EDITORIAL COMMENTARY

# The sympathetic nervous system and arrhythmogenic right ventricular cardiomyopathy: Further evidence of a strong tie

Veronica Dusi, MD,*† Gaetano M. De Ferrari, MD*†

*From the *Department of Molecular Medicine, Section of Cardiology, University of Pavia, Pavia, Italy, and †Cardiac Intensive Care Unit, Arrhythmia and Electrophysiology and Experimental Cardiology, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy.*

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited cardiac disorder characterized by a progressive fibrofatty replacement predominantly affecting the right ventricle (RV) with an epicardium to endocardium gradient. The cardiac sympathetic nervous system (SNS) is deeply involved in the pathogenesis of the disease, suggesting a potential role for neuromodulation among the possible therapeutic approaches.

ARVC is mainly caused by mutations in desmosomal proteins that increase cardiac susceptibility to mechanical stressors, particularly to wall stretch. During physical exercise, the RV wall stress increases much more than the left ventricular (LV) wall stress, providing a mechanical trigger for right-sided onset ventricular arrythmias (VAs) in ARVC. Acute recurrent mechanical stress in susceptible hearts may lead to cardiomyocyte damage and death, promoting local inflammatory processes, further increasing the arrhythmic risk. In addition to exercise, mental stress and intravenous catecholamine infusion reproducibly trigger VAs in ARVC. Accordingly, VAs in ARVC typically improve with β-blockers, which usually represent the first-line treatment with sotalol. Altogether, these clinical features strongly support a role for the SNS in favoring arrhythmias in ARVC. Regional myocardial sympathetic dysfunction in patients with ARVC and recurrent monomorphic VAs of right-sided origin was first reported in 1994.[1] More than 80% of 48 patients with ARVC studied showed regional reductions or defects of $^{123}$I-*meta*iodobenzylguanidine (MIBG) uptake (expression of presynaptic noradrenergic uptake in vivo) in the LV as compared with no healthy controls and 22% of patients with idiopathic ventricular tachycardia (VT). Insufficient spatial resolution prevented visualization of the RV. In 2000[2] a significant global reduction of ~40% in postsynaptic β-adrenergic receptor density of patients with ARVC compared with controls was shown, despite similar levels of plasma norepinephrine. A secondary downregulation caused by increased firing rates of SNS efferent neurons rather than an impaired presynaptic catecholamine uptake was proposed to explain the abnormal β-adrenergic receptor density in ARVC. Intriguingly, even areas with preserved myocardial perfusion, inconsistent with local fibrofatty replacement, were affected. These findings argue against anatomic denervation of sympathetic fibers (running in the subepicardium) being the unique mechanism of SNS dysfunction in ARVC. Also, patients with abnormal $^{123}$I-MIBG uptake had a much higher risk of VAs during long-term follow-up, independently of the extent of RV dysfunction.[3] Recently, using state-of-the-art single photon emission computed tomography/computed tomography (SPECT/CT) hybrid imaging, RV and LV sympathetic innervation was separately assessed in ARVC,[4] showing reduced $^{123}$I-MIBG accumulation in the RV of patients with ARVC; the RV-to-mediastinum uptake ratio accurately predicted ARVC diagnosis.

The mechanisms leading to SNS dysfunction independently of the extent of fibrofatty replacement and RV dysfunction are still unsettled, although functional mechanisms are likely to play a major role. Frequent right-sided premature ventricular contractions and pathological increase in wall stress may increase afferent sympathetic activity, leading in turn to a significant reflex increase in the global cardiac sympathetic efferent drive. Moreover, ARVC-related mutations in desmosomal proteins may affect a broad spectrum of cellular functions in addition to cell-cell adhesion, including intracellular calcium cycling,[5] potentially contributing to an increased sensitivity to catecholamines. Finally, the progressive fibrofatty replacement of the RV is expected to induce anatomic denervation and reinnervation processes, further increasing the arrhythmic susceptibility to catecholamines.

The management of refractory VAs in ARVC is challenging because of the young age of patients and the progressive, albeit largely unpredictable, course of the disease.

This study was funded by the European Union's Horizon 2020 research and innovation programme under grant agreement no. 733381. **Address reprint requests and correspondence:** Dr Gaetano M. De Ferrari, Cardiac Intensive Care Unit, Arrhythmia and Electrophysiology and Experimental Cardiology, Fondazione IRCCS Policlinico San Matteo, Viale Golgi, 19 – 27100 Pavia, Italy. E-mail address: g.deferrari@smatteo.pv.it.

 https://doi.org/10.1016/j.hrthm.2019.02.004

Recently, a multicenter retrospective study[6] focused on the outcome of 110 patients with ARVC (mean age 38 years; 83% men) with >3 VT episodes/implantable cardioverter-defibrillator (ICD) shocks: 70% were initially treated with antiarrhythmic drugs and/or β-blockers escalation, and the remaining underwent VT ablation (mainly endocardial) as first-choice therapy. The 3-year recurrence rate was similar (28% vs 35%); 43 patients in the pharmacological-only group underwent subsequent VT ablation. Overall, among the 75 patients who had ablation, 56% were free of VT recurrence at 3 years, with a borderline significant difference between the endo/epicardial vs the endocardial-only approach (71% vs 47%, p=0.05). These results, consistent with previous findings on the limitations of VT ablation in ARVC, underline the need of additional therapeutic strategies, particularly in patients with a failed endo/epicardial approach or in patients where VT ablation is contraindicated/refused.

