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Electroanatomic Relationships in Patients With Primum Atrioventricular Septal Defect

Nina Hakacova, MD, PhD,*‡ Galen S. Wagner, MD,* Salim F. Idriss, MD, PhD†
Durham, North Carolina; and Lund, Sweden

OBJECTIVES The objective of this study was to test the hypothesis that patients with primum atrioventricular septal defect (AVSD) have an imbalance in the positions of the left ventricular papillary muscles compared with healthy subjects, and that this anatomic imbalance correlates with left deviation of the QRS axis.

BACKGROUND The function and contraction pattern of the heart is best predicted when cardiac anatomy is considered together with its electrical activation sequence. Understanding the electroanatomic relationships is essential for discovering the developmental relationships between the conduction system and heart structures. Left deviation of the QRS axis is typically present in patients with primum AVSD. However, the pathophysiology of this phenomenon is not understood.

METHODS Thirty-five patients with primum AVSD and 35 healthy subjects were included in the study. Echocardiographic images were used to determine the papillary muscle positions. A 12-lead electrocardiogram was used to determine the QRS axis in the frontal plane in both patients and healthy subjects.

RESULTS An imbalance between papillary muscle positions in primum AVSD patients was defined as the position of the anterior papillary muscle closer to the septum and/or the position of the posterior papillary muscle further from the septum compared with the position of the papillary muscles in healthy subjects. In primum AVSD patients compared with control subjects, there was significant imbalance in the positions of the papillary muscles ($p = 0.0007$). The imbalance of papillary muscles correlated with deviation of the QRS ($r = 0.5$, $p = 0.0019$).

CONCLUSIONS Abnormality in the position of the papillary muscles changes continuously with the abnormality of the QRS axis. Understanding the electroanatomic relationships provides important insight into developmental relationships between the conduction system and the trabecular structures in primum AVSD patients. These results may provide insights in understanding the continuity of primum AVSD abnormality, in estimating the best surgical approach, and predicting the prognosis of primum AVSD patients. (J Am Coll Cardiol Img 2009;2:1357–65) © 2009 by the American College of Cardiology Foundation

From the Divisions of *Cardiology and †Pediatric Cardiology, Duke University Medical Center, Durham, North Carolina; and the ‡Children's Heart Centre, Lund University Hospital, Lund, Sweden.
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The heart function and contraction pattern is best understood and predicted when heart anatomy is considered together with its electrical activation sequence. However, there is limited information on the electroanatomic relationship in the presence of cardiac malformations. Patients with congenital primum atrioventricular septal defect (AVSD) have abnormalities of heart morphology involving both the atrioventricular junction and the atrioventricular valve complex (1). From the perspective of electrical activation, left deviation of the QRS axis (LAD) in the frontal plane is frequently present and suggests an alteration in the electrical activation sequence of the left ventricle (LV) (2–5). Understanding the electroanatomic relationships in the heart is essential for appropriate diagnosis and management of heart conditions and for shedding light on the developmental relationships between the conduction system and heart structures (6,7).

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ABBREVIATIONS AND ACRONYMS

ASD = atrial septal defect

AVSD = atrioventricular septal defect

ECG = electrocardiogram

echo = echocardiography

LAD = left deviation of the QRS axis

LBB = left bundle branch

LV = left ventricle/ventricular

PM = papillary muscle

Papillary muscles (PMs), as part of the atrioventricular valve complex, have recently been studied in relation to the variability of QRS complex characteristics in healthy individuals (6). The findings suggest that variations of the QRS axis are caused by variations in the location of the Purkinje conduction system (specifically left bundle branch [LBB] fascicles), as indicated by the locations of the respective LV PMs, toward which the borders of the fan-like fascicles course. Because these borders are formed by the anterior and posterior LBB fascicles, the abnormalities in the QRS axis associated with primum AVSD may be related to their anatomic displacement, which results in major alterations in the LV electrical activation sequence.

