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Article

Improvement in Left Ventricular Function of the Resected Myocardium after Septal Myectomy in Patients with Aortic Valve Replacement

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Abstract

Background: Some surgeons have previously advocated for a more aggressive concomitant septal myectomy to address left ventricular outflow tract obstruction; however, concerns about the surgical complications of post-septal myectomy remain. Here, we aimed to assess the clinical, echocardiographic, and pathological findings following concomitant septal myectomy with surgical aortic valve replacement. **Methods**: We reviewed 21 patients who underwent surgical aortic valve replacement and concomitant septal myectomy from April 2014 to September 2019. The global and regional left ventricular ejection fraction changes between the perioperative periods were analyzed using two-dimensional speckle-tracking echocardiography. The resected myocardium was pathologically assessed. **Results**: No operative mortality was observed during the study period. Transthoracic echocardiography showed no significant differences in preoperative and postoperative left ventricular ejection fraction (68.1 $\pm$ 9.9% *vs.* 68.6 $\pm$ 6.0%, $p = 0.82$) or interventricular septum thickness (11.9 $\pm$ 1.4 mm *vs.* 11.5 $\pm$ 1.5 mm, $p = 0.23$). Interventricular septum thickness at the end-systolic phase, which is the maximum septal wall thickness, was significantly reduced postoperatively (27.7 $\pm$ 9.3 mm *vs.* 22.6 $\pm$ 5.5 mm, $p < 0.05$). The basal, mid, and apical septal areas improved with septal myectomy by 80%, 230%, and 27%, respectively, compared to perioperative echocardiography (basal septal, 80 $\pm$ 23%; mid septal, 230 $\pm$ 830%; apical septal, 27 $\pm$ 350%). Pathological examination of the resected myocardium revealed marked endocardial thickness (mean, 914 µm) with focal fibrosis. **Conclusions**: In aortic valve stenosis patients with septal hypertrophy, concomitant septal myectomy with surgical aortic valve replacement improved regional myocardial function and eliminated left ventricular outflow tract obstruction by removing thickened endocardium and prominent fibrosis.

Keywords

aortic valve stenosis; left ventricular outflow tract obstruction; strain; myocardial fibrosis

Introduction

The number of patients with aortic valve stenosis (AS) is increasing owing to an aging population and changing lifestyles, leading to a rise in surgical aortic valve replacements (SAVR). Approximately 10% of patients with severe AS exhibit asymmetric basal septal thickening in relation to the left ventricular posterior wall [1]. Moreover, patients with severe AS, concentric left ventricular hypertrophy (LVH), and a sigmoid septum are at risk of developing left ventricular outflow tract obstruction (LVOTO) after SAVR, even in patients with no preoperative indication for LVOTO [2]. Furthermore, reports show that 14–25% of patients experience abnormal intracavitary flow velocities after SAVR [3,4]. While some surgeons have previously advocated for a more aggressive concomitant septal myectomy to address LVOTO because its retention or progression is associated with a poor prognosis [5], there remain concerns about the surgical complications of post-septal myectomy, including ventricular septum rupture or pacemaker implantation (PMI), associated with the surgical intervention for LVOTO concomitant with SAVR [6]. In this study, we retrospectively analyzed patients who underwent SAVR with concomitant septal myectomy to determine the surgical indications and assess the surgical benefit, complications, and cardiac function outcomes.

Materials and Methods

This retrospective single-center study was approved by the institutional review board (approval number: E21-0341-H01), and the requirement to obtain informed consent

