

Late-onset atrioventricular block after transcatheter aortic valve replacement



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BACKGROUND Conduction disturbances leading to permanent pacemaker implantation (PPI) rarely occur late after transcatheter aortic valve replacement (TAVR). The clinical features of this phenomenon and its association with periprocedural conduction disturbances remain uncertain.

OBJECTIVES We aimed to determine the incidence and characteristics of late-onset atrioventricular block (AVB) after TAVR.

METHODS This single-center study included 246 patients undergoing TAVR. Late-onset AVB was defined as AVB ≥ 1 month after the TAVR.

RESULTS Periprocedural AVB (periAVB) occurred in 43 patients (17%). Patients with periAVB had a higher rate of right bundle branch block (47% vs 7%, $P < .0001$). Of the 43 patients with periAVB, 15 underwent PPI (35%) at a median duration of 6 days, whereas 1 of the remaining 203 patients without periAVB underwent PPI within 1 month (0.5%). During a median follow-up duration of 365 days, late-onset AVB occurred in 10 of 230 patients without PPI within 1 month (4%) at a median duration of 76

days. All 10 patients presented transient periprocedural atrioventricular conduction disturbances, including 8 patients with periAVB (80%), all of whom recovered within 1 month, and 9 patients underwent self-expanding valve implantation (90%). The mortality rate in patients with PPI within 1 month was higher than in those without, although the difference was not statistically significant (hazard ratio 2.68, 95% confidence interval 0.97–9.05, log-rank $P = .09$).

CONCLUSION Late-onset AVB occurred in a minority of patients undergoing TAVR. Greater vigilance is warranted, particularly in patients with transient conduction disturbances during the periprocedural period following self-expanding valve implantation.

KEYWORDS Complete atrioventricular block; Late-onset pacemaker implantation; Late-onset atrioventricular block; Transcatheter aortic valve implantation; Transcatheter aortic valve replacement

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Introduction

Transcatheter aortic valve replacement (TAVR) is a widely accepted, less invasive procedure than surgical aortic valve replacement for symptomatic severe aortic stenosis (AS).¹ As the safety and utility of TAVR have improved with advances in techniques and devices, the indication of TAVR has expanded to include patients with low surgical risk.^{1–3}

Conduction disturbances, including atrioventricular block (AVB) requiring permanent pacemaker implantation (PPI), are a major complication of TAVR.⁴ Preexisting complete right bundle branch block (RBBB) on electrocardiogram (ECG),⁵ depth of valve implantation,⁶ angles between the annulus and aorta,⁷ short membranous septum,⁸ and oversizing of implanted valves⁹ are known predictors of PPI, and the reported incidence of PPI is 15%.¹⁰ The mortality rate has

been shown to be higher in patients undergoing PPI than in those without PPIs.^{11,12} Delayed AVB 2 days after TAVR, assessed using 30-day ambulatory event monitoring, has been reported.¹³ However, the incidence of late-onset AVB occurring later than 30 days after TAVR, the clinical features of this phenomenon, and its association with periprocedural conduction disturbances within 30 days after TAVR remain uncertain. In this study, we aimed to determine the incidence and clinical characteristics of late-onset AVB in patients undergoing TAVR.

Methods

Study subjects

The present study was a single-center retrospective cohort study of symptomatic patients with severe AS who underwent TAVR between February 2017 and June 2020 at Tokai University Hospital (Isehara, Japan). Patients were prospectively enrolled in the Tokai Valve Registry

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KEY FINDINGS

- Late-onset atrioventricular block (AVB), defined as high-grade AVB ≥ 1 month after the transcatheter aortic valve replacement, occurred in 4% of patients without permanent pacemaker implantation (PPI) within 1 month, all of whom presented with new-onset atrioventricular conduction disturbances during the periprocedural period, including transient periprocedural AVB.
- A self-expanding valve was implanted in the majority of patients presenting with late-onset AVB.
- Periprocedural AVB occurred in 17% of patients, and PPI was performed in 7% of patients within 1 month. Patients with periprocedural AVB had a higher prevalence of right bundle branch block than those without.

