

Left Cardiac Sympathetic Denervation in Patients with CASQ2-Associated Catecholaminergic Polymorphic Ventricular Tachycardia

Ibrahim Marai MD¹, Monther Boulos MD¹ and Asaad Khoury MD²

¹Division of Pacing and Electrophysiology and ²Department of Pediatric Cardiology, Rambam Health Care Campus, affiliated with Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel

ABSTRACT: **Background:** Left cardiac sympathetic denervation (LCSD) was reported to be effective in patients with intractable ryanodine receptor mutation-associated catecholaminergic polymorphic ventricular tachycardia (CPVT).

Objectives: To report our experience with LCSD in calsequestrin (*CASQ2*) mutation-associated CPVT.

Methods: LCSD was performed in three patients with *CASQ2* mutation-associated CPVT with symptoms and exercise-induced ventricular arrhythmia despite high dose beta-blocker.

Results: None of them experienced symptoms or exercise-induced ventricular arrhythmia after LCSD. However, all had recurrence of symptoms and/or exercise-induced ventricular arrhythmia after 6 months (6–18 months).

Conclusions: LCSD conferred short-term suppression but less than optimal long-term suppression of exercise-induced ventricular arrhythmia among *CASQ2*-associated CPVT patients.

IMAJ 2015; 17: 538–540

KEY WORDS: catecholaminergic polymorphic ventricular tachycardia (CPVT), calsequestrin (*CASQ2*), left cardiac sympathetic denervation (LCSD)

For Editorial see page 576

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a primary electrical disease characterized by exercise- and stress-induced ventricular tachycardia manifested as syncope and sudden death in young individuals with structurally normal hearts [1]. Beta-blockers are the mainstay medical treatment for CPVT patients. Implantable cardioverter defibrillator (ICD) is recommended for patients who remain symptomatic despite medical treatment. Beta-blockers do not completely suppress CPVT-associated ventricular tachycardia [2] and may not prevent recurrent ICD shocks [3]. Left cardiac sympathetic denervation (LCSD) was reported to be effective in intractable ryanodine receptor mutation-associated CPVT (CPVT1) cases

[4]. We report three patients with calsequestrin (*CASQ2*) mutation-associated CPVT (CPVT2) who underwent LCSD.

PATIENTS AND METHODS

The patients described here presented with known homozygous *CASQ2-D307H* mutation described previously [5,6]. All of them had a positive stress or isoproterenol test. The isoproterenol test is used mainly in children or patients who cannot do exercise. Isoproterenol is infused at an increasing dose of 0.05–2.0 µg/kg/min while the patient is monitored in the intensive cardiac care unit until the appearance of ventricular arrhythmia or reaching the target heart rate (about 180 beats/minute in children). Ventricular arrhythmia is reproducibly induced during stress or the isoproterenol test.

All patients received the highest tolerated propranolol dose at a range of 5–6 mg/kg/day (240–320 mg/day). LCSD was offered because of both the severity of their symptoms despite optimal medical treatment and evidence of ventricular arrhythmia during exercise test. All patients and their families gave written informed consent.

The surgery was performed in 2010 by an experienced surgeon as described previously [7]. Briefly, LCSD, also referred to as left cervicothoracic sympathectomy or high thoracic left sympathectomy, involves ablation of the lower half of the left stellate ganglion together with the thoracic ganglia T2 to T4. This technique involves a supraclavicular and retropleural approach without opening the chest. The patients were followed in the outpatient clinic every 3 months, including exercise test and ICD interrogation.

