Left Atrial Stiffness Index as a Predictor of Effort Intolerance and Hemodynamics Evaluated by Invasive Exercise Stress Testing in Degenerative Mitral Regurgitation

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In patients with degenerative mitral regurgitation (DMR), peak oxygen consumption is the significant prognostic factor, and exercise intolerance has been considered a trigger for surgical intervention. The significant mitral regurgitation (MR) induces left atrial (LA) remodeling, but the significance of LA stiffness calculated by the ratio of E/e′ to LA reservoir strain in degenerative MR has not been elucidated. A total of 30 patients with asymptomatic or minimally symptomatic grade ≥III + DMR underwent the cardiopulmonary exercising test simultaneously with invasive hemodynamic assessment. LA stiffness index significantly correlated with exercise hemodynamic deterioration, including pulmonary arterial wedge pressure ($r = 0.71$, $p < 0.01$), systolic pulmonary arterial pressure at peak exercise ($r = 0.73$, $p < 0.01$), and pulmonary circulatory reserve (mean pulmonary arterial pressure/cardiac output slope, $r = 0.45$, $p = 0.012$). Multiple linear regression analysis revealed that the higher LA stiffness index was significantly associated with decreased percent predicted peak oxygen consumption (per 0.1 increase, β −4.0, 95% confidence interval −6.9 to −1.3, $p < 0.01$) independently of MR deterioration during exercise. In conclusion, increased LA stiffness was associated with exercise intolerance through hemodynamic deterioration during exercise in patients with asymptomatic or minimally symptomatic severe DMR. **(Am J Cardiol 2023;208:65−71)**

Keywords: left atrial stiffness index, left atrial strain, mitral regurgitation, exercise stress echocardiography

Exercise capacity assessed by cardiopulmonary exercise test (CPET) has been considered as a prognosticator in severe degenerative mitral regurgitation (DMR).[1] Exercise stress testing is recommended by the current guidelines for determining the indication of surgical repair.[2] We previously reported that pulmonary circulatory reserve was a determinant of exercise tolerance in patients with DMR with few symptoms, independently of exercise-induced mitral regurgitation (MR) deterioration.[3] However, the mechanism that influences pulmonary circulation and afterload of the right ventricle other than MR severity has not been fully understood. Thus, we focused on the left atrium as an important target intervening between the mitral valve and pulmonary circulatory system in this study. DMR causes left atrial (LA) enlargement through continuous volume overload.[4] The LA stiffness index using LA strain has been reported to be a predictor of exercise intolerance and prognosis in patients with heart failure with preserved ejection fraction,[5,6] although the significance in DMR has not been fully elucidated. In the present study, we sought to investigate the hypothesis that LA stiffness is associated with effort intolerance with hemodynamic deterioration during exercise.

Methods

We examined the patients with grade ≥III + DMR referred for functional assessment and who underwent invasive exercise stress testing at Hiroshima University Hospital between April 2016 and March 2021. We included the patients with minimal symptoms within New York Heart Association (NYHA) functional class II when their symptom was so mild that it was difficult to determine whether the symptom was due to MR. The exclusion criteria were (1) NYHA functional class ≥III, (2) left ventricular ejection fraction <50%, (3) respiratory exchange ratio <1.0 as insufficient workload, (4) ischemia or paroxysmal arrhythmia during exercise, and (5) inadequate image at rest or during exercise. The patients with minimally symptomatic grade III + DMR or asymptomatic severe DMR were included in the study group. Written informed consent approved by the local ethical committee was obtained from all participants.

The patients had a 4 F Balloon Wedge-Pressure Catheter (Teleflex, Wayne, Pennsylvania) inserted and advanced to

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See page 71 for Declaration of Competing Interest.

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the pulmonary artery with fluoroscopic guidance. The catheter was fixed at the position where it would be wedged just by inflating the balloon, under confirmation with fluoroscopic guidance. Next, we confirmed the wedge position while watching the change of pressure waveform in the monitor at rest and repositioned as needed. The experienced cardiologist checked the waveform during exercise. A 4 F arterial sheath was also inserted into the patients' right radial artery. We positioned the pressure transducer as reference, 5 cm below the axillary fold. pulmonary arterial pressure (PAP) and pulmonary arterial wedge pressure (PAWP) were measured at rest and during exercise using a hemodynamic monitoring (IntelliVue MP70; Philips, Andover, Massachusetts), with calibration before each study. We measured these pressures at end-expiratory at rest, and continuously obtained and averaged over 3 beats during exercise. Cardiac output (CO) was calculated with the Fick method using direct measurement of oxygen consumption (VO_2) and arteriovenous VO_2 difference with blood samples obtained at rest and peak exercise. CO reserve was defined as the CO increase from rest to peak exercise. Heart rate (HR) reserve was calculated by the following formula: [(HR at peak − HR at rest)/(220 − Age −HR at rest)] × 100.[7]

