Novel Strategy for Predicting Conduction Abnormalities During Transcatheter Closure of Perimembranous Ventricular Septal Defect in Adults

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Background: In this study we evaluated the feasibility and efficacy of predicting conduction system abnormalities under 3-dimensional (3D) electroanatomic mapping guidance during transcatheter closure of perimembranous ventricular septal defects (pmVSDs) in adults.

Methods and Results: The distribution of the His-Purkinje system (HPS) close to the margins of pmVSDs in the left ventricle was identified using 3D electroanatomic mapping and near-field HPS was further confirmed by different pacing protocols. Of the 20 patients in the study, 17 (85%) were successfully treated by transcatheter intervention. The minimum distance between the margins of the pmVSD and near-field HPS, as measured by 3D electroanatomic mapping, ranged from 1.3 to 3.9 mm (mean \[± SD\] 2.5±0.7 mm). Five patients with a minimum distance <2 mm had a higher risk (3/5; 60%) for adverse arrhythmic events, whereas patients with a distance >2 mm were at a much lower risk (1/15; 6.7%) of procedure-related conduction block (P=0.032). No other adverse events were recorded during the follow-up period (median 30 months).

Conclusions: A minimum distance between the pmVSD and near-field HPS <2 mm was associated with a relatively high risk of closure-related conduction block. 3D electroanatomic mapping may be helpful in guiding decision making for transcatheter closure and reduce the incidence of adverse arrhythmic events.

Key Words: Adults; His-Purkinje system; Perimembranous ventricular septal defect; Three-dimensional electro-anatomic mapping; Transcatheter closure
near-field HPS, and clarify its proximity to the margins of the pmVSD, it may be possible to guide procedural decision making and reduce the risk of arrhythmic events. In this study, we prospectively applied this technique to transcatheter closure in adults with pmVSDs and further explored its feasibility and efficacy.

Methods

Study Subjects

Between January 2016 and August 2018, 20 adults with pmVSD were eligible for transcatheter closure in Guangdong Cardiovascular Institute. The study included 8 male and 12 female patients ranging in age from 18 to 48 years. The study was approved by the Ethics Committee of Guangdong Provincial People's Hospital and was performed in accordance with the Declaration of Helsinki. Patients provided written informed consent to take part in the study. All patients underwent clinical examination, chest radiography, electrocardiography (ECG), and transthoracic echocardiography (TTE) before the intervention.

The inclusion criteria were as follows: (1) age ≥ 18 years; (2) pmVSD diagnosed by TTE with a diameter between 2 and 14 mm; (3) a significant left-to-right shunt across the defect; (4) a distance of ≥ 2 mm from the VSD to the aortic valve; and (5) mean pulmonary artery pressure < 70 mmHg, as evaluated by catheterization. Exclusion criteria were: (1) severe aortic or tricuspid regurgitation; (2) severe pulmonary hypertension (≥ 70 mmHg); (3) a right-to-left shunt across the defect; (4) New York Heart Association (NYHA) Class III and IV; and (5) the presence of other types of congenital heart disease and/or previous surgery.

Procedures

The catheterization procedure was performed in patients under local anesthesia. Heparin (100 IU/kg) was administered intravenously during the procedure. Access was created through the right femoral vein and right femoral artery. Right heart catheterizations were performed to assess the degree of shunting and to evaluate pulmonary vascular resistance. Angiography in the left ventricle (LV) at a 60°/20° left anterior oblique projection/cranial view was performed to detect the location, shape, and size of the pmVSD. The diameter of the pmVSD was measured during end diastole, and an occluder was selected based on this measurement. A mapping catheter was positioned in a pmVSD through a retrograde approach. The MC was located at the margins of the pmVSD, as confirmed by transthoracic echocardiography. LVG before releasing the occluder.
Bipolar pacing from the mapping catheter was performed. The pacing protocol consisted of different pacing current (20, 15, 10, and 5 mA) at a different pulse widths (2.0, 1.5, 1.0, and 0.5 ms). Pacing with a cycle length of 400 ms was performed at the sites recording HPS activation adjacent to the pmVSD. QRS morphology during pacing was interpreted as follows: (1) narrow QRS complexes indicated both myocardial and near-field HPS capture; (2) wide QRS complexes indicated only myocardial capture; and (3) paced QRS morphology identical to that during sinus rhythm and long-stimulus QRS morphology indicated only pure His capture. The left-sided near-field HPS was further defined as the presence of His capture with minimal pacing output (<10 mA/2 ms).

