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Title: Feasibility of His-Bundle Pacing in patients with conduction disorders following Transcatheter Aortic Valve Replacement

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/jce.14371.

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Funding: A. Noel was supported by a grant from the "Fédération Française de Cardiologie" for this work.

Disclosures: none

Word count: 2904

Abstract

Background

Conduction disorders requiring permanent pacemaker implantation occur frequently after transcatheter aortic valve replacement (TAVR). This multicenter study explored the feasibility and safety of His bundle pacing (HBP) in TAVR patients with a pacemaker indication to correct a TAVR induced left bundle branch block (LBBB).

Methods

Patients qualifying for a permanent pacemaker implant post TAVR were planned for HBP implant. HBP was performed using the Select Secure (3830, Medtronic) pacing lead, delivered through a fixed curve or deflectable sheath (C315HIS or C304; Medtronic).

Successful HBP was defined as selective or non-selective HBP, irrespective of LBB recruitment. Successful LBBB correction was defined as selective or non-selective HBP resulting in paced QRS morphology similar to pre-TAVR QRS and paced QRS duration <120ms with thresholds <3.0V at 1.0ms pulse width.

Results

The study enrolled 16 patients requiring a permanent pacemaker post TAVR (age 85±4yrs, 31% female, all LBBB, QRS duration 161±14ms). Capture of the His bundle was achieved in 13/16 (81%) patients. HBP with LBBB correction was achieved in 11/16 (69%) and QRS duration narrowed from 162±14ms to 99±13ms and 134±7ms during S-HBP and NS-HBP respectively (p=0.005). At implantation, mean threshold for LBBB correction was 1.9±1.1V at 1.0ms. Thresholds remained stable at 11±4 months follow up (1.8±0.9V at 1.0ms, p=0.231 for comparison with implant thresholds). During HBP implant, one temporary complete atrioventricular block occurred.

Conclusion

Permanent His bundle pacing is feasible in the majority of TAVR patients requiring a permanent pacemaker with the potential to correct a TAVR-induced LBBB with acceptable pacing thresholds.

KeyWords: His bundle pacing, TAVR, Complication, Left Bundle Branch Block, Conduction disturbance

1. Introduction

Transcatheter aortic valve replacement (TAVR) is an effective catheter-based treatment for severe aortic valve stenosis. Large registries and randomized trials have proved its effectiveness in patients at low, intermediate or high surgical risk.(1-6) Unfortunately, atrioventricular block (AVB) and new left bundle branch block (new LBBB), resulting from encroachment of the conduction system by the aortic valve prosthesis, are frequent complications that could mitigate the advantage of TAVR. Whereas AVB requires permanent pacemaker implantation, occurrence of new LBBB after TAVR has been associated with an increased risk of mortality, heart failure and progression to third degree AVB.(7-13) Therefore, patients with new conduction disturbances after TAVR frequently undergo pacemaker implantation. However, the best pacing modality in these patients has not yet been defined. Previous case reports demonstrated that His bundle pacing (HBP) might correct LBBB, including TAVR-induced new LBBB.(14-16) As HBP can restore the normal myocardial activation and avoid ventricular dyssynchrony during pacing, HBP might be the preferred strategy of pacing in TAVR patients. The aim of the present study was to assess the feasibility and short-term safety of HBP in patients with new conduction disturbance occurring after TAVR.

2. Methods

Population and study protocol

This study is a multicenter prospective cohort study conducted between April 2018 and April 2019. All consecutive patients who presented with an indication for permanent pacemaker implantation within 48 hours after TAVR were considered eligible. TAVR indication was based on the presence of a severe and symptomatic aortic valve stenosis in patients at increased risk for open heart surgery and good candidates for TAVR according to multidisciplinary heart-team evaluation. Patients with previously implanted pacemaker were excluded from the present study. All patients were implanted with the Evolut™ R valve

(Medtronic, Minneapolis, MN, USA).

Pacemaker indication was based on the occurrence of AVB, PR or QRS prolongation or new LBBB at the discretion of the treating cardiologist in agreement with the electrophysiologist and recent recommendations regarding post TAVR pacemaker policy.(17-19) HBP was performed by electrophysiologists. The study was approved by both Institutional Committees on human research and written informed consent was obtained in all patients.