(UMIN000036671). Patients with preexisting cardiac implantable electronic devices, such as permanent pacemakers, implantable cardioverter-defibrillators, or cardiac resynchronization therapy, were excluded from this study. Severe AS was defined as a peak velocity (V_{max}) >4 m/s, a mean transvalvular pressure gradient >40 mm Hg, and aortic valve area <1 cm² on transthoracic echocardiography.¹ The baseline characteristics, including echocardiographic, ECG, and computed tomography (CT) properties, were analyzed in patients with periprocedural AVB (peri-AVB), which was defined as the occurrence of high-grade AVB including second-degree Mobitz type II, advanced AVB, atrial fibrillation with slow response, or third-degree AVB within 5 days after TAVR.¹⁴ Late-onset AVB was defined as the high-grade AVB occurring greater than 1 month after the TAVR procedure. Written informed consent was obtained from all patients before the procedure. This study complied with the Declaration of Helsinki regarding investigation in humans and was approved by the Institutional Ethics Committees at Tokai University Hospital.

TAVR procedure

The TAVR prosthesis type, sheath size, vascular access, and pre- and post-balloon dilation were at the discretion of the operating physicians and TAVR team, which included interventional imagers, interventional cardiologists, and cardiothoracic surgeons. The TAVR valve types used were the Evolut series (Evolut-R and Evolut Pro; Medtronic, Dublin, Ireland) and Sapien 3 (Edwards Lifesciences, Irvine, CA). Indications for postprocedure PPI were determined after consultation with cardiac electrophysiologists. Oversizing of the implanted valve was calculated as the implant prosthesis size/aortic annulus on multislice CT, measured using the method of calculated average annulus diameter derived from the cross-sectional area assessed by mean of planimetry.¹⁵ In attempt to investigate the influence of oversizing on the occurrence of periAVB and late-onset AVB, we

compared the oversizing rate between patients with periAVB or late-onset AVB and those without.

Postprocedural rhythm monitoring

Continuous ECG monitoring was performed in all patients after the TAVR procedures until discharge. Patients were seen in our clinic at 1, 3, 6, and 12 months post procedure for reassessment with 12-lead ECG regardless of symptoms or ambulatory ECG recording if patients experienced presyncope, syncope, dizziness, or loss of consciousness. Patients were subsequently seen thereafter every 3–6 months, either at our clinic or by primary care physicians, for reassessment of symptoms and ECG.

Statistical analysis

Categorical variables were analyzed using the χ^2 statistic and expressed as percentages. Continuous variables were analyzed using the Wilcoxon signed rank sum test and Student *t* test. Normality of distribution was assessed using the Shapiro-Wilk test. Variables with a normal distribution were expressed as mean \pm standard deviation. Variables with non-normal distribution were expressed as median and 25th to 75th percentiles. Statistical significance was set at $P < .05$. The Kaplan-Meier estimate was performed to analyze the survival rate. All statistical analyses were performed using JMP Statistics (version 14.2; SAS Institute, Cary, NC).

