Two-to-one Purkinje-to-myocardium activation during ventricular fibrillation associated with hypertrophic cardiomyopathy

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Introduction

The role of the Purkinje network in the cardiac vulnerability to ventricular fibrillation (VF) has been extensively studied in experimental conditions. The Purkinje system represents a tiny fraction of the myocardial mass, but its pathogenic role is disproportionally high. It may contribute to VF by triggering ectopy initiating spontaneous VF or by reentrant mechanisms maintaining VF, both scenarios having been demonstrated in experimental or clinical studies.[1,2] However, significant limitations are present in the clinical capabilities to demonstrate the contribution of the Purkinje system in arrhythmias because of the need for multiple invasive recordings. This case report presents a novel arrhythmogenic manifestation/phenotype of the Purkinje system exhibiting a 2-to-1 response to ventricular myocardium in a young patient with hypertrophic cardiomyopathy (HCM).

Case report

A 4-year-old girl was diagnosed with nonobstructive HCM after a heart murmur check-up in March 2016. On initial evaluation, the maximum interventricular septum thickness was 11 mm on transthoracic echocardiography and 15 mm on cardiac magnetic resonance without late gadolinium enhancement. No ventricular arrhythmias were recorded on 24-hour Holter electrocardiogram (ECG) and during exercise testing. A double mutation in the *MYBPC3* gene was identified, with 1 variant inherited from each parent, but no other family member had HCM.

In December 2021, at the age of 9 years, she presented with sudden cardiac arrest during exercise. The initial rhythm was VF and she was successfully resuscitated without any neurological sequelae (no flow <1 minute, low flow 20 minutes). After several recurrences of VF recorded in the intensive care unit, amiodarone was introduced in combination with beta-blockers (nadolol). Maximum wall thickness was 20 mm on magnetic resonance imaging with diffuse fibrosis of the septum and anterolateral wall of the left ventricle (Figure 1A). Given the patient's size (132 cm, 30 kg) and the need for pacing (sinus bradycardia associated with antiarrhythmic pharmacological therapy), a dual-chamber epicardial implantable cardioverter-defibrillator (ICD) was implanted for secondary prevention.

In June 2022, after a moderate exertion, she presented with syncope requiring cardiopulmonary resuscitation by her parents, with spontaneous recovery (without ICD intervention) before the arrival of emergency medical services. ICD interrogation revealed an irregular slow

KEY TEACHING POINTS

- In hypertrophic cardiomyopathy, the Purkinje system may play a driver role in ventricular fibrillation.
- A slow ventricular tachycardia may be caused by 2:1 activation ratio between the peripheral Purkinje system and the ventricular myocardium.
- The Purkinje system appears as a potential target for catheter ablation of ventricular fibrillation in hypertrophic cardiomyopathy.