Electrogram analysis

Twelve-lead electrograms (ECG) were acquired before, during and after both TAVR and pacemaker implantation. Electrocardiographic data included recording of baseline rhythm (sinus rhythm or atrial fibrillation), PR and RR intervals, QRS duration (QRSd) and QRS morphology. Diagnosis of bundle branch blocks was made according to the AHA guidelines.(20) All of the ECG measurements were performed twice and the mean value was used for analysis.

His bundle pacing procedure

All patients were implanted with the Select Secure pacing lead (model 3830, 69cm, Medtronic Inc., Minneapolis, MN) at the level of the His bundle, using a fixed sheath (C315-HIS, Medtronic) or deflectable sheath (C304; Medtronic) inserted via a 7 or 9 French introducer sheath placed in the subclavian or axillary vein. His bundle electrograms were mapped in a unipolar configuration at the tip of the pacing lead and recorded with the Medtronic pacing system analyzer and an electrophysiologic recording system. The lead was screwed in at the optimal His bundle position by 4 to 5 clockwise rotations. His bundle capture thresholds and bundle branch recruitment thresholds were assessed at pulse width of 1.0ms. In case of threshold <1V, pulse width of 0.5ms was equally tested. The choice of placing a backup pacing lead was left to the discretion of the implanting electrophysiologist. In that case, the HBP lead was connected to either the right ventricular (RV) or left ventricular port (LV) port of a cardiac resynchronization therapy (CRT) device.

Defining HBP success

All ECGs during HBP were blindly analyzed by two readers (JDP and JBLPDW). To characterize His bundle pacing, the following measurements were obtained during the implant procedure: relationship of the His-QRS and stimulus-QRS intervals, the presence or absence of direct capture of the local ventricular electrogram on the pacing lead, the QRS duration and morphology and the capture thresholds. Accordingly, selective and non-selective HB capture with or without LBBB recruitment were annotated as recommended by previously published criteria.(21)

Successful HBP was defined as either selective or nonselective HB capture, irrespective of LBBB correction. HBP with correction of LBBB was defined as selective or nonselective HBP with LBB recruitment resulting in a QRS morphology similar to pre-TAVR QRS morphology and QRSd < 120ms (in case of S-HBP). HBP with LBB recruitment was accepted if recruitment thresholds were lower than 3.0V at 1.0ms. Higher thresholds were considered acceptable if the excepted longevity (calculated from the actual threshold, the pulse duration and the impedance) exceeded the Belgian governmental warranty (>6 years).

Noninvasive epicardial ventricular activation mapping during HBP

In one patient with TAVR-induced new LBBB and CRT indication, the impact of HBP on the reduction of QRSd, total left ventricular activation time (LVAT) and ventricular electrical uncoupling (VEU) was evaluated by using noninvasive epicardial ventricular activation mapping. Immediately before the implant procedure, this patient was fitted with a 252-electrode electrocardiographic imaging vest (Medtronic CardioInsight, Minneapolis, Minnesota) and submitted to a low-dose thoracic computed tomography to acquire electrode and cardiac positions. The patient was then submitted to various pacing configurations (ODO, RV, LV, biventricular pacing and His bundle pacing). For each pacing modality QRSd, LVAT and (VEU) was derived from 5 consecutive beats.

Statistical Analysis

Quantitative data were presented as mean ± standard deviation (SD) or median [interquartile range (IQR)] if not normally distributed. Quantitative variables were compared with the Student t-test or Mann-Whitney test. Paired student T-test and Wilcoxon signed rank test were performed for paired comparisons. Categorical variables were expressed as numbers and percentages and compared by use of the Pearson Chi-Square or Fisher's Exact test. All reported p values are 2-sided and p values <0.05 were considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 24.0 (IBM Corp., Armonk, New York, USA).

Results

Baseline characteristics

The study enrolled 16 patients (mean age 85±4 years, 31% female). Patient characteristics are summarized in table 1. Forty-four percent of patients had normal LV ejection fraction (LVEF), and 31% of patients had a history of ischemic heart disease. All patients underwent TAVR with the Evolut™ R. (Diameter range: 23 to 34 mm). QRSd pre-TAVR was 101±20ms and prolonged to 162±14ms after TAVR (p=0.007). All patients in the present study experienced a new LBBB after TAVR.

