

Role of Bilateral Sympathectomy in the Treatment of Refractory Ventricular Arrhythmias in Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy

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Ventricular arrhythmias in arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) are precipitated by an increase in sympathetic activity, typically physical exercise. As such, β blockade is the cornerstone of medical treatment. However, some patients are either intolerant or refractory to β -blockers, and many continue to have arrhythmias despite catheter ablation. This report presents the case of an ARVD/C patient with severe ventricular arrhythmias refractory to β -blockade, antiarrhythmic drugs, and 3 endocardial/epicardial ventricular tachycardia (VT) ablations, who was successfully treated with bilateral sympathectomy.

A previously healthy 16-year-old male triathlete presented with a sudden cardiac arrest while swimming. He was diagnosed with ARVD/C based on T-wave inversions V1–V4, 7216 premature ventricular complexes on 24-hour Holter monitoring, left bundle inferior axis VT, and subtricuspid dyskinesia with right ventricular ejection fraction 33% (Figure 1). Genetic testing revealed no pathogenic mutation in a 76-gene cardiomyopathy panel (including all 5 desmosomal genes), and he had no familial history of disease. He received a single-chamber implantable cardioverter–defibrillator (ICD) and was discharged on sotalol. Five months after discharge, the patient received his first shock for VT at 233 beats per minute while dancing. He underwent an endocardial/epicardial VT ablation (Figure 2) and was noninducible at the end of the procedure during programmed stimulation with and without isoproterenol. He was discharged on long-acting metoprolol. Flecainide was added when palpitations recurred soon after discharge. Five months later, he experienced a VT storm requiring 43 ICD shocks after climbing stairs. He received cardiopulmonary resuscitation and regained consciousness 2 days later. He underwent a second endocardial/epicardial ablation. A stress test before discharge was normal. Amiodarone was initiated for further arrhythmia control. VT recurred 6 months later when he received 8 appropriate ICD shocks while running. In the electrophysiology laboratory, he developed spontaneous VT that promptly terminated on deep sedation.

Electroanatomic mapping showed minimal signs of scar progression. Open chest epicardial cryoablation was performed with no inducible VT 5 days post ablation. One month later, the patient experienced 6 ICD shocks during exercise, and a decision was made to perform bilateral sympathectomy. Using a video-assisted thoracoscopic surgery approach, the bilateral lower half of the stellate ganglia were removed together with the second through fourth thoracic ganglia. The procedure was well tolerated and no complications occurred.

To assess the impact of sympathectomy, the patient underwent noninvasive neurophysiologic testing before and after 8 weeks of sympathectomy while on the same medications (Figure 3). After sympathectomy, diastolic blood pressure responses to sympathetic stressors were similar to presympathectomy levels, whereas systolic blood pressure responses were attenuated, confirming denervation (Figure 3A). Similarly, resting heart rate was lower after sympathectomy, but augmented robustly to sympathetic stress to levels below presympathectomy values (Figure 3B). After sympathectomy, levels of finger pulse volume, the amplitude of the finger plethysmograph (Figure 3C), were higher, reflecting an overall decrease in sympathetic drive. Responses to sympathetic stress were, however, preserved. Interestingly, although finger pulse volume did not recover to baseline during the final rest period before sympathectomy, the finger pulse volume values returned to baseline after sympathectomy, showing restored capacity to attenuate sympathoexcitation when stress is withdrawn. As shown in Figure 3D, baseline skin conductance was also significantly attenuated by sympathectomy. Spectral analysis of heart rate variability demonstrated an overall reduction in sympathovagal balance (low-frequency/high-frequency ratio) from 0.58 to 0.46 (Figure 3E) because of a decrease in the low-frequency sympathetic component (1.84×10^{-4} versus 1.42×10^{-4}); but not the high-frequency parasympathetic component (3.17×10^{-4} versus 3.10×10^{-4} ; Figure 3F).

During 1-year follow-up after sympathectomy, the patient remains asymptomatic on metoprolol. His ventricular ectopy

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levels have significantly decreased, and he remains free of ICD therapy (Figure 4).