KEYWORDS Hypertrophic cardiomyopathy; Ventricular fibrillation; Catheter ablation; Purkinje system; Sudden death; Ventricular arrhythmia
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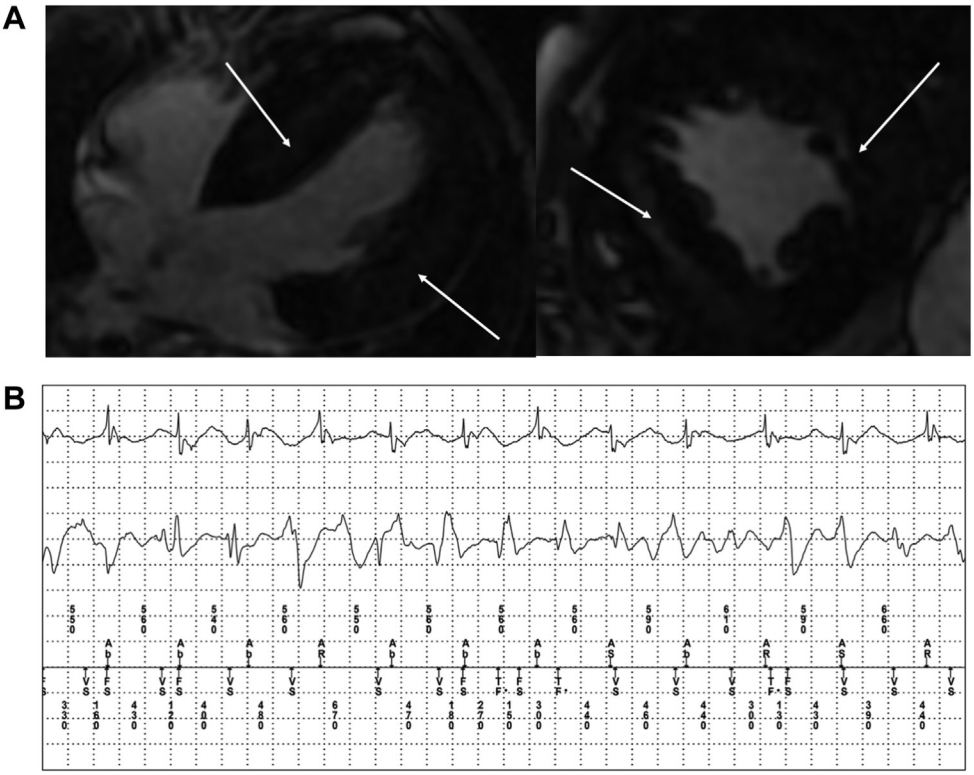

Figure 1 Cardiac magnetic resonance imaging and slow polymorphic ventricular arrhythmia. **A:** Four-chamber (left) and short-axis (right) views of cardiac magnetic resonance imaging showing diffuse fibrosis of the septum and anterolateral wall of the left ventricle. Fibrosis areas are shown by the arrows. **B:** The recordings from implantable cardioverter-defibrillator show atrial (upper) and ventricular electrograms (lower). The annotations at the bottom show a slow polymorphic irregular ventricular arrhythmia (mean cycle length 387 ms, 155 beats/min), sometimes undersensed, and slower than the therapy zones (VT zone 182 beats/min, FV zone 231 beats/min). VF = ventricular fibrillation; VT = ventricular tachycardia.

polymorphic ventricular arrhythmia labeled as nonsustained ventricular arrhythmia (Figure 1B). The ICD parameters were modified with lower therapy zones and shorter detection durations, but VF could not be induced by ICD burst pacing, so we could not evaluate whether these new ICD programming parameters would effectively treat a new episode of slow polymorphic ventricular arrhythmia.

The electrophysiological study was performed after informed consent of the patient and her parents. The procedure was performed under general anesthesia with 2 right venous femoral accesses (7-8F). After a transseptal puncture, a Vizigo guiding sheath (Biosense Webster Inc, Irvine, CA, USA) was used and a voltage map of the left ventricle was performed during sinus rhythm using a PentaRay catheter (2563 sites mapped, Figure 2). Purkinje potentials were specifically tagged for anatomical location (Figure 2, in yellow). No spontaneous premature ventricular complexes were observed. Slow polymorphic ventricular arrhythmias, similar to the arrhythmia recorded by the ICD during cardiac arrest, were easily and reproducibly induced by slow ventricular bursts (400–450 ms) from the right ventricle. On the PentaRay catheter placed on the posterior fascicule of the Purkinje network, Purkinje activation was clearly faster than the adjacent ventricular myocardium, with mean cycle lengths of 328 ± 53 ms vs 537±82 ms, respectively, during the first 5 seconds of the first induced VF. The majority of QRS complexes showed a 2:1 ratio between Purkinje potentials and ventricular electrograms, as well as QRS complexes on surface ECG (Figure 3A). Long conduction times were also observed between ventricular electrograms in contiguous bipoles, suggesting severe alterations in myocardial structure and connections (Figure 3A). Two episodes of spontaneous VF also occurred after cardioversion of induced VFs, and in both cases, Purkinje activation preceded ventricular activation (Figure 3B) with a faster rate.