The patients underwent a symptom-limited graded ramp bicycle exercise test with a dedicated ergometer (Echo Stress Table 750 EC; Lode, Groningen, The Netherlands). They pedaled at a constant cadence (50 rotations/min) in a semisupine position at 30° angle lateral decubitus. The test started with 3 minutes of unloaded cycling; next, the load was increased using a 10 W/min ramp protocol.[8] The 12-lead electrocardiogram was monitored during the test. Blood pressure was measured with the oscillometric method at rest and during exercise. Breath-by-breath analysis was performed to measure minute ventilation, carbon dioxide production (VCO_2), and VO_2 with a commercially available metabolic cart (MINATO 2,805; Minato Ikagaku, Osaka, Japan). We defined peak VO_2 as the highest averaged 30-second VO_2 during exercise, and the respiratory exchange ratio as the VCO_2/VO_2 ratio provided by ventilatory expired gas analysis. We manually determined anaerobic threshold level using the modified V-slope method.

Transthoracic echocardiography was performed using a commercially available ultrasound system (Vivid E9, GE Vingmed Ultrasound, Horten, Norway) at rest and during exercise. We measured the echocardiographic parameters according to the American Society of Echocardiography (ASE) recommendations.[9] At rest, we obtained LA volume and left ventricular (LV) volume by apical 2- and 4-chamber views. These were indexed by body surface area. The LV ejection fraction (EF) was calculated with a modified Simpson method. Tricuspid annular plane systolic excursion was recorded by M-mode and defined as the travel distance of the junction between the tricuspid valve and the right ventricular free wall.[10] We also obtained Doppler blood flow parameters including transmitral inflow velocity (E wave and A wave), tricuspid regurgitation velocity, and LV outflow tract velocity time integral. Early mitral annular (e′) velocity was measured with tissue Doppler image.

LA strain was analyzed retrospectively by apical 4-chamber view using commercially available speckle-tracking software (EchoPac version 112, GE Healthcare, Horten, Norway). The measurement was performed by the cardiologist (T.K.) blinded to the exercise stress testing. The QRS onset was taken as a reference point, and we used the positive peak atrial longitudinal strain as the LA reservoir strain.[11] LA stiffness index was assessed by the ratio of E/e′ to LA reservoir strain.[12] MR severity was assessed by regurgitant fraction, vena contracta (VC) width, VC area by 3-dimensional imaging, and pulmonary venous flow pattern.[13] A regurgitant fraction was obtained by the Doppler hemodynamic parameters of transmitral and LV outflow tract flow. The etiology of DMR was defined according to the ASE guideline.[13]

Continuous variables are expressed as mean ± SD or median (interquartile range: twenty-fifth and seventy-fifth percentile). Categorical variables are expressed as number (%). The Kolmogorov-Smirnov test was performed to confirm normal distribution. Correlations between echocardiographic and hemodynamic CPET parameters were assessed using Pearson or Spearman's correlation coefficient. We performed multiple linear regression analysis to confirm the associated factors of percent predicted VO_2. Given the small number of patients (n = 30), 2 independent factors, including LA stiffness index, were calculated in each model. We considered that age and gender were adjusted using percent predicted peak VO_2. All statistical analyses were performed using EZR software version 1.36 (http://www.jichi.ac.jp/saitama-sct/SaitamaHP.files/statmed.html).[14] We considered a 2-tailed $p < 0.05$ as statistically significant.

Result

A total of 44 patients were enrolled in this study. We eventually included 30 patients, excluding 1 with NYHA class III, 1 with EF ≤50%, 4 with respiratory exchange ratio <1.0, 1 with atrial fibrillation with tachycardia during exercise, and 7 with inadequate image quality unable to perform LA strain analysis. The patients' characteristics are listed in Table 1; the information including MR mechanism, etiology, and severity is listed in Table 2, and hemodynamic parameters by right-sided cardiac catheterization are listed in Table 3.

