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REVIEW ARTICLE

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Anatomical Considerations and Emerging Strategies for Reducing New Onset Conduction Disturbances in Percutaneous Structural Heart Disease Interventions

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ABSTRACT

Transcatheter procedures offer an alternative to cardiac surgery in select patients with structural heart disease (SHD). Unfortunately, inadvertent disruption of electrical pathways and subsequent development of new onset conduction disturbances can occur in up to 5–70% of percutaneous interventions, result in pacemaker implantation, and confer a worse prognosis. The physical proximity between the conduction system (atrioventricular node, bundle of His, and bundle branches) and the site of percutaneous repair is increasingly recognized as a key factor influencing new onset conduction disturbance development in procedures located near the conduction system. This review covers the incidence, clinical significance, and mechanisms of new onset conduction disturbances and discusses current and emerging strategies to address this complication in these populations.

Abbreviations: SHD: structural heart disease; AVN: atrioventricular node; AVB: atrioventricular block; LBBB: left bundle branch block; PPM: permanent pacemaker

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KEYWORDS New onset conduction disturbances; structural heart disease; percutaneous interventions

Introduction

In the last two decades, innovations in device technology, patient selection, imaging guidance, and procedural technique have propelled transcatheter-based therapies to the forefront of treating patients with a wide spectrum of structural heart diseases (SHD). The location of the heart's conduction system (atrioventricular node (AVN), bundle of His, and bundle branches) with respect to the inferior aspect of the interatrial septum, membranous interventricular septum, and coronary sinus have important implications for the risk of new onset conduction disturbances following various percutaneous structural heart interventions.[1,2] In the current paper, we review the incidence and clinical significance of new onset conduction disturbances in patients undergoing percutaneous structural heart interventions with an emphasis on transcatheter aortic valve replacement (TAVR). We then explore electroanatomical mechanisms of new onset conduction disturbances including device interactions with the conduction system and discuss the unmet need for novel approaches to reduce the risk for new onset conduction disturbances following structural heart interventions.

Discussion

Atrial and ventricular septal defects

In patients with appropriate anatomy and indications for closure, percutaneous device-based closure of atrial septal defects (ASDs) and ventricular septal defects (VSDs) may be preferred over surgery due to similar efficacy, reduced invasiveness and associated complications, and improved patient satisfaction.[3–5] Early clinical experience with transcatheter closure of atrial and ventricular septal defects provided the field of SHD with an introduction to the importance of cardiac electrophysiologic anatomy (Figures 1 and 2). Persistent high-grade AVB requiring permanent pacemaker

