Frequent His-Purkinje discharges with longitudinal dissociation in a case with multiple premature ventricular contractions suppressed by co-treatment with verapamil and quinidine

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A female patient in her fifties was referred to our institution due to frequent palpitations and several syncope attacks. A 12-lead electrocardiogram (ECG) showed multiple premature ventricular contractions (PVCs) and Holter 24-h monitoring revealed approximately 30,000 beats/day of PVCs with maximum four-beat runs of non-sustained polymorphic ventricular tachycardia (VT) (Figure 1). Figure 2 shows the characteristics of PVC. Echocardiogram revealed normal ventricular function without obvious structural abnormalities. Coronary angiography, cardiac magnetic resonance imaging, cardiac 18F-fluorodeoxyglucose positron emission tomography, and endomyocardial biopsy also revealed no specific findings. Oral administration of bisoprolol, mexiletine, and amiodarone failed to suppress multiple PVCs and symptom. Therefore, catheter ablation was attempted.

In electrophysiologic study, multielectrode catheters were placed in the right atrium, His bundle region, and proximal left bundle (LB) region (Figure 3). PVCs with multiple QRS morphologies were mainly right bundle branch block type with various axes and various coupling intervals. His and proximal LB electrogram recordings revealed that His or LB potential always preceded multiple PVCs (Figure 4). Some LB discharges showed exit block inside the proximal LB after which a following His potential and PVC did not appear. His bundle discharge was followed by LB potential and a subsequent PVC after which a following His potential and PVC did not appear. His bundle pacing restores electrical synchronization in LB branch. Several studies have reported longitudinal dissociation in the His bundle.1 This concept is further supported by the recent finding that His bundle pacing restores electrical synchronization in LB branch block.2

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Oral administration of amiodarone, mexiletine, verapamil, and quinidine alone were all ineffective; however, co-treatment with verapamil 240 mg/day and quinidine 300 mg/day could suppress PVCs and eliminated symptoms. Holter monitoring revealed only 260 beats/day of single PVCs under oral administration of verapamil and quinidine. Because of polymorphic VT and several syncope attacks, an implantable cardioverter defibrillator (ICD) was placed, and ICD discharge was absent during a follow-up period of 12 months under verapamil and quinidine administration.

Next-generation sequencing was performed for 56 genes associated with inherited primary arrhythmia syndromes and cardiomyopathy. This revealed a rare variant in LMNA in this patient. Finally, using Sanger sequencing, we then confirmed a novel LMNA nonsense mutation, c.1789A>T, K597Ter.

Several studies have reported longitudinal dissociation in the His bundle.1 This concept is further supported by the recent finding that His bundle pacing restores electrical synchronization in LB branch block.2 In this case, some ectopic LB discharges showed exit block...
inside the proximal LB and a following His potential and QRS complex were not demonstrated. This appears to implicate pathological His-Purkinje tissue with longitudinal dissociation as the origin of the multiple PVCs in this case. Some ectopic LB potentials showed prolongation and fractionation, which also indicate abnormal His-Purkinje tissue with delayed conduction. The precise mechanism is unclear; however, longitudinal dissociation in the His bundle with pathological His-Purkinje tissue-related multifocal discharges and conduction delay may be associated with multiple PVCs.

Frequent multiple PVCs and polymorphic VT arising from hyperexcitability of the fascicular-Purkinje system associated with SCN5A variants which respond to quinidine have been reported as multifocal ectopic Purkinje-related premature contractions (MEPPC). The manifestations of ventricular arrhythmia in our case are quite similar to those in MEPPC, although SCN5A variant was negative. The His-Purkinje network has been reported to cause PVCs and VT through abnormal automaticity and/or triggered activity with delayed post-depolarization due to calcium overload in Purkinje tissues. It is possible that verapamil administration affects this abnormal automaticity and triggered activity. Low bioavailability might be the major reason why oral verapamil alone was ineffective. Quinidine has been also reported to be effective in patients with MEPPC and short-coupled ventricular fibrillation originating from the His-Purkinje system. Quinidine is known as a strong blocker of transient outward potassium current (Ito), and the fascicular-Purkinje hyperexcitability with prominent Ito channel expression in fascicular-Purkinje fibers is reported to be suppressed by quinidine. However, the precise mechanism by which quinidine suppresses Purkinje-related PVCs and polymorphic VT is still unclear. Moreover, the appropriate dose of quinidine is a critical issue and should be explored in future research. In this case, a daily dose of 300 mg of quinidine was low; however, we chose not to increase it because gastrointestinal symptoms occurred at a dose of 400 mg. As we recently reported, adding verapamil to low-dose quinidine in patients with Purkinje-related PVCs and polymorphic VT is a possible therapeutic approach when the adverse effects of quinidine are a concern. We should also note that verapamil can increase plasma quinidine levels by inhibiting CYP3A4. Great care should be taken regarding the interaction of verapamil and quinidine and their inhibitory effects on the conduction system.

Cardiac laminopathy associated with LMNA mutation generally demonstrates a wide spectrum of clinical phenotypes, including...
FIGURE 2  Analysis of multiple premature ventricular contractions (PVCs). (A) Relationship between QRS axis and coupling interval (CI) of PVC. All PVCs with left axis deviation (LAD) showed CI > 400 ms and all PVCs with right axis deviation (RAD) showed CI < 400 ms. (B) Relationship between QRS duration and CI of PVC. A weak inverse relationship was observed.

FIGURE 3  Fluoroscopic right anterior oblique (RAO) and left anterior oblique (LAO) views of the position of the catheters at the right atrium (RA), His bundle region (HBE), and proximal left bundle region (LBos)
FIGURE 4 Intracardiac recording (upper panel) and schematic representation of possible mechanism of the His-Purkinje discharge and premature ventricular contractions (PVCs) (lower panel). (A) The first His-Purkinje discharge (☆) originating from the LBos was blocked and was not followed by a PVC and His potential. The second His-Purkinje discharge (☆) originating from LBos was followed by a PVC with right axis deviation and His potential. The third His-Purkinje discharge (•) originating from the LBos showed fragmentation. This discharge was followed by an His potential but a following PVC did not appear. (B) His-Purkinje discharge (☆) originating from the LBos was followed by a PVC with left axis deviation. (C) His-Purkinje discharge (☆) originating from the His bundle was followed by a PVC with normal axis deviation.
mechanical and electrical alterations of cardiomyocytes. Dilated cardiomyopathy, conduction system disease, and atrial/ventricular tachyarrhythmias are major manifestations in cardiac laminopathy. The \textit{LMNA} variant in this case (c.1789A>T, K597Ter) is located at the end of the tail of the lamin A protein, which is far from the pathogenic \textit{LMNA} variants reported in the Japanese laminopathy, and might be less severe than the typical cardiac laminopathy.\(^5\) Although this variant is classified as pathogenic by Varsome (https://varsome.com/) using the ACMG classification, it is still unclear whether this variant is actually associated with multiple PVCs and polymorphic VT. However, in general, non-missense mutations in the \textit{LMNA} are associated with fatal arrhythmias leading to sudden cardiac death. Accordingly, in this case, though the PVCs and polymorphic VT were almost entirely suppressed by oral anti-arrhythmic drugs, we recommended prophylactic ICD implantation.

\textbf{CONFLICT OF INTEREST}

Dr. Satoshi Nagase is affiliated with a department endowed by Japan Medtronic Inc. The others have nothing to disclose.

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