Efficacy of a pure Ikr blockade with nifekalant in refractory neonatal congenital junctional ectopic tachycardia and careful attention to damaging the atrioventricular conduction during the radiofrequency catheter ablation in infancy

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Introduction

Congenital junctional ectopic tachycardia (JET) is a rare idiopathic disorder that presents during infancy. It is caused by abnormal automaticity near the atrioventricular (AV) node or proximal His bundle.[1] Although the survival rate has improved because of progress in medical treatment and catheter ablation (CA), JET is still associated with a high morbidity and mortality.[2–4] There are some reports about the efficacy of medications such as amiodarone (AMD)[2–4] and CA, but no reliable treatment has been established thus far. We experienced 2 cases of congenital JET, which were refractory to various antiarrhythmic agents, including AMD, but were well controlled with a nifekalant (NIF) infusion and successively underwent CA. The effectiveness of NIF for postoperative JET has been previously reported.[5] However, to the best of our knowledge, this is the first report on the effectiveness of an NIF infusion in infants with congenital JET. Further, there have been only 5 case reports about CA during infancy for JET.[2–4,6,7] An accumulation of a case series is needed to improve the outcome of CA during infancy. Here we describe 2 infants that underwent radiofrequency CA (RFCA) and clarify the successful ablation site and their complications.

KEYWORDS Catheter ablation; Ikr blocker; Infant; Nifekalant; Neonatal congenital junctional ectopic tachycardia (Heart Rhythm Case Reports 2017;3:298–301)

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Case 1

This patient was diagnosed with a fetal tachycardia, and a definitive diagnosis of JET was made just after birth. AMD infused at a dose of 5 mg/kg over 15 minutes induced cardiogenic shock. The JET did not improve with the administration of propranolol, aprindine, sotalol, bepridil, and landiolol. However, the JET rate was controlled by an intravenous NIF infusion at a rate of 0.8 mg/kg/h. Although we tried to replace NIF with an oral administration of AMD (20 mg/kg), the JET rate could not be controlled by AMD despite an adequate blood concentration of 784 ng/mL. The patient was subsequently referred to our institution for RFCA at the age of 5 months with a body weight of 5.8 kg, and the patient had received a continuous infusion of NIF (0.8 mg/kg/h). Figure 1 shows the response to the NIF during the RFCA. The JET rate was markedly controlled by the NIF administration. The QT interval and corrected QT interval using Freidericia formula (FQTc) markedly increased from 268 ms and 384 ms to 389 ms and 483 ms, respectively, as the JET rate decreased from 178 beats per minute (bpm) to 115 bpm with the NIF administration. The diagnosis of JET was confirmed based on the following electrophysiological study findings: (1) a similar QRS morphology was observed between the tachycardia and atrial captured beat; (2) junctional beats were preceded by His bundle electrograms (HBEs) of which the His-ventricular (HV) interval was similar to the HV interval of the junctional beat captured by sinus beats; and (3) ventriculoatrial dissociation was present during the tachycardia. A radiofrequency (RF) application was delivered

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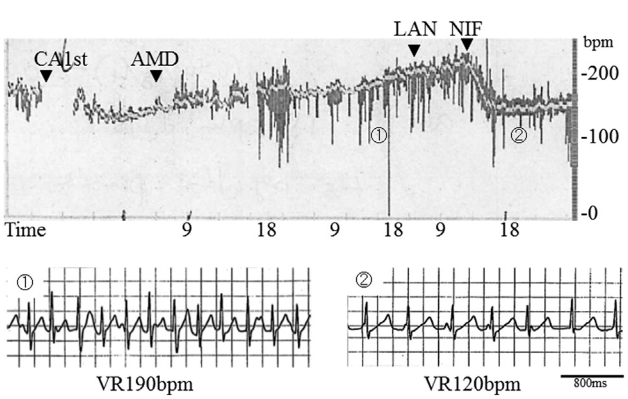
KEY TEACHING POINTS

- Nifekalant, which creates a pure Ikr blockade, could be effective in treatment of congenital junctional ectopic tachycardia.
- A catheter ablation for congenital junctional ectopic tachycardia is a treatment option even in infancy.
- It is key to prevent complications by using various strategies during the catheter ablation.

