Long term clinical outcome of Cardiac Sympathetic Denervation in patients with refractory ventricular arrhythmias

Parag Barwad[1], Kunal Sinkar[2], Neeta Bachani[2], Rushil Shah[3], Vihang Shah[2], Binay Kumar[2], Shrikant Bhoskar[2], Neeraj Desai[2], and Yash Lokhandawala[4]

[1]Post Graduate Institute of Medical Education and Research
[2]Bandra Holy Family Hospital and Research Centre
[3]Johns Hopkins University School of Medicine
[4]Arrhythmia Associates

June 22, 2020

Abstract

Background: Cardiac Sympathetic Denervation (CSD) involves surgical removal of lower half of the stellate ganglion and the T1-T4 ganglia for reducing sympathetic discharge to the heart. CSD is a useful therapeutic option in patients with ventricular tachycardia (VT) when they are non-responsive to standard drug therapy or catheter ablation. We report here the clinical profile and long-term outcome of all our patients who underwent CSD for refractory VT or VT storm. Method: Data of all patients who underwent CSD from 2010 to 2019 was analysed. They were regularly followed up, focusing on arrhythmia recurrence. Complete response to CSD was defined as more than 75% decrease in the frequency of VT. Results: A total of 65 patients (50 male, 15 female) underwent CSD in the above-mentioned period and the duration of follow-up was 27 ± 24 months. The underlying substrate was for VT was coronary artery disease in 30 (46.2%) patients and 35 (53.8%) patients had a variety of other causes. Complete response to CSD was attained in 47 (72.3%) patients. There was a significant decline in the incidence of number shocks after CSD (24 ± 37 vs 2 ± 4; p <0.01). Freedom from a combined end point of ICD shock or death at the end of two years was 51.5%. Advanced NYHA class (III and IV) was the only parameter shown to have significant association with this combined end point. Conclusion: The current retrospective analysis reemphasize the role of surgical CSD in the treatment of patients with refractory VT or VT storm.

Introduction

The intracardiac cardioverter-defibrillator (ICD) is shown to play an important role in preventing sudden cardiac death (SCD) in patients with structural heart disease (1). However, ICD shocksare associated with significant increase in morbidity and also have a negative impact on quality of life (2,3). Thus, every effort needs to be taken to reduce the incidence of ICD shocks without affecting their efficacy. The autonomic nervous system has a very important role in genesis and maintenance of cardiac arrhythmias, especially ventricular tachycardia VT (4,5). Cardiac sympathetic denervation (CSD) is thus, an interesting therapeutic option in many patients with VT when they are non-responsive to standard treatment. Though it's role is established in managing hereditary channelopathies like long QT syndrome and catecholaminergic VT, an increasing volume of recent literature is consolidating its role as a viable therapeutic option in the management of refractory VT (6-10) in structural heart disease. The mechanism underlying the benefit of CSD in VT is by reducing the dispersion of myocardial repolarization and increasing the threshold of VT inducibility, as studied in animal models of myocardial infarction (11,12). There are only few studies assessing the long term efficacy of CSD in patients with refractory VT or VT storm (13,14). In the current article we aim to describe a relatively large single centre experience of long term effect of CSD in patients with refractory VT or VT storm.

1

Method

Study site: This is a retrospective analysis of all patients who underwent CSD at a tertiary hospitalfrom January 2010 to June 2019.

Data compilation: Data was collected from all patients during their index hospitalization, out-patient visit charts, telephonic conversation, hospital records, telemetry and ICD interrogation details (wherever available). Apart from patient demographics, the type of ventricular arrhythmia, etiology of ventricular arrhythmia, medication details, thoracic epidural anesthesia (TEA), immediate peri-CSD outcomes, procedural complications and follow-up data were noted. In case the patients did not come for follow-up, they were contacted telephonically at regular intervals.

Definitions:

VT storm: [?] 3 sustained episodes of VT within a 24 hour period, each requiring termination by an intervention (1).

