Hypertrophic Cardiomyopathy and Ventricular Preexcitation in the Young: Etiology and Accessory Pathway Characteristics

Robert Przybylski, MD,

Sakethram Saravu Vijayashankar, MD, MRCPCH,

Edward O'Leary, MD,

Robyn J. Hylind, MS, CGC,

Jennifer Noon, MSN, CPNP-PC,

Audrey Dionne, MD,

Elizabeth S. DeWitt, MD,

Vassilios J. Bezzerides, MD, PhD,

Dominic J. Abrams, MD, MRCP MBA

Boston Children's Hospital, Department of Cardiology, Harvard Medical School, Boston, MA

Abstract

Background: The etiology of hypertrophic cardiomyopathy (HCM) in the young is highly varied. Ventricular preexcitation (preexcitation) is well recognized, yet little is known regarding the specificity for any etiology, and the characteristics of the responsible accessory pathways (APs).

Methods: Retrospective cohort study of patients <21 years of age with HCM/preexcitation from 2000–2022. Etiology of HCM was defined as isolated HCM, storage disorder, metabolic disease, or genetic syndrome. Atrioventricular APs (true APs) were distinguished from fasciculoventricular fibers (FVF) using standard invasive EP study (EPS) criteria. APs were defined as high-risk if any of the following were <250 ms: shortest preexcited RR interval in AF, shortest paced preexcited cycle length, or anterograde AP effective refractory period.

Results: We identified 345 patients with HCM and 28 (8%) had preexcitation (isolated HCM 10/220, storage disorder 8/17, metabolic disease 5/19, genetic syndrome 5/89). Six (21%) had clinical AF (1 with SPRRI <250 ms). Twenty-two underwent EPS which identified 23 true APs and 16 FVFs. Preexcitation was exclusively FVF-mediated in 8 (36%) patients. Five (23%) patients had APs with high-risk conduction properties (including 1 patient in each etiologic group). Multiple APs were seen in 8 (36%) and AP plus FVF in 10 (45%). Ablation was acutely successful in 13/14 patients with recurrence in 3. One procedure was complicated by CHB after ablation of a high-risk midseptal AP. There were significant differences in QRS amplitude and delta wave amplitude between groups. There were no surface ECG features which differentiated APs from FVFs.

Correspondence: Robert Przybylski, MD, Inova Fairfax Hospital, Department of Pediatrics, 3600 Gallows Road, Falls Church, VA 22042, Tel: 703-573-0504, robert.przybylski@inova.org.

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Conclusions: Young patients with HCM and preexcitation have a high likelihood of underlying storage disease or metabolic disease. Non-isolated HCM should be suspected in young patients with very large QRS and delta wave amplitudes. Surface ECG is not adequate to discriminate preexcitation from a benign FVF from that secondary to potentially life-threatening APs.

Graphical Abstract
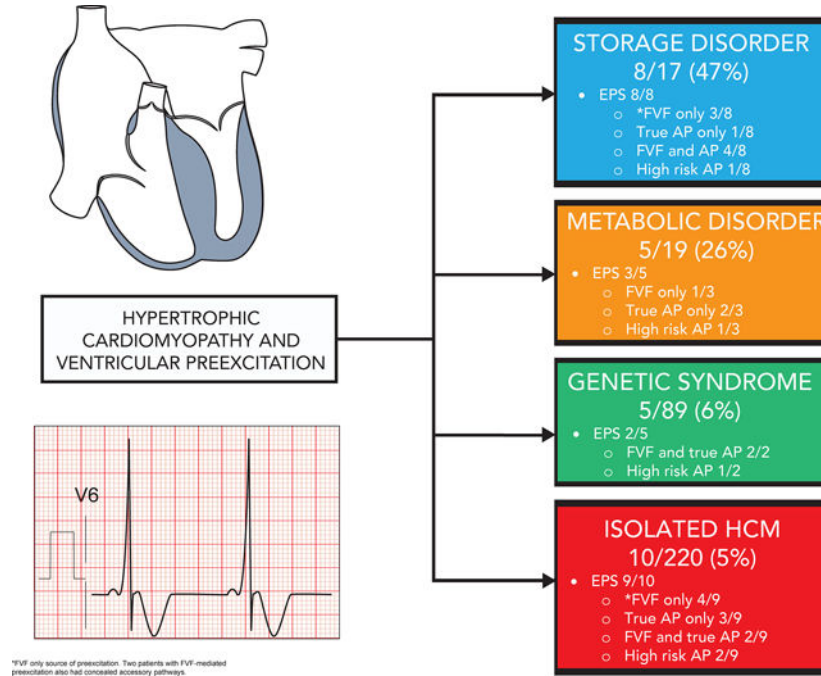
Keywords

Hypertrophic cardiomyopathy; accessory pathway; Wolff-Parkinson-White syndrome; fasciculoventricular fiber

Introduction

Ventricular preexcitation (preexcitation) has long been known to occur at increased frequency in patients with hypertrophic cardiomyopathy (HCM)[1,2]. This appears to be true in patients with sarcomeric/non-sarcomeric HCM not related to an underlying syndrome (isolated HCM) and in patients with several distinct systemic disorders which result in an HCM phenotype. These include storage diseases such as *PRKAG2* cardiomyopathy[3–5] and *LAMP2*-mediated Danon disease[6–9] as well as metabolic disease including cardioskeletal mitochondrial myopathies[10–13]. It is crucial to identify patients with these phenocopies as their prognosis and management differ from patients with isolated HCM.