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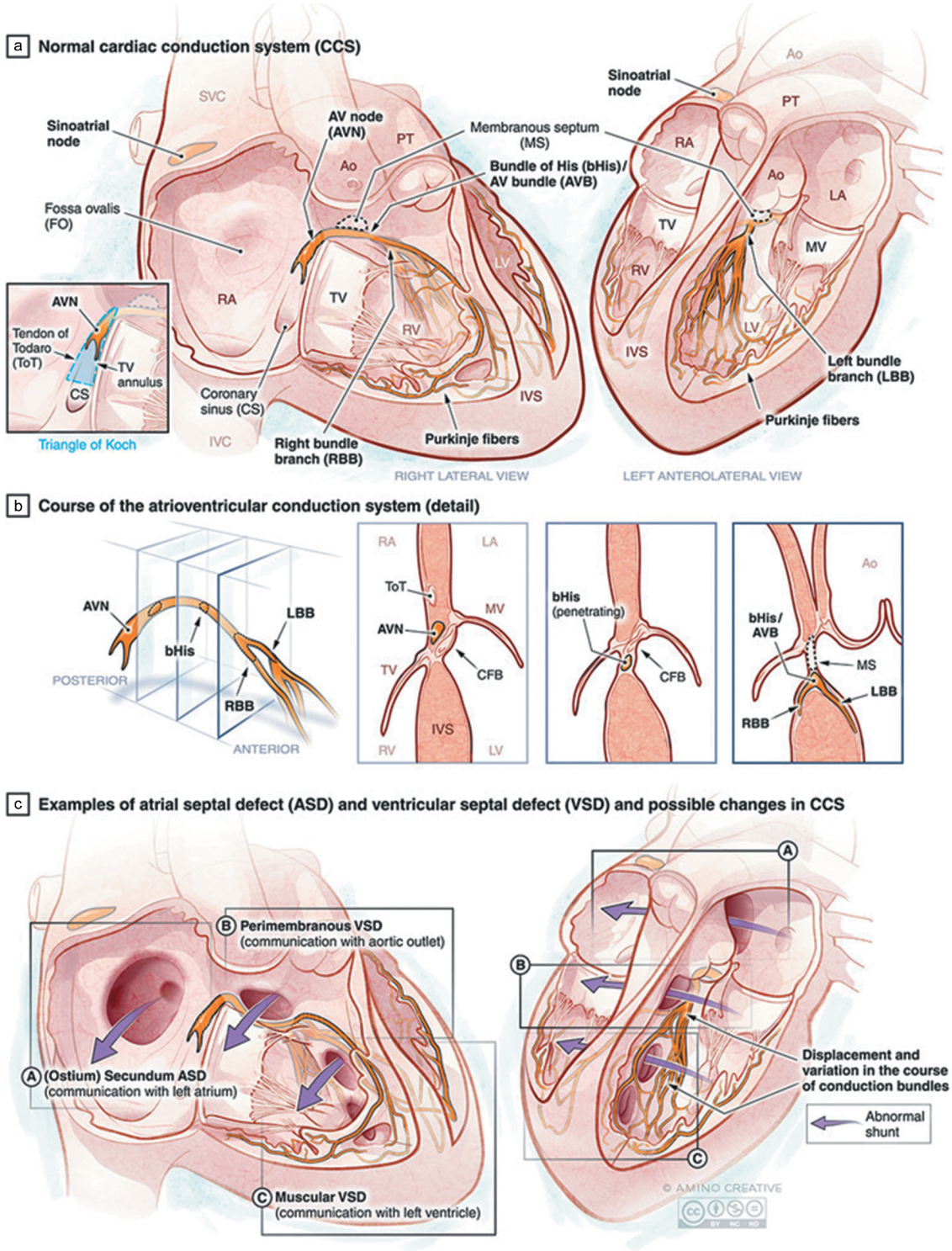

Figure 1. Normal cardiac conduction system (CCS) anatomy and in patients with atrial and ventricular septal defects. (a) The normal CCS is comprised of the atrioventricular node (AVN) which arises within the triangle of Koch a region located at the base of the right atrium defined by the following anatomical landmarks: the coronary sinus (CS), Tendon of Todaro (ToT), and septal leaflet of the tricuspid valve (TV). The AVN gives rise to the bundle of His (bHis) continuing into the AV bundle, and right (RBB) and left bundle branches (LBB) and subsequently the Purkinje fibers. The bHis/AV bundle is located just below the membranous septum at the crest of the interventricular septum. (b) The central fibrous body (CFB) serves as the demarcation between the AVN and bHis. The course of the AVN travels from postero-inferiorly to antero-superiorly and divides into the LBB and RBB at the crest of the interventricular septum at the site of the inferior attachment of the membranous septum. (c) The presence of an ASD or VSD may displace the usual course of normal CCS anatomy.

Abbreviations: AV, atrioventricular; SVC, superior vena cava; IVC, inferior vena cava; PT, pulmonary trunk; Ao, aorta; TV, tricuspid valve; MV, mitral valve; IVS, interventricular septum; RA, right atrium; RV, right ventricle; LA, left atrium; LV, left ventricle; CFB, central fibrous body.

