

BRIEF REPORT

Left Cardiac Sympathetic Denervation for Catecholaminergic Polymorphic Ventricular Tachycardia

Arthur A.M. Wilde, M.D., Ph.D., Zahurul A. Bhuiyan, M.D., Ph.D., Lia Crotti, M.D., Ph.D., Mario Facchini, M.D., Gaetano M. De Ferrari, M.D., Thomas Paul, M.D., Chiara Ferrandi, B.Sc., Dave R. Koolbergen, M.D., Attilio Odero, M.D., and Peter J. Schwartz, M.D.

SUMMARY

Catecholaminergic polymorphic ventricular tachycardia is a potentially lethal disease characterized by adrenergically mediated ventricular arrhythmias manifested especially in children and teenagers. Beta-blockers are the cornerstone of therapy, but some patients do not have a complete response to this therapy and receive an implantable cardioverter–defibrillator (ICD). Given the nature of catecholaminergic polymorphic ventricular tachycardia, ICD shocks may trigger new arrhythmias, leading to the administration of multiple shocks. We describe the long-term efficacy of surgical left cardiac sympathetic denervation in three young adults with catecholaminergic polymorphic ventricular tachycardia, all of whom had symptoms before the procedure and were symptom-free afterward.

From the University of Amsterdam, Amsterdam (A.A.M.W., Z.A.B., D.R.K.); the University of Pavia (L.C., A.O., P.J.S.) and the Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Fondazione Policlinico S. Matteo (L.C., G.M.D.F., C.F., A.O., P.J.S.) — both in Pavia, Italy; the IRCCS Istituto Auxologico, Milan (M.F., P.J.S.); University Children's Hospital, Georg-August-University, Göttingen, Germany (T.P.); and the University of Cape Town, Cape Town, South Africa (P.J.S.). Address reprint requests to Dr. Wilde at the Department of Cardiology, Academic Medical Center, Meibergdreef 9, B2-238, Amsterdam 1105 AZ, the Netherlands, or at a.a.wilde@amc.uva.nl.

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CATECHOLAMINERGIC POLYMORPHIC VENTRICULAR TACHYCARDIA, FIRST recognized in the 1970s,^{1,2} is a genetic disorder caused by mutations in genes involved in the calcium homeostasis of cardiac cells. After initial observations linked catecholaminergic polymorphic ventricular tachycardia to chromosome 1,³ two disease-causing genes were identified: the ryanodine receptor 2 gene (*RYR2*)^{4,5} and the cardiac calsequestrin 2 gene (*CASQ2*).^{6,7} Catecholaminergic polymorphic ventricular tachycardia is characterized by life-threatening ventricular arrhythmias, usually polymorphic ventricular tachycardia or ventricular fibrillation, especially under conditions of increased sympathetic activity, including physical exercise and emotional stress.^{8,9} It is often manifested at a young age, and the first event may be lethal.

The management of catecholaminergic polymorphic ventricular tachycardia is difficult. Most patients are protected by taking β -adrenergic blocking agents, but many continue to have symptoms, documented exercise-induced ventricular tachycardias, or both. For these patients, it is currently believed that the only additional therapy available is the ICD.¹⁰ However, since even modest exercise initiates fast ventricular tachycardias that trigger ICD shocks, the quality of life of these patients is often diminished. In addition, ICDs do not protect all patients,¹¹ and physicians sometimes resort to the extreme measure of cardiac transplantation.¹²

We present evidence that left cardiac sympathetic denervation, an antifibrillatory intervention that largely prevents norepinephrine release in the heart,^{13,14} may reduce these adrenergically mediated life-threatening arrhythmias. We also propose that left cardiac sympathetic denervation may be an effective treatment for young patients with catecholaminergic polymorphic ventricular tachycardia who are not fully protected by beta-blockers.

CLINICAL CASES

Patient 1 carried a de novo RYR2 amino acid missense mutation, Phe4511→Leu, which was absent in his relatives and in 117 controls. Since the age of 10 years, he had had frequent syncope, and at 17 years of age, an episode of polymorphic ventricular tachycardia was documented during exercise stress testing on a bicycle at a workload of 50 W. Despite the use of propranolol (240 mg), he had a cardiac arrest due to ventricular fibrillation after an emotional encounter. In 1988, at 18 years of age, he underwent left cardiac sympathetic denervation. During the subsequent 20 years, he remained asymptomatic, although nonsustained ventricular tachycardia could still be induced by exercise, but only at a workload of 120 W or more.

