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Original Research

# The Ozaki Procedure: Standardized Protocol Adoption of a Complex Innovative Procedure

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ABSTRACT

*Background:* The Ozaki procedure using autologous pericardium is an interesting but complex alternative for aortic valve replacement. We present a standardized approach to minimize the learning curve and confirm reproducibility.
*Methods:* After careful preparation, from May 2015 to February 2021, an Ozaki procedure was performed on 46 patients age 51 ± 14 years. Seven had unicuspid (15%), 29 bicuspid (63%), and 10 tricuspid (22%) aortic valves, and 2 patients had endocarditis. Endpoints were operative learning curves, perioperative outcomes, intermediate-term valve hemodynamics, reintervention, health-related quality of life (MacNew Heart Disease Health-Related Quality of Life questionnaire), and mortality.
*Results:* Cardiopulmonary bypass and aortic clamp times decreased from 145 to 125 minutes and 120 to 100 minutes, respectively, over the first 20 cases, reflecting the learning curve. There was no major perioperative morbidity or mortality. Median postoperative stay was 6.9 days. Aortic regurgitation was mild or less in all but 2 patients who developed moderate aortic regurgitation. Mean aortic valve gradient was 7.9 mmHg postoperatively, 9.2 mmHg by 6 months, and constant thereafter. Left ventricular ejection fraction was 58% preoperatively, 60% at 6 months, and remained stable thereafter. One patient developed infective endocarditis 7 months postoperatively, failed medical management, and underwent valve replacement at 14 months. Two-year survival was 96%, with 1 noncardiac death at 16 months. Health-related quality of life in mental, physical, and emotional domains was better than matched norms, global 6.2 vs. 5.0 ($p < 0.0001$).
*Conclusions:* Using a well-prepared standardized approach, the Ozaki procedure is reproducible with a short learning curve, excellent hemodynamic performance, and good quality of life.

ABBREVIATIONS

4DCT, 4-dimensional computed tomography.; HALT, hypoattenuated leaflet thickening.

## Introduction

The Ozaki procedure is a new alternative for aortic valve replacement that uses autologous pericardium to reconstruct a 3-cusp aortic valve within the native annulus and root. Ozaki and colleagues[1] had developed a tool set that included sizers and a cusp template and described the operation stitch by stitch to obtain reproducibility. Cusps were designed to create a large zone of coaptation to minimize cusp strain and stress while providing a large effective orifice area. As of 2021, Ozaki and his group's pioneering series spans 1196 patients aged 11 to 90 years. At 10-year follow-up, this original series showed a mean gradient of 8 mmHg, 93.4% freedom from moderate or greater aortic regurgitation, 91.2% freedom from reoperation, and 75%

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survival.[2,3] They also noticed that the valves did not calcify rapidly in patients on chronic renal dialysis.[4] Compared with Edwards Lifescience's PERIMOUNT bovine pericardial valve, Ozaki valves exhibited lower valve gradients but greater aortic regurgitation.[5]

Encouraged by promising early outcomes and use of autologous tissue in combination with available tools and a detailed description, the Ozaki procedure was introduced at Cleveland Clinic in 2015. We hypothesized that although the procedure was complex and innovative, with proper preparation and a standardized approach it would have a short learning curve, be reproducible, and provide excellent hemodynamics. Given its use of autologous tissue and potential for longer durability, we believed the procedure would be of particular interest to younger patients with aortic valve disease wishing to avoid the anticoagulation required for mechanical prostheses and the medium-term deterioration of bioprostheses. We describe our disciplined approach to adoption of this new procedure, its operative learning curves, perioperative outcomes, intermediate-term hemodynamic performance, and cusp remodeling observations, reintervention, postoperative health-related quality of life, and mortality.

## Patients and Methods

### *Patients*

From May 2015 to February 2021, 50 patients underwent an Ozaki procedure under an institutional review board–monitored innovative therapy protocol. The procedure was offered to any normal-risk patient age 75 years or younger with aortic valve disease requiring valve replacement. The only exclusion criterion was more than mildly dilated aortic sinuses, which for an average size individual is > 40 mm. One pediatric patient and 3 patients undergoing single-cusp replacement were excluded from the study, resulting in a final cohort of 46 patients.

The mean patient age was 51 ± 14 years and 83% had New York Heart Association class II or III symptoms (Table 1). Seven patients had unicuspid, 29 bicuspid, and 10 tricuspid aortic valves. Twenty-seven patients had isolated aortic stenosis (59%) with a median aortic valve area of 0.7 (0.50/0.94) $cm^2$ and a mean gradient of 53 ± 18 mmHg, and 3 had mixed stenotic and regurgitant lesions (6.5%) with a median aortic valve area of 0.78 (0.53/1.04) $cm^2$, mean gradient of 42 ± 17 mmHg, and moderate regurgitation. Sixteen patients had severe regurgitation (35%), 5 of whom had evidence of active (n = 2) or healed (n = 3) infective endocarditis.

