Aortic valve replacement in patients with amyloidosis

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ABSTRACT

Background: Outcome data on aortic valve replacement in patients with amyloidosis are limited. To address this issue, we reviewed our experience of patients with amyloidosis who underwent aortic valve replacement.

Methods: We retrospectively reviewed the records of 16 patients with amyloidosis who underwent aortic valve replacement between May 2000 and February 2017.

Results: The cohort comprised 11 males (69%) and 5 females (31%). The median patient age was 76 years (interquartile range [IQR], 71-82 years), and Society of Thoracic Surgeons predicted rate of mortality was 5.0% (IQR, 2.4%-8.7%). Amyloidosis type was immunoglobulin light chain in 6 patients (38%), age-related in 6 (38%), and localized in 4 (25%). The operation was surgical aortic valve replacement in 11 patients (69%) and balloon-expandable transfemoral transcatheter aortic valve insertion in the other 5. There was no procedure-related stroke, need for new-onset dialysis or pacemaker, or death within 30 days of surgery. The median length of hospital stay was 1 day (IQR, 1-2 days) in the transcatheter valve insertion group and 6 days (IQR, 6-8 days) in the surgical group ($P = .002$). Follow-up was available for all patients at a median of 1.9 years (IQR, 1.2-4.8 years). During the follow-up period, there were 4 deaths, all occurring >1 year after surgery.

Conclusions: Aortic valve replacement can be performed with low risk of operative morbidity and mortality in patients with amyloidosis. Transcatheter valve insertion has the advantage of reduced hospital length of stay. The 1-year survival is excellent. (J Thorac Cardiovasc Surg 2018;156:98-103)

Amyloid protein (green) in atrial myocytes (yellow).

Central Message

Aortic valve replacement can be done safely and with good intermediate-term mortality outcome in patients with amyloidosis.

Perspective

In this series of 16 patients with amyloidosis, most of the patients were elderly, with an intermediate risk profile for surgical aortic valve replacement. Outcomes were excellent following both transcatheter and surgical aortic valve replacement. These data support the safety of aortic valve replacement in patients with amyloidosis.

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Cardiac amyloidosis is an infiltrative restrictive cardiomyopathy that portends a poor prognosis.¹⁻⁶ Although involvement of the myocardium is the most frequent cause of death, some patients also may be affected by valvular or other cardiac pathologies.⁷⁻¹² There are limited data on the risk of aortic valve replacement in patients with amyloidosis.^{8,9,13-17} Because the disease

often causes severe diastolic dysfunction and affects other organ systems (eg, kidney, liver), we hypothesized that there was potential for increased risk of perioperative morbidity and mortality during aortic valve replacement.³ The focus of the present study was on operative and longer-term mortality outcomes in patients with amyloidosis who underwent aortic valve replacement.

METHODS

The Mayo Clinic's Institutional Review Board approved this study (approval no. 16-010399; February 13, 2017). We performed a retrospective review of the Department of Cardiovascular Surgery's database for

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Abbreviations and Acronyms

AL	= immunoglobulin light chain type amyloidosis
ATTR	= transthyretin/prealbumin type amyloidosis
IQR	= interquartile range

all patients who underwent aortic valve replacement between January 2000 and February 2017. This group of 6437 patients was then cross-referenced with the Department of Medicine's amyloidosis database, which at that time contained 2626 patients. There were 16 patients with a diagnosis of amyloidosis any time before or within 3 months of the aortic valve replacement.

Baseline demographic, comorbidity, operative, and follow-up data were recorded as defined in the Society of Thoracic Surgeons Adult Cardiac Database. Vital status was checked through the electronic medical record and an Internet search that included the Social Security Death Index and a general obituary query (accessed October 21, 2017). The primary endpoint of the study was all-cause mortality.

The diagnosis of amyloidosis was based on noncardiac tissue biopsy in 10 patients (63%), cardiac tissue biopsy in 5 patients (32%), and ^{99m}Tc -PYP single-photon positive emission computed tomography cardiac imaging in 1 patient (6%). The cardiac tissue specimens were evaluated by light microscopy using standard clinical protocols. The patients' aortic valves were examined with staining with hematoxylin and eosin (4 μm), Verhoeff-van Gieson (4 μm), sulfated Alcian blue (4 μm), and Congo red (10 μm). Only 1 valve showed amyloid deposition, but with only a micro-focal deposit of endocardial amyloid identified. All histological analyses were performed by a cardiovascular pathologist (J.J.M.).