Preexcitation can be caused by fasciculoventricular fibers (FVFs) originating distal to the atrioventricular (AV) node or by true AV accessory pathways (AP) spanning the AV junction. While FVFs are considered benign and do not predispose to sudden cardiac death (SCD) or participate in AV reciprocating tachycardia (AVRT), true AP can participate in AVRT and, in some cases, predispose to SCD secondary to rapid conduction of

atrial fibrillation (AF) and degeneration to ventricular fibrillation[14]. Furthermore, it is well known that both preexcitation and HCM predispose to the development of AF[15,16]. While the relationship between preexcitation and HCM is established, data are sparse regarding the relative frequency of preexcitation in different etiologies of HCM expressed in young people, the electrophysiological properties of the responsible APs, and risk for life-threatening arrhythmia.

Methods

We performed a single-center retrospective cohort study of patients aged <21 years with both HCM and preexcitation with a clinical encounter at Boston Children's Hospital between January 1, 2000 and October 31, 2022. This study was approved by our Institutional Review Board with a waiver of informed consent and the data supporting the findings of this study are available upon request from the corresponding author. Preexcitation was defined as the presence of a PR interval less than the lower limit of normal for age with a delta wave. HCM was defined according to the 2020 AHA/ACC Guideline for the Diagnosis and Treatment of Patients with Hypertrophic Cardiomyopathy[17]:

- Maximal left ventricular wall thickness z-score 2.5 in children without a family history of HCM and no pathogenic or likely pathogenic (P/LP) variant in a gene known to cause HCM

- Maximal left ventricular wall thickness z-score >2 in a child with a P/LP variant in a gene known to cause HCM or a positive family history and no hemodynamic explanation for left ventricular hypertrophy.

The etiology of HCM was classified into one of the following mutually exclusive categories:

1. Storage disease including *PRKAG2* cardiomyopathy and Danon disease (*LAMP2*) if patients had a P/LP variant in either of these genes or histopathologic evidence of storage disease on endomyocardial biopsy.

2. Metabolic disease if patients had a P/LP variant in a gene associated with known metabolic disease including those associated with mitochondrial myopathy or a clear phenotype indicative of metabolic disease.

3. Genetic syndrome associated with HCM if patients had a clear syndromic phenotype with extracardiac manifestations without features suggestive of storage or metabolic disease.

4. Isolated HCM if patients had a P/LP genetic variant in a gene encoding a sarcomeric protein known to be associated with HCM or HCM in the absence of features suggestive of an underlying systemic disorder.

Clinical data on all patients in our internal database of children with HCM was examined to determine the frequency of preexcitation within each etiologic group. Demographic and clinical data collected included age at diagnosis of preexcitation and age at diagnosis of HCM as well as sex assigned at birth. A history of clinical AF and supraventricular tachycardia (SVT) was recorded, and in those with documented AF the shortest preexcited RR interval (SPRRI) was recorded. Additional data collected included family history of

preexcitation and/or HCM. Heart transplantation or death during the study period was also recorded.

ECG data were abstracted from the first available 12-lead ECG with preexcitation and included PR interval, QRS duration, QRS amplitude (average of V1 and V6), V6 R-wave and S-wave V1 amplitude, and delta wave amplitude (DWA) 40 ms after delta wave onset (highest amplitude in any limb lead). R-wave amplitude in V6 and S-wave amplitude in V1 were normalized (amplitude divided by age-specific upper limit of normal from our institutional database) to account for differences in age.

In patients who underwent invasive electrophysiology study (EPS) data including the cause of preexcitation (classified as FVF if the HV interval was <35 ms and did not change with decremental atrial extrastimulus testing, or true AP if the HV was <35 ms and the HV interval decreased with decremental atrial extrastimulus testing[18]) as well as number and location of APs were collected. APs with anterograde conduction were defined as high risk if any of the following characteristics were met at baseline (i.e. not during isoproterenol infusion): SPRRI during AF <250 ms, shortest paced preexcited cycle length (SPPCL) during atrial pacing <250 ms, or anterograde AP effective refractory period <250 ms. Use of isoproterenol and AP characteristics during isoproterenol infusion were also collected.

Kruskal-Wallis tests were used to evaluate variability in continuous variables between etiologic groups while Fisher's exact test was used for binary variables. Given the small size of our cohort, post-hoc analyses were not performed. Comparison was made of ECG characteristics in patients with preexcitation exclusively due to an FVF to those with preexcitation secondary to a true AP using Fisher's exact test for binary variables and the Wilcoxon rank-sum test for continuous variables. ECG preexcitation patterns were analyzed using the Arruda algorithm[19] to estimate the likely AP location and compared to the invasively determined location. The Arruda algorithm was classified as correct if it correctly predicted the location of at least one AP with anterograde conduction.

Results

We identified 28 patients with preexcitation from a total of 345 HCM patients (8%). The frequency of preexcitation differed significantly between HCM etiologies [isolated HCM 10/220 (5%), storage disease 8/17 (47%), metabolic disease 5/19 (26%), genetic syndrome 5/89 (6%), p <0.001]. Clinical characteristics are summarized in table 1. There were significant differences between groups at age of both preexcitation and HCM diagnosis, and between groups with regards to average QRS amplitude, DWA, and normalized V6 R-wave amplitude. Clinical and ECG characteristics are summarized by HCM etiologic group in table 2.

We constructed receiver operating characteristic curves to explore the relationships between average QRS amplitude, DWA, and etiology of HCM. The area under the curve (AUC) for the relationship between average QRS amplitude and storage disease was 0.83. Youden's J-statistic was maximized at a threshold value of 33.5 mm which was 87.5% sensitive and 85.0% specific for the presence of storage disease (figure 1A). The AUC for the relationship

between DWA and non-isolated HCM was 0.81 and Youden's J-statistic was maximized at a threshold of 4.8 mm which was 72.2% sensitive and 90.0% specific for non-isolated HCM (figure 1B).