with a temperature control below 55°C and power limit of 30 W with a 5F ablation catheter (Ablaze 5F, Japan Lifeline, Tokyo, Japan). A successful ablation was achieved after 2 sessions. The JET did not convert to sinus rhythm with an RF delivery to the distal HBE and slow pathway potential (SPP) recording sites. The successful ablation was achieved at a site proximal to the previous delivery site, where the HBE was recorded by the bipolar electrodes and a relatively large atrial wave was recorded (Figure 2). Although a complete right branch block occurred during the RFCA, the AV conduction was preserved by atrial pacing at a rate faster than the junctional tachycardia rate during the applications (Supplementary Figure S1). Transient AV block occurred during atrial pacing at 150 paces per minute, so the energy delivery was immediately terminated. There has been no recurrence of the JET for 4 years.

Case 2

The patient had a fetal tachycardia, and a definitive diagnosis of congenital JET was made after birth. This patient had a clinical course similar to that of case 1 and was resistant to



CA: catheter ablation, AMD: amiodarone, LAN: landiolol, NIF: nifekalant

Figure 1 The effectiveness of nifekalant (NIF) in case 1. The trends, heart rate variability, and electrocardiography results are shown. After the first session of radiofrequency catheter ablation (CA1st), the junctional ectopic tachycardia rate gradually increased with the amiodarone (AMD) and landiolol (LAN) administration. However, it was dramatically controlled after the administration of NIF at a dose of 0.8 mg/kg/h. bpm = beats per minute; VR = ventricular rate.

various antiarrhythmic drugs (atenolol, flecainide, sotalol, bepridil, and landiolol). AMD at a dose of 5 mg/kg/d was also ineffective, and only an NIF infusion at 0.4 mg/kg/h successfully reduced the JET rate from 185 bpm to 93 bpm. The patient was referred to a different hospital for RFCA; however, the JET was not resolved, and complete atrioventricular block (CAVB) developed. The patient was subsequently referred to our hospital for RFCA at the age of 9 months with a body weight of 7.4 kg. Figure 3 shows 2:1 exit block during the JET after the NIF administration. The JET rate decreased from 220 bpm to 110 bpm. The QT interval and FQTc changed from 347 ms and 534 ms to 368 ms and 450 ms, respectively, as the heart rate decreased from 220 bpm to 110 bpm. In our hospital, an electrophysiological study confirmed the diagnosis of JET and CAVB. The JET did not improve with an RF application to the proximal and distal HBE recording (Figure 2) and SPP sites. The RF applications were delivered in the same manner as in case 1. A successful ablation was achieved at the midseptal region of the tricuspid annulus, which was lower and more proximal than the previous unsuccessful site. No HBE was recorded, and the atrial electrograms were larger than the ventricular electrograms at that site (Figure 2). An epicardial pacemaker implantation was performed for the CAVB after the RFCA. No further JET has recurred for 2 years.

Discussion

Efficacy of nifekalant

Mechanism of slowing a JET by an Ikr blocker

NIF is a pure class III antiarrhythmic drug, which mainly blocks the Ikr current.[8] The recommended therapeutic dose ranges from 0.2 to 0.4 mg/kg/h.[9] It has a dose-dependent Ikr channel–blocking effect in the ventricles, sinoatrial node, and atrioventricular node, without affecting the L-type calcium channel current, sodium current, or inward rectifier potassium current. The attenuation of the time-dependent repolarization and increase in the action potential duration resulting from Ikr inhibition may increase the cycle length of the nodal automaticity.[10–12] Interestingly, case 1 presented with a gradual decrease in the JET rate without QT prolongation. This may have been caused by the Ikr-blocking effect on the abnormal foci by suppression of the automaticity. In contrast, case 2 presented with a 2:1 exit block without a reverse rate-dependent QT response. This conduction block could have occurred between the abnormal foci and proximal His bundle because of the absence of an HBE at the time of the block.