### *Ozaki Procedure*

The Ozaki procedure was performed by 2 surgeons (G.B.P., S.U.) who adhered to a strict, uniform operative protocol described by Ozaki and colleagues.[1] Only autologous pericardium was used. Surgeon preparation included visiting Professor Ozaki in Tokyo to observe several procedures and wet lab practice. The first 2 Ozaki procedures in Cleveland, first in the United States, were performed under Ozaki's personal presence and guidance.

Briefly, a large piece of autologous pericardium was harvested, and redundant tissue and fat removed. The excised pericardium was mounted, stretched on a metal plate, and treated with a 0.6% glutaraldehyde solution for 10 minutes, followed by rinsing 3 × 6 minutes in normal saline. Diseased valve cusps were excised and annulus calcification meticulously removed. Cusp size was determined by intercommissural distance measured with Ozaki sizers (Tokyo Research Center for Advanced Surgical Technology Co., Ltd, Tokyo).

Initially, in patients with unicuspid and bicuspid valves, visible raphes were used for commissure locations and unequal cusp sizes accepted; however, from patient #29 on, all received equal-sized cusps (equal tricuspidization), a technical modification introduced by Ozaki (personal communication). For patients with unequal commissural/raphe distance, new commissures were created to accommodate 3 equal-sized cusps. Cusps were drawn and cut from treated and dried pericardium using the Ozaki template. They were then implanted with the smooth surface of the pericardium facing the ventricle and individually sutured to the annulus with running 4 to 0 monofilament suture according to dots on the template, creating a cusp belly.

Thirty patients had isolated Ozaki procedures, and 16 had concomitant procedures (Table 2). Of the 16 patients, 4 underwent

**Table 1**
Preoperative patient characteristics (N = 46)

| Characteristics | n* | Value† |
|---|---|---|
| Demographics | | |
| Age (y) | 46 | 51 ± 14 |
| Female | 46 | 19 (41) |
| Body mass index (kg/$m^2$) | 46 | 30 ± 5.2 |
| Symptoms | | |
| NYHA functional class | 46 | |
| I | | 8 (17) |
| II | | 31 (67) |
| III | | 7 (15) |
| Aortic valve pathology | | |
| Regurgitation | 46 | |
| None | | 11 (24) |
| Mild | | 11 (24) |
| Moderate | | 7 (15) |
| Severe | | 17 (37) |
| Stenosis | 46 | 33 (72) |
| Aortic valve morphology | | |
| Number of cusps | 46 | |
| Unicuspid | | 7 (15) |
| Bicuspid | | 29 (63) |
| Tricuspid | | 10 (22) |
| Cusp symmetry | 46 | |
| Equal | | 28 (61) |
| Nonequal | | 18 (39) |
| Aortic valve etiology | | |
| Degenerative | 46 | 12 (26) |
| Endocarditis | 46 | 2 (4.3) |
| Bicuspid or unicuspid | 46 | 33 (72) |
| Left ventricular function | | |
| Ejection fraction (%) | 46 | 58 ± 7.8 |
| Cardiac comorbidity | | |
| Atrial fibrillation or flutter | 46 | 5 (11) |
| Complete heart block/pacer | 46 | 0 (0) |
| Ventricular tachycardia or fibrillation | 46 | 1 (2.2) |
| Prior cardiovascular surgery | 46 | 7 (15) |
| Noncardiac comorbidity | | |
| Hypertension | 46 | 23 (50) |
| Diabetes | | |
| Pharmacologically treated | 46 | 6 (13) |
| Insulin treated | 46 | 2 (4.3) |
| Renal dialysis | 46 | 2 (4.3) |
| Stroke | 46 | 1 (2.2) |
| Creatinine (mg/dL) | 46 | 0.96 (0.71/1.2) |

NYHA, New York Heart Association.
* Patients with data available.
† No. (%), mean ± standard deviation, or median (15th/85th percentiles).

**Table 2**
Operative details (N = 46)

| Details | No. (%) or mean ± SD |
|---|---|
| Isolated Ozaki procedure | 30 (65) |
| Concomitant procedure | |
| Ascending aorta replacement | 2 (4.3) |
| Reduction aortoplasty | 4 (8.6) |
| Coronary artery bypass grafting | 2 (4.3) |
| Mitral valve repair | 1 (2.2) |
| Maze | 2 (4.3) |
| Left atrial appendage ligation/excision | 3 (6.5) |
| Intraoperative conversion to prosthetic valve | 0 (0) |
| Second cardioplegic arrest | 2 (4.3) |
| Support | |
| Aortic clamp time (min) | 110 ± 18 |
| Cardiopulmonary bypass time (min) | 129 ± 24 |

reduction aortoplasty, 2 ascending aorta replacement, 1 mitral valve repair, 3 biatrial maze or left atrial appendage ligation, and 2 coronary artery revascularization, 1 with a left internal thoracic artery to the left anterior descending coronary artery plus explant of a transcatheter aortic valve device, maze procedure, and left atrial appendix ligation, and the other patient having complete arterial revascularization with 3 arterial grafts.