Preexcited AF was seen in 6 patients during the study period, including at presentation in 2. In 4 patients preexcitation was secondary to an FVF and the average ventricular rate during preexcited AF was <150 bpm. In 2 patients, anterograde conduction during preexcited AF was, at least in part, over an AP with more rapid conduction: one patient with Danon disease and a SPRRI 315 ms presented in congestive heart failure and one patient with isolated HCM had a SPRRI of 210 ms; figure 2A). Two patients presented with reentrant SVT and two patients had syncope. There were no cases of cardiac arrest or sudden death.

Twenty-two patients underwent invasive EPS. A total of 39 total AP (including both FVF and true AP) were identified – 23 true AP (including 5 with retrograde only conduction) and 16 FVF. In 8 patients preexcitation was secondary to an FVF only, and in 2 of these patients there was at least 1 additional concealed AP with retrograde only conduction (all retrograde only APs were along the left AV groove). EPS data are summarized by HCM etiologic group in table 2. EPS indications and patient-level EPS data are presented in table 3. AP location and nature are depicted for each etiologic group in figure 3. Five patients had AP with high-risk characteristics at baseline including at least one patient from each etiologic category. AP were characterized during isoproterenol infusion in 6 (27%) patients. Anterograde AP conduction was rapid during isoproterenol infusion (AP ERP, SPRRI, or SPPCL <250 ms) in 2 of these patients, though both of these AP met high-risk criteria under baseline conditions. Radiofrequency/cryoablation was performed in 14 patients targeting 19 true AP, with acute success in 13 (93%). A subsequent recurrence of AP conduction was seen in 3 (23%) patients. No FVF were ablated. One patient with isolated HCM who presented with rapidly conducted preexcited AF was found to have midseptal and right lateral true APs with anterograde-only conduction as well as an FVF and experienced complete AV block as a result of radiofrequency ablation of the midseptal AP. There were no other procedural complications.

Two patients with storage disease who underwent true AP ablation subsequently developed QRS widening during follow up and repeat EPS were performed due to concern for AP recurrence. However, preexcitation was confirmed to be secondary to known FVF in both cases and the QRS widening was attributed to evolving cardiac conduction disease and resultant intraventricular conduction delay.

In patients who underwent invasive EPS, the Arruda algorithm[19] correctly predicted the location of an AP with anterograde conduction in only 11 (50%) patients. Notably 10 (45%) patients had >1 source of preexcitation, though this did not appear to impact the accuracy of the Arruda algorithm (correct in 5/12 (42%) with one AP with anterograde conduction and 6/10 (60%) with more than one AP with anterograde conduction, p = 0.67). In the group of patients whose preexcitation was exclusively secondary to an FVF, the Arruda algorithm localized the surface ECG preexcitation pattern to a site outside the anteroseptal region in 3 of 6 cases (right anterior/anterolateral in 2 cases and left lateral/anterolateral in 1 case). There were no clinical or ECG characteristics which differentiated patients with

preexcitation secondary to an FVF versus those with true AP-mediated preexcitation (table 4).

Over the course of a median follow up of 5.1 years (range 0.0–13.4 years), 1 patient with a genetic syndromic etiology of HCM died from a non-cardiac cause. Three patients (2 patients with Danon disease and 1 with a mitochondrial myopathy) underwent heart transplantation during follow up.

Discussion

In this cohort of young patients with HCM and comorbid preexcitation, we make a number of important observations regarding the underlying etiology of HCM and AP characteristics which include the following:

1. The frequency with which preexcitation is comorbid with HCM differs markedly between HCM etiologic groups.

2. Evaluation of QRS and delta wave amplitude may be useful for differentiation between underlying etiologies of HCM.

3. Surface electrocardiography cannot reliably distinguish between preexcitation secondary to a benign FVF and that due to a potentially life-threatening true AP in this population.

4. Young patients with HCM and preexcitation have a high frequency of both multiple true AP and high-risk AP as well as frequent coexistence of FVF and true AP.

Although isolated disease is the most common etiology of pediatric HCM, only 5% of these patients had associated preexcitation in our cohort. This contrasts strikingly with the approximately 50% of patients with HCM secondary to storage disease and 25% of children with HCM secondary to metabolic disease who had comorbid preexcitation. These findings are consistent with prior reports of relatively rare preexcitation in isolated HCM cohorts[1] and high rates of preexcitation in patients with storage disease[7,20–22]. Thus, identification of preexcitation in a young patient with HCM should raise suspicion for an underlying storage or metabolic disease. While evidence of an underlying systemic disorder may be obvious in some patients with dysmorphic features, anomalies in other visceral organs, musculoskeletal weakness, or developmental delay, others may have no extracardiac features. This is particularly true of patients with *PRKAG2* cardiomyopathy as most patients do not have extracardiac manifestations aside from mild skeletal myopathy in a minority[23], and females with Danon disease in whom extracardiac manifestations occur in less than 40% and may be quite subtle including transaminitis, mild/sub-clinical skeletal myopathy, and visual disturbances[24].