Patient 2 carried the RYR2 mutation Glu4076→Lys, which was absent in 100 controls and segregated strongly within the patient's family. The patient's family was characterized by adrenergically dependent symptoms and premature sudden death under typical circumstances. She became symptomatic at 10 years of age and remained symptomatic despite full-dose beta-blockade (2.5 mg of metoprolol per kilogram of body weight [i.e., 100 mg]) and continued to have ventricular tachycardia during exercise. Other family members were successfully treated with beta-blockers. Because of the negative effect of these exercise-induced arrhythmias on her quality of life, in 2005, at 17 years of age, she underwent left cardiac sympathetic denervation. During the next 30 months, she remained asymptomatic, and ventricular arrhythmias occurred only at high workloads. Figure 1 shows recordings from an exercise stress test before and immediately after surgery. Figure 2 shows the total arrhythmia burden, defined as the number of ventricular extrasystoles per minute, for all available exercise stress tests for this patient (while she was taking a consistent dose of metoprolol). Frequent extrasystoles (>50 per minute) occurred during all tests before surgery but were clearly reduced in number in the tests after surgery, with fewer than 20 per minute during peak exercise.

Patient 3 carried the RYR2 Gly3946→Ser mutation. Since the age of 11 years, he had had many episodes of syncope, with documented polymorphic ventricular tachycardia related to exercise. An ICD was implanted in 1995, when he was 13 years of age. Despite treatment with high doses of pro-

pranolol and mexiletine, he received numerous shocks, including five consecutive, appropriate shocks. For this reason, he underwent left cardiac sympathetic denervation in 1998. He was discharged while receiving the same pharmacologic therapy as he had before surgery. During the subsequent 10 years, he remained fully asymptomatic, without any ICD discharge.

Left cardiac sympathetic denervation is performed in 35 to 40 minutes, after an incision is made at the base of the neck; an extrapleural approach is used, without opening the chest. The lower part of the stellate ganglion is ablated together with the second and third thoracic ganglia; the fourth ganglion is cauterized. Preserving the upper half of the stellate ganglion prevents the occurrence of Horner's syndrome.

DISCUSSION

Catecholaminergic polymorphic ventricular tachycardia is a malignant disorder affecting young people, in some of whom current therapies are unsatisfactory. Adrenergic stimuli trigger life-threatening arrhythmias that are difficult to treat. Treatment with β -adrenoreceptor blockade does not provide full protection, nor does ICD implantation.¹¹ The use of an ICD is particularly ill-suited for treating catecholaminergic polymorphic ventricular tachycardia, because the pain and fear generated by the shocks may initiate arrhythmic storms and result in multiple shocks, with major psychological consequences in children.¹⁵ Left cardiac sympathetic denervation may be a viable solution for patients with catecholaminergic polymorphic ventricular tachycardia who are not fully protected by beta-blockers, such as the patients described here.

The arrhythmogenic mechanism in catecholaminergic polymorphic ventricular tachycardia has been shown to involve the catecholamine-induced activation of cyclic AMP-dependent protein kinase A, which phosphorylates several key Ca^{2+} -handling proteins, including RYR2. This increases the calcium-activated release of calcium from the sarcoplasmic reticulum. Mutant RYR2 channels have a gain-of-function effect, resulting in excessive calcium release during sympathetic activation that generates depolarizing membrane currents, which in turn lead to delayed afterdepolarizations and cardiac arrhythmia.^{16,17} Hence, the two most critical steps in the arrhythmogen-