**3D Mapping and Pacing Protocol**

Point-by-point 3D electroanatomic mapping (CARTO; Biosense Webster) was performed to identify a relatively large area of HPS activation adjacent to the pmVSD. During the high-density mapping, the pmVSD, its adjacent HPS activation, and left anterior and posterior fascicular potential sites in the LV were identified and tagged on the 3D map (Figure 2). The sites of near-field HPS potential in the LV were initially defined as the sites with the longest interval from the Purkinje potential to ventricular activation.

For patients who presented with arrhythmic events after the procedure, corticosteroid therapy was administered to reduce occluder-related mechanical compression and myocardial edema. Dexamethasone was given at a dose of 10 mg/day for 3–7 days. All patients received oral aspirin (100 mg) daily for 6 months after the procedure.

VSD Occluders

Two types of occluder devices were used in this study: a double-disk symmetrical concentric pmVSD occluder (Lifetech Scientific, Shenzhen, China) and a double-disk thin-waist pmVSD occluder (Starway Medical Technology, Beijing, China). These 2 devices are self-expanding double-disk devices composed of 0.127 mm nitinol wire mesh with fabric inside. The waist diameters of the occluders ranged from 5 to 12 mm. The diameters of the right and left disks were uniformly 4 mm larger than the waist of the symmetrical concentric pmVSD occluder. The diameters of the right and left disks were 4 and 8 mm larger, respectively, than the waist of the thin-waist pmVSD occluder. The
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exact test. Statistical analyses were performed using SPSS version 24.0 (IBM Corp., Armonk, NY, USA). All tests were 2-sided, and P<0.05 was considered significant.

Results

Clinical and Procedural Patient Data
Of the 20 patients in whom transcatheter closure of the pmVSD was attempted, 17 (85%) were successfully treated by transcatheter intervention. The mean age of the patients was 28±10 years. During the procedure, the mean defect size measured by angiography was 4.9±1.6 mm (range 2.9–8.5 mm), and the mean size of the implanted device was 6.5±1.9 mm (range 5–12 mm). The thin-waist occluder device was selected for 9 patients, and the symmetric occluder device was selected for 8 patients. A septal aneurysm accompanied the defect in 13 patients (65%), as confirmed by TTE (Table 1).

Definition of Adverse Arrhythmic Events and New-Onset Arrhythmic Events
Adverse arrhythmic events were defined as second- and/or third-degree atrioventricular block, complete right bundle branch block (CRBBB), CLBBB, and accelerated junctional rhythm (AJR) during the procedure. Any of the above conduction abnormalities persisting for more than 48 h after the procedure was also regarded as an adverse arrhythmic event. New-onset arrhythmic events were defined as newly developed conduction blocks after the procedure where there had been no conduction block or a different conduction block before the procedure.

Follow-up Protocol
Continuous ECG monitoring was performed during the entire hospitalization period. A standard 12-lead ECG examination was performed within 6 h after the procedure, and subsequently on Days 1, 3, and 7 after the procedure. Clinical examination, TTE, ECG, and/or Holter ECG were performed at 1, 3, 6, and 12 months after the procedure and yearly thereafter. The findings at each visit were recorded in an electronic database by well-trained personnel. All patients were regularly followed-up at the outpatient clinic.