Feasibility of His bundle recruitment and correction of TAVR-induced LBBB

His bundle capture post TAVR could be achieved in 13/16 (81%) patients. Selective HBP (S-HBP) was achieved in 38% of patients and nonselective HBP (NS-HBP) in 62%. Overall, HB capture threshold was 1.2±1.5V at 1ms at implant. HBP with LBBB correction could be achieved in 11/16 (69%) patients. In figure 1 and 2 we show examples of patients with TAVR-induced new LBBB which could be corrected by HBP. In figure 3, the fluoroscopic image of a patient with successful correction of TAVR-induced new LBBB by HBP is shown and positions of the HBP lead of all successful implanted patients are marked by red dots. LBBB correction thresholds measured 1.9±1.1V at 1.0ms. In patients with successful LBBB correction, QRSd narrowed from 162±14ms to 99±13ms and 134±7ms during S-HBP and NS-HBP respectively (p=0.005) (Figure 4). QRSd during S-HBP with LBBB correction was comparable to pre-TAVR QRSd (99±13ms versus 101±20ms, p= 0.581).

In patients with no correction of TAVR-induced new LBBB (n=5), HBP was abandoned and patients were switched to RV apical pacing or biventricular pacing (RV + LV pacing). HBP was accepted as final pacing configuration in all patients with successful LBBB correction (n=11). In those patients, 1(9%) received single chamber pacemaker, 4(36%) a dual chamber pacemaker and 6(55%) a CRT-device. In patients implanted with a CRT device, the HBP lead was connected to the LV port with RV apex or outflow tract back up pacing (n=4) or to the RV port with an additional LV implanted in a posterolateral side branch of the coronary sinus. All pacing characteristics at implant are summarized in table 2.

Correction of left ventricular activation time during HBP

Noninvasive epicardial ventricular activation maps of a patient during different pacing configurations (ODO, RV, LV, RV+LV and HBP) are shown in figure 5, the largest benefit in terms of reduction of LVAT, VEU and QRSd was obtained during His bundle pacing.

Procedural characteristics and complications.

Procedural characteristics are summarized in Table 2. Mean procedure time was 93±33 min and mean fluoroscopy time was 15±11 min. During HBP implant, one complete heart block developed, which resolved within 24 hours after implant. No tamponade or vascular access complications occurred.

Follow up of HBP in TAVR patients

At a mean follow up of 11±4months, HB capture thresholds remained stable 1.0±0.7V at 1.0ms (p=0.223 compared to implant HBP thresholds). Bundle branch recruitment thresholds also remained stable (1.8±0.9V at 1.0ms, p=0.231 compared to implant LBBB correction threshold). One patient experienced a significant rise in LBBB correction threshold (>2V), but no lead revision was required. No lead dislocations or exit blocks occurred. No deaths or heart failure hospitalizations were observed in the enrolled patients.

Reason for non-successful or non-corrective HBP post TAVR

Reasons for non-successful HBP (n=3) were: inability to locate the His bundle combined with unsuccessful pace mapping (n=2) and inability to recruit the His bundle despite successful His mapping (n=1). In two additional patients the His bundle could be paced, but either no correction of LBBB could be achieved (n=1) or LBBB correction could only be achieved with unacceptable high output (6V) (n=1). Patients in whom HBP was not successful were similar in terms of age, sex and TAVR characteristics.

4. Discussion

Main findings

In the present study, we evaluated the feasibility of treating patients with TAVR-induced conduction disorders and new LBBB by pacing the His bundle. Our results can be summarized as follow: First, His bundle recruitment after implantation of the Medtronic Evolut™ R aortic valve is feasible and was achieved in 81% of patients with acceptable threshold values. Second, in 69% of patients, the TAVR-induced new LBBB could be corrected with significant reduction in QRS duration. Third, thresholds remained stable at short-term follow-up without the need for lead revision. This limited series of patients might serve as a proof of concept and demonstrates that His bundle pacing has the potential for correcting the most frequent iatrogenic complication resulting from TAVR.