With the new ICD programming/parameters (notably a ventricular tachycardia [VT] zone set at 90 beats per minute [bpm]), the majority of induced ventricular arrhythmias were correctly sensed and treated; however, some induced ventricular arrhythmias were too slow and irregular (80–100 bpm) to be detected and they were associated with hemodynamic collapse. Anatomical ablation of the posterior Purkinje fascicle was attempted in the left ventricle using an irrigated-tip radiofrequency catheter (ThermoCool SmartTouch; Biosense Webster); 35 applications were delivered at 30 watts for a total of 985 seconds of energy delivery (Figure 2). Unfortunately, slow and irregular polymorphic ventricular arrhythmias were still inducible at the end of the procedure (cycle length range between 400 and 750 ms). We did not target other Purkinje areas or myocardial scar to avoid an overly long procedure with potential complications and because the indication for heart transplantation

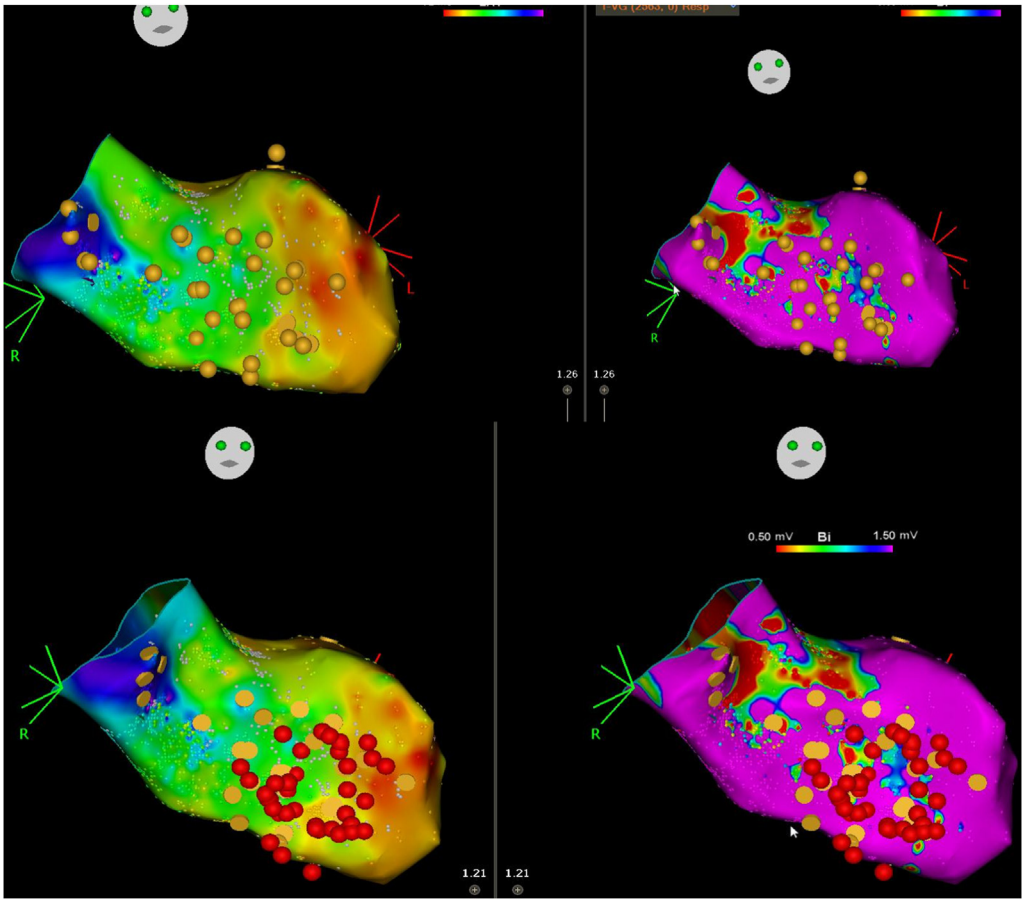

Figure 2 Activation and voltage maps of the left ventricle in anteroposterior views during sinus rhythm. Purkinje potentials are tagged in yellow. Radiofrequency applications are tagged with red dots.

was under discussion. Given the potential risk of recurrence of untreated ventricular arrhythmias, and after further discussion with the patient's family, the patient was placed on the national transplant waiting list for arrhythmic motive. She underwent heart transplantation 2 weeks later.