There were no correlations of LA stiffness index with MR regurgitant fraction ($p = 0.17$), MR VC at rest ($p = 0.55$), LVEF ($p = 0.73$), or LA volume index ($p = 0.41$). In contrast, the LA stiffness index correlated well with PAWP ($r = 0.63$, $p < 0.01$) and systolic PAP ($r = 0.72$, $p < 0.01$), and negatively with CO at rest ($r = -0.40$, $p = 0.027$; Figure 1). As for hemodynamic parameters during exercise, the LA stiffness index was positively correlated with PAWP ($r = 0.71$, $p < 0.01$) and systolic PAP at peak exercise ($r = 0.73$, $p < 0.01$; Figure 2). CO at peak exercise was negatively correlated with LA stiffness ($r = -0.59$, $p < 0.01$; Figure 2). We also assessed the cardiac reserve during exercise. LA stiffness was significantly associated with ΔPAWP ($r = 0.50$, $p < 0.01$) and mean PAP/CO slope ($r = 0.45$, $p = 0.012$; Figure 1) but not with CO reserve ($p = 0.15$; Figure 1).

Table 1
Baseline characteristics

	N = 30
Age, y	61 (11)
Male	23 (77%)
Body mass index, kg/m^2	23.7 (2.6)
NYHA functional class	
Class I	11 (37%)
Class II	19 (63%)
Hypertension	14 (47%)
Diabetes mellites	2 (6.7%)
Atrial fibrillation	0
β-blocker	4 (13%)
ACE inhibitor/ARB	12 (40%)
Hemoglobin, g/dL	14.1 (0.9)
NT-pro BNP, pg/mL	97 (42 - 200)
Creatinine, mg/dL	0.82 (0.15)
Echocardiography at rest	
LV end-diastolic volume, mL	126 (25)
LV end-systolic volume, mL	42 (10)
LV ejection fraction, %	66 (4.4)
LA volume index, mL/m^2	50 (14)
LA reservoir strain, %	37 (11)
E/e' average	14 (6.4)
LA stiffness index	0.40 (0.19)
TAPSE, mm	24 (3.7)
Cardiopulmonary exercise test	
peak VO_2, ml/min per kilogram	19.8 (4.4)
percent predicted peak VO_2, %	80 (15)
peak load, watt	110 (26)
VE vs VCO_2 slope	29.6 (27.6 - 32.5)
Respiratory exchange ratio	1.10 (1.06 - 1.18)

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; LA = left atrial; LV = left ventricular; NT-pro BNP = N terminal-pro brain natriuretic peptide; NYHA = New York Heart Association; TAPSE = tricuspid annular plane systolic excursion; VE vs VCO_2 slope = ventilatory equivalent versus carbon dioxide output slope; VO_2 = oxygen consumption.

Table 4 shows the correlations of LA stiffness index, E/e′, and LA reservoir strain with hemodynamic and CPET parameters. LA stiffness index (the ratio of E/e' to LA reservoir strain) was better correlated with hemodynamic and CPET parameters than was E/e′ or LA reservoir strain alone. Pulmonary circulatory reserve as assessed by mean PAP/CO slope was significantly associated with LA stiffness index but not with E/e′ and LA reservoir strain (Table 4).

Table 2
Mechanism, etiology and severity of mitral regurgitation

	N = 30
Mechanism, Etiology	
Flail leaflet	20 (67%)
Prolapse	9 (30%)
Restricted leaflet motion	1 (3%)
Fibroelastic deficiency	10 (33%)
Advanced fibroelastic deficiency	8 (27%)
Forme fruste	6 (20%)
Barlow's disease	5 (17%)
Multi-scallop	9 (30%)
Severity	
Regurgitant fraction, %	54 (14)
VC, mm	5.4 (1.2)
3D-VC area, cm^2	0.62 (0.22)
PV systolic flow reversal	18 (60%)

PV = pulmonary venous; VC = vena contracta.

Table 3
Hemodynamic parameters obtained by right heart catheterization

Hemodynamic parameter	N = 30
at rest	
Systolic blood pressure, mmHg	141 (126 - 150)
Heart rate, bpm	64 (9.3)
Systolic PAP, mmHg	26 (21 − 33)
Mean PAP, mmHg	17 (6.6)
PAWP, mmHg	12 (8.6 − 16)
CO, L/min	4.5 (1.1)
Pulmonary vascular resistance (Wood Unit)	1.2 (0.7)
at peak exercise	
Systolic blood pressure, mmHg	208 (183 − 232)
Heart rate, bpm	132 (18)
Systolic PAP, mmHg	53 (13)
Mean PAP, mmHg	36 (9.8)
PAWP, mmHg	24 (9.9)
CO, L/min	10.9 (2.9)
Pulmonary vascular resistance (Wood Unit)	1.1 (0.7)

CO = cardiac output; PAP = pulmonary arterial pressure; PAWP = pulmonary arterial wedge pressure.