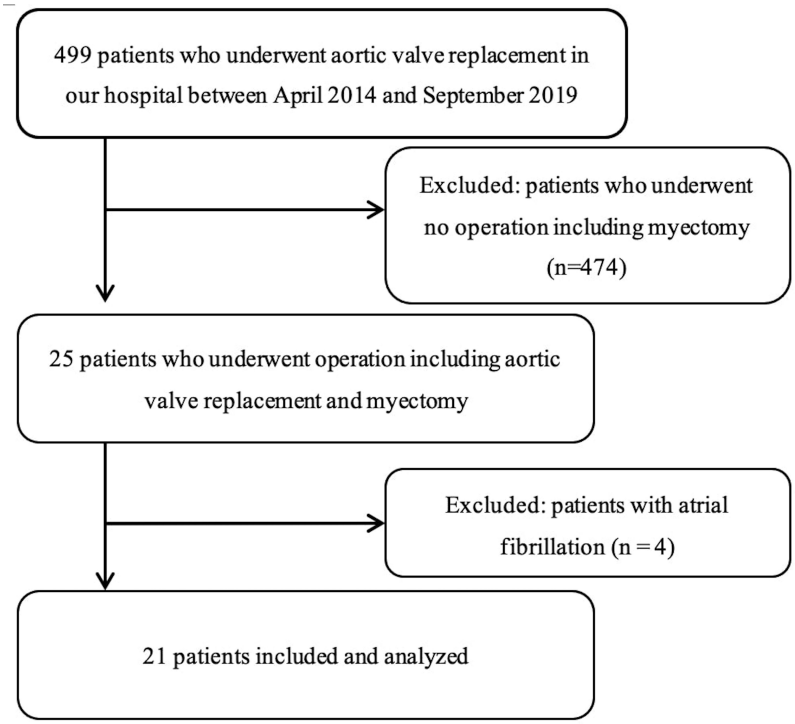

Fig. 1. Flowchart of patient selection.

was waived. The study information, including the study's purpose, was posted on the hospital's website. The patients were guaranteed the opportunity to refuse to participate in this study.

Study Design

We retrospectively identified 499 patients with AS who underwent SAVR at the Department of Cardiovascular Surgery at Juntendo University Hospital between April 2014 and September 2019. Twenty-five patients who underwent concomitant septal myectomy in addition to SAVR were potentially eligible for the study. The criterion for septal myectomy was left ventricular pressure gradient ≥50 mmHg, according to the guidelines [7]. In addition, septal myectomy was performed at the surgeon's discretion based on the following findings: preoperative echocardiographic findings of septal myocardial deformity, e.g., Sigmoid septum; intraoperative findings of the deformity (protrusion) through the transapical aortic valve; or color changes in septal tissue that suggests fibrosis. A total of 25 cases were eligible per the inclusion criteria. Patients with atrial fibrillation (n = 4) were excluded this analysis because an accurate functional measurement would not be possible for such cases. Finally, 21 cases were analyzed in this study (Fig. 1).

Echocardiography

The patients underwent preoperative and postoperative transthoracic echocardiographic studies performed in our hospital laboratory. Basic measurements included left ventricular (LV) wall thickness and LV diameter by two-dimensional-guided linear measurement. Using echocardiography, the interventricular septal thickness (IVST) was measured on a parasternal long-axis view at the end-diastole phase. An electronic caliper was positioned at the interface of the compacted myocardium of the interventricular septum, and a line extending perpendicular to the long axis of the LV to the inner border of the compacted myocardium of the posterior wall was drawn. The measurement was obtained at a level just below the tips of the mitral valve leaflet. Additionally, we measured the IVST at the end-systolic phase (IVSTs) representing the maximum septal wall thickness. The left ventricular ejection fraction (LVEF) was measured using the modified biplane Simpson method, as recommended by the American Society of Echocardiography [8]. To determine the timing of cardiac events, the mitral inflow and LV outflow were recorded using pulsed Doppler echocardiography. Two-dimensional echocardiography (2DE) images of the LV were acquired at the basal, mid, and apical levels using the same echocardiography machine. Three consecutive cardiac cycles were recorded and averaged. We defined the onset of the QRS complex (at ventricular end-diastole) as the zero strain, and all longitudinal LV strain values were expressed as absolute values. The recordings were processed using acoustic-tracking dedicated software (Two-Dimensional Cardiac Performance Analysis, TomTec Imaging System, Munich, Germany). This is an offline myocardial performance analysis system that uses digital imaging and communications in medicine