Refractory VT: Incessant sustained VT that recurred promptly despite repeated intervention over several hours (15).

Arrhythmia management prior to CSD: All the patients were put on maximum tolerated antiarrhythmic drugs prior to considering CSD (table 1). The ICDs were programmed on individual case basis to minimize shock discharges, such as longer detection duration for first VT zone, more antitachycardia pacing (ATP) for VT, no shocks for the 1^{st}VT zone, etc. Reversible factors such as myocardial ischemia and electrolyte disturbances were addressed. Deep sedation or general anesthesia (GA) with endotracheal intubation was taken on case to case basis depending upon the clinical status. Radiofrequency ablation of VT was also performed in suitable patients prior to CSD. Despite the above measures, arrhythmias persisted in all these patients and thus were subjected to CSD. TEA was attempted in few patients prior to CSD.

CSD Operative details: A video assisted thoracoscopic surgical (VATS) approach under GA was utilized in all patients for CSD. Three 1.5 cm incisions were made in the sub-axillary area to access the pleural cavity. The ipsilateral lung was collapsed with single lung ventilation except in 4 patients where conventional intubation was performed and CO_2 insufflation of the pleural cavity was used. The thoracic sympathetic chain was identified in the pre-vertebral region. The lower half of the stellate ganglion along with thoracic sympathetic ganglia from level T2 to T4 were resected out and cauterized. The chest drain was removed after confirmation of lung re-expansion. Histological confirmation of the tissue removed was also obtained.

Definition of response to CSD: Response to CSD was assessed on the basis of occurrence of sustained VT requiring ICD shocks or external defibrillator after two weeks of CSD. We did not take into account anyshocks between CSD till two weeks after CSD and considered that period as 'blanking period'. This is because we postulated that CSD would take atleast two weeks for decreasing the circulating levels of epinephrine and norepinephrine.

Complete response: Defined as>75% reduction in the episodes of VT requiring ICD shockor external defibrillationcompared to before CSD.

Partial response: Defined as 50-75% reduction in the episodes of VT requiring ICD shock or external defibrillation in the follow-up period after CSD compared to before CSD.

No response: Defined as < 50% reduction in the episodes of VT requiring ICD shock or external defibrillation in the follow-up period after CSD compared to before CSD.

Delayed response: It was observed from our earlier case results that, patients usually show clinical response to CSD within 2 weeks of surgery. However lateron we also observed some patients continued to have shocks after CSD till three months but no requirement of shocks after three months. We considered such patients as delayed responders.

Statistical methods: Continuous variables were expressed as mean±SD or median and interquartile ranges [IQRs] and categorical variables, as percentages. The Kolmogorov-Smirnov test was performed which showed the data to be not normally distributed. Wilcoxon Signed Ranks test was used to determine differences between groups. Kaplan-Meier survival curves were used to estimate freedom from recurrent ICD shock and death. Log-rank test was used to compare Kaplan- Meier curves. For Kaplan- Meier analysis of freedom from ICD shock and death, patients who were lost to follow-up were censored at the time of last follow-up. A p value of <0.05 was considered significant. Statistical analysis was performed using SPSS software (Version 26, Chicago, IL, USA)

Results:

Data of 65 patients who underwent CSD during the above mentioned period for refractory VT / VT storm and had at least six months of clinical follow-up was available for analysis and interpretation. There were 50 (77%) males and 15 (23%) females,age 50 ± 18 (range 1-81) years in the cohort. The duration of follow-up was 27±24 months[median 20 (IQR 12-36)months]. The baseline characteristics are shown in Table 1. The left ventricular ejection fraction (LVEF) was 0.28 ± 0.13 prior to CSD. 25 (38.5%)patients had severe (LVEF 0.20-0.35) LV dysfunction and 29 (44.6%)patients had very severe (LVEF <0.2) LV dysfunctionprior to CSD.