LA stiffness index, HR reserve, and CO reserve were significantly correlated with percent predicted peak VO_2 (Figure 3). Table 5 lists multiple linear regression analyses to explore the factors related to percent predicted peak VO_2. In addition to LA stiffness index, LVEF (model 1), LA volume index (model 2), ΔMR-VC (model 3), HR reserve (model 4), and CO reserve (model 5) were adjusted separately as the independent factors. Therefore, the LA stiffness index was the significant determinant of percent predicted peak VO_2, independently of these confounding factors. HR reserve and CO reserve were also associated with exercise tolerance.

The representative case with higher LA stiffness index and exercise-induced hemodynamic deterioration and effort intolerance is presented in Figure 4.

Discussion

To the best of our knowledge, this is the first report to examine the association of LA stiffness index with the backward transmission of intracardiac pressure and exercise tolerance in patients with asymptomatic or with minimally symptomatic grade ≥III + DMR. In this study, we assessed exercise hemodynamics precisely by right-sided cardiac catheterization. This study suggested that LA stiffness may cause an excessive increase in LA and pulmonary artery pressure, which may worsen the pulmonary circulatory reserve. Consequently, LA stiffness was a significant associated factor with effort intolerance in severe DMR.

Kurt et al[12] first reported the LA stiffness index with the ratio of E/e′ to LA reservoir strain as a noninvasive marker. They showed the correlation of the LA stiffness index with PAP by right-sided cardiac catheterization, similarly to our result. Furthermore, the LA stiffness index was also

