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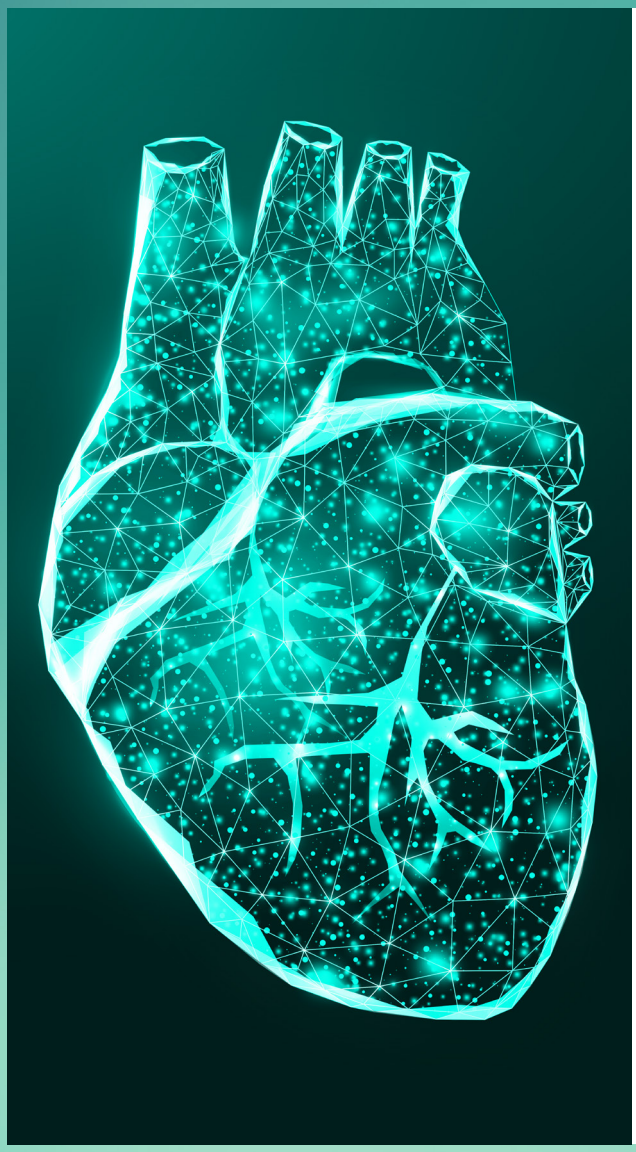

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RESEARCH ARTICLE

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Int J Cardiovasc Acad 2026;12(3):141-146

Clinical and Metabolic Factors Associated with Heart Rate Recovery in Patients Undergoing Exercise Stress Testing: A Cross-sectional Study from Southwest Iran

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Abstract

Background and Aim: Heart rate recovery (HRR) after exercise is a simple marker of autonomic function. Attenuated HRR has been linked to increased cardiovascular risk and mortality. This study examined the associations between traditional cardiovascular risk factors, exercise-induced ischemia, and HRR at one minute (HRR1) in a population from southwest Iran.

Materials and Methods: This cross-sectional study included 342 patients (mean age 50.7±10.3 years) referred for Bruce protocol treadmill testing due to non-specific symptoms and clinical suspicion of ischemia. HRR1 was calculated as peak heart rate minus heart rate at one minute after exercise cessation. Bivariate analyses were performed for age, sex, hypertension, diabetes, smoking, high plasma low-density lipoprotein (LDL) cholesterol (>130 mg/dL), family history of coronary artery disease, and exercise-induced ischemia. Variables with $P < 0.25$ were entered into multivariate linear regression. Multicollinearity was assessed using the variance inflation factor, and standard linear regression assumptions were verified.

Results: The mean HRR1 was 31.4±10.4 beats per minute. In multivariate analysis, higher HRR1 was significantly and independently associated with normotension (B=4.52, $P = 0.001$), absence of diabetes (B=3.81, $P = 0.010$), LDL cholesterol ≤130 mg/dL (B=2.67, $P = 0.011$), and a negative exercise test for ischemia (B=3.94, $P = 0.016$). No significant associations were found with age, sex, smoking, or family history of coronary artery disease.

Conclusion: Impaired HRR1was independently associated with hypertension, diabetes mellitus, elevated LDL cholesterol, and exercise-induced ischemia in this population. These findings suggest that HRR1 can serve as a simple, useful integrative marker of cardiovascular risk during routine exercise stress testing. Due to the cross-sectional design, causality cannot be inferred, and prospective studies are warranted.

Keywords: Heart rate recovery, exercise stress test, myocardial ischemia

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INTRODUCTION

Heart rate recovery (HRR), the rate at which heart rate slows down after the termination of exercise, is defined by the parasympathetic recovery along with the withdrawal of the sympathetic branch of the autonomic nervous system.[1] HRR reflects the integrated function of the cardiovascular, respiratory, and metabolic systems, collectively referred to as cardiorespiratory fitness.[1-3]

Lower HRR values have been associated with adverse outcomes, including systemic inflammation, arrhythmia-related mortality,[4,5] hypertension, and insulin resistance.[6,7] Furthermore, established demographic and lifestyle factors such as advanced age,[8] as well as smoking and caffeine consumption,[9,10] have been identified as influential variables in previous studies.

Beyond its established diagnostic utility for detecting ischemia via electrocardiography, exercise stress testing also provides prognostic information through HRR determination, which is of considerable relevance in primary prevention. These dual capabilities continue to be investigated by the scientific community.[2,3]

Objectives

Cardiovascular diseases remain a leading cause of mortality both globally and in Iran. Considering the differences in lifestyle and the varying prevalence of risk factors across regions, the aim of this study was to investigate the relationship between HRR, an important component of cardiovascular risk assessment, and traditional risk factors including age, smoking, diabetes, and hypertension in the Dezful region of western Iran, a population for which such data have not previously been reported.

Notably, this study simultaneously examines the associations of HRR with both traditional risk factors and exercise-induced ischemia a combined assessment that has been infrequently reported in the existing literature. It is expected that the results from the current research will prove helpful in designing effective preventive measures for improved health outcomes in the region.

METHODS

This cross-sectional study was conducted in a specialized cardiac clinic in Dezful, Southwest Iran, between October 2021 and October 2022.

Patients aged 30-70 years who were referred for exercise stress testing due to non-specific symptoms and clinical suspicion of ischemia were eligible for inclusion. Inclusion criteria comprised: no known cardiovascular disease; normal baseline electrocardiogram and echocardiogram; controlled blood pressure (<140/90 mmHg) at the time of testing; and ability to complete the test until reaching the age-predicted maximum heart rate. Patients taking beta-blockers or other medications known to significantly affect heart rate were excluded. Additional exclusion criteria included premature test termination due to chest pain, arrhythmias, or other limiting symptoms, and incomplete HRR data. A total of 342 patients met the inclusion criteria and were enrolled using convenience sampling.

The study protocol was approved by the Institutional Review Board and Ethics Committee of Dezful University of Medical Sciences (approval no: IR.DUMS.REC.1401.086, dated: 17.01.2023). Written informed consent was obtained from all participants after explanation of the study objectives and procedures. Participants were assured of confidentiality and their right to withdraw at any time. The study was conducted in accordance with the Declaration of Helsinki.

Exercise Testing Protocol: Exercise testing was performed using the BPL Dynatrac Neo Stress Test System treadmill according to the standard Bruce protocol, following ACC/AHA recommendations.[11]

Heart rate and blood pressure were recorded at the end of each stage. The exercise testing equipment was regularly calibrated by the center's biomedical engineer, and its proper function was verified before each test.

HRR1 was calculated as peak heart rate minus heart rate measured at the first minute after exercise cessation, with the patient in the standing position. Measurements were performed by trained personnel under the supervision of a cardiologist, according to a standardized protocol.

Data Collection: Demographic and clinical data including age, sex, history of hypertension, diabetes mellitus, smoking status, family history of coronary artery disease (CAD), and low-density lipoprotein (LDL) cholesterol levels were extracted from medical records. Definitions were as follows:

Hypertension: Blood pressure ≥140/90 mmHg on repeated measurements in clinic or use of antihypertensive medication.[11]

Diabetes: Fasting blood glucose ≥126 mg/dL or 2-hour postprandial glucose ≥200 mg/dL or use of antidiabetic medication.[11]

Hypercholesterolemia: Plasma LDL cholesterol >130 mg/dL.[12]

Positive family history: CAD in first-degree male relative <55 years or female relative <65 years.[12]

Smoking: Lifetime consumption of ≥100 cigarettes.[12]

Ischemic response: Defined according to standard electrocardiographic criteria during testing.[11]

Statistical Analysis

Data were analyzed using SPSS version 26. Continuous variables are presented as mean ± standard deviation, and categorical variables as frequency (percentage). The Kolmogorov-Smirnov test was used to assess normality. Pearson correlation and independent t-tests (or analysis of variance) were applied for bivariate analyses. Variables with $P < 0.25$ in bivariate analysis were considered for inclusion in the multivariate linear regression model. This liberal threshold was selected given the exploratory nature of the study in a specific regional population, to reduce the risk of prematurely excluding potentially relevant variables.

Prior to regression, assumptions of linear regression were verified, including linearity, homoscedasticity, normality of residuals, and independence of errors. Multicollinearity was assessed using the variance inflation factor; all values were below 2.0, indicating no significant multicollinearity. A *P*-value < 0.05 was considered statistically significant in the final model. All beta coefficients are unstandardized unless otherwise specified.

RESULTS

Study Population

As shown in Table 1, a total of 342 patients were included in this study. The mean age was 50.7±10.3 years, and 182 (53.2%) were male. The mean HRR at one minute (HRR1) was 31.4±10.4 bpm.

The prevalence of cardiovascular risk factors was as follows: hypertension in 131 patients (38.3%), diabetes mellitus in 55 (16.1%), smoking history in 57 (16.7%), positive family history of CAD in 68 (19.9%), and LDL cholesterol >130 mg/dL in 133 (38.9%). A positive exercise test for ischemia was observed in 21 patients (6.1%). Seventy-one participants (20.8%) had no cardiovascular risk factors (not mentioned in the table).

Lower HRR1 values were significantly associated with the presence of hypertension, diabetes mellitus, elevated LDL cholesterol, and a positive exercise test for ischemia. No statistically significant associations were observed between HRR1 and age (r=-0.09, $P = 0.11$), sex, smoking status, or family history of CAD.

Multivariate Analysis

Variables with $P < 0.25$ in the bivariate analysis were entered into the multivariate model (Table 2). The final model included age, hypertension, diabetes mellitus, LDL cholesterol level, and exercise test result. The "number of risk factors" variable was not included in the regression model to avoid conceptual redundancy and multicollinearity with the individual risk factors.

All regression assumptions were satisfied (linearity, homoscedasticity, normality of residuals, and no significant multicollinearity). Beta coefficients reported below are unstandardized.

Table 1. The relationship between hypertension, diabetes, plasma LDL, and the result of the exercise test with heart rate recovery

Variable	Category	No (%)	Heart rate recovery, mean ± SD	*P*-value
Blood pressure	High	131 (38.3)	28.5±10.14	0.01
	Normal	211 (61.7)	33.15±10.13	
Diabetes	Yes	55 (16.1)	28.33±11.66	0.03
	No	287 (83.9)	31.96±10.17	
LDL level	LDL >130 mg/dL	133 (38.9)	30.2±11.1	0.01
	Normal	209 (61.1)	32.13±9.82	
Exercise test	Positive for ischemia	21 (6.1)	29±12.29	0.03
	Negative	321 (93.9)	31.5±10.23	
Smoking	Positive	57 (16.7)	30.33±10.27	0.41
	negative	285 (83.3)	31.59±10.39	
Family history of CAD	Positive	68 (19.9)	32.9±11.61	0.21
	Negative	274 (80.1)	31±10.02	
Sex	Male	182 (52.2)	31.25±10.19	0.81
	Female	160 (46.8)	31.52±10.59	

LDL: Low-density lipoprotein, CAD: Coronary artery disease, SD: Standard deviation

Table 2. Multiple linear regression analysis of factors associated with heart rate recovery

Variable	B (unstandardized)	SE	β (standardized)	t	*P*-value	95% CI for B
Age (years)	-0.38	0.26	-0.09	-1.46	0.145	-0.89 - 0.13
Normotensive (vs. hypertensive)	4.52	1.12	0.22	4.04	0.001	2.32 - 6.72
Non-diabetic (vs. diabetic)	3.81	1.48	0.14	2.57	0.010	0.90 - 6.72
LDL ≤130 mg/dL (vs. >130)	2.67	1.05	0.13	2.54	0.011	0.60 - 4.74
Negative exercise test (vs. positive)	3.94	1.62	0.11	2.43	0.016	0.75 - 7.13
Constant	38.76	3.45	-	11.24	0.001	31.97 - 45.55

LDL: Low-density lipoprotein, CAD: Coronary artery disease, CI: Confidence interval, SE: Standard error

DISCUSSION

This study demonstrated significant associations between lower HRR1 and several major cardiovascular risk factors, including hypertension, diabetes mellitus, elevated LDL cholesterol, and the presence of exercise-induced ischemia, in patients from southwest Iran. An inverse association with age was observed in the bivariate analysis; however, this relationship did not remain statistically significant in the multivariate model. No significant associations were found with sex, smoking history, or family history of CAD.

Our findings regarding hypertension, diabetes, and dyslipidemia are consistent with previous reports. For instance, Sydó et al.[3] followed over 20,000 patients and observed that slower HRR was associated with older age, diabetes, hypertension, obesity, and smoking, whereas sex showed no statistically significant effect on HRR levels. Similarly, Hughes and Chaturvedi[13] reported inverse associations between HRR and systolic blood pressure, blood glucose, and body mass index. Grad and Zdrenghea[11] also noted associations between reduced HRR1 and older age, male sex, high plasma triglycerides, and ischemic response during exercise testing. In some prior studies, reduced HRR was significantly related to both cardiac and non-cardiac mortality.[3] However, the association between HRR and mortality was not evaluated in our study, as such an analysis requires large cohort studies.

The present results align with these studies regarding most metabolic risk factors and extend them by providing data from an Iranian population in the Dezful region. More than one-third of the individuals in the study area had hypertension and elevated LDL cholesterol, which warrants attention in primary prevention health programs in the region.

In the study by Ulleryd et al.,[14] an association between autonomic dysfunction and carotid plaque and cardiac inflammation was observed. Our research demonstrated a significant correlation between low HRR and exercise-induced ischemia, which is consistent with the findings of Ulleryd et al.[14] and Grad and Zdrenghea.[11]

This possible association may not be limited to overt ischemia, as the literature suggests that reduced HRR values have also been observed in cases of silent ischemia or microvascular disease, even in the presence of normal stress testing.[15,16]

Given the possibility of cardiac ischemia in the presence of low HRR, the routine use of this parameter in sports centers for ischemia screening is more prominently recommended.

Previous research has suggested that men tend to have higher fitness levels than women across all age groups, possibly due to higher haemoglobin levels, greater muscle mass, and higher cardiac output.[16,17]

Furthermore, a study by Beltrame et al.[18] observed that estradiol levels in women of all ages may play a role in HRR and autonomic nervous system response. In 2021, Zubac et al.[19] indicated that the HR recovery rate continuously declined with age in both males and females. However, in a very comprehensive study by Jackson et al.,[8] the HR recovery rate decreased in association with age (primarily due to reduced sympathetic response), but the pace of decline hastened beyond the age of 45 years. Nevertheless, lower body mass index, greater levels of physical activity, and being a non-smoker attenuated the reductions in fitness levels and HR recovery rate associated with aging.[8] The lack of a significant association between age and HRR1 in the multivariate analysis differs from some earlier reports. This discrepancy may be related to the relatively narrow age range of our sample (30-70 years), sample size, or unmeasured genetic and environmental factors specific to this population.[20,21]

The absence of sex differences in HRR1 is consistent with some prior investigations that found no clear gender effect after adjusting for other variables.

