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Could Mitral Valve and Mitral Annular Velocities and Left Atrial and Left Ventricular Wall Strain Predict the Presence of Coronary Artery Disease? A Case-Control Echocardiographic Study

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ABSTRACT

Background: Coronary Artery Disease (CAD) is a major cause of morbidity and mortality world-wild. Thus, its early diagnosis and treatment could be life-saving. Mitral Valve (MV) and mitral annular velocities as well as left atrial and left ventricular wall strain have been claimed to be helpful for prediction of the presence of CAD.

Objectives: This case-control study aimed to assess the predictive value of these echocardiographic parameters for detection of CAD.

Methods: Eighty consecutive individuals referring with acute angina-like chest pain and requiring diagnostic coronary angiography and had a concomitant echocardiographic Left Ventricular Ejection Fraction (LVEF) ≥ 50% were divided into two groups: those with significant CAD (n = 45) and those with non-significant CAD (n = 35). Tissue Doppler Imaging (TDI) was employed for all participants. Peak early and late MV velocities (E and A, respectively), peak longitudinal systolic myocardial velocity (mitral S′), peak early and late diastolic velocities (e′ and a′, respectively) from medial mitral annulus, E/e′ ratio, peak Left Atrial (LA) strain, and Left Ventricular Global Longitudinal Strain (LV GLS) were measured and compared in the two groups. Chi-square and t-test were used to compare the two groups as appropriated. Multiple logistic regression was also performed to detect the impact of categorical variables on the predictors of the presence of CAD. Receiver operating characteristic curves were constructed as needed. A P value ≤ 0.05 was considered to be statistically significant.

Results: Mitral S′ and E/e′ were significantly different in the two groups. Mitral S′ was lower and E/e′ was higher in the patients with CAD compared to the control group (P = 0.01 and P = 0.03, respectively). Considering 5.3 cm/sec as the cut-off point for mitral S′, sensitivity and specificity for significant CAD were 67.40% and 68.60%, respectively with an odds ratio of 0.275. The cut-off point for mitral E/e′ was defined as 12.65, with sensitivity and specificity for significant CAD to be 52.17% and 77.14%, respectively with an odds ratio of 1.249.

Conclusion: This study showed that mitral S′ and E/e′ could predict the presence of significant CAD in patients with chest pain and preserved LVEF. Thus, TDI could be used as a simple, reliable, and non-invasive tool to achieve this goal.

1. Background

Coronary Artery Disease (CAD), the most common type of heart disease, is characterized by atherosclerosis in epicardial coronary arteries. Despite improvements in treatment for CAD, its prevalence has been increasing in the recent years. Globally, CAD is the leading cause of death and has been predicted to remain so for the next 20 years (1). In addition to its mortality burden, CAD is the leading cause of morbidity and loss of quality of life. This makes CAD a major public health problem, which exerts heavy economic costs (1). Despite a decline in CAD mortality, it remains the main cause of heart failure worldwide (2). CAD is also the first cause of death and disability in both genders in Iran. It accounts for nearly half of all deaths per year (3). This signifies the importance of early CAD diagnosis and treatment to reduce the occurrence of heart failure and its associated complications and mortality.

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To date, there are several ways to evaluate coronary arteries. Doppler echocardiography has found widespread application for evaluation of systolic and diastolic function of the left ventricle. Additionally, early and late mitral inflow velocities (E and A, respectively) measured by pulse wave Doppler echocardiography have been used to assess Left Ventricular (LV) diastolic performance as well as LV filling pressure.

Recently, tissue Doppler imaging has been successfully applied for assessment of all cardiac chambers. It is a cheap, non-invasive test that has been clearly shown to be an excellent prognostic tool in individuals with cardiovascular disease (4, 5). It has also been shown to be a useful diagnostic test for detection of CAD (6-8). In addition, the potential usefulness of Tissue Doppler Imaging (TDI) to assess left atrial function in cardiac diseases including CAD has been recently demonstrated (9, 10).

Deformation characteristics of longitudinally oriented myocardial fibers are sensitive markers of early derangements of cardiac function caused by various pathological disorders, such as ischemia (11). Recently, quantification of LV longitudinal strain using Two-Dimensional Speckle-Tracking Echocardiography (2D STE) was shown to be a sensitive method for identifying significant CAD (11).