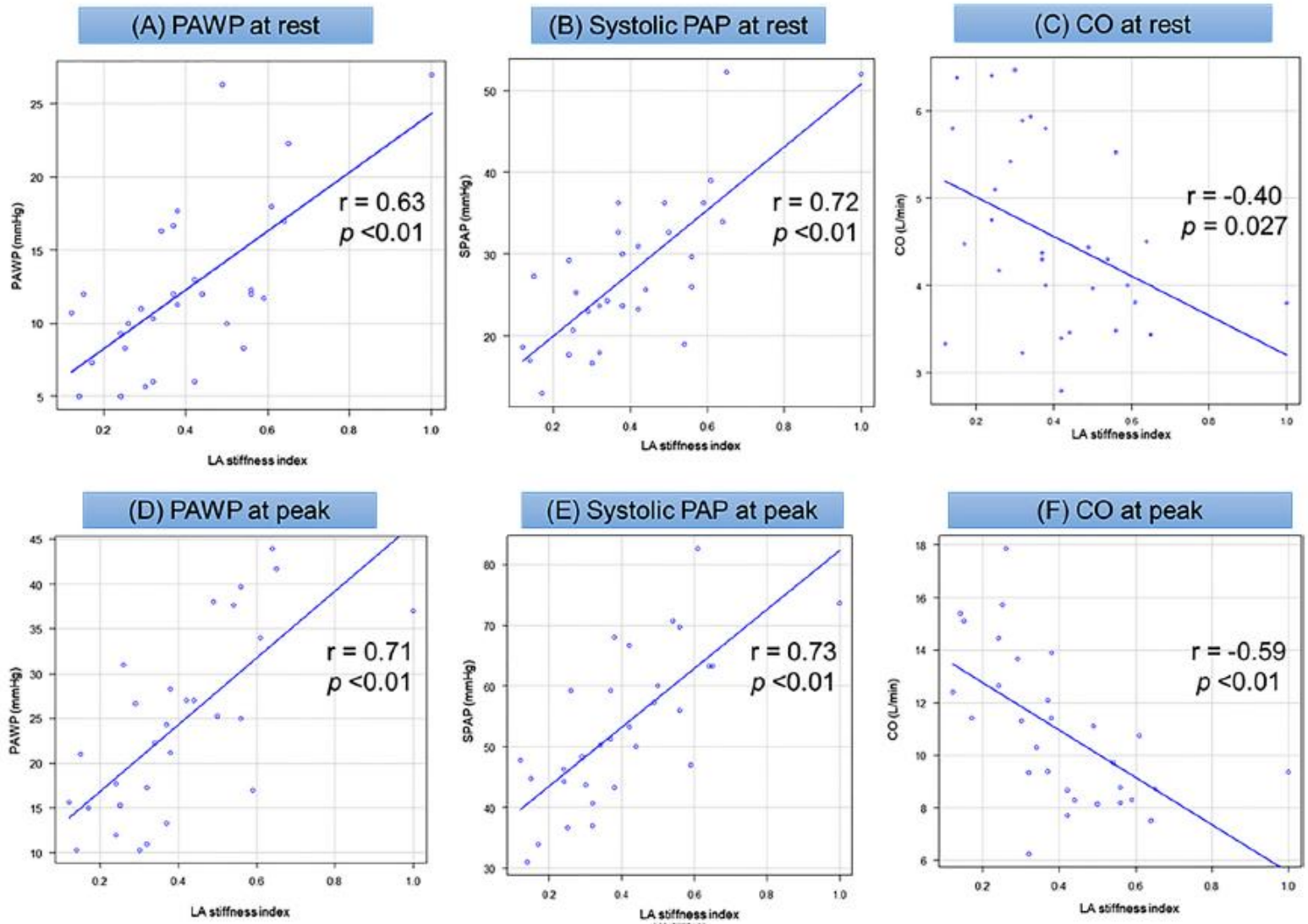

Figure 1. The association of LA stiffness index with hemodynamic parameters at rest and during exercise. The association of LA stiffness index with hemodynamic parameters obtained by right-sided cardiac catheterization was assessed using Spearman's correlation coefficient (*A, B*) or Pearson correlation coefficient (*C–F*). (*A*) PAWP at rest, (*B*) Systolic PAP at rest, (*C*) CO at rest, (*D*) PAWP at peak exercise, (*E*) Systolic PAP at peak exercise, (*F*) CO at peak exercise.

significantly associated with PAWP v wave (r = 0.61, p <0.01; data not shown) in our study, which was considered as supporting the significance as a marker of LA stiffness.

The previous study showed the inverse correlation of LA strain with LA fibrosis as detected by delayed-enhancement magnetic resonance imaging.[15] In the patients with paroxysmal and persistent atrial fibrillation, LA reservoir strain was reported to be associated with low voltage area obtained by electroanatomical mapping, which was considered to represent LA fibrosis.[16] Moreover, the LA reservoir strain has shown correlation with pathologic LA fibrosis confirmed by LA tissue biopsy samples obtained at mitral valve surgery for severe MR[17] and after heart transplantation.[18] The patients with a higher LA stiffness index may have a left atrium with impaired compliance due to LA fibrosis.