Previous studies have shown a link between smoking and decreased HRR, and autonomic dysfunction has been identified as the underlying cause.[22,23]

Likewise, the non-significant association with smoking, despite lower mean HRR1 values among smokers, could be attributed to the modest number of smokers (16.7%) and variations in smoking intensity and duration that were not captured in this study. While previous studies have described these relationships, The present study uses regional data from southwestern Iran, where cardiovascular risk profiles and lifestyles differ across populations. The results of the above studies suggest that HRR1 may serve as a useful integrative marker associated with traditional risk factors and cardiac ischemia and could be applied in clinical practice.

Study Limitations

Several limitations should be considered when interpreting these findings. First, the cross-sectional design allows only for the identification of associations and does not permit conclusions about causality or temporal relationships. Second, this was a single-center study conducted in one cardiac clinic in Dezful, which may limit generalizability. Although participants were classified as asymptomatic, they were referred to a cardiac clinic for ischemia evaluation, indicating a clinical suspicion that may not represent the general healthy population. Third, this referral pattern introduces potential selection bias, and the results may not fully represent asymptomatic community-dwelling individuals. Due to the relatively small sample size (n=342) and the low prevalence of certain factors—such as smoking (16.7%) and positive ischemic response (6%) the study may have been underpowered to detect statistically significant associations for these specific variables. Additionally, objective measures of cardiorespiratory fitness, such as VO_2max or METs, were not available, as gas exchange analysis was not performed. We did not collect detailed information on physical activity levels, dietary patterns common in the Western Iran region, educational level, socioeconomic status, or caffeine consumption, all of which could act as residual confounders. Medication history was limited to the exclusion of beta-blockers, and other drugs potentially affecting autonomic function were not fully stratified. Heart rate was recorded manually from the monitor screen at exactly one minute, a method susceptible to minor human error or equipment lag compared to automated digital beat-to-beat analysis. HRR was measured in a standing position; different recovery postures (e.g., supine or active cool-down) significantly alter parasympathetic reactivation, potentially limiting the comparability of these results to studies using different protocols. Finally, no formal sample size or power calculation was performed, as this was a convenience sample. Despite these limitations, the integration of HRR as an inexpensive and practical risk stratification tool after exercise testing is recommended. However, large-scale, cohort-based complementary studies are still needed.

CONCLUSION

This cross-sectional study showed that impaired HRR1 is significantly associated with hypertension, diabetes mellitus, high LDL cholesterol, and exercise-induced ischemia among patients undergoing treadmill testing in Southwest Iran. HRR1 appears to be a simple and practical physiological marker associated with cardiovascular risk profiles in routine exercise stress testing. Due to the associative nature of the findings and the limitations inherent in the study design, larger prospective studies are needed to further evaluate the clinical utility of HRR1 in diverse populations and to explore its relationship with long-term cardiovascular outcomes and primary prevention

Ethics

Ethics Committee Approval: The study protocol was approved by the Institutional Review Board and Ethics Committee of Dezful University of Medical Sciences (approval no: IR.DUMS.REC.1401.086, dated: 17.01.2023).

Informed Consent: Written informed consent was obtained from all participants after explanation of the study objectives and procedures.

Footnotes

Authorship Contributions

Surgical and Medical Practices: H.S., M.K., A.K., M.H., S.S., Concept: H.S., M.K., A.K., M.H., S.S., Design: H.S., M.K., A.K., M.H., S.S., Data Collection or Processing: H.S., M.K., A.K., M.H., Analysis or Interpretation: H.S., M.K., A.K., M.H., Literature Search: H.S., M.K., M.H., S.S., Writing: H.S., M.K., A.K., M.H., S.S.

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RESEARCH ARTICLE

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Serum Lipoprotein(a) as a Marker of Severity of Coronary Artery Disease in Aortic Valve Sclerosis Patients

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Abstract

Background and Aim: Aortic valve sclerosis (AVS) and severity of coronary artery disease (CAD) share common risk factors, but not all patients have the same severity of coronary lesions. Lipoprotein(a) [Lp(a)] is a significant, causal, and non-modifiable indicator of valvular outcomes and CAD in the general population. This study aimed to evaluate the correlation between serum Lp(a) level and CAD severity in individuals with AVS.

Materials and Methods: This cross-sectional study was conducted in 100 individuals with an established diagnosis of AVS who had chest pain and/or dyspnea and were provisionally diagnosed with CAD. Participants were subdivided into two groups: the normal-level group (n=42), with a cut-off serum Lp(a) level of 30 mg/dL. High level group (n=58): high-risky Lp(a) level.

Results: A significant correlation was observed between the number of diseased epicardial coronary arteries and high Lp(a) levels [51.73% vs. 4.77% for 3-vessel disease, and 3.45% vs. 66.66% for one-vessel disease, in the high and normal Lp(a) groups, respectively] ($P < 0.001$). SYNTAX score had been elevated (35.07±6.08) in those with elevated Lp(a) level contrasted to reduced Lp(a) (14.76±4.5 SD) ($P < 0.001$).

Conclusion: Elevated serum Lp(a) was significantly associated with greater coronary lesion severity and higher SYNTAX scores among patients with AVS.

Keywords: Lipoprotein(a), aortic valve, lipid marker, coronary artery disease.

INTRODUCTION

Aortic valve sclerosis (AVS) is characterized by focal or diffuse aortic valve thickening without significant hemodynamic obstruction.[1,2] Despite its lack of effect on aortic valve function and subsequent benign classification, multiple studies in the last several years have linked AVS to an escalated risk of cardiovascular (CV) death in the general population and at-risk subsets.[3]

There is an initial stage of AVS pathophysiology that includes lipid infiltration, inflammation, and oxidation, and a subsequent stage that includes calcification and fibrosis of the aortic cusps.[4] Bicuspid aortic valve is the primary etiology of AVS in persons aged 70 years or younger and results in a more intense progression of AVS.[5]

No medical therapy existed to lessen the manifestations or to halt or slow the AVS progression.[6] Currently, surgery or transcatheter AV replacement is the only technique known

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to improve survival rates. Half of all patients exhibiting AVS symptoms will die over the next 12 to 18 months unless surgical intervention is attempted.[7]

In recent years, there has been growing interest in lipoprotein(a) [Lp(a)] as an important, largely genetically determined, and relatively non-modifiable biomarker associated with valvular outcomes and coronary artery disease (CAD)s in the general population.[8,9]

Lp(a) is a cholesterol-dense particle comprising the large glycoprotein apolipoprotein (a) [apo(a)], which is covalently linked to apolipoprotein B-100 by a single disulfide bond. The genetic background is the primary determinant of circulating serum Lp(a) levels, mediated by the *LPA* gene that encodes apo(a).[10] Apo(a) has a protease-like domain, a kringle V domain, and a kringle IV repeat domain (KIV), all of which share a high degree of sequence similarity with plasminogen. A strong inverse association existed between Lp(a) concentration in plasma and the number of KIV2 repeats, which are responsible for the substantial size variation in apo(a) isoforms. The apo(a) sequence only contains one repeat of KIV2.[11]

The pathophysiological mechanism of Lp(a) activity remains under investigation. Lp(a) has been suggested to transport cholesterol to the leaflets of the valves, thus promoting the microcrystals formation, that could lead to calcification.[12] Elevated inflammation and oxidative stress are prevalent pathophysiological contributors to vascular endothelial dysfunction and to the earliest phases of valvular osteogenesis. Lp(a) is additionally the principal carrier of oxidized phospholipids, that cause these conditions.[13]

Numerous researchers have proposed that Lp(a) might serve as an independent risk factor for cardiovascular system (CVS) illness[14,15] and have noted a favorable correlation between serum Lp(a) levels and both the severity and frequency of CV disease.[16]

Consequently, we aimed to ascertain the relationship between serum Lp(a) levels and the degree and complexity of coronary lesions as assessed by the SYNTAX score in individuals with AVS.

METHODS

Design and Population

This cross-sectional study was conducted on 100 participants with an established diagnosis of AVS who had chest pain and/or dyspnea and were provisionally diagnosed as CAD.

The study was conducted following approval by the Local Research Ethics Committee of the Faculty of Medicine, Sohag University, in accordance with the Declaration of Helsinki (approval no: Soh-Med-24-09-5PD, date: 11.09.2024). Verbal informed consent was obtained from all participants. ClinicalTrials registration was not required for this study.

Eligibility Criteria

Exclusion criteria were aortic stenosis, previous aortic valve prosthesis, chronic kidney failure, untreated hypothyroidism, pregnancy, and regular use of systemic immunosuppressive or anti-inflammatory medications, including chronic corticosteroids, disease-modifying antirheumatic drugs, biologic immunosuppressive agents, or long-term non-steroidal anti-inflammatory drugs for more than four weeks before enrollment.

Grouping

Participants were subdivided into two groups: the normal-level group (n=42), with a cut-off of serum Lp(a) level of 30 mg/dL. High level group (n=58): high-risky Lp(a) level.[17]

Clinical Evaluation and Baseline Data Collection

All of them had been exposed to comprehensive taking of history, clinical examinations, laboratory tests [blood sugar, kidney function tests (creatinine and blood urea nitrogen), full blood picture and lipid profile] and radiological investigations.

Assessments

Detailed echocardiography was performed to evaluate aortic valve structure and function, and to assess ejection fraction and segmental wall motion abnormalities.

Age, sex, the most prevalent risk factors for CV disease such as hypertension, dyslipidemia, diabetes mellitus (DM) and smoking in addition to the clinical justification for coronary angiography were all noted for each patient.

Coronary angiography was performed at a rate of 12.5 frames per second; digital angiographic images were captured using an angiography system (Philips Harvey IL 60426, USA, 2000).

Detailed analysis of coronary lesions by two observers was done to assess: [the diseased coronary arteries number, the severity of epicardial coronary lesions (significant lesions if >70%) and SYNTAX scoring for complexity of coronary lesions of each patient (low score (<22), moderate (22-33) and high score (≥34)].[18]

A venous blood sample was obtained from each patient during a scheduled follow-up visit approximately one month (4 weeks) after hospital discharge to measure serum Lp(a) levels. The samples were centrifuged for 10 minutes at 2-8 °C; the serum was then divided into aliquots and stored at -20 °C. The human

Lp(a) kit (Biotang Inc., HU9148) was used to determine the Lp(a) levels. We utilized the enzyme-linked immunosorbent assay.

No participants initiated PCSK9 inhibitors or underwent major changes in lipid-lowering therapy during this interval. As Lp(a) concentrations are predominantly genetically determined and relatively stable over time, major short-term fluctuations were considered unlikely.

Sample Size Calculation

Sample size was calculated using G*Power 3.1.9.2 (Universität Kiel, Germany). We conducted a pilot study (5 cases in each group) and found that the incidence of significant coronary lesions according to Lp(a) level was 40% in participants with normal Lp(a) levels and 70% in those with high Lp(a) levels. The sample size was based on the following considerations: an α error of 0.05, 80% power, and the addition of sixteen instances to account for dropout. Therefore, we recruited 100 cases for this study.

Statistical Analysis

Data were analyzed using STATA version 14.2 (Stata Statistical Software: Release 14.2 College Station, TX: StataCorp LP.). Quantitative data were expressed as mean and standard deviation (SD) and analyzed using the Student's t-test. Qualitative data were reported as numbers and percentages and analyzed using the chi-square test. Graphs were produced using Excel or STATA. Univariate regression was used to estimate the relationship between a dependent variable and one independent variable. Multivariate regression was also used to estimate the relationship between a dependent variable and multiple independent variables. A two-tailed *P*-value ≤0.05 will be considered statistically significant.

RESULTS

The mean age of the subjects in our research was 60.76 years with SD ±5.39 years, and 68% of them were males. We assessed the conventional CV risk factors and discovered their overlap. Among patients, 54% had dyslipidemia and 56% had arterial hypertension. DM also represented 56% of our population. Fifty percent of the patients were smokers. The mean low-density lipoprotein (LDL) of the subjects in our research was 116.9 mg/dL with SD ±32.35 mg/dL. Forty percent of the study population had a high SYNTAX score, 18% had an intermediate score, and 42% had a low score. The mean Lp(a) concentration was 39.8 mg/dL; 58% of patients had high blood levels of Lp(a) (>30 mg/dL), with a mean of 55.68 mg/dL, and 42% had low blood levels of Lp(a), with a mean of 16.68 mg/dL Table 1.

Patients with high levels of LP(a) had significantly higher rates of smoking (75.86% vs. 14.29%), hypertension (89.66% vs. 9.52%), DM (86.21% vs. 14.29%), and dyslipidemia (89.66% vs. 4.76%), a higher prevalence of a high SYNTAX score (68.97% vs. 0%), a higher proportion of males (75.86% vs. 57.14%), and higher mean age (63.83 vs. 56.52 years) and higher LDL (139.79 vs. 85.29 mg/dL) than patients with normal levels of LP(a) ($P < 0.05$) Table 2.

Hypertension and DM were more common in patients with significant lesions than in patients without significant lesions, but the difference was not statistically significant Table 3.

Additionally, we found that high serum Lp(a) levels showed a significant direct relationship with the number of diseased coronary arteries ($P < 0.001$), with 51.73% in three-vessel disease versus 3.45% in single-vessel disease. A significant increase in serum Lp(a) levels ($P < 0.001$) was associated with the severity of coronary lesions, with severe lesions accounting for 75.88% of individuals in the high Lp(a) group versus 24.12% with non-severe lesions in that group Table 4.

In univariate regression analysis, age, sex, smoking, hypertension, LDL, and Lp(a) were independent predictors of a high syntax score ($P < 0.05$). In multivariate regression analysis, LDL and Lp(a)were independent predictors of high syntax score ($P = 0.001$), while age, sex, smoking, and hypertension were not Table 5.

SYNTAX score had been significantly greater in the group with high Lp(a) level (35.07±6.08) than normal Lp(a) group (14.76±4.5) ($P < 0.001$) Figure 1.

Table 1. Demographic data and cardiovascular risk factors distribution of the studied population

		n=100
Age (years)		60.76±5.39
Sex	**Female**	32 (32.0%)
	Male	68 (68.0%)
Risk factors	**Smoking**	50 (50.0%)
	Hypertension	56 (56.0%)
	DM	56 (56.0%)
Lipid profile	**Normal**	46 (46.0%)
	High (dyslipidemia)	54 (54.0%)
LDL (mg/dL)		116.9±32.35
SYNTAX score	**Intermediate**	18 (18%)
	Low	42 (42%)
	High	40 (40.0%)
Lp(a)	**Normal level**	42 (42.0%)
	High level	58 (58.0%)

Data are presented as mean ± SD or frequency (%)

DM: Diabetes mellitus, LDL: Low-density lipoprotein, Lp(a): Lipoprotein(a), SD: Standard deviation

Table 2. Relation between demographic data and cardiovascular risk factors and Lp(a)

		Lp(a)		*P*-value
		Normal level (n=42)	High level (n=58)	
Age (years)		56.52±2.51	63.83±4.77	<0.001*
Sex	Female	18 (42.86%)	14 (24.14%)	0.048*
	Male	24 (57.14%)	44 (75.86%)	
Risk factors	Smoking	6 (14.29%)	44 (75.86%)	<0.001*
	Hypertension	4 (9.52%)	52 (89.66%)	<0.001*
	DM	6 (14.29%)	50 (86.21%)	<0.001*
Lipid profile	Normal	40 (95.24%)	6 (10.34%)	<0.001*
	High (dyslipidemia)	2 (4.76%)	52 (89.66%)	
LDL (mg/dL)		85.29±12.8	139.79±20.75	<0.001*
SYNTAX score	Intermediate	6 (14.29%)	12 (20.69%)	<0.001*
	Low	36 (85.71%)	6 (10.34%)	
	High	0 (0%)	40 (68.97%)	

Data are presented as mean ± SD or frequency (%)

DM: Diabetes mellitus, LDL: Low-density lipoprotein, Lp(a): Lipoprotein(a), SD: Standard deviation, *: Significant as $P < 0.05$

Table 3. Relation of angiographic significance of coronary lesions to conventional risk factors

		Non-significant lesions	Significant lesions	*P*-value
Hypertension	Yes	22 (39.28%)	34 (60.72%)	0.284
	No	22 (50%)	22 (50%)	
DM	Yes	28 (40%)	42 (60%)	0.218
	No	16 (53.33%)	14 (46.67%)	

Data are presented as frequency (%)

DM: Diabetes mellitus

Table 4. Comparison of the number of diseased epicardial vessels and angiographic significance of coronary lesions in relation to Lp(a) level

	Lp(a) *levels		*P*-value
	Normal level (n=42)	High level (n=58)	
Number of diseased epicardial vessels			
One vessel	28 (66.66%)	2 (3.45%)	<0.001*
Two vessels	12 (28.57%)	26 (44.82%)	
Three vessels	2 (4.77%)	30 (51.73%)	
Angiographic significance of coronary lesions			
Non-significant	30 (71.42%)	14 (24.12%)	<0.001*
Significant	12 (28.58%)	44 (75.88%)	

Data are presented as frequency (%)

Lp(a): Lipoprotein(a), *: Significant $P < 0.05$

DISCUSSION

Serum Lp(a) is a separate macromolecular lipoprotein characterized by significant homology and particular antigenicity, having an essential impact in the onset and progression of atherosclerosis and thrombosis by disrupting the lipid metabolism and fibrinolytic system, which is peculiar for Lp(a) other than alternative apolipoproteins.[19]

To our knowledge, our study is one of the few studies to use SYNTAX scores to assess the correlation between the severity of coronary lesions and Lp(a) in AVS patients.