Table 1. Clinical and Procedural Characteristics of Patients

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<th>Device type</th>
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waist length of the symmetrical concentric occluder and thin-waist occluder were 3 and 5 mm, respectively. The selection of the occluder was based primarily on the location and characteristics of the defect. The device size chosen was usually 1–4 mm larger than the maximum defect size as assessed by either echocardiography or angiography, depending on which was judged most reliable.

Definition of Adverse Arrhythmic Events and New-Onset Arrhythmic Events
Adverse arrhythmic events were defined as second- and/or third-degree atrioventricular block, complete right bundle branch block (CRBBB), CLBBB, and accelerated junctional rhythm (AJR) during the procedure. Any of the above conduction abnormalities persisting for more than 48 h after the procedure was also regarded as an adverse arrhythmic event. New-onset arrhythmic events were defined as newly developed conduction blocks after the procedure where there had been no conduction block or a different conduction block before the procedure.

Follow-up Protocol
Continuous ECG monitoring was performed during the entire hospitalization period. A standard 12-lead ECG examination was performed within 6 h after the procedure, and subsequently on Days 1, 3, and 7 after the procedure. Clinical examination, TTE, ECG, and/or Holter ECG were performed at 1, 3, 6, and 12 months after the procedure and yearly thereafter. The findings at each visit were recorded in an electronic database by well-trained personnel. All patients were regularly followed-up at the outpatient clinic.

Statistical Analysis
Continuous variables are expressed as the mean±SD and were compared by Student’s t-test or the Mann-Whitney U-test (non-parametric). Categorical variables are reported as counts or percentages and were compared by the Fisher’s exact test. Statistical analyses were performed using SPSS version 24.0 (IBM Corp., Armonk, NY, USA). All tests were 2-sided, and P<0.05 was considered significant.

3D Mapping and Pacing Characteristics
On average, 718±320 points were taken for 3D mapping of the LV. Figure 2 shows the 3D electroanatomic mapping of the HPS distribution and the relative location of the pmVSD. As shown in the map, no Purkinje potential was recorded in the pmVSD, with a relatively large area of HPS activation along the defect margins. Pacing with lower outputs (10 mA at 1 ms in 8 patients and 5 mA at 1 ms in 12 patients) in the sites recording HPS potential adjacent to the pmVSD resulted in a narrower QRS morphology by capturing the HB and some myocardium, indicating these sites are near-field HPS that are close to the anatomic HB (Figure 3). The HB-ventricular (HV) and QRS intervals of the sites before pacing were 44±5 ms (range 35–54 ms) and 87±9 ms (range 72–109 ms), respectively. The duration of narrower paced QRS complexes was 90±9 ms (range 76–112 ms). A mean distance of 2.5±0.7 mm (range 1.3–3.9 mm) between the pmVSD and
Adverse Arrhythmic Events

Adverse arrhythmic events were noted in 4 patients (2 with CLBBB, 1 with CRBBB, and 1 with AJR and CLBBB). In 3 cases the adverse arrhythmic events occurred during the procedure, whereas in 1 case the event occurred 4 days after the procedure. A 31-year-old female without conduction abnormality before the procedure developed CLBBB immediately when the occluder was ready to be released (Case 9; Figure 4A). Similarly, a 26-year-old male with left anterior hemiblock (LAH) before the procedure progressed to AJR and CLBBB when maneuvering the long sheath to release the occluder (Case 18; Figure 4B). The minimum distance between the pmVSD and near-field HPS in these 2 patients was 1.4 and 1.3 mm, respectively. Sinus rhythm was automatically restored in these 2 patients after removal of the device and delivery system. The first patient (Case 9) refused surgical repair for personal reasons and remained without any symptoms. A conventional surgical repair was conducted in the second patient (Case 18) via the median sternotomy approach under cardiopulmonary bypass. No new-onset arrhythmic events were shown during this patient’s follow-up visits. CRBBB was observed in a 37-year-old female when establishing the arteriovenous circuit during the procedure (Case 20; Figure 4C), with 3D electroanatomic mapping showing that the minimum distance between the pmVSD and near-field HPS was 2.8 mm. After the delivery sheath was withdrawn, sinus rhythm quickly recovered. Therefore, the procedure was canceled, and subsequent surgical repair was performed in this patient. During the next 12 months of follow-up, neither CRBBB nor other conduction blocks were observed.