While previous work has described large QRS amplitudes in patients with preexcitation and *PRKAG2* cardiomyopathy[23], ours is the first to quantify and directly compare ECG characteristics between different etiologic groups in young patients with HCM and preexcitation. We found DWA 4.8 mm was 90% specific for non-isolated HCM and average QRS amplitude 33.5 mm demonstrated approximately 85% sensitivity and

specificity for storage disease. Representative ECGs from patients with storage disease and isolated HCM are shown in figure 2 (C&D). The only patient with storage disease who had an average QRS amplitude <33.5 mm and DWA <4.8 mm was an adolescent male with Danon disease whose cardiac phenotype had progressed to a hypokinetic stage with congestive heart failure at the time of presentation. He had significant fibrotic myocardial replacement apparent on cardiac magnetic resonance imaging explaining his diminished QRS and delta wave amplitudes. Additionally, younger age at presentation was more common in patients with metabolic or genetic syndromic etiologies. That said, infantile presentation does not exclude isolated HCM or storage disease and remarkably one previously described patient with *PRKAG2* cardiomyopathy in our cohort was noted to have cardiac hypertrophy *in utero*[25]. Furthermore, while we did not have any patients with Pompe disease (glycogen storage disease type II) in our cohort, neonatal presentation with HCM and preexcitation is described[26].

Identifying the etiology of HCM in patients with HCM and preexcitation is crucial for several reasons. Genetic syndromes, storage disorders, and metabolic disease often involve disease processes in other organ systems that require identification and appropriate management. The cardiac phenotype is also varied across different etiologic groups. Both Danon disease and *PRKAG2* cardiomyopathy are associated with an increased likelihood of atrial arrhythmias as well as cardiac conduction disease and early systolic dysfunction leading to congestive heart failure[20,22–24,27]. Etiology-specific disease-modifying therapy is presently available for conditions such as Pompe disease[28] and gene therapy for other conditions such as Danon disease is under investigation[29]. Thus, early identification of patients who may benefit from these therapies is important.

FVFs are APs which arise distal to the AV node and typically connect the bundle of His to the ventricular myocardium in the paraHisian/anteroseptal region[18,30]. FVFs are not thought to predispose to life-threatening rapidly conducted preexcited AF or participate in SVT, though sudden death in a patient with *PRKAG2* cardiomyopathy and FVF-mediated preexcitation with documented rapidly conducted preexcited AF has been described, possibly secondary to enhanced AV nodal conduction[3]. Previous work in individuals without HCM has demonstrated FVF-mediated preexcitation can be differentiated from that secondary to a true AP by a longer PR interval, shorter QRS duration, and smaller DWA[31,32]. While O'Leary et al found DWA >5 mm was 96% specific for true AP-mediated preexcitation and DWA <2 mm was 96% specific for FVF-mediated preexcitation in a cohort of children without structural heart disease, in our cohort 3 of 8 patients with FVF-mediated preexcitation had DWA >5 mm and the only patient with DWA <2 mm had true AP-mediated preexcitation. Additionally, we found no difference in PR interval or QRS duration between patients with FVF and true AP-mediated preexcitation and, concordant with a prior report in patients with Danon disease[6], no ECG characteristic reliably differentiated these two groups. Furthermore, while preexcitation secondary to FVF conduction typically results in a surface ECG pattern suggestive of an anteroseptal location[30], 50% of patients in our cohort with FVF-mediated preexcitation had a preexcitation pattern inconsistent with an anteroseptal location using the Arruda algorithm[19], which performed poorly overall in our cohort. The limited utility of the Arruda algorithm in our cohort is consistent with a prior report which found the Arruda algorithm

and multiple additional AP localization algorithms to be of limited utility in pediatric patients[33]. Administration of intravenous adenosine has previously been shown to be useful in distinguishing between FVF and true AP-mediated preexcitation[32], however other authors have reported up to 20% of true APs are adenosine sensitive[34] and AV nodal conduction may be relatively adenosine insensitive in patients with *PRKAG2* cardiomyopathy[3]. Thus, we conclude invasive EPS is required to definitively characterize preexcitation in patients with HCM.

Previous studies have provided detailed characterization of APs in patients with Danon disease[6] and *PRKAG2* cardiomyopathy[3] and the present study expands upon these findings. Darden et al reported on a cohort of patients with Danon disease including 9 patients with preexcitation who underwent invasive EPS[6]. Concordant with our findings, they described several patients with multiple true AP, the coexistence of FVF and true AP, and the presence of true AP with high-risk anterograde conduction characteristics in two patients. While Sternick et al previously reported on a cohort of *PRKAG2* cardiomyopathy patients with exclusively FVF-mediated preexcitation with no co-occurrence of FVF and true AP[3], others have reported preexcitation secondary to true AP in this population[21,35–37]. Here we describe 3 patients with *PRKAG2* cardiomyopathy and true AP -- 1 patient with both an FVF and true AP anterograde conduction, 1 patient with exclusively true AP-mediated preexcitation, and an additional patient with FVF-mediated preexcitation as well as two true AP with retrograde-only conduction. Darden et al additionally reported a patient with Danon disease who underwent successful AP ablation and subsequently developed QRS widening and PR prolongation 4 years later[6]. We observed a similar phenomenon in 2 patients with *PRKAG2* cardiomyopathy both of whom underwent repeat EPS which ruled out true AP-mediated preexcitation, suggesting distal conduction system disease or intraventricular conduction delay as the etiology of QRS widening.

While preexcitation has long been described in a minority of patients with isolated HCM[1,2], reports including detailed AP characterization are sparse and lack true APs[38]. Notable findings from this subset of our cohort include the finding of true AP with high-risk anterograde conduction in 2 of 10 patients, frequent coexistence of FVFs and true AP, multiple true AP in several patients, and true AP located in both septal as well as both right and left free wall locations. Additionally, two patients in this group had documented AF including one patient who presented with rapid preexcited AF (figure 2A), highlighting the potential for life-threatening arrhythmias in these patients. Our study additionally characterizes preexcitation in a small group of patients with HCM associated with metabolic and genetic syndromes in whom previous reports are sparse[39]. As with the other etiologic groups described in the present study, notable findings in these groups include patients with high-risk true AP, multiple true AP, and the coexistence of FVF and true AP in multiple patients.