2. Objectives

This study aims to assess the predictive capabilities of peak Mitral Valve (MV) inflow and mitral annular velocities and left atrial and LV strain for prediction of the presence of significant CAD.

3. Patients and Methods

3.1. Study Design and Population

This case-control study was conducted on 80 consecutive individuals fulfilling the study inclusion criteria who had referred with acute chest pain and required coronary angiography. Patient selection was done via convenient, referral-based sampling. The sample size was determined to be 80 using the following formula $N = 2\delta^2 (Z1\text{-}\alpha/2 + Z1\text{-}\beta)^2 / D^2$ to yield a 95% confidence interval, power of 80%, $\alpha = 0.05$, and effect size of 20%.

All participants underwent full history taking, clinical examination, electrocardiography, echocardiography, and routine laboratory investigations. Demographic data and risk factors, including the presence of diabetes mellitus, hypertension, cigarette smoking, hyperlipidemia, and premature CAD in the family members, were also recorded. Coronary angiography was done by an expert cardiologist for all participants who were subsequently divided into two groups. The control group contained individuals with no or non-significant CAD, while the case group included those with significant CAD defined as luminal narrowing $\geq$ 50%. The exclusion criteria of the study were cardiac rhythms other than normal sinus, left bundle branch block, acute myocardial infarction, recent or prior Percutaneous Coronary Intervention (PCI) or Coronary Artery Bypass Graft (CABG) surgery, regional wall motion abnormality in echocardiography, moderate to severe valvular pathologies, Left Ventricular Ejection Fraction (LVEF) less than 50%, and unwillingness to cooperate.

3.2. Standard Two-Dimensional (2D) Echocardiography

All participants underwent echocardiography by an expert echocardiographer who was kept blind to the patients' angiographic results. Standard 2D images, strain data, and color-coded TDI data were saved in cine loop format. All analyses were done offline. It should be noted that the study was conducted among patients with sinus rhythm.

Standard M-mode and 2D echocardiographic studies were performed using a high quality echocardiograph (Vivid E9, General Electronic, USA). The patients were examined in the left lateral recumbent position. For each patient, apical four-chamber, parasternal long axis, and parasternal short axis views images were obtained. In the apical 4-chamber view, Pulsed Wave Doppler (PW-Doppler) sample volume was placed at the tip of the MV. E-wave velocity (m/sec), A-wave velocity (m/sec), and E/A ratio were recorded. By tracing MV inflow, MV Velocity Time Integral (MV VTI) in centimeters and mean and maximum MV diastolic pressure gradient (mmHg) were measured during breath hold. All parameters were measured in three consecutive beats and the mean value for each parameter was used for analysis.

3.3. Tissue Doppler Imaging

Color-coded TDI loops were obtained in the apical four-chamber view at the highest possible frame rate with a 1-2 mm sample volume placed at the septal side of the MV annulus. Using color-coded TDI, peak longitudinal systolic myocardial velocity (S′) and peak early and late diastolic velocities (e′ and a′) from medial mitral annulus were measured in centimeters per second. Time to peak contraction (q-S′) was also measured in milliseconds.

3.4. Left Atrial Strain

A sample volume was placed at the mid part of the Left Atrium (LA) lateral wall. Each sample was obtained by averaging at least three consecutive heart cycles. From the reconstructed strain curves, the peak left atrial strain was identified as the peak negative strain value.

3.5. Left Ventricular Global Longitudinal Strain

Left Ventricular Global Longitudinal Strain (LV GLS) was assessed by speckle tracking modality. Apical two-chamber, four-chamber, and long axis views were obtained using conventional 2D gray scale echocardiography with a stable electrocardiography recording. Each sample was obtained by averaging at least three consecutive heart beats at the highest frame rate possible. In doing so, each patient was asked to hold one's breath for as long as possible. End-diastolic frame was selected from apical 3, 4, and 2 chamber views. The inner endocardial border was delineated by Automated Function Imaging (AFI) and was tracked by speckle tracking software for Vivid (Vivid E9, EchoPAC 11). The echocardiographic images were accepted for analysis when all segments approved for speckle analysis were tracked reliably. The software automatically generated a topographic representation of all 17 analyzed segments (bull's-eye) and global longitudinal strain was measured for each patient.