Involvement of the sympathetic nervous system in ARVD/C has been suspected since the first reports of the disease.¹ The right ventricle and the proximal pulmonary artery are richly innervated by sympathetic nerves from the ventromedial cardiac nerves. High-frequency stimulation in the pulmonary artery induces PVCs from the right ventricular outflow tract, and these nerves have been implicated in the pathophysiology of idiopathic VT. Indeed, the VTs in our patient exhibit features suggestive of catecholamine-mediated focal VT. VTs were easily inducible by minimal exercise and isoproterenol infusion, had fast cycle lengths, and VT salvos on electrophysiology study had similar morphology but different cycle lengths, favoring a triggered over reentrant mechanism. Of note, every previous ablation in this patient had been successful, and exercise stress testing and noninvasive programmed stimulation were normal after 2 of 3 ablation procedures. This questions the role of these tests in the setting of catecholamine-sensitive recurrent arrhythmias. The success of bilateral sympathectomy in controlling arrhythmias in our patient after 3 previous endocardial/epicardial ablations reveals that sympathectomy may achieve arrhythmia control after all other treatment options have been exhausted. Because bilateral sympathectomy involves the removal of postganglionic soma, intramyocardial sympathetic neural regeneration does not occur, leading to a durable antiarrhythmic effect. Unilateral sympathectomy may be less effective in the long-term, as remodeling may occur in the contralateral ganglion,² and may include sprouting within

the heart. Furthermore, left and right sympathetic nerves have been demonstrated to innervate unique regions of the heart, with overlap.³ As such, implementation of this technique early in the disease course may prevent recurrent VT storms and incapacitating psychosocial symptoms associated with ICD shocks. Although this does not eliminate the need for an ICD, it may result in lower arrhythmia burden, lower medication dependence, and increased quality of life. Future studies in a large number of patients should confirm the role of cardiac sympathectomy in ARVD/C and investigate its optimal timing and use in ARVD/C management.

Disclosures

None.

References

1. Wichter T, Hindricks G, Lerch H, Bartenstein P, Borggrefe M, Schober O, Breithardt G. Regional myocardial sympathetic dysinnervation in arrhythmogenic right ventricular cardiomyopathy. An analysis using 123I-metaiodobenzylguanidine scintigraphy. *Circulation*. 1994;89:667–683.
2. Fioretto ET, Rahal SC, Borges AS, Mayhew TM, Nyengaard JR, Marcondes JS, Balieiro JC, Teixeira CR, de Melo MP, Ladd FV, Ladd AA, de Lima AR, da Silva AA, Coppi AA. Hypertrophy and neuron loss: structural changes in sheep SCG induced by unilateral sympathectomy. *Int J Dev Neurosci*. 2011;29:475–481. doi: 10.1016/j.ijdevneu.2011.02.002.
3. Vaseghi M, Zhou W, Shi J, Ajjola OA, Hadaya J, Shivkumar K, Mahajan A. Sympathetic innervation of the anterior left ventricular wall by the right and left stellate ganglia. *Heart Rhythm*. 2012;9:1303–1309. doi: 10.1016/j.hrthm.2012.03.052.

KEY WORDS: ablation ■ arrhythmogenic right ventricular dysplasia-cardiomyopathy ■ sympathetic nervous system ■ ventricular tachycardia

