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VALVULAR HEART DISEASE (V NKOMO, SECTION EDITOR)

Clinical Implications of Conduction Abnormalities and Arrhythmias After Transcatheter Aortic Valve Implantation

Robert M. A. van der Boon · Patrick Houthuizen · Rutger-Jan Nuis · Nicolas M. van Mieghem · Frits Prinzen · Peter P. T. de Jaegere

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Abstract Transcatheter aortic valve implantation (TAVI) has become an established treatment option for patients with aortic stenosis at prohibitive risk to undergo surgical aortic valve replacement. Despite conveying obvious clinical benefits and a decreasing frequency of complications, the occurrence of new conduction abnormalities and arrhythmias remains an important issue. Generally considered a minor complication, they may have a profound impact on prognosis and quality of life after TAVI. Therefore the purpose of this review is to assess and discuss the available information on clinical implications of both new conduction abnormalities and arrhythmias after TAVI.

Keywords Transcatheter aortic valve implantation (TAVI) · Conduction abnormalities · Arrhythmias · Left bundle branch block · Atrioventricular block · Permanent pacemaker implantation · Atrial fibrillation

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R. M. A. van der Boon · R.-J. Nuis · N. M. van Mieghem · P. P. T. de Jaegere
Department of Interventional Cardiology, Thoraxcenter, Erasmus Medical Center, Rotterdam, The Netherlands

P. Houthuizen
Department of Cardiology, Catharina Hospital, Eindhoven, The Netherlands

P. Houthuizen · F. Prinzen
Cardiovascular Research Institute Maastricht, Maastricht, The Netherlands

P. P. T. de Jaegere (✉)
's-Gravendijkwal 230, 3015 CE Rotterdam, The Netherlands
e-mail: p.dejaegere@erasmusmc.nl

Introduction

Transcatheter aortic valve implantation (TAVI) has become an established treatment option for patients with aortic stenosis who cannot undergo surgical aortic valve replacement (SAVR) [1••]. In these patients, TAVI has shown to significantly decrease all-cause mortality, repeat hospitalization and cardiac symptoms when compared to the standard treatment, including medical and invasive therapy [2••, 3]. For patients at high surgical risk, TAVI has been shown to have a similar outcome compared to SAVR [4••, 5]. The prospect of treating younger and less sick patients exist in whom the effectiveness and safety of TAVI is currently studied in randomized clinical trials (SUrgical Replacement and Transcatheter Aortic Valve Implantation; SURTAVI and Placement of AoRTic traNscathetER valve-2; PARTNER-2). However, TAVI is associated with a number of vexing complications that need to be resolved. This paper in particular focuses on the frequently encountered problem of conduction abnormalities and arrhythmias after TAVI. Although generally considered benign and correctable, these complications may have profound clinical and economic effects [6•, 7•, 8•]. This is among others reflected by the inclusion of these complications in the updated Valve Academic Research Consortium Guidelines (VARC 2) published in 2012 [9••]. The scope of this review article is to assess the available information on the occurrence, predictors and clinical implications of newly acquired conduction and arrhythmic disorders after TAVI.

Left Bundle Branch Block

New left bundle branch block (LBBB) is reported in 29–65 % of patients after the implantation of the self expanding

Medtronic CoreValve ® system (MCV; Medtronic CV Luxembourg S.a.r.l., Luxembourg), and in 4–18 % of patients receiving the balloon-expandable Edwards SAPIEN ® valve (ESV; Edwards Lifesciences Corporation, Irvine, CA, USA) [10•, 11–13]. Considering the cellular architecture of the base of the aortic root and left ventricular outflow tract where these bioprostheses are being implanted, on one hand and the differences in the geometry, physical characteristics and mode of implantations of these valves, on the other, may explain the reported frequencies. Although unproven, the main cause of LBBB after TAVI is presumed to be mechanical injury inflicted upon the atrioventricular conduction tissue. Understanding the (physiological) anatomical relationship between both valve and the surrounding tissue allows the understanding of the pathophysiological mechanism of new arrhythmias, as has been reported previously by our group [10•].

