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Conduction abnormalities after transcatheter aortic valve implantation

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Abstract

In the last few years, transcatheter aortic valve implantation (TAVI) has become an alternative procedure in patients with severe aortic stenosis and high risk for surgical aortic replacement. Due to the anatomic correlation between aortic valve structure and conduction system of the heart, one of the most common complications after TAVI is conduction system disturbances which including bundle branch block, complete heart block and need for permanent pacemaker implantation. Although these disturbances are usually not lethal, they may have a great influence on patients' state and long term-survival. Several risk factors for conduction disturbances have been identified which including age, anatomy of the heart, periprocedural factors, type of implanted valve, preexisting abnormalities and comorbidities. As this technique becomes more familiar to physicians, patients should be carefully screened for risk factors for the development of conduction abnormalities after TAVI in order to provide effective prevention and proper treatment.

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1 Introduction

Degenerative calcific aortic stenosis, which is an active inflammatory process, is the most frequent valvular heart disease in the Western world. It is estimated that 1%–2% of patients aged over 65 years have moderate to severe aortic stenosis, whereas this rate increases up to 12% in patients aged over 85 years.[1] Aortic valvular stenosis is well recognized as being associated with abnormalities of cardiac conduction, which including prolonged PR, AH and HV intervals and higher degrees of atrioventricular (AV) block.[2–4] Aortic valve replacement (AVR) can result in the development of further conduction abnormalities and the incidence of intraventricular conduction defects after surgical replacement of the aortic valve has been reported in as many as 33% of patients, and has been associated with an increased incidence of adverse events.[5,6] Transcatheter aortic valve implantation (TAVI) is an expanding, catheter-based technology that allows the implantation of a prosthetic valve without requiring open-heart surgery for the treatment of severe aortic stenosis. This technique was developed more than one decade ago to minimize surgical risk in high-risk patients with severe symptomatic aortic stenosis, such as elderly or with contra-indication for open AVR. With the anatomical proximity of the AV node to the aortic annulus, conduction disorders caused by calcification or mechanical trauma might result in AV block with subsequent pacemaker requirement. In literature, this is described in 6% of cases after surgical aortic valve replacement, but varies after TAVI between 5.7% and 42.5%, while new left bundle branch block (LBBB) occurs in up to 50%–70%.[7–11] The Valve Academic Research Consortium (VARC) 2 criteria provide definitions of frequently encountered complications.[12] Among these complications, the development of post-procedural conduction disturbances may not be the strongest predictor of mortality but has a significant influence on long-term prognosis and patients' quality of life.[13,14]

Whilst initial TAVI experiences were limited to a small number of devices, the rapid adoption of TAVI has generated a major impetus to refine and improve available devices, resulting in a wide selection now being available. The two most frequently used devices are the balloon-expandable Edwards SAPIEN XT valve (Edwards Lifesciences, Irvine, CA, USA) and the self-expanding Medtronic CoreValve (Medtronic, Minneapolis, MN, USA).

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2 Aortic valve and conduction system anatomy

Since the 16th century, when Leonardo da Vinci conducted the first known cadaveric studies of the heart, the aortic root complex has been studied extensively. The aortic valve, which consists in the majority of cases of three cusps, is attached to the aortic wall. The valvular leaflets and their supporting sinuses, which together make up the root, are related to all four cardiac chambers. Within the right atrium, the AV node is located within the triangle of Koch. This important triangle is demarcated by the tendon of Todaro, the attachment of the septal leaflet of the tricuspid valve, and the orifice of the coronary sinus. The apex of this triangle is occupied by the atrioventricular component of the membranous septum. The AV node is located just inferior to the apex of the triangle adjacent to the membranous septum, and therefore the AV node is in fact in close proximity to the subaortic region and membranous septum of the left ventricular outflow tract. Thus, severe calcification, infectious diseases, and mechanical trauma to this region can induce conduction abnormalities like complete heart block. The AV node continues as the bundle of His, which is located in the membranous septum and branches into the left and right bundle. The antero-posterior relationship of the AV node with respect to the apex of the triangle of Koch varies between individuals as does the length of the non-penetrating (or most proximal) portion of the His bundle. The non-penetrating portion of the His bundle traverses the membranous septum to become the penetrating His bundle, which then physically divides into the respective bundle branches. Inter-individual variation in the penetrating bundle length and depth of septal penetration and variation in the location of the proximal portion of left bundle determine how susceptible these structures are to injury during TAVI. Kawashima and Sato[15] described three major variants that, depending on which is present, determine the susceptibility of a patient to developing complete block or LBBB. In an autopsy series of 115 elderly patients, 50% were found to have a relatively right-sided AV bundle, 30% a left-sided AV bundle, and in around 20%, the bundle coursed under the membranous septum just below the endocardium. In the latter two variants, the AV bundle is particularly exposed and susceptible to injury. LBBB susceptibility is determined by how soon the left bundle appears on the left side of the septum, and injury to both is further affected by the relative positioning of the membranous septum with respect to the aortic cusps.