Discussion

We report here the case of a 9-year-old girl with HCM and VF or polymorphic VT, in whom left ventricular mapping demonstrated an intermittent 2:1 activation ratio between the peripheral Purkinje system and the local ventricular myocardium.

The patient initially presented with episodes of VF leading to combined amiodarone and beta-blocker therapy, and was referred for arrhythmia recurrences in the form of slow polymorphic VT undersensed by ICD and associated with cardiac arrest/hemodynamic collapse. The clinical ventricular arrhythmia was reproducible during electrophysiological study, with mapping showing a part of left posterior fascicle driving the arrhythmia. To our knowledge, such a clinical observation showing a 2:1 ratio between Purkinje and local ventricular activations has not been previously reported. This finding was confirmed by the reproducibility of induction in our patient and the consistency of Purkinje potentials preceding changes in ventricular activation. The mechanism cannot be specified but could be reentry rather than triggered activity because of the consistency and prolonged duration of the phenomenon. The polymorphic QRS morphology was suggestive of a progressive shift in trajectory or ventricular exit from the Purkinje network, which has been demonstrated in computer modeling studies.[3,4]

The Purkinje system is increasingly recognized as a common cause of VF associated with various forms of structural heart disease and channelopathies.[2] Its role as a trigger has been demonstrated particularly in the context of ischemic heart disease and in idiopathic VF, but also in a variety of other types of cardiac disease, including HCM.[5–7] Its role as a maintaining driver has been the subject of controversy, because experimentally induced VF could evolve either with or without Purkinje fiber involvement. These apparent discrepancies may be related to distinct experimental and structural conditions and the timing of VF recordings. Most recent experimental studies indicate that the Purkinje system is involved at a late stage (>2 minutes) of ongoing VF.[8–10] In humans, the Purkinje system appears to be involved at the initial stage of VF in some patients with dilated cardiomyopathy or HCM, and then the myocardial excitation evolves to a state in which Purkinje fibers are not required to maintain the arrhythmia because complex