This study is based on the following assumptions: 1) assessment of the positions of the PMs between the interventricular septum and the LV free wall can localize the lateral borders of the LBB fascicular fan and thus indicate the most lateral 2 of the primary starting points of LV activation; and 2) imbalance of the position of the PMs, with the anterior PM relatively closer to the septum than the posterior PM, would be expected to produce a delay of activation of the anterior LV free wall, causing the frontal QRS axis to be directed leftward (LAD). The relationship between the LV PM positions and the direction of the frontal QRS axis in patients with primum AVSD has not been shown previously. Elucidation of this relationship in this patient population may have implications for understanding the nature of this electrical phenomenon, and may help to facilitate diagnostic and therapeutic approaches.

The objective of the study was to test the hypothesis that in patients with primum AVSD, an anatomic imbalance of the positions of the LV PMs correlates with electrophysiological LAD.

METHODS

The research protocol was approved by the Institutional Review Board Committee, and the study complies with the Declaration of Helsinki.

Definitions of key terms. Primum AVSD was defined as an anatomic defect of the atrioventricular junction above the level of the atrioventricular valve with no detectable defect below the valve (8). Primum AVSD is sometimes also called primum atrial septal defect (ASD). However, because primum AVSD is distinctly different from ASDs and is characterized by a defect in the atrioventricular junction rather than the atrial septum, we avoid the term primum ASD in this report. Primum AVSD also differs from the complete form of AVSD defect because of dense septal attachments that effectively close the ventricular communication and prevent shunting at the ventricular level. Patients with the complete form of AVSD were not included in the study.

Imbalance between the PM positions was defined as the position of the anterior PM closer to the septum and/or the posterior PM further from the septum, compared with the positions of PMs in healthy subjects. A position of the PM closer to the septum was present when its distance from the middle of the septum was smaller than its distance from the midpoint of the free wall. The position of the PM further from the septum was present when its distance from the middle of the septum was smaller than its distance from the midpoint of the free wall.

Study population. Thirty-five patients with a diagnosis of primum AVSD followed up at the Duke University Medical Center from 1996 until 2007 were identified from the Duke Information System for Cardiovascular Care database. The diagnosis of primum AVSD was confirmed in the following steps: 1) echocardiography (echo) images were reviewed independently by an investigator and an echo expert for the presence of the defect of the atrioventricular junction above the level of the atrioventricular valve with no detectable defect below the valve to confirm the diagnosis of primum AVSD; 2) echo reports of patients from all available encounters at the Duke University Medical Center were reviewed for confirmation of the diagnosis; 3) when available, surgical reports were reviewed for the presence of the surgical anatomic description of primum AVSD. Thirty-five healthy control subjects were randomly selected from children who had structurally normal hearts proven by echo as part of the evaluation before noncardiac surgery or for other purposes.

Inclusion criteria for AVSD patients and control subjects. Inclusion criteria were: 1) age range from 6 months to 25 years; 2) 12-lead surface electrocardiogram (ECG) and echo records for procedures performed on the same day; 3) available echo images of parasternal short-axis views of the heart at the level of the origins of the PMs; and 4) visible endocardial origins of both PMs and septal free-wall junction points on the echo image.

Exclusion criteria for primum AVSD patients. Exclusion criteria were: 1) history or ECG signs of myocardial infarction; 2) ECG signs of complete right bundle branch or LBB block, a ventricular rhythm, or a paced rhythm; 3) severe heart failure; and 4) diagnosis other than primum AVSD.

Data acquisition. Clinical, echo, and surgical reports were extracted electronically from the Duke Information System for Cardiovascular Care database at Duke University Medical Center. The echo images and ECGs were extracted from the respective electronic databases. All available ECGs were reviewed in each patient.