3 Conduction disorders

Aortic valve stenosis has been associated with both prolonged AV conduction times and higher degrees of AV conduction disorders. The anatomical vicinity of the aortic valve and the AV node as well as the His bundle will lead to complete AV block in 5.7% and new LBBB in 18% at long term after open-heart surgery.[5,16] Such complications are caused by surgical trauma to the cardiac conduction tissue during the preparation of the calcified annulus. Similarly, one of the major complications with TAVI is the damage of the conduction system.[17] Therefore, it's not surprising when AV block also occurs after TAVI. Thus, new-onset LBBB, third-degree AV block, and the need for new permanent pacemaker implantation (PPI) constitute an important clinical problem during TAVI.

The susceptibility to AV block in the TAVI setting is in some degree device specific, as has been well-described in meta-analyses, with incidence ranging between 24.5% and 25.8% in the CoreValve device compared with 5.9% to 6.5% in the SAPIEN valve.[18] On the other hand, TAVI constitutes a complex and multi-step procedure including crossing of the aortic valve and exchange and manipulation of various guide wires and bulky catheter systems in the left ventricular outflow tract (LVOT), which may inflict temporary or permanent injury to the conduction system. Hence, procedure-related causes of conduction abnormalities during TAVI may not necessarily relate to the prosthesis itself but to many other actions inherently associated with TAVI.

In patients undergoing TAVI, conduction disturbances occur early during the procedure,[19,20] and data on recovery from an AV block are poor. More than half of the new conduction abnormalities seems to occur before the actual valve implantation,[20] and this observation is in accordance with the incidence of new conduction abnormalities reported after isolated aortic balloon valvuloplasty.[21,22] Besides of this, new conduction abnormalities may occur not only during but also at some time after the procedure.[20] Widening of QRS is observed almost in 50% of patients during the procedure; in the majority of them, the widening occurred after implantation of the device and in one third occurred before implantation but after percutaneous aortic balloon valvotomy or guidewire crossing of the native aortic valve.[23]

Previous studies have documented a significant increase in the frequency of LBBB after TAVI, which indicates direct injury of the intraventricular conduction system during valve implantation.[23,24] As a result, any additional damage to the conduction system in patients with AV conduction abnormalities before intervention may lead to complete AV block. In a meta-analysis, patients with right bundle branch block (RBBB), first-degree AV block, or left anterior hemiblock at baseline were at higher risk for PPI after the inter-

vention.[25] New-onset LBBB is the most frequently observed conduction abnormality, which is explained by the very superficial location of the left bundle branch in the uppermost part of the leftward ventricular septum. The incidence of new-onset LBBB varies considerably, from 25% to 85% after implantation of the self-expandable CoreValve (Medtronic Inc, Minneapolis, Minnesota) and from 8% to 30% after the implantation of a balloon-expandable valve.[26] Although new onset LBBB is frequent after TAVI, its clinical significance is unclear in the literature. Overall, mortality data in patients who develop new LBBB after TAVI are conflicted. The largest study published to date (n = 1151) showed no association between new LBBB and death, but led to an increase in pacemaker insertion and failure of left ventricular ejection fraction (LVEF) to improve at 1-year follow-up.[27] In contrast, a Dutch registry (n = 679) followed patients for a median of 450 days showed that new LBBB was an independent predictor of all-cause mortality (37.8 % *vs*. 24 %, P = 0.002). The authors postulate that LBBB-induced desynchrony and progression to higher degree heart block are two possible mechanisms behind the higher mortality rates.[28] Similarly, another study identified persistent new onset LBBB as an independent predictor of all-cause mortality.[29] Other studies demonstrated similar rates of mortality at 1-year follow-up but an increase in syncopal events and PPI in patients with persistent LBBB and may be related to the progression of LBBB toward complete heart block.[30,31]

