Aborted Sudden Cardiac Death in a Pediatric Patient with Hypertrophic Cardiomyopathy and a Novel MYH7 Mutation

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A 14-year-old boy with hypertrophic cardiomyopathy experienced ventricular fibrillation while running in his schoolyard. He was resuscitated and admitted to our hospital. Delayed enhancement cardiac magnetic resonance imaging revealed asymmetric ventricular septal hypertrophy and delayed enhancement of the ventricular septum. Monomorphic ventricular tachycardia (VT) was induced by double ventricular extrastimuli. During electroanatomical mapping, a low voltage area was found in the right ventricle, but none was found in the left ventricular endocardium. Pace-mapping from the anterior right ventricular outflow tract, i.e., the low voltage area, revealed delayed potentials, and pacing at this site generated an 85% morphological match to the induced VT. Endomyocardial biopsy of the right ventricular septum revealed differences in myocyte size and myocardial disarray, along with moderate interstitial fibrosis. A cardioverter defibrillator (ICD) was implanted. Genetic testing identified a novel heterozygous missense mutation in the cardiac myosin heavy chain gene.

Key words: hypertrophic cardiomyopathy, sudden cardiac death, gene mutation

Introduction
Ventricular noncompaction cardiomyopathy (NCCM) often leads to heart failure, lethal arrhythmia, or thromboembolism, and therefore the prognosis is poor.1-3 With improvements in the diagnostic accuracy of cardiac echocardiography, an increasing number of adult cases of NCCM have been reported. NCCM involves mainly the left ventricle (LV). We encountered a rare case of hypertrophic cardiomyopathy (HCM) associated with right ventricular (RV) NCCM and a novel heterozygous missense mutation in the cardiac myosin heavy chain gene.

Case Report
The patient was a 14-year-old boy who suffered cardiac arrest while running in his schoolyard. A teacher immediately grabbed an AED, and the boy was defibrillated and then transported to Nihon University Hospital. HCM had been diagnosed at another hospital, and he was being treated with aspirin, furosemide, and enarapril. There was no family history of cardiomyopathy or sudden cardiac death. Electrocardiography (ECG) performed on arrival showed sinus rhythm at a heart rate of 86 bpm, marked LV hypertrophy, and left atrial overload (Fig. 1). Chest X-ray revealed enlargement of the heart and moderate lung congestion (Fig. 2). Transthoracic echocardiography yielded an LV end-diastolic dimension of 62.4 mm, LV end-systolic dimension of 46.1 mm, and LV ejection fraction of 53.3%. Asymmetric hypertrophy of the interventricular septum (IVS) was seen from the mid-portion to the apex, with a maximum thickness of 19.6 mm at the apex. Furthermore, prominent myocardial trabeculations and deep intertrabecular recesses were seen in the apical portion of the RV, and color Doppler imaging revealed blood flow within the intertrabecular recesses (Fig. 3a, 3b). Delayed enhancement cardiac magnetic resonance imaging also showed asymmetric hypertrophy of the IVS. The maximum measured thickness upon late gadolinium enhancement (LGE) of the hypertrophied IVS was 20 mm (Fig. 4). Monomorphic ventricular tachycardia (VT) at a cycle length of 230 ms with a left bundle branch block morphology and inferior axis was induced by means of double programmed premature ventricular stimuli at 400/250/240 msec delivered from the RV apex (Fig. 5a). Because the patient was suffering hemodynamic deterioration, DC cardioversion was performed. RV and LV endocardial electroanatomical mapping performed with a CARTO 3 system (Biosense-Webster, Inc., Diamond Bar, CA, USA) revealed normal LV voltage but low voltage at the anterior outflow tract and lateral RV (Fig. 6). A bipolar electrogram recorded from the anterior wall of the RV outflow tract showed delayed potentials...
Fig. 1 Twelve-lead electrocardiogram obtained on admission. Heart rate: 86 bpm. Marked left ventricular hypertrophy and left atrial overload are evidenced.

Fig. 2 Chest X-ray on admission. The cardiothoracic ratio is 60%, and mild pulmonary congestion is seen.

Transthoracic echocardiogram

Fig. 3 Echocardiographic images. Hypertrophy of the interventricular septum and hypertrabeculation of the right ventricular apex are evident in the transthoracic echocardiogram (3a: left upper panel, arrows), and deep intertrabecular recesses perfused with blood from the ventricular cavity are also seen (3b: right upper panel, arrows). 3c: Hypertrabeculation of the right ventricular apex is evident on the intracardiac echocardiogram (bottom panel, arrows).