Categorical data are reported as count (percentage), and continuous data are reported as median (interquartile range [IQR]). A comparative analysis of length of stay between procedure types was done with a nonparametric rank-sum test. Matched pairs analysis was performed by using Wilcoxon-signed rank test comparing preoperative and postoperative echocardiography characteristics. Follow-up was calculated using the reverse Kaplan-Meier method, whereas long-term mortality was calculated using the standard Kaplan-Meier method. Statistical significance was set at $\alpha = 0.05$. Data analysis was done with JMP Pro 10.0.0 (SAS Institute, Cary, NC).

RESULTS

The median patient age was 76 years (IQR, 71-82 years), 5 patients were female (31%), and Society of Thoracic Surgeons predicted risk of mortality was 5.0% (IQR, 2.4%-8.7%). Aortic valve stenosis was present in all patients. Additional baseline patient characteristics are reported in Table 1.

The type of amyloidosis was immunoglobulin light chain in 6 patients (38%), age-related in 6 patients (38%), and localized in 4 patients (25%; seminal vesicle in 2, skin in 1, and pharynx in 1). The diagnosis was confirmed with mass spectrometry in 7 patients and demonstrated transthyretin/prealbumin-type amyloidosis (ATTR; ie, transthyretin; Figure 1) in 5 patients and immunoglobulin light chain-type amyloidosis (AL; ie, immunoglobulin light chain) in 2 patients. The diagnosis of amyloidosis was known before aortic valve replacement in 14 patients (88%). In the remaining 2 patients (12%), the diagnosis

of amyloidosis was made at 47 and 76 days after aortic valve replacement, respectively.

Baseline patient echocardiography demonstrated a median ejection fraction of 60% (IQR, 59%-65%). Aortic stenosis was present in all patients. The mean systolic aortic transvalvular gradient was 46 mmHg (IQR, 36-51 mm Hg), and the median aortic valve area index was 0.51 cm^2/m^2 (IQR, 0.39-0.55 cm^2/m^2). The median septal wall thickness was 13 mm (IQR, 11-14 mm), and that of the posterior ventricular wall was 11 mm (IQR, 10-13 mm).

Transfemoral transcatheter aortic valve insertion was performed in 5 patients (31%), all with balloon-expandable valves. Surgical aortic valve replacement was done in the remaining 11 patients (69%), using a stented biological valve in 10 patients and a mechanical valve in 1 patient. Concomitant surgical procedures included coronary artery bypass graft operation in 4 patients. The median cardiopulmonary bypass time was 114 minutes (IQR, 69-168 minutes), and median aortic cross-clamp time was 99 minutes (IQR, 57-125 minutes).

Procedure-related complications occurred in 3 patients (19%). There was a single femoral artery pseudoaneurysm following transcatheter aortic valve insertion in a patient with immunoglobulin light chain amyloidosis (patient 15 in Table 2). In the surgical aortic valve replacement group, there was a case of postoperative tamponade in a patient with age-related amyloidosis (patient 9 in Table 2) and a case of low-output syndrome in a patient with immunoglobulin light chain amyloidosis who presented in cardiogenic shock (patient 6 in Table 2). There were no cases of stroke, new-onset dialysis, or permanent pacemaker implantation.

There was a single case of mild paravalvular regurgitation in the surgical valve replacement group (patient 5 in Table 2), whereas in the transcatheter valve replacement group, paravalvular regurgitation was graded none/trivial in all patients. The median length of hospital stay was 6 days (IQR, 1-8 days) for all patients, 1 day (IQR, 1-2 days) for the transcatheter valve replacement group, and 6 days (IQR, 6-8 days) for the surgical valve replacement group ($P = .002$). There was also no in-hospital or 30-day mortality.

Follow-up echocardiography data were available in all patients, at a median of 0.6 years (IQR, 0.1-2.4 years). Matched-pairs analysis demonstrated no change from preoperative to last follow-up ejection fraction ($P = .815$), septal wall thickness ($P = .837$), or posterior wall thickness ($P = .709$); however, there was a significant decrease in mean systolic aortic valve gradient from 46 mm Hg to 14 mm Hg (median difference, -31 (-31 – -20) mm Hg; $P < .001$).

Vital status follow-up was complete for all patients at a median of 1.9 years (IQR, 1.2-4.8 years). One patient underwent subsequent tricuspid valve repair 4 months after the initial surgical aortic valve replacement (patient 12 in Table 2). During the follow-up period, there were 4 deaths,