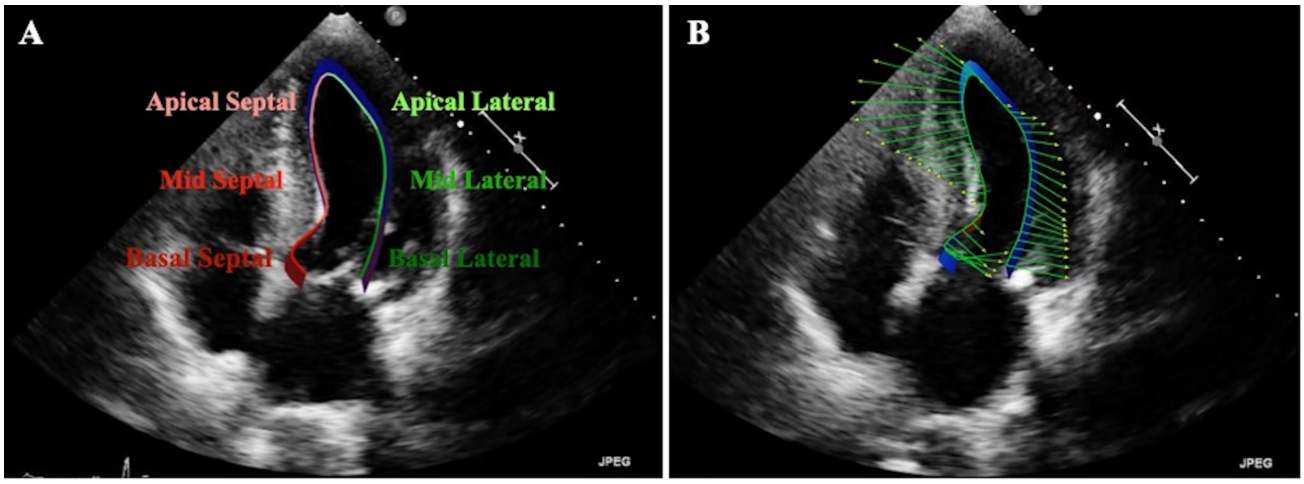

Fig. 2. Strain measurement. (A) Measurements were obtained using automatic boundary detection and manual correction, tracing the endocardial boundaries of each chamber at end-diastole and end-systole. (B) Left ventricular myocardial longitudinal strain was measured by segment site, and the strain data of each segment were compared with the preoperative and postoperative differences.

(DICOM) files from any echocardiography machine. Endocardial borders were traced in the end-systolic frame, and we created a region of interest after manual adjustment of the endocardial layer from 2DE images of the LV in apical 4-chamber (4ch), 2-chamber (2ch), and 3-chamber (3ch) views. LV myocardial longitudinal strain was measured by 18 segment sites (6 basal, 6 mid, and 6 apical segments) from each chamber apical view (Fig. 2). The strain data at each segment was compared between the postoperative and preoperative differences.

Septal Myectomy Procedure

The septal myectomy process was to observe the septal myocardium through the transaortic valve in all cases. If septal myocardial protrusion or tissue with color changes suggestive of fibrosis was observed, resection was performed to eliminate the protrusion.

Pathological Analysis

The resected myocardium tissue samples were submitted to the pathology laboratory, rather than evaluated in the operating room, and processed according to the laboratory protocol. In brief, the tissue was fixed in 4% paraformaldehyde in 0.1-M phosphate buffer (Trichrome stain (Masson) Kit, SLBK9565V, Sigma-Aldrich, Tokyo, Japan) for 48 hours, dehydrated, and embedded in paraffin. The remaining tissue block was transported to the cardiovascular surgery laboratory, sectioned to a thickness of 4-μm, and mounted on glass slides. Masson's trichrome staining was subsequently performed according to the manufacturer's protocol (Sigma-Aldrich, Tokyo, Japan) to assess the extent of fibrosis in the cardiac muscle.

Table 1. Baseline clinical and demographic data.

Variable	
Patients (n)	21
Age, years (range)	74.2 ± 6.4
Male (%)	6 (29)
BMI, kg/m^2 (range)	23.3 ± 5.1
Hypertension, n (%)	15 (71)
Dyslipidemia, n (%)	12 (57)
Diabetes, n (%)	4 (19)
Chronic kidney disease, n (%)	10 (48)
Hemodialysis, n (%)	2 (10)

BMI, body mass index.

Statistical Analysis

All data are presented as the mean ± standard deviation. Statistical analyses were performed using SPSS Statistics, version 27 (IBM, Tokyo, Japan). Paired *t*-test was used to compare the significant differences between the pairs after ascertaining homogeneity of variance by Levene's test. Chi-square tests were used to compare the proportions of categorical variables between the two groups. A p-value $<$ 0.05 was considered statistically significant.

Results

Characteristics of the Patients

The baseline characteristics of the participants are presented in Table 1. The mean age at operation was 74.2 ± 6.4 years. There were 6 male patients (29%), with comorbidities of hypertension (71%), dyslipidemia (57%), and chronic kidney disease (48%) (estimated glomerular filtration rate <60) respectively. Among them were two dialysis patients.

Table 2. Echocardiographic variables.

Variable	Preoperative (n = 21)	Postoperative (n = 21)	*p*-value
LVDd, mm (range)	43.6 ± 4.2	41.7 ± 4.0	0.11
LVDs, mm (range)	26.2 ± 3.6	25.7 ± 3.1	0.48
IVST, mm (range)	11.9 ± 1.4	11.5 ± 1.5	0.23
IVSTs, mm (range)	27.7 ± 9.3	22.6 ± 5.5	<0.05
PWT, mm (range)	11.7 ± 1.4	11.0 ± 1.4	0.06
SV, mm (range)	31.3 ± 3.2	31.1 ± 3.1	0.83
AoD, mm (range)	35.4 ± 4.6	30.7 ± 4.7	0.75
LAD, mm (range)	39.8 ± 8.8	39.3 ± 5.2	0.76
RVD, mm (range)	22.7 ± 2.5	23.4 ± 2.3	0.31
LVEF, % (range)	68.1 ± 9.9	68.6 ± 6.0	0.82
Vmax, m/s (range)	3.9 ± 1.3	2.2 ± 0.5	<0.05
MPG, mmHg (range)	42.7 ± 7.2	10.8 ± 4.7	<0.05
eRVP, mm (range)	29.5 ± 7.2	28.7 ± 5.9	0.56