The effect of LBBB on clinical outcome, however, remains subject of debate. Clinical studies have shown that LBBB is associated with increased morbidity and mortality in healthy individuals and patients with established heart failure [14]. The latter can be explained by the abnormal activation of the ventricles (i.e., intraventricular dyssynchrony) which may be associated with reduced cardiac function [15–17]. Cardiac function has been shown to be diminished in patients with new LBBB after TAVI [7•, 18, 19]. Yet, the effects on all-cause and cardiac mortality remain equivocal. Houthuizen et al. reported on the outcome of 697 patients undergoing TAVI with both MCS and ESV [6•]. Multivariate analysis revealed that new LBBB was associated with a ~55 % increased risk of mortality during follow-up. Despite a significantly higher frequency of LBBB after MCS implantation, no association between mortality and valve type was found in the multivariate analysis. In contrast, two observational studies from Italy (on MCS) and Canada (on ESV) found no effect of new LBBB on mortality during follow-up [7•, 8•]. The discrepancy between these studies may be explained by differences in the application of diagnostic criteria for LBBB and ECG assessment. The reported duration of the QRS complex in the Italian registry (lower interquartile range < 130 ms) suggests that some patients, diagnosed with a new LBBB, may in fact not have had LBBB after TAVI. The Italian registry also included patients with new permanent pacemaker > 48 hrs after TAVI and, are therefore, protected from death due to the eventual development of complete AV block or bradycardia during follow-up. Yet, it should be acknowledged that a pacemaker may protect a patient from brady-arrhythmic death, it is still associated with interventricular dyssynchrony. In addition, differences in baseline risk of the populations may have played a role. Patients in the Italian registry had a higher median EuroSCORE than in the other two studies. This means that prognostic factors other than LBBB may have played a more dominant role in the outcome of these patients.

There is little information on the persistence and eventual late development of new conduction abnormalities after TAVI. In the Canadian multi-center study encompassing 202 patients without baseline conduction abnormalities a new LBBB was found in 30.2 % (n=61) of the patients after the implantation of the ESV [7•]. At discharge, recovery was observed in 23 (37.7 %) of these 61 patients. After 6 to 12 months of follow-up LBBB had resolved in 12 (48.0 %) of the remaining 25 patients with LBBB at hospital discharge. Patients with persistent LBBB at discharge had a higher incidence of syncope (16.0 % vs. 0.7 %, p=0.001) and complete atrioventricular block requiring permanent pacemaker (PPM) implantation (20.0 % vs. 0.7 %, p<0.001). These results show the need for more elaborate electrocardiographic follow-up of patients with or without new LBBB after TAVI and the need of differentiation between persistent and transient conduction abnormalities. Moreover, it should be studied whether this effect is also seen after implantation with the MCS which is among others the subject of the multicenter ADVANCE II registry. This information will help to improve recommendations of pacemaker implantation after TAVI in clinical practice, which will be discussed below.

Atrioventricular Block and Permanent Pacemaker Implantation

Similar to LBBB, a higher frequency of high degree atrioventricular block (HDAVB; second (AV2B) or third degree (AV3B) atrioventricular block) after TAVI is reported after MCS valve implantation (14 – 44 %) than after ESV implantation (0 – 12 %) explaining the new PPM implantation in 18 – 49 % of the patients after MCS valve implantation and 0 – 12 % after ESV implantation [10•, 20–23]. Although generally considered a minor issue, PPM implantation not only implies an additional intervention that is not free from complications by itself, it may also have physiological effects on cardiac function and, therefore, patient well being. In particular, atrioventricular and interventricular dyssynchrony may alter ventricular hemodynamics, which has been reported to be an independent predictor of adverse long-term clinical outcome in addition to increase in costs [24–29, 30•, 31]. Yet, one study in which a new PPM was implanted in 98 out of the 305 patients (32.1 %) revealed no difference in clinical outcome at 30-days and 1-year. Interpretation of the available data is not easy, given differences in populations and thresholds for PPM implantation [32]. It might well be that the implantation strategy in this cohort was too liberal which could have led to a population consisting of patient with persistent AVB and patients that recovered from AVB, thus leading to inhibition of pacemaker function [33]. Also, detrimental effects of PPM to cardiac function may only appear during longer-term follow up and therefore may become a particular issue if TAVI technology would move to younger and lower-risk patient populations who have a longer life expectancy.