TABLE 1. Patient baseline characteristics

Characteristic	Value
Continuous data, median (interquartile range)	
Age, y	76 (71-82)
Body mass index, kg/m ²	28 (26-31)
Creatinine, mg/dL	1.2 (1.0-1.7)
Ejection fraction, %	60 (59-65)
Society of Thoracic Surgeons predicted risk of mortality, %	5.0 (2.4-8.7)
Categorical data, n (%)	
Female sex	5 (31)
Caucasian race	16 (100)
Diabetes	4 (25)
Dialysis	1 (6)
Hypertension	15 (94)
Infectious endocarditis	0 (0)
Chronic lung disease	
None	11 (69)
Mild	3 (19)
Moderate	1 (6)
Severe	1 (6)
Immunosuppression	1 (6)
Peripheral vascular disease	3 (19)
Cerebrovascular disease	1 (6)
Previous pacemaker	2 (13)
Previous coronary artery bypass graft operation	0 (0)
Previous valve procedure	1 (6)
Previous percutaneous coronary intervention	3 (19)
Previous myocardial infarction	0 (0)
New York Heart Association class	
I	1 (6)
II	8 (50)
III	5 (31)
IV	2 (13)
Cardiogenic shock	1 (6)
Resuscitation	1 (6)
Atrial arrhythmia	2 (13)
Medical inotropes	1 (6)
Number of diseased coronary vessels	
None	7 (44)
1	3 (19)
2	4 (25)
3	2 (13)
Left main coronary artery stenosis >50%	4 (25)
Aortic stenosis	16 (100)
Mitral stenosis	4 (25)
Aortic valve regurgitation	
None	2 (13)
Trivial	4 (25)
Mild	6 (38)
Moderate	2 (13)
Severe	2 (13)
Mitral valve regurgitation	
None	1 (6)
Trivial	6 (38)
Mild	4 (25)

(Continued)

TABLE 1. Continued

Characteristic	Value
Moderate	5 (31)
Severe	0 (0)
Tricuspid valve regurgitation	
None	1 (6)
Trivial	9 (56)
Mild	4 (25)
Moderate	2 (13)
Severe	0 (0)
Incidence of cardiac operation	
First	15 (94)
Second	1 (6)
Status elective	15 (94)
Mechanical assistance	0 (0)

all of which occurred >1 year after surgery. One patient with immunoglobulin light chain amyloidosis died at 3.8 years after surgery (patient 1 in Table 2; cause not specified). One patient with age-related amyloidosis died at 1.7 years after surgery (patient 4 in Table 2; cause not specified), 2 patients with localized amyloidosis died, 1 at 1.5 years after surgery (patient 8 in Table 2; cause not specified) and the other at 7.4 years after surgery (patient 2 in Table 2; cause, giant cell arteritis).

DISCUSSION

This study reports our experience with 16 patients with amyloidosis who underwent aortic valve replacement. This group of patients was relatively elderly, with a median age of 76 years, and at intermediate risk for surgical aortic valve replacement, with a Society of Thoracic Surgeons predicted risk of mortality of 5%. Aortic valve replacement was surgical in 11 patients and via transfemoral transcatheter in 5. Procedure-related outcomes were outstanding, with no strokes, no need for new-onset dialysis or pacemaker implantation, and no 30-day mortality. Additional longer-term follow-up demonstrated the first postoperative mortality occurring 1.5 years after surgery.

Most of the available literature on amyloidosis and cardiac surgery is focused on the infiltrative cardiomyopathy and the role of heart transplantation in affected patients.¹⁸ In our institution, between 1992 and 2011, 12% of heart transplant recipients had amyloidosis (R.C. Daly, personal communication, October 20, 2017). Data are limited on the role of valve surgery in the treatment of patients with amyloidosis, however, with previous reports limited to case reports or small case series.^{7-9,13-17} In a study of 6 patients reported by Treibel and colleagues,⁸ at a median follow-up of 2.3 years after aortic valve replacement, 50% of patients with amyloidosis had died. The present case series adds additional important data and analysis for patients with amyloidosis who underwent aortic valve replacement.

TABLE 2. Patient specific operative and outcome data in chronological operative order

Patient	Age at operation, y	Amyloid type	Aortic valve replacement	Duration of follow-up, y	Vital status at last follow-up
1	71	AL	Surgical	3.8	Dead
2	75	Localized (skin)	Surgical	7.3	Dead
3	81	Localized (seminal vesicle)	Surgical	8.6	Alive
4	83	Age-related	Surgical	1.7	Dead
5	67	Age-related	Surgical	4.8	Alive
6	70	AL	Surgical	3.9	Alive
7	82	Age-related	Surgical	3.1	Alive
8	78	Localized (seminal vesicle)	Surgical	1.5	Dead
9	82	Age-related	Surgical	1.9	Alive
10	79	AL	Transcatheter	1.7	Alive
11	75	Localized (pharynx)	Surgical	1.7	Alive
12	70	Age-related	Surgical	1.5	Alive
13	95	Age-related	Transcatheter	0.8	Alive
14	68	AL	Transcatheter	0.8	Alive
15	74	AL	Transcatheter	0.8	Alive
16	72	AL	Transcatheter	0.7	Alive

AL, Immunoglobulin light chain–type amyloidosis.