Conduction disorders after TAVR

According to the type of valve implanted, the need for permanent pacing after TAVR ranges from 4-65%, which is higher than what is observed after surgical aortic valve replacement(17). Previous reports have identified the use of the CoreValve™ prosthesis as a risk factor for damage to the conduction system.(17) Unfortunately, predictors for recovery of cardiac conduction after TAVR are poorly described. Damage resulting from mechanical displacement by calcium deposits during aortic valve deployment might be permanent. In contrast, conduction disturbances related to tissue edema and reaction to ischemia and inflammation after TAVR might have the potential to recover. Beyond AVB, de novo LBBB is also a frequent complication after TAVR. According to the current literature, approximately one third of patients implanted with the Medtronic CoreValve™ will develop TAVR-induced LBBB.(22) Although, the clinical impact of this complication remains a matter of debate, growing evidence suggest that TAVR-induced new LBBB is associated with adverse outcomes. First, Urena and colleagues studied 3729 TAVR patients with or without new LBBB and identified an increased risk of late sudden cardiac death (SCD) among patients with a new LBBB.(11) In this study, patients with a new LBBB and a QRS>160ms carried a 5-fold increased risk of SCD at 1-year follow-up. This risk of SCD was partially corrected by the implantation of a pacemaker, suggesting that a considerable amount of deaths are related to late progression towards complete AVB. Two recent studies confirmed that new LBBB is associated with an increase in both all-cause and cardiovascular mortality.(7, 8) Similarly, in a recent meta-analysis including 7 studies exploring the clinical impact of TAVR-induced new LBBB, Regueiro and colleagues found an increased risk of death from cardiac (OR:1.5) and non cardiac (OR 1.3) causes in those patients.(12) Finally, in the PARTNER registry, de novo LBBB after TAVR was also associated with a higher rate of permanent pacemaker implantation.(10) However, in this study, the implantation of a prophylactic pacemaker in this population only attenuated the overall mortality, which remained significantly higher when compared to non-LBBB and non-pacemaker patients. The authors speculated that excess of mortality in new LBBB patients and TAVR patients implanted with a permanent pacemaker resulted from a combination of dyssynchrony induced systolic dysfunction, followed by clinical heart failure and arrhythmias. Despite the important consequences of TAVR-induced conduction disturbances, there are currently no guidelines for the management of AVB and new LBBB after TAVR. Moreover, when the clinical decision is made to implant a pacemaker, no consensus exists on the best pacing modality. Dual-chamber pacing will resynchronize the atrial and ventricular chambers, but given the significant expected need for ventricular pacing in these patients, RV pacing will in turn promote interventricular dyssynchrony which can result in heart failure and worse outcomes.

Biventricular pacing represents an option but often appears as a complex strategy in those older patients with comorbidities and still normal LVEF at the time of implant. Moreover, as illustrated in figure 5, biventricular pacing only fuses two abnormal wavefronts, whereas HBP restores the normal intrinsic activation leading to less dyssynchrony. Indeed in a recent study by Arnold et al., using noninvasive epicardial electrocardiographic imaging, it was shown that HBP was more effective at delivering ventricular resynchronization and produced greater acute hemodynamic benefit as compared to biventricular pacing. (23) In the recent context of the Partner III (5) and Evolut low risk trials (4), which included lower risk patients, the search for better pacing solutions in this population has therefore become crucial. In this context, direct left bundle branch pacing might be considered a promising pacing option as it has the potential to correct LBBB with higher success rates and lower pacing thresholds as compared to His bundle pacing. (24, 25)

His bundle pacing post TAVR

In the present study, we demonstrated that pacing the bundle of His in patients with heart block and TAVR-induced new LBBB can restore the normal physiological pattern of ventricular activation and normalize QRS duration accordingly. Pacing the bundle of His after TAVR is associated with a moderate but reasonable success rate. In the current study, both implanters had experience with HBP, but found that despite the anatomical landmark represented by the inferior edge of the Evolute™ R prosthesis, His bundle pacing in this specific clinical context remains particularly challenging from a technical point of view. The occasional occurrence of complete AVB while mapping and more difficult recording of the His electrogram added to the challenge. To overcome difficulties of mapping the His bundle after TAVR, a mapping catheter can be considered which helps to maximize ability for pacemapping and might serve as a backup pace in the event of intraprocedural heart block. Alternatively, given the observation of complete heart block during implant, a temporary pacing catheter might be prudent to consider prior to attempt active fixation on the His bundle. Acute pacing thresholds for new LBBB correction were relatively high. Both the difficulty to map the His bundle and the relative high pacing thresholds might be related to TAVR-induced tissue edema. On the other hand, in the recent HIS-SYNC trial, LBBB correction thresholds also remained high in a population with longstanding pre-existent LBBB, where tissue edema was unlikely to be present.(26) Our results are however in line with those from Sharma and colleagues who implanted 4 patients with conduction disturbances after TAVR, among a larger series of patients.(15) In contrast to our patients, however, they were all implanted with the EDWARDS Sapien valve. Still, they report that half of these patients benefited from a HBP.