Intracardiac echocardiogram

Fig. 4 Delayed enhancement cardiac magnetic resonance images. Note the late gadolinium enhancement in the hypertrophied interventricular septum (right panel, arrows).
Fig. 5
Twelve-lead electrocardiogram of the induced ventricular tachycardia (a: *left panel*) and bipolar electrogram recorded from the anterior wall of the RV outflow tract (b: *right panel*). Ventricular tachycardia induced by the programmed ventricular stimulation shows left bundle branch block and an inferior axis at a cycle length of 230 ms. The Intracardiac electrocardiogram recorded from the low voltage site shows isolated delayed potentials (*arrows*).

Fig. 6
Electroanatomical maps of the right ventricle (*upper panels*) and left ventricle (*lower panel*). There is no low voltage zone in the left ventricular endocardium, but low voltage zones are located at the anterior outflow tract and lateral right ventricle.

RV septum biopsy sections

(A) H-E staining
(B) PTAH staining

Fig. 7 RV septum biopsy sections. Endocardial biopsy of the RV septum revealed myocardial cells of various sizes, some that were hypertrophied, disarray (hematoxylin-eosin staining, *left panel*), and some collagenous fibers and adipose tissue (PTAH staining, *right panel*: collagenous tissue: red, myocardial tissue: blue).
(Fig. 5b). Pacemapping during sinus rhythm at the site of delayed potentials yielded an 85% morphological match to the induced VT.

Because of the episode of sudden cardiac arrest, the presence of structural heart disease, and the hemodynamic instability upon induced VT, catheter ablation was not performed. Instead the patient was given an implantable cardioverter defibrillator (ICD). Intracardiac echocardiography demonstrated hypertrabeculation of the RV apex (Fig. 3c). Endocardial biopsy specimens from the RV septum showed myocardial cells of various sizes, some appearing hypertrophied, disarray, and some collagenous fibers and adipose tissue deposition in the interstitial tissue (Fig. 7). Genetic testing (approved by the Human Genome/Gene Analysis Ethics Committee of Nihon University, approval #103-0, and the Clinical Research Institutional Review Board of Nihon University Itabashi Hospital, approval #RK-101112-10) identified a novel cardiac myosin heavy chain (MYH7) mutation (Met 593 lle; ATG ATA). We observed marked LGE at the IVS in our patient. LGE (OR: 2.52; 95% CI: 1.44–4.4, p = 0.001). All-cause mortality and cardiac death rates are also significantly increased in patients with LGE. We observed marked LGE at the IVS in our patient. NCCM is a rare and unique congenital disorder that is designated an unclassified cardiomyopathy. It is characterized by prominent trabeculations and deep intertrabecular recesses that extend to the ventricular wall and are without any communication with the coronary circulation. Echocardiography is commonly used to diagnose NCCM. The echocardiographic criteria for a diagnosis of NCCM are four-fold: (1) absence of coexisting cardiac anomalies; (2) myocardium consisting of two layers, a thick, non-compacted endocardial layer showing a trabecular meshwork with deep endocardial spaces and a much thinner, compacted epicardial layer, with a maximum ratio of ≥2 for the former measured against the latter at end-systole. (3) predominant localization of the abnormality at the left ventricular apex, lateral and inferior wall, and (4) color Doppler-echocardiographic evidence that deep intertrabecular recesses are perfused with blood from the ventricular cavity. Isolated RV NCCMs have also been reported. 

Our case was characterized by hypertrabeculation within the RV apex.

RV NCCM is difficult to diagnose because differentiation between normal variants of the usually highly trabeculated RV is at best challenging and at worst impossible. NCCM sometimes occurs in association with arrhythmogenic RV cardiomyopathy/dysplasia (ARVC/D), but results of the endocardial RV biopsy were not suggestive of ARVC/D in our patient. The unique features of our case were the absence of a low voltage area in the LV and presence of a low voltage area in the RV. Delayed potentials were recorded from the low voltage area at the RVOT, and the QRS morphology during pacemapping at the site of delayed potentials was similar to the morphology of the induced VT.

Genetic testing of all exons of 67 genes linked to hereditary heart diseases identified a novel heterozygous missense mutation in the cardiac myosin heavy chain gene (Met 593 lle; ATG → ATA). MYH7 mutations have been reported in patients with HCM, dilated cardiomyopathy (DCM), and LV NCCM. Left ventricular noncompaction has also been associated with HCM. We believe association between LV/RV NCCM and HCM/DCM warrants clinical evaluation.

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References