Data analysis. Demographic, ECG, and anatomic data were compared between patients with primum AVSD and normal subjects. The association between QRS axis deviation and PM positions in patients with primum AVSD was tested. Primum AVSD patients were also divided into 3 groups according to the direction of the QRS axis (LAD [−31° to −90°], horizontal axis [+30° to −30°], inferior axis [+60° to +29°]). The difference in PM positions between the groups of primum AVSD patients with regard to the degree of QRS axis deviation was studied.

QRS axis. The QRS axis was analyzed by visual inspection by 2 independent physicians blinded to echo data. Evaluation of the direction of the average QRS axis was performed by projection of the maximum average QRS vector on the axis scale in the frontal plane. Numbering of the degree of the axis was performed in a clockwise direction (positive axis) and a counterclockwise direction (negative axis). Each observer estimated the QRS axis twice, using different QRS complexes each time.

Echo data. The echo data were analyzed by 2 independent observers. The parasternal short-axis view at the level of the PM origins was used to measure the length and thickness of the LV and to determine the relative positions of anterior and posterior PMs in relation to the interventricular septum and LV free wall.

The method of determination of the PM positions was previously described (9). In short, using Figure 1 as a reference, the insertions of the right ventricular free wall (labeled W1) and septum (labeled W2) as borders of the interventricular septum were determined. A line was drawn perpendicularly to the line between W1 and W2 going through its middle to determine the intersection midpoint of the septum (labeled S) and the respective intersection of the free wall (labeled F). The septal sides of the PM origins were identified (labeled A and P). The location of the septal origin was identified for each PM by consideration of all available short-axis views of the heart from the base

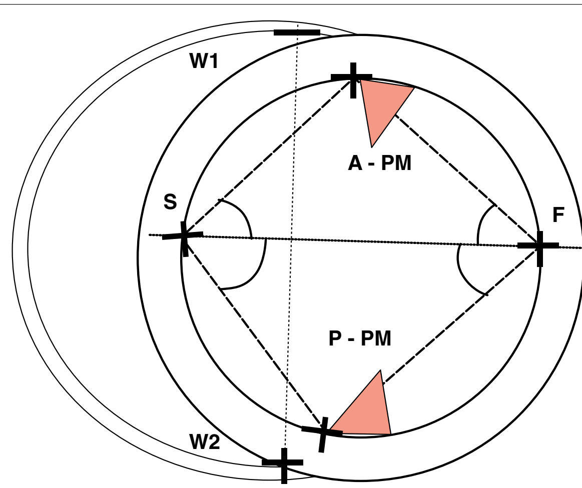

Figure 1. Determination of the PM Positions in the Parasternal Short-Axis View

Method of determination of the papillary muscle (PM) positions, described in detail previously (9). First, the insertions of the right ventricular free wall and septum as borders of the interventricular septum were determined (W1, W2). A line was drawn perpendicularly to the line between W1 and W2 going through its middle to determine the intersection midpoint of the septum (S) and respective intersection of the free wall (F). The septal sides of the PM origins were identified (anterior PM [A-PM] and posterior PM [P-PM]). The distance of the A-PM from the septum and free wall (A-PM position) was calculated by considering the ratio between the septal wall angle (ASF) and the free wall angle (AFS). Similarly, the distance of the P-PM position from the septum and free wall (P-PM position) was calculated as the ratio between the septal wall angle (PSF) and the free wall angle (PFS) of the P-PM.

to the apex and by considering cine images throughout the cardiac cycle. This approach served to distinguish between the PMs and the endocardial trabeculae.

The distance of the anterior PM from the septum and free wall (anterior PM position) was calculated by considering the ratio between the septal wall angle and the free wall angle. Similarly, the distance of the posterior PM position from the septum and the free wall (posterior PM position) was calculated as the ratio between the septal wall angle and the free wall angle of the posterior PM. Therefore, if the PM was closer to the midpoint of the septum, the ratio between the septal angle and the free wall angle had a relatively higher value. Balance between the positions of PMs was determined by measuring the ratio between the free wall angle of the anterior PM and that of the posterior PM. Therefore, if the anterior PM was displaced closer to the midpoint of the septum than the posterior PM, the ratio between the free wall angle of the anterior PM and the free wall angle of the posterior PM was smaller.