5. Limitations

The tools for HBP are still in evolution. The Medtronic Select Secure lead has an exposed helix screw with no inner lumen and must be delivered through a fixed sheath (Medtronic C315-His), or a deflectable sheath (Medtronic SelectSite C304-L or C304-His). It is probable, that in the future better tools and techniques will result in better implant results. As discussed earlier, post TAVR patients might represent a particularly difficult subset of HBP candidates. Only one balloon-expendable valve type was used in this cohort. Therefore our findings have to be considered particular to CoreValve^{TM} design. Other valve types might cause a different form of injury to the conduction system with distinct temporal characteristics compared to the CoreValve^{TM}. Another limitation concerns the relatively limited documentation of the potential benefit of HBP in this particular population. Although encouraging and theoretically valid, our results focus mainly on electrical measurements and may lack invasive blood pressure measurement or invasive LV dp/dt measurements. Finally, the number of patients enrolled in the present study is relatively small. Given the relatively short follow up in this study, caution should be taken as progression of TAVR induced damage to the conduction system might occur at longer follow up. Progression of periaortic root or artificial valve fibrosis, calcification and inflammation might lead to loss of LBBB correction in some patients at a later time. Larger trials and longer follow up are mandatory to confirm our encouraging results.

6. Conclusion

Permanent His bundle pacing can safely correct TAVR-induced new LBBB in the majority of patients with acceptable thresholds. Further studies are needed to assess the potential benefits of LBB recruitment with His bundle pacing over conventional right ventricular pacing.

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Figures

Figure 1: **Correction of TAVR induced LBBB with selective His bundle pacing**. Twelve lead electrocardiogram (ECG) from a patient with transcatheter aortic valve replacement (TAVR) induced left bundle branch block (LBBB) corrected by selective His bundle pacing (HBP)**.**

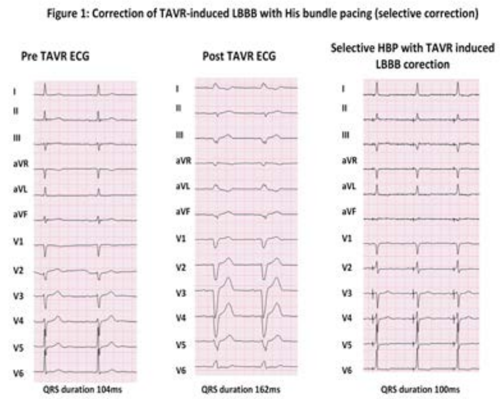

Figure 2: **Correction of TAVR induced LBBB with non-selective His bundle pacing**. Twelve lead electrocardiogram (ECG) from a patient with transcatheter aortic valve replacement (TAVR) induced left bundle branch block (LBBB) corrected by non-selective His bundle pacing (HBP)**.**

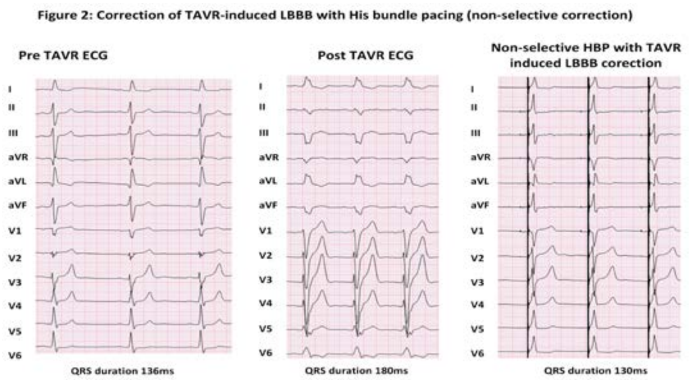

Figure 3: **Fluoroscopic views of His bundle pacing lead implant to correct TAVR-induced new conduction disorders.** The His bundle pacing lead (HBP) lead was implanted on the right side of the septum just below the inferior edge of Evolut^{TM} R prosthesis. Red points indicate final positioning of the His bundle pacing lead for all patients successfully implanted. TAVR: Transcatheter aortic valve replacement

