



Effect of transcatheter aortic valve replacement on P-wave duration, P-wave dispersion and left atrial size

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Abstract

Background P-wave dispersion (PWD), a measure of heterogeneity of atrial refractoriness, is defined as the difference between the maximum and minimum P-wave duration. In patients with severe aortic stenosis (AS), P-wave duration and PWD were shown to be increased, indicating atrial electrical remodeling. However, the effect of transcatheter aortic valve replacement (TAVR) on P-wave morphology has not been established yet. The aim of this study is to assess the short and long-term effects of TAVR with two types of bioprosthetic valves on P-wave duration and PWD in association with left atrial (LA) size. **Methods** Fifty-two (36 female) eligible patients in sinus rhythm who underwent transfemoral TAVR between June 01, 2012 and July 31, 2014 with either a Medtronic CoreValve (MCV) ($n = 32$) or an Edwards SAPIEN XT Valve ($n = 20$) were enrolled. Standard 12-lead electrocardiogram and echocardiographic evaluations were performed pre-procedurally, post-TAVR day one and 6 months post-TAVR. P-wave duration and PWD were measured and correlation analyses with echocardiographic variables were performed. **Results** P-wave duration and PWD were significantly decreased on post-TAVR day one ($P < 0.05$). They continued to decrease during the six month follow-up period, but were not significantly different from short-term values ($P > 0.05$). The decrease of LA diameter was found significant at the sixth-months of follow-up ($P < 0.05$). These changes were independent from the types of bioprosthetic valves implanted ($P > 0.05$). A positive correlation was detected between minimum P-wave duration and maximum aortic valve gradients at post-TAVR day one ($r = 0.297$, $P = 0.032$). **Conclusions** P-wave duration and PWD were significantly reduced early after TAVR indicating early reverse atrial electrical remodeling. Moreover, structural reverse remodeling of atrium was detected at the 6-months of follow-up. The effects of two types of bioprosthetic valves on atrial remodeling were similar.

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1 Introduction

P-wave dispersion (PWD) is defined as the difference between the maximum and minimum P-wave duration.^[1] It is a new electrocardiographic marker that reflects an inhomogeneous and discontinuous propagation of sinus impulses and indicates heterogeneous intra-atrial and inter-atrial conduction, providing a substrate that favors reentry mechanisms.^[2–4] Several studies used this electrocardiographic parameter in various clinical settings, especially in the prediction risk of atrial fibrillation (AF).^[5–8]

Aortic stenosis (AS) results in chronically increased afterload that is accompanied by left atrial (LA) enlargement

and dysfunction indicating atrial remodeling.^[9,10] These patients reported to have longer maximum P-wave duration and higher PWD than healthy control subjects which possibly explains AF as being the most common arrhythmia in these patients.^[11–13]

Transcatheter aortic valve replacement (TAVR) has been a reliable treatment modality alternative to surgery for high-risk patients with AS.^[14,15] Two types of bioprosthetic valves most commonly used worldwide are the self-expandable Medtronic CoreValve (MCV) (Medtronic, Minneapolis, Minnesota), and balloon-expandable Edwards SAPIEN XT valve (ESV) (Edwards Lifesciences, Irvine, California). TAVR provides significant reductions in transvalvular aortic pressure gradients equivalent to reductions in left ventricular afterload.

Atrial structural remodeling secondary to AS reported to improve after TAVR with the relief in pressure overload.^[16] However, there is no study so far evaluating the effect of TAVR on P wave parameters. Thus, we aimed to determine

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the effects of TAVR with two types of devices on both atrial electrical and structural remodeling over short and long-term periods.

2 Methods

2.1 Study design and population

Between June 01, 2012 and July 31, 2014, 77 patients who underwent transfemoral TAVR with MCV (Medtronic, Minneapolis, Minnesota) or ESV (Edwards Lifesciences, Irvine, California) in our clinic were included in this retrospective cohort analysis. Patients who had atrioventricular conduction abnormalities, an undetectable P-wave in ≥ 3 leads, sustained atrial or ventricular arrhythmias, AF, and a permanent pacemaker were excluded. Thus, 21 patients with AF, and eight patients with a permanent pacemaker (four had both AF and pacemaker) were excluded and the remaining 52 (36 female) eligible patients were enrolled.

The present study was a single center study. All examinations were performed in the Dokuz Eylul University, Department of Cardiology. The study protocol was approved by the ethics committee of the institution.

