Prognostic Significance of Occult Transthyretin Cardiac Amyloidosis in Patients With Severe Aortic Stenosis Undergoing Surgical Aortic Valve Replacement

An Unrecognized Disease Modifier

Jun Koyama, MD, PhD

Aortic stenosis (AS), a common condition affecting 3% of individuals aged >75 years, leads to heart failure and death unless the valve is replaced.\(^1\) Recently, patients with concomitant degenerative AS and transthyretin-related cardiac amyloidosis have been reported.\(^2\) One prospective study investigated the coexistence of cardiac amyloidosis in elderly patients with AS who were referred for an aortic valve replacement (surgical or transcatheter), by using echocardiography, \(^{99m}\)Tc-3, 3-diphosphono-1, 2-propanodicarboxylic acid scintigraphy, and endomyocardial biopsy, but no cardiac magnetic resonance; 5 of the 43 patients were diagnosed with wild-type transthyretin-related amyloidosis (wtATTR). Of the 5 patients with wtATTR, only 1 was female (median age, 84 years; range, 76–90 years), and all had advanced heart failure (New York Heart Association III/IV).\(^2\) One retrospective analysis included 171 patients with wtATTR, on the basis of clinical presentation, in addition to endomyocardial biopsy, cardiac magnetic resonance, echocardiography with an apical sparing strain pattern, and \(^{99m}\)Tc-pyrophosphate scintigraphy; 27 were determined to have AS (mean age, 79 years; 70% male).\(^1\) The 2-year mortality rate was not different between patients with and without AS, suggesting that the mortality in patients with both diseases may be driven by ATTR as opposed to a stenotic aortic valve or its treatment.\(^3\)

Another retrospective study reported 16 patients (mean age, 79±6 years; 81% were men) with concomitant AS and transthyretin cardiac amyloidosis (wtATTR, \(n=13\); Val122I, \(n=1\); no genetic test, \(n=3\)).\(^4\) After valve replacement (surgical in 63% and via transcatheter in 13%), mortality was 44% (\(n = 7\)) during the median 33-month follow-up period.\(^4\) These were small cohort or retrospective studies; larger prospective studies are needed to systematically know the prevalence of wtATTR in patients with severe AS and the mortality of these concomitant diseases after aortic valve replacement. Thus, the frequency of wtATTR cardiac amyloidosis and its mortality in patients with severe AS is a hot topic.

See Article by Treibel et al

To examine the prevalence and clinical significance of dual pathology (severe AS and wtATTR), Treibel et al,\(^5\) in this issue of Circulation: Cardiovascular Imaging, examined a cohort of 146 patients with severe AS requiring surgical valve replacement (sAVR) as part of the RELIEF-AS study (Regression of Myocardial Fibrosis After Aortic Valve Replacement), in which intraoperative myocardial biopsy and comprehensive multimodality imaging were performed in a single center. The echocardiography was performed as a clinical test and the cardiovascular magnetic resonance (CMR) as a research study preoperatively, whereas \(3, 3\)-diphosphono-1, 2-propanodicarboxylic acid bone scintigraphy was conducted during subsequent specialist clinical evaluations of subjects found to have amyloid on the biopsy. Exclusion criteria comprised contraindications to CMR, including glomerular filtration rate of <30 mL/min and CMR-incompatible devices. All subjects underwent CMR at 1.5 Tesla using a standard clinical protocol with late gadolinium imaging by using PSIR and T1 mapping before and after a bolus of gadolinium for extracellular volume fraction quantification. Of 146 patients, 112 had calcified AS (mean age, 75±6 years; 58% male), 32 had bicuspid AS (mean age, 59±6 years; 66% male), 1 patient each had rheumatic and unicuspid AS. An intraoperative septal biopsy was harvested from the basal left ventricular septum, under direct vision of the surgical team, by using a 14-gauge coaxial needle; the formalin was fixed and paraffin embedded. Histological analysis was performed by using Congo red staining on formalin-fixed and paraffin embedded sections and viewing in bright field and cross polarized light. When amyloid was confirmed by displaying apple green birefringence under cross polar, immunohistochemistry was carried out using a panel of nonspecific antibodies against known amyloid-forming proteins, in an attempt to identify the amyloid fibril. Cardiac amyloidosis was identified in myocardial biopsies of 6 of 146 patients (mean age, 77 years; 67% male), all with calcified AS and >65 years, which had not been suspected at preoperative echocardiography. Preoperative CMR findings were of definite cardiac amyloidosis in 2 of 6, and postoperative \(^{99m}\)Tc-3, 3-diphosphono-1, 2-propanodicarboxylic acid scans demonstrated cardiac localization in all 4 surviving patients (2 patients died before). At a median follow-up of 2.3 years, 11 calcified AS patients had died whereas all of the bicuspid AS were alive. Three of 6 calcified AS with

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

From the Department of Cardiovascular Medicine, Shinshu University School of Medicine, Matsumoto, Japan.