Clinical factors correlated with aortic sclerosis including age, male gender, hypertension, smoking, diabetes, elevated serum Lp(a) levels and low-density lipoprotein.[20]

The Lp(a) concentrations varies significantly across various populations and it is mainly determined by hereditary factors.[21] However, its individual concentration remains relatively stable and is not influenced by the use of statins, patients' age, gender, diet, environment, smoking habit or lipid metabolism.[22]

AVS and the severity of CAD share common risk factors, but not all patients have coronary lesions of the same severity. Previous investigators did not clearly establish this relationship.

The present study is designed to identify the correlation between serum Lp(a) levels and the extent of CAD and the severity of coronary lesions in individuals with AVS.

A previous, similar study examined the impact of elevated Lp(a) levels on CAD. Maranhão et al.[23] proposed that Lp(a) might serve as an independent risk factor for CVS illness, whereas Nordestgaard et al.[22] noted a positive relationship between serum Lp(a) levels and both the incidence and severity of CV illness.

This outcome was comparable to the findings of Lima et al.,[24] Maher et al.,[25] Utermann,[26] and other prior research, which indicated that blood levels of Lp(a) gradually escalate in accordance with the severity of coronary atheromatosis.

Rajasekhar et al.,[27] noted that serum Lp(a) levels had been considerably elevated in triple vascular disease compared to single vessel disease, corroborating findings from earlier research.

Conversely, Schwartzman et al.[28] observed no significant variation in plasma Lp(a) levels across different CAD categories based on the number of affected arteries or angiographic disease severity, findings that were comparable to those of other researchers.[29] The discrepancy between their findings and ours may be explained by differences in study population and assessment methods. Our cohort specifically included patients with AVS, a condition that shares inflammatory, lipid-

Table 5. Univariate and multivariate logistic regression analyses of factors associated with high SYNTAX score

	Univariate			Multivariate		
	OR	**95% CI**	***P*-value**	**OR**	**95% CI**	***P*-value**
Age (years)	1.591	1.35: 1.87	**<0.001***	1.1442	0.891: 1.47	0.292
Sex (female)	0.375	0.148: 0.951	**0.039***	0.405	0.039: 4.16	0.447
Smoking	15.58	5.51: 44.07	**<0.001***	3.15	0.664: 14.96	0.149
Hypertension	44.33	9.64: 203.79	**<0.001***	0.544	0.043: 6.93	0.639
DM	1.72	---	0.997	---	---	---
LDL (mg/dL)	1.089	1.06: 1.12	**<0.001***	1.086	1.038: 1.136	**0.001***
Lp(a)	1.277	1.134: 1.438	**0.001***	1.249	1.099: 1.421	**0.001***

CI: Confidence interval, DM: Diabetes mellitus, LDL: Low-density lipoprotein, OR: Odds ratio, LP(a): Lipoprotein(a), *: Significant $P < 0.05$

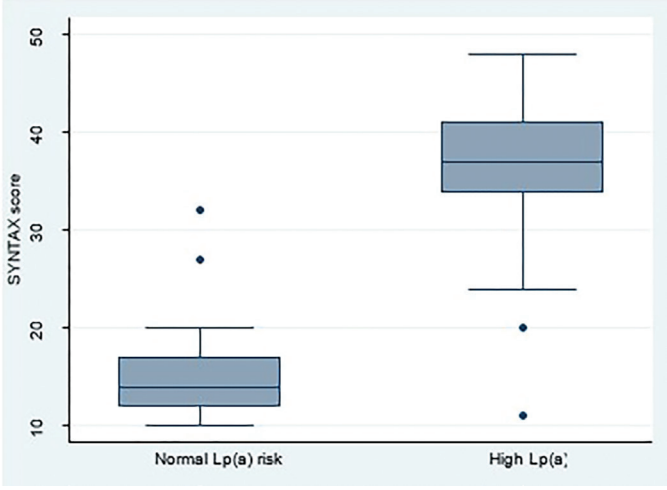

Figure 1. Comparison of mean serum lipoprotein(a) [Lp(a)] levels according to SYNTAX score categories, demonstrating significantly higher levels among patients with greater coronary lesion complexity

mediated, and calcific pathways with CAD. In addition, we assessed coronary disease complexity using the SYNTAX score rather than relying solely on traditional vessel counts, allowing a more detailed evaluation of lesion burden, anatomical complexity, and overall angiographic severity.

Although conventional CV risk factors are established determinants of CAD severity, our findings demonstrate marked differences in coronary lesion burden and the SYNTAX score across Lp(a) levels. However, interpretation of these findings requires caution because the elevated Lp(a) group was older and had higher LDL levels and a higher prevalence of smoking, hypertension, DM, and dyslipidemia. To address this potential confounding, multivariate logistic regression was performed; Lp(a) remained independently associated with a high SYNTAX score after adjustment for relevant covariates. Nevertheless, residual confounding cannot be excluded, and causality cannot be inferred from the present observational design.

The present investigation revealed a significant increase in the frequency and severity of coronary atherosclerosis, as identified by CA, among individuals with elevated blood levels of Lp(a) over 30 mg/dl compared with individuals with normal levels.

Coronary angiography demonstrated a significant increase in the number of affected coronary arteries in individuals with elevated Lp(a) levels compared with those with normal Lp(a) levels.

The SYNTAX score, the most recent and reliable angiographic tool for quantifying the severity and complexity of CAD and predicting outcomes of coronary interventions depending on anatomical complexity, was employed in our current study to mitigate bias and enhance decision-making. It was substantially elevated in individuals with high Lp(a) levels contrasted to those with normal levels of Lp(a), with cut-off values of 22 for mild risk and 34 for high-risk scores.[30,31]

Study Limitations

Some limitations should be acknowledged. First, the sample size was relatively small, and the study was conducted at a single center, which may limit external validity. Second, baseline characteristics were not homogeneous between study groups: patients with elevated Lp(a) levels were older and had higher LDL levels and a higher prevalence of smoking, hypertension, DM, and dyslipidemia. Although multivariate regression analysis was performed to adjust for potential confounders, residual confounding cannot be completely excluded. Third, selection bias may have occurred because the study included symptomatic AVS patients referred for coronary angiography, thereby limiting generalizability to asymptomatic populations. Fourth, the Lp(a) measurement was performed approximately one month after discharge, which may have introduced variability, although no major changes in lipid-lowering therapy occurred and Lp(a) levels are generally stable over time. Finally, the absence of longitudinal clinical outcomes precludes assessment of prognostic implications. Therefore, larger prospective multicenter studies with longitudinal follow-up are warranted.

CONCLUSION

Elevated serum Lp(a) levels were independently associated with greater CAD severity and higher SYNTAX scores among individuals with AVS. By applying the SYNTAX score to this AVS population, the present study highlights the potential clinical value of Lp(a) as a marker of angiographic disease burden and of coronary lesion complexity. Larger multicenter longitudinal studies are warranted to validate these findings.

Ethics

Ethics Committee Approval: The study was conducted following approval by the Local Research Ethics Committee of the Faculty of Medicine, Sohag University, in accordance with the Declaration of Helsinki (approval no: Soh-Med-24-09-5PD, date: 11.09.2024).

Informed Consent: Verbal informed consent was obtained from all participants.

Footnotes

Authorship Contributions

Surgical and Medical Practices: R.S.A., S.M.T., S.P.A., A.I.B., Concept: R.S.A., S.M.T., S.P.A., A.I.B., Design: R.S.A., S.M.T., S.P.A., A.I.B., Data Collection or Processing: R.S.A., S.M.T., S.P.A., A.I.B., Analysis or Interpretation: R.S.A., S.M.T., S.P.A., A.I.B., Literature Search: R.S.A., S.M.T., S.P.A., A.I.B., Writing: R.S.A., S.M.T., S.P.A., A.I.B.

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RESEARCH ARTICLE

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Impact of Digoxin Therapy on Cardiac Mechanical Dyssynchrony in Patients with Non-ischemic Heart Failure

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Abstract

Background and Aim: Mechanical dyssynchrony is a key determinant of impaired cardiac performance, adverse remodeling, and prognosis in heart failure (HF). Digoxin is widely used in HF because of its positive inotropic and neurohormonal effects; however, its impact on mechanical dyssynchrony remains poorly defined.

Materials and Methods: In this prospective, randomized, single-center study, 50 patients with newly diagnosed non-ischemic dilated cardiomyopathy, left ventricular ejection fraction (LVEF) <45%, and documented mechanical dyssynchrony by tissue Doppler imaging were randomized to guideline-directed medical therapy (GDMT) alone (control) or GDMT plus digoxin (0.125-0.25 mg/day). Echocardiographic parameters, including intraventricular and interventricular dyssynchrony, left ventricular volumes, LVEF, and QRS duration, were assessed at baseline and at three months.

Results: At three months, intraventricular dyssynchrony decreased significantly in both groups, with a greater reduction in the digoxin group ($P < 0.001$ within-group; $P = 0.044$ between-group). Interventricular dyssynchrony improved significantly only in the digoxin group ($P = 0.002$). Digoxin therapy was associated with increased LVEF ($P = 0.006$), reduced left ventricular volumes, and shorter QRS duration ($P < 0.001$). No significant changes were observed in the control group for these parameters.

Conclusion: Digoxin therapy appears to improve cardiac mechanical synchrony, systolic function, and electrical conduction in patients with non-ischemic HF. These findings suggest that the therapeutic effects of digoxin may extend beyond symptom relief and neurohormonal modulation to include favorable mechanical remodeling.

Keywords: Heart failure, imaging, left ventricular dysfunction

INTRODUCTION

Heart failure (HF) remains a major public health problem, associated with substantial morbidity, mortality, and healthcare burden.[1] Mechanical dyssynchrony—defined as a temporal mismatch in regional myocardial contraction—plays a critical role in the pathophysiology of HF and is associated with adverse ventricular remodeling, impaired hemodynamic efficiency, and worse clinical outcomes.[2,3] Intraventricular and interventricular dyssynchrony have been identified as independent predictors of poor prognosis in patients with HF, particularly those with reduced ejection fraction (HFrEF).[3]

Pharmacologic and device-based strategies targeting dyssynchrony have demonstrated beneficial effects on clinical outcomes. Beta-blockers have been shown to reduce mechanical dyssynchrony in selected patients with dilated cardiomyopathy,[4] while cardiac resynchronization therapy

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(CRT) has become a cornerstone therapy for patients with electrical dyssynchrony and advanced HF.[5,6] Despite these advances, many patients remain symptomatic or ineligible for device therapy, highlighting the need for adjunctive pharmacologic strategies.

Digoxin, a cardiac glycoside, has been used for decades in the management of HF, primarily for rate control in atrial fibrillation and for symptomatic improvement in HFrEF. Its mechanism of action involves inhibition of the Na^+/K^+-ATPase, resulting in increased intracellular calcium and enhanced myocardial contractility. Digoxin also exerts neurohormonal effects, including modulation of sympathetic activity and vagal tone, which may influence myocardial electrical and mechanical function.[7] Digoxin inhibits the Na^+/K^+-ATPase pump, thereby increasing intracellular calcium availability through the $Na^+/Ca2^+$ exchanger. Improved calcium cycling may reduce regional disparities in myocardial contraction, shorten electromechanical delay, and ultimately improve ventricular mechanical synchrony. These effects may also interact with autonomic modulation and with the reversal of electrical remodeling. However, the effect of digoxin on mechanical dyssynchrony has not been systematically evaluated. Given its electrophysiological and hemodynamic effects, we hypothesized that digoxin may reduce mechanical dyssynchrony in patients with non-ischemic HF. Although digoxin has gradually shifted from a first-line therapy to an adjunctive treatment in contemporary HF guidelines because of concerns regarding its narrow therapeutic window and arrhythmogenic potential, low-dose therapy remains recommended for selected patients for symptom control and reduction in hospitalizations for HF. Whether digoxin can improve ventricular mechanical synchrony beyond its established positive inotropic and neurohormonal effects has not been adequately investigated. Demonstrating such an effect could provide additional mechanistic insight into the role of digoxin in selected patients with non-ischemic HF. We hypothesized that low-dose digoxin therapy (0.125-0.25 mg/day), administered within the currently recommended therapeutic range, would improve mechanical synchrony by enhancing intracellular calcium handling and myocardial contractile coordination without increasing the risk of digoxin-related toxicity.

METHODS

This study was designed as a prospective, single-center, randomized controlled trial conducted between August 2016 and March 2017. The study protocol was reviewed and approved by the Local Ethics Committee of Erciyes University (decision no. 2016/381; date: 24 June 2016). All participants provided written informed consent in accordance with the principles of the Declaration of Helsinki.

A total of 312 patients presenting with newly diagnosed HF were screened. Patients were eligible if they were older than 18 years, had non-ischemic dilated cardiomyopathy, were in sinus rhythm, had left ventricular ejection fraction (LVEF) <45%, and had mechanical dyssynchrony documented by tissue Doppler imaging (TDI). All patients were treatment-naïve with respect to HF therapy. Patients were excluded if they had ischemic heart disease (defined as ≥50% stenosis in a major epicardial coronary artery on coronary angiography), significant valvular disease, prior cardiac surgery, prior CRT or permanent pacemaker implantation, or any contraindication to digoxin.

After applying the eligibility criteria, 50 patients were enrolled and randomized to two groups. The control group received guideline-directed medical therapy (GDMT), including angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, beta-blockers, and mineralocorticoid receptor antagonists, as appropriate. The digoxin group received digoxin in addition to GDMT; digoxin was initiated at 0.125 mg/day and titrated up to 0.25 mg/day according to clinical tolerance and renal function.

All patients underwent transthoracic echocardiography at baseline and after three months using standardized protocols. Echocardiographic assessments were performed by two experienced cardiologists blinded to treatment allocation. Left ventricular volumes and LVEF were calculated using the modified Simpson's biplane method. Mechanical dyssynchrony was assessed using pulsed-wave TDI. Intraventricular dyssynchrony was defined as a time difference >60 ms between peak systolic velocities of the basal septal and lateral or posterior segments.[8] Interventricular dyssynchrony was defined as a delay >56 ms between peak systolic velocities of the right ventricular free wall and left ventricular basal segments.[9]

Clinical and echocardiographic parameters, including LV end-diastolic and end-systolic volumes, LVEF, QRS duration, and dyssynchrony indices, were recorded at baseline and follow-up. In addition to within-group comparisons, analysis of covariance (ANCOVA) was performed to compare post-treatment echocardiographic parameters between groups after adjustment for baseline values. The treatment group was entered as the fixed factor, and the baseline measurements were entered as covariates.