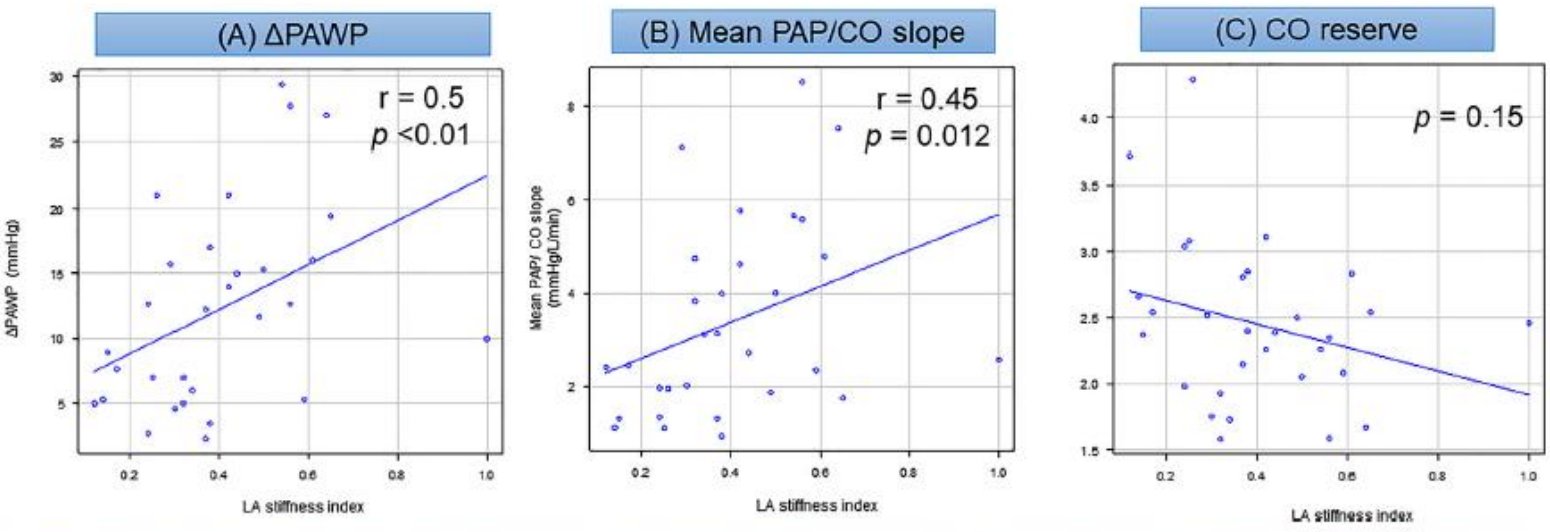

Figure 2. The association of LA stiffness index with exercise-induced hemodynamic response. The association of LA stiffness index with exercise-induced hemodynamic response was assessed using Spearman's correlation coefficient. (*A*) PAWP, (*B*) mean PAP/CO slope, (*C*) CO reserve.

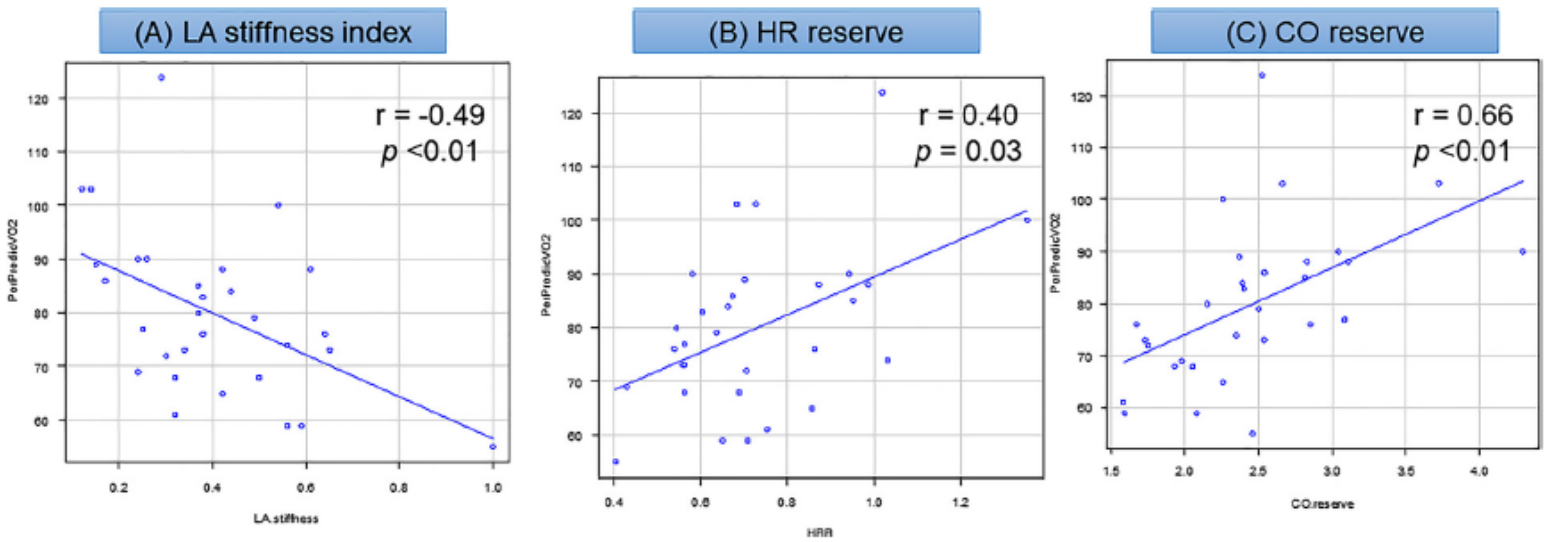

Figure 3. The factors associated with percent predicted peak VO_2. The association of percent predicted peak VO_2 were assessed with (*A*) LA stiffness index, (*B*) HR reserve, (*C*) CO reserve, using Spearman's correlation coefficient.

Table 4
Correlations of left atrial stiffness index, E/e', and left atrial reservoir strain with hemodynamic and cardiopulmonary exercise test parameters

	LA stiffness index		E/e'		LA reservoir strain	
	r	p-value	r	p-value	r	p-value
%predicted peak VO_2, %	−0.49	< 0.01	−0.21	0.28	0.42	0.02
VE vs VCO_2 slope	0.64	< 0.01	0.43	0.02	−0.17	0.36
PAWP at rest, mmHg	0.63	< 0.01	0.55	< 0.01	0.42	0.02
PAWP v-wave, mmHg	0.61	< 0.01	0.49	< 0.01	−0.041	0.83
PAWP at peak, mmHg	0.71	< 0.01	0.53	< 0.01	−0.36	0.0502
ΔPAWP, mmHg	0.50	< 0.01	0.24	0.21	−0.21	0.27
Systolic PAP at rest, mmHg	0.72	< 0.01	0.56	< 0.01	−0.24	0.21
Systolic PAP at peak, mmHg	0.73	< 0.01	0.47	< 0.01	−0.43	0.019
Mean PAP/CO slope, mmHg/L/min	0.45	0.012	0.12	0.51	−0.25	0.18

CO = cardiac output; PAP = pulmonary arterial pressure; PAWP = pulmonary arterial wedge pressure; VE vs VCO_2 slope = ventilatory equivalent versus carbon dioxide output slope; VO_2 = oxygen consumption.