(PPM) implantation appears to be uncommon (~1–5%) with percutaneous ASD[5–9] and VSD[10–13] closure. These observations are limited by a paucity of long-term outcome data in large numbers of patients and the true incidence may be confounded by the fact that many patients with post-closure AVB are frequently converted to surgical closure. Although

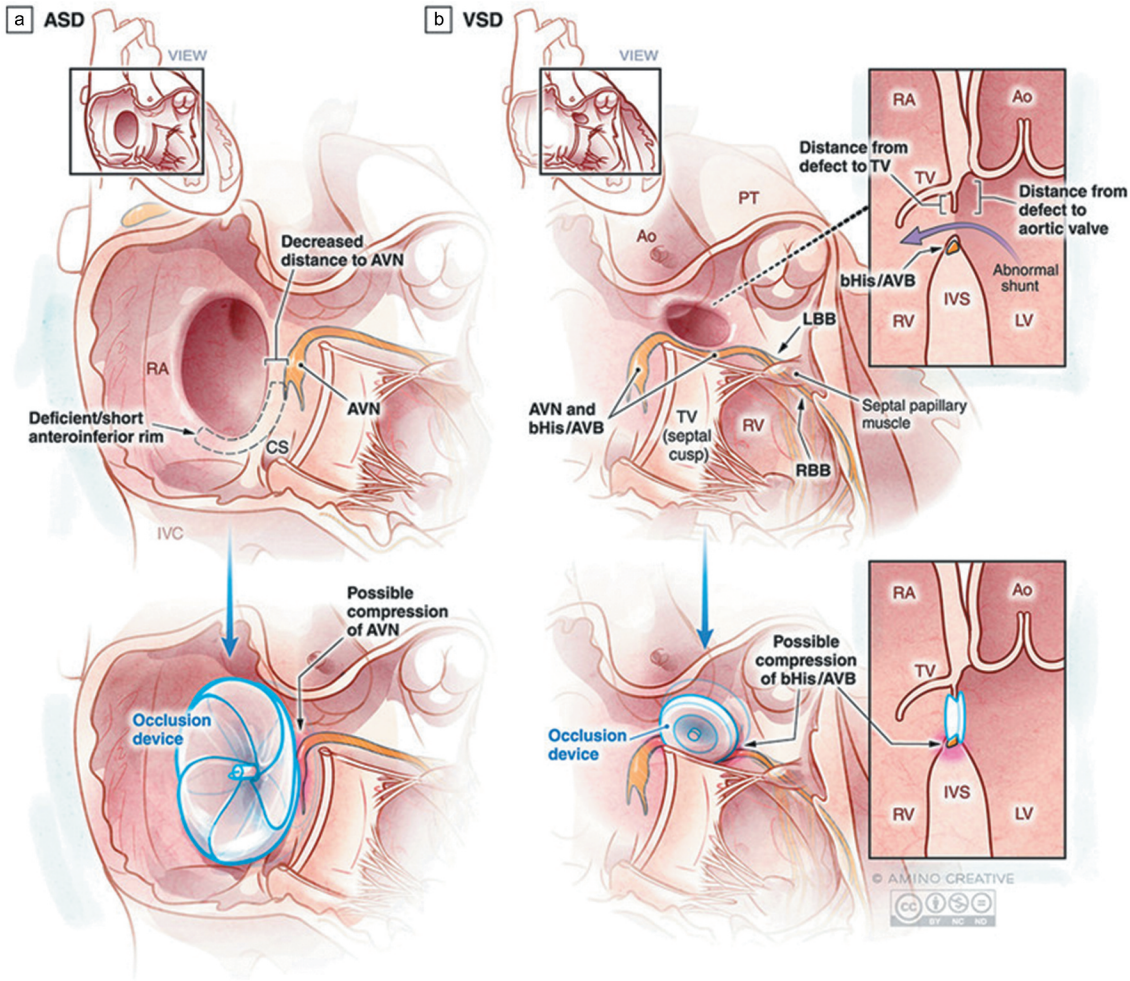

Figure 2. Anatomical considerations in ASD and VSD for device sizing and risk of new onset conduction disturbances. (a) Deficiency of the inferior or posterior rim of the ASD refers to a shortened length of septal tissue between the ASD and posterior free wall of the atria. Deficiency of the antero-inferior rim reduces the proximity of the defect to the AVN and thus increases the risk of compression by ASD closure devices. (b) In patients with perimembranous VSDs, the proximity of the VSD to the crest of the interventricular septum (IVS) and thus bHis/AV bundle increases the risk of device compression of the AV bundle and subsequent development of new onset conduction disturbances (NOCDs).