Statistical Analysis

Statistical analyses were performed using standard software. Continuous variables are presented as mean ± standard deviation or median (interquartile range), as appropriate. Categorical variables are expressed as counts and percentages. Between-group comparisons were conducted using one-way analysis of variance or the Kruskal-Wallis test; post-hoc analyses were conducted using Tukey's test or the Bonferroni

correction, as applicable. Categorical variables were compared using the chi-square or Fisher's exact test. Correlations were assessed using Pearson or Spearman correlation coefficients. All statistical tests were two-tailed, and a *P*-value < 0.05 was considered significant. Statistical analyses were performed using SPSS software (version 25.0; IBM Corp., Armonk, NY, USA).

RESULTS

A total of 49 patients completed the study (25 in the digoxin group and 24 in the control group), while one patient withdrew from the study after randomization. Baseline demographic, clinical, and echocardiographic characteristics were comparable between the two groups, including age, sex distribution, baseline heart rate, blood pressure, QRS duration, left ventricular volumes, and baseline mechanical dyssynchrony indices. No statistically significant differences were observed between groups baseline LVEF, intraventricular dyssynchrony, interventricular dyssynchrony, or concomitant medical therapies. Detailed baseline demographic, clinical, echocardiographic, and pharmacological characteristics of the study population are presented in Table 1.

At the end of the three-month follow-up period, both groups exhibited reductions in intraventricular dyssynchrony; however, the magnitude of improvement was more pronounced in the digoxin group. Intraventricular dyssynchrony decreased from 76.56±18.35 ms to 63.68±16.94 ms in the digoxin group ($P < 0.001$), representing a clinically and statistically significant improvement. In the control group, intraventricular dyssynchrony decreased from 70.79±14.03 ms to 64.50±13.59 ms ($P = 0.013$). The between-group comparison demonstrated that the digoxin group experienced a significantly greater reduction ($P = 0.044$), suggesting a treatment-specific effect beyond that achieved with standard therapy alone.

Interventricular dyssynchrony followed a similar trend. Patients receiving digoxin demonstrated a significant reduction in interventricular dyssynchrony from 71.84±22.53 ms to 62.32±21.64 ms ($P = 0.002$), whereas the control group showed no significant change (69.50±21.14 ms to 66.63±18.36 ms; $P = 0.324$). This finding indicates that digoxin may exert specific effects on biventricular mechanical coordination, influencing interventricular timing and efficiency.

Left ventricular systolic function improved significantly in the digoxin group. LVEF increased from 36.81%±7.24% to 40.28%±7.85% ($P = 0.006$), whereas no significant change was observed in the control group (39.42%±6.89% to 39.98%±9.19%; $P = 0.577$). This improvement was accompanied by significant reductions in left ventricular end-diastolic volume (LVEDV) and left ventricular end-systolic volume (LVESV) in the digoxin group, consistent with favorable reverse remodeling. No significant volumetric changes were observed in the control group. After adjustment for baseline values using ANCOVA, the beneficial effects of digoxin remained significant. Adjusted post-treatment intraventricular dyssynchrony was significantly lower in the digoxin group than in the control group (adjusted mean difference -6.1 ms, F=4.42, $P = 0.041$). Likewise, interventricular dyssynchrony remained significantly reduced (F=6.31, $P = 0.015$). Adjustment for baseline LVEF confirmed that post-treatment LVEF was significantly higher in the digoxin

Table 1. Baseline demographic, clinical, echocardiographic characteristics and pharmacological therapies

Variable	Digoxin group (n=25)	Control group (n=24)	*P*-value
Age, years	61.2±10.4	60.5±11.2	0.812
Male sex, n (%)	17 (68.0)	16 (66.7)	0.919
Heart rate, bpm	78.4±9.6	77.8±10.1	0.829
Systolic BP, mmHg	118.6±12.4	120.1±11.8	0.665
Diastolic BP, mmHg	74.2±8.1	75.0±7.6	0.731
QRS duration, ms	127.1±15.2	125.8±16.1	0.773
LVEF, %	36.81±7.24	39.42±6.89	0.203
LVEDV, mL	168.4±32.6	165.7±30.8	0.761
LVESV, mL	106.2±25.4	101.8±24.1	0.535
Intraventricular dyssynchrony, ms	76.56±18.35	70.79±14.03	0.211
Interventricular dyssynchrony, ms	71.84±22.53	69.50±21.14	0.716
Beta-blocker therapy, n (%)	21 (84.0)	20 (83.3)	0.946
ACE inhibitor/ARB/ARNI, n (%)	23 (92.0)	22 (91.7)	0.966
Mineralocorticoid receptor antagonist, n (%)	18 (72.0)	17 (70.8)	0.924

Values are presented as mean ± standard deviation or n (%), as appropriate

BP: Blood pressure, LVEF: Left ventricular ejection fraction, LVEDV: Left ventricular end-diastolic volume, LVESV: Left ventricular end-systolic volume, ACE: Angiotensin-converting enzyme, ARB: Angiotensin receptor blocker, ARNI: Angiotensin receptor-neprilysin inhibitor

group (F=7.18, P = 0.010). Similar findings were observed for LVEDV (F=5.27, P = 0.026), LVESV (F=6.94, P = 0.011), and QRS duration (F=10.84, P = 0.002), indicating that the observed treatment effects were independent of baseline differences.

Furthermore, a significant reduction in QRS duration was observed in the digoxin group (from 127.08 ms to 117.96 ms; P < 0.001), while QRS duration remained unchanged in the control group. The temporal changes in mechanical dyssynchrony parameters and left ventricular systolic function during the three-month follow-up period are illustrated in Figure 1. This finding suggests a potential electrophysiological effect of digoxin that may contribute to improved mechanical synchrony. This finding suggests that the reduction in QRS duration may reflect secondary improvements in ventricular geometry, reverse remodeling, and autonomic modulation rather than a direct electrophysiological action.

DISCUSSION

This study provides important insights into the potential role of digoxin in modulating mechanical dyssynchrony in patients with non-ischemic HF. The findings demonstrate that digoxin therapy is associated with significant improvements in both intraventricular and interventricular dyssynchrony, as well as in systolic function, parameters of ventricular remodeling, and electrical conduction. Mechanical dyssynchrony is increasingly recognized as a key determinant of disease progression in HF. It contributes to impaired contractile efficiency, increased wall stress, and progressive ventricular remodeling, all of which are associated with adverse clinical outcomes.[2,3] The prognostic relevance of dyssynchrony has been highlighted in prior studies, which demonstrated that patients with significant mechanical dyssynchrony experience higher rates of hospitalization, ventricular arrhythmias, and mortality.[10,11]

The mechanisms underlying the observed improvements with digoxin are likely multifactorial. Digoxin exerts a positive inotropic effect through inhibition of Na^+/K^+-ATPase, leading to increased intracellular calcium and enhanced myocardial contractility.[7] Improved contractile performance may facilitate more synchronous contraction patterns, thereby reducing temporal dispersion of myocardial shortening. Additionally, digoxin has well-established neurohormonal effects, including attenuation of sympathetic overactivity and enhancement of parasympathetic tone. These autonomic effects may influence myocardial conduction velocity and electromechanical coupling, contributing to improved mechanical synchrony.[11-17]

The significant reduction in QRS duration observed in the digoxin group supports the hypothesis that digoxin may exert favorable effects on electrical conduction pathways. While digoxin is not traditionally considered a primary electrophysiological agent affecting ventricular conduction, its indirect effects on autonomic tone and intracellular calcium handling may promote more coordinated ventricular activation. Improved electrical synchrony may, in turn, translate into improved mechanical synchrony, creating a positive feedback loop that enhances overall cardiac performance.[12-14] The observed reduction in QRS duration following digoxin therapy should not necessarily be interpreted as a direct electrophysiological effect. Instead, improved ventricular synchrony may reflect

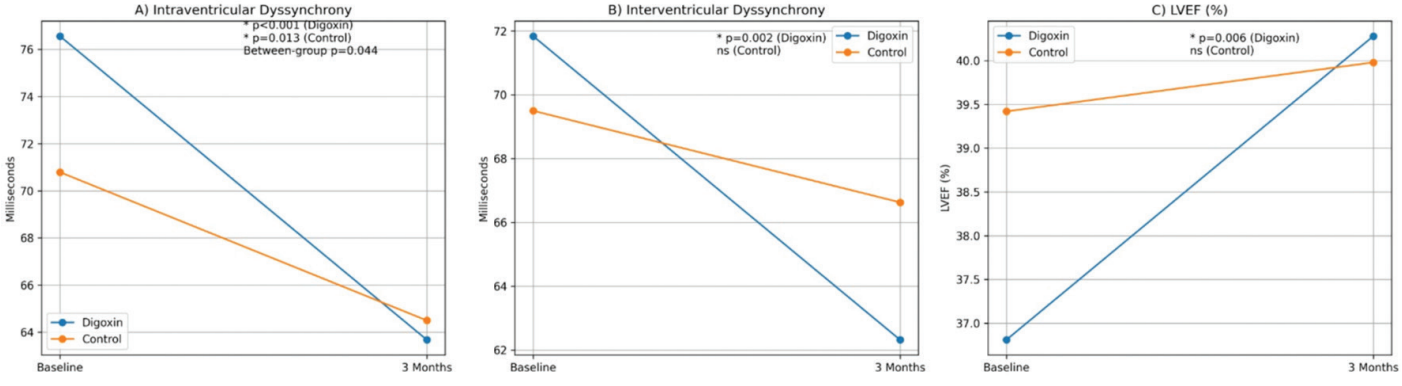

Figure 1. Changes in cardiac mechanical dyssynchrony and systolic function over three months

(A) Intraventricular dyssynchrony significantly decreased in both groups, with a greater reduction observed in the digoxin group (P < 0.001) compared with the control group (P = 0.013); the between-group difference was significant (P = 0.044)

(B) Interventricular dyssynchrony improved significantly only in the digoxin group (P = 0.002), while no significant change was observed in the control group

(C) Left ventricular ejection fraction (LVEF) increased significantly in the digoxin group (P = 0.006) with no significant change in the control group

**: Values are expressed as mean values, asterisks indicate statistical significance, ns: Not significant*

enhanced myocardial contractile coordination, mediated by improved intracellular calcium handling, enhanced autonomic modulation through increased vagal tone, and early reverse ventricular remodeling. These mechanisms may collectively contribute to a reduction in electromechanical delay, although further mechanistic studies are required.

The observed improvements in left ventricular volumes and LVEF suggest that digoxin may also contribute to reverse remodeling. Reverse remodeling is a critical therapeutic goal in HF management, as it is associated with improved functional capacity, reduced hospitalizations, and improved survival. The reduction in LV volumes observed in this study indicates a potential structural benefit associated with digoxin therapy, potentially complementing its functional effects.

Notably, the improvements observed in the digoxin group occurred in the context of GDMT, which included beta-blockers, renin-angiotensin system inhibitors, and mineralocorticoid receptor antagonists. This suggests that digoxin may provide incremental benefit when added to contemporary medical therapy.[11,17] In contrast, patients in the control group, who received guideline-directed therapy alone, demonstrated only modest improvements in mechanical parameters and no significant improvements in systolic function or remodeling indices. According to contemporary ESC and AHA/ACC HF guidelines, digoxin is recommended as an adjunctive therapy in selected patients who remain symptomatic despite optimal GDMT, rather than as a routine first-line treatment. Therefore, the present findings should be interpreted as providing mechanistic support for the use of digoxin in carefully selected patients rather than advocating its broader use.

The clinical implications of these findings are potentially important. While CRT remains the gold standard for patients with electrical dyssynchrony and wide QRS complexes, many patients with mechanical dyssynchrony do not meet criteria for device therapy. Pharmacologic strategies capable of improving mechanical synchrony could therefore have a meaningful impact on patient outcomes. The present findings raise the possibility that digoxin may serve as a useful adjunct in selected patients, particularly those with mechanical dyssynchrony who are not candidates for device-based therapies.

Study Limitations

This study has several limitations. This was a hypothesis-generating pilot trial, and the relatively small sample size limited statistical power and generalizability. First, the study was single-center, with a relatively small sample size and a short, three-month follow-up period, which limited statistical power and long-term generalizability. Second, mechanical dyssynchrony was assessed using TDI rather than speckle-tracking echocardiography; the latter may provide a more comprehensive assessment of myocardial mechanics. Although TDI is a well-established and widely available echocardiographic technique, it has technical limitations, including angle dependence and limited ability to assess global myocardial deformation compared with speckle-tracking echocardiography (STE). STE may provide a more comprehensive evaluation of myocardial deformation and mechanical function by enabling the assessment of strain parameters with less angle dependency. Therefore, in the present study, the absence of STE-based strain analysis may have limited characterization of subtle changes in myocardial mechanics. Prospective studies with larger sample sizes and advanced echocardiographic techniques, including STE, are warranted to further validate and extend our findings. Third, serum digoxin concentrations were not measured; therefore, the relationship between therapeutic drug levels and improvement in mechanical synchrony could not be evaluated. Fourth, echocardiographic measurements were not analyzed in a blinded core laboratory, introducing the possibility of observer bias. Finally, indices of left ventricular filling pressure, such as the E/e' ratio, were not systematically incorporated into the analysis, although they may influence ventricular mechanical delay.

CONCLUSION

This study demonstrates that digoxin therapy is associated with significant improvements in mechanical synchrony, systolic function, ventricular remodeling, and electrical conduction in patients with non-ischemic HF. The observed reductions in intraventricular and interventricular dyssynchrony, combined with improvements in left ventricular performance and QRS duration, suggest that digoxin may exert beneficial effects on both mechanical and electrical aspects of cardiac function.

These findings support a broader therapeutic role for digoxin beyond symptom control and neurohormonal modulation, highlighting its potential as an adjunctive therapy aimed at improving mechanical efficiency and structural remodeling in HF. While the results are promising, larger, multicenter studies with longer follow-up and advanced imaging modalities are required to confirm these findings and to determine their impact on clinical outcomes such as hospitalization rates, functional capacity, and survival.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Local Ethics Committee of Erciyes University (decision no. 2016/381; date: 24 June 2016).

Informed Consent: All participants provided written informed consent in accordance with the principles of the Declaration of Helsinki.

Footnotes

Authorship Contributions

Surgical and Medical Practices: H.O., A.O.B., C.K., Concept: H.O., A.O.B., C.K., Design: H.O., A.O.B., C.K., Data Collection or Processing: H.O., A.O.B., C.K., Analysis or Interpretation: H.O., A.O.B., C.K., Literature Search: H.O., A.O.B., C.K., Writing: H.O., A.O.B., C.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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RESEARCH ARTICLE

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Impact of Transcatheter Aortic Valve Replacement in Cases with Bicuspid Aortic Valve Stenosis Compared with Tricuspid Aortic Valve Stenosis

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Abstract

Background and Aim: Transcatheter aortic valve implantation (TAVI) is a well-established intervention for severe aortic stenosis (AS). The bicuspid aortic valve (BAV) continues to pose a technical challenge because of altered valve geometry, asymmetric calcification, and larger annular dimensions. Objectives to compare the early in-hospital clinical and procedural outcomes of TAVI in patients with bicuspid versus tricuspid aortic valve (TAV) stenosis using new-generation self-expanding Evolut R and Evolut PRO valves. We hypothesized that early in-hospital outcomes would be broadly comparable between the two groups despite the more complex bicuspid anatomy.

Materials and Methods: This prospective observational cohort study enrolled 60 patients with significant symptomatic AS who underwent TAVI and were categorized by valve morphology into a BAV group (n=15) and a TAV group (n=45).

Results: Diabetes mellitus was more prevalent in the TAV group than the BAV group (64.4% vs. 33.3%, $P = 0.035$; odds ratio 0.28, 95% confidence interval 0.08-0.95, favoring a lower prevalence in the BAV group). Annular dimensions, including the minimum, maximum, and mean annular diameters, the derived perimeter, and the annular area, were significantly larger in the BAV group (all $P < 0.05$). Post-procedural conduction abnormalities, complete heart block, atrial fibrillation, aortic regurgitation, and paravalvular leak did not differ significantly between groups. Mean and maximal pressure gradients after TAVI were significantly higher in the BAV group. Early adverse events were infrequent overall, with vascular complications and stroke occurring in 3.3% and 1.7% of the whole cohort, respectively, and did not differ significantly between groups.