Left cardiac sympathetic denervation is an effective strategy in genetic diseases in which malignant arrhythmias are favored by sympathetic activity in structurally normal hearts.[7,8] Left and, better, bilateral cardiac sympathetic denervation (BCSD) markedly reduced the VA burden in an international cohort of 121 patients with cardiomyopathy (mean age 55 years; LV ejection fraction 30%), including 6 patients with ARVC.[9] Overall, 1-year freedom from VT/ICD shocks was 58%. In multivariable analysis, New York Heart Association (NYHA) class I-II and shorter VT cycle length were the only independent predictors of efficacy.

In this issue of **Heart**Rhythm, Assis et al[10] report a single-center analysis of 8 consecutive patients with ARVC undergoing BCSD (mean age 38 years; 62% women; 75% with a history of vigorous exercise and 88% with previous electrical storm), with all except 1 in NYHA class I. All of them had failed multiple antiarrhythmic drugs (including amiodarone in half) and had undergone at least 1 VT ablation attempt (mean 2.7) before BCSD, including epicardial ablation in 7 and open-chest cryoablation in 1. In these extremely high-risk and already aggressively treated patients, 63% freedom of VT/ICD shocks was reported 1 year after BCSD, unaltered at the end of follow-up (mean 1.9 years), together with a 92% reduction in ICD shocks. Notably, no electrical storm occurred after BCSD. Patients were protected despite all but 1 were taking only low-dose β-blockers at follow-up (metoprolol in 6 patients; mean dose 21 mg/d).

These favorable results are in good agreement with the acknowledged pathophysiological role of the SNS. Despite the anecdotal nature of the report, few comments may be appropriate. Of the 3 patients who had recurrences, 2 (patients 4 and 2) had extensive electroanatomic scar throughout the RV, the latter also advanced NYHA class and very slow VTs— 2 already described negative predictors. These 2 patients, however, showed a marked decrease in the number of ICD shocks after BCSD. Altogether, we could define 5 patients as full responders, 2 as partial responders, and 1 as nonresponder to BCSD. In some patients, BCSD was performed shortly after VT ablation, underlining the current uncertainty in the ideal timing of this new therapeutic approach. The 2 approaches should be rather viewed as synergistic: while ablation of a stable substrate with reproducibly inducible VTs appears warranted, the disproportionate inhomogeneity in sympathetic innervation and the progressive nature of the disease make BCSD particularly attractive in this population of patients.

In conclusion, the strong pathophysiological rationale, the lack of major safety concerns, and these promising preliminary data make BCSD an option that should always be considered in the antiarrhythmic strategy of drug-resistant ARVC.

## References


1. Wichter T, Hindricks G, Lerch H, et al. Regional myocardial sympathetic dysinnervation in arrhythmogenic right ventricular cardiomyopathy: an analysis using $^{123}$I-*meta* iodobenzylguanidine scintigraphy. Circulation 1994;89:667–683.
2. Wichter T, Schäfers M, Rhodes CG, et al. Abnormalities of cardiac sympathetic innervation in arrhythmogenic right ventricular cardiomyopathy: quantitative assessment of presynaptic norepinephrine reuptake and postsynaptic beta-adrenergic receptor density with positron emission tomography. Circulation 2000;101:1552–1558.
3. Paul M, Wichter T, Kies P, et al. Cardiac sympathetic dysfunction in genotyped patients with arrhythmogenic right ventricular cardiomyopathy and risk of recurrent ventricular tachyarrhythmias. J Nucl Med 2011;52:1559–1565.
4. Todica A, Siebermair J, Schiller J, et al. Assessment of right ventricular sympathetic dysfunction in patients with arrhythmogenic right ventricular cardiomyopathy: an $^{123}$I metaiodobenzylguanidine SPECT/CT study [published online ahead of print December 17, 2018]. J Nucl Cardiol, https://doi.org/10.1007/s12350-018-01545-3.
5. Cerrone M, Montnach J, Lin X, et al. Plakophilin-2 is required for transcription of genes that control calcium cycling and cardiac rhythm. Nat Commun 2017;8:106.
6. Mahida S, Venlet J, Saguner AM, et al. Ablation compared with drug therapy for recurrent ventricular tachycardia in arrhythmogenic right ventricular cardiomyopathy: results from a multicenter study. Heart Rhythm 2019;16:536–543.
7. Schwartz PJ, Priori S, Cerrone M, et al. Left cardiac sympathetic denervation in the management of high-risk patients affected by the long-QT syndrome. Circulation 2004;109:1826–1833.
8. De Ferrari GM, Dusi V, Spazzolini C, et al. Clinical management of catecholaminergic polymorphic ventricular tachycardia: the role of left cardiac sympathetic denervation. Circulation 2015;131:2185–2193.
9. Vaseghi M, Barwad P, Malavassi Corrales FJ, et al. Cardiac sympathetic denervation for refractory ventricular arrhythmias. J Am Coll Cardiol 2017;69:3070–3080.
10. Assis FR, Krishnan A, Zhou X, et al. Cardiac sympathectomy for refractory ventricular tachycardia in arrhythmogenic right ventricular cardiomyopathy. Heart Rhythm 2019;16:1003–1010.