Results

Two-hundred sixty-six patients who underwent TAVR were originally enrolled, 20 of whom were excluded from the study population, including 15 patients who had undergone PPI before TAVR. In the remaining 5 excluded patients, 2 patients were excluded because of procedure-related reasons—1 patient with failed TAVR procedure and the other died within 2 days after the TAVR owing to procedural complication—and 3 patients were excluded because of the other PPI indications: symptomatic sick sinus syndrome in 2 patients and hypertrophic obstructive cardiomyopathy in 1 patient. Among the remaining 246 patients, periAVB occurred in 43 patients (17%). There were no differences in the baseline characteristics between the patients with and without peri-AVB (Table 1), except for lower estimated glomerular filtration rate (46 vs 52 mL/min/1.73 m²) in the patients with periAVB. Table 2 summarizes the baseline echocardiographic, CT, and ECG characteristics. Patients with periAVB had a larger left ventricular outflow tract velocity time integral (23.6 ± 9.1 vs 21.1 ± 6.4 , $P = .04$), longer QRS duration (113 ± 26 ms vs 96 ± 19 ms, $P < .01$), longer corrected QT interval (456 ± 35 ms vs 443 ± 34 ms, $P = .03$), higher rate of RBBB (47% vs 7%, $P < .01$), and a larger oversizing rate ($24.8\% \pm 14.6\%$ vs $17.5\% \pm 11.5\%$, $P < .01$) than those without periAVB. Of the 43 patients with periAVB, 15 (35%) underwent PPI at a median duration of 6 days (interquartile range [IQR] 5, 9 days), whereas 1 of 203 patients (1%) without periAVB underwent PPI within 1 month (Figure 1). In the remaining 28 patients with periAVB,

Table 1 Baseline characteristics

	Total (n = 246)	Patients with periAVB (n = 43)	Patients without PeriAVB (n = 203)	P value
Age, y (IQR)	85 (82–88)	85 (83–88)	85 (81–88)	.23
Male sex, n (%)	85 (35)	11 (26)	74 (36)	.16
Body mass index, kg/m ² (IQR)	22.1 (19.5–24.5)	21.3 (20.1–24.8)	22.2 (19.4–24.4)	.84
Hypertension, n (%)	193 (78)	32 (74)	161 (79)	.49
Diabetic mellitus, n (%)	79 (32)	16 (37)	63 (31)	.44
Dyslipidemia, n (%)	145 (59)	21 (48)	124 (61)	.14
Prior coronary intervention, n (%)	69 (28)	8 (19)	61 (30)	.12
Cerebral infarction, n (%)	32 (13)	6 (14)	26 (13)	.84
Peripheral artery disease, n (%)	21 (9)	6 (15)	15 (8)	.18
Atrial fibrillation, n (%)	54 (22)	14 (33)	40 (20)	.07
STS score	6.4 (4.7–8.8)	6.6 (4.7–8.5)	6.4 (4.6–8.9)	.68
Clinical frailty scale	3 (3–4)	3 (3–4)	3 (3–4)	.33
Hemoglobin, g/dL (IQR)	11.6 (10.4–12.7)	11.3 (10.3–12.5)	11.6 (10.5–12.7)	.57
Albumin, U/L (IQR)	3.8 (3.5–4.1)	3.7 (3.4–4.1)	3.8 (3.5–4.1)	.65
BNP level, pg/mL (IQR)	212 (96–524)	245 (104–697)	210 (95–490)	.67
Estimated GFR, mL/min/1.73 m ² (IQR)	50 (38–61)	46 (34–54)	52 (39–61)	.04

BNP = brain natriuretic peptide; GFR = glomerular filtration rate IQR = interquartile range; PeriAVB = periprocedural atrioventricular block; STS = Society of Thoracic Surgeons.

median recovery time from the onset of the AVB was 1 day (IQR 1, 1 day), with no AVB prior to discharge at median 8 days (IQR 6, 12 days). Overall, the incidence of PPI within 1 month after TAVR was 16 of 246 patients (7%): persistence of periprocedural AVB in 12 patients, recurrence of high-grade AVB after recovering the periprocedural AVB in 3 patients, and complete AVB in 1 patient without periprocedural AVB. Of the 16 patients, 14 patients underwent PPI before discharge (6% of 246 patients). The mortality rate in patients who underwent PPI within 1 month tended to be higher than that in those who did not undergo PPI, although the difference was not statistically significant (hazard ratio 2.68, 95% confidence interval 0.97–9.05, log-rank $P = .09$, Figure 2).