Conclusion: TAVI using contemporary self-expanding valves produced early in-hospital outcomes in BAV patients that were statistically comparable to those in TAV patients, despite significantly greater anatomical complexity, thereby supporting the feasibility of TAVI in carefully selected bicuspid patients. These early, hypothesis-generating findings from a two-center cohort warrant confirmation in larger, adequately powered, multicenter studies with longer follow-up.

Keywords: TAVI, bicuspid aortic valve, tricuspid aortic valve, aortic stenosis, Evolut PRO

INTRODUCTION

Transcatheter aortic valve implantation (TAVI) is now a well-established therapeutic option for patients with severe aortic stenosis (AS).[1]

Since its introduction, TAVI has undergone remarkable advancement, with over 300,000 procedures performed and an annual growth rate of approximately 40% reported by 2016.[2]

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Bicuspid aortic valve (BAV) is the most common congenital heart defect in adults, affecting approximately 0.5-2% of the general population, and is closely linked to the development of AS, a condition that often necessitates intervention.[3]

Patients with BAV frequently have enlarged annular dimensions, may show variations in coronary architecture, often have bulky, calcified and irregular aortic valve leaflets, and exhibit altered aortic geometry and haemodynamics. [4]

Multiple randomized trials have shown that transcatheter aortic valve replacement (TAVR) is effective for patients with symptomatic severe AS across surgical-risk categories. Although patients with BAV anatomy were excluded from these trials, the use of TAVR in BAV-associated AS has increased over time, and recent observational studies suggest that outcomes after TAVR are broadly similar in patients with BAV-AS and those with tricuspid aortic valve (TAV) stenosis.[5]

Compared with early-generation devices, TAVI with new-generation valves in BAV patients is associated with better postprocedural results and a lower incidence of paravalvular leak (PVL).[6]

The Valve Academic Research Consortium (VARC)-2 provides standardized definitions for the complications most frequently encountered in this field. Although post-procedural conduction abnormalities may not be the strongest predictor of mortality, they can substantially affect long-term prognosis and quality of life.[6]

This study assessed the early in-hospital clinical impact of the latest-generation self-expanding prostheses, Evolut PRO and Evolut R, in patients with BAV compared with patients with TAV stenosis.

We hypothesized that using these contemporary self-expanding valves, early in-hospital procedural and clinical outcomes of TAVI would be broadly comparable between patients with bicuspid and TAV stenosis, notwithstanding the greater anatomical complexity of the bicuspid valve. This was formulated and tested as a descriptive comparison rather than as formal non-inferiority or superiority hypotheses, as the study was not powered for either.

METHODS

Study Design and Population

This prospective observational cohort study was conducted according to routine clinical practice and did not require ClinicalTrials registration; it included 60 patients who underwent TAVI in the Cardiology Departments of Nasr City Insurance Hospital and Benha University Hospital between April 2024 and April 2025.

Patients presenting to the heart valve team at both centers who met the eligibility criteria below were enrolled prospectively and consecutively; those excluded by the heart valve team for the anatomical or clinical reasons detailed in the eligibility criteria were not entered into the registry. Screening and enrollment followed a standardized clinical pathway through the heart valve team, described above under eligibility criteria. A formal STROBE-style numerical flow diagram was not part of the original data-collection instrument but will be incorporated into the prospective case-report form for future cohorts from this registry.

Ethical Statement

The study received ethical clearance from the Research Ethics Committee of the Faculty of Medicine, Benha University (approval code: M.S 15-2-2024, date: 27.05.2026) and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants after a thorough explanation of the study's nature and objectives.

Eligibility Criteria

Inclusion criteria comprised patients with a clinical indication for TAVI due to symptomatic, severe AS, pathologically defined by constriction of the aortic orifice causing left ventricular outflow obstruction and risk of heart failure.[7] Patient selection followed the European Society of Cardiology (ESC) guidelines, which prioritize TAVI over surgical aortic valve replacement (SAVR) in patients older than 70 years with high-risk features, such as a porcelain aorta, previous chest radiation, or significant comorbidities (e.g., severe pulmonary, hepatic, or renal disease). Exclusion criteria comprised elevated frailty scores, limited life expectancy (<1-2 years), severe irreversible left ventricular systolic dysfunction, or anatomical features favoring SAVR, including complex coronary artery disease, unsuitable annular dimensions, or the need for concomitant myomectomy.

Grouping

Patients were categorized into two groups according to valve morphology: Group A: patients with BAV (n=15); Group B: patients with TAV (n=45).

Study Protocol

The indication for TAVI was established by the heart valve team, in line with current guidelines and technical suitability. Baseline assessment, performed by an experienced TAVI cardiologist, included frailty evaluation (Short Physical Performance Battery), cognitive screening (Mini-Mental State Examination), and nutritional assessment, in collaboration with a geriatric specialist. Patients with major comorbidities,

marked frailty, projected life expectancy of less than 1-2 years, severe cognitive impairment, or anatomical/technical contraindications were not offered TAVI and were excluded from the registry. Demographic, clinical, electrocardiographic, echocardiographic, and multislice CT (MSCT) data were collected prospectively at baseline.

Study Procedure

All patients gave written informed consent and underwent comprehensive history-taking, physical examination, laboratory testing, baseline electrocardiography (ECG), baseline echocardiography, baseline MSCT, and in-hospital monitoring after TAVI. The medical history included the following: age, sex, smoking status, hypertension (HTN), diabetes mellitus (DM), prior cardiac intervention, chronic kidney disease (CKD) or chronic liver disease (CLD), prior cerebrovascular accident, prior coronary artery disease, and AS-related symptoms.

Clinical Definitions and Medical History

The 2024 ESC Guidelines define HTN as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg on repeated measurement.[8] DM was defined per standard glycaemic thresholds: fasting plasma glucose ≥126 mg/dL (7.0 mmol/L), 2-hour oral glucose tolerance test glucose ≥200 mg/dL (11.1 mmol/L), HbA1c ≥6.5%, or random plasma glucose ≥200 mg/dL with classic symptoms.[9]

Particular attention was paid to AS-related symptoms, including chest tightness, signs of heart failure, and syncope. Clinical assessment included measurement of pulse and blood pressure, cardiopulmonary auscultation for signs of pulmonary venous congestion, and functional classification according to the New York Heart Association system. Cardiac auscultation was performed to assess murmurs (e.g., ejection systolic murmur) and additional heart sounds (e.g., fourth heart sound). Laboratory testing included complete blood count, serum urea, and serum creatinine.

Baseline ECG and Echocardiography

A standard 12-lead ECG was obtained for every patient before the procedure to assess baseline rhythm and conduction (PR interval, QRS duration).

Transthoracic echocardiography was performed before and during TAVI using a Vivid Ultra Edition ultrasound system with an M5Sc-D matrix probe and simultaneous ECG recording. In accordance with the 2021 ESC/EACTS Guidelines for valvular heart disease, patients were assessed using two-dimensional and color Doppler echocardiography in the left lateral decubitus position. Ejection fraction was measured by M-mode (parasternal long-axis view) and Simpson's method (apical four-chamber view). Left ventricular mass, left atrial diameter, aortic root diameter, and septal and posterior wall thicknesses (PWT) were also recorded. Diastolic function was assessed using E/e' and E/A ratios. Additional measurements included left ventricular end-diastolic and end-systolic dimensions, mean and peak transaortic pressure gradients, maximum transaortic velocity, stroke volume, and aortic valve area.

Aortic valve area was derived using the continuity equation. The left ventricular outflow tract (LVOT) diameter was measured at the aortic annulus in mid-systole. Pulsed-wave Doppler in the LVOT provided the velocity-time integral (VTI), peak velocity, and stroke volume (LVOT-VTI×LVOT area). Continuous-wave Doppler across the aortic valve was used to determine peak aortic jet velocity, peak and mean pressure gradients, and aortic valve area.

Baseline Multislice Computed Tomography

A baseline MSCT was performed before the procedure. This study used 320-slice MSCT technology, which provides accurate whole-heart coverage in a single rotation and is advantageous for functional and perfusion imaging. Dual-source CT, which uses two X-ray tubes and detectors aligned at 90 degrees, can further improve temporal resolution, particularly at higher heart rates.

Patient Preparation for MSCT

Before coronary/cardiac CT angiography, the procedure, potential risks, and the need to comply with breath-holding instructions were explained, and informed consent was obtained. Contraindications assessed included iodinated-contrast allergy, renal failure, pregnancy, and severe arrhythmia. Patients fasted for 4-6 hours before scanning, with permission to ingest small amounts of water, to reduce the risk of aspiration and to improve image quality.

A target heart rate of ≤60 beats per minute was sought using oral or intravenous metoprolol where not contraindicated (e.g., by asthma, high-grade atrioventricular block, or hypotension), with ivabradine as an alternative when beta-blockers were unsuitable. Sublingual nitroglycerin 0.4 mg was commonly administered before scanning to improve coronary visualization, unless contraindicated by hypotension, severe AS, allergy, or recent phosphodiesterase-5-inhibitor use. An 18-20G intravenous cannula was placed in the antecubital vein for high-flow contrast injection (typically 80-100 mL at 4-6 mL/s), and a saline flush was then administered to reduce artifacts. During acquisition, patients avoided speaking, moving, or swallowing and held their breath for 8-12 seconds. Renal function (serum creatinine, estimated glomerular filtration rate) was checked before contrast administration; patients with thyroid disease had thyroid function assessed, and metformin was withheld on the day of the scan and for 48 hours afterward

in patients with renal impairment, per ESC/European Society of Radiology guidance.[10]

MSCT Measurements and Anatomical Assessment

Aortic annular mean diameter, perimeter, and area were measured using MSCT. On modified coronal views, the heights of the left main and right coronary ostia and the length of the membranous septum were measured. The aortic valvular complex was characterized by leaflet-sector involvement, and the extent of basal septal and aortic-valve calcification was graded using a threshold of 850 Hounsfield units.

Aortic valve calcification was graded II-IV in this cohort. Sievers classification, raphe-specific calcification, calcium-asymmetry scoring, and eccentricity index were beyond the scope of the anatomical protocol used for this registry and are identified below as priorities for the prospective, dedicated bicuspid-imaging protocol now being implemented at our center.

Procedural Characteristics

Valve size was selected according to manufacturer-recommended annular sizing charts; balloon pre-dilatation and post-dilatation were performed at the operator's discretion, and final implantation depth was confirmed by fluoroscopy and transthoracic echocardiography prior to closure. Formal quantitative summaries of prosthesis oversizing, implantation depth, fluoroscopy time, contrast volume, total procedural duration, valve-repositioning frequency, cerebral embolic protection use, and vascular closure technique are being compiled for a dedicated analysis of procedural characteristics and are not included as a separate results table in the present manuscript, which was designed and powered to compare early clinical and anatomical outcomes rather than procedural technique. This scope is clarified in the Study Limitations section.

In-hospital Follow-up and Outcomes

After TAVI, patients were monitored in the hospital to assess early post-procedural and procedure-related outcomes, focusing on conduction abnormalities, PVL, and the post-procedural mean pressure gradient across the implanted valve.

The primary endpoint was the composite incidence of early (in-hospital) VARC-2-defined procedure-related adverse events, comprising permanent pacemaker implantation (PPI) for high-grade conduction disturbance, moderate-or-greater PVL, major vascular complication, stroke, and death. Secondary endpoints were the individual components of this composite, together with the post-procedural mean and peak transvalvular pressure gradients. The safety and efficacy of TAVI in BAV stenosis relative to TAV stenosis, as assessed against these endpoints, were the study's primary objectives.

Sample Size Calculation

The minimum required sample size was estimated using Cochran's formula, informed by the methodology of Nanjundeswaraswamy and Divakar,[11] to characterize the expected prevalence of BAV among patients undergoing TAVI for severe AS. In this calculation, Z is the z-score for the selected confidence level (1.96 for 95% confidence), P is the estimated population proportion (0.151, based on prior reported BAV prevalence among TAVI recipients[8]), and E is the margin of error (0.05).

This calculation estimates the sample size required to characterize a population prevalence and is not, by itself, a power calculation for the subsequent between-group (BAV vs. TAV) outcome comparisons reported in Results; no dedicated effect size, expected event rate, alpha, or power specific to those comparisons were pre-specified. This is acknowledged as a limitation, and the resulting BAV subgroup (n=15) should be understood as prevalence-driven rather than power-driven, which materially limits the ability to detect true between-group differences and increases the risk of Type II error.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics for Windows (version 27.0; IBM Corp., Armonk, NY, USA). Continuous variables are reported as mean ± standard deviation (SD) and range; categorical variables as frequencies and percentages. Normality of continuous data was assessed using the one-sample Kolmogorov-Smirnov test.

The Kolmogorov-Smirnov test has reduced power to detect departures from normality in small samples, such as the 15-patient BAV group, and the Shapiro-Wilk test would have been more appropriate for this subgroup. This is noted as a methodological limitation of the original analysis, and Shapiro-Wilk testing is recommended for future adequately powered analyses of this cohort.

Categorical variables were compared using the chi-square test or Fisher's exact test when expected cell counts were below 5. Normally distributed continuous variables were compared between the two independent groups using the independent-samples t-test. Statistical significance was defined as $P < 0.05$, and results were reported with a 95% confidence interval (CI) and a 5% margin of error.

Group comparisons were performed using univariate methods appropriate to this cohort size. Multivariable adjustment (e.g., logistic regression, propensity-score matching, or inverse-probability weighting) was carefully considered and deliberately not pursued: the limited number of events for several outcomes (e.g., stroke, n=1; vascular complications, n=2; moderate PVL,

n=1) relative to the number of candidate covariates would not support stable, generalizable model estimates, and an unstable adjusted model was judged less informative—and potentially misleading—than the transparent unadjusted comparisons reported here. The prevalence of DM and several annular dimensions differed significantly between groups at baseline and were identified as potential confounders to be considered when interpreting the univariate findings. No correction for multiple testing was applied across the comparisons performed, and *P*-values are, accordingly, best interpreted as hypothesis-generating, consistent with the exploratory intent of this early comparative cohort.

RESULTS

Patients were categorized by aortic valve morphology into two groups: Group A, 15 patients with BAV; and Group B, 45 patients with TAV.

There were no statistically significant differences between the two groups in gender distribution and age ($P = 0.283$ and 0.213, respectively), nor in weight, height, or BMI ($P = 0.087$, 0.585 and 0.208, respectively). DM was significantly more prevalent in Group B (29/45, 64.4%) than in Group A (5/15, 33.3%; $P = 0.035$). Groups did not differ significantly in the proportion of smokers or in the prevalence of HTN, chronic coronary syndrome, CKD, prior cerebrovascular/cardiovascular disease, or CLD (all $P > 0.05$), nor in other clinical or laboratory parameters ($P > 0.05$; Table 1).

Regarding pre-TAVI ECG findings, there were no significant between-group differences in atrial fibrillation, QRS morphology, or the proportion of patients with prolonged QRS ($P = 0.619$, 0.080, and 0.230, respectively). On pre-TAVI echocardiography, Group A had a significantly greater mean PWT than Group B (13.53±1.41 mm vs. 12.27±1.84 mm; $P = 0.018$; mean difference 1.26 mm, 95% CI 0.22-2.30 mm), with no significant between-group difference in other echocardiographic parameters ($P > 0.05$; Table 2).

On CT aortography, the minimum annular diameter, maximum annular diameter, derived perimeter, mean annular diameter and annular area were all significantly greater in Group A than Group B (minimum diameter 22.29±2.45 vs. 20.55±2.41 mm, $P = 0.019$; maximum diameter 28.45±2.99 vs. 26.83±2.35 mm, $P = 0.035$; perimeter 24.8±2.6 vs. 23.38±1.97 mm, $P = 0.029$; mean diameter 25.51±2.46 vs. 23.8 ± 2.02 mm, $P = 0.011$; area 533.1±35.3 vs. 473.8±54.3 mm^2, $P < 0.001$). There were no significant between-group differences in left main and right coronary ostial heights ($P = 0.235$ and 0.572, respectively; Table 3).

No statistically significant between-group differences were observed in the incidence of early in-hospital adverse events after the procedure ($P > 0.05$; Table 4).