Correspondence to Jun Koyama, MD, PhD, Department of Cardiovascular Medicine, Shinshu University School of Medicine, Asashi 3-1-1, Matsumoto, 390-8621, Japan. E-mail jkoyama@shinshu-u.ac.jp


Circ Cardiovasc Imaging is available at http://circimaging.ahajournals.org

DOI: 10.1161/CIRCIMAGING.116.005320
wtATTR (50%) died compared with 8 of 106 (7.5%) in the remaining calcified AS cohort. The presence of wtATTR amyloid had the highest hazard ratio for all-cause mortality (hazard ratio, 9.5 [2.5–35.8], P=0.001, univariable Cox regression analysis). This study provides important information on the prevalence of wtATTR in patients with severe AS requiring sAVR; the frequency of wtATTR cardiac amyloidosis in patients with severe AS was 5.6%.

Furthermore, univariate analysis demonstrated that wtATTR amyloid deposit is a prognosticator in patients with AS after sAVR, and perioperative mortality was not affected by the presence of wtATTR. This finding is the first and largest prospective report in patients with severe AS after sAVR.

In previous studies, several prognostic markers were reported in patients undergoing sAVR or transcatheter aortic valve replacement (TAVR). Advanced chronic kidney disease was associated with a higher rate of early and late mortality and bleeding events after TAVR, with atrial fibrillation and dialysis therapy determining a high risk in 2075 consecutive patients. Severity of coexisting coronary artery disease was associated with impaired clinical outcomes at 1 year after TAVR in 445 patients with severe AS (mean age, 82.5 years; 56% female).7 Severe AS and left ventricular ejection fraction of <50% with or without aortic valve replacement,8,9 low-flow, low-gradient AS with reduced stroke volume index,10–11 and reduced global longitudinal strain by speckle-tracking echocardiography12 have increased risk of mortality after sAVR or TAVR in patients with severe AS. Midwall myocardial fibrosis that can be detected by late gadolinium enhancement,13 and prosthesis–patient mismatch14,15 have also been reported as prognosticators in patients with severe AS after sAVR or TAVR.

Thus, the existence of wtATTR may be a newly recognized disease modifier in patients with AS requiring sAVR or TAVR,7–5 which may have affected patients included in previous studies.6–17 The coexistence of wtATTR and severe AS may cause severe hypertrophy and left ventricular functional impairment, which can be misdiagnosed as low-flow, low-gradient severe AS.10–13 Recent studies have suggested that patients with wtATTR are characterized by lower left ventricular ejection fraction, stroke volume index, left ventricular basal, and midradial strains compared with age and wall thickness matched mutant ATTR patients.18 These findings may be helpful in distinguishing wtATTR cardiac amyloidosis from patients with other causes of left ventricular hypertrophy. The lower 1-year mortality in women was reported in patients undergoing TAVR (mean age, 84 years for women and 82 years for men).19 This phenomenon may be accounted for by the male dominance of wtATTR (male:female=20–50:1), which may lead to the poorer prognosis in male sex in these population.20 In the study by Treibel et al,2 patients with CMR-incompatible devices were excluded from the study. Because wtATTR patients may have advanced aortoventricular block requiring CMR-incompatible devices,20 some wtATTR patients with devices may have been possibly excluded from this study, may have resulted in an underestimation in the prevalence of wtATTR in patients with severe AS.

The prognostic significance of the existence of myocardial wtATTR should be considered in future studies on the prognosis of patients with severe AS. The age of patients in Treibel et al’s2 study is younger than that of patients who underwent TAVR (>80 years of age).21 Histologically significant cardiac wtATTR occurs in 8% to 16% of people >80 years of age.22 Thus, AS patients requiring TAVR may include more wtATTR patients than AS patients requiring sAVR. The prevalence of wtATTR in patients with severe AS requiring TAVR is of interest, and further systematic prospective studies should be performed in patients with severe AS being considered for TAVR, especially in elderly patients >80 years of age.

Disclosures

None.

References


Koyama  Cardiac Amyloid in Severe Aortic Stenosis


**KEY WORDS**: Editorials ◼ aortic valve ◼ atrial fibrillation ◼ gadolinium ◼ heart failure
Prognostic Significance of Occult Transthyretin Cardiac Amyloidosis in Patients With Severe Aortic Stenosis Undergoing Surgical Aortic Valve Replacement: An Unrecognized Disease Modifier
Jun Koyama

*Circ Cardiovasc Imaging*, 2016;9:
doi: 10.1161/CIRCIMAGING.116.005320
*Circulation: Cardiovascular Imaging* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2016 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-9651. Online ISSN: 1942-0080

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circimaging.ahajournals.org/content/9/8/e005320

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation: Cardiovascular Imaging* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at: http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Circulation: Cardiovascular Imaging* is online at: http://circimaging.ahajournals.org/subscriptions/