Our study was limited by its small size as only 22 included patients underwent invasive EPS over the 22-year study period. It is further limited by its retrospective nature and is subject to the biases inherent to this sort of study design. Additionally, our institution is a referral center for pediatric HCM, and our patient population may not be generalizable.

In summary, the presence of preexcitation in a young patient with HCM should raise suspicion for underlying storage, metabolic, or syndromic disease and identifying these etiologies has significant implications for prognosis and management of these patients and their families. Very large QRS and delta wave amplitudes should further heighten the suspicion for an underlying storage disease. Invasive EPS is required for characterization of preexcitation in this population as surface ECG characteristics do not reliably distinguish between preexcitation secondary to benign FVF and potentially life-threatening true AP in this population with a high incidence of high-risk true AP, multiple true AP, and coexistence of FVF and true AP.

Sources of Funding:

Nonstandard Abbreviations and Acronyms:

preexcitation	Ventricular preexcitation
HCM	hypertrophic cardiomyopathy
FVF	fasciculoventricular fiber
AP	accessory pathway
AV	atrioventricular
SCD	sudden cardiac death
AVRT	atrioventricular reciprocating tachycardia
AF	atrial fibrillation
P/LP	pathogenic or likely pathogenic
SVT	supraventricular tachycardia
SPRRI	shortest preexcited RR interval
DWA	delta wave amplitude
EPS	electrophysiology study
SPPCL	shortest paced preexcited cycle length

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What is Known:

- A subset of patients with hypertrophic cardiomyopathy (HCM) have associated ventricular preexcitation (preexcitation) which can be due to atrioventricular accessory pathways (AP) or benign fasciculoventricular fibers (FVF).

What this Study Adds:

- In patients with HCM, the prevalence of preexcitation is 10 times higher in patients and underlying storage disease and 5 times higher in patients with underlying metabolic disease than in patients with isolated HCM.

- Atrioventricular AP with high-risk characteristics, multiple AP, and the coexistence of AP and FVF can be found in patients with HCM secondary to underlying storage disease, metabolic disease, genetic syndromes, and in patients with isolated HCM.

- No surface ECG characteristic reliably discriminates between potentially life-threatening atrioventricular AP-mediated preexcitation and benign FVF-mediated preexcitation in patients with HCM.
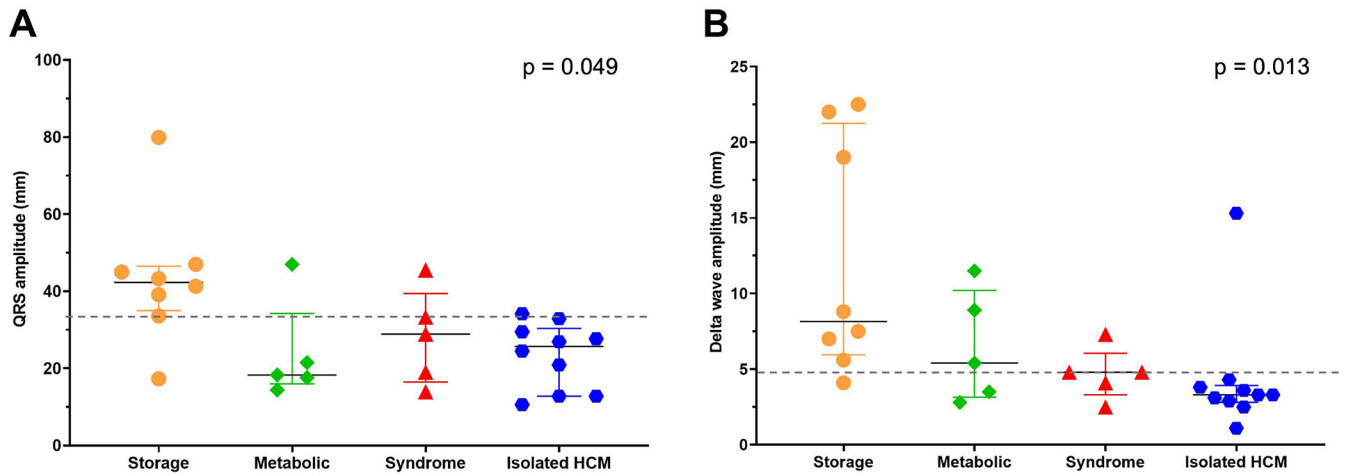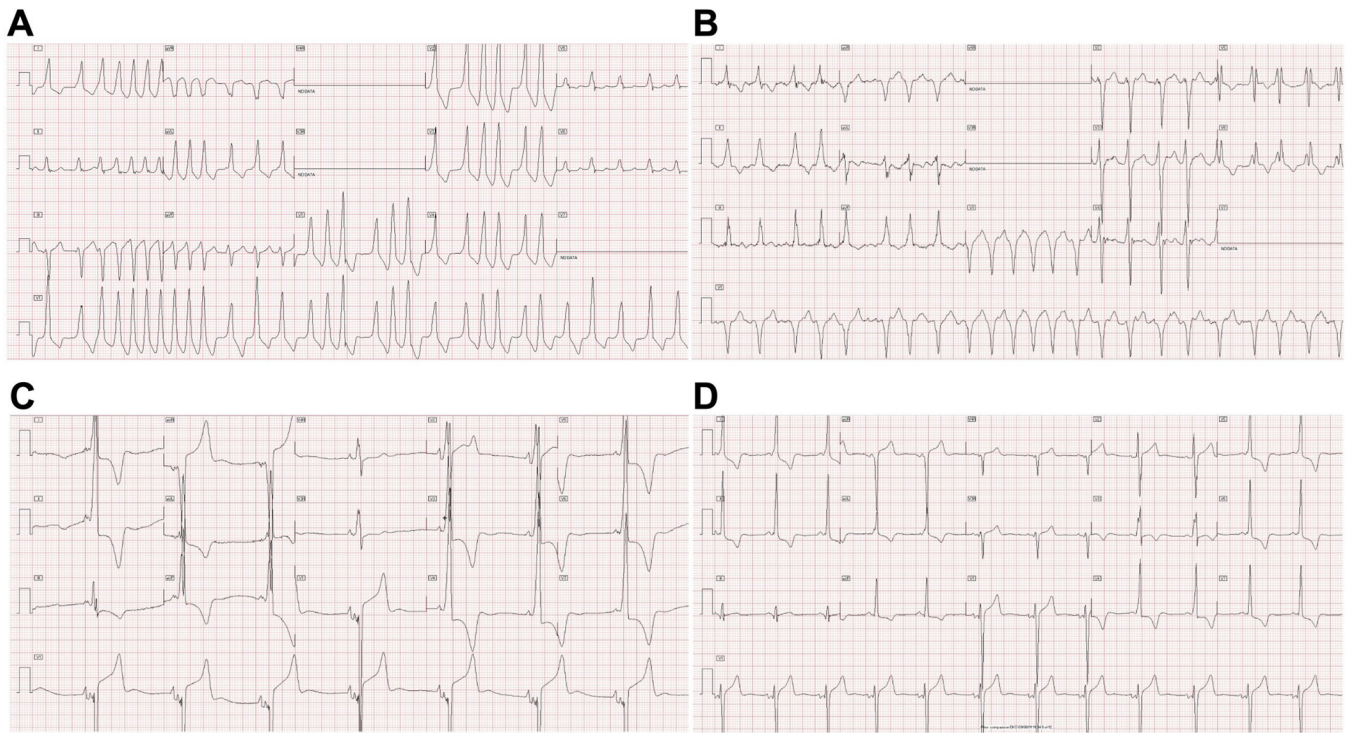
Figure 1.