LVDd, left ventricular end-diastolic diameter; LVDs, left ventricular end-systolic diameter; IVST, interventricular septum thickness; IVSTs, interventricular septum end-systolic thickness; PWT, posterior left ventricular wall thickness; SV, sinus of Valsalva diameter; AoD, aorta diameter; LAD, left atrium diameter; RVD, right ventricular diameter; LVEF, left ventricular ejection fraction; Vmax, maximum aortic jet velocity; MPG, mean aortic valve pressure gradient; eRVP, estimated right ventricular pressure.

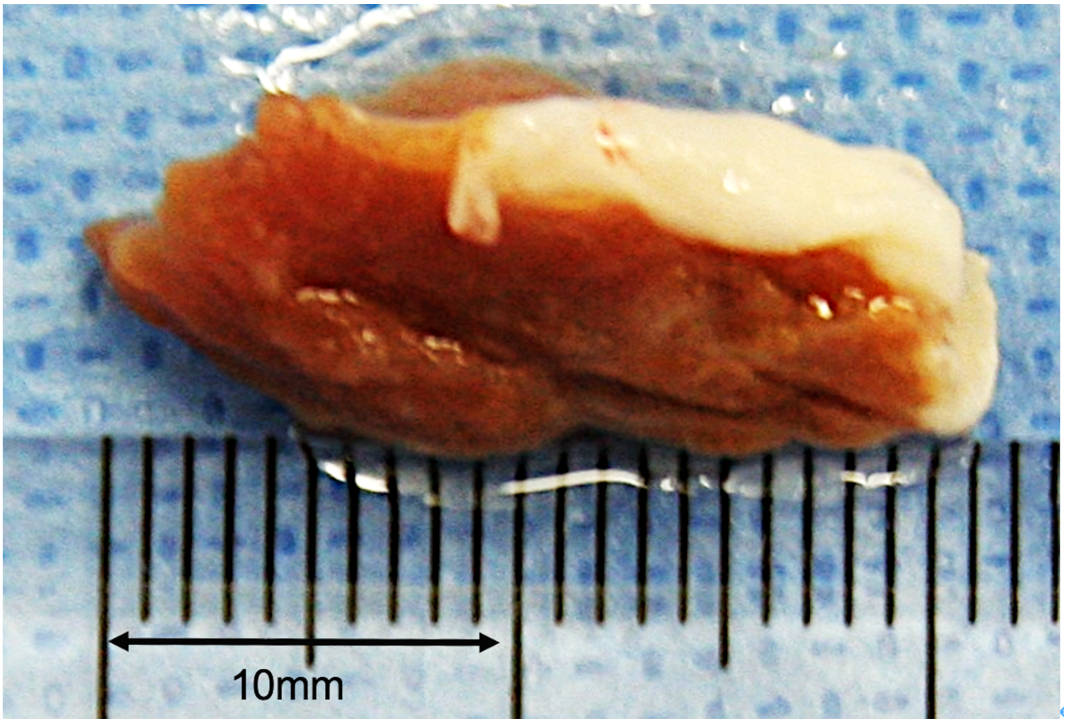

Fig. 3. Morphology of resected myocardium. The white tissue represents the endocardium. Resected myocardium. Thickened fibrotic tissue on the endocardial side.

Echocardiogram

Cardiac function was assessed preoperatively using echocardiography and at around 1 week postoperatively (Table 2). Preoperative and postoperative transthoracic echocardiography showed no significant differences in LVEF (68.1 ± 9.9% *vs.* 68.6 ± 6.0%, $p = 0.82$), left ventricular end-diastolic diameter (LVDd), and left ventricular end-systolic diameter (LVDs) between preoperative and postoperative periods. There were significant differences in the aortic valve maximum blood flow velocity (Vmax, 3.9 ± 1.3 m/s *vs.* 2.2 ± 0.5 m/s, $p < 0.05$) and mean aortic valve pressure gradient (MPG, 42.7 ± 7.2 mmHg *vs.* 10.8 ± 4.7 mmHg, $p < 0.05$) between preoperative and postop-

Table 3. Regional myocardial strain.