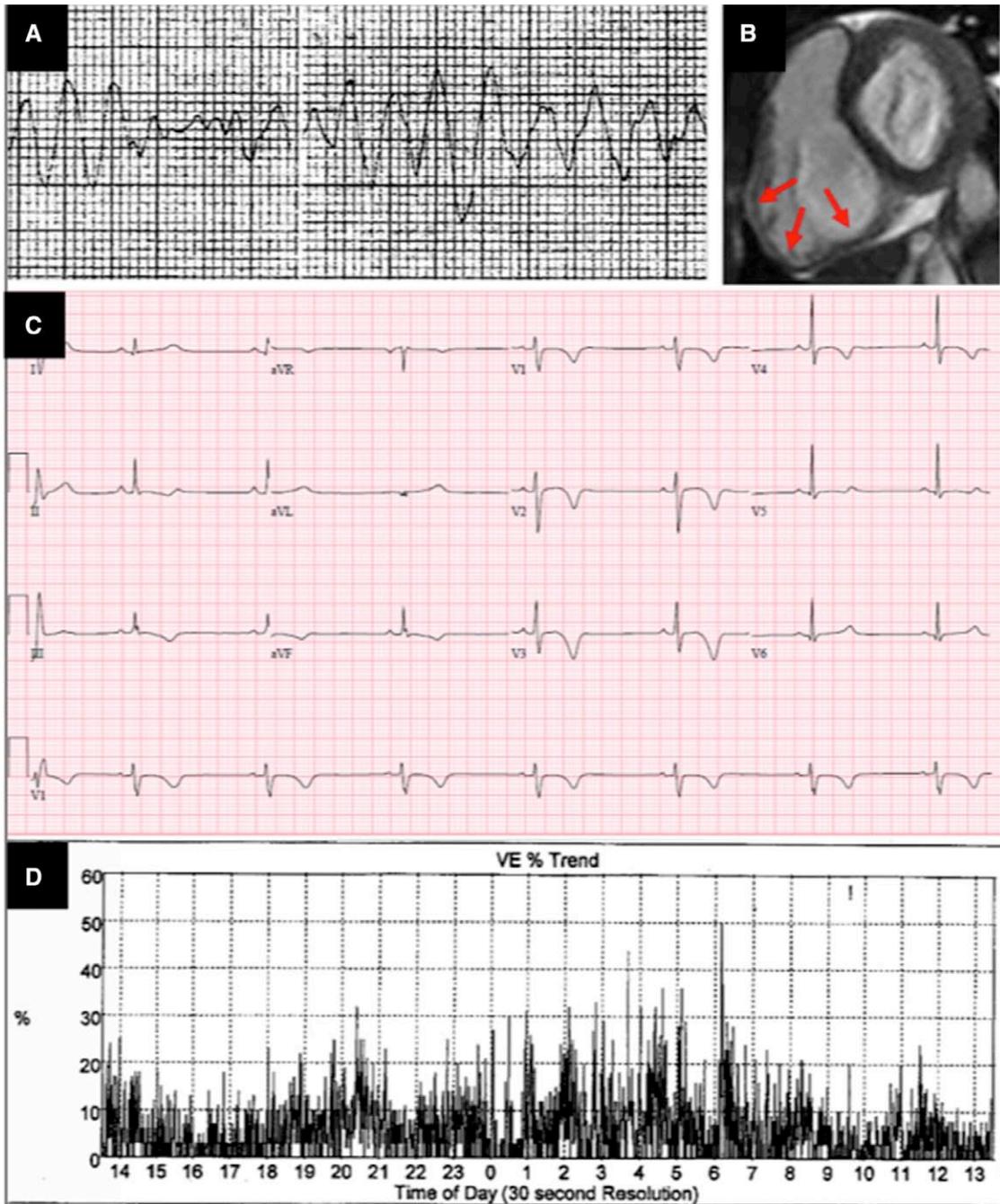


Figure 1. Clinical evaluation of the 16-year-old male arrhythmogenic right ventricular dysplasia/cardiomyopathy patient. **A**, The patient presented with sudden cardiac arrest while swimming. An automated external defibrillator detected monomorphic ventricular tachycardia, which degenerated into ventricular fibrillation successfully treated by defibrillation. **B**, Cine cardiac magnetic resonance imaging showed an enlarged right ventricle with dyskinesia in the inferior, acute angle, and anterior walls (arrows) under the tricuspid valve. **C**, 12-lead ECG revealed T-wave inversion V1–4. **D**, Hourly premature ventricular complex (PVC) counts on 24-hour Holter monitoring 1 month after presentation (total 24-hour PVC count: 7216). VE indicates ventricular ectopy.