4 Pacemaker implantation as an adverse event after TAVI

AV conduction disturbances and a subsequent requirement for PPI are more common after Medtronic CoreValve System than Edwards SAPIEN valve implantation,[24,25,32] with a requirement of permanent pacing ranging from 2% to 51% (with a median of 28% for the Medtronic CoreValve System and 6% for the Edwards SAPIEN valve).[25] The increased risk of AV block with Medtronic CoreValve System has been attributed to the valve design (self-expanding *vs*. balloon-expandable) and the potential of a deeper implantation into the LVOT. This may result in more injury to the AV node and left bundle branches, which may be delayed because of the self-expanding nature of the prosthesis and tissue edema.[33] The challenge with peri-procedural heart block is determining when to implant a permanent pacemaker. Guidelines on continuous monitoring or related to timing for pacemaker implantation do not exist and for obvious reasons AV block after TAVI exhibits dynamic properties. Most of the disturbances occur within the first week after the procedure. Therefore, some researchers recommend at least 7-day ECG monitoring.[34] ESC guidelines on cardiac pacing also recommend a 7-day period of clinical observation to assess the type and significance of disturbances. The observation period could be shortened in case of permanent or recurring complete AV block with slow escape rhythm. In such patients, the PPI can be performed earlier (class of recommendation I, evidence level C).[35] There is a lack of consensus and data regarding PPI in case of occurrence of TAVI-related 2nd degree AV block, bundle branch blocks or combination of AV block and bundle blocks. Although PPI is indicated for asymptomatic patients with acquired second- or third-degree type 2 AV block,[34–36] absolute and relative indications for TAVI patients have not been established. In patients with aortic stenosis and severe comorbidities undergoing TAVI, a somewhat more aggressive approach may have been adopted, although a proportion of AV conduction disturbances after the intervention have been shown to recover over time.[37–39] Currently, the median time to the clinical decision of implantation is five days. Due to the possibility of resolution of conduction abnormalities, some authors recommend a longer observation period and a more conservative approach to PPI.[36]

The TAVI-related conduction disturbances may resolve not only during the hospital stay but also in a longer period. Results of the investigations concerning patients with pacemaker implanted after TAVI are conflicting. For instance, Piazza, *et al*.[40] showed that at one year, most patients were paced for > 10% of time, but van Der Boon, *et al*.[39] showed that more than 50% of patients were pacemaker independent after a median of 11.5 months of follow-up. Similarly, Kostopoulou, *et al*.[38] and Renilla, *et al*.[41] also showed a significant decrease in pacing dependency after 1 and a median of 35 months, respectively. Compared to conduction abnormalities seen after surgical aortic valve replacement, the evolution of conduction disorders after TAVI tends to be more favorable.[42] The lowest ventricular pacing rate was observed in patients in whom PPI was performed due to bundle branch blocks.[36,43]

However, interpretation of pacing statistics from devices on the first check can be misleading because for complete heart block, devices are usually programmed in a pacing mode with relatively short AV delays. Statistics on pacing needs should be used only if the device has been programmed in a mode with a preference for intrinsic rhythm. Therefore, in many previous studies, even if partial recovery of the underlying rhythm was evident, it is possible that it was not observed on the ECG, and it can only be observed during pacemaker assessment. Furthermore, in patients with rhythm on pacemaker check, it is not possible to determine

the exact time of rhythm recovery because in all studies follow up and testing of underlying rhythm was performed at significant days, usually day 1, 7 and 1 month or even later and not in between. It is not known when rhythm recovers and if we have to wait how many days will be needed.

A meta-analysis of 49 studies which included a total of over 16,000 patients demonstrated that heart block requiring PPI was the most frequent adverse outcome among patients who underwent TAVI.[32] Although PPI constitutes a significant proportion of procedure-related complications among patients undergoing TAVI, it is widely considered a benign event as compared with other major adverse cardiac and cerebrovascular events such as death, stroke, and myocardial infarction. Nevertheless, its clinical significance is still controversial. An analysis by Buellesfeld, *et al*.[44] revealed that the 12-month all-cause mortality rate was similar among patients without PPI, patients with PPI before TAVI, and patients with PPI after TAVI. Pereira, *et al*.[45] also reported that new PPI did not affect 1-year survival rates. In accordance with these data, despite the higher rate of PPI among recipients of the CoreValve prosthesis, in the UK TAVI registry, 30-day, 1- and 2-year mortality rates were not different between patients treated with the CoreValve versus the Sapien prosthesis.[46] Moreover, a study by Urena, *et al*.[47] in patients without previous PPI provided further insight into the influence of PPI on clinical outcomes. After a mean follow-up of 22 months, the requirement for PPI at 30 days did not increase the rate of all-cause mortality, cardiovascular mortality, and all-cause mortality or re-hospitalization because of heart failure. Indeed, the rate of sudden or unknown death was lower in patients with new PPI relative to those without. Nevertheless, new PPI correlated with a lesser improvement in LVEF, and was predictive of a reduction in LVEF at 6- to 12-month follow-up. On the other hand, in the sub-analysis of the PARTNER trial, the presence of PPI was associated with worse outcomes and higher 1-year mortality when compared to non-PPI patients.[48]