### Endpoints

Endpoints included procedural learning curves, perioperative outcomes, intermediate-term valve hemodynamics, aortic valve reintervention, health-related quality of life assessed by the MacNew Heart Disease Health-Related Quality of Life questionnaire, and mortality.[6]

#### Procedural Learning Curves

Learning curves were evaluated using aortic clamp time and cardiopulmonary bypass time as proxies for procedural learning among patients undergoing an isolated Ozaki procedure.

#### Perioperative Outcomes

Perioperative outcomes were defined as for the Society of Thoracic Surgeons Adult Cardiac Surgery Database. These included operative mortality, use of mechanical circulatory support, reoperation for any reason, sepsis, deep sternal wound infection, stroke, need for prolonged mechanical ventilation, renal failure, atrial fibrillation, need for a pacemaker, and postoperative length of stay.

#### Valve Hemodynamics

Aortic valve mean gradient, regurgitation grade (none, mild, moderate, severe), and left ventricular ejection fraction were assessed by routine transthoracic echocardiography before hospital discharge and at the discretion of referring physicians during follow-up. All available serial follow-up echocardiograms for each patient were included, but for those undergoing reintervention, were censored at the time of reintervention. A total of 118 postoperative and follow-up echocardiogram records were available for the 46 patients (Supplemental Figure 1).

Any patient with a persistently elevated mean gradient $>15$ mmHg ($n = 6$), greater than mild regurgitation ($n = 2$), or evidence of cusp thickening ($n = 2$) on postoperative echocardiograms was considered for 4-dimensional computed tomography (4DCT) to assess for cusp thickening or restricted or otherwise abnormal cusp motion.

#### Time-Related Events

Cross-sectional follow-up was performed to identify any valve-related reintervention. Fifty percent of patients were followed more than 8.7 months, 25% more than 2.1 years, and 10% more than 3.7 years. Cross-sectional follow-up supplemented with outpatient visit dates was used to ascertain vital status. Fifty percent of patients were followed for vital status more than 1.3 years, 25% more than 2.5 years, and 10% more than 4 years. No patient was lost to follow-up.

#### Health-Related Quality of Life

All patients except one who had died before the time of cross-sectional follow-up completed the MacNew Heart Disease Health-Related Quality of Life questionnaire,[6] a 27-item tool covering 3 quality of life domains: physical limitation, emotional function, and social function. It is valid, reliable, and responsive in assessing quality of life for patients with heart disease.[7]

### Data Analysis

All analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC). Continuous variables are summarized as mean ± standard deviation or median (15th/85th percentiles). Categorical variables are summarized as frequencies and percentages.

#### Learning Curves

Learning curves were constructed for 30 patients undergoing isolated Ozaki procedures. Each patient's sequence number within the entire series of 46 patients was used as the sole independent variable with aortic clamp time and cardiopulmonary bypass time as dependent variables in locally weighted scatterplot smoothing estimation.

#### Longitudinal Hemodynamic Trends

Multiphase nonlinear mixed effects regression models were used to assess the temporal trend of longitudinal postoperative hemodynamics and left ventricular function.[8] These longitudinal models were implemented using PROC NLMIXED. Longitudinal postoperative aortic regurgitation grades are depicted using patient-specific observed profiles.

#### Health-Related Quality of Life

Scores for emotional, physical, and social MacNew domains were obtained by averaging across nonmissing responses. Domains with more than 50% of the items missing were set to missing. For the global domain, scores were averaged over all scored domains unless one was missing. One-sample nonparametric sign tests were performed to test for deviations from population norm reported by Dixon and colleagues.[9] Given our limited sample size, we also used 1000 bootstrap data sets to generate 95% percentile confidence intervals around the observed means.

## Results

### Learning and Learning Curve

There was a slow but steady rise in annual volume, with 19 Ozaki procedures performed in 2020.

Initially, we performed Ozaki procedures only on tricuspid valves and bicuspid valves with a well-defined raphe, accepting unequal cusp sizes. From patient 30 onward, commissures were symmetrical or realigned to create equal-sized cusps.