Abbreviations: ASD, atrial septal defect; VSD, ventricular septal defect; NOCD, new onset conduction disturbance; AVN, atrioventricular node; PT, pulmonary trunk; Ao, aorta; TV, tricuspid valve; MV, mitral valve; IVS, interventricular septum; RA, right atrium; RV, right ventricle; LA, left atrium; LV, left ventricle; bHis, bundle of His

high-grade AVB can safely be treated with PPM implantation in most patients, the impact on patient quality of life and healthcare expenditures due to device cost and long-term complications such as infection are not trivial.[14,15]

A critical aspect of percutaneous septal defect closure is the detailed anatomical characterization of the septal defect and its surrounding tissue (Figure 1c). Adjunctive pre-procedural imaging helps to determine the feasibility of percutaneous closure and to guide appropriate device sizing and positioning, that may then reduce the risk of new onset conduction disturbances.[7] In patients with an ASD, deficiency of the inferior rim of the septal defect may be an important determinant of successful defect closure due to the risk of device embolization.[9,16,17] In addition to device oversizing, however, this may also be an important predictor of AVB following closure.[5,7,9,18] In patients with a deficient inferior rim, the distance between AVN and ASD occluder devices becomes increasingly small and therefore the risk of mechanical compression, post-procedural edema, and thus AVB theoretically becomes greater (Figure 2a). Similarly, the distance from the VSD to the aortic valve and septal leaflet of the tricuspid valve as well as device over-sizing may be important determinants of AVB in patients undergoing percutaneous closure (Figure 2b).[19] It is important to distinguish the multiple types of VSDs including post-myocardial infarction, perimembranous, and muscular VSD as these defects may carry differential risk of new onset conduction disturbances following device-based closure given differences in their proximity to the conduction system. Indeed, despite high procedural success rates, transcatheter device closure of isolated perimembranous VSDs is associated with an approximately 10% increased risk of complete AVB.[20,21]

These observations highlight the implications of device sizing and selection on the risk of new onset conduction disturbances in patients undergoing percutaneous septal defect closure as a function of the anatomic characteristics of the cardiac conduction system. Variations in the position of the

AVN have been described in individuals with and without septal defects.[2] Existing imaging modalities are not currently able to characterize these individual variations and underscore the unmet need for peri-procedural tools to reduce the risk of new onset conduction disturbances following ASD and VSD closure.

Incidence, impact, and mechanism of new onset conduction disturbances

Aortic stenosis

In patients with severe aortic stenosis (AS) who are at high or intermediate surgical risk, transcatheter aortic valve replacement (TAVR) is currently recommended over surgical aortic valve replacement (SAVR) according to consensus guidelines.[22,23] TAVR has also been approved in the United States and much of Europe for patients at low-risk and is expected to become the favored therapy for many of these patients as well.[24–26] Improved pre-procedural planning, device innovations, operator experience, and evolution of implantation technique have reduced the incidence of serious peri-procedural complications including death, bleeding, and paravalvular leak following TAVR.[27–31] Unfortunately, the occurrence of new onset conduction disturbances including high-grade AVB requiring PPM implantation and new-onset LBBB remains the most common significant complications following TAVR.[32,33]