PATIENT 1

A 17 year old female with CPVT2 (diagnosed at age 8 years following a positive stress test) suffered from syncope while on high dose beta-blocker (240 mg/day propranolol). Stress test showed ventricular arrhythmia including ventricular premature beats (VPBs) and short run of non-sustained polymorphic ventricular tachycardia (PMVT). She had refused ICD and underwent LCSD, which was complicated by partial Horner

syndrome (ptosis of left eyelid). Repeated stress test 3, 6 and 12 months after surgery showed no arrhythmia and the dosage of beta-blocker was tapered down to 40 mg twice a day. Eighteen months after surgery she had syncope during a period of emotional stress. Repeated stress test after increasing the dosage of propranolol to 320 mg/day showed recurrence of arrhythmia (polymorphic VPBs). Combination therapy of beta-blocker and flecainide 100 mg twice daily suppressed the exercise-induced arrhythmia. The Horner syndrome resolved simultaneously with the recurrence of arrhythmia. Several months later, she had syncope while dancing, despite combination therapy with beta-blocker and flecainide. An ICD was implanted later on.

PATIENT 2

A 17 year old male with CPVT 2 (diagnosed at age 3 years following a positive isoproterenol test) had an ICD implanted because of syncope while on propranolol, 320 mg/day, at age 14. While on the same dosage of beta-blockers, a stress test showed frequent ventricular VPBs and non-sustained PMVT. The patient underwent LCSD without complications. Repeated stress tests 3 and 6 months after LCSD showed no arrhythmia. Six months after surgery the dosage of propranolol was reduced to 80 mg twice a day due to fatigue and weakness. However, 15 months after surgery the arrhythmia relapsed (frequent VPBs and couplets) during stress test. It was therefore decided to return to the initial dosage of 320 mg/day beta-blocker. Repeated stress test on this dosage showed only a few VPBs. There was no ICD activation during follow-up.

PATIENT 3

An 18 year old male with CPVT2 (diagnosed at age 5 years following a positive isoproterenol test) was under treatment with propranolol, 320 mg/day. At age 14, an ICD was implanted due to syncope despite propranolol treatment. Following appropriate ICD shock due to rapid PMVT and having frequent VPBs during stress test, he underwent LCSD. A stress test 3 months after LCSD with the same propranolol dose showed no arrhythmia. The dosage of propranolol was reduced to 160 mg/day 3 months post-surgery. Repeated stress test after propranolol dose reduction (6 months post-surgery) showed recurrence of arrhythmia (frequent VPBs). The dosage of propranolol was restored to the pre-LSCD level. However, he continued to have frequent VPBs during stress, which were suppressed by adding flecainide 100 mg twice a day to propranolol.

DISCUSSION

Although LSCD suppressed exercise-induced arrhythmias in these three patients in the short term, it failed to do so after 6 months. In two patients (# 1 and 3), exercise-induced arrhythmia recurred despite the high dose of propranolol. The addition of flecainide successfully suppressed the exercise-induced

arrhythmia but did not prevent syncope in patient 1. Patient 2 had recurrence of exercise-induced arrhythmia about 9 months after the beta-blocker dose was reduced.

LCSD largely prevents norepinephrine release in the heart at the myocardial level. Since LCSD is a preganglionic denervation, there is no re-innervation [4]. In addition, there is no post-denervation supersensitivity because the surgery does not completely eliminate catecholamines in the ventricles [8]. The surgery increases the threshold for ventricular fibrillation and increases ventricular refractoriness [9]. Therefore, LSCD seems to be an optimal option in cases of drug failure in CPVT patients. Limited data on the role of LCSD in the treatment of CPVT are available and are based mainly on case series of patients with CPVT1.

Wilde et al. [4] reported three cases of symptomatic CPVT1 patients despite medical treatment who became asymptomatic following LCSD during a long-term follow-up (30 months, 10 years, 20 years). Minimally invasive video-assisted thoracoscopic LCSD provided a safe and novel therapeutic option for children with intractable ventricular arrhythmias (four long QT syndrome, four CPVT, and one idiopathic ventricular arrhythmia) [10]. Three of the patients with CPVT experienced significant symptomatic improvement. However, two patients had only short-term follow-up (2 months and 1 month), and the type of CPVT of these patients is not clear.