2.2 Electrocardiographic measurement

Standard 12-lead ECG was obtained using a recorder set at 50 mm/s paper speed and calibration of 1 millivolt/centimeter in the supine position. This was recorded for each patient on the day before TAVR and repeated on post-TAVR day one and six months post-TAVR. Measurements of P-waves were done by two investigators who were unaware of the subjects' data. To improve accuracy, measurements were performed with calipers and magnifying lenses for defining the electrocardiographic deflection. P-wave duration was measured from the onset to the offset of the P wave. The average P-wave of three consecutive beats from each lead was determined. Maximum P-wave duration was defined as the longest P-wave duration and minimum P-wave duration was defined as the shortest P-wave duration in all derivations. PWD was defined as the difference between the maximum and minimum P-wave durations from the 12 leads. The standard deviation of the P-wave duration (PSD) in all measurable leads were also measured.^[1-4,17]

2.3 Echocardiographic evaluation

Standard transthoracic echocardiography was performed for each patient before TAVR and repeated on post-TAVR day one and six months post-TAVR. Left ventricular ejection fraction (LVEF), LA diameter, and left ventricular wall

thicknesses were measured by M-mode echocardiography. Maximum and mean aortic gradients were calculated by Doppler studies.

2.4 Statistical analysis

All analyses were performed using statistical package for the social sciences version 17.0 statistical software (SPSS Inc., Chicago, IL, USA). Continuous data were expressed as mean \pm SD and categorical data were expressed as percentage. Comparisons of continuous variables between two groups were based on the Student's *t*-test for parametric variables, and the Mann Whitney *U* test for nonparametric variables. Analysis of variance was performed for the comparison of repeated measurements of electrocardiographic and echocardiographic values using ANOVA for parametric variables and Friedman test with Bonferroni corrections for nonparametric variables. Spearman correlation coefficients were used to investigate the associations between P wave parameters and echocardiographic variables. $P < 0.05$ was regarded as statistically significant.

3 Results

The mean age of our study population was 79.1 ± 6.8 years. MCV was implanted to 32 (62%) and ESV to 20 (38%) patients. Mean post-TAVR duration of hospitalization was 4.0 ± 1.2 days, blood pressure levels were in normal range, and no paroxysmal AF attack was observed in patients until discharge. Within the six months of follow-up, three patients (two with MCV, one with ESV) died due to non-cardiac causes; two patients had an AF attack and were both successfully converted to sinus rhythm. Baseline characteristics and types of bioprosthetic valves implanted are presented at Table 1.

P_{\max} (123.3 ± 13.4 vs. 114.5 ± 11.9 , $P < 0.05$), P_{\min} (70.1 ± 11.0 vs. 66.3 ± 11.5 , $P < 0.05$), PWD (53.2 ± 12.4 vs. 48.4 ± 12.8 , $P < 0.05$), and PSD (11.4 ± 0.7 vs. 9.4 ± 0.6 , $P < 0.05$) were significantly decreased on post-TAVR day one compared to pre-TAVR values. However, when compared to post-TAVR values, no significant difference was detected for P-maximum (114.5 ± 11.9 vs. 113.3 ± 10.0 , $P > 0.05$), P-minimum (66.3 ± 11.5 vs. 66.9 ± 10.5 , $P > 0.05$), PWD (48.4 ± 12.8 vs. 46.6 ± 11.6 , $P > 0.05$), and PSD (9.4 ± 0.6 vs. 9.0 ± 0.7 , $P > 0.05$) at six months post-TAVR control. The LA diameter at post-TAVR day one was not significantly different compared to pre-TAVI values (4.5 ± 0.5 vs. 4.4 ± 0.5 , $P > 0.05$) but found significantly different at six months post-TAVR compared to post-TAVR day one (4.4 ± 0.5 vs. 4.3 ± 0.4 , $P < 0.05$) (Table 2, Figure 1).

Table 1. Baseline characteristics of the patients and types of valves implanted (n = 52).

Age, yrs	79.1 ± 6.8
Hypertension	44 (84.6%)
Diabetes	14 (26.9%)
COPD	22 (42.3%)
STS score	8.2 ± 4.5
Logistic Euroscore	34.8 ± 13.1
Euroscore II	11.0 ± 7.6
LA diameter, cm	4.5 ± 0.5
IVS, cm	1.5 ± 0.3
PW, cm	1.3 ± 0.2
Peak AV gradient, mmHg	76.3 ± 18.6
Mean AV gradient, mmHg	48.0 ± 12.0
AV area, cm ²	0.6 ± 0.1
LVEF, %	50.3 ± 15.6
Medtronic CoreValve	32 (68%)
26 mm	11
29 mm	15
31 mm	6
Edwards Sapien Valve	20 (32%)
23 mm	4
26 mm	15
29 mm	1

Data are shown as n or mean ± SD or n (%); AV: aortic valve; COPD: chronic obstructive pulmonary disease; IVS: interventricular septum; LA: left atrium; LVEF: left ventricular ejection fraction; PW: posterior wall; STS: Society of Thoracic Surgery.