In our previous study, mean PAP/CO slope was an independent predictor of effort intolerance in patients with asymptomatic severe DMR.[3] Mean PAP/CO slope is considered the reserve function influenced by both LA function and the pulmonary circulatory system. The present study has suggested that mean PAP/CO slope may be determined more by LA stiffness than by pulmonary vascular remodeling in patients with early stage DMR because mean PAP/CO slope correlated with LA stiffness index, although the pulmonary vascular resistance, both at rest and at peak exercise, was in the normal range in this study (Table 3).

Table 5
Multiple linear regression analysis for the determinant of %predicted peak VO_2

	model 1				model 2			
	β	95% CI	SE	p-value	β	95% CI	SE	p-value
LA stiffness index (per 0.1 increase)	−3.9	−6.6 — -1.1	1.3	< 0.01	−3.7	−6.5 – −8.8	1.4	0.012
LVEF	−0.21	−1.4 – 0.98	0.58	0.72				
LAVI					−0.25	−0.62 – 0.13	0.18	0.19

	model 3				model 4				model 5			
	β	95% CI	SE	p-value	β	95% CI	SE	p-value	β	95% CI	SE	p-value
LA stiffness index (per 0.1 increase)	−4.0	−6.9 – −1.3	1.4	< 0.01	-3.5	−5.9 – −1.1	1.2	< 0.01	−3.0	−5.5 – −0.46	1.2	0.013
log_eΔMR VC	2.8	−8.8 – 14.4	5.7	0.62								
loge HR reserve					24	7 – 41	8.3	< 0.01				
ΔCO									10.3	2.4 – 18.2	3.9	0.022

CO = cardiac output; HR = heart rate; LA = left atrial; LAVI = left atrial volume index; LVEF = left ventricular ejection fraction; MR VC = mitral regurgitation vena contracta.