Statistical analysis. Data are presented as either mean ± SD or median (range). A Mann-Whitney *U* test was performed to compare PM positions between the primum AVSD patients and healthy control subjects, as well as the degree of the QRS axis deviation between those groups. A Spearman correlation test was used to assess the correlation between the PM positions and the QRS axis in the frontal plane. One-way analysis of variance was used to compare the subgroups of primum AVSD patients according to the QRS axis deviation. A 2-sided p value <0.05 was considered statistically significant. The level of interobserver and intraobserver agreement was assessed for echo-related measurements and QRS axis measurement by calculating the percentage of difference from the agreement by dividing the difference between measurements over the average of the measurements (10). A difference <5% was assumed to be within the agreement limits. Then, 2 groups were made: the first group had measurements that agreed (were within 5% of difference), and the second group had measurements that did not agree (were above 5% of difference). A kappa statistic was used to assess the level of agreement.

Table 1. Characteristics of Primum AVSD Patients and Healthy Control Subjects

	Primum AVSD Patients (n = 35)	Healthy Control Subjects (n = 35)	p Value
Demographic characteristics			
Sex (F/M)	26/9	11/24	0.0007*
Age (yrs)	9.3 ± 7.6	8.5 ± 4.3	NS†
Weight (kg)	31.1 ± 26.3	34.3 ± 22.7	NS†
Body surface area (m^2)	1.01 ± 0.54	1.09 ± 0.45	NS†
Echo measurements			
LV length	6.17 ± 1.8	6.9 ± 1.2	NS†
LV posterior wall thickness	0.65 ± 0.21	0.65 ± 0.18	NS†
Mitral regurgitation (degree/number of patients)	Trivial/8 Mild/17 Moderate/5 Severe/5		

*McNerman test. †Mann-Whitney *U* test.
AVSD = atrioventricular septal defect; Echo = echocardiography; LV = left ventricle; NS = not significant; PM = papillary muscle.

RESULTS

Thirty-five patients and 35 healthy control subjects were included in the study. Table 1 shows demographic characteristics and LV size measurements of both patients and control subjects. The mean age of patients was 9.3 ± 7.6 years, mean weight was 31.5 ± 26.3 kg, mean length of the LV was 6.17 ± 1.8 cm, and mean thickness of the LV was 0.65 ± 0.21 cm. Patients and control subjects did not differ significantly in demographic characteristics and LV size measurements.

A comparison of the direction of the QRS axis between patients and control subjects is shown in Figure 2. The median of the QRS axis in patients was −30° (range −70° to +70°) and +65° (+45° to +70°) in control subjects. Patients had significantly more leftward direction of the QRS axis direction compared with control subjects (p = 0.001). All control subjects had direction of the QRS axis within the normal range.

The comparison of the positions of the PMs between the patients with primum AVSD and normal subjects is summarized in Table 2 and schematically shown in Figure 3. Both the anterior PM (p = 0.0084) and the posterior PM (p < 0.0001) were significantly further from the septum in primum AVSD patients compared with healthy control subjects. However, in assessing the balance between both PMs, the anterior PM was positioned closer to the interventricular septum than the posterior PM in primum AVSD patients compared with healthy control subjects (anterior PM/posterior PM free wall angle ratio between patients and control subjects, p = 0.0021). Neither the length nor the thickness of the LV as correlated with deviation of the QRS axis. Measurements of angles of PMs as well as the QRS axis showed excellent intraobserver and interobserver agreements (kappa = 95%).

Relationship between PM positions and QRS axis. Figure 4 shows the relationship between anatomic characteristics (position of PMs) and electrophysiological characteristics (QRS axis) in patients with primum AVSD. The imbalance between the positions of PMs, with the anterior PM positioned closer to the septum than the posterior PM, correlated with LAD ($r = 0.5$, $p = 0.0019$).