Table 2. Early and late post-procedural effects of TAVR on electrocardiographic and echocardiographic variables.

	Pre-TAVR	Post-TAVR 1 st day	Post-TAVR 6 th month
P _{min} , ms	70.1 ± 11.0	66.3 ± 11.5*	66.9 ± 10.5*
P _{max} , ms	123.3 ± 13.4	114.5 ± 11.9*	113.3 ± 10.0*
PWD, ms	53.2 ± 12.4	48.4 ± 12.8*	46.6 ± 11.6*
PSD, ms	11.4 ± 0.7	9.4 ± 0.6*	9.0 ± 0.7*
LA, cm	4.5 ± 0.5	4.4 ± 0.5	4.3 ± 0.4* [#]
LVEF, %	50.3 ± 15.6	50.8 ± 15.2	55.3 ± 13.3* [#]

*P < 0.05 versus pre-TAVR values; [#]P < 0.05 versus post-TAVR day one values. LA: left atrial diameter; LVEF: left ventricular ejection fraction; PWD: P wave dispersion; PSD: standard deviation of P wave duration in all leads; TAVR: transcatheter aortic valve replacement.

Table 3. Comparison of the effects of two bioprosthetic valves on electrocardiographic and echocardiographic variables.

Variable	Pre-TAVR			Post-TAVR day 1			Post-TAVR 6 month		
	MCV (n = 32)	ESV (n = 20)	P-value	MCV (n = 32)	ESV (n = 20)	P-value	MCV (n = 30)	ESV (n = 19)	P-value
P _{min} , ms	70.78 ± 12.1	69.0 ± 9.1	NS	66.1 ± 12.5	66.5 ± 9.9	NS	66.1 ± 11.7	68.0 ± 8.3	NS
P _{max} , ms	123.1 ± 15.1	123.5 ± 10.4	NS	113.6 ± 12.5	116.0 ± 11.0	NS	112.2 ± 10.1	115.0 ± 10.0	NS
PWD, ms	52.3 ± 12.8	54.5 ± 11.9	NS	47.6 ± 12.8	49.5 ± 13.2	NS	46.4 ± 11.4	47.0 ± 12.2	NS
LA, cm	4.5 ± 0.5	4.4 ± 0.5	NS	4.5 ± 0.5	4.4 ± 0.5	NS	4.3 ± 0.4	4.3 ± 0.5	NS
LVEF, %	48.5 ± 16.2	53.1 ± 14.5	NS	48.9 ± 16.3	53.8 ± 13.0	NS	54.2 ± 14.5	57.2 ± 11.2	NS

ESV: Edwards Sapien XT Valve; LA: left atrium; LVEF: left ventricular ejection fraction; MCV: Medtronic Core Valve; NS: non-significant; PWD: P wave dispersion; TAVR: transcatheter aortic valve replacement.

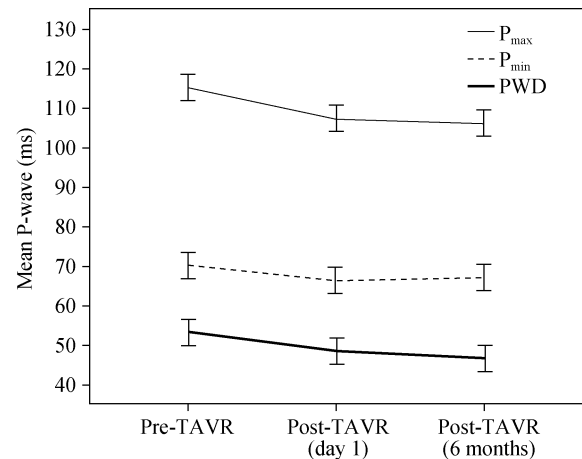


Figure 1. P-wave measurements at pre-TAVR, post-TAVR day one and six months post-TAVR controls. PWD: P-wave dispersion; TAVR: transcatheter aortic valve replacement.

Comparison of P wave and echocardiographic parameters between MCV and ESV groups are shown in Table 3. P-maximum, P-minimum and PWD values (at pre-TAVR, at post-TAVR day one, at six months post-TAVR) were similar in both groups (P > 0.05). Also, LA diameter and LVEF (pre-TAVR, post-TAVR day one, six months post-TAVR) were similar in both groups (P > 0.05), (Table 3).