An expert panel statement and meta-analysis have recently summarized the available data on the management, incidence, and prognosis of new onset conduction disturbances following TAVR which provides an excellent overview of the available data and current consensus.[32,34] The reported incidence of a new onset conduction disturbance after TAVR varies widely ranging from 5% to 65% in studies using various types of transcatheter heart valves (THVs).[32,35] The risk of new onset conduction disturbances requiring a PPM is generally thought to be higher following TAVR with a self-expanding valve compared to a balloon-expandable THV.[36,37] The wide range of reported NOCD events may also, in part, reflect the heterogeneity of definitions used for a new onset conduction disturbance, the duration (in-hospital vs. ambulatory) and timing of their ascertainment (procedural vs. delayed vs. any), modality used for the detection (surface electrocardiographic monitoring vs. implantable loop recorders) new onset conduction disturbances, and lack of standardized criteria for PPM implantation.[32,34] Whereas a new onset conduction disturbance requiring PPM implantation has generally been observed to be associated with an adverse prognosis following TAVR, the impact of a new onset conduction disturbance in the form of LBBB on clinical outcomes has been controversial. However, a recent meta-analysis of 12 TAVR studies found that new onset LBBB occurred in 22.7% of patients and PPM implantation was reported in 6% to 32% of patients, and that both types of new onset conduction disturbances were associated with an increased risk of all-cause death and heart failure hospitalization at 1-year follow-up.[32] PPM implantation following TAVR is not only associated with increased risk of death and heart failure, but is associated with a reduction in quality of life and increased cost.[38,39] Thus, an emerging body of clinical research indicates the persistence and negative prognostic significance of new onset conduction disturbances following TAVR.

Table 1. Modifiable vs non-modifiable risk factors associated with conduction disturbance and/or pacemaker implantation following TAVR.

Modifiable	Non-modifiable
• Device type (self-expanding vs balloon-expandable)	• Baseline RBBB • Age
• Radial force	• Preexisting cardiovascular risk factors
• Implantation depth, per 1 mm	• Biological sex
• Prosthesis: LVOT diameter ratio, per 0.1 increment	• Anatomical variability of the conduction system
	• LVED diameter, per 1 cm
	• Noncoronary cusp calcium

An increasing awareness of the mechanisms underlying the interaction between the conduction system and THVs has permitted identification of modifiable risk factors (Table 1) and thus the opportunity for reducing the risk of post-TAVR new onset conduction disturbances. Among patients treated with a self-expanding THV who experience new onset conduction disturbances in the peri-procedural period, approximately 50% occur before valve implantation, possibly due to balloon valvuloplasty causing impingement of valvular calcium on the conduction system and/or manipulation of the conduction by the stiff wire and catheter delivery system. However, another 25% of new onset conduction disturbances occur intra-procedurally following valve implantation, presumably due to an interaction between the THV and the heart's conduction system[40] (Figure 3). Several procedural characteristics have been associated with an increased risk of new-onset LBBB and/or the need for PPM implantation following TAVR including depth of valve implantation, valve overexpansion relative to the native annulus, use of self-expanding THVs, and larger THVs in general.[34] Collectively, these findings suggest that direct physical disruption of the conduction system prior to and during device implantation leads to development of conduction disturbances.[41,42]

Given these factors above, an understanding of the electrophysiologic anatomy of the cardiac conduction system is vital to understanding the risk for new onset conduction disturbances in patients treated with TAVR. An increasing appreciation for the importance of the proximity of the aortic annulus to the bundle of His on the risk of post-TAVR new onset conduction disturbances has recently emerged.[43,44] A comprehensive pathologic study of the conduction system anatomy from 115 human hearts emphasized the close proximity of the atrioventricular (AV) bundle to the aortic root complex and described important inter-individual variations in the location of the bundle branches with respect of the membranous and ventricular septum that may contribute to differences in the risk of NOCDs between individuals. The investigators noted that the AV bundle traverses the caudal border of the membranous septum and superior aspect of the ventricular septum in 46.7% of