Potential differences in the efficacy between AMD and NIF

Why was NIF more effective than AMD in reducing the JET rate despite having a similar mechanism of blocking the Ikr current? AMD is lipid soluble and a multichannel drug that includes a potassium channel–blocker effect, whereas NIF is water soluble with a rapid onset of action and a pure Ikr blocker. Therefore, the drug concentration of an Ikr blockade

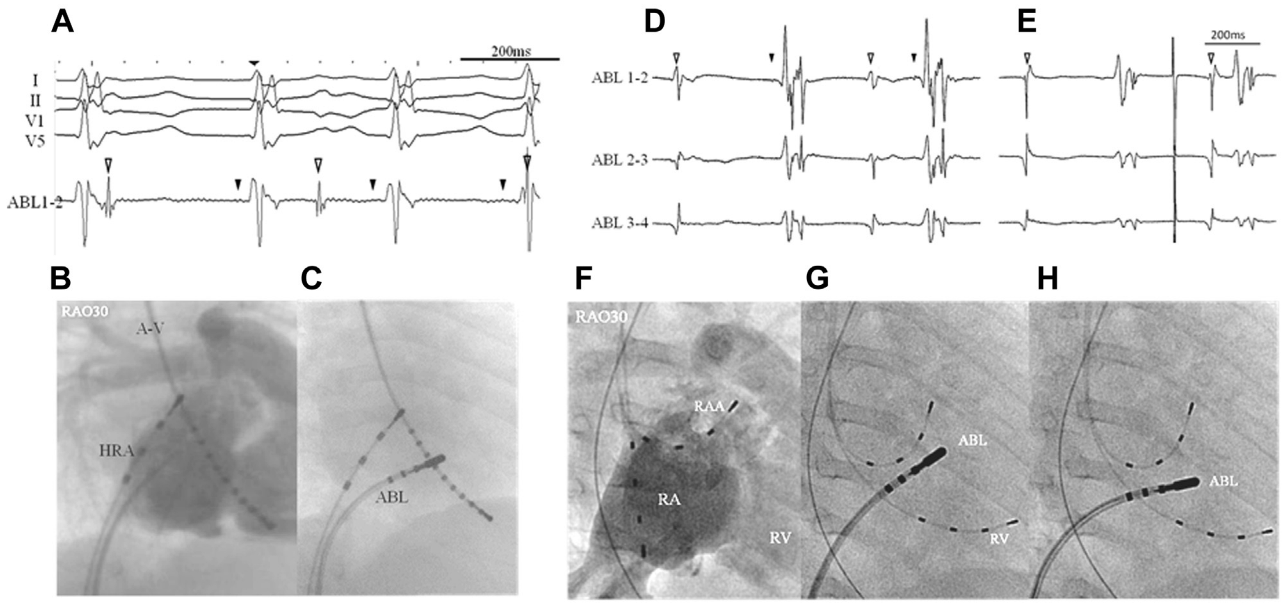


Figure 2 Results of intracardiac electrocardiography and fluoroscopy at the successful ablation sites. ABL = ablation catheter; A-V = atrio-ventricular; HRA = high right atrium; RA = right atrium; RAA = right atrial appendage; RV = right ventricle; Open triangle = atrial electrogram; filled triangle = His bundle electrogram (HBE). **A:** In case 1, an HBE was recorded from the distal bipolar electrodes, but was unclear when recorded from the unipolar electrodes. The atrial wave was half the amplitude of the ventricular wave and the HBE was small. **B:** The atrial angiography in case 1. **C:** The ablation catheter was positioned on the anterior septum of the tricuspid annulus during fluoroscopy in case 1. **D–H:** Results of intracardiac electrocardiography and fluoroscopy at the ablation site in case 2. **D, G:** The unsuccessful site where an HBE was recorded from the distal bipolar electrodes. The ablation catheter was positioned on the anterior septum of the tricuspid annulus. The ratio of the atrial and ventricular waves was 1:6, and there was a small HBE. **E, H:** Successful site where an HBE was not recorded and the atrial wave was equal to the ventricular wave when recorded from the distal bipolar electrodes; the ablation catheter was positioned on the midseptum of the tricuspid annulus, which was lower than and toward the atrial side of the prior unsuccessful site. **F:** The right atrial angiography and each catheter's position.