3.6. Coronary Angiography

All participants underwent standard coronary angiography before entering the study because of their anginal pain or angina-like symptoms. Coronary angiography was performed via either femoral or radial approach by an expert angiographer.

3.7. Statistical Analysis

The data have been expressed as mean ± Standard Deviation (SD) for continuous variables and as percentage for categorical ones. T-test and chi-square test were used to compare normal participants and patients, as appropriated. In addition, multiple logistic regression was performed to identify the impact of categorical variables on the anticipated predictors of the presence of CAD (E/A, mitral S′, mitral e′, mitral E/e′, and LV GLS). Moreover, Receiver Operating Characteristic (ROC) curves were constructed for mitral E/e′ and mitral S′. Area under the ROC curves (AUC) were compared by the Henley and McNeil's test (12). A P value ≤ 0.05 was considered to be statistically significant. All analyses were performed using the SPSS software for Windows (version 16.0, Chicago, IL, SPSS Inc.).

3.8. Ethics

The study protocol was approved by the Regional Ethics Committee. Indeed, written informed consent forms were obtained from all participants.

4. Result

This study was conducted on 80 participants (40 females and 40 males) aged between 43 and 85 years (57.42 ± 10.56). Among the participants, 45 (56%) had significant CAD (≥ 50% stenosis) in at least one major coronary artery or its branches, while 35 (44%) had either less than 50% stenosis or no stenosis in their coronary arteries (Table 1). There was no major gender difference between the two groups. However, a significant difference was found between the two groups with regard to age distribution (P = 0.003) since the control group was on average seven years younger than the patients.

Among the risk factors, there was a statistically significant difference between the two groups regarding the prevalence of diabetes, smoking, and family history of CAD (P = 0.011, 0.031, and 0.003, respectively). The prevalence of these risk factors was higher in cases than in normal controls. However, no significant differences were observed between the two groups concerning the prevalence of hypertension and hyperlipidemia (Table 2).

Among M-mode echocardiographic parameters, only the LA diameter was significantly larger in cases than in normal controls (P = 0.02). The results indicated no significant differences between the two groups with respect to the other elements.

Among MV conventional parameters, there was a statistically significant difference between the two groups regarding the E/A ratio (P = 0.039). Other parameters, such as MV VTI, mitral diastolic maximum and mean gradient, and E and A velocities, were similar in the two groups (Table 3).

Considering mitral TDI parameters, the results demonstrated a statistically significant difference between the two groups concerning mitral S′, mitral E', and mitral E/e′ (P = 0.01, 0.008, and 0.039, respectively). Accordingly, mitral S′ and mitral e′ were higher in controls than in cases, while mitral E/e′ was higher in cases than in the control group. However, LA-S and mitral a′ were similar in the two groups (Table 4). Moreover, the results showed no significant difference between the two groups regarding the peak LA strain, while LV GLS tended to be minimally higher in the normal group (P = 0.049) (Table 4).

To assess the impact of confounding factors (including the risk factors) on the anticipated predictors of the presence of CAD, multivariate logistic regression analysis was performed for E/A, mitral S′, mitral e′, mitral E/e′, and LV GLS. The results showed a significant relationship between the disease and mitral S′ and mitral E/e′, but not E/A, mitral e′, and LV GLS (Table 5).

The results of multivariate analysis demonstrated that the odds of the disease were lower in the individuals with higher mitral S′ levels (odds ratio = 0.275). In other words,

Table 1. Demographics of the Participants

Parameter	Groups	Number/Range	Mean	SD	P
Gender (F/M)	Case	19/26 (41.3%/58.7%)			0.595
	Control	21/14 (60.0%/40.0%)			
Age (years)	Case	39 - 81	60.44	10.89	0.003
	Control	34 - 75	53.54	8.84	
BMI (kg/m²)	Case	16 - 31.14	24.90	3.10	0.729
	Control	17.84 - 38.22	25.27	3.80	

Abbreviations: F, female; M, male; BMI, body mass index; SD, standard deviation; P, P value