ECG features which aid in differentiation between HCM etiologic groups: A) QRS amplitude v. HCM etiologic group: an average QRS amplitude 33.5 mm (dashed line) is 87.5% sensitive and 85.0% specific for an underlying storage disorder. B) Delta wave amplitude v. HCM etiologic group: a DWA amplitude 4.8 (dashed line) mm is 72.2% sensitive and 90.0% specific for non-isolated HCM. P-values determined using Kruskall-Wallis test.

Figure 2.
ECG examples: A) Rapidly conducted preexcited atrial fibrillation (SPRRI 210 ms) in a
patient with isolated HCM. B) Preexcited atrial fibrillation (SPRRI 315 ms) in a patient with
Danon disease and an FVF. C) Preexcitation with massive QRS and delta wave amplitudes
in a patient with *PRKAG2* cardiomyopathy. D) Preexcitation in a patient with isolated HCM
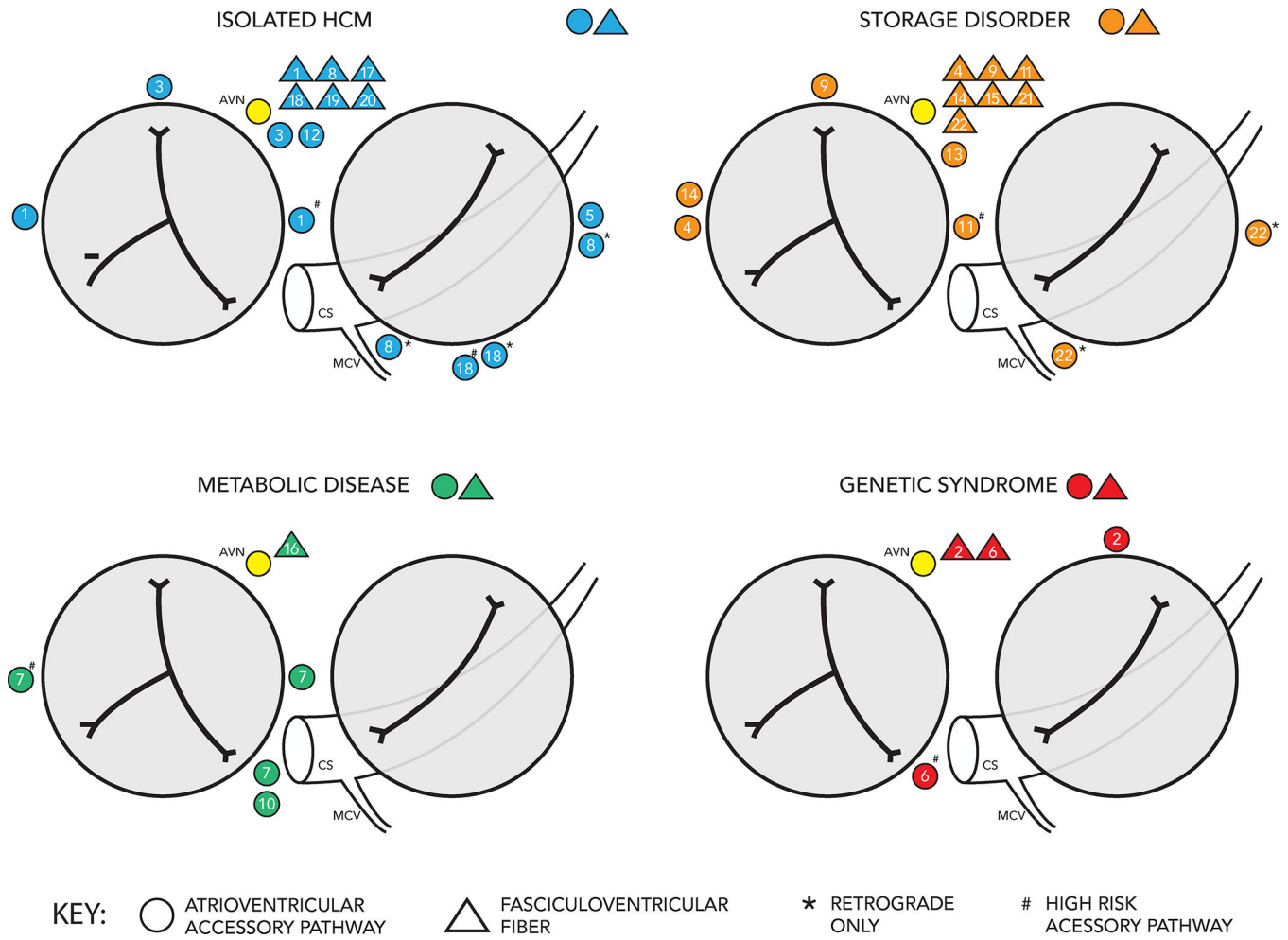with more modest QRS and delta wave amplitudes.