Over the first 20 isolated Ozaki cases, aortic clamp and cardiopulmonary bypass times for isolated Ozaki procedures decreased from 125 and 145 minutes, respectively, to about 100 and 120 minutes, respectively (Figure 1). Times remained constant thereafter.

### Native Aortic Valve Morphology and Operative Details

Seven patients had unicuspid valves (15%), 29 bicuspid valves (63%), and 10 tricuspid valves (22%). Of the first 29 patients, 10 had equal-sized cusps. The remainder received cusp sizes true to the intercommissural distances, including 2 patients with a $>2$ size difference between the smallest and largest cusps. After initiation of equal tricuspidization, 13 patients had nonequal intercommissural distances requiring commissural repositioning.

Two patients with prior bicuspid valve repair underwent the Ozaki procedure as a reoperation. One had a remote history of valve repair but was still found to have healthy pericardium suitable for use. The second had a bicuspid valve and underwent the Ozaki procedure for recurrent severe aortic regurgitation within a week after attempted repair.

No patient required intraoperative conversion to an alternative valve procedure. Two patients required a second cardioplegic arrest, the first because of severe regurgitation due to suture breakage and the second to resolve moderate regurgitation by shortening the cusp free margins using additional figure-of-8 commissural sutures.[10] Both patients left the operating room with no regurgitation.

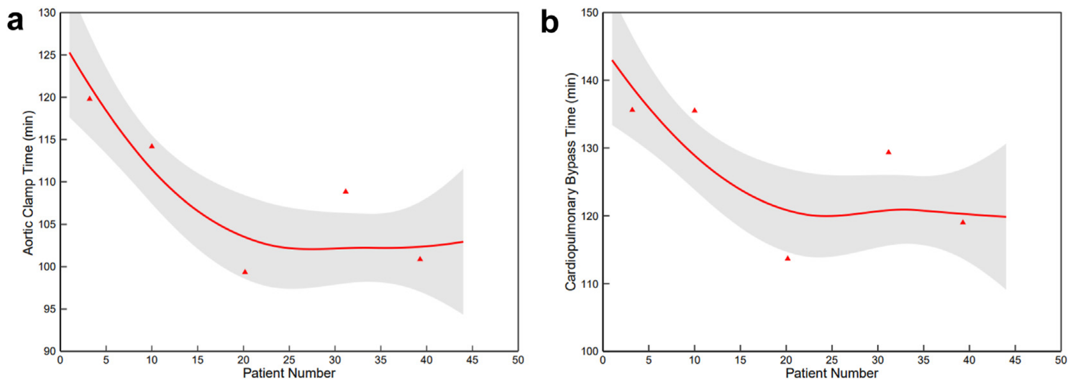


**Figure 1. Ozaki procedure learning curves.** Numbers on horizontal axis are sequence number of patients undergoing an isolated produce. Solid line is a nonparametric lowess smoothed estimate of the learning curve enclosed within a shaded 68% confidence interval. Symbols are average of grouped data. (a) Aortic clamp time. (b) Cardiopulmonary bypass time.

*Perioperative Outcomes*

There was no operative mortality or major morbidity. Twenty patients (43%) received blood products, 13 (29%) intraoperatively and 7 (15%) postoperatively. Ten patients (24%) experienced episodes of postoperative atrial fibrillation. The median postoperative length of stay was 6.9 days.

*Aortic Valve Gradients*

Overall mean aortic valve gradient was 8.0 mmHg (68% CI: 7.4-8.5 mmHg) immediately postoperatively, increasing to 9.2 mmHg (8.4-9.9 mmHg) by 6 months (Figure 2); it remained nearly constant thereafter.

Six patients had a mean aortic valve gradient >15 mmHg at some time postoperatively or during follow-up. Two had a reduction in gradient on subsequent echocardiograms. Two had persistently elevated gradients: the one with a mean gradient of 22 mmHg did not undergo 4DCT; the other, with mean gradient 19 mmHg, had a thick hyperdynamic ventricle and small annulus, and 4DCT showed cusps without thickening and with good motion, valve area of 1.9 $cm^2$, and no regurgitation. Despite the elevated gradients, regression of left ventricular mass was observed, from 460 to 318 g. In the fifth patient with a mean gradient of 15 mmHg, 4DCT revealed mild thickening of the bases of 2 cusps, but the upper portions were of normal thickness with unrestricted motion. The last patient, with a mean gradient of 12 mmHg on discharge, had an outside echocardiogram showing a mean gradient of 18 mmHg 1 year postoperatively; this patient has not undergone 4DCT. Two additional patients had echocardiographic evidence of mild cusp thickening but had mean gradients <15 mmHg and have not undergone 4DCT.