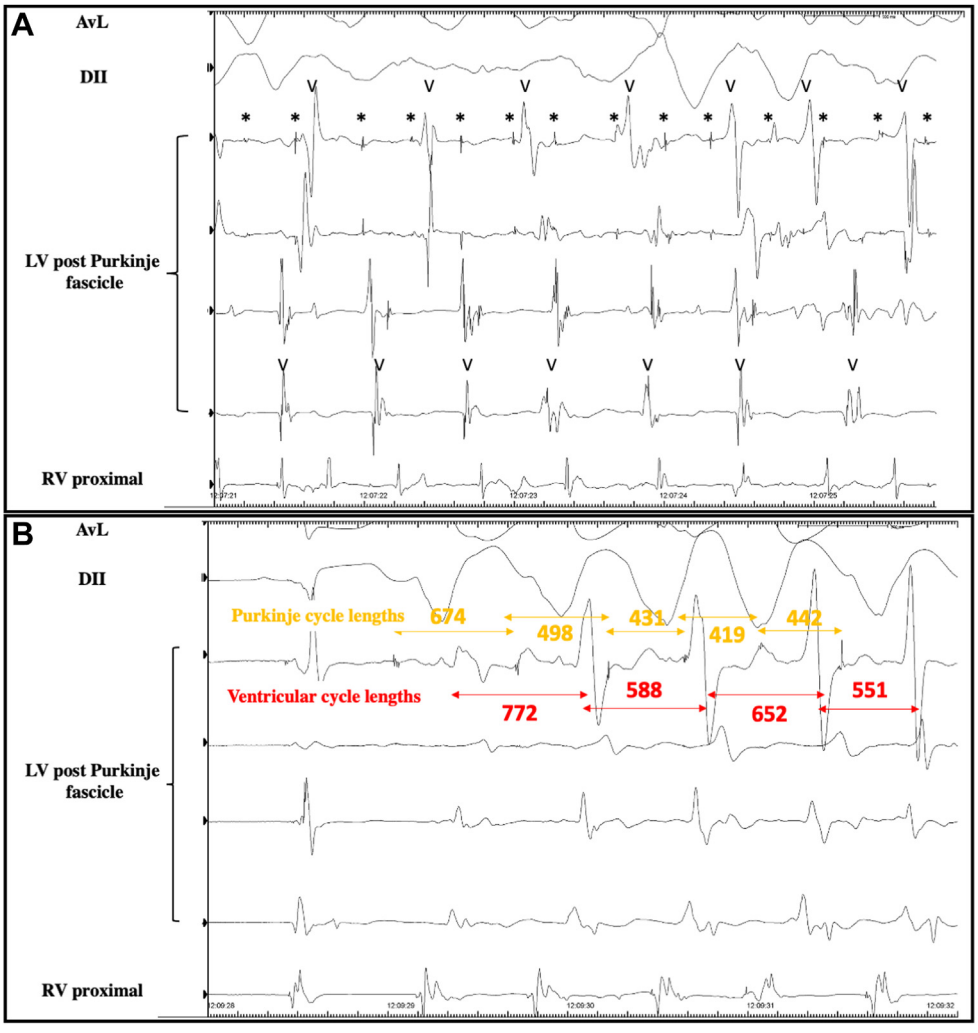

Figure 3 Purkinje activation during ventricular fibrillation initiation. ECG leads aVL and DII are shown at the top. Intracardiac electrograms show recordings from the PentaRay electrodes (Biosense Webster) in the Purkinje network area. **A:** Ventricular fibrillation initiation after ventricular stimulation. Purkinje activation (*) has a mean cycle length of 328 ± 53 ms as compared to 537 ± 82 ms in the local ventricular (V) complexes. Significant delays can be observed in local ventricular activations (V) in this area with electrograms occurring out of phase (sometimes half cycle activation difference between the different bipoles), suggestive of severe alterations in the myocardial connections. **B:** Spontaneous ventricular fibrillation after cardioversion of induced ventricular fibrillation. The ventricular fibrillation is initiated by a trigger from the Purkinje network (Purkinje signal preceding ventricular electrogram at the beginning of the arrhythmia). The changes in Purkinje activation precede changes in ventricular activation, and shorter cycle lengths are measured in Purkinje activation relative to myocardial activation in the PentaRay (Purkinje in yellow, ventricle in red). Of note, the third V-V interval is longer than the second despite a shorter Purkinje-to-Purkinje interval related to a 2:1 Purkinje-to-ventricle conduction. LV = left ventricle; RV = right ventricle.

reentrant patterns have developed in the ventricular myocardium. At later stages, human VF may be maintained again by Purkinje activity.[6,8,10]

In HCM, the largest catheter ablation series published to date included 8 patients.[11] Purkinje activity was observed in electrically induced VF during a median of 14 initial cycles (ie, approximately 3 seconds of VF), with a 1:1 ventricular response. In our patient, several factors may have led to severe alterations in Purkinje and myocardial connectivity (Purkinje-muscle junctions), resulting in a 2:1 conduction. These include increased muscle mass and disarray typical of HCM fibers, the presence of significant fibrosis on magnetic resonance imaging, the presence of 2 variants in *MYBPC3*, or the impact of amiodarone.[7]

In conclusion, we report a case of HCM with VF and polymorphic ventricular arrhythmias, which was associated with a 2:1 activation ratio between the peripheral Purkinje system and the ventricular myocardium. This arrhythmic phenotype is a strong manifestation of the potential driver role of the Purkinje system in VF associated with HCM.

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