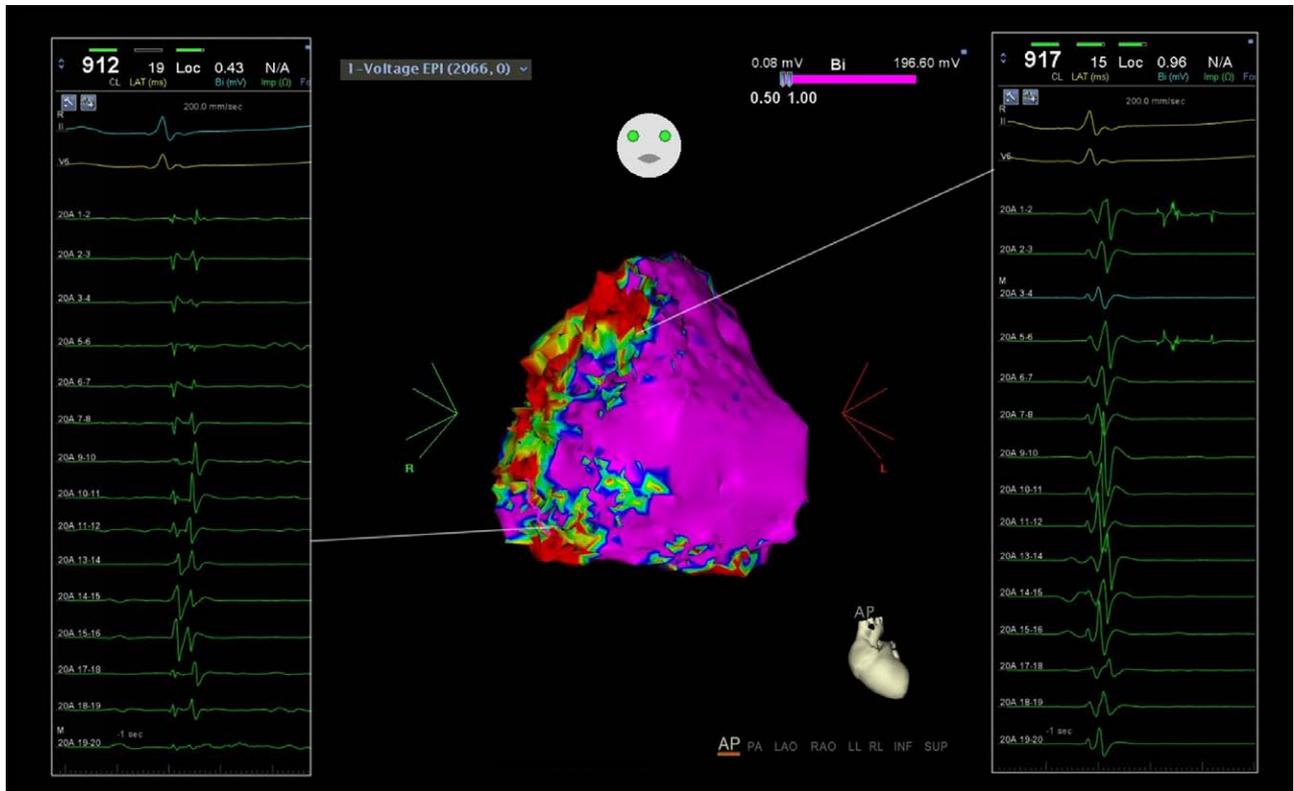


Figure 2. Electroanatomic voltage mapping during first endocardial/epicardial ventricular tachycardia ablation. Voltage mapping revealed scar (<0.5 mV) in the epicardial right ventricular (RV) basal lateral-free wall and anterior RV outflow tract with double and late potentials in the border zone merging into normal myocardium. AP indicates anteroposterior; INF, inferior; LAO, left anterior oblique; LL, left lateral; PA, posteroanterior; RAO, right anterior oblique; RL, right lateral; and SUP, superior.