*Aortic Valve Regurgitation*

Two patients developed greater than mild regurgitation at some time perioperatively or during follow-up (Figure 3). One had moderate regurgitation and underwent 4DCT that revealed abnormal thickening of the right coronary cusp with severely restricted cusp motion; the other 2 cusps had thickening of their bases but preserved motion. During the operation, this patient had a second cardioplegic arrest for regurgitation, interpreted as caused by excessive length of the free margins of the cusps; the regurgitation resolved after shortening the free margin with a figure-of-8 suture at the commissure. The other patient with moderate regurgitation on follow-up had also required a second pump run intraoperatively due to suture break, resulting in severe regurgitation; after the cusp was resutured to the annulus there was trace residual regurgitation. This second patient has not undergone 4DCT, has continued left ventricular reverse remodeling, and remains asymptomatic. Neither of these 2 patients received unequal cusps.

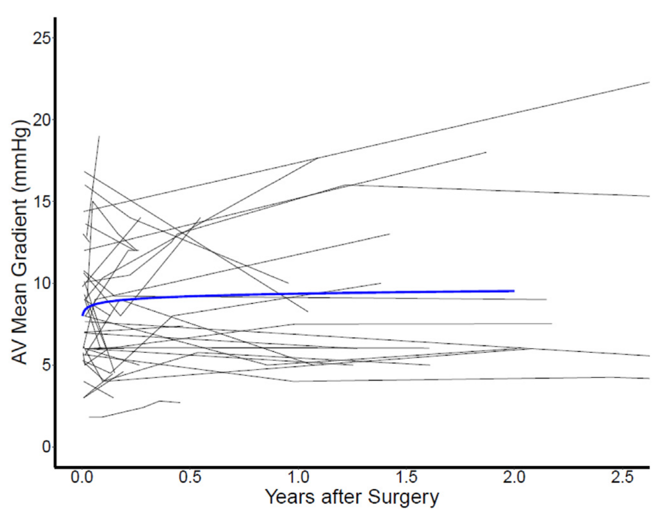


**Figure 2. Temporal trend of aortic valve (AV) mean gradient after Ozaki procedure in the entire cohort.** Solid blue line depicts ensemble average of postoperative AV mean gradient. Thin gray lines depict individual patient-observed longitudinal mean gradients.

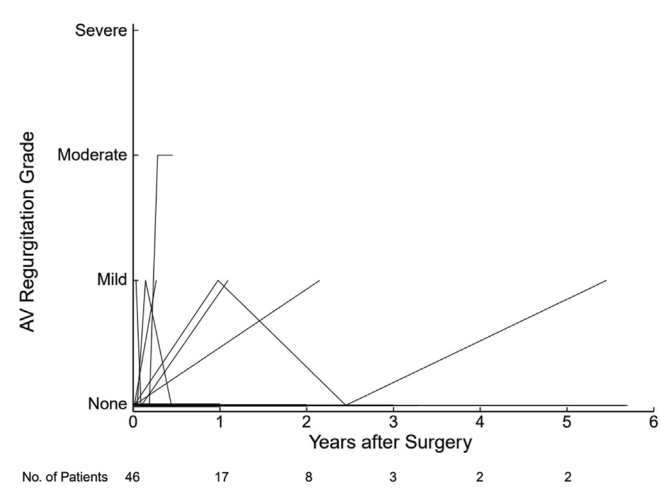


**Figure 3. Spaghetti plot depicting temporal trends of prevalence of postoperative aortic valve (AV) regurgitation grade after Ozaki procedure in the entire cohort.** Numbers below the horizontal axis depict the number of patients eligible for an echocardiogram at the beginning of each year and number of echocardiograms available within each yearly interval.

### Left Ventricular Function and Remodeling

Left ventricular ejection fraction, 58% ± 7.8% preoperatively, was 55% (68% CI: 53–56%) immediately postoperatively but 60% (59–61%) at 6 months. Thereafter, it remained stable (Supplemental Figure 2).

### Infective Endocarditis and Reintervention

One patient developed infective endocarditis 7 months postoperatively, failed conservative medical management with antimicrobial therapy, and ultimately underwent reoperation 14 months after the Ozaki procedure with allograft root replacement.

### Health-Related Quality of Life

In each domain, MacNew scores were higher (better) in the Ozaki cohort than population norms (Figure 4): emotional, 6.2 (95% CI: 5.9-6.4) vs. 5.04; physical, 6.2 (5.9-6.5) vs. 4.8; social, 6.3 (5.9-6.6) vs. 5.2; and global, 6.2 (5.9-6.4) vs. 5.0 (all $p < 0.0001$).

### Survival

One patient, on chronic dialysis, died at 16 months. Mode of death was a dialysis-related complication.