Careful assessment of patients with new conduction abnormalities and/or new PPM after TAVI may help to improve outcome and patient comfort by patient tailored reduction of ventricular pacing, thereby, sustaining or restoring normal atrioventricular and intraventricular conduction. Also, prolonged right ventricular pacing may induce heart failure as shown in the DAVID trial [34]. Right ventricular pacing induced dyssynchrony is known to increase morbidity and mortality, especially if the patients are paced for > 40 % of the time [35]. Noteworthy, a few studies report a reduction of pacemaker dependency after TAVI. One study including 36 out of 167 patients who received a new PPM implantation after TAVI (21.6 %) revealed that during a median follow-up of 11.5 months, 20 (55.6 %) of the patients were independent of their pacemaker. When specifically assessing the patients with HDAVB (n=30), 16 (53.5 %) were independent during the follow-up visit [36]. This was confirmed by Simms et al. who found that after a follow-up of 8 months only 33.3 % of the patients still had a HDAVB [37]. Pereira et al. reported that 3 of the 16 (18.8 %) patients who received a new PPM for HDAVB remained pacemaker dependent at follow-up [38]. It must be acknowledged that the studies summarized above concern single center observations in small number of patients with only one time point of PPM assessment after TAVI. These studies do not elucidate at what time after TAVI the patient becomes PPM independent and whether this phenomenon is transient or permanent. Secondly, the findings only pertain to the MCS. The time of PM dependence during follow-up may be explained by the nature and degree of the injury inflicted on the conduction tissue which may lead to either permanent disruption or only peri-procedural edema and inflammation as seen in post-mortem examinations [39].

It is clear that more detailed information in larger series of patients are needed before making sound proposals of criteria for new PPM implantation after TAVI. It should also be acknowledged that in clinical practice logistic problems and the risk of local infections due to the presence of a temporary pacemaker lead may render the application of a watchful waiting policy difficult. Yet, it might be safe to say that a restrictive PPM implantation policy and regular follow-up visits, with readjustments of the pacemaker settings, is recommended. With a growing body of evidence it might be possible to create more absolute indications for PPM implantation after TAVI, as proposed by Fraccaro et al. [40]. However, the final decision whether to implant or not a PPM in a patients with a new conduction abnormality should be customized to the individual patient.

Atrial Fibrillation

Atrial fibrillation (AF) is the most common arrhythmia in the general population, characterized by uncoordinated electrical activation of the atria [41]. Its prevalence increases with the age and reaches a frequency > 9.0 % in patients aged 80 years or older [42]. AF has been shown to coexist in more than 50 % of the patients suffering from aortic stenosis undergoing TAVI [43, 44]. Similar to AV and intraventricular conduction abnormalities, AF may affect cardiac performance as a result of the loss of atrioventricular synchrony and atrial kick leading to a reduction in cardiac output and increased ventricular filling pressure [45]. Conversely, aortic stenosis results in left ventricular hypertrophy and diastolic dysfunction, which itself may lead to the development AF, due to a change in left atrial pressures and dimensions. In addition to the effects on cardiac performance, AF is associated with an increased risk of cerebrovascular events (CVEs) and systemic embolisms (SE) as well as impaired long-term survival compared to the general population [46, 47]. The presence of pre-existent AF in patients undergoing SAVR has been associated with mortality, late adverse cardiac events and CVEs [48, 49]. The inflammatory response and/or increase in beta-adrenergic tone after thoracotomy and surgical repair of the heart, with concomitant myocardial injury, are responsible for the occurrence of new onset AF (NOAF) [50]. Whereas, the pathophysiological mechanism and effects of AF in the general population and in patients undergoing SAVR have been extensively studied, little is known on the impact of pre-existing AF and NOAF in patients undergoing TAVI, especially considering the risk of stroke in this population [51•, 52, 53].

In both PARTNER studies, AF was present in 41.6 % (TAVI 40.8 %, SAVR 42.7 %) and 40.6 % (TAVI 32.9 %, medical treatment 48.8 %) of the patients. NOAF within 30 days from the procedure was reported 8.6 % of the patients who underwent TAVI, which was significantly lower when compared to patients who underwent SAVR (16.0 %, p= 0.006) [2••, 4••]. The pathophysiologic mechanisms explaining this difference between TAVI and SAVR remain speculative. It may be due to the less invasive nature of TAVI and potentially a lesser inflammatory and adrenergic response to/after TAVI. This - in combination with the reduction of the afterload after TAVI - may explain the observation by Motloch in 84 patients that two-thirds of the patients with pre-procedural AF had a stable sinus rhythm during the first 72-hours after TAVI [54]. Notably, there were no cases with AF after transfemoral TAVI in this study which is somewhat remarkable and deviant from most observations in the literature. Two retrospective studies have reported on the effects of pre-existing AF on outcomes after TAVI, reporting a prevalence of 34.0 % and 50.0 % respectively [55, 56]. Whereas, Salines et al. found no effect on prognosis after TAVI, Stortecky et al. showed that AF was associated with a two-fold increase in all-cause and cardiac mortality (and no effect of AF on the risk of stroke and life-threatening bleeding complications). Both studies reported an incidence of 6-7 % NOAF after TAVI. Despite careful and complete assessment

of patient data, the above mentioned studies did not include extensive rhythm monitoring and could therefore miss short periods of NOAF after TAVI. Showing substantial evidence for the clinical impact of AF after TAVI, one should be careful in extrapolating data from these studies.