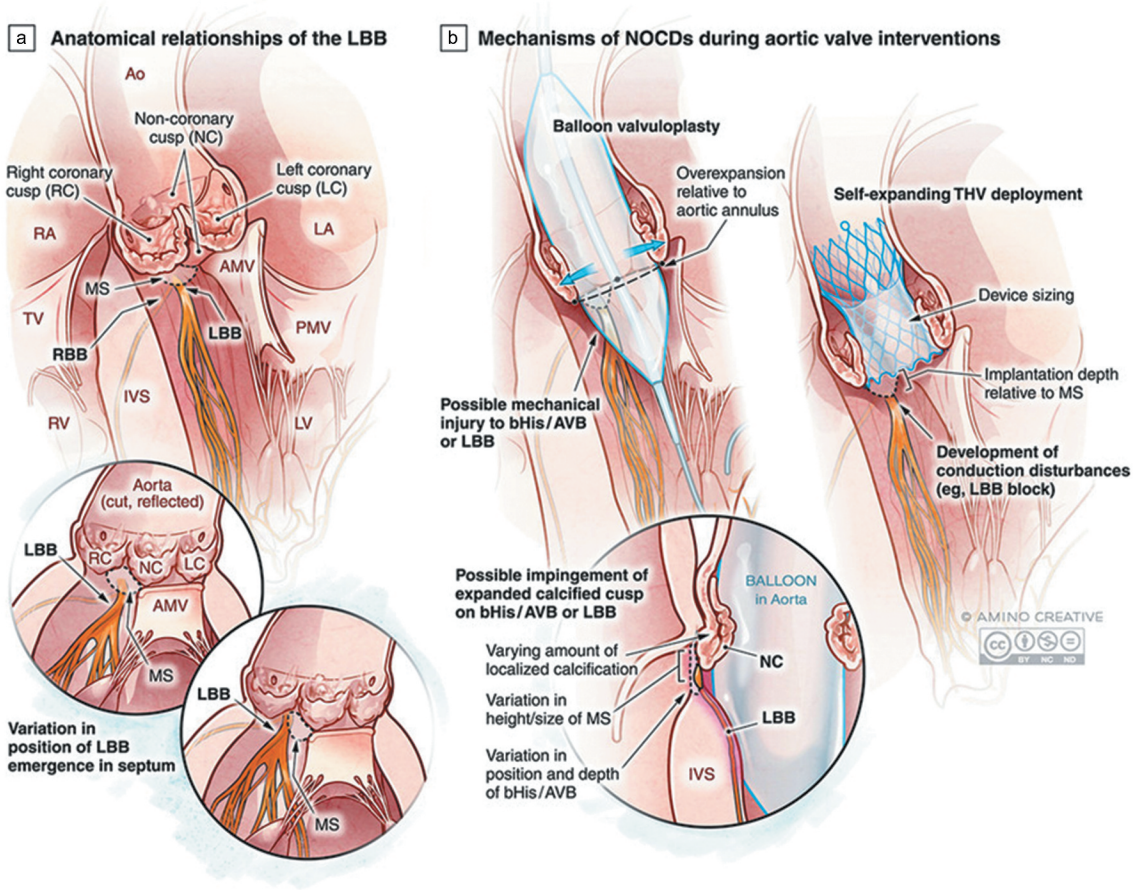

Figure 3. Anatomical considerations in aortic stenosis for TAVR and the risk of new onset conduction disturbances. (a) The AV bundle emerges on the left side sandwiched between the crest of the interventricular septum (IVS) and the membranous septum. The anatomical guide to the membranous septum is between the right and non-coronary cusps. From there the origin of the LBB varies, depending on the length of the common (non-branching) AV bundle. (b) During balloon aortic valvuloplasty (BAV) or transcatheter heart valve (THV) deployment, the LBB may be impinged due to compression from the wire, balloon, or delivery system used for BAV or TAVR. In addition, calcific nodules may compress the left bundle branch block (LBBB) leading to new onset AVB in patients with underlying right bundle branch block (RBBB) or even complete AVB in patients with variations in individual variations in the anatomy of the cardiac conduction system that cannot be discerned with existing imaging modalities used to guide TAVR. In addition, transcatheter heart valve positioning and sizing are key determinants of the risk of NOCDs, particularly with self-expanding THVs.