	Variable	Preoperative strain	Postoperative strain	Strain change
		% (Mean ± SD)	% (Mean ± SD)	% (Mean ± SD)
		(n = 21)	(n = 21)	(n = 21)
4ch view	Basal septal	–13 ± 8	–11 ± 7	80 ± 23
	Mid septal	–11 ± 7	–10 ± 7	230 ± 830
	Apical septal	–30 ± 21	–16 ± 12	27 ± 350
	Apical lateral	–29 ± 13	–21 ±14	73 ± 450
	Mid lateral	–17 ± 8	–13 ± 10	–12 ± 94
	Basal lateral	–19 ± 8	–18 ± 10	8 ± 78
2ch view	Basal inferior	–15 ± 8	–15 ± 8	52 ± 140
	Mid inferior	–11 ± 7	–9 ± 5	140 ± 520
	Apical inferior	–34 ± 11	–25 ± 13	–8 ± 85
	Apical anterior	–27 ± 12	–22 ± 12	31 ± 170
	Mid anterior	–15 ± 7	–14 ± 8	2 ± 57
	Basal anterior	–22 ± 13	–13 ± 8	18 ± 190
3ch view	Basal posterior	–18 ± 10	–17 ±12	90 ± 380
	Mid posterior	–14 ± 9	–15 ± 10	120 ± 350
	Apical lateral	–23 ± 15	–18 ± 19	52 ± 340
	Apical anterior	–28 ± 15	–21 ±11	110 ± 450
	Mid anteroseptal	–14 ± 7	–9 ± 6	14 ± 150
	Basal anteroseptal	–10 ± 7	–9 ± 7	80 ± 260

4ch, four-chamber; 2ch, two-chamber; 3ch, three-chamber.

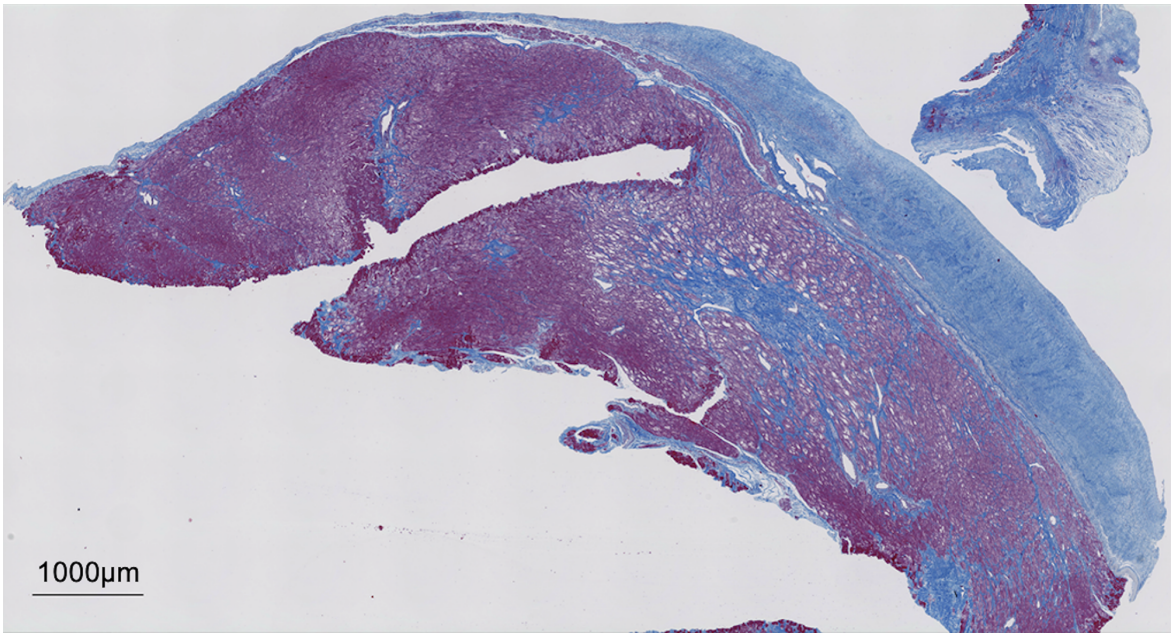

Fig. 4. Masson's trichrome staining of the resected myocardium. Thickened fibrotic tissue is seen on the endocardial side (Scale bar, 1000 μm).

erative periods. IVST was not reduced, despite the addition of concomitant septal myectomy. We measured and compared IVSTs, which was significantly reduced postoperatively (27.7 ± 9.3 mm *vs*. 22.6 ± 5.5 mm, $p < 0.05$).

Strain Analysis

Strain analyses using the echocardiography images were performed, and the wall motion during the postoperative period was compared with the preoperative data in each section. The analyses were performed at three different views: 4ch, 2ch, and 3ch (Table 3). The basal septal,

Table 4. Operative outcomes.