During a median follow-up of 365 days (IQR 169, 669 days), late-onset AVB occurred in 10 of 230 patients who had not already required PPI within the first 30 days post TAVR (4%): advanced AVB in 4 patients and complete AVB in the remaining 6 patients. Presyncope ($n = 1$), syncope ($n = 2$), dizziness, heart failure ($n = 1$), and fatigue ($n = 1$) were clinical features of the late-onset AVB. Although periAVB did not occur in 2 of these patients, new-onset conduction disturbance developed during the periprocedural period in both patients—namely, left bundle branch block and nonspecific intraventricular conduction disturbance, respectively (Table 3). Self-expanding valves were implanted in 9 of the 10 patients with late-onset AVB (90%), whereas they were implanted in 151 of the remaining 220 patients (69%, $P = .11$). Patients with late-onset AVB had similar oversizing rate compared with those without (20.6% \pm 9.6% vs 18.3% \pm 12%, $P = .60$). The median date of PPI for late-onset AVB was 76 days (IQR 45, 134 days). Overall, PPI was implanted in 26 of the 246 patients (11%) enrolled in our study. Self-expanding valves were implanted in 22 of the 26 patients who underwent PPI (85%), whereas they were implanted in 151 of the remaining 220

patients (69%) ($P = .07$). Twenty patients without PPI died after the TAVR during the follow-up period. Unexplained sudden cardiac deaths occurred in 3 of the 20 patients, none of whom presented periAVB. The mortality rate in patients with periAVB tended to be higher than in those without, although the difference was not statistically significant (hazard ratio 2.22, 95% confidence interval 0.91–5.39, log-rank $P = .07$, Figure 2).

Discussion

Our major findings were as follows: (1) Late-onset AVB occurred in 4% of patients without PPI within 1 month, all of whom presented with new-onset atrioventricular (AV) conduction disturbances during the periprocedural period, including 8 patients with periAVB, all of whom recovered within 1 month. A self-expanding valve was implanted in 90% of patients presenting with late-onset AVB. (2) PeriAVB occurred in 17% of patients, and PPI was performed in 7% of patients within 1 month following TAVR. (3) Patients with periAVB had a higher prevalence of RBBB than those without. (4) The mortality rate in patients with periAVB or PPI within 1 month tended to be higher than in those without, although it was not significant.

Periprocedural conduction disturbances, including AVB, remain one of the most important complications of TAVR procedures.^{16,17} In accordance with previously reported risk factors, the prevalence of RBBB was significantly higher in patients with periAVB,¹⁸ whereas the angle between the annulus and aorta⁷ was not different between patients with and without periAVB. Furthermore, a prolonged QRS interval in patients with periAVB may be associated with a higher incidence of RBBB. Although the mortality rate was reported to be higher in patients who underwent PPI within 1 month than in those without PPI,^{11,12,19} it was not significant in this study, potentially owing to the low incidence of PPI within 1 month