Abbreviations: TAVR, transcatheter aortic valve replacement; NOCD, new onset conduction disturbance; MS, membranous septum; bHis, bundle of His; LBB, left bundle branch; RBB, right bundle branch; RC, right coronary cusp; LC, left coronary cusp; NC, non-coronary cusp; PT, pulmonary trunk; Ao, aorta; TV, tricuspid valve; AMV, anterior mitral valve; PMV, posterior mitral valve; IVS, interventricular septum; RA, right atrium; RV, right ventricle; LA, left atrium; LV, left ventricle; THV, transcatheter heart valve.

patients where it is insulated from mechanical injury by a thin layer of myocardium and fibrous tissue. In 32.4% of patients, the AV bundle was observed to course within the muscular aspect of the ventricular septum. In the remaining 21% of patients, the AV bundle was found to be immediately beneath the endocardium and coursing onto the membranous septum, which prompted the investigators to call this AV bundle variant the "naked AV bundle" due to the lack of protective insulating tissue[45] (Figure 3a and b, insets).

After branching off the AV bundle and entering the deep ventricular septum, the left bundle branch (LBB) enters the superficial portion of the left ventricular endocardium where it lacks protective tissue insulation and is therefore more prone to physical insults. However, the position at which the LBB emerges from the septum varies between individuals and is associated with the depth and position of the AV bundle, thereby contributing to a differential risk of new onset conduction disturbances between individuals following SHD interventions.[1] These pathologic findings were underscored by a subsequent cardiac CT study of patients undergoing TAVR with a self-expanding THV.[44] The investigators observed wide variation in membranous septum length among patients with aortic stenosis referred for TAVR and noted that this variation correlated with the risk of subsequent conduction disturbances post-TAVR. In patients with shorter membranous septum length (i.e., short distance from the aortic annulus to the His bundle), the risk of AV block and PPM was greater compared to those with a longer membranous septum length.[44] The patient-specific importance of membranous septum length and risk of new onset conduction disturbances were further emphasized in a recent study from these same investigators – compared to patients with tricuspid valves, patients with bicuspid aortic valves were observed to have significantly shorter membranous septum length which was predictive of a developing a new LBBB or requiring a PPM post-TAVR.[46]

The insights afforded by these key pathologic observations and imaging-based insights were leveraged in a novel study characterizing the depth of valve implantation in relation to the membranous septum as defined by cardiac computed tomography (CT) and was utilized as a landmark for the anatomic location of the AV nodal conduction system in patients undergoing TAVR.[43] Jilaihawi et al. observed that deployment of a self-expanding THV at a depth less than that of the membranous septum length based on a patient-specific CT-derived risk score was associated with a reduced risk of PPM and LBBB compared to retrospective cohort comparator group (Figure 3, right panel).[43] However, as the authors acknowledge, the membranous septum is a surrogate marker for the location of the AV bundle and given the aforementioned individual variability in the anatomic position of the AV bundle and LBB, the membranous septum may not be a reliable surrogate in a significant proportion of patients. In addition, pre-procedural CT does not afford the interventionalist with the opportunity to guide intra-procedural valve positioning on the basis of variations in conduction system anatomy.

Tricuspid regurgitation

Several hundred thousand patients in the United States are diagnosed with tricuspid regurgitation (TR) each year. However, few patients undergo isolated tricuspid valve intervention, in part, because of the high operative mortality rate (~10%).[47,48] Therefore, percutaneous repair or replacement offers an attractive alternative to surgery. Indeed, several new percutaneous devices (coaptation, annuloplasty, and newer bioprosthetic valves) have been developed in recent years that have demonstrated promise in addressing TR.[49]

The recent introduction of percutaneous TV implantation limits our understanding of the incidence and impact of a new onset conduction disturbance with this emerging approach. However, conduction disturbances are a known complication after surgical repair, with studies describing an incidence of a new onset conduction disturbance as high as 40% in patients with combined mitral and tricuspid valve surgery.[50] Studies further report that PPM is required in 25–30% of patients following surgical TV repair, emphasizing the particularly high susceptibility to electrical disruption at this site.[48]

Similar to the aortic valve, the tricuspid valve is in close proximity to the conduction system, particularly the AV node, bundle of His, and right bundle branch.[51] The bundle of His traverses the right trigone of the central fibrous body to reach the ventricular septum which is near the commissure of the septal and anterior tricuspid leaflets.[52] Percutaneous interventions may increase the risk of injury to the conduction system; however, the incidence and prognostic significance of new onset conduction disturbances following percutaneous repair of the tricuspid valve remain unknown.[51] Considering that this approach is gaining recognition as a favorable alternative to surgery,[49] future studies will help to delineate the incidence and impact of arrhythmias on short-term and long-term outcomes following this intervention.