Variable	n = 21
Incubation time, hours (range)	8.1 ± 4.0
ICU stay, days (range)	4.0 ± 3.8
Hospital stays, days (range)	21.8 ± 17.4
Prosthetic valve size, mm (range)	21.8 ± 2.2
Follow-up period, years (range)	3.7 ± 2.0
Mortality (%)	2 (9.5)
PMI (%)	6 (28.6)
Postoperative LVOTO (%)	0 (0.0)

ICU, intensive care unit; LVOTO, left ventricular outflow tract obstruction; PMI, pacemaker implantation.

mid septal, and apical septal areas of septal myectomy improved by 80%, 230%, and 27%, respectively, compared to the preoperative and postoperative echocardiography (basal septal; 80 ± 23%, mid septal; 230 ± 830%, apical septal; 27 ± 350%). The overall area also improved by 61% (61 ± 59%).

Pathological Examination

The macroscopic appearance of the resected myocardium is shown in Fig. 3. White tissue indicates the endocardium. Masson's trichrome staining revealed that the endocardium became thickened by marked fibrosis (Fig. 4). The average thickness by fibrosis was 914 µm (108–2946 µm of range). No correlation was detected between the thickness of the fibrotic tissue and septum wall thickness measured using echocardiogram (IVSTs) (Fig. 5).

Early and Long Operative Outcomes

The early and long operative outcomes are presented in Table 4. The follow-up period at operation was 3.7 ± 2.0 years. The intensive care unit (ICU) and hospital stays were 4.0 ± 3.8 days and 21.8 ± 17.4 days, respectively. There were two deaths during the follow-up period (9.5%): one was caused by infection, and the other was noncardiac related. Postoperative PMI was performed in six cases (28.6%); of these, four cases had complete atrioventricular blocks, one case had symptomatic bradycardia due to AF, and one case had sick sinus syndrome. No cases of postoperative LVOTO were observed.

Discussion

In this study, we used strain analysis to retrospectively assess the regional function at the site of the resected septum in patients who underwent SAVR with concomitant septal myectomy. A thorough histological assessment of the resected tissue was performed, demonstrating the functional benefits of septum resection. Our findings suggest that concomitant septal myectomy should be considered for patients with AS requiring SAVR, particularly those with a thickened or deformed septal wall, such as a sigmoid septum.

Fibrotic Change in the Endocardium

Fibrotic changes in the endocardium were observed during our histological analysis, revealing a notable thickening due to fibrosis, with a maximum thickness of approximately 3000 µm. Previous studies have shown that patients with hypertrophic cardiomyopathy (HCM) are more likely to develop septal wall thickening accompanied by fibrotic remodeling of the endocardium [9]. However, approximately 50% of HCM cases are caused by mutations in sarcomere genes [10]. Although mutant sarcomere genes are known to trigger myocardial changes leading to hypertrophy and fibrosis, the mechanism behind fibrotic alterations in non-genetic hypertrophy remains poorly understood. Shear stress has been proposed as a potential mechanism, as stress can activate angiotensin II, subsequently enhancing tumor growth factor-beta, which is an inducible factor for fibrosis [11]. Furthermore, our study population included not only hypertrophic cases but also included individuals with a sigmoid septum. A sigmoid septum, characterized by an angulation between the basal ventricular septum and the ascending aorta, was first reported in 1969 by Goor *et al*. [12]. Although a sigmoid septum alone lacks pathological or clinical significance [13], a hypercontractile cardiac state coupled with a decrease in intravascular blood volume can lead to narrowing of the left ventricular outflow tract (LVOT), resulting in dynamic obstruction, particularly under physical stress. This deformity is also susceptible to shear stress from blood flow, which can result in fibrotic changes at the site. Progressive fibrosis contributes to increased ventricular stiffness, ultimately restricting wall motion. By resecting the fibrotic tissue, the regional wall motion was improved, although the global LVEF did not significantly improve during this study period.

Strain Analysis

Two-dimensional speckle tracking echocardiography (2D-STE) is a recent technique for tracking myocardial wall motion using cardiac imaging [14]. It is considered the most accurate and sensitive parameter for the assessment of early left ventricular dysfunction [15]. In this study, we used a strain analysis to assess regional myocardial function. Our results indicated that the strain analysis clearly demonstrated an improvement in the wall motion at the resected site. In contrast, the global LVEF was not affected by myectomy. Furthermore, the improvement had already appeared in the acute phase after surgery when the myocardial damage induced by the surgery remained. These results suggest that the benefit was not from the improvement