Collura and team [11] reported their experience with LCSD using video-assisted thoracic surgery for the treatment of 20 patients (18 long QT, 2 CPVT1). The procedure was performed as a secondary prevention strategy in 11 patients (1 CPVT), which led to a marked reduction in cardiac events. Recently, Schneider and co-authors [12] reported a marked reduction in arrhythmia burden and cardiac events in five CPVT patients (three with CPVT1 and two with genotype-negative CPVT) after LSCD while on medication.

All three patients had recurrence of exercise-induced arrhythmia post-LSCD: in two of them while being treated with high dosage beta-blockers (patients 1 and 3) and in one (patient 2) after reduction of beta-blocker dosage. We do not know the reason for breakthrough (patients 1 and 3) after several months, in contrast to the long-term effect in the CPVT1 patients described by Wilde et al. [4]. CPVT2 seems to be more fatal than CPVT1 [1] and therefore may be more prone to failure. It is interesting that post-LSCD long-term breakthrough was reported among high risk long QT syndrome patients. Schwartz et al. [7] reported that LCSD was associated with a significant reduction in the incidence of aborted cardiac arrest and syncope in high risk long QT syndrome patients when compared with pre-LSCD events. However, LSCD was not entirely effective in preventing cardiac events, including sudden cardiac death during long-term follow-up. In another study, it was reported that about 50% of high risk long QT syndrome patients had experienced at least one post-LSCD

breakthrough [13]. Therefore, LCSD must not be viewed as curative or as an alternative to ICD for high risk patients.

Given the risk associated with treatment failure in CPVT patients, it seems that LCSD should be offered to CPVT2 patients only after failure of medical treatment, which should probably include both a high dose beta-blocker and flecainide. Flecainide, an approved antiarrhythmic drug, was reported to reduce exercise-induced ventricular arrhythmias in patients with CPVT, mainly RyR2-associated CPVT [14]. Recently, we reported our experience of combining flecainide and beta-blockers in CPVT2 patients and showed that flecainide may completely prevent ventricular arrhythmia during exercise and partially prevent recurrent ICD shocks in high risk CPVT2 patients [15]. Furthermore, flecainide was reported to be effective also in patients with genotype-negative CPVT [16].

LCSD is not available in many centers as it requires a qualified facility, well-trained surgeons and dedicated techniques. Therefore, the place of LCSD in the therapeutic management of CPVT patients resistant to optimal pharmacological therapy has yet to be proven [1].

LIMITATIONS

This is a single-center, uncontrolled, observational study that included only three patients with a specific mutation. Therefore, we must be cautious before drawing conclusions based on these data. In addition, we did not assure completeness of sympathetic denervation. However, it should be noted that most previous clinical studies did not assure completeness of sympathetic denervation. Moreover, the surgeries were performed by an experienced surgeon, and all patients exhibited a clinical response for several months after surgery. Thus, we could assume completeness of sympathetic denervation. We believe that placebo-controlled prospective studies should be conducted to further explore the effectiveness of LCSD in CPVT2 patients.

SUMMARY

LCSD reduced exercise-induced ventricular arrhythmias in three patients with CPVT2 for a relatively short time post-surgery but became less effective after about a year. Beta-blocker dosage should not be reduced post-LCSD in those patients. Flecainide should probably be added to beta-blockers before resorting to LCSD.

Correspondence

Dr. I. Marai

Division of Pacing and Electrophysiology, Dept. of Cardiology, Rambam Medical Center, Haifa 31096, Israel