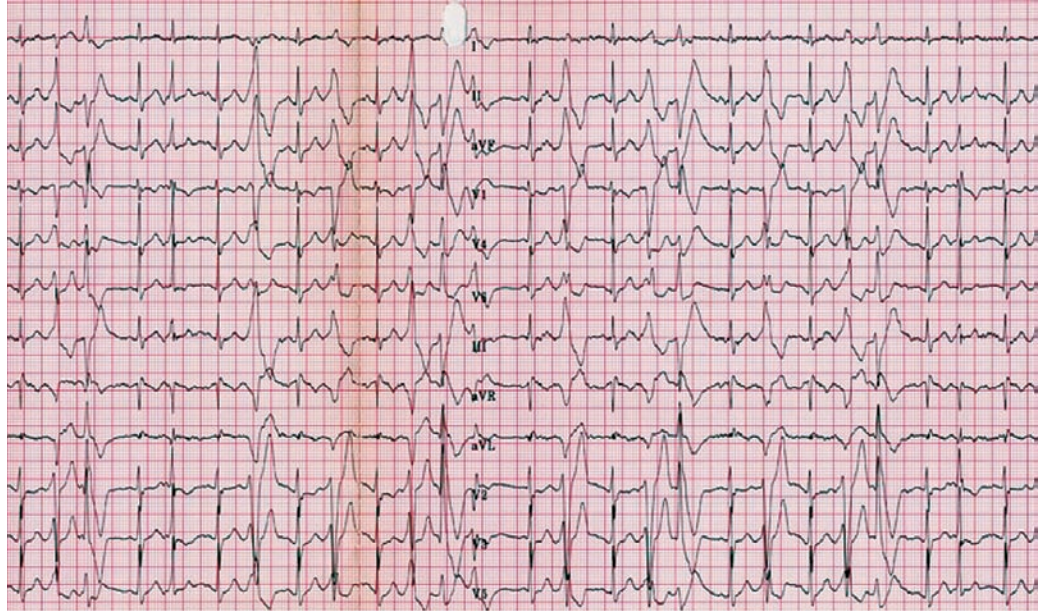
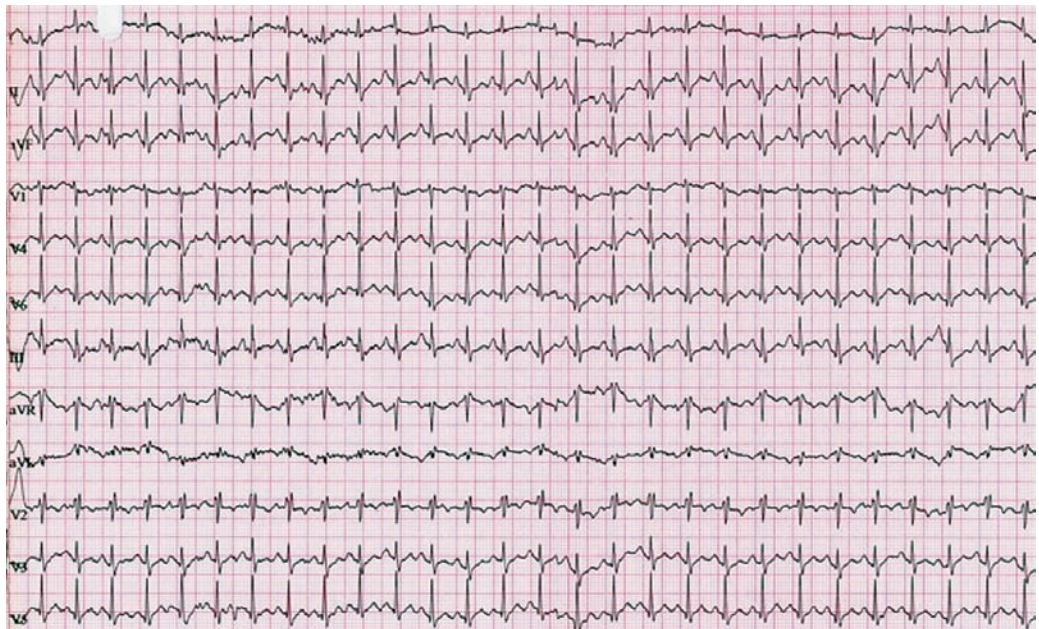
A 16 Months before LCSD**B 2 Days after LCSD**

Figure 1. Twelve-Lead Electrocardiograms (ECGs) Obtained from Patient 2 during Exercise Stress Tests before and after Left Cardiac Sympathetic Denervation (LCSD).

Panel A shows an ECG from the patient with a heart rate of 120 beats per minute (after 4 minutes and 42 seconds of exercise); the first extrasystoles appeared quickly, followed by polymorphic doublets and triplets. Panel B shows an ECG obtained from the patient, this time with a heart rate of 164 beats per minute (after 10 minutes and 32 seconds of exercise), 7 days after LCSD; no ectopy was observed. Standard calibration was performed for both ECGs.

esis of catecholaminergic polymorphic ventricular tachycardia are the increase in the catecholamine level and the attendant increased release of calcium. The therapeutic strategy of left cardiac sympathetic denervation is focused on interfering with the release of norepinephrine at the myocardial level.