## Discussion

### Principal Findings

Although a complex operation, the Ozaki procedure was reproducible and safe, with good outcomes for varying aortic valve morphologies and pathologies. With good preparation and strict discipline, learning was quick and surgical complications few and minor. Aortic valve mean gradients remained low, but development of aortic regurgitation and risk of endocarditis may still be a concern. Intermediate-term survival and patient health-related quality of life were excellent.

### Use of Autologous Pericardium for Aortic Valve Repair: Why the Ozaki Procedure?

Various methods to repair and reconstruct aortic valves using autologous pericardium have been reported since the 1960s.[11] In 1986, Love and Love[12] introduced tanning the pericardium with 0.6% glutaraldehyde to prevent retraction and scarring. Al Halees and colleagues applied this treatment of autologous pericardium to reconstruct aortic valves, reporting 16-year results in 2005, followed by Chan and colleagues in 2011.[13,14] Both groups provided sizers and simple templates for cutting the pericardium and suturing the cusps to the annulus. However, superiority compared with outcomes after replacement with bovine pericardial prostheses was never demonstrated, and their techniques were not widely adopted.

In 2011, Ozaki and colleagues[15] reported a new technique to reconstruct the aortic valve with autologous pericardium. There were several reasons to believe that the Ozaki procedure could be better than the previously described attempts to reconstruct the aortic valve with autologous pericardium:

1. **Autologous tissue:** Autologous pericardium is attractive to patient and surgeon.
2. **Better valve design:** The Ozaki design included a generous zone of co-aptation, low stress, and preserved annulus mobility. The ideas behind it were the result of Ozaki's own thesis studies of bioprosthetic valve failure.[1,16] Better design should translate into better function and durability.
3. **Reproducibility:** Ozaki provided a tool set, instructions for preparing the pericardium, and detailed stitch-by-stitch instructions for performing the operation. The tool set included a plate on which to stretch the pericardium before tanning, sizers for determining cusp dimensions, and a template to shape and cut the cusps with marks showing where to place each individual stitch.[1,16]
4. **Results:** Ozaki's early and midterm outcomes were better than those after previously described operations to repair and reconstruct aortic valves with autologous pericardium.[1,2]
5. **Cost:** Autologous pericardium costs less than prosthetic valves.

### Adoption of the Ozaki Procedure and the Learning Curve

The Ozaki procedure is not yet widely used. It is perceived as technically complex, requiring full sternotomy and longer cardiopulmonary bypass and clamp times than conventional valve replacement. Recognizing this complexity, we took the preparation very seriously, working in close collaboration with Professor Ozaki. After reading his manuscripts and studying the technique, one coauthor (G.B.P.) visited Ozaki in Japan and observed several cases, then practiced the procedure on a model. In 2015, we invited Ozaki to our institution and performed the first 2 cases under his guidance. Since then, the majority of our Ozaki procedures have been performed by 2 staff surgeons, 1 of whom is Japanese (S.U.), which enabled us to communicate directly with Ozaki and receive regular feedback from him. S.U. has also visited Ozaki to observe several cases.

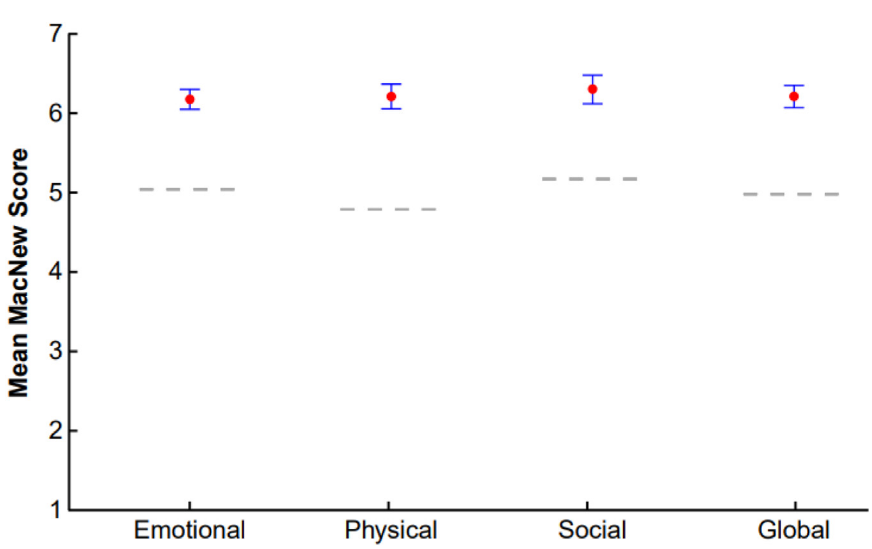


**Figure 4. Quality of life measurements in the entire Ozaki cohort.** Mean (95% CI) plots for MacNew domains. Our observed means (red circles) and corresponding 95% bootstrap confidence intervals (blue lines) are plotted along with domain-specific population norms (gray dashed lines; 5.04, 4.79, 5.17, and 4.98 for the emotional, physical, social, and global domains, respectively). No CIs contain their respective population norms. Therefore, our observed estimates are significantly different from population norms.