In patients with PPI, the right ventricle is activated first and then crosses the interventricular septum via cell-to-cell conduction, bypassing physiological activation by the native His-Purkinje system. As a result of asynchronous conduction, abnormal septal wall motion and alterations in regional blood flow in the LV myocardium have been demonstrated.[49] Clinically, several trials have highlighted the detrimental effects of long-term RV pacing on LV function. MOST (Mode Selection Trial) identified a significant correlation between frequency of RV pacing with the development of heart failure, noting that the lowest risk patients had a ventricular pacing burden < 10% (DDDR mode).[50]

5 Risk factors for conduction disorders

The pathophysiology of new conduction abnormalities has not yet been elucidated. A number of studies indicate that both patient and procedure-related factors such as septal wall thickness, non-coronary cusp thickness, pre-existing RBBB, depth of valve implantation within the LVOT, post-implant prosthesis expansion, and the type of prosthesis play a role.[37,40,51–56]

Irrespective of prosthesis type, one of the most frequently identified procedural factors is the depth of prosthesis implantation, with deeper implantation being correlated with a higher risk of new conduction disturbances. A Spanish study (n = 65; CoreValve only) reported a frame depth in the LVOT of 11.1 mm as an independent predictor of PPI with 81% sensitivity and 84.6% specificity.[57] Similarly, another study revealed that if the proximal end of the valve frame was positioned < 6.7 mm from the lower edge of the noncoronary cusp, no prosthesis-related left bundle branch block would occur.[58] Among studies in which the CoreValve prosthesis was used, Baan, *et al*.[51] demonstrated that the incidence of new LBBB was associated with deeper prosthesis implantation (10.2 ± 2.3 *vs*. 7.7 ± 3.1 mm). Similarly, Mouillet, *et al*.[59] found that patients with delayed high-grade AV block had deeper prosthesis implantation (12 ± 4 *vs*. 9 ± 5 mm). Predictors of new PPI following CoreValve implantation further evaluated by Toutouzas, *et al*.[60] demonstrated that the depth of prosthesis implantation was significantly greater in patients who required new PPI. For patients in whom optimal prosthesis placement was achieved, defined as an implantation depth of < 8 mm, the rate of new PPI was 27% compared with 74% for patients without optimal placement. A multi-center comparative study aimed to evaluate the new Accutrak CoreValve delivery system found the mean depth of valve implantation as a strong predictor, for both new PPI and new LBBB after TAVI, but also pre-existing RBBB and pre-existing 1st degree AV-block confirmed to be strong predictors of the need for new PPI.[61]

With regard to the Sapien prosthesis, Urena, *et al*.[30] demonstrated that persistent, new-onset LBBB correlated with the depth of prosthesis implantation and each 1-mm increase in the ventricular depth of prosthesis implantation corresponded to a 1.37 increase in the odds ratio for developing persistent new LBBB.

Although deeper valve implantation seems to be associated with a higher risk of AV block, implantation depth, however, does not reflect patient propensity for conduction abnormalities. It is a procedural outcome and thus only a

predictor post-factum. Membranous septum length represents an anatomic surrogate of the distance between the aortic annulus and the bundle of His and may therefore be inversely related to the risk of conduction system abnormalities after TAVI. In a study by Hamdan, *et al*.[62] membranous septum length was the single most powerful independent pre-procedural predictor, not just of pacemaker implantation but of higher degree AV block and complete AV block, inversely related to these risks.

The impact of LVOT dimensions on conduction disturbances has been investigated in several studies. Toutouzas, *et al*.[60] found a low LVOT/annulus ratio (< 0.89) as a strong indicator of the need for PPI. Among patients who had the CoreValve prosthesis implanted at an optimal depth, the frequency of PPI was 8.0% and 53% for those with a high LVOT/annulus ratio and a low LVOT/annulus ratio, respectively. The authors suggested that a low LVOT/annulus ratio may cause greater tension and edema in the intraventricular septum which would exacerbate underlying conduction disturbances.