Table 2 Morphologic, electrocardiographic, and procedural parameters

	Total (n = 246)	Patients with periAVB (n = 43)	Patients without periAVB (n = 203)	P value
Echocardiographic parameters				
EF (%)	66 ± 13	68 ± 14	66 ± 13	.27
LVDD (mm)	44 ± 7	42 ± 7	44 ± 7	.09
LVDs (mm)	28 ± 8	26 ± 8	28 ± 8	.09
Aortic valve max velocity (m/s)	4.5 ± 0.8	4.5 ± 0.7	4.5 ± 0.8	.78
Aortic valve max PG (mm Hg)	82 ± 28	77 ± 28	83 ± 28	.20
Aortic valve mean PG (mm Hg)	46 ± 17	44 ± 19	47 ± 17	.38
AVA (cm ²)	0.6 ± 0.2	0.6 ± 0.2	0.6 ± 0.2	.31
LVOT-VTI (cm)	21.6 ± 7.0	23.6 ± 9.1	21.1 ± 6.4	.04
CT parameters				
Mean LVOT (mm)	23.2 ± 10.2	24.5 ± 18	22.9 ± 7.4	.37
Aortic annulus (mm)	20.3 ± 6.4	19.4 ± 6.2	20.6 ± 6.4	.29
LVOT / aortic annulus	1.06 ± 0.48	1.17 ± 0.79	1.04 ± 0.38	.12
Valve size (mm)	26 ± 2	26 ± 2	26 ± 2	.44
ECG parameters				
PR interval (ms)	178 ± 31	174 ± 31	179 ± 31	.38
QRS interval (ms)	99 ± 21	113 ± 26	96 ± 19	<.01
QTc (ms)	446 ± 34	456 ± 35	443 ± 34	.03
RBBB, n (%)	35 (14)	20 (47)	15 (7)	<.01
LBBB, n (%)	5 (2)	2 (5)	3 (1)	.23
LAFB, n (%)	13 (5)	4 (9)	9 (4)	.23
LPFB, n (%)	0 (0)	-	-	-
NIVCD, n (%)	10 (4)	0 (0)	10 (5)	.047
Procedural parameters				
Oversizing of implanted valves	18.8 ± 12.4	24.8 ± 14.6	17.5 ± 11.5	<.01
Self-expanding valve, n (%)	173 (70)	33 (77%)	140 (69)	.30
Angle (degrees)	50 ± 10	52 ± 9	49 ± 10	.07
Pre-BAV, n (%)	166 (67)	28 (65)	138 (68)	.71
Post-BAV, n (%)	51 (21)	8 (19)	43 (21)	.70
Valve in valve, n (%)	4 (2)	1 (2)	3 (1)	.70

AVA = aortic valve area; BAV = balloon aortic valvuloplasty; CT = computed tomography; ECG = electrocardiography; EF = ejection fraction; LAFB = left anterior fascicular block; LBBB = left bundle branch block; LPFB = left posterior fascicular block; LVDD = left ventricular end-diastolic diameter; LVDs = left ventricular end-systolic diameter; LVOT = left ventricular outflow tract; NIVCD = nonspecific intraventricular conduction disturbance; PeriAVB = periprocedural atrioventricular block; PG = pressure gradient; RBBB = right bundle branch block; VTI = velocity time integral.

compared with previous studies.¹¹ According to a previous study by Ream and colleagues,¹³ delayed high-grade AVB (DH-AVB) >2 days after the procedure occurred in 10% of patients who underwent 30-day ambulatory event monitoring. Although preexisting RBBB was a risk factor for DH-AVB,

the sensitivity in predicting DH-AVB was only 27%, and other predictors remain unclear. The present study revealed that late-onset AVB occurring >30 days occurred in 5% of patients who underwent TAVR. This highlights the importance of long-term follow-up of periprocedural conduction disturbances even after

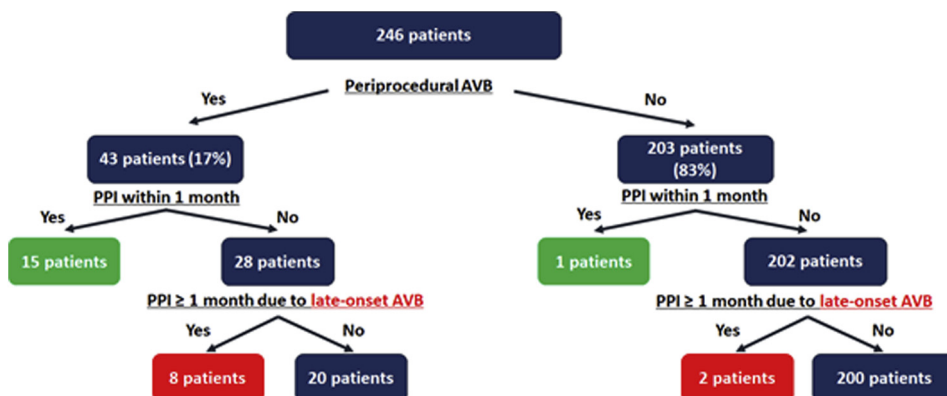


Figure 1 Study population. Among the 246 patients, periprocedural atrioventricular block (periAVB) after transcatheter aortic valve replacement (TAVR) occurred in 43 patients (17%). Of these 43, 15 patients underwent permanent pacemaker implantation (PPI) at a median duration of 6 days (35%), whereas 1 of 203 patients without periAVB underwent PPI (1%). Late-onset AVB, defined as AVB occurring 1 month after the TAVR procedure, occurred in 10 of 230 patients without PPI during the periprocedural period (4%), 8 of whom had transient periAVB.