Figure 3: Fluoroscopic views of His bundle pacing lead implant to correct TAVR-induced new conduction disorders

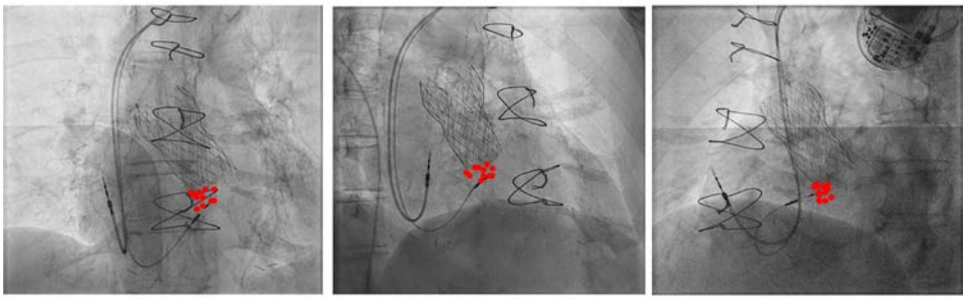

Figure 4: **QRS duration pre and post TAVR and after left bundle branch block correction with His bundle pacing.** QRS duration (QRSd) increased significantly after transcatheter aortic valve replacement (TAVR). With His bundle pacing (HBP), QRSd could be significantly reduced.

Figure 4: QRS duration pre and post TAVR and after left bundle branch block correction with His bundle pacing

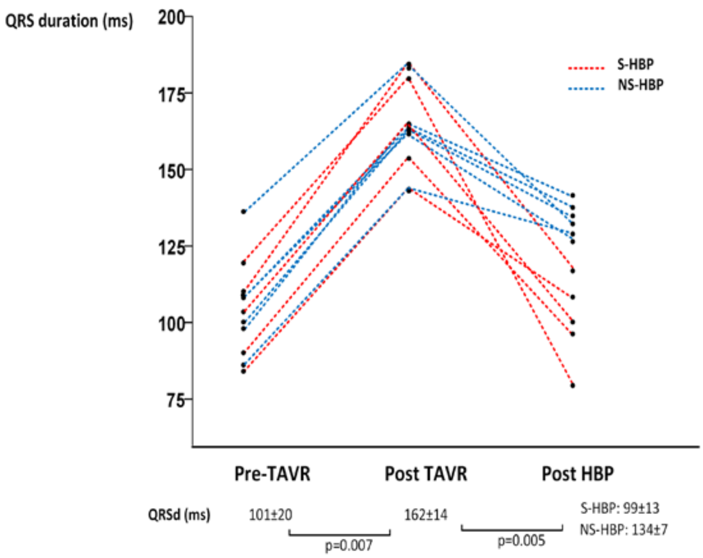

Figure 5: Noninvasive epicardial ventricular activation mapping and 12 lead ECGs in a patient with TAVR-induced LBBB and different pacing configurations . Maps are acquired during (A) intrinsic rhythm (ODO), (B) Right ventricular apical pacing, (C) Left ventricular pacing, (D) Biventricular pacing (B + C), (E) His bundle pacing. With intrinsic rhythm (panel A), due to left bundle branch block (LBBB), the color scale demonstrates a late (blue) activation occurring at the lateral wall of the left ventricle. A similar latency is found during right ventricular apical pacing (B) and reverted during pure left ventricular pacing (C). During biventricular pacing (D), ventricular activation results from the fusion of 2 non-physiological wave fronts, with no reduction in QRS duration (QRSd) in this patient. In contrast during selective His bundle pacing (E), a complete correction of the LBBB pattern of activation is observed which translated into a normalized QRS duration and reduction in both left ventricular activation time (LVAT) and ventricular electrical uncoupling (VEU) compared to the intrinsic LBBB rhythm. ECG: electrocardiogram, TAVR: Transcatheter aortic valve replacement