can be more effectively increased with NIF than with AMD. Furthermore, the action potential duration, effective refractory period, and QT interval were significantly prolonged during the NIF administration compared with those for AMD.[13]

Adverse events

Neither case had any adverse event, such as torsade de points or hypotension, during the NIF administration. A high dose of AMD (10-mg load during the first hour plus a maintenance dose of 10 mg/kg/d) is frequently associated with adverse events (90%) such as hypotension, bradycardia, and vomiting,[14] but a modest dose and titration of AMD can be safe. A dose of 5 mg/kg over 15 minutes might have been associated with hypotension in case 1. Because NIF has a positive inotropic effect,[12] it was easily administered during the hemodynamic instability of the JET.

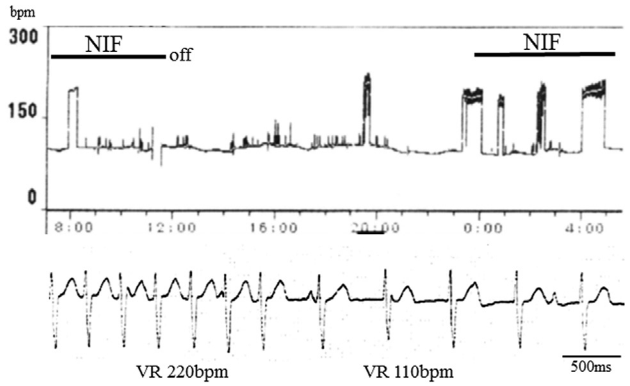


Figure 3 The effectiveness of nifekalant (NIF) in case 2. The tachycardia occurred after the discontinuation of nifekalant prior to the radiofrequency catheter ablation. After the readministration of nifekalant at a dose of 0.4 mg/kg/h, 2:1 block of the junctional ectopic tachycardia from a ventricular rate of 220 to 110 beats per minute (bpm) was observed.

CA of JET in infancy

There have been only 5 cases previously reported that have required CA during a patient's infancy.[2–4,6,7] All 5 cases were successfully ablated, but the incidence of complications was high. Among those 5 cases, 1 permanent and 2 temporary occurrences of CAVB were reported.

Successful ablation site

The successful ablation sites were the para-Hisian area and midseptal region of the tricuspid annulus, as reported in previous studies.[3,4,6] There are several ways to resolve JET, such as applying energy at the HBE recording site where the tachycardia rate can be decreased by the mechanical manipulation of the ablation catheter[15] or by the application of energy at the earliest retrograde atrial activation site when ventriculoatrial conduction is present.[16] In the first case, the JET converted to sinus rhythm by delivering RF energy at the HBE recording site, and there was no effect when RF applications were delivered at the distal HBE recording and SPP sites. In the second case, ablation at the midseptal region of the tricuspid annulus had no effect when delivered at the proximal HBE recording site.

Prevention of complications

It is beneficial to preserve the AV conduction by performing atrial pacing during the energy application[17] or delivering the application from a low-dose energy.[18] In our case, monitoring the AV conduction by atrial pacing contributed to preventing CAVB. Cryoablation would be a better choice for avoiding CAVB. However, RF ablation with 5F or 6F catheters was used in the previous reports, because a 7F cryoablation catheter is too big for small infants. We performed RFCA in the 2 infants because cryoablation was unavailable in Japan at that time. The success rates of cryoablation and RFCA are similar, but AV block is more frequent with RFCA than with cryoablation in older patients with JET.[19] Although 4- and 6-mm-tip, 7F cryoablation catheter s are currently available, they cannot be used below a certain body size. Cryoablation cannot be performed until an adequate body size is met. RF energy delivered with a 5F ablation catheter may be required for patients with body weights of less than approximately 5 kg.

Conclusions

To the best of our knowledge, this is the first report of the effectiveness of an NIF infusion to control the rate of congenital JET with 2 different mechanisms of action. Thus, in the future, a pure Ikr blocker may contribute to treating these arrhythmias. As a last resort, CA of JET in infancy is possible, however, it is associated with a very high risk of AV block. Cryoablation is preferred when the infant is large enough for a 7F cryoablation catheter to be used. Further studies are required to establish a better treatment for congenital JET.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.hrcr.2017.03.005.

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