Current and novel strategies to address conduction disturbances

Considering the high rates of new onset conduction disturbances following these interventions, there has been increased interest in identifying strategies to address this complication. Much emphasis has been placed on approaches to better predict and detect which patients develop new LBBB and high-grade AV block, as well as improved selection of patients who will most benefit from PPM. Some tools include more intensive intraoperative and postoperative monitoring algorithms, general demographic-based prediction factors (age, sex, other conditions),[11] more specific risk score calculators for PPM, preoperative evaluation of anatomical risk factors like septal wall thickness or existing electrical disorders,[53] and technique-based prediction methods such as depth or site of implantation.[54]

While these strategies are valuable, the prevalence of new onset conduction disturbances will continue to rise – particularly as percutaneous SHD interventions expand to an increasingly broader population of patients – unless novel strategies to *prevent* conduction disturbances are identified. Based on the studies outlined above, this pathogenic mechanism is best described for TAVI[55] but is likely relevant to a broader range of procedures given the well-known anatomical proximity of the conduction system to the atrial and ventricular septa, tricuspid valve, and aortic valve.[1,56] Improved device design to minimize physical impingement on the conduction system is one such strategy to prevent new onset conduction disturbances. Unfortunately, although newer-generation transcatheter heart valve systems have been associated with a decrease in the risk of conduction disturbances, some newer devices have been actually been associated with an increased risk of new LBBB and PPM implantation.[57,58] Since each patient's electroanatomy is highly variable and complex,[59] it may be difficult to appropriately design a device that is suitable for each patient. Although some have proposed that super-personalized device design based on an individual patient's anatomy could help reduce conduction block,[1] this is likely to be expensive, logistically cumbersome, and non-pragmatic. The most tailored device could still be inadvertently placed on top of a conduction pathway due to lack of real-time visualization of the conduction system. Thus, it remains unclear if iterative developments in valve design alone will address the root causes of new onset conduction disturbances in these patients.

Emerging imaging approaches such as hybrid technology allowing fusion of TEE and/or CT with fluoroscopy improve 3D visualization; however, a key feature absent from these innovative strategies is simultaneous real-time imaging of the conduction pathways.[60,61] That is, although anatomy may be depicted with greater detail, the operator remains blind to the exact location of the conduction pathways, which can vary greatly between patients. Therefore, the introduction of 3D imaging approaches that display both electrical pathways (e.g. AV node, bundle of His, and bundle branches) and 3D soft tissue anatomy, in conjunction with novel valve designs, will be necessary to avoid physical disruption to the conduction system. Increased focus on the development of intra-procedural

imaging tools may help to advance the field of image guidance for structural heart disease interventions and hopefully improve outcomes for patients.

Conclusion

Percutaneous approaches to SHD intervention are rising as a favorable alternative to traditional surgical methods for a range of indications as diverse as valve intervention and congenital heart disease repair. However, the utility of this approach is limited by the potential for conduction system disorders induced by direct electroanatomical damage arising from the intervention itself. New devices may be designed to avoid impinging on the conduction system, but current imaging tools used during percutaneous SHD interventions are incapable of providing the operator with the necessary combination of anatomical and electrical information necessary to guide device deployment in a way that maximally attenuates new onset conduction disturbances. Introducing new imaging modalities that can generate electro-anatomical real-time data could equip operators with useful information that is unavailable with TEE and fluoroscopy alone. This comprehensive intraoperative imaging approach may help to improve percutaneous technique and decrease incidence of conduction disturbances, ultimately facilitating the spread of promising non-surgical methods for SHD interventions.

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