The occurrence of post-TAVI PVL did not differ significantly between patients receiving Evolut R and those receiving Evolut PRO ($P = 0.509$; Table 5).

Table 1. Comparison between Group A (bicuspid aortic valve) and Group B (tricuspid aortic valve) regarding baseline demographic and clinical characteristics

Variable		Group A (BAV), n=15	Group B (TAV), n=45	Test value	*P*-value	Sig.
Gender	Male	11 (73.3%)	26 (57.8%)	1.152*	0.283	NS
	Female	4 (26.7%)	19 (42.2%)			
Age (years)	Mean ± SD	73.47±4.12	75.22±4.84	-1.260•	0.213	NS
Weight (kg)	Mean ± SD	83.27±11.09	77.42±11.29	1.744•	0.087	NS
Height (cm)	Mean ± SD	168.93±8.71	167.49±8.85	0.549•	0.585	NS
BMI (kg/m^2)	Mean ± SD	29.14±4.67	27.59±3.86	1.272•	0.208	NS
Smoking	Yes	7 (46.7%)	10 (22.2%)	3.311*	0.069	NS
Diabetes mellitus	Yes	5 (33.3%)	29 (64.4%)	4.434*	0.035	S
Hypertension	Yes	10 (66.7%)	38 (84.4%)	2.222*	0.136	NS
CCS	Yes	7 (46.7%)	26 (57.8%)	0.561*	0.454	NS
CKD	Yes	1 (6.7%)	7 (15.6%)	0.769*	0.380	NS
Prior CVS event	Yes	0 (0%)	3 (6.7%)	1.053*	0.305	NS
CLD	Yes	3 (20%)	5 (11.1%)	0.769*	0.380	NS
NYHA class III-IV	Yes	11 (73.3%)	35 (77.8%)	1.788*	0.617	NS

*: Chi-square test; •: Independent-samples t-test, BAV: Bicuspid aortic valve, TAV: Tricuspid aortic valve, NS: Not significant ($P > 0.05$); S: Significant ($P < 0.05$), SD: Standard deviation, CCS: Chronic coronary syndrome, CKD: Chronic kidney disease, CVS: Cerebrovascular, CLD: Chronic liver disease, NYHA: New York Heart Association

Table 2. Comparison between Group A and Group B regarding pre-TAVI electrocardiographic and echocardiographic parameters

Variable		Group A (BAV), n=15	Group B (TAV), n=45	Test value	*P*-value	Sig.
Prolonged QRS	Yes	2 (13.3%)	4 (8.9%)	0.247*	0.619	NS
QRS morphology	Normal	12 (80%)	40 (88.9%)	6.769*	0.080	NS
Atrial fibrillation (pre-TAVI)	Yes	4 (26.7%)	6 (13.3%)	1.440*	0.230	NS
Ejection fraction (%)	Mean ± SD	61.80±9.63	62.51±9.72	-0.246•	0.807	NS
SWT (mm)	Mean ± SD	13.67±1.76	12.84±1.78	1.552•	0.126	NS
PWT (mm)	Mean ± SD	13.53±1.41	12.27±1.84	2.435•	0.018	S
LVEDD (mm)	Mean ± SD	50.13±6.57	50.93±8.02	-0.349•	0.729	NS
LVESD (mm)	Mean ± SD	33.40±7.15	33.44±7.45	-0.020•	0.984	NS
PPG (mmHg)	Mean ± SD	90.27±18.76	81.04±19.48	1.602•	0.115	NS
MPG (mmHg)	Mean ± SD	56.93±8.05	50.44±13.01	1.813•	0.075	NS
Aortic valve area (cm^2)	Mean ± SD	0.69±0.09	0.74±0.13	-1.197•	0.236	NS
Significant AR	Yes	6 (40%)	11 (24.4%)	1.341*	0.247	NS

*: Chi-square test; •: Independent-samples t-test, BAV: Bicuspid aortic valve, TAV: Tricuspid aortic valve, NS: Not significant, S: Significant, TAVI: Transcatheter aortic valve implantation, SWT/PWT: Septal/posterior wall thickness, LVEDD/LVESD: Left ventricular end-diastolic/systolic dimension, SD: Standard deviation, PPG/MPG: Peak/mean pressure gradient, AR: Aortic regurgitation

Table 3. Comparison between Group A and Group B regarding CT aortographic (annular) parameters

Variable	Group A (BAV), n=15	Group B (TAV), n=45	Test value	*P*-value	Sig.
Minimum annular diameter (mm)	22.29±2.45	20.55±2.41	2.412•	0.019	S
Maximum annular diameter (mm)	28.45±2.99	26.83±2.35	2.158•	0.035	S
Annular derived perimeter (mm)	24.80±2.60	23.38±1.97	2.235•	0.029	S
Mean annular diameter (mm)	25.51±2.46	23.80±2.02	2.615•	0.011	S
Aortic annular area (mm^2)	533.07±35.31	473.79±54.31	3.946•	<0.001	HS
Aortic valve calcification grade II-IV	Predominantly III-IV	Predominantly II-III	-	-	-
LMCA height (mm)	14.27±4.68	13.14±2.48	1.201•	0.235	NS
RCA height (mm)	16.19±2.51	15.71±2.91	0.568•	0.572	NS

•: Independent-samples t-test, CT: Computed tomography, BAV: Bicuspid aortic valve, TAV: Tricuspid aortic valve, NS: Not significant; S: Significant, HS: Highly significant ($P < 0.01$), LMCA/RCA: Left main/right coronary artery

Sievers classification, raphe status, calcium-asymmetry and eccentricity index were not systematically recorded for this cohort (see Limitations)

Table 4. Comparison between Group A and Group B regarding early in-hospital adverse events after TAVI

Variable		Group A (BAV), n=15	Group B (TAV), n=45	Test value	*P*-value	Sig.
Conduction abnormality	Any	6 (40%)	11 (24.4%)	3.795*	0.285	NS
	CHB	2 (13.3%)	3 (6.7%)			
Permanent pacemaker	Yes	2 (13.3%)	4 (8.9%)	0.247*	0.619	NS
Paravalvular leak	Any	2 (13.3%)	3 (6.7%)	1.721*	0.423	NS
Vascular complication	Yes	0 (0%)	2 (4.4%)	0.690*	0.406	NS
Hb drop	Yes	0 (0%)	2 (4.4%)	0.690*	0.406	NS
Renal impairment	Yes	0 (0%)	2 (4.4%)	0.690*	0.406	NS
Stroke	Yes	0 (0%)	1 (2.2%)	0.339*	0.560	NS
Death (in-hospital)	Yes	0 (0%)	0 (0%)	-	-	-

*: Chi-square/Fisher's exact test as appropriate, BAV: Bicuspid aortic valve, TAV: Tricuspid aortic valve, NS: Not significant, CHB: Complete heart block, TAVI: Transcatheter aortic valve implantation

Table 5. Comparison between Evolut R and Evolut PRO regarding incidence of paravalvular leak					
	Evolut R, n=40	**Evolut PRO, n=20**	**Test value**	***P*-value**	**Sig.**
Paravalvular leak, no	36 (90.0%)	19 (95.0%)	0.436*	0.509	NS
Paravalvular leak, yes	4 (10.0%)	1 (5.0%)			
*: Chi-square test, NS: Not significant ($P > 0.05$)					

Effect Sizes for the Principal Significant Comparisons

To supplement the *P*-values above, mean differences (for continuous variables) and an odds ratio (for DM prevalence) with 95% CIs were derived from the reported group means, SDs, group sizes, and test statistics, assuming the pooled-variance independent t-test that was used for the original comparisons: PWT, mean difference 1.26 mm (95% CI 0.22-2.30); minimum annular diameter, 1.74 mm (0.30-3.18); maximum annular diameter, 1.62 mm (0.12-3.12); annular derived perimeter, 1.42 mm (0.15-2.69); mean annular diameter, 1.71 mm (0.40-3.02); annular area, 59.3 mm^2 (29.2-89.4); and DM, odds ratio 0.28 (95% CI 0.08-0.95) for Group A relative to Group B (equivalently, a risk difference of -31.1%, 95% CI -58.8% to -3.5%). All CIs exclude the null value, consistent with the $P < 0.05$ findings reported above. However, the intervals are wide, reflecting the small BAV sample.

DISCUSSION

After the procedure and during the hospital stay, most patients maintained normal conduction; conduction abnormalities included right bundle branch block, left bundle branch block (LBBB), intraventricular conduction delay, and complete heart block (CHB) at rates consistent with prior reports. These findings are broadly in line with Zaid et al.,[12] who reported new-onset LBBB rates of 20.6% and 17.8% after Evolut R and Evolut PRO implantation, respectively, and with Forrest et al.,[8] who reported 30-day PPI rates of 19.6% and 17.1% for Evolut R and Evolut PRO, respectively.

CHB occurred in 5 patients (8.3%) in our cohort, consistent with Al-Ogaili et al.,[13] who reported CHB in 10.4% of 35,500 TAVR procedures, with a significant increase in incidence from 8.4% to 11.8% between 2012 and 2014.

CHB did not differ significantly between BAV and TAV patients in our study (13.3% vs. 6.7%, respectively; Table 4). PPI was required in 6 patients overall (10.0%), comparable to rates reported in the PARTNER trial.[14] Prior studies suggest pacemaker implantation after TAVI may be more frequent in BAV patients, with large series reporting rates of 17-29%;[15] however, direct comparisons with TAV patients are limited, and many earlier reports used older-generation devices, complicating interpretation.[16] The non-significant difference observed here may reflect the small sample size and the use of newer-generation self-expanding prostheses.

Most patients had no postoperative PVL (91.7% no leak, 6.7% mild PVL, and 1.7% moderate PVL). Reported PVL rates after TAVI vary widely (7-40%), depending on imaging modality, timing, and grading method.[1] Earlier observational studies reported moderate-or-greater PVL in 10-25% of patients, and randomized trials reported approximately 12%; this variability largely reflects the absence of uniform grading in earlier work. Contemporary studies more commonly apply VARC-2 criteria, which grade PVL by the circumferential extent of the regurgitant jet.[17]

The low rate of moderate PVL observed here is consistent with Popma et al.[18] The mild-PVL rate in our cohort was lower than reported elsewhere (29% with balloon-expandable and 36% with self-expanding valves at 30 days),[19] which may reflect differences in assessment timing, valve type, grading method, and patient operative risk.

PVL did not differ significantly between BAV and TAV patients in our cohort (13.3% vs. 6.7%, respectively), in contrast to Montalto et al.,[20] who reported a higher risk of moderate-to-severe PVL in BAV patients, and to Yoon et al.,[4] who found comparable two-year mortality between BAV and TAV patients but lower procedural success and more frequent moderate-or-greater PVL in the bicuspid group. This difference may be related to our small sample size, a low overall PVL burden, and the use of newer-generation valves.

Aortic regurgitation (AR) was absent in 83.3% of patients, mild in 13.3%, and moderate in 3.3%; no cases of severe AR were observed. These findings are consistent with Popma et al.[18] (moderate AR in 3.5%) and with the European Sentinel Registry (grade 2 AR in 7.7%, grade 3 in 1.3%, among >4,500 patients);[21] the lower AR rate in our study may relate to differences in sample size, valve type and procedural approach—Di Mario et al.[21] included both SAPIEN XT/CoreValve prostheses and transapical/transfemoral approaches, whereas our study used only the transfemoral route.

Vascular adverse events occurred in 3.3% of patients, consistent with contemporary reports of ≈4% or less,[1,18] and markedly lower than the PARTNER trial's reported rate of major (15.3%) and minor (11.9%) vascular events.[17] This likely reflects advances in delivery-system profiles, improved vascular closure devices (e.g., Perclose ProGlide), and growing operator experience.

Stroke occurred in 1 patient (1.7%), consistent with Eggebrecht et al.[22] (mean 30-day stroke/TIA rate 3.3±1.8%, range 0-6%) and Okuno et al.[23] (30-day stroke incidence 3.0% in 11,957 patients, with most events within the first 48 hours).

Overall, early in-hospital adverse events did not differ significantly between groups ($P > 0.05$), consistent with Gasecka et al.,[24] who found similar device success, in-hospital and long-term mortality, procedural adverse events, and moderate-to-severe PVL at discharge in propensity-matched BAV and TAV cohorts, albeit with a non-significant trend toward more stroke in BAV patients. Similarly, contemporary-technology studies report comparable procedural and one-year outcomes between BAV and TAV patients, supporting TAVI as a viable option for selected BAV patients.[24,25]

PVL did not differ significantly between Evolut R and Evolut PRO ($P = 0.509$), though it was numerically lower with Evolut PRO (2.5% vs. 10.0%), consistent with Gozdek et al.,[26] who reported a 35% relative reduction in moderate-to-severe PVL with Evolut PRO, and with Bhogal et al.,[27] who found comparable moderate-PVL rates between the two devices at 1 year. Although not statistically significant here, this numerical trend is plausibly attributable to the external pericardial sealing skirt, which is unique to Evolut PRO and designed to reduce paravalvular flow at the frame-annulus interface.

Mechanistic Considerations

The larger, more elliptical bicuspid annulus and its typically greater and asymmetric calcium burden are likely to underlie several of the differences observed between groups. Asymmetric leaflet calcification can cause uneven frame expansion of a self-expanding nitinol stent, producing an oval rather than a circular final frame geometry; this incomplete circularization is a recognized mechanism for residual paravalvular regurgitation and elevated post-implant gradients, consistent with the higher mean and peak gradients seen in the BAV group in this study. Calcium located near the membranous septum and the LVOT can mechanically compress the conduction axis during frame expansion, which is a plausible contributor to new conduction disturbances and the need for permanent pacing, independent of implantation depth. The pericardial outer wrap, incorporated into the Evolut PRO platform, is designed to fill the irregular space between an asymmetric calcified annulus and the valve frame; this provides a mechanistic rationale for the numerically—if not statistically—lower PVL rate observed with Evolut PRO in this cohort. These mechanisms are discussed in greater detail in recent bicuspid-specific TAVI reviews and registries.[3,4,20]

Study Limitations

This study provides early, real-world comparative data from a two-center cohort on contemporary self-expanding TAVI in bicuspid and tricuspid anatomy; several methodological considerations should inform the interpretation and extension of these findings.

Sample size and power: The BAV group comprised only 15 patients, substantially limiting statistical power for most comparisons and increasing the risk of Type II error. Non-significant results should not be interpreted as evidence of equivalence between groups.

Design: This was a single-center (two affiliated hospitals within one study team), non-randomized, observational cohort study. Selection bias related to heart valve team decision-making cannot be excluded, and no independent, blinded adjudication of clinical events was performed.

Confounding and adjustment: The prevalence of DM and several annular dimensions differed significantly between groups at baseline. No multivariable adjustment, propensity-score matching, inverse-probability weighting, or sensitivity analysis were performed because the small BAV group and low event counts for several outcomes made such modeling statistically unreliable; residual confounding cannot be excluded, and the reported associations should be interpreted as unadjusted and hypothesis-generating.

Statistical methodology: The Kolmogorov-Smirnov test, rather than the more appropriate Shapiro-Wilk test, was used to assess normality in a small subgroup; no correction was applied to account for the large number of statistical comparisons performed, increasing the risk of false-positive findings. Although 95% CIs and effect sizes for the principal significant comparisons have now been added (see Results), these were derived post hoc from reported summary statistics rather than from a re-analysis of the original patient-level dataset with these estimates pre-specified.

Sample size calculation: The reported calculation estimated the sample size needed to characterize BAV prevalence rather than to power the between-group comparisons that were ultimately performed (see Sample Size Calculation).

Follow-up outcomes were assessed only during the index hospital stay. Clinically important endpoints—30-day, 6-month, and 1-year mortality, valve durability, structural valve deterioration, rehospitalization, and late pacemaker dependency—could not be evaluated and therefore require dedicated longer-term follow-up.

Anatomical and procedural detail: Annular sizing was not standardized across operators; a formal Sievers classification, raphe-specific calcification, calcium-asymmetry scoring and eccentricity index were not systematically recorded; and fluoroscopy time, contrast volume, total procedural duration, valve-repositioning frequency, cerebral embolic protection use, vascular closure technique, and individual operator case-volume were not available in the dataset used for this analysis.