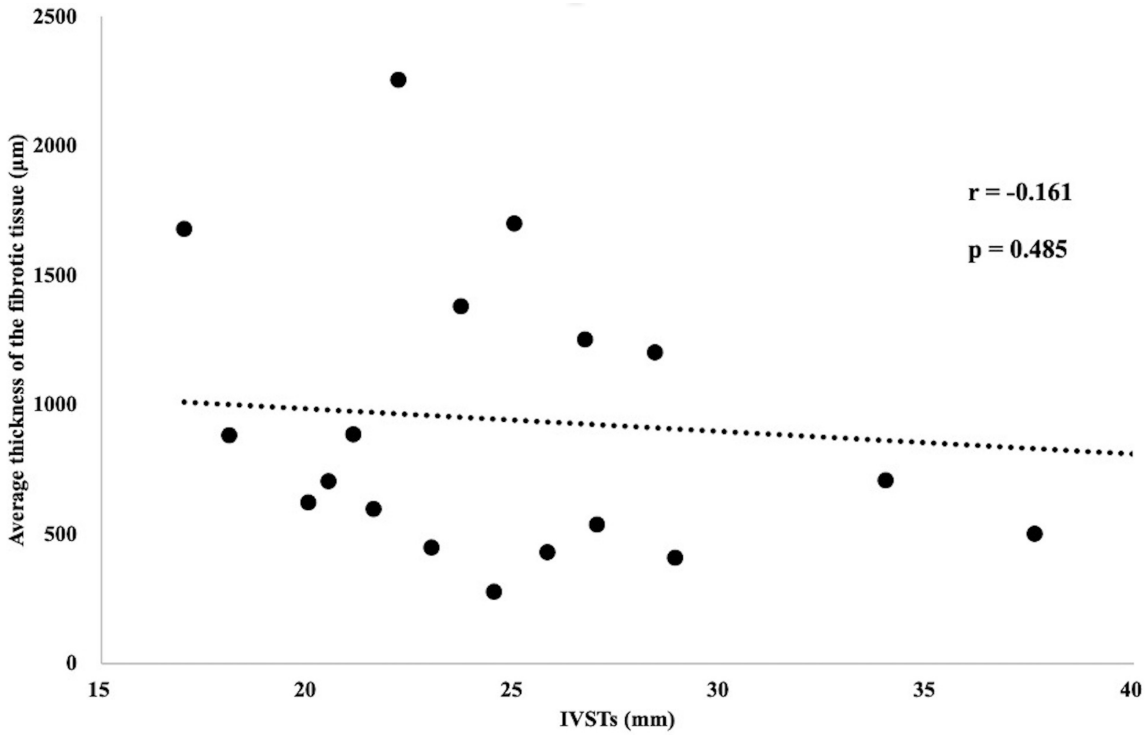

Fig. 5. Maximum septal wall thickness and fibrosis. Correlation curve between IVSTs and fibrosis; correlation was not significant. r = Pearson's correlation coefficient; IVSTs, interventricular septum end-systolic thickness.

of hemodynamics owing to the release of the stenosis, but may have been derived from the resection of the stiff endocardium itself.

Surgical Indication for Concomitant Septal Myectomy with AS

Current guidelines for septal reduction therapy in hypertrophic cardiomyopathy recommend considering concomitant surgical septal myectomy in cases of aortic valve disease requiring surgical treatment. However, there are no established criteria for determining the extent of septal myocardial hypertrophy that should be resected [1,6,7,13,16]. According to past publications, concomitant septal myectomy in SAVR was often performed in cases of marked septal hypertrophy identified through echocardiography or by the surgeon's intraoperative judgment. The purpose of septal myectomy is to relieve LVOTO or for postoperative prevention. The indication for septal myectomy is defined in the guidelines as LVOT pressure gradient >50 mmHg according to HCM treatment. In this study, one of the indication criteria for concomitant septal myectomy was based on the intraoperative judgment of the surgeon in addition to the guidelines of isolated septal myectomy. Notably, 6 out of 21 cases (28.5%) matched the indication of the guideline. However, a previous report also recommended septal myectomy for those at high risk for future LVOTO [2]. Retrospective review of the patients' data revealed that IVST was >15 mm in all cases, consistent with the Japanese guidelines that a maximum LV wall thickness of ≥15 mm was considered a clinical feature of hypertrophic cardiomyopathy [17]. In addition, IVST is conventionally measured at end-diastole, however one report found a greater correlation between IVSTs than IVST at the end-diastolic phase (IVSTd) in a comparison of echocardiographic and necropsy [18]. In the present case, preoperative IVSTs were 2.32 times greater than IVSTd. This was 1.6 times greater than the group that underwent SAVR without septal myectomy at the same period. This difference in the ratio of IVSTd to IVSTs suggests septal deformity. It is thought that the risk factors for LVOTO following SAVR were LV septal hypertrophy (sigmoid septum) and a relatively narrow LVOT [2]. This indicated that the cohort in this study may have been at higher risk for LVOTO after surgery. As mentioned above, blood flow to the deformed region causes some stress on the myocardium, which may lead to further thickening and fibrosis. According to previous reports [19,20], the thickness of fibrotic tissue in the LV septum of normal patients is approximately 17.7–26.4 μm. In contrast, the thinnest septum was 108 μm in this cohort. In addition, as shown in Fig. 5, there was no correlation of thickness between IVSTs and fibrosis. These results indicate that even a very small deformity induced the fibrotic change in the septum tissue. If left untreated, further blood flow stress may accelerate the progression of fibrosis, suggesting that the myocardium should be resected if fibrosis is present. However, the evaluation method for fibrosis is difficult with echocardiography, and cardiac mag-