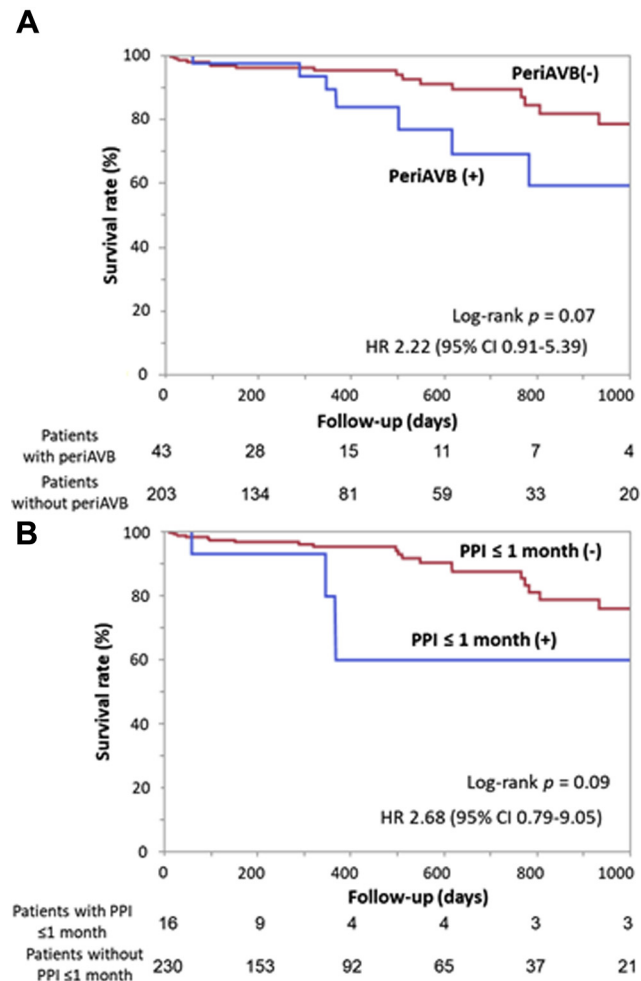


Figure 2 Long-term outcome in patients with transient periprocedural atrioventricular block (pAVB) and permanent pacemaker implantation (PPI) within 1 month. **A:** The mortality rate in patients with periAVB tended to be higher than in those without, although the difference was not statistically significant (hazard ratio [HR] 2.22, 95% confidence interval [CI] 0.91–5.39, log-rank $P = .07$). **B:** The mortality rate in patients with PPI within 1 month tended to be higher than in those without, although the difference was not statistically significant (HR 2.68, 95% CI 0.97–9.05, log-rank $P = .09$).

recovery during hospitalization. Although there was no sudden cardiac death documented in this study during follow-up, it remains unclear whether late-onset AVB could be a potential cause of sudden cardiac death; 50% of patients had symptomatic AVB, suggesting a risk of sudden cardiac death in such patients without subsequent PPI.

In general, conduction system fibrosis and/or sclerosis causes conduction disturbance in chronic conduction system disease.²⁰ In contrast, previous reports have demonstrated edematous changes and increased leukocyte counts around the AV nodal region following valve implantation in patients who underwent TAVR.^{21,22} The traumatic effect of the implanted valve may damage myocardial cells around the AV nodal region, leading to irreversible scarring of the surrounding tissue; therefore, it is recommended to implant the valve higher to avoid damage to the conduction system. Several

studies have demonstrated that membranous septum length and valve depth in relation to this length are highly predictive of PPI.^{8,23} Whether membranous septum-guided TAVR reduces the incidence of late-onset AVB requires further investigation. In a recent report by Krishnaswamy and colleagues,²⁴ patients receiving self-expanding valves required PPI more frequently than those receiving balloon-expandable valves within 30 days. Of note, self-expanding valves were implanted in the majority of the patients with late-onset AVB in our study, suggesting that continuous pressure overload to the conduction system caused insidious progression of tissue fibrosis over time.