Operator-dependent decisions—valve and device selection, sizing, and implantation strategy—were based on individual operator discretion rather than on a standardized, pre-specified protocol, which may have introduced variability not captured by the recorded covariates.

CONCLUSION

This study contributes early, prospectively collected comparative data on TAVI with contemporary self-expanding valves (Evolut R/PRO) in patients with bicuspid versus tricuspid AS, a clinical scenario for which comparative evidence using new-generation devices remains limited. Early in-hospital clinical and safety outcomes in patients with bicuspid anatomy were statistically similar to those in patients with tricuspid valves, despite significantly larger and more complex annular dimensions in the bicuspid group, which supports the feasibility of TAVI in carefully selected bicuspid patients when procedures are guided by detailed pre-procedural imaging and individualized device selection. TAVI in tricuspid anatomy remains the benchmark for procedural predictability, given its more symmetrical anatomy; the bicuspid findings reported here should be regarded as hypothesis-generating rather than confirmatory, a status that reflects the single-center design and modest bicuspid sample size inherent to this still-evolving area of practice. These results support the rationale for conducting larger, multicenter, adequately powered studies that incorporate standardized bicuspid anatomical characterization (including Sievers classification) and mid- to long-term follow-up to confirm and extend the encouraging early signal observed in this cohort.

Ethics

Ethics Committee Approval: The study received ethical clearance from the Research Ethics Committee of the Faculty of Medicine, Benha University (approval code: M.S 15-2-2024, date: 27.05.2026) and was conducted in accordance with the Declaration of Helsinki.

Informed Consent: Written informed consent was obtained from all participants after a thorough explanation of the study's nature and objectives.

Footnotes

Authorship Contributions

Surgical and Medical Practices: H.I.A., O.S.A., M.S.A.E., Concept: M.A.H., H.I.H., Design: M.A.H., H.I.H., Data Collection or Processing: H.I.A., O.S.A., Analysis or Interpretation: M.S.A.E., H.I.H., Literature Search: M.A.H., Writing: H.I.A., M.S.A.E., O.S.A.

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CASE REPORT

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Primary Brock Procedure for Pulmonary Atresia with Intact Ventricular Septum in a Neonate: A Case Report from a Resource-limited Cardiac Center

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Abstract

Pulmonary atresia with intact ventricular septum (PA-IVS) is a rare cyanotic congenital heart disease characterized by unstable neonatal physiology and considerable perioperative complexity. We report the case of an 8-day-old male neonate with PA-IVS who presented with fluctuating oxygen saturation despite receiving prostaglandin E1 infusion. Alternative strategies include transcatheter pulmonary valvuloplasty and a systemic-to-pulmonary shunt. However, primary surgical pulmonary valvotomy was selected in this case, given the favorable right ventricular (RV) growth potential and the physiological imperative to establish antegrade pulmonary blood flow while avoiding shunt-dependent circulation. Perioperative management emphasized preserving RV preload, maintaining systemic vascular resistance, and maintaining balanced pulmonary-to-systemic blood flow. Intraoperative reassessment supported the chosen surgical strategy. The patient achieved sustained hemodynamic stability and progressive improvement in oxygenation throughout the postoperative period. This case underscores the critical role of multidisciplinary decision-making in determining the optimal palliation strategy for PA-IVS, particularly in centers with limited access to advanced congenital cardiac services.

Keywords: Pulmonary atresia with intact ventricular septum, Brock procedure, duct-dependent circulation, perioperative management, resource-limited setting

INTRODUCTION

Pulmonary atresia with intact ventricular septum (PA-IVS) is a rare cyanotic congenital heart defect characterized by right ventricular (RV) outflow tract obstruction, with survival dependent on preserved RV function and a balanced pulmonary-to-systemic blood flow ratio (Qp:Qs).[1,2]

Early palliation is required to maintain pulmonary perfusion. Contemporary management options include transcatheter valvuloplasty or a modified Blalock-Taussig (BT) shunt. In selected neonates with favorable RV morphology, surgical valvotomy using the Brock procedure may restore antegrade flow without cardiopulmonary bypass (CPB).[3] This report describes the perioperative management of a neonate with PA-IVS undergoing the Brock procedure at a center with limited resources.

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CASE REPORT

An 8-day-old male neonate with a birth weight of 2600 g, born at 35-36 weeks of gestation (Apgar 7/8), was referred for early respiratory distress and persistent hypoxemia. Initial management included continuous positive airway pressure (CPAP).

Physical examination revealed peripheral cyanosis. Respiratory rate was 45-55 breaths/min, oxygen saturation fluctuated between 50-85%, and there was a significant pre- and post-ductal gradient (64% vs. 51%). Heart rate was 135-145 beats/min, S1S2 were normal, and a cardiac murmur was present.

Arterial blood gas showed severe hypoxemia with mild metabolic acidosis (pH 7.31, PaO_2 31 mmHg, HCO_3 18.6 mmol/L). Given the marked desaturation and a ductal gradient, a duct-dependent congenital heart defect was suspected. Echocardiography identified PA-IVS, a 6-7 mm secundum atrial septal defect (ASD) with bidirectional shunt, patent ductus arteriosus (PDA), along with hypoplastic pulmonary arteries, and moderate tricuspid regurgitation. Further assessment demonstrated a tripartite RV with preserved inlet, trabecular, and outlet components; the ventricles appeared relatively balanced, without severe RV hypoplasia. The tricuspid annulus measured approximately 13 mm, which is within the normal range for age. Although a formal tricuspid valve Z-score was not available, the echocardiographic findings supported the feasibility of a biventricular repair pathway. The absence of a Z-score is acknowledged as a limitation of this assessment (Figure 1). The neonate was admitted to the neonatal intensive care unit (NICU) and was started on a prostaglandin E1 (PGE1) infusion to maintain ductal patency.

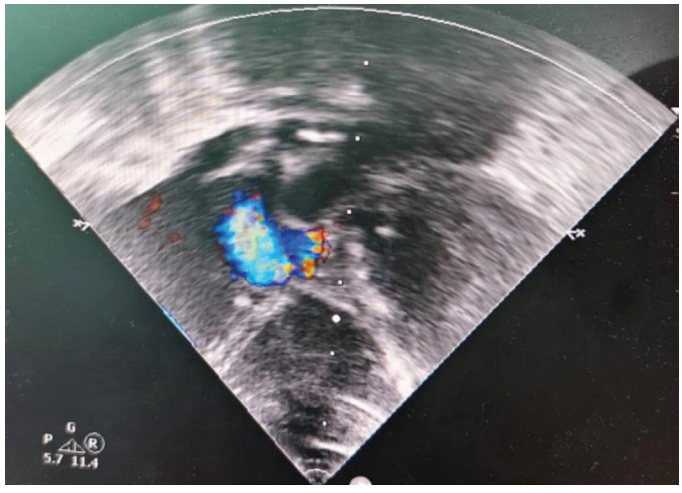

Figure 1. Preoperative echocardiography demonstrating pulmonary atresia with intact ventricular septum, secundum atrial septal defect with bidirectional shunt, patent ductus arteriosus, hypoplastic pulmonary arteries, right-sided chamber dilation with moderate tricuspid regurgitation and preserved left ventricular systolic function

Urgent surgical palliation was planned because persistently unstable oxygenation despite PGE1 infusion and non-invasive respiratory support indicated duct-dependent pulmonary blood flow. The patient was classified as ASA physical status IV; informed consent was obtained, and standard preoperative fasting was followed.

Preoperatively, the patient remained on CPAP under continuous monitoring and received premedication with intravenous atropine sulfate 0.1 mg and fentanyl 10 mcg. General anesthesia was induced with an additional 10 mcg of fentanyl and 1 mg of atracurium, and was maintained with inhaled oxygen and sevoflurane at approximately 1%. An opioid-based technique was used to maintain hemodynamic stability, with invasive arterial and central venous monitoring. Mean arterial pressure was maintained between 45-55 mmHg with a stable heart rate; central venous pressure ranged from 8 to 10 mmHg. Pressure-controlled ventilation, aimed at maintaining normocapnia with an FiO_2 of 40-50% and positive end-expiratory pressure of 4 cmH_2O, ensures balanced Qp:Qs and stable SVR while avoiding excessive drops in pulmonary vascular resistance (PVR).

The surgical procedure was performed via median sternotomy without CPB. Intraoperative observations revealed hypoplastic branch pulmonary arteries and a diminutive main pulmonary artery. A Brock procedure, which included commissurotomy and dilation of fused valve leaflets, was performed. A purse-string suture was placed near the pulmonary annulus, and transventricular perforation of the atretic pulmonary valve was then performed using a 14-gauge catheter. Subsequent dilation using a 5 mm Hegar dilator restored antegrade flow across the RV outflow tract. After restoration of antegrade pulmonary flow, oxygen saturation improved to approximately 80% at FiO_2 of 50%. Blood loss was minimal. The patient was transferred to the NICU, mechanically ventilated and receiving a dobutamine infusion (10 mcg/kg/min).

The postoperative course was hemodynamically stable. Echocardiography showed preserved left ventricular systolic function (ejection fraction 75%), moderate tricuspid regurgitation, PDA (+), and residual ASD (Figure 2). Mechanical ventilation was maintained until postoperative day 7 to allow for gradual cardiopulmonary adaptation after RV decompression. The patient was subsequently extubated and discharged on day 9 post-surgery. At outpatient follow-up, antegrade RV-PA flow remained patent, although the channel was relatively small. The patient remained under serial cardiology surveillance and was being evaluated for future staged palliation with a modified BT shunt, if required.

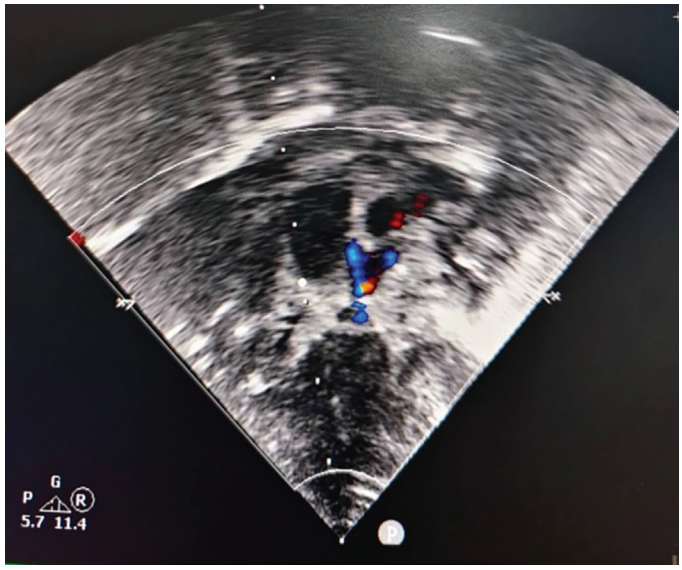

Figure 2. Postoperative echocardiography showing restored antegrade pulmonary blood flow, preserved left ventricular systolic function (ejection fraction 75%), persistent moderate tricuspid regurgitation, residual secundum atrial septal defect with bidirectional shunt and patent ductus arteriosus

DISCUSSION

PA-IVS is a complex, cyanotic congenital heart disease. The therapeutic strategy depends on RV morphology, coronary anatomy, pulmonary artery development, and institutional resources.[4] Determining the optimal initial palliation for neonates weighing less than 3 kg remains a formidable clinical challenge, as duct-dependent physiology carries risks of severe morbidity and mortality. Although the modified BT shunt is widely employed to augment pulmonary blood flow, it is associated with significant morbidity and mortality in low-birth-weight neonates. Lower body weight and complex anatomy have been associated with unfavorable early outcomes after shunt placement.[5,6]

The risk of postoperative hemodynamic instability is further amplified by a decline in PVR following shunt placement. In our 2.6 kg patient, the smallest available graft (4 mm) raised concerns about potential overshunting. Treatment selection was further influenced by local resource constraints. Ideally, pulmonary blood supply, including major aortopulmonary collateral arteries, should be evaluated by cardiac catheterization.[3,4] In resource-limited centers, inadequate pediatric cardiac intensive care and limited access to extracorporeal membrane oxygenation (ECMO) can exacerbate postoperative instability.[7] Undetected collateral flow may lead to unpredictable pulmonary overcirculation after shunt placement.[6]

Transcatheter pulmonary valvuloplasty is an alternative to RV decompression in selected patients.[8] However, surgical valvotomy remains more reliable in cases with complex anatomy or limited catheter capabilities.[9] At the time of the intervention, neonatal transcatheter procedures, hybrid procedures, and ECMO were not available, further influencing treatment decisions. In this patient, duct-dependent hemodynamic instability, uncertain pulmonary vascular anatomy, and concerns regarding shunt-related hemodynamic imbalance favored the primary Brock procedure as the initial palliative strategy. This decision was further supported by anatomical considerations, namely the presence of a tripartite RV, balanced ventricular dimensions, and preserved tricuspid annular size, all of which favored RV decompression and the potential for biventricular circulation. Furthermore, echocardiography demonstrated no evidence of major coronary sinusoids, coronary fistulae, or right-ventricle-dependent coronary circulation, thereby reducing concerns about myocardial ischemia after decompression.[2]

Although a modified BT shunt was initially considered, concerns regarding overshunting in a low-weight neonate with favorable RV morphology supported an initial decompressive strategy using the Brock procedure. Given the anatomical findings, a single-ventricle approach was not pursued as the initial strategy because these features were deemed supportive of biventricular circulation and RV decompression.[3]

Collectively, these findings support the Brock procedure as a suitable initial strategy for establishing antegrade pulmonary blood flow. This technique permits transventricular valvotomy without CPB, thereby avoiding capillary leak, coagulopathy, and inflammatory sequelae associated with CPB.[3,10] Compared with the modified BT shunt, which carries vascular, prosthetic and antithrombotic risks, the primary Brock procedure preserves native pulmonary blood flow and may simplify postoperative care.[6]

Urgent intervention was required because the neonate was dependent on continuous PGE1 infusion to maintain ductal patency. Despite pharmacological and non-invasive ventilatory support, oxygen saturation fluctuated between 50-75%, with persistent respiratory distress and metabolic acidosis, reflecting a critically limited cardiopulmonary reserve.

Nevertheless, important physiological trade-offs must be recognized following RV decompression. Sudden decompression may alter ventricular load and increase pulmonary blood flow, potentially precipitating systemic hypotension, pulmonary overcirculation, or transient ventricular dysfunction in neonates with a hypertrophied, non-compliant RV.[1,11] Restoration of antegrade pulmonary flow improved hemodynamic responsiveness during the perioperative period and permitted

modulation of the Qp:Qs balance by adjusting ventilation, SVR, and inotropic support.[1]

In this patient with a hypertrophied and relatively non-compliant RV, anesthetic management prioritized the maintenance of RV performance and coronary perfusion. Anesthetic induction was conducted gradually to avoid abrupt reductions in SVR, and ventilatory parameters were carefully titrated to prevent decreases in PVR.[2,12]

Perioperative priorities included oxygenation control, SVR maintenance, RV preload preservation, and continuous invasive hemodynamic monitoring. An opioid-based induction combined with low-dose inhalational anesthesia was selected to reduce sympathetic responses while maintaining hemodynamic stability.[1,13] Prolonged mechanical ventilation, in this case, reflected the physiological challenges associated with acute decompression of a hypertrophied and relatively non-compliant RV, including the potential for persistent diastolic dysfunction and the need for gradual hemodynamic adaptation. Mechanical ventilation was progressively weaned while maintaining adequate oxygenation and hemodynamic stability, with transition to non-invasive ventilation and then to low-flow supplemental oxygen prior to discharge. This staged approach facilitated progressive cardiopulmonary adaptation while avoiding abrupt perturbations in RV loading conditions.

Study Limitations

This report has several limitations. Formal tricuspid valve Z-score calculations and quantitative RV volume measurements were not available in the retrospective echocardiographic records. During follow-up, serial quantitative assessments of RV growth and residual pulmonary regurgitation could not be consistently obtained.