Another CLBBB occurred 4 days after placement of a 6-mm pmVSD occluder in a 30-year-old female (Case 12; Figure 4D). This patient had a normal ECG before and during the procedure. A minimum distance of 1.5 mm from the defect to the near-field HPS was measured by 3D electroanatomic mapping. After intravenous administration of dexamethasone (10 mg/day) for 7 days, sinus rhythm was restored in this patient and she was discharged.

Risk Factors for Adverse Arrhythmic Events

Univariate analysis was conducted between the groups with and without adverse arrhythmic events (Table 2). Variables, including age, sex, pmVSD diameter, threshold of His capture, and presence of septal aneurysm, were compared between the 2 groups. The results revealed that there were no significant differences in age, sex, defect size, threshold of His capture, and the presence of septal aneurysm between the 2 groups (all P>0.05).

The minimum distance between the pmVSD and near-field HPS measured by 3D electroanatomic mapping was also compared between the 2 groups using univariate analysis. These results indicated that a distance <2 mm was correlated with procedure-related adverse arrhythmic events (P=0.032).
New-Onset Arrhythmic Events

Four patients had conduction abnormalities before the procedure (3 with LAH and 1 with LAH plus incomplete right bundle branch block [IRBBBl]). One patient with LAH developed AJR and CLBBB during the procedure, and the remaining 3 patients did not develop adverse arrhythmic events progressively during the follow-up period (Table 3).

New-onset arrhythmic events occurred in 7 patients, with 10 events after the procedure. The time between device placement and the development of new-onset conduction block was usually ≤3 days. Among these cases, LAH was the most common type of arrhythmic event (5/17; 29.4%), followed by right bundle branch block (RBBB; 2/17; 11.7%), AJR (2/17; 11.7%), and left bundle branch block...
the univariate analysis of potential predisposing factors for new-onset arrhythmic events are summarized in Table 4. Of note, a shorter distance between the pmVSD and near-field HPS (2.5±0.7 vs. 2.7±0.7 mm) seems to be associated with a higher risk of new-onset arrhythmic events, but this difference was not statistically significant (P=0.568).

Other Follow-up Results
Except for the arrhythmic events mentioned above, there were no deaths, incidents of infective endocarditis, device embolizations or malpositions, thrombus formations, or other morbidities during the follow-up period (median 30 months; range 12–48 months).

Table 4. Risk Factors for New-Onset Arrhythmic Events After the Procedure

<table>
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<th>New-onset arrhythmic events</th>
<th>Yes (n=7)</th>
<th>No (n=10)</th>
<th>P-value*</th>
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<td>Female sex</td>
<td>5 (71.4)</td>
<td>5 (50.0)</td>
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<tr>
<td>Age (years)</td>
<td>23±6</td>
<td>30±12</td>
<td>0.128</td>
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<tr>
<td>Diameter of the pmVSD (mm)</td>
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<td>Septal aneurysm</td>
<td>4 (57.1)</td>
<td>7 (70.0)</td>
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<td>Thin-waist occluder</td>
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<td>Occluder size (mm)</td>
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<tr>
<td>Distance between the pmVSD and near-field HPS (mm)</td>
<td>2.5±0.7</td>
<td>2.7±0.7</td>
<td>0.568</td>
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</table>

Values are presented as the mean±SD or as n (%). *P-values are based on the Student’s t-test, the Mann-Whitney U-test, or Fisher’s exact test, as appropriate. P<0.05 was considered significant. HPS, His-Purkinje system; pmVSD, perimembranous ventricular septal defect.
Main Findings
In the present study we showed that mapping of the distribution of the HPS facilitates visualization of its 3D location in relation to the location of pmVSD. By combining 3D electroanatomic mapping and pacing techniques, the site with denoted His potentials can be further confirmed as near-field HPS. By measuring the distance between the pmVSD and near-field HPS, we reached the conclusion that a minimum distance <2 mm was associated with a higher risk of adverse arrhythmic events related to the procedure.