Table 2. Distribution of the Major Risk Factors among the Participants

Risk Factors	Case (n = 45)	Control (n = 35)	P
Diabetes	13 (28.3%)	2 (5.9%)	0.011
Hyperlipidemia	9 (25.7%)	7 (23.3%)	0.824
Hypertension	19 (52.8%)	16 (47.1%)	0.632
Smoking	12 (28.6%)	3 (8.8%)	0.031
FM HX of PCAD	11 (25%)	0 (0%)	0.003

Abbreviations: FM HX of PCAD, family history of premature coronary artery disease; N, number; P, P value

Table 3. Conventional Echocardiographic LA and LV Findings

Parameter	Groups	N	Range	Mean	SD	P
Peak E velocity (m/sec)	Case	45	0.28 - 1.03	0.53	0.16	0.240
	Control	35	0.32 - 1.07	0.58	0.16	
Peak A velocity (m/sec)	Case	45	0.31 - 1.29	0.69	0.17	0.230
	Control	35	0.3 - 1.14	0.65	0.15	
E/A ratio	Case	45	0.4 - 1.41	0.80	0.25	0.039
	Control	35	0.14 - 2.34	0.96	0.44	
Max gradient (mmHg)	Case	45	0.39 - 6.78	2.31	1.10	0.634
	Control	35	0.93 - 4.53	2.20	0.77	
Mean gradient (mmHg)	Case	45	0.15 - 2.97	0.79	0.45	0.282
	Control	35	0.31 - 1.31	0.70	0.28	
VTI (cm)	Case	45	10.20 - 42.7	17.55	5.39	0.978
	Control	35	12.25 - 27.55	17.53	3.22	

Abbreviations: E, E-wave velocity; A, A-wave velocity; Max gradient, maximum gradient; VTI, velocity time integral of mitral valve; P, P value; SD, standard deviation

Table 4. Tissue Doppler Echocardiographic LA and LV Strain Findings

Parameter	Groups	N	Range	Mean	SD	P
Mitral S′ (cm/sec)	Case	45	2.61 - 7.72	4.86	1.02	0.010
	Control	35	2.53 - 7.14	5.43	0.91	
Mitral S′: q-S (sec)	Case	45	0.07 - 0.19	0.12	0.02	0.376
	Control	35	0.07 - 0.19	0.12	0.02	
Mitral e′ (cm/sec)	Case	45	10.40 - 1.28	4.22	1.84	0.008
	Control	35	10.8 - 2.00	5.34	1.79	
Mitral a′ (cm/sec)	Case	45	8.94 - 3.04	6.50	1.35	0.667
	Control	35	8.25 - 2.07	6.37	1.38	
Mitral E/e′	Case	45	6.26 - 69.96	15.18	9.77	0.039
	Control	35	4.49 - 29.57	11.78	4.36	
LA-S (cm/sec)	Case	45	3.16 - 9.64	6.05	1.77	0.152
	Control	35	3.40 - 10.45	6.60	1.57	
LA-S: q-S (sec)	Case	45	0.06 - 0.23	0.12	0.02	0.456
	Control	35	0.09 - 0.20	0.12	0.02	
Peak LA strain (%)	Case	45	5.08 - 21.18	11.05	3.68	0.959
	Control	35	6.01 - 16.19	11.02	2.66	
LV GLS (%)	Case	45	9.20 - 23.20	2.90	17.06	0.049
	Control	35	11.20 - 22.8	18.29	2.61	

Abbreviations: Mitral S′, peak longitudinal systolic myocardial velocity; Mitral S′: q-S, time to peak contraction for mitral S′; Mitral e′, peak early diastolic velocities from medial mitral annulus; Mitral a′, peak late diastolic velocities from medial mitral annulus; LA-S, left atrial maximum tissue velocity; LA-S: q-S, time to peak contraction for LA-S; Peak LA strain, peak left atrial strain; LV GLS, left ventricular global longitudinal strain; N, number; SD, standard deviation; P, P value

Table 5. The Results of Multivariate Analysis on the Anticipated CAD Predictors

Parameter	BC	SE	P	OR	95% CI	
					Lower	Upper
Mitral S′	-1.292	0.485	0.008	0.275	0.106	0.710
Mitral E/e	0.222	0.108	0.039	1.249	1.011	1.542
Mitral e′	0.340	0.218	0.120	1.405	0.916	2.156
LV GLS	0.227	0.133	0.088	1.254	0.967	1.627
E/A	-0.91	1.145	0.937	0.913	0.097	8.617

Abbreviations: BC, beta coefficient; SE, standard error; P, p-value; OR, odds ratio; CI, confidence interval; Mitral S′, peak longitudinal systolic myocardial velocity; Mitral e′, peak early diastolic velocities from medial mitral annulus; LV GLS, left ventricular global longitudinal strain

the odds of CAD were 260% lower per unit increase in mitral S′. On the other hand, the odds of CAD were higher among the individuals with higher E/e' values (odds ratio = 1.249) (Table 5).