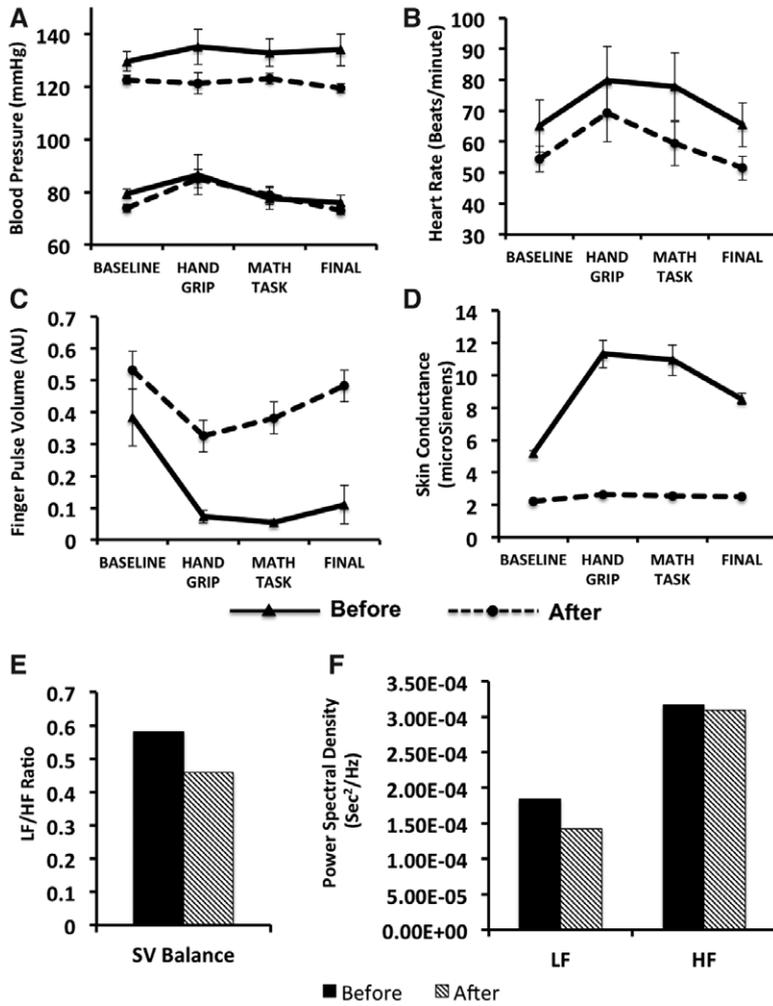


Figure 3. Provocative autonomic testing before and after sympathectomy. Continuous noninvasive blood pressure (A), heart rate (B), finger pulse volume (C), and skin conductance (D) were recorded at baseline, and during 2 sympathetic stressors (handgrip exercise and mental stress induced by a Trier test) before (solid line) and after (dashed lined) bilateral cardiac sympathectomy. Recordings were also made during a final baseline to assess recovery from sympathetic stress. Spectral analysis of heart rate variability (E and F) was also performed on electrocardiographic tracings recorded at baseline before and after sympathectomy. In composite, testing revealed the hemodynamic and neurophysiologic responses to stress after sympathectomy. HF indicates high frequency; and LF, low frequency.

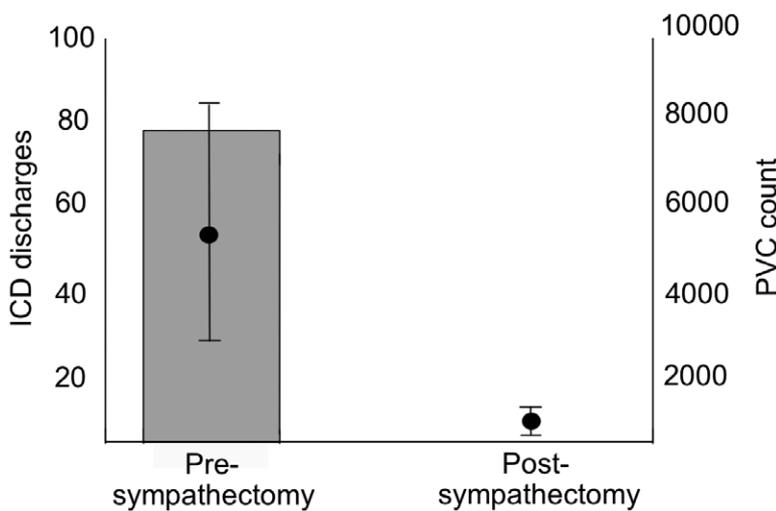


Figure 4. Number of implantable cardioverter-defibrillator (ICD) discharges and median premature ventricular complex (PVC) burden on 24-hour Holter monitoring during 16 months pre sympathectomy and 12 months post sympathectomy. Bars indicate ICD discharges; dots indicate PVC count with error bars indicating range. The patient experienced 78 discharges presympathectomy compared to none postsympathectomy; PVC count decreased from 5697 per 24 hours (range, 3029–8767 per 24 hours; n=4) presympathectomy to 676 per 24 hours (range, 673–679 per 24 hours; n=2) postsympathectomy.

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