Figure 3.
Location and nature of APs in 22 patients who underwent invasive electrophysiology study organized by HCM etiologic group.

Table 1.

Clinical characteristics.

Patients	28
Male sex	15 (52)
Age at preexcitation diagnosis (years)	9.5 (4.2–13.8)
Age at HCM diagnosis (years)	11.2 (0.9–14.4)
Concomitant VPe & HCM diagnosis	14 (48)
Etiology of HCM	
Storage disease	8 (29)
Metabolic disease	5 (18)
Genetic syndrome	5 (18)
Isolated HCM	10 (36)
History of reentrant supraventricular tachycardia	6 (21)
History of atrial fibrillation	6 (21)
History of syncope	2 (7)

Data expressed n (%) or median (IQR)

HCM = hypertrophic cardiomyopathy

Table 2.

Clinical, ECG, and invasive electrophysiology study characteristics by HCM etiologic group.

Clinical Characteristics	Overall (n = 28)	Storage disorder (n = 8)	Metabolic disease (n = 5)	Genetic syndrome (n = 5)	Isolated (n = 10)	p-value
Age at preexcitation diagnosis (years)	9.5 (0.0–17.2)	14.6 (7.2–17.2)	3.4 (0.5–10.7)	1.3 (0.0–12.9)	11.6 (1.7–17.0)	**0.008**
Age at HCM diagnosis (years)	11.2 (0.0–19.3)	13.4 (0.0–17.2)	0.3 (0.0–5.7)	11.0 (0.0–14.4)	13.0 (0.9–19.3)	**0.048**
Male sex	15 (52)	2 (25)	4 (80)	2 (40)	7 (70)	0.188
Family history of preexcitation	7 (25)	2 (25)	3 (60)	0 (0)	2 (20)	0.222
Family history of HCM	8 (29)	2 (25)	1 (20)	2 (40)	3 (30)	1.000
*Atrial fibrillation	6 (21)	4 (50)	0 (0)	0 (0)	2 (20)	0.126
*Reentrant SVT	6 (21)	1 (13)	1 (20)	1 (20)	3 (30)	0.916
Syncope	2 (7)	0 (0)	1 (20)	0 (0)	1 (10)	0.499
ECG Characteristics						
PR interval	93 (55–145)	95 (80–116)	82 (55–90)	88 (80–108)	107 (65–145)	0.121
QRS duration	110 (85–192)	120 (95–192)	108 (100–140)	100 (85–108)	110 (96–160)	0.057
DWA 40 ms after delta onset (mm)	4.6 (1.1–22.5)	8.2 (4.1–22.5)	5.4 (2.8–11.5)	4.8 (2.5–7.3)	3.3 (1.1–15.3)	**0.013**
QRS amplitude (average V1 and V6, mm)	28.3 (10.6–79.9)	42.3 (22.8–79.9)	18.3 (14.4–47.0)	28.8 (11.6–47.5)	25.7 (10.6–34.2)	**0.049**
V6 R-wave amplitude (mm)	25.2 (4.4–65.0)	39.7 (11.6–65.0)	16.4 (4.4–46.3)	28.8 (11.0–44.0)	17.5 (11.4–35.1)	0.062
Normalized V6 R-wave amplitude	1.0 (0.3–2.5)	1.6 (0.5–2.5)	0.6 (0.3–2.0)	1.1 (0.5–1.8)	0.7 (0.4–1.5)	**0.046**
V1 S-wave amplitude (mm)	20.7 (0.0–75.3)	31.8 (0.0–75.3)	18.4 (5.9–40.9)	9.2 (2.6–30.5)	20.3 (0.0–30.5)	0.194
Normalized V1 S-wave amplitude	1.0 (0.0–3.1)	1.3 (0.0–3.1)	0.8 (0.2–2.0)	0.4 (0.1–1.3)	0.9 (0.0–1.4)	0.237
EPS Characteristics	Overall (n = 22)	Storage disorder (n = 8)	Metabolic disease (n = 3)	Genetic syndrome (n = 2)	Isolated (n = 9)	
Patients with AP with anterograde conduction	14 (64)	5 (63)	2 (66)	2 (100)	5 (66)	0.912
Patients with multiple true APs	8 (36)	2 (25)	1 (33)	0 (0)	5 (56)	0.470
Patients with high risk true AP	5 (23)	1 (13)	1 (33)	1 (50)	2 (22)	0.653
Patients with FVF	16 (73)	7 (88)	1 (33)	2 (100)	6 (66)	0.307
Patients with FVF-mediated preexcitation	8 (36)	3 (38)	1 (33)	0 (0)	4 (44)	0.912