To further explore the applicability of mitral S′ and mitral E/e′ as the potential predictors of CAD, ROC analyses were performed. The cut-off point for mitral S′ was considered to be 5.3 cm/sec. Hence, values ≥ 5.3 cm/sec were considered to be normal and those < 5.3 cm/sec were considered to be abnormal. The cut-off point for mitral E/e' was considered to be 12.65. Thus, the absolute values ≤ 12.65 were normal and those > 12.65 were abnormal. Based on these cut-off points, sensitivity, specificity, AUC, Positive Predictive Value (PPV), Negative Predictive Value (NPV), and accuracy were calculated and enlisted in Table 6.

AUCs for both mitral S′ and mitral E/e′ have been depicted in Figure 1. Pairwise comparison of mitral S′ and E/e′ ROC curves was also done, which did not show any significant

Table 6. Parameters regarding Mitral S′ and Mitral E/e′

Parameter	Mitral S′	Mitral E/e′
Cut-off point	5.3	12.65
Sensitivity (%)	67.4	52.17
Specificity (%)	68.6	77.14
AUC	0.68	0.64
95% CI for AUC	0.57 - 0.78	0.53 - 0.74
PPV (%)	51.85	75.00
95% CI for PPV	40.54 - 62.98	56.60 - 88.54
NPV (%)	48.14	55.10
95% CI for NPV	37.01 - 59.45	40.23 - 69.33
Accuracy (%)	67.65	62.96
95% CI for accuracy	51.16 - 80.89	52.97 - 72.08

Abbreviation: AUC, area under ROC curve; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value

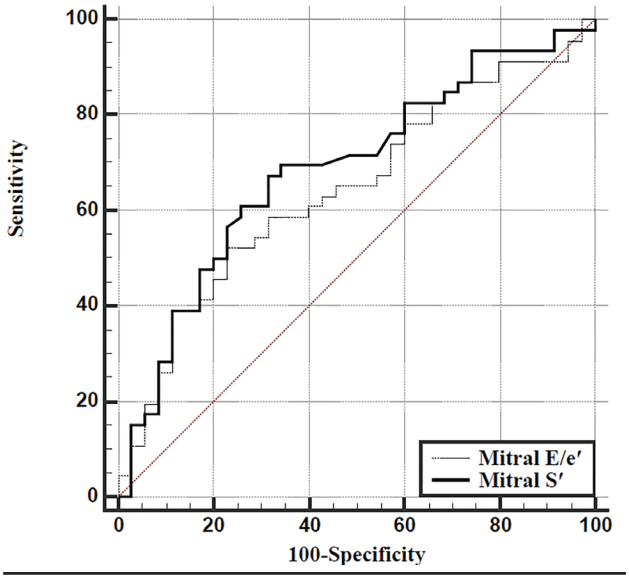

Figure 1. Comparison of Mitral S′ and E/e′ ROC Curves

differences between the two curves (P = 0.56, Figure 1). The two curves also had similar predictive powers for prediction of CAD.

5. Discussion

The current study findings revealed that the two major TDI parameters, namely S′ and E/e′ ratio, could be used to predict the presence of CAD. After multivariate adjustment for confounding parameters, including demographic features and risk factors, only S′ and E/e′ ratio turned to be the independent predictors of the presence of CAD among the individuals presenting with chest pain and having normal LVEF. This means that the longitudinal systolic function of the left ventricle, as shown by S′, is significantly depressed in individuals with CAD despite the presence of a normal EF. This, of course, could happen as a result of the compensatory intensification of the radial myocardial function as reported by Fang et al. (13).