When comparing the position of each PM separately with deviation of the QRS axis, displacement of the posterior PM further from the septum correlated significantly with the QRS axis ($r = 0.4$, $p = 0.03$). Correlation between the position of the anterior PM and the QRS axis was not significant ($r = 0.1$, $p = 0.4$).

Figure 5 shows the difference in PM positions between the 3 primum AVSD patient subgroups, formed according to the direction of the QRS axis. Forty-six percent of the patients with primum AVSD had LAD. A horizontal QRS axis was present in 37% of primum AVSD patients, and 17% of the patients had an inferior QRS axis. When comparing the balance between anterior and posterior PM positions among the 3 groups, significant differences were found. Patients with LAD had anterior PMs closer to the septum and posterior PMs further from the septum compared with patients with a horizontal or inferior QRS axis ($p = 0.0013$).

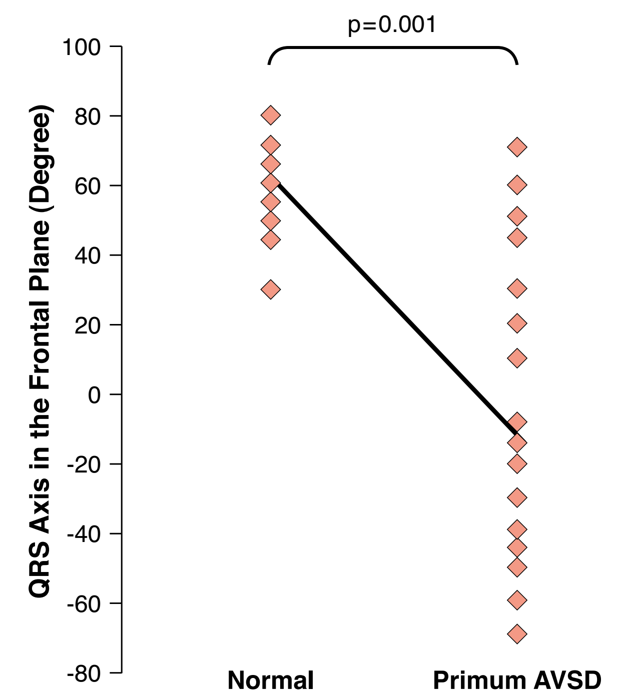

Figure 2. Comparison of the Degree of the QRS Axis Between Healthy Children (Normal) and Primum AVSD Patients

The degree of the QRS axis in normal subjects **(left)** and primum atrioventricular septal defect (AVSD) patients **(right)**, emphasizes the abnormality in the deviation of the QRS axis in primum AVSD patients. It can be seen that in contrast with normal subjects, who had a direction of the QRS axis within the normal range, primum AVSD patients had a significantly more left-deviated QRS axis. A Mann-Whitney *U* test was used for comparison of the 2 groups.

DISCUSSION

The results of this study show that, in primum AVSD patients, LAD of the QRS axis correlates with an imbalance of the positions of the LV PMs. The study provides an insight into understanding the electroanatomic relationships in the heart and sheds light on the developmental relationships between the conduction system and heart structures and appropriate diagnosis and management of heart conditions.

Deviation of the QRS axis suggests alteration in the electrical activation sequence of the LV and may reflect abnormalities within the specialized (Purkinje) LV conduction system (11–13) and/or abnormalities of conduction through the LV myocardium (14,15). The latter could be caused by changes of the normal sequence of LV myocardial activation produced by changes in the sites of the junctions of the LBB fascicles on the LV endocardium. A relationship between the PM positions and the QRS complex characteristics has been recently described in healthy subjects (6). It was suggested that an individual's PM positions can serve as a marker of the borders of the endocardial area directly supplied by the left fascicles. This area has been shown by Durrer et al. (11) to be activated earlier than the remainder of the LV endocardium. It is known that the left fascicles have a fan-like distribution, with its central part positioned on the septal wall and its lateral parts extending toward the origins of the anterior and posterior PMs (left anterior and left posterior LBB fascicles) (16,17). Therefore, the points of PM endocardial origin can potentially serve as anatomic landmarks of the borders of the LBB fascicular fan. The anatomic positions of the 2 LV PMs could thereby significantly determine an individual's QRS complex characteristics. The results of the current study support these concepts and provide a new view into the anatomic mechanism of LAD in primum AVSD patients. This opens a new dimension of using PMs as predictors of cardiac electrophysiological characteristics.