Our procedural outcomes were excellent, with minimal procedure-related morbidity and no 30-day mortality. Galat and colleagues¹⁷ also reported no procedure-related deaths in their series of 11 patients with amyloidosis who underwent aortic valve replacement, and Terada and associates¹⁵ published a case report with a successful outcome. Outcomes following aortic valve insertion or surgical replacement in patients with amyloidosis have not been uniformly good, however. Previous reports have described deaths from left ventricular apical rupture after transapical transcatheter

aortic valve insertion (n = 1) and from low cardiac output syndrome after surgical valve replacement (n = 2).^{13,14,16}

Our reported mortality outcome was also encouraging, with no mortality within 1 year of operation. This is in contrast to the relatively high early mortality reported by Galat and colleagues⁸ (post hoc Kaplan–Meier 1-year mortality estimate, 19.1% ± 10.0%) and Treibel and colleagues¹⁷ (50% mortality at a median follow-up of 2.3 years). In another study of 171 patients with ATTR-type cardiac amyloidosis, Sperry and colleagues⁷ reported a 2-year mortality rate of 37% in patients with aortic valve stenosis. Our reported outcomes should be viewed in the context of natural history data of patients with symptomatic severe aortic valve stenosis, transcatheter aortic valve insertion, and amyloidosis.^{1,4,7,8,19}

Two types of amyloidosis commonly affect the heart: immunoglobulin light chain–associated amyloidosis and age-related transthyretin amyloidosis (most commonly wild-type transthyretin, previously called “senile” cardiac amyloidosis). The presence of immunoglobulin light chain cardiac amyloidosis carries a particularly poor prognosis, with a median survival of 6 months after the onset of overt heart failure in untreated patients.^{1,6,14,20} In contrast, patients with age-related (wild-type transthyretin) amyloidosis have a more indolent clinical course, although the median survival of approximately 3.5 years from diagnosis is significantly worse than predicted.²

The possible role of amyloid protein in the development of aortic stenosis is unknown. Although some series have reported high incidences of valvular involvement by

FIGURE 1. Transthyretin/prealbumin (ATTR)-type cardiac amyloidosis. This photomicrograph shows discrete pericellular deposition of amyloid protein (green) in the interstitium between the atrial myocytes (yellow) (sulfated Alcian blue stain; original magnification, 400×).

amyloid in the setting of aortic stenosis, histopathological examination of a subset of our cohort revealed only 1 patient with microfocal deposition (Figure 1).^{12,21} On critical analysis, those previous studies do not definitively prove the presence of amyloid in these specimens. Given the fact that abundant collagen (such as seen in aortic valves) can produce a false-positive Congo red stain, ultrastructural or proteomic data should be used to confirm the presence of amyloid, and neither previous study proffered such data.

Operative decision making is complex in these patients. The decision to operate depends on the type of amyloidosis, severity of cardiac involvement, and overall prognosis, which can be determined using cardiac biomarker staging systems.⁵ The majority of our patients would be classified as intermediate risk for surgical aortic valve replacement. These patients would qualify for US Food and Drug Administration–approved transcatheter aortic valve insertion.²² The technique appears to be an acceptable option in this group, given the relatively advanced age combined with the lack of procedure-related morbidity, associated short length of hospital stay, and excellent 1-year mortality outcome.

All of our patients who underwent transcatheter valve insertion had a good outcome, but of note, insertion was performed via transfemoral arterial access in all these patients. A good operative outcome was also reported in the 2 patients with transcatheter valve insertion reported by Galat and colleagues,¹⁷ but the authors did not specify the method of arterial access. In the previously mentioned transapical access case report by Monticelli and colleagues,¹⁶ the outcome was poor, however. In that case, the patient died from left ventricular apical rupture presumably related to amyloid infiltration of the ventricular apex and weakening of the access puncture repair site. At present, we urge caution with the transapical approach in patients with cardiac amyloidosis.

This study has several limitations, the most important of which is our small cohort of only 16 patients, representing only a minor percentage (<1%) of the patients with amyloidosis seen at our institution during the study period. Given the limited number of patients, this study is at risk for type II statistical error in accepting the null hypothesis that valve replacement is safe. In addition, this single-center study is subject to local referral and treatment biases that might not apply to other health care institutions. Finally, there are varying degrees of amyloidosis and cardiac involvement. The diagnosis of amyloidosis is not simple, and thus our rate of presentation is likely an underestimate.

CONCLUSIONS

There are limited data available on aortic valve replacement in patients with amyloidosis. Our procedural outcomes were excellent following both transcatheter aortic valve insertion and surgical valve replacement. In this

series, most of the patients were elderly, with an intermediate operative risk profile for surgical aortic valve replacement. Transfemoral transcatheter aortic valve insertion appears to be an excellent option in these patients, and the operation should not be denied.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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