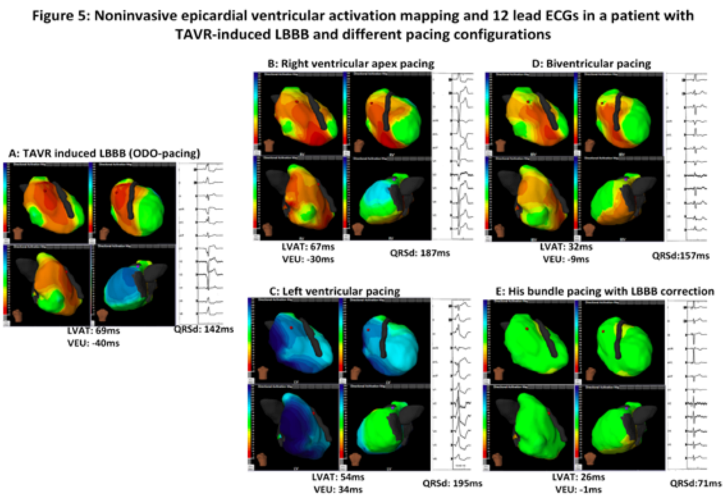

Table 1: Baseline patient and TAVR procedural characteristics	All patients (n=16)
Baseline patient characteristics	
Age, yrs	85±4
Female gender, n (%)	5 (31)

BMI, kg/m^2	27±4
Height, cm	167±8
Weight, kg	76±13
Arterial hypertension, n (%)	14 (88)
Ischemic heart disease, n (%)	5 (31)
Atrial fibrillation, n (%)	6 (38)
Aortic stenosis, n (%)	16 (100)
Aortic valve area (before TAVR), cm²	0.79±0.20
Left ventricular ejection fraction (EF), %	51±10
Patients with EF ≥55%, n (%)	7(44)
Patients with EF 36-54%, n (%)	8(50)
Patients with EF ≤ 35%, n (%)	1(6)
Pre TAVR electrocardiographic findings	
Pre-TAVR Rhythm	
Sinus, n (%)	14(87)
Atrial fibrillation, n (%)	2(13)
Pre-TAVR QRS duration	101±20
Pre-TAVR QRS morphology	

Narrow QRS, n (%)	13(81)
Right bundle branch block, n (%)	1(6)
Incomplete Left bundle branch block, n (%)	2(13)
TAVR procedural characteristics	
Valve Type	
Evolute™ R	16(100)
Diameter of Valve (mm)	30±4
Post TAVR electrocardiographic findings	
Post TAVR rhythm	
Sinus, n (%)	13(81)
Atrial fibrillation, n (%)	3(19)
Post TAVR QRS duration (ms)	162±14
Post TAVR QRS morphology, n (%)	
New left bundle branch block, n (%)	16(100)

BMI: Body mass index; TAVR: transcatheter aortic valve replacement; EF: ejection fraction

Table 2: Pacing and pacemaker implant characteristics

HBP characteristics (n=16)	
Successful HBP, n (%)	13(81)
Non-selective HBP, n (%)	8(62)
Selective HBP, n (%)	5(38)
Unipolar HBP threshold at 1.0ms (V)	1.2±1.5
Bipolar HBP threshold at 1.0ms (V)	1.4±2.1
Unipolar sensing (mV)	4.5±1.4
Bipolar sensing (mV)	3.4±1.9
Unipolar Impedance (Ohm)	323±86
Bipolar impedance (Ohm)	427±75
Successful LBBB correction, n (%)	11(69)
Unipolar LBBB correction threshold at 1.0ms (V)	1.9±1.1
Bipolar LBBB correction threshold at 1.0ms (V)	2.4±1.3
Paced QRS duration Selective HBP (ms)	99±13
Paced QRS duration Non-selective HBP (ms)	134±7

HB Pacemaker characteristics (n=11)	
RV back up lead, n (%)	4(36)
Type of pacemaker	
Single chamber, n (%)	1 (9)
Dual chamber, n (%)	4 (36)
Triple chamber, n (%)	6 (55)
His lead in RV port, n (%)	2 (33)
His lead in LV port, n (%)	4 (67)
Procedural characteristics (n=16)	
Procedural time, (min)	93±33
Fluoroscopic time, (min)	15±11
Complications (n=16)	
New 3th degree atrioventricular block	1(6)
Tamponade	0(0)

HBP: His bundle pacing; LBBB: Left bundle branch block; RV: Right ventricular; LV: Left ventricular