Our cohort of patients underwent their Ozaki procedures with no deviation from the techniques described. Before making modifications, we wanted to understand the operation and reproduce Ozaki's outcomes. In contrast to some other groups, we have used only autologous pericardium.[12,17]

As our case numbers gradually rose and outcomes were excellent, we became increasingly comfortable offering the operation to more patients. Initially, we performed Ozaki procedures only on tricuspid valves and bicuspid valves with a well-defined raphe, accepting unequal cusp sizes, but after the learning curve ended, we began including patients with symmetrical bicuspid valves without a raphe (Sievers' type 0). We have since invited Ozaki back to Cleveland and performed several cases under his guidance. We adopted the technically more demanding equal tricuspidization for unicuspid and bicuspid valves, wherein the commissures are repositioned, providing symmetrical cusps rather than accepting unequal ones.

Our disciplined approach has resulted in a short learning curve, no intraoperative conversions to a prosthetic valve, and little perioperative morbidity. In Ozaki's own series, learning curves were observed for aortic clamp time (which for isolated procedures decreased from >2 hours to about 105 minutes by the 300th case), occurrence of aortic regurgitation, and the early phase of mortality risk.[5] In Ozaki's case, the learning curve also includes the technical evolution of the procedure.

### Perioperative Outcomes

Length of stay was shorter than in other studies, median 6.9 days compared with >10 days in contemporary Ozaki series.[17–21] Importantly, no patient in our series required a permanent pacemaker; this mirrors other studies and could be uniquely related to the Ozaki operation given that sutures are placed following the original base of the cusps.[12,13,22] The Ozaki procedure puts no pressure on the annulus and does not "shoehorn" in large valves.

### Valve Gradients

Our low postoperative aortic valve mean gradient aligns with other Ozaki series.[17–21] Low gradients have been attributed to preservation of normal annulus size and motion, without a rigid prosthetic ring preventing normal increase in valve area during systole.[23,24] Rosseykin and colleagues compared immediate postoperative echocardiographic findings of patients undergoing the Ozaki procedure (n = 20) with those of patients undergoing prosthetic aortic valve replacement (Hancock II [n = 41], PERIMOUNT [n = 35]) and reported lower gradients and larger valve area ($p < 0.001$) after the Ozaki procedure.[25]

### Aortic Regurgitation

Patients undergoing the Ozaki procedure may be prone to developing regurgitation; Ozaki reported a 7% 8-year prevalence of aortic regurgitation, but it was largely related to endocarditis. To address the issue, Ozaki modified the technique twice, first by adding a 5-mm "wing" extension to the cusps for better fixation of the commissures, and second by adopting equal tricuspidization (also to reduce the risk of endocarditis), creating "new commissures" as needed in patients with unicuspid and bicuspid valves. Until 2012, tricuspidization for these valves was done by accepting the positions of the raphes as commissures, thereby also accepting unequal cusp sizes.[2] Ozaki's learning curve related to regurgitation suggests that these 2 modifications worked.[5] We adopted the equal tricuspidization modification mid-series.

So far, only 2 of our patients have developed moderate regurgitation. Although both required second pump runs, they had no regurgitation at hospital discharge. The mechanism in the patient with cusp thickening could have been "hypoattenuated leaflet thickening" (HALT; see text that follows), while the other patient had a second pump run to shorten the free margins of the cusps, suggesting cusp oversizing leading to rolling of the free margin as a cause of regurgitation.

### Cusp Thickening and Mobility

Early cusp thickening, or HALT, has been described for bioprosthetic valves,[26] particularly transcatheter replacement valves, but has not been previously described or studied for the Ozaki valves constructed from autologous pericardium. Three patients with mildly elevated gradients in our cohort underwent 4DCT to evaluate cusp thickening. One had minimal symmetrical cusp thickening, the second showed mild thickening of the cusp bases, and the third had single cusp thickening and immobility associated with moderate regurgitation (the patient mentioned above). Anticoagulation was initiated for the third patient and has resulted in decreased thickening and improved mobility on echocardiogram and 4DCT, as well as decreased regurgitation and improved effective orifice area. The causes and implications of these findings on long-term valve function are unknown, but HALT warrants further investigation regarding prevalence, causes, consequences, need for anticoagulation, and patient and technical risk factors.

### Intermediate-Term Outcomes

Our follow-up is too short to say anything about structural valve degeneration. Outcomes extending to 8 years in the original Ozaki cohort show low occurrence of valve degeneration, although some valve regurgitation.[2] Resistance to calcification was most impressive in the subgroup of patients on dialysis, with no observed cusp calcification. Long-term outcome data are needed to confirm longevity of the procedure and the patients.