CONCLUSION

In neonates with PA-IVS, the selection of the primary Brock procedure should be guided by patient-specific anatomy and physiology, especially the presence of unstable duct-dependent circulation and the risk of shunt-related imbalance. Restoration of antegrade pulmonary blood flow enabled more physiologic perioperative regulation of Qp:Qs. In resource-limited cardiac settings, optimal outcomes depend on close multidisciplinary collaboration and careful perioperative anesthetic management to preserve systemic perfusion.

Ethics

Informed Consent: Written informed consent for publication of this case report and accompanying clinical information was obtained from the patient's parents.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A., Y.W., Concept: B.I., A.H., Design: B.I., A., A.H., Data Collection or Processing: B.I., A., Y.W., Analysis or Interpretation: B.I., A., Y.W., A.H., Literature Search: B.I., Writing: B.I., A., Y.W., A.H.

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EDITORIAL COMMENT

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From CKM to CKLM: Why the Liver may be the Missing Fourth Pillar

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Keywords: CKM, CKLM, liver

An Organ Recognized, but Not Yet Fully Integrated

When the American Heart Association (AHA) formally defined cardiovascular-kidney-metabolic (CKM) syndrome in 2023, it reframed obesity, type 2 diabetes, chronic kidney disease (CKD), and cardiovascular disease as manifestations of an interconnected pathophysiological continuum rather than four separate conditions.[1,2] The 2026 AHA/ACC/ADA/ASN guideline has taken an important further step by explicitly recognizing metabolic dysfunction-associated steatotic liver disease (MASLD) within CKM care and recommending non-invasive liver fibrosis assessment, including the Fibrosis-4 (FIB-4) index, in selected patients.[3] Yet an important conceptual question remains unresolved: Should this clinical recognition evolve into formal recognition of the liver as a fourth structural axis of CKM syndrome? The central argument is straightforward. The liver is now clinically recognized within the CKM framework, but it has not yet been formally integrated as a fourth structural axis of the syndrome.

The timing of this evolution is relevant to understanding the current CKM framework. The original CKM construct was developed before the 2023 international consensus established the contemporary MASLD/MASH nomenclature.[4] Subsequent work has increasingly emphasized the liver as an integral component of the cardiometabolic continuum, including within broader conceptualizations of CKM syndrome.[5] This temporal context may partly explain why hepatic disease was not explicitly incorporated as a distinct axis in the original CKM framework; however, it does not resolve whether the liver should now be formally integrated into the syndrome. The biological rationale for such an integration is substantial. MASLD and MASH share major pathophysiological drivers with CKM syndrome, including insulin resistance, visceral adiposity, ectopic lipid accumulation, and chronic low-grade inflammation. Moreover, liver disease is closely and bidirectionally linked to both CKD and cardiovascular disease, while increasing hepatic fibrosis is associated with adverse cardiovascular and cardiorenal outcomes.[6,7] These relationships support viewing hepatic disease not simply as a comorbidity accompanying CKM syndrome, but as part of the interconnected multisystem disease process. This concept has increasingly emerged across several recent frameworks, including MALCKS,[8] cardiovascular-renal-hepatic-metabolic syndrome,[6] cardiovascular-kidney-liver-metabolic (CKLM),[9] CKLMS,[10] and CARDIAL-MS.[11] Although these proposals differ in terminology, scope, and intended clinical application, they share a common premise: hepatic disease may warrant a more explicit and integrated position

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within cardiometabolic disease models. More recently, a 2026 JACC communication proposed extending the CKM framework toward CKML and emphasized the role of the liver within the cardiometabolic clinical workflow.[12] Taken together, these developments do not necessarily establish that the CKM acronym should be changed. Rather, they indicate that the transition from clinical recognition of liver disease in CKM care to its formal conceptualization as a fourth structural axis deserves careful consideration.

The CKLM Paradigm: From Clinical Recognition to Structural Integration

Nomenclature alone will not change practice. The practical task is to embed hepatic evaluation into the existing CKM staging architecture, as illustrated in Figure 1. The 2026 guideline already provides a framework for doing so.[3] Among adults with CKM syndrome and diabetes or at least two cardiometabolic risk factors, FIB-4 calculation every 1-2 years is recommended; among adults with CKM stage 1 due to prediabetes, calculation every 2-3 years is considered reasonable.[3] FIB-4 is derived from age, aspartate aminotransferase, alanine aminotransferase, and platelet count, and therefore can be incorporated into routine CKM assessment without requiring additional laboratory infrastructure. In adults aged 35-64 years, a FIB-4 below 1.3 identifies a group at low-risk for clinically significant fibrosis, whereas age-adjusted interpretation is required in adults aged 65 years or older, for whom a threshold of 2.0 is used.[3] Intermediate or high-risk results should prompt sequential assessment, commonly with vibration-controlled transient elastography or enhanced liver fibrosis testing, with specialist referral when clinically significant fibrosis is suspected.[3]

This sequential approach also illustrates why the liver could be conceptualized as a parallel axis rather than an ancillary component. The analogy with the kidney is instructive: epidermal growth factor receptor and albuminuria provide organ-specific information that is integrated into CKM risk assessment without replacing the broader syndrome framework.[1-3] FIB-4 is useful, but it is not a definitive diagnostic test and has important limitations. Its prognostic value has been demonstrated in populations with obesity and/or type 2 diabetes, while discordance with elastography can occur and may be clinically relevant.[13,14] In selected patients, elastography and, when appropriate, magnetic resonance imaging (MRI)-based techniques can refine fibrosis assessment.[14,15] MRI-based techniques should be interpreted according to their

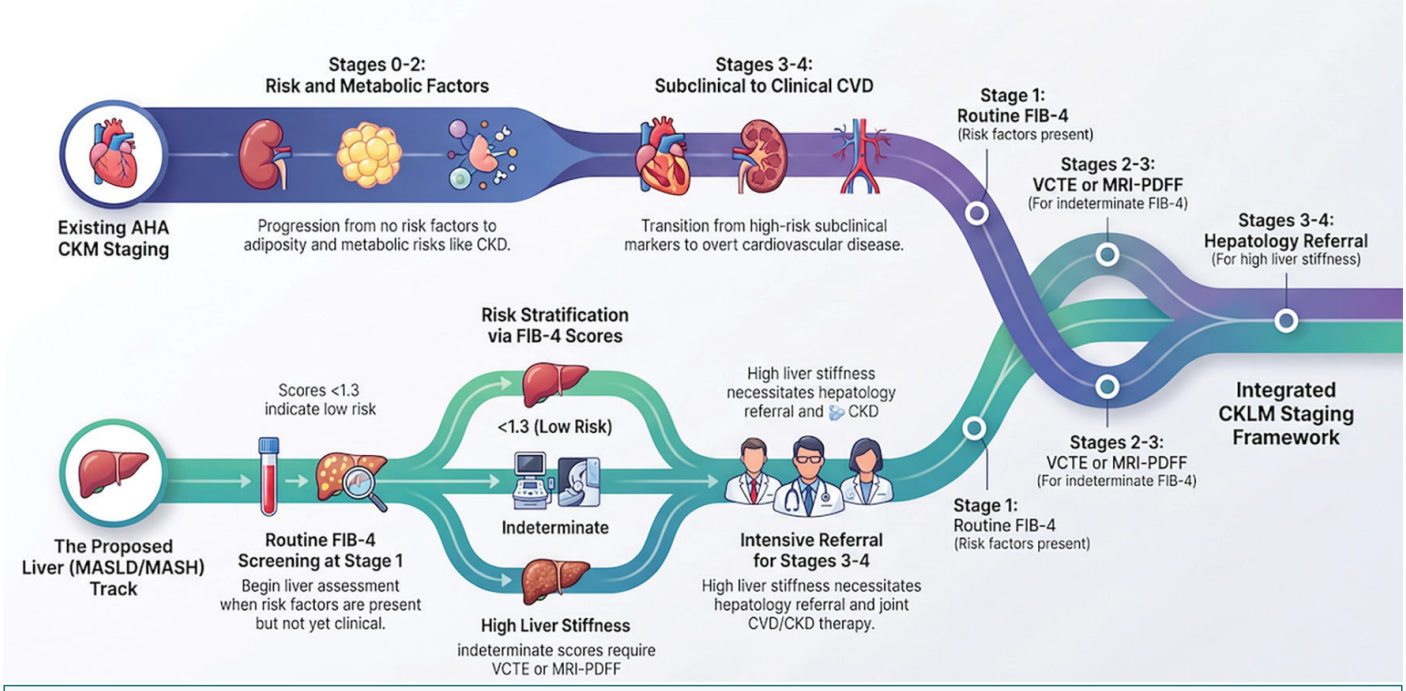

Figure 1. FIB-4 and sequential non-invasive liver assessment layered onto existing CKM stages to illustrate a practical CKLM pathway, running parallel to rather than replacing the established CKM framework

FIB-4: Fibrosis-4, CKLM: Cardiovascular-kidney-liver-metabolic, MRI: Magnetic resonance imaging, CKM: Cardiovascular-kidney-metabolic, CKD: Chronic kidney disease, MRI: Magnetic resonance imaging, CVD: Cardiovascular disease

specific purpose: magnetic resonance elastography provides an imaging-based assessment of liver stiffness and fibrosis, whereas MRI-based proton density fat fraction is primarily used to quantify hepatic steatosis.[15] The appropriate response is therefore a structured, sequential assessment rather than exclusion of the liver.

Conclusion

Among the proposed names, I favor CKLM over the alternative ordering, CKML, recently proposed in JACC.[12] Both formulations recognize the liver alongside the cardiovascular and renal axes. CKLM, however, preserves the cardiovascular-kidney sequence established by the original CKM construct while introducing the liver as the newly emphasized organ axis and retaining the metabolic domain as a central driver of the syndrome.

The original CKM framework was built around systemic interconnection rather than isolated organ silos.[1,2] The 2026 guideline has now taken an important clinical step by explicitly recognizing MASLD and incorporating FIB-4-based liver fibrosis assessment into CKM care.[3] The next question is whether this clinical recognition should evolve into structural recognition of the liver as a fourth axis of the syndrome. Future AHA scientific statements and international consensus documents should consider whether MASLD/MASH and liver fibrosis warrant formal incorporation into CKM nomenclature and staging, with prospective evaluation of how liver status modifies cardiovascular and kidney risk prediction, therapeutic decisions, and multiorgan clinical trial design.[9,10,12] The goal should not be to create another acronym for its own sake but to develop a more complete disease model in which cardiovascular, kidney, liver, and metabolic diseases are assessed as interconnected manifestations of systemic cardiometabolic disease (Figure 2).

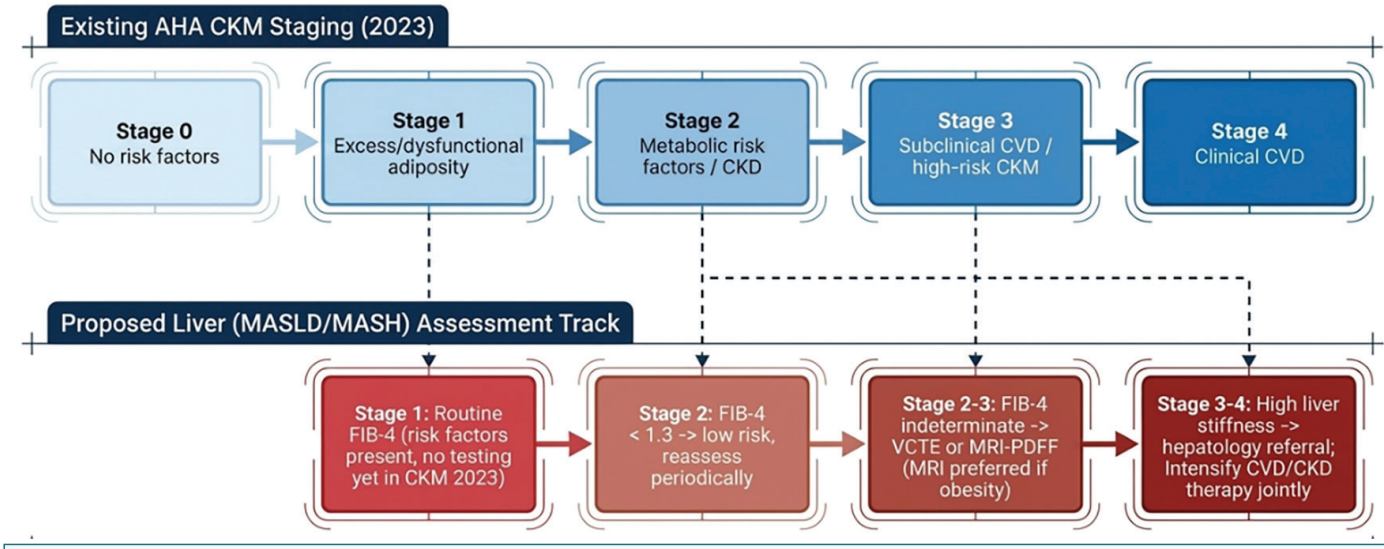

Figure 2. Proposed integration of non-invasive liver fibrosis assessment into existing AHA CKM syndrome staging, illustrating the conceptual basis of a CKLM framework

AHA: American Heart Association, CKM: Cardiovascular-kidney-metabolic, CKLM: Cardiovascular-kidney-liver-metabolic, CKD: Chronic kidney disease, FIB-4: Fibrosis-4, CVD: Cardiovascular disease

Footnotes

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LETTER TO THE EDITOR

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Letter to the Editor: A Study of Clinical Profile, Chest X-ray, ECG Changes, and 2D Echocardiography in Patients with Chronic Cor Pulmonale

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Keywords: Cor pulmonale, electrocardiography, echocardiography, right heart

To the Editor,

I read with interest the article by Haq et al.[1] titled "A study of clinical profile, chest X-ray, ECG changes, and 2D echocardiography in patients with chronic cor pulmonale," published in the recent issue of the *International Journal of Cardiovascular Academy*. The authors provide a pragmatic evaluation of chronic cor pulmonale (CCP), emphasising that conventional diagnostic findings retain considerable significance, particularly in settings characterised by resource limitations.[1]

What caught my attention was that all patients in this group had right atrial (RA) and right ventricular (RV) dilatation. This is a sobering clinical observation, suggesting that CCP is often a "silent traveler" diagnosed only in its advanced stages.[1] The study effectively highlights the diagnostic value of fundamental tools; specifically, the prevalence of dyspnoea and peripheral oedema as primary clinical markers, the presence of "P-pulmonale" and right axis deviation on electrocardiography, and the classic radiographic signs of pulmonary artery enlargement.[1] These findings show that a high level of suspicion is important even before advanced imaging. While the authors' focus on two-dimensional (2D) echocardiography internal diameters is relevant, it also highlights the need to think about how we can improve our diagnosis.

The authors rightly emphasise that 2D echocardiography is the most accessible and time-effective diagnostic modality for these patients.[1,2] Indeed, advanced modalities such as RV/RA longitudinal strain or three-dimensional (3D) volume analysis, while powerful, are often time-consuming, highly dependent on image quality, and require significant operator experience.[3,4] In a busy clinical context, the simplicity of the 2D measurements employed in this study is likely to be the key factor contributing to their significant clinical utility.[1]

From a constructive standpoint, however, it may be logical to consider a more multiparametric approach, if time and image quality permit. The integration of parameters such as tricuspid annular plane systolic excursion, tricuspid annular systolic velocity (S' wave), fractional area change and RV deformation imaging (RV Strain), 3D RV assessment provides a more detailed understanding of RV systolic performance, even in the subclinical stages.[3,5] Furthermore, the assessment of RA volume and RA deformation imaging can provide early indicators of pressure overload, even prior to the development of overt RV failure.[3,4]

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Congratulations to the authors for documenting this clinical profile so thoroughly. Their work provides a solid foundation for future research into the correlation between these simpler, accessible tools and newer, more advanced functional metrics.

Footnotes

The corresponding author(s) of the original article were contacted by e-mail on 3 February 2026, 18 March 2026, and 16 June 2026 and were given the opportunity to respond to this letter. However, despite repeated attempts, no response was received.

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