Limitations

First, the present study was a small, single-center, retrospective, observational cohort study. Therefore, a prospective multicenter study with a larger sample size is warranted to elucidate our findings. Second, it is likely that some of the patients we regarded as free from late-onset AVB had undetected asymptomatic AVB in the absence of continuous monitoring devices. These false-negatives, if detected, should have been included in patients with late AVB. Third, a prolonged follow-up period may have increased the incidence of late-onset AVB. In future studies, close long-term follow-up using implantable loop recorder may reduce the overlooking of late AVB in patients undergoing TAVR, particularly those with transient conduction disturbances during the periprocedural period.

Conclusion

Late-onset AVB occurred in a minority of patients undergoing TAVR and was associated with new-onset atrioventricular conduction disturbances during the periprocedural period, including transient high-grade AVB. Caution should be taken for late-onset AVB, particularly in patients receiving self-expanding valves, even after recovering from transient conduction disturbances.

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Disclosures

Dr Ohno served as a proctor for Medtronic. All other authors have reported that they have no relationships to disclose that are relevant to the contents of this paper.

Authorship

All authors attest they meet the current ICMJE criteria for authorship.

Patient Consent

Written informed consent was obtained from all patients before the procedure.

Table 3 Characteristics of patients with late-onset atrioventricular block

Age	Sex	AVB	Symptom	EF (%)	LVDd (mm)	LVDs (mm)	Aortic annulus (mm)	LVOT/annulus	Valve size (mm)	Self-expanding valve	Angle (°)	Over-sizing (%)	Pre-conduction disturbances	Post-conduction disturbances	PPI (days)
83	F	Complete	Syncope	67	41	26	24.2	0.94	26	+	49	14.8	-	periAVB	36
86	F	Complete	None	82	34	17	18.9	1.16	26	+	51	19.3	-	periAVB	36
88	F	Advanced	Dizziness	72	35	21	25.4	NA	29	+	68	14.2	LAFB	NIVCD	48
87	F	Advanced	Syncope	41	50	40	23.3	0.94	26	+	47	18.5	LBBB, first-degree AVB	periAVB	61
88	F	Advanced	None	57	44	31	22.2	1.01	26	+	59	16.1	RBBB	periAVB	73
85	F	Complete	HF	76	45	25	19.4	1.05	23	-	64	12.5	RBBB, LAFB	periAVB	79
85	M	Advanced	None	70	55	33	21.3	1.03	26	+	53	18.7	Second-degree AVB	periAVB	84
83	M	Complete	Presyncope	43	43	34	26.5	NA	29	+	42	9.6	-	periAVB	111
85	F	Complete	Fatigue	65	32	21	19.2	1.08	23	+	69	11.1	LAFB	LBBB	204
82	F	Complete	None	67	38	24	20.1	1.09	26	+	59	19.0	-	periAVB	294

AVB = atrioventricular block; EF = ejection fraction; HF = heart failure; LAFB = left anterior fascicular block; LBBB = left bundle branch block; LVDD = left ventricular end-diastolic diameter; LVDS = left ventricular end-systolic diameter; LVOT = left ventricular outflow tract; NA = not available; NIVCD = nonspecific intraventricular conduction disturbance; PeriAVB = periprocedural atrioventricular block; PPI = permanent pacemaker implantation; RBBB = right bundle branch block.

Ethics Statement

This study complied with the Declaration of Helsinki regarding investigation in humans and was approved by the Institutional Ethics Committees at Tokai University Hospital.

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