfunction and may provide prognostic information beyond conventional clinical variables. Shafran et al. (2024) reported that longitudinal changes in ADMA were associated with disease progression and survival in pulmonary arterial hypertension [3]. In addition, Rodríguez-Chiaradía et al. (2023) demonstrated that endurance exercise training was associated with a more favorable endothelial repair profile [5], characterized by increased circulating progenitor cells and reduced endothelial microvesicles. These findings support the biological plausibility that structured exercise may promote endothelial adaptation, even when changes in a single biomarker do not reach statistical significance.

The nonsignificant increase in uric acid should be interpreted within its broader metabolic and hemodynamic context. In CHD-associated pulmonary arterial hypertension, higher uric acid levels have been associated with worse pulmonary hemodynamics, higher risk categories, impaired functional status, and response to PH-specific therapy [2]. Experimental evidence also suggests that uric acid may participate in pulmonary vascular dysfunction through effects on endothelial nitric oxide signaling and oxidative pathways [7]. However, uric acid is influenced by several processes, including purine turnover, renal handling, tissue oxygen utilization, oxidative stress, hydration, dietary intake, and concurrent medications. Accordingly, its increase after exercise should not be interpreted in isolation as evidence of worsening pulmonary vascular disease.

Exercise may alter systemic and pulmonary metabolism through changes in oxygen delivery, skeletal-muscle energy use, and redox balance. Metabolomic studies have highlighted the close interaction between altered pulmonary vascular metabolism and impaired exercise physiology in pulmonary arterial hypertension [8]. Oxidative stress is also recognized as an important contributor to pulmonary vascular remodeling and right ventricular dysfunction, providing a potential mechanistic link between metabolic biomarkers and clinical disease expression [9]. Preclinical data further suggest that exercise can modify systemic metabolic pathways in pulmonary hypertension, although translation of these findings to circulating biomarkers in adults requires further study [10].

The divergent responses of ADMA and uric acid reinforce the importance of evaluating endothelial and metabolic markers as complementary, rather than interchangeable, measures. ADMA may better reflect endothelial regulation, whereas uric acid may capture metabolic, oxidative, and hemodynamic burden. A multidimensional assessment that includes biomarkers, functional capacity, symptoms, quality of life, echocardiographic measures, and hemodynamic parameters may therefore be more informative than reliance on a single laboratory outcome [6,11].

Current evidence supports supervised exercise-based rehabilitation as an adjunct to optimized medical therapy in selected patients with PH. Recent systematic reviews have reported improvements in exercise capacity and health-related quality of life, with no clear increase in serious adverse events during supervised programs [4,12]. The present study extends this literature by examining ADMA and uric acid in adults with CHD-associated PH. These findings suggest that biomarker-based assessments may complement functional outcomes when evaluating the response to structured exercise in this population.

This study used a single-arm pre–post design without a control group; therefore, the observed directional changes cannot be attributed specifically to the exercise program and may reflect natural variation, regression to the mean, or concurrent clinical factors. The small sample of 13 participants limited statistical power and precision, so the nonsignificant findings should be interpreted as an absence of a statistically detectable effect rather than as confirmation that exercise has no effect on these biomarkers. These constraints also limit the generalizability of the findings. In addition, the evaluation was restricted to ADMA and uric acid and did not include functional capacity, symptom burden, quality of life, or other clinically relevant outcomes. Potential confounding factors affecting both biomarkers, including metabolic status, renal function, hydration, dietary intake, medication use, and interindividual clinical variation, were not comprehensively controlled. Finally, because the intervention combined supervised aerobic exercise with daily incentive spirometry, any observed biomarker changes reflect the combined program rather than aerobic training alone.

4. CONCLUSION

In adults with CHD-associated PH, a 12-week structured and supervised exercise program was not associated with statistically significant changes in ADMA or uric acid levels. The contrasting directional changes and individual variability indicate that endothelial and metabolic responses to exercise may differ within this population. Further controlled studies are needed to evaluate the effects of this combined exercise program on circulating biomarkers in adults with CHD-associated PH.

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AUTHOR CONTRIBUTIONS

RKP contributed to conceptualization, methodology, investigation, data curation, formal analysis, interpretation of findings, and writing of the original draft. **PT and YP** contributed to conceptualization, methodology, supervision, interpretation of findings, and critical revision of the manuscript. **ZD and MW** contributed to methodology, clinical supervision, interpretation of findings, and critical revision of the manuscript. **AAZ** contributed to methodology, statistical analysis, interpretation of findings, and critical revision of the manuscript. All authors read and approved the final manuscript.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

ETHICS STATEMENT

The study protocol was approved by the Universitas Hasanuddin Research Ethics Committee, Faculty of Medicine, Universitas Hasanuddin, Makassar, Indonesia (approval no. 1083/UN4.6.4.5.31/PP36/2025; protocol no. UH25100937; approved on 8 December 2025). Written informed consent was obtained from all participants before enrollment.

DATA AVAILABILITY STATEMENT

The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request, subject to ethical and institutional approval.

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Supplementary Table S1. Baseline right heart catheterization and oximetry characteristics of participants

Variable	Mean ± SD	Minimum	Maximum
High superior vena cava oxygen saturation, %	62.08 ± 12.13	42	79
Low superior vena cava oxygen saturation, %	60.08 ± 8.35	46	72
Inferior vena cava oxygen saturation, %	66.38 ± 8.19	53	84
Right atrial systolic pressure, mmHg	12.17 ± 4.26	6	18
Right atrial diastolic pressure, mmHg	11.25 ± 4.62	4	22
Mean right atrial pressure, mmHg	8.23 ± 4.21	3	16
Right atrial oxygen saturation, %	71.15 ± 11.52	52	87
Right ventricular systolic pressure, mmHg	88.67 ± 39.30	19	150
Right ventricular diastolic pressure, mmHg	10.33 ± 14.08	1	40
Mean right ventricular pressure, mmHg	19.92 ± 17.04	4	61
Right ventricular oxygen saturation, %	74.38 ± 13.23	49	90
Pulmonary artery systolic pressure, mmHg	96.42 ± 35.10	31	146
Pulmonary artery diastolic pressure, mmHg	38.08 ± 19.46	1	71
Mean pulmonary artery pressure, mmHg	61.00 ± 22.51	12	96
Pulmonary artery oxygen saturation, %	73.31 ± 12.30	49	95
Left atrial systolic pressure, mmHg	14.25 ± 4.59	8	23
Left atrial diastolic pressure, mmHg	13.50 ± 4.34	8	21
Mean left atrial pressure, mmHg	10.82 ± 3.95	6	17
Aortic systolic pressure, mmHg	106.92 ± 22.83	70	142
Aortic diastolic pressure, mmHg	63.00 ± 18.58	36	109
Mean aortic pressure, mmHg	79.42 ± 16.59	50	109
Aortic oxygen saturation, %	88.17 ± 7.90	72	98
Pulmonary-to-systemic vascular resistance ratio	1.19 ± 0.92	0.11	2.70

Values are mean ± standard deviation.