### Endocarditis

One of our patients developed endocarditis, eventually requiring allograft root replacement. In Ozaki's series, occurrence of endocarditis was slightly higher than observed with standard bioprostheses.[2] Although with use of autologous tissue resistance to endocarditis could be anticipated, previous experiences using glutaraldehyde-treated autologous pericardium have also raised concerns about the risk of endocarditis. Chan and colleagues[14] used a single piece of glutaraldehyde-treated autologous pericardium to reconstruct the aortic valve and reported a 27% occurrence of endocarditis by 7.5 years (notably, in two-thirds of these patients the indication for surgery was endocarditis). Al Halees and colleagues[13] reported an 11% occurrence of endocarditis by 16 years, and this risk continued beyond the early postoperative phase, while a comparable group undergoing aortic valve reconstruction with bovine pericardium had less postoperative endocarditis. Our conclusion is that there is reason to recommend endocarditis prophylaxis after the Ozaki procedure. Whether the modification "equal tricuspidization" will reduce the risk of endocarditis remains to be seen.

### Health-Related Quality of Life

After an Ozaki procedure, patients should expect a quality of life like that of persons without aortic valve disease, with no anticoagulation and no foreign material implanted. MacNew health-related quality of life in social, mental, and physical domains was significantly higher than population reference data provided in Dixon and colleagues'[9] study. This is in keeping with recent findings that young (age <60 years) patients show similar physical and better mental quality of life than age-matched control subjects after bioprosthetic aortic valve replacement. It suggests that they recover and experience few limitations from their past aortic valve disease and experience this as better than normal health-related quality of life.[27] We also speculate that by self-selection, patients undergoing an Ozaki procedure are particularly happy to have avoided prosthetic valves and anticoagulation and expect longevity of the valve. Quality of life is of particular importance, because managing aortic valve disease may span a patient's lifetime. Further studies are thus warranted to determine which characteristics of the Ozaki procedure contribute most to health-related quality of life, and to compare quality of life outcomes after other available treatment options. In addition, these findings further underscore the importance of shared decision-making in treatment strategy.

### *Worldwide Experience and Application*

Since Ozaki and colleagues first published their results in 2011, the Ozaki procedure has been adopted worldwide, with a growing body of literature supporting its use. To date, centers from the United Kingdom, Italy, Germany, Switzerland, India, and Vietnam have published their results with the procedure.[17–21] Our cohort is similar to these in that patients undergoing the Ozaki procedure are younger (mean age in the 50s), span a large age range, including pediatric populations, and typically have fewer comorbidities than the standard aortic valve replacement population.[5]

Opening the door to further innovation and improved outcomes, Nguyen and colleagues have reported 9 Ozaki procedures performed with a minimally invasive approach ($n = 9$). They used thoracic endoscopy to harvest the pericardium during cardiopulmonary bypass.[28]

Concerns have been expressed about the suitability of transcatheter aortic valve replacement in case of failure of Ozaki valves, because of the tall cusps and risk of coronary obstruction and lack of annulus calcification. Only one transcatheter aortic valve replacement after an Ozaki procedure has been reported, but new technology (such as BASILICA) should be able to alleviate the tall cusp problem.[29,30]

### *Limitations*

This is a single-center study that reflects Cleveland Clinic's initial experience with the Ozaki procedure, and thus the sample size is small; our primary objectives were to confirm safety and reproducibility. To prove the concept and reproducibility, our protocol required learning directly from Ozaki and strict adherence to his technique and principles. Comparisons are limited and follow-up short. Although outcomes are comparable to other series performed internationally, it is more important that outcomes are comparable to Ozaki's series. The growing number of procedures performed over time is evidence we have become increasingly comfortable with the operation.

## Conclusion

The Ozaki procedure is an interesting addition to our armamentarium to manage aortic valve disease. We have confirmed that with good preparation and discipline, the Ozaki procedure is a safe and reproducible alternative to prosthetic valve replacement for a variety of aortic valve pathologies, with a short learning curve and excellent hemodynamic performance, intermediate-term outcomes, and health-related quality of life. Further studies are required to determine long-term outcomes, patient selection, and surgical and patient factors associated with untoward outcomes, such as valve regurgitation, cusp thickening (HALT), and endocarditis.

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## Ethics Statement

The research reported has adhered to all relevant ethical guidelines.

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## Disclosure Statement

Dr Blackstone had statistical consultation related to valve trials with Edwards Lifesciences and Abiomed. The other authors had no conflicts to declare.

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## Supplementary Material

Supplemental data for this article can be accessed on the publisher's website.

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