Left cardiac sympathetic denervation interrupts the major source of norepinephrine released in the heart and has multiple antiarrhythmic effects.¹⁴ The surgery increases the threshold for ventricular fibrillation¹³ and increases ventricular refractoriness.¹⁸ Since left cardiac sympathetic denervation is a preganglionic denervation, there is no reinnervation. Also, since left cardiac sympathetic denervation does not completely eliminate catecholamines in the ventricles, the surgery does not lead to postdenervation supersensitivity (i.e., excessive response to catecholamines).¹⁹

Left cardiac sympathetic denervation was shown to be highly effective in a high-risk subgroup of patients who had had a myocardial infarction.²⁰ Among patients with the long-QT syndrome who were not protected by full-dose beta-blocker therapy, major arrhythmic events were reduced by 90% after a mean follow-up period of 8 years.²¹

Left cardiac sympathetic denervation does not preclude implantation of an ICD. When appropriate, the clinical strategy would be to use the ICD as a safety net together with left cardiac sympathetic denervation, in conjunction with beta-blockers, to minimize the risk of life-threatening arrhythmias.

Beta-blockers, universally regarded as first-line therapy for catecholaminergic polymorphic ventricular tachycardia, have been reported to have a high success rate by some,^{8,22} but not all,^{9,23} investigators. Recently, verapamil has been successfully added to the treatment regimen for five patients with catecholaminergic polymorphic ventricular tachycardia who have not undergone screening for RYR2 mutations.²⁴ Asymptomatic persistence of frequent premature ventricular beats during exercise does not justify a major change in therapy. The main clinical issue is what to do when patients continue to have frank syncope or sustained ventricular tachycardia under stress. The current recommendation^{10,25} is to implant an ICD in any patient with catecholaminergic polymorphic ventricular tachycardia who has arrhythmias despite

taking the maximal tolerated doses of beta-blockers. However, physicians need to address what happens after the ICD is implanted.

Given the nature of catecholaminergic polymorphic ventricular tachycardia, appropriate ICD shocks are potentially lifesaving but also cause pain and fear. Both result in the release of catecholamines, which can initiate a new episode of ventricular tachycardia or ventricular fibrillation and a second shock, sometimes resulting in a vicious cycle. Furthermore, since inappropriate defibrillator shocks are not infrequent, they may also lead to arrhythmia storms, in which case the ICD actually becomes proarrhythmic. The apparent lack of alternatives for patients with catecholaminergic polymorphic ventricular tachycardia who are not adequately protected by the use of beta-blockers led to cardiac transplantation in a 17-year-old patient reported to have had "innumerable" ICD shocks.¹² In the period between denervation and the subsequent reinnervation, the boy's clinical condition improved considerably, with an absence of arrhythmic episodes. Complete denervation may cause denervation supersensitivity, with serious unwarranted effects.

There are several important advantages of left cardiac sympathetic denervation. Once the procedure is performed, the effects are permanent, because preganglionic denervation precludes reinnervation. Patients with the long-QT syndrome who underwent the surgery more than 30 years ago have remained completely free of cardiac events.²¹ Denervation avoids limitations of medical therapy such as incomplete compliance, especially among teenagers. The surgery can also complement the use of an ICD, because denervation markedly decreases the probability of arrhythmic events, and the ICD is likely to interrupt ventricular fibrillation and restore sinus rhythm.

As shown by the case reports on our three patients, left cardiac sympathetic denervation results in marked improvement in the quality of life for patients with catecholaminergic polymorphic ventricular tachycardia. This surgery is associated with the reduction of adrenergically mediated cardiac arrhythmias.

The ability to antagonize or reduce cardiac sympathetic activity seems to be the cornerstone of successful therapeutic interventions in patients with catecholaminergic polymorphic ventricular tachycardia, with β -adrenoreceptor blockade as the