Recently, Amat-Santos et al. reported on 138 consecutive patients with no prior history of atrial fibrillation who underwent TAVI (ESV only) after which patients were under continuous electrocardiogram monitoring until hospital discharge [57•]. In this cohort NOAF was encountered in 31 % of all cases, of which 36 % of the occurred during the procedure and 27 % between the procedure and day 2. A third of NOAF episodes lasted less than 1 h, emphasizing that they are likely to be ignored if not diagnosed using systematic ECG monitoring. Together with left atrial enlargement (OR 1.21, 95 % C.I.: 1.09 – 3.04, $p<0.0001$), the transapical approach (OR 4.08, 95 % C.I.: 1.35 – 12.41, $p=0.019$) was an independent predictor of the occurrence of NOAF. The latter might support the hypothesis that myocardial injury is the underlying factor. Clinically, NOAF was associated with a higher frequency of CVEs and SE after TAVI, but not with an increased risk of mortality. The results of this study will need to be confirmed in larger, prospective cohorts involving both valve systems. Dedicated research in to the mechanisms underlying NOAF might help reducing the frequency of this complication. However, a certain amount will always occur. For these patients it will be necessary to develop uniform guidelines on post-TAVI anticoagulative therapy focused on minimizing the risk of in-hospital bleeding events and CVEs. A recent statement article by Rodes-Cabau et al. may be of guidance to evolve the current concepts [58•].

Future Perspectives

Better understanding of the predictive factors, pathophysiologic mechanisms of the etiology and possible detrimental effects of new conduction abnormalities after TAVI help to formulate changes in valve design, patient selection, procedural planning and execution. Ensuring minimal contact between the valve frame and surrounding tissue may decrease the frequency of conduction abnormalities. This can be achieved by reduction of the height of the frame that extends into the left ventricular outflow tract and, possibly, by minimizing radial force of the frame on surrounding tissue. As mentioned above, little is known about the exact mechanisms of the development of new conduction abnormalities. For instance, it is conceivable that the moment of mechanical contact (and trauma) during implantation play a more dominant role in the onset of these abnormalities than the (continuous) radial force after full expansion of the valve. It remains to be seen whether a fully retrievable valve system, thereby, allowing a correct position with little contact of the frame with the subannular tissue, will be associated with less conduction abnormalities. Also, changes in design to address paravalvular leak may have unwanted effects on the conduction tissue. Increased data from observational studies involving new valve technologies, such as the Direct Flow Medical, Inc (Santa Rosa, CA, USA), Lotus Valve (Sadra Medical Inc., Los Gatos, CA, USA), JenaValve (JenaValve Technology Inc., Delaware, USA)) and Portico System (St. Jude Medical Inc., St. Paul, Minnesota, USA) are becoming available and are showing promising results [59–62]. Moreover, currently available valve technologies are continuously improving [63, 64]. Yet, their effect on the frequency of conduction abnormalities and PPM remain to be established. The incorporation of pre-procedural multimodality imaging for proper balloon and valve sizing algorithms [13, 65–67] may help to improve patient-planning and the execution of TAVI. Some advocate performing TAVI without balloon predilatation [68]. This may be feasible in patients with a low calcium load. Yet, the risk of atherosclerotic embolization and stroke need to be clarified [69]. Another solution might be to improve the accuracy and precision of implantation, especially with the MCS given the mode of implantation and anchoring in the aortic root. This can be achieved using novel software, which offers the possibility of tracking the annulus during the procedure, allowing the physician to make tiny adjustments while releasing the valve [70]. Also, extra stability incorporated in novel delivery systems such as the Accutrak System, which is designed for optimal positioning of the MCS. There is some evidence from non-randomized observations that such a system is associated with less PPM implantations [71, 72]. The question is to what extent operator experience has played a (confounding) role.

Conclusion

New conduction abnormalities and subsequent PPM implantation frequently occur after TAVI. Although the body of evidence regarding these complications is growing, their etiology and pathophysiologic and clinical implications remain equivocal. Carefully designed prospective studies might further elucidate the relationship between both and help to further aid in procedural refinements.

Compliance with Ethics Guidelines

Conflict of Interest Robert M.A. van der Boon, Patrick Houthuizen, Rutger-Jan Nuis, Nicolas M. van Mieghem, Frits Prinzen, and Peter P.T. de Jaegere declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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