netic resonance imaging (MRI) is now considered useful [9,21,22]. The pressure gradient was difficult to evaluate because it was not measured in all cases. Furthermore, the hard tissue covering the myocardium could have caused impaired myocardial motion. In this study, regional myocardial function was improved by resection of the fibrotic tissue. Contrastingly, concomitant septal myectomy resulted in a longer postoperative hospital stay (mean: 22 days, median: 17 days), mainly due to six cases of PMI. However, the purpose of the hypertrophic myocardial resection was to prevent LVOTO, and no case of LVOTO occurred after the procedure, suggesting its effectiveness. Our findings represent a breakthrough as they introduce the concept of fibrosis as a quality factor in the indication for surgery, which was previously evaluated solely based on the pressure gradient. In the future, the preoperative assessment of fibrosis may be an important factor in determining whether concomitant septal myectomy should be performed.

Limitations

This study had some limitations. First, this was a retrospective, single-center study with a small sample size. Second, the decision for septal myectomy was mostly based on an intraoperative assessment by the operating surgeon, except for the patients who met the surgical indication for septal myectomy (N = 6). Lastly, no control group was available to compare outcomes and determine whether septal myectomy had a significant impact. Because the potential selection bias could not be eliminated due to variations in the surgical indications, this study was performed as a descriptive analysis. Therefore, future studies should aim to develop a method for evaluating preoperative fibrosis and establishing criteria for determining whether resection is necessary.

Conclusions

Resection of endocardial thickening and prominent fibrosis significantly improved the regional strain in the septum. In AS patients with LVH or a sigmoid septum, concomitant septal myectomy with SAVR improved the regional myocardial function and eliminated LVOTO.

Abbreviations

IVSTs, interventricular septum thickness at the end-systolic phase; AS, aortic valve stenosis; SAVR, surgical aortic valve replacement; LVH, left ventricular hypertrophy; LVOTO, left ventricular outflow tract obstruction; PMI, pacemaker implantation; AF, atrial fibrillation; LV, left ventricular; IVST, interventricular septum thickness; 2DE, Two-dimensional echocardiography; DICOM, digital imaging and communications in medicine; 4ch, four-chamber; 2ch, two-chamber; 3ch, three-chamber; LVDd, left ventricular end-diastolic diameter; LVDs, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction; Vmax, maximum aortic jet velocity; MPG, mean aortic valve pressure gradient; ICU, Intensive care unit; HCM, hypertrophic cardiomyopathy; LVOT, left ventricular outflow tract; 2D-STE, two-dimensional speckle tracking echocardiography; IVSTd, interventricular septum thickness at the end-diastolic phase; MRI, magnetic resonance imaging; BMI, body mass index; PWT, posterior left ventricular wall thickness; SV, sinus of Valsalva diameter; AoD, aorta diameter; LAD, left atrium diameter; RVD, right ventricular diameter; eRVP, estimated right ventricular pressure.

Availability of Data and Materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

YK and SMa contributed to the design of the study, the analysis of the data, the interpretation of the results, and the writing the manuscript. SMi contributed to the acquisition of and maintaining the data, the analysis of the data, the interpretation of the result, and critically reviewed the manuscript. RM contributed to the acquisition of and maintaining the data and critically reviewed the manuscript. KK, HI and AA contributed to the acquisition of samples, the design of the study, the interpretation of the results, and critically reviewed the manuscript. TM contributed to the interpretation of the results and critically reviewed the manuscript. MT contributed to the design of the study, interpretation of the results, and critically reviewed the manuscript. All authors finally approved the final version of the manuscript. All authors contributed to editorial changes in the manuscript. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

This study was approved by the ethics committee of Juntendo University Department of Medicine, Research and Ethics Committee on February 24, 2022 (Approval number: E21-0341-H01). The requirement to obtain informed consent was waived. The study information, in-

cluding the study's purpose, was posted on the hospital's website. The patients were guaranteed the opportunity to refuse to participate in this study.

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Conflict of Interest

The authors declare no conflict of interest.

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