Table 2. Comparisons of PM Positions Between the Primum AVSD Patients and Control Subjects

	Primum AVSD Patients (n = 35)	Healthy Control Subjects (n = 35)	p Value
Position of the anterior PM (septal to free wall angle ratio)	0.64 ± 0.23	0.83 ± 0.22	0.0084*
Septal angle of anterior PM	31.4 ± 10.2°	36.7 ± 7.8°	
Free wall angle of anterior PM	49.4 ± 10.6°	57.2 ± 6.9°	
Position of the posterior PM (septal to free wall angle ratio)	1.67 ± 0.47	1.84 ± 0.5	0.0001*
Septal angle of posterior PM	51.9 ± 11.4°	45.4 ± 7.3°	
Free wall angle of posterior PM	44.5 ± 11.8°	31.8 ± 5.2°	
Balance between anterior and posterior PM (anterior over posterior PM free wall angle ratio)	1.2 ± 0.29	1.46 ± 0.31	0.0021*

*Mann-Whitney *U* test.
Abbreviations as in Table 2.

Developmental studies in animals suggest that cardiac morphogenesis and conduction system formation are linked. It follows that by understanding abnormal electrical activation patterns, one could further increase our understanding of the pathogenesis of congenital heart disease (18). It has been suggested previously that the conduction system develops from the trabecular system of the ventricle (19,20). The trabecular system in lower vertebrates serves for the rapid propagation of excitation within the ventricle (21). The main trabecular bands spanning the entire ventricle from the atrioventricular junction to the apex were found to be the functional equivalent of the His bundle and its branches in the zebrafish, and their ablation resulted in complete heart block (22). The PMs are part of the trabecular component, and therefore, the position of the PMs may be anatomically associated with the location of the conduction system. Our data support this idea. The question arises whether in primum AVSD patients displacement of the conduction system together with displacement of the PMs is part of a developmental abnormality associated with malformation of the atrioventricular junction. There is increasing evidence showing that development of AVSDs can be explained by alteration in the configuration of the heart tube, with inadequate remodeling of the inner heart curvature rather than simple failure of fusion between the atrioventricular endocardial cushions (23). Inadequate remodeling of the inner heart curvature may lead to altered posi-

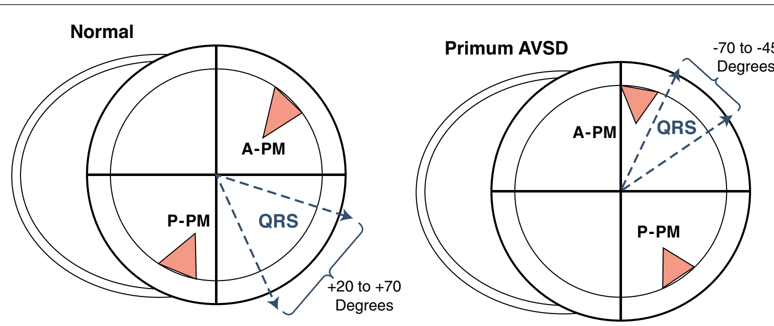

Figure 3. Schematic Depiction of the Mean Position of PMs in Normal Subjects and Primum AVSD Patients and the Range of the QRS Axis

