Sympathectomy - A "one hit wonder" for life?

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The role of the sympathetic nervous system in the genesis and perpetuation of ventricular arrhythmias is well recognized. Cardiac sympathetic denervation (CSD) has been shown to benefit patients with recurrent ventricular tachycardia (VT) who failed conventional therapy regardless of the underlying etiology[1]. Despite this, CSD is currently utilized as a last option after failing drugs and catheter ablation. Lack of randomized data on outcomes, short term follow up in the published literature, cross-cultural nature of the intervention, misconceptions of the effects on ventricular function in the setting of advanced structural disease are some of the reasons for this underutilization. A whole another question is the durability of the effect. Most studies published so far have had limited follow up and whether CSD is a one-time effect or not is unknown.

In this issue of JCE, Barwad and colleagues [4]investigated the long-term outcomes of 65 patients who underwent CSD due to refractory ventricular arrhythmias from 2010 to 2019 (reference). Most patients were men (77%), and the mean age was 50 +/- 18yo. In a study comprising mostly patients with structural heart disease (SHD), the authors reported a 92% reduction in shock burden (median 16 [IQR 11-25) to 0 [IQR 0-2] shocks) over a median follow-up of 20 months (IQR 12 – 36 months). Further, forty-five (69.2%) patients

were rendered free of shocks at two years. To our knowledge, this is one of the largest studies to assess a more extended follow-up duration in patients with SHD.

This study shed some light on a critical issue: the sustainability of the anti-arrhythmic effects of CSD in the long run. The development of compensatory adrenergic activation, nerve regrowth, and disease progression are time-dependent variables, and whether they may compromise CSD benefits later in the follow-up is yet to be determined. Over a median follow-up of 20 months, the authors found that over 2/3rds of patients remained shock-free. Such results suggest sustained anti-arrhythmic properties long after the procedure, even when considering all the unassessed factors in question. However, due to data availability limitations, arrhythmic outcomes were given only by shock recurrence. Sustained VT episodes requiring other types of therapies, such as anti-tachycardia pacing or chemical cardioversion were not included in the analyses, and may have contributed to overestimating the overall benefit. Along the same lines, it is not clear whether the comparison between the number of shocks before and after the procedure involved similar time windows. Nevertheless, all these considerations collectively do not outshine the importance of Barwad and colleagues' findings, as almost $\frac{3}{4}$ of patients achieved a lasting shock burden reduction following CSD. Additionally, consistent with existing data, the underlying etiology did not predict arrhythmic outcomes, and the presence of Class III-IV heart failure was associated with a worse prognosis.

Most patients (92.3%) enrolled in the study underwent bilateral CSD. Although the systematic use of bilateral CSD (BCSD) is still debatable, prior reports suggest a superior anti-arrhythmic profile of BCSD compared to left-only CSD.[1] In a recent systematic review including 173 patients with SHD who underwent CSD, Shah and colleagues described 82% of the procedures as bilateral. This is in consonance with our own experience, wherein BCSD has been employed as the preferred technique.

The study has some limitations. Most patients (79%) underwent CSD without a prior VT ablation attempt. Despite the author's arguments on cost-effectiveness of ablation and VT recurrence rates, we believe that some points should be carefully pondered before advocating one strategy over the other. We must recognize that VT ablation holds an overall safer profile than surgical sympathectomy, even when considering epicardial procedures. In turn, epicardial ablations have dramatically contributed to improved catheter ablation (CA) outcomes in patients with complex substrates [2,3]. Both strategies, CSD and CA, work synergically in refractory cases, but whether CSD yields superior arrhythmic outcomes enough to disregard the benefits derived from a stepwise approach, from the less to the most invasive intervention, has not been yet assessed. Further, it is fair to consider that, although patients who failed CA seem to benefit from CSD, most patients undergoing CA do not require adjunctive denervation. On the other hand, we do acknowledge that there is no strong reason to delay adjunctive sympathetic denervation in those patients who failed to respond to standard care. In our institution, we have a low threshold to perform CSD in eligible patients with refractory VT.

Another important take by the authors resides in the methodology. All shocks occurring within a 2-week blanking period immediately after CSD were disregarded as to account for the residual circulation of neurotransmitters after the procedure. Despite the lack of definitive information on the exact duration of such vulnerability window, VT recurrence early after CSD is not a synonym of procedural failure and may not predict worse late arrhythmic outcomes.

Barwad and colleagues also assessed the long-term hemodynamic impact of CSD in patients with SHD. The acute and chronic effects of CSD on cardiovascular performance have been evaluated randomly and thereby remain a source of concern in this specific population. With a mean left ventricular ejection fraction (LVEF) of 0.28 +/- 0.13, Barwad and colleagues showed that LVEF alone was not associated with worse arrhythmic outcomes. More importantly, LVEF remained stable one year after CSD. Nevertheless, although these findings corroborate to demystify low LVEF as a limitation to CSD, further consideration is necessary while individually weighing the net benefit against the risks. Five patients in the cohort died from progressive pump failure, and the presence of advanced heart failure (Class III and IV) was associated with lower survival rates from shock or death (combined endpoint).

Finally, we congratulate the authors for the outstanding work on some of the missing CSD puzzle pieces. Evidence of long-term sustained anti-arrhythmic effects and preserved cardiac function after CSD contribute to support the expanding role of SCD in the management of patients with complex arrhythmias. Nonetheless, additional research is still warranted to optimize patient selection and the optimal timing.

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