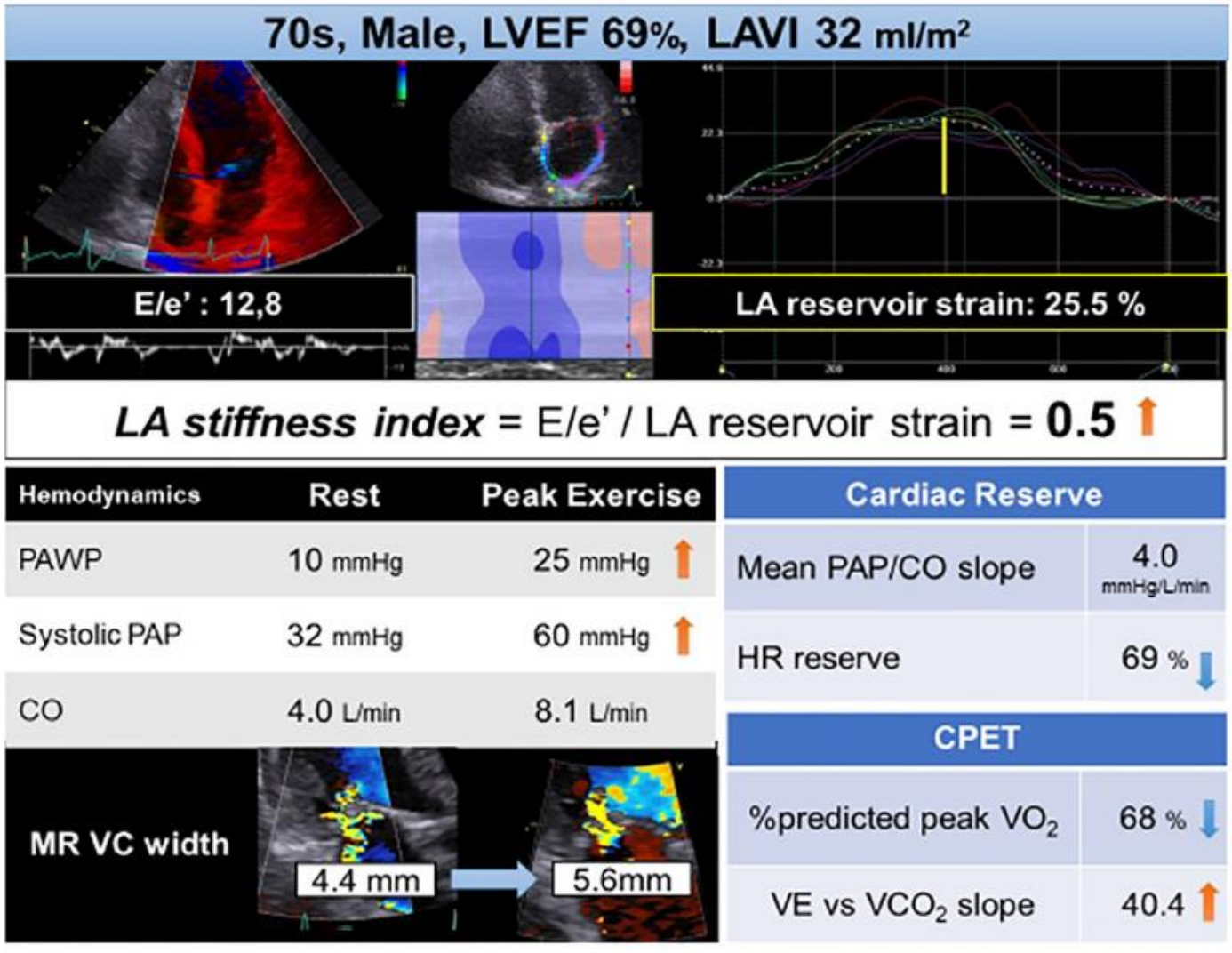

Figure 4. Representative case with a higher LA stiffness index and effort intolerance, and increased PAWP and Systolic PAP. The subject was a male patient in his 60s with grade III + DMR and higher LA stiffness index of 0.5. The result of invasive CPET showed effort intolerance and exercise-induced PAWP and Systolic PAP increase.

This study had some limitations. First, this was a single-center retrospective study with a small number of participants. Therefore, the confounding factors may have been inadequately adjusted. Second, of the 44 participants, 7 patients could not be assessed for inadequate image quality. This was influenced by the 4-chamber view focused on the left atrium not always being obtained for the retrospective study. Third, the severity of MR during exercise was evaluated by the VC and not based on the ASE recommendation. Fourth, we excluded atrial fibrillation because it was considered the trigger of the surgery, and the significance of LA stiffness index was confirmed only in the patients with sinus rhythm. Fifth, the systolic blood pressure at rest was higher than that of the patients with DMR in the previous study.[19,20] Hypertension may have influenced LA stiffness in the small population in this study. Sixth, we used the catheter-measured PAWP, not the direct LA pressure. In addition, the clinical usefulness including the prognostic value of the LA stiffness index has not been shown in this cross-sectional study although the impact of LA stiffness on hemodynamics and exercise capacity in patients with DMR was evaluated. A previous study reported that LA reservoir strain predicted the prognosis after mitral valve surgery in patients with DMR,[21] and another has shown that LA stiffness index was the significant prognosticator in patients with heart failure with preserved EF.[6] Whether early detection of LA dysfunction using the LA stiffness index in this population translates into better outcomes and appropriate timing of surgical intervention remains to be addressed in prospective, larger-scale, and longer-term studies.

In conclusion, LA stiffness as assessed by speckle-tracking echocardiography was significantly associated with hemodynamic deterioration during exercise in patients with asymptomatic/minimally symptomatic severe DMR. In our study population, effort intolerance was associated with LA stiffness in addition to chronotropic incompetence and CO reserve, but not by MR deterioration.

Authors' Contributions

Dr. Takahari is responsible for visualization, investigation, and writing—original draft preparation. Dr. Susawa is responsible for investigation. Dr. Utsunomiya is responsible for ensuring that the descriptions are accurate and agreed by all authors and for conceptualization, methods, funding acquisition, and writing—review and editing. Dr. Tsuchiya is responsible for validation. Dr. Mogami is responsible for investigation. Dr. Takemoto is responsible for investigation. Dr. Izumi is responsible for investigation. Dr. Ueda is responsible for investigation. Dr. Itakura is responsible for formal analysis. Dr. Nakano is responsible for project administration and supervision.

Declaration of Competing Interest

The authors have no competing interests to declare.

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