This figure emphasizes the presence of electroanatomic relationships and the difference in those relationships between normal subjects **(left)** and primum AVSD patients **(right)**. The frontal electrocardiogram plane, represented as a horizontal and vertical line, is superimposed on the short-axis view of the heart. The PMs are shown as **triangles**. The area between the 2 **arrows** represents the mean ± 1 SD of the QRS axis direction. In normal subjects, the P-PM is positioned closer to the septum than the A-PM. In contrast, in primum AVSD patients, imbalance of the PMs is present, with P-PM further from the septum than A-PM. Associated with this, the QRS axis is deviated inferiorly in normal subjects and leftward in primum AVSD patients. This electroanatomic relationship can be explained as follows. Because LBB block fascicles cover the septal area between PMs, PMs reflect borders of the LBB block fascicles. The area not covered by the LBB block fascicles is depolarized slowly, cell by cell, and causes deviation of the average QRS axis to that direction. This area can be appreciated to be inferior in normal subjects and more superior in primum AVSD patients. Deviation of the QRS axis therefore can be appreciated to be inferior in normal subjects and leftward in primum AVSD patients. LBB = left bundle branch; other abbreviations as in Figures 1 and 2.

tions of PMs within the heart and may consequently alter the position of the septal fascicles of the conduction system.

Interestingly, in this study, 17% of primum AVSD patients had an inferior QRS axis and had positioning of the PMs that was similar to that of the normal subjects. There are reports of intermediate or right-axis deviation in AVSDs. Certain anatomic features were described within that group, such as a milder downward displacement of the atrioventricular valves and a shorter length of the primum atrioventricular defect compared with the group with the LAD (24). From a developmental perspective, it may be that there exists a continuum of electroanatomic abnormalities in AVSDs. Understanding this continuum and the electroanatomic relationship may help in predicting functional consequences in the heart. It also may be that the patients with a normal QRS axis and normal PMs may belong to a different developmental entity that does not involve abnormally developed atrioventricular junction (8,25). Distinguishing between different developmental entities is essential because disturbance of the atrioventricular canal is a complex abnormality with the need for a specific surgical approach, and there is potential for a severe outcome (1).

The mechanism of QRS axis deviation in primum AVSD patients was previously studied. The data regarding the influence of hemodynamics are controversial. Kulbertus et al. (4) did not find a relationship between volume overload and deviation of the QRS axis in primum AVSD patients. On the other hand, Borkon et al. (2) found that with the persistence of ventricular hypertrophy post-operatively or the surgical induction of right bundle branch block, the abnormal QRS either remains unchanged, or in the latter instance, moves in a more superior direction. We surmise that the primary influence on the QRS axis is the sequence of LV depolarization. Hemodynamic factors, such as right ventricular overload, can secondarily influence the QRS axis. However, right ventricular overload present in primum AVSD patients would rather explain shift of the QRS axis to the right, as suggested by Borkon et al. (2). Biventricular overload would rather cancel the electrical forces, and the QRS axis would be primarily dependent on the activation sequence. Down syndrome is often associated with AV canal defect. This supports the suggestion of a potential genetic origin of electroanatomic abnormality associated with the diagnosis of AV canal defect.

Detailed morphological and functional study of the atrioventricular valve complex and heart function in association with electrophysiological abnormalities may be beneficial in predicting the degree of LV and valve disturbance. This may lead to new insights into predicting the outcomes of patients with AVSDs based on PM positions and disturbances of the conduction system.

Study limitations. The identification of the septal origin of PMs using echo images has limitations because of difficulty identifying adjacent structures

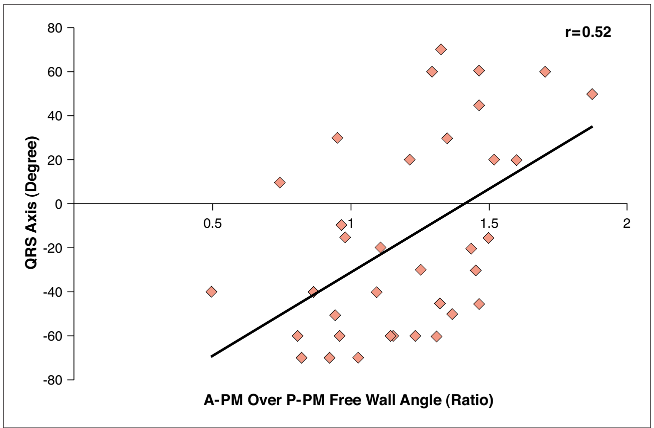

Figure 4. **Correlation Between the PM Position and QRS Axis Deviation in Primum AVSD Patients**