Phone: (972-4) 854-2180

Fax: (972-4) 854-2354

email: i_marai@rambam.health.gov.il

References

- Priori SG, Wilde AA, Horie M, et al. HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes: document endorsed by HRS, EHRA, and APHRS in May 2013 and by ACCF, AHA, PACES, and AEPC in June 2013. *Heart Rhythm* 2013; 10: 1932-63.
- Leenhardt A, Lucet V, Denjoy I, et al. Catecholaminergic polymorphic ventricular tachycardia in children. A 7-year follow-up of 21 patients. *Circulation* 1995; 91: 1512-19.
- Marai I, Khoury A, Suleiman M, et al. Importance of ventricular tachycardia storms not terminated by implantable cardioverter defibrillators shocks in patients with CASQ2 associated catecholaminergic polymorphic ventricular tachycardia. *Am J Cardiol* 2012; 110: 72-6.
- Wilde AA, Bhuiyan ZA, Crotti L, et al. Left cardiac sympathetic denervation for catecholaminergic polymorphic ventricular tachycardia. *N Engl J Med* 2008; 358: 2024-9.
- Lahat H, Eldar M, Levy-Nissenbaum E, et al. Autosomal recessive catecholamine- or exercise-induced polymorphic ventricular tachycardia: clinical features and assignment of the disease gene to chromosome 1p13-21. *Circulation* 2001; 103: 2822-7.
- Lahat H, Pras E, Olender T, et al. A missense mutation in a highly conserved region of CASQ2 is associated with autosomal recessive catecholamine-induced polymorphic ventricular tachycardia in Bedouin families from Israel. *Am J Hum Genet* 2001; 69: 1378-84.
- Schwartz PJ, Priori SG, Cerrone M, et al. Left cardiac sympathetic denervation in the management of high-risk patients affected by the long-QT syndrome. *Circulation* 2004; 109: 1826-33.
- Schwartz PJ, Stone HL. Left stellectomy and denervation supersensitivity in conscious dogs. *Am J Cardiol* 1982; 49: 1185-90.
- Schwartz PJ, Verrier RL, Lown B. Effect of stellectomy and vagotomy on ventricular refractoriness in dogs. *Circ Res* 1977; 40: 536-40.
- Atallah J, Fynn-Thompson F, Cecchin F, et al. Video-assisted thoracoscopic cardiac denervation: a potential novel therapeutic option for children with intractable ventricular arrhythmias. *Ann Thorac Surg* 2008; 86: 1620-5.
- Collura CA, Johnson JN, Moir C, Ackerman MJ. Left cardiac sympathetic denervation for the treatment of long QT syndrome and catecholaminergic polymorphic ventricular tachycardia using video-assisted thoracic surgery. *Heart Rhythm* 2009; 6: 752-9.
- Schneider HE, Steinmetz M, Krause U, et al. Left cardiac sympathetic denervation for the management of life-threatening ventricular tachyarrhythmias in young patients with catecholaminergic polymorphic ventricular tachycardia and long QT syndrome. *Clin Res Cardiol* 2013; 102: 33-42.
- Bos JM, Bos KM, Johnson JN, et al. Left cardiac sympathetic denervation in long QT syndrome: analysis of therapeutic nonresponders. *Circ Arrhythm Electrophysiol* 2013; 6: 705-11.
- van der Werf C, Kannankeril PJ, Sacher F, et al. Flecainide therapy reduces exercise-induced ventricular arrhythmias in patients with catecholaminergic polymorphic ventricular tachycardia. *J Am Coll Cardiol* 2011; 57: 2244-54.
- Khoury A, Marai I, Suleiman M, et al. Flecainide therapy suppresses exercise-induced ventricular arrhythmias in patients with CASQ2-associated catecholaminergic polymorphic ventricular tachycardia. *Heart Rhythm* 2013; 10: 1671-5.
- Watanabe H, van der Werf C, Roses-Noguer F, et al. Effects of flecainide on exercise-induced ventricular arrhythmias and recurrences in genotype-negative patients with catecholaminergic polymorphic ventricular tachycardia. *Heart Rhythm* 2013; 10: 542-7.

“Be who you are and say what you feel, because those who mind don’t matter and those who matter don’t mind”

Dr. Seuss (1904-1991), pen name for American writer and cartoonist Theodore Geisel, most widely known for his children’s books (e.g., *Green Eggs and Ham*, *The Cat in the Hat*, *The Lorax*, *One Fish Two Fish Red Fish Blue Fish*), characterized by imaginative characters, rhyme, and frequent use of anapestic meter