Studies have shown that the oversizing of the balloon used (high balloon/annulus ratio) is an independent predictor for a new AV block after TAVI but without an influence on pacemaker requirement in multivariate analysis.[20,56] Bleiziffer, *et al*.[56] also reported the link between the balloon size and the incidence of new conduction disturbances. Similarly to this, a large valve implanted into a small annulus was reported as a factor increasing the frequency of conduction disturbances. Finally, the prosthesis/LVOT diameter ratio was identified as a novel predictor for PPI even among patients undergoing TAVI with SAPIEN valve (for each 0.1 increment, OR = 1.29; 95% CI: 1.10–1.51; $P = 0.002$).[18]

It is easy to generalize conduction abnormalities to mechanical factors alone, but the involved patient population has multiple comorbidities that are probably relevant to this issue. Patients undergoing TAVI are a priori characterized by an exceptionally high risk profile because of the presence of severe cardiac pathological features in conjunction with other non cardiac comorbidities. As with any operation, procedural complications increase with a patient's age and comorbidities. In severe aortic stenosis, common cardiac risk factors including diabetes mellitus, hypertension and congestive heart failure have been associated with the development of LBBB and bradyarrhythmias, irrespective of whether or not these patients underwent surgical or transcatheter AVR. Indeed, in a study by Buellesfeld, *et al*.,[44] patients with previous PPI before TAVI had a higher risk profile, with notable differences in various baseline characteristics, including hypertension, coronary artery disease, myocardial infarction, prior percutaneous coronary intervention, renal failure, and atrial fibrillation compared with patients without a history of PPI.

In the analysis conducted by Piazza, *et al*., [40] male sex and history of myocardial infarction were risk factors for new-onset LBBB but not predictors of new PPI. However, the requirement for PPI was significantly higher in patients with higher logistic EuroSCORE.[63] Patients' age is one of the variables included in the logistic EuroSCORE formula. Age itself was also described as an independent predictor of conduction disturbances after TAVI. Patients older than 75 years have a significantly higher rate of PPI when compared to the younger group.[64] In a meta-analysis by Siontis, *et al*.[25] men had a higher risk for PPI. Male patients undergoing TAVI tend to have more comorbidities and higher procedural risk, furthermore they also receive larger bioprostheses, which may have an impact on AV conduction.

Several ECG abnormalities have been associated with PPI. In one study, the predictive factors for pacemaker requirement were determined, among others, by left axis deviation at baseline and LBBB.[54] Although isolated RBBB is generally considered to be a benign condition, extrapolating the results across multiple studies, baseline RBBB is a consistent predictor of PPI irrespective of the device used (CoreValve *vs*. SAPIEN valve).[34,18] As previously discussed, new LBBB manifests frequently after TAVI and when compounded with RBBB it will lead to complete heart block. The duration of the QRS interval at baseline has also been identified as a predictor of persistent LBBB and the need for PPI.[30,40] One could suspect that any increase in QRS duration may have an influence on development of conduction disturbances. Indeed, one of the studies described post-procedural QRS duration > 128 ms as associated with permanent pacemaker requirement.[59]

In studies using invasive ECG studies to evaluate TAVI effects on the conduction system, also significant prolongation of His-ventricle interval and the Wenckebach point was found.[65,66] A basic ECG study would predict complete heart block after TAVI because patients with preexisting abnormalities are at higher risk for this complication. Kostopoulou, *et al*.[38] showed that the basic predictor of a PPI after TAVI was the baseline HV interval. There were no patients with normal second electrophysiological study who underwent PPI over the long term. In contrast, in patients who developed complete heart block relatively late, HV significantly increased > 70 ms, indicating worsening in conduction. Infrahisian damage, either pre-existing or occurring post-procedurally, was non-reversible, which was in concordance with other electrophysiological studies.[66]

6 Conclusions

The development of TAVI has provided inoperable pa-

tients with severe aortic stenosis, a viable treatment option with meaningful survival benefit over medical therapy alone. However, the benefit of this procedure comes at the cost of a substantially increased risk of conduction disturbances that may necessitate the placement of a permanent pacemaker. TAVI results in worsening of conduction parameters, especially the occurrence of new LBBB, in most patients. This worsening is the result of direct damage on the AV node or His bundle and is related to the initial valvuloplasty or prosthesis deployment. Several risk factors have been associated with the occurrence of conduction disturbances after TAVI. Therefore, patients should be carefully screened for risk factors in order to provide effective prevention and proper treatment. Pacemaker implantation is the most common treatment option for severe abnormalities, but data regarding its use and influence on outcome remain ambiguous. By improving our ability to predict conduction disturbances and our understanding of the mechanism by which this occurs, we could improve overall outcomes after TAVI.

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