Data expressed n (%) or median (range); n = number of patients

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*
One patient had both SVT and AF

AF = atrial fibrillation, AP = accessory pathway, DWA = delta wave amplitude, EPS = electrophysiology study, HCM = hypertrophic cardiomyopathy, SVT = supraventricular tachycardia.

Table 3.

Invasive EP study indications and AP characteristics by patient.

Patient number	HCM etiology	Age at EPS (years)	Indication for EPS	AP nature[‡]/location	High risk AP
1	Isolated	13.8	Preexcited AF	1) FVF 2) right lateral 3) midseptal [*]	Yes
2	Genetic syndrome	12.9	Asymptomatic preexcitation	1) FVF 2) left anterior	No
3	Isolated	13.6	SVT	1) right anterior 2) anteroseptal	No
4	Storage disorder	14.6	SVT, preexcited AF	1) FVF 2) right lateral	No
5	Isolated	10.0	SVT	Left lateral	No
6	Genetic syndrome	6.5	Asymptomatic preexcitation	1) FVF 2) right posteroseptal [*]	Yes
7	Metabolic disease	12.1	SVT	1) right lateral [*] 2) midseptal 3) right posteroseptal	Yes
8	Isolated	12.6	SVT	1) FVF 2) left posteroseptal [†] 3) left lateral [†]	No
9	Storage disorder	16.8	Preexcited AF	1) FVF 2) right anterior	No
10	Metabolic disease	7.0	Syncope	Right posteroseptal	No
11	Storage disorder	12.6	Asymptomatic preexcitation	1) FVF 2) midseptal [*]	Yes
12	Isolated	15.4	Asymptomatic preexcitation	Anteroseptal	No
13	Storage disorder	11.0	Syncope	Anteroseptal	No
14	Storage disorder	7.5	Asymptomatic preexcitation	1) FVF 2) right lateral	No
15	Storage disorder	17.6	Preexcited AF	FVF	No
16	Metabolic disease	11.5	Asymptomatic preexcitation	FVF	No
17	Isolated	16.8	Preexcited AF	FVF	No
18	Isolated	3.8	Asymptomatic preexcitation	1) FVF 2) left posterior [*] 3) left posterior [†]	Yes
19	Isolated	19.6	Asymptomatic preexcitation	FVF	No
20	Isolated	16.9	Palpitations	FVF	No
21	Storage disorder	16.4	Preexcited AF	FVF	No
22	Storage disorder	10.4	Asymptomatic preexcitation	1) FVF 2) left posteroseptal [†] 3) left lateral [†]	No

[*] high risk AP

[†] retrograde only AP

[‡] true atrioventricular AP with anterograde conduction unless otherwise noted

HCM = hypertrophic cardiomyopathy, EPS = electrophysiology study, SVT = supraventricular tachycardia, AF = atrial fibrillation, FVF = fasciculoventricular fiber, AP = accessory pathway

Table 4.

Characteristics of patients with ventricular preexcitation exclusively due to FVF conduction versus patients with at least one true AP with anterograde conduction.

	FVF (n = 8)	**True anterograde AP (n= 14)**	**p-value**
Age at preexcitation diagnosis (years)	15.0 (1.7–17.2)	11.6 (0.5–16.7)	0.172
Age at HCM diagnosis (years)	14.1 (0.3–19.3)	12.5 (0.3–16.7)	0.633
Male sex	4 (50)	8 (57)	1.000
PR interval (ms)	103 (80–125)	95 (65–145)	0.560
QRS duration (ms)	115 (96–125)	113 (95–192)	0.946
DWA 40 ms after delta onset (mm)	4.1 (3.3–15.3)	4.9 (1.1–22.5)	0.838
Average QRS amplitude (mm)	29.9 (14.4–47.0)	31.4 (10.6–79.9)	0.811
V6 R-wave amplitude (mm)	30.6 (12.8–39.3)	28.1 (11.4–65.0)	0.918
Normalized V6 R-wave amplitude	1.2 (0.5–1.6)	1.1 (0.4–2.5)	0.891
V1 S-wave amplitude (mm)	22.6 (5.9–41.8)	27.0 (0.0–75.3)	0.891
Normalized V1 S-wave amplitude	1.1 (0.2–2.0)	1.1 (0.0–3.1)	0.946
Storage disease	3 (38)	5 (26)	1.000
Metabolic disease	1 (13)	2 (14)	1.000
Syndromic	0 (0)	2 (14)	0.491
Isolated HCM	4 (50)	5 (38)	ref
Supraventricular tachycardia	0 (0)	5 (36)	0.115
Atrial fibrillation	3 (38)	3 (21)	0.624

data expressed as n (%) or median (range)

HCM = hypertrophic cardiomyopathy, DWA = delta wave amplitude, FVF = fasciculoventricular fiber, AP = accessory pathway