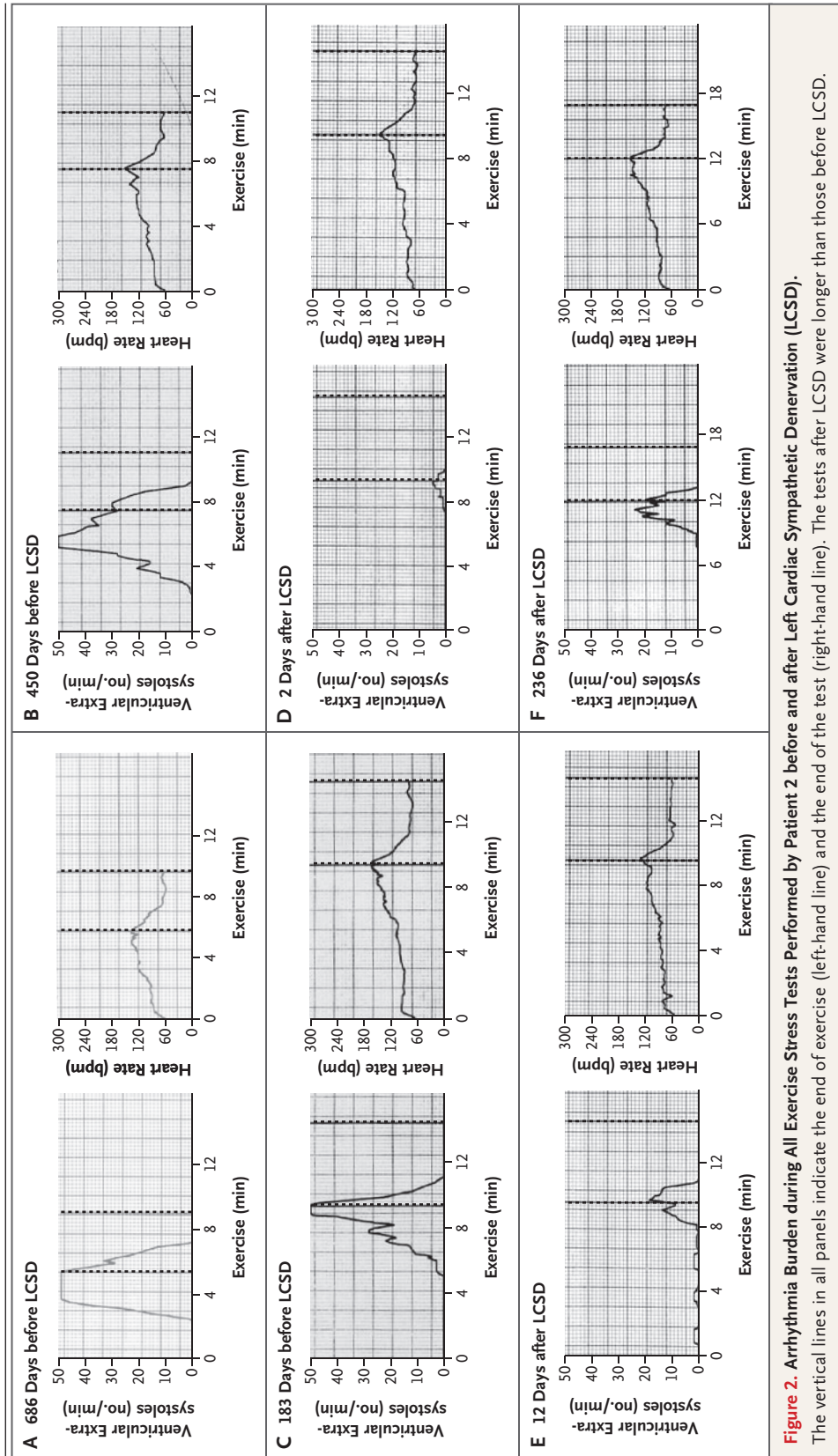


Figure 2. Arrhythmia Burden during All Exercise Stress Tests Performed by Patient 2 before and after Left Cardiac Sympathetic Denervation (LCSD).

The vertical lines in all panels indicate the end of exercise (left-hand line) and the end of the test (right-hand line). The tests after LCSD were longer than those before LCSD.

standard treatment. If use of beta-blockers fails to protect patients, the current recommendation is to implant an ICD. Although ICD therapy may indeed effectively guard against life-threatening arrhythmias, in patients with catecholaminergic polymorphic ventricular tachycardia, this treatment may trigger arrhythmic storms and result in multiple shocks, with negative effects on the patient's quality of life. Our study provides evidence that left cardiac sympathetic denervation may be an effective alternative treatment, especially for patients whose symptoms are not ade-

quately controlled by means of beta-blockade. Data from a larger number of patients with catecholaminergic polymorphic ventricular tachycardia treated with left cardiac sympathetic denervation are needed to properly assess the effect of this physiologically based method of treatment for catecholaminergic polymorphic ventricular tachycardia.

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