Using 3D Electroanatomic Mapping and Pacing Techniques to Identify the Near-Field HPS
To the best of our knowledge, this is the first report on the use of 3D electroanatomic mapping to guide transcatheter closure of pmVSD in adults. This novel strategy may help improve our understanding of the anatomy of the pmVSD and its adjacent conduction system, as well as guide the decision making process regarding transcatheter closure. It is known that the HB passes through the central fibrous body before it reaches the lower edge of the membranous septum, and then continues into the penetrating portion of the HB (PHB) that bifurcates into the left and right bundle branches. All pmVSDs share the feature that the HB and PHB pass posterior and inferior to them, and the distance between the PHB and the margins of the pmVSD is approximately 2–4 mm. In a previous study we demonstrated that the site where an HB potential is recorded and the HB can be captured with minimal output represents near-field His activation, indicating close proximity to the HB. According to the present study, HPS activation based on 3D mapping can be found in a relatively large area adjacent to the pmVSD. We prospectively applied this technique in left-sided HPS, and further corroborated that pacing at the sites recording HPS activation adjacent to the pmVSD could produce a narrower QRS complex by capturing the HB with a low pacing output (<10 mA/2 ms).

Discussion
Potential Mechanisms of New-Onset Arrhythmic Events
New-onset bundle branch block, including LAH and RBBB, was quite common in the present study, probably due to the delicate and fragile features of bundle branch that increase the risk of injury. Most of the new-onset arrhythmic events occurred within 6 h after the procedure, which also confirms that mechanical stimuli may be important causes of arrhythmia. A previous study indicated that asymmetric occluders and large device sizes increased the risk of new-onset arrhythmic events. An enlarged left disc of the thin-waist occluder and large device sizes logically increase the risk of compression onto the conduction system. However, no difference was found in occluder type and device size between the 2 groups in the present study. Although the mean distance between the pmVSD and near-field HPS was less in patients with than without new-onset arrhythmic events (2.5 ± 0.7 vs. 2.7 ± 0.7 mm), this difference was not significant. Therefore, larger sample sizes and longer follow-up periods are needed to verify the relationship between new-onset arrhythmic events and their related risk factors.

Possible Mechanisms of New-Onset Arrhythmic Events
Conduction block has been commonly reported in transcatheter closure of pmVSDs due to the proximity of the conduction system to the defect. Some previous studies reported that bundle branch block and CAVB occurred in 3.5–8.6% of cases. In the present study, no CAVB was recorded during the entire follow-up period, whereas other adverse arrhythmic events were noted in 4 patients. Of these, 1 patient with a minimum distance of 2.8 mm from the defect to the near-field HPS was found to have CRBBB when establishing the arteriovenous circuit during the procedure. The patient quickly recovered to normal conduction after the delivery system was withdrawn, suggesting that mechanical stimulation may result in conduction abnormality. Of the other 3 patients with adverse arrhythmic events during closure and after the procedure, there was a minimum distance between the pmVSD and near-field HPS of <2 mm in all cases. These events may be due to the direct compression of the device on the conduction system with a relatively short distance from the pmVSD to the near-field HPS, explaining why the sinus rhythm recovered quickly in patients after removal of the device and delivery system and the initiation of steroid therapy. Notably, CLBBB has been proven to induce left ventricular remodeling and to cause heart failure. Left ventricular motion is significantly delayed and often dysynchronous in patients with CLBBB. Meanwhile, the ejection fraction can decrease gradually because of the impaired left ventricular motion, leading to LBBB-induced left ventricular enlargement and cardiomyopathy. Therefore, CLBBB should be regarded as an adverse arrhythmic event, underscoring the need for lifelong follow-up.