The study results indicated that the absolute value of mitral S′ was lower in the cases than in the controls. Considering 5.3 cm/sec as the cut-off point for mitral S′ (the values above 5.3 as normal and those below 5.3 as abnormal), sensitivity, specificity, PPV, NPV, AUC, and accuracy for significant CAD were 67.4%, 68.6%, 51.85%, 48.14%, 0.68, and 67.65%, respectively. The results of multivariate analysis also showed that the odds of the presence of CAD were lower in the individuals with higher mitral S′ levels. Accordingly, each unit increase in mitral S′ caused the chance of CAD to reduce by 260% (odds ratio = 0.275, 95% CI = 0.106 - 0.710, P = 0.008).

Mitral E/e′ was significantly higher in the patients with CAD compared to the control group, signifying the presence of diastolic impairment. The cut-off point for mitral E/e′ was defined as 12.65. Using this cut-off point, sensitivity, specificity, PPV, NPV, AUC, and accuracy for significant CAD were about 52.17%, 77.14%, 75.00%, 55.10%, 0.64, and 62.96%, respectively. The results of multivariate analysis also showed that higher values of mitral E/e' were associated with higher odds for the presence of CAD. Accordingly, for each unit increase in mitral E/e′, the odds of CAD increased by 24% (odds ratio = 1.249, 95% CI = 1.011 - 1.542, P = 0.039).

The results of pairwise comparison of mitral S′ and E/e′ ROC curves did not show any significant differences between the two curves (P = 0.56). It seemed they had similar power for prediction of CAD.

The study results regarding the difference between the case and control groups with respect to mitral S′ and E/e′ are in line with those of the previous investigations. Hoffman et al. demonstrated in 2010 that color TDI performed at rest revealed both diastolic and systolic dysfunction in patients with stable angina pectoris even when the EF was preserved. They reported significantly reduced S′ and significantly increased E/e′ in patients with significant CAD (7). Ma et al. also conducted a study in 2017 and disclosed that E/e′ ratio was a practical predictor of CAD. By considering 8.153 as the cut-off point, specificity of 72.4% and sensitivity of 57.4% were achieved. Indeed, the results of multivariate analysis showed that E/e′ was closely associated with CAD with an odds ratio of 1.350 and p-value of 0.008 (14).

The current study results indicated no significant differences between the two groups with respect to LA-S and mitral A'. Time to peak systolic velocity in LA and MV annulus was also similar in the study groups. Moreover, the results showed no significant differences between the two groups concerning the peak LA strain. Both groups had clinical risk factors, such as diabetes mellitus and hypertension, which could influence the peak LA strain values. There are controversial issues regarding the peak LA strain in patients with and without significant CAD

with preserved LVEF. In 2003, Yuda et al. concluded that segments subtended by significant CAD were not different in strain parameters (15). In 2012, Yan et al. showed that the peak atrial longitudinal strain of LA tended to decrease among CAD patients even though the differences did not reach statistical significance (16). In a study performed by Sergio Mondillo et al. in 2011, the peak atrial longitudinal strain was lower in patients with hypertension and those with diabetes with normal LA size compared to the controls. Indeed, there were no interactions between hypertension and diabetes (17).

In the present study, LV GLS tended to be higher in the normal group (P = 0.049). However, this was rejected by the results of multivariate analysis. Thus, more reliable results may be achieved by increasing the sample size.

Overall, further larger scale studies are needed to determine whether peak LA strain can predict the presence of significant CAD in patients with chest pain and preserved LVEF. It is also necessary to measure peak LA strain in the presence of significant LAD/LCX/RCA stenosis and in one vessel, two-vessel, and three-vessel CAD and left main disease to explore differences in peak LA strain among these groups. Future investigations are also required to measure regional LV strain in patients with specific epicardial CAD to assess the correlation between the presence of significant CAD and LV GLS.

5.1. Conclusion

The study findings indicated that mitral TDI parameters (mitral S′ and mitral E/e′) were better predictors of significant CAD compared to MV conventional parameters, LA systolic velocity measured by TDI (LA-S), and peak LA strain in individuals with preserved LVEF.

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Authors' Contribution

S. A. did the angiographies and their interpretations. F. A. carried out all echocardiographies and their interpretations. A. Y. gathered all patients' data and actively participated in writing the primary version of the manuscript. G. R. initiated the research program, developed the study concept, and wrote the final paper.

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