This figure emphasizes the presence of continual abnormality of both QRS axis deviation and position of papillary muscles (PMs). The position of the PMs correlates with the degree of left deviation of the QRS axis ($r_s = 0.52$). A Spearman correlation test was used for calculation of the correlation.

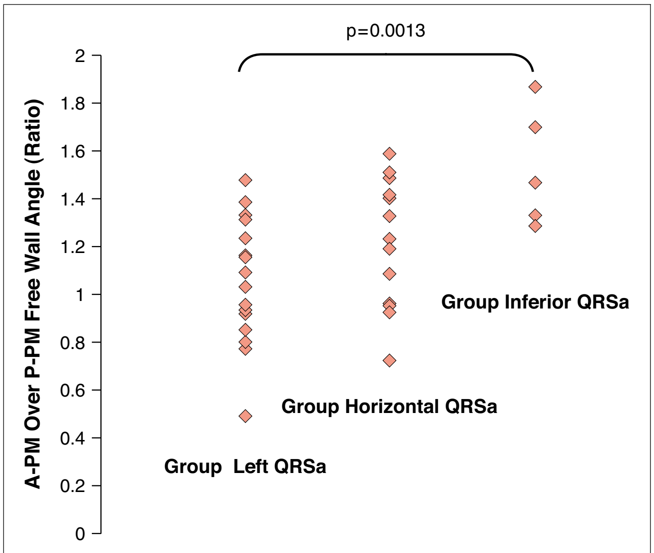

Figure 5. **Comparison of the Position of PMs in Primum AVSD Patients Grouped According to the Deviation of the QRS Axis**

Patients with a left QRS axis (−31° to −90°) had a more imbalanced position of the PMs (higher A-PM over P-PM ratio) compared with patients who had a horizontal QRS axis (+30° to −30°) and compared with patients who had an inferior QRS axis (+60° to +29°). This finding suggests the presence of several degrees of both electric and anatomic abnormality as well as the presence of an electroanatomic relationship in each QRS axis group. An analysis of variance test was used for comparison of the groups. Abbreviations as in Figures 1 and 2.

with similar echogenicity. This limitation was somewhat alleviated by using cine echo images to serially identify the borders of the PMs adjacent to the endocardium.

It may be that cardiac magnetic resonance may be more precise in the assessment of PM positions because of superior contrast between tissues. However, reproducibility of the assessment of the positions of PMs between echo and the cardiac magnetic resonance modality was tested previously, and it was found that there was excellent agreement between imaging modalities. This supports the use of echo for reproducible assessment of PM positions (9). Although the positions of the PMs and the QRS axis were not shown to be age dependent, it should be mentioned that in this study significantly more female subjects were in the population with primum ASD compared with the control group.

CONCLUSIONS

The most important finding of this study is the relationship between PMs and electrophysiological characteristics in the human heart. This relationship suggests developmental relationships between the conduction system and trabecular structures. The understanding of the relationships between the conduction system and anatomy in primum AVSD may help in understanding alterations of the electrical activation of the heart. This knowledge may have important diagnostic implications. The findings of the study can have important clinical applications in providing a patient-specific diagnosis or in the planning of patient-specific treatment.

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Reprint requests and correspondence: Dr. Salim F. Idriss, Pediatric Electrocardiographic Services, Pediatric Cardiology and Electrophysiology, Duke University Medical Center, Durham, North Carolina 27710. *E-mail: idris002@mc.duke.edu*.

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