Guide to Decision Making and Treatment Options
In the present study we confirmed that the distance between the pmVSD and near-field HPS measured by 3D mapping is crucial. A minimum distance <2 mm was associated with a higher risk of procedure-related adverse arrhythmic events. Therefore, the choice of treatment should be individualized based on the minimum distance between the pmVSD and near-field HPS. If the minimum distance between the pmVSD and near-field HPS is ≥2 mm, transcatheter closure is considered to be a relatively safe treatment. If the minimum distance is <2 mm, caution should be exercised when deciding transcatheter closure for the pmVSD. Surgical repair of the pmVSD should be an alternative to transcatheter closure in this situation.

Surgical repair with cardiopulmonary bypass and median sternotomy has been the standard treatment for VSDs. However, this procedure has many complications, such as postoperative pain, thoracostomy scars, infection, a prolonged hospital stay, and psychological trauma. With
the recent development of various devices and improvements in interventional techniques, device closure for VSD using a transthoracic or transcatheter approach is more widely performed, and good clinical outcomes have been obtained.\textsuperscript{19,20} A recent meta-analysis found no significant difference between transcatheter closure and surgical repair of pmVSD with regard to the incidence of adverse arrhythmic events; however, double the number of patients developed adverse arrhythmic events after transcatheter compared with surgical repair.\textsuperscript{21} Moreover, Fang et al\textsuperscript{20} reported a similar success rate and comparable rates of adverse arrhythmic events in the different device groups compared with the surgical repair group. Compared with surgical repair, device closure procedures such as transcatheter and percutaneous device closure involve real-time monitoring of changes in cardiac rhythm due to the delivery and release of the occluder. On the basis of the findings of the present study, we speculate that the occurrence of adverse arrhythmic events during and after the procedure may be related to the mechanical compression caused by the occluder, because a relatively short distance was found between the pmVSD and near-field HPS in these patients. Therefore, at Guangdong Cardiovascular Institute, surgical repair of pmVSDs with an autologous patch instead of an inserted device is still the preferred method in patients with failed transcatheter closure.

Based on the experience from our previous para-Hisian studies,\textsuperscript{20} we believe that 3D electroanatomic mapping can be of considerable importance in transcatheter closure of pmVSDs. The total mapping time itself was relatively short (20 min) in the present study. High-density 3D electroanatomic mapping can improve our understanding of the local anatomy of the pmVSD and its adjacent conduction system before the procedure, which is critical for all practitioners, including interventional cardiologists, cardiac electrophysiologists, and cardiac surgeons. The time required for mapping is minimal, and 3D electroanatomic mapping should not lengthen the procedure considerably. Additional costs associated with 3D electroanatomic mapping could be an issue, but may be offset by improvements in procedural outcomes and reductions in the incidence of conduction injury.

Study Limitations
Although the present study demonstrated significant benefits of 3D electroanatomic mapping for transcatheter pmVSD closure, it nevertheless has some limitations. First, an ultrasound catheter was not used in the study to improve the local anatomy of the pmVSD and near-field HPS could also play an important role in predicting conduction disturbance related to the procedure, but was not evaluated in the present study. Despite these limitations, the methods used in this study can improve the prediction of adverse arrhythmic events during and after transcatheter pmVSD closure.

Conclusions
Transcatheter closure of pmVSDs in adults guided by 3D electroanatomic mapping and pacing techniques is feasible and useful for delineation of the cardiac conduction system in close proximity. It allows for intracardiac identification of the near-field HPS adjacent to the pmVSD, thus guiding occlusion procedures and possibly reducing the incidence of procedure-related adverse arrhythmic events.

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Conflict of Interest
The authors do not have any conflicts of interest to declare.

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