In the correlation analysis between P-wave variables and echocardiographic parameters including LA diameter, mean aortic gradients, LVEF, left ventricular posterior wall and interventricular septal thicknesses before and after TAVR, a positive correlation between minimum P-wave duration and maximum aortic gradients at post-TAVR day one (r = 0.297, P = 0.032) was found.

4 Discussion

The main finding of our study was P-wave duration and PWD were significantly reduced early after TAVR indicating reverse atrial electrical remodeling. We also observed reverse structural remodeling by decrease in LA diameter at

long-term follow-up. The effects of two types of bioprosthetic valves on atrial remodeling were similar. To our knowledge, this is the first study describing reverse atrial electrical remodeling after TAVR.

Myocardial stretch due to volume or pressure overload causes changes in electrical signaling that is described as the mechano-electric feedback.^[18,19] The stretch in atrium was shown to cause a reduction in conduction velocity, altered action potential duration, prolongation of atrial refractoriness and PWD, all of which indicates atrial electrical remodeling and confers an increased vulnerability to AF.^[20-22] Atrial overload also effects stretch-activated ion channels (SACs) to produce potentially arrhythmogenic electrophysiological changes and blockage of the SACs was found to suppress stretch-facilitated AF.^[19,23,24] In a previous study, relief from chronic atrial stretch with mitral commissurotomy reported to cause reverse atrial remodeling in patients with mitral stenosis.^[25]

Aortic stenosis leads raised left ventricular filling pressure which results in increased LA pressure overload and dilatation.^[26] Increased LA stretch promotes arrhythmogenic events including AF that is an important prognostic indicator for clinical deterioration in these patients.^[9,12,13] In a recent study, P-wave duration and PWD were found to be significantly longer in patients with AS than control subjects. Further, if these patients have coexisting paroxysmal AF, they have higher values of maximum P-wave duration and PWD than those without paroxysmal AF.^[11] Since TAVR provides the relief of left ventricular pressure overload and reported to improve LA functions with structural remodeling previously,^[16] it may also be expected to cause reverse atrial electrical remodeling.

In this study, we observed reverse atrial electrical remodeling early after TAVR. Since the relation between P-wave duration, PWD and AF is well-known improvement on atrial electrical remodeling might have prevented new-onset AF attacks in our patients. Despite of the limited number of patients and relatively short in-hospital stay, no patient had new-onset AF until discharge. During six months of follow-up only two patients had a paroxysmal AF attack who were both successfully converted to sinus rhythm.

The reductions in LA diameter indicating reverse atrial structural remodeling was observed at the six months of follow-up. We think that structural reverse remodeling of LA starts long before that we have detected by LA diameter since D'Ascenzi, *et al.*^[16] reported structural reverse remodeling of LA as early as 40 days post-TAVR using additional echocardiographic parameters for LA functions. Since LA diameter is an important predictor on P wave size and it was found to be significantly decreased, we had expected the

persistence of significant reductions on P-wave parameters at six months post-TAVR. However, maximum P wave duration and PWD were decreased but not reached a significant value. We think that this was possibly due to our small sized population.

The two types of bioprosthetic valves, self-expandable MCV and balloon-expandable ESV are structurally quite different which may have consequences as an increased incidence of conduction disorders with MCV.^[27] However in our study, P wave duration and PWD before and after TAVR were similar between patients in whom MCV or ESV were implanted. The positive changes in P wave duration were observed in a short period of time and independent from the type of bioprosthetic valves.

One of the major limitations of our study was the limited number of patients that have been evaluated in a relatively short period of time. Lack of a control group was another limitation. Comparison of the electrocardiographic effects of TAVR with patients who underwent medical therapy or aortic valve surgery would have improved our study. Also, we observed patients with new-onset AF only after their admissions to hospital, a long-term Holter recording could be better to exactly determine the incidence of paroxysmal AF in these patients. The absence of the intra-LA pressure recordings before or after the procedure was also a limitation since we think reverse electrical remodeling were mostly due to the relief of LA pressure overload. Finally, using a high resolution ECG instead of standard 12-lead ECG would have been better for the measurements. We suggest long-term and larger prospective studies on this topic.

In conclusion TAVR caused a significant reduction on P-wave duration and PWD in a short period of time indicating early reverse atrial electrical remodeling. Reverse structural remodeling of atrium was also occurred at post-TAVR follow-up. The effects of two types of bioprosthetic valves on atrial reverse remodeling were similar.

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