Three (4.6%) patients were in NYHA class I, 20 (30.8%) in class II, 35 (53.8%) in class III and 7 (10.8%) in class IV. The underlying substrate was for VT was coronary artery disease in 30 (46.2%) patients and 35 (53.8%) patients had a variety of other non-ischemic causes, prominent ones being dilated cardiomyopathy and old myocarditis(Table 2).Nineteen (29.2%) patients had sustained monomorphic (single morphology) VTs, 38 (58.5%) patient had pleomorphic ([?]2 VT morphologies) and 8 (12.3%) had polymorphic VTs. An ICD or a CRT-D had been implanted in the past in 57 (87.7%) patients. After CSD, no further ICDs were implanted.Eight patients in the initial study period underwent TEA before subjecting them to CSD. This led to control of arrhythmia in 6 patients while 2 patients showed no response to TEA. However, after our initial experience of encouraging results of CSD, we changed our strategy and directly considered CSD without waiting to see the response to TEA.

Only 14(21.5%) patients had previous attempt of catheter ablation of VT while the other 51 (78.5%) patients were considered for CSD without a prior catheter based ablation. Seventeen (25.8%) of patients were on single, 37 (56.1%) on two and 11 (16.7%) on three antiarrhythmic drugs (AADs)prior to CSD. The most frequently used AAD was amiodarone in 55(83.3%) followed bybeta-blockers in 41 (62.1%) of patients(Table 3).60 (92.3%) of our patients underwent bilateral CSD and only 5 (7.7%) underwent unilateral left sided CSD.

Success of CSD: By the definition described earlier in the methods section, 47 (72.3%) patients fulfilled criteria of complete responder, 4(6.1%) were partial responders and 14 (21.5%) were non-responders. Amongst patients with complete and partial response, (6.1%) were delayed responders as they continued to have appropriate shock till 3 months after CSD but not thereafter. For analysiswe combined the complete and partial responders and compared them with non-responders. The comparison has been shown in Table 1. The only significant difference was that non-responders were predominantly in NYHA III and IV.

Efficacy of CSD:

Effect on ICD or external shocks: The average number of shocks received by a patient prior to CSD was compared to shocks received after the CSD at the end of follow up. It showed a very significant decrease from a 24+-37 {median 16(IQR 11-25)} prior to CSD to 2+-4 {median 0(IQR 0-2); p<0.01}. Thus, CSD led to a 92% reduction in requirement of defibrillation shocks.

Freedom from shock or death : At the end of 2 years, 46 (70.8%) patients were free of any sustained VT requiring ICD or external shock(Figure 1).However, at the end of follow-up (27+-23 months), this number had decreased to 43 (66%).

There were total 11 (16.9%) deaths in the complete cohort of patients up to the end of follow-up. Four

patients died during the index hospitalization for CSD, 3 related to progressive pump failure and congestive heart failure and one patient due to electro-mechanical dissociation soon after the CSD. Another 4 patients died in the first year of CSD, 2 because of pump failure and 2 because of sepsis. Thus, freedom from death at the end of 1 year was87.7% and at 2 years was 83.1% (Figure2) Three patients died subsequently during follow-up, 2 because of heart failure and 1 due to VT recurrence. Freedom from a combined end point of ICD shock or death at the end of two years was 52.3% (Figure 3).

Patient characteristics associated with outcome: We observed from the Kaplan-Meier curve that the number of shocks declined consistently till 1 year and after that the slope seems to have stabilized. Therefore, we tried assessing patient characteristics which were associated with ICD shock, as well as the combined endpoint of ICD shock and death were assessed whether certain populations were less likely to benefit from CSD. Kaplan-Meier analysis did not show any difference in outcomes between patients with ischemic cardiomyopathy and non-ischemic etiology [Log Rank (Mantel-Cox) p = 0.435] in relation to ICD shock recurrence or the combined end-point of ICD shock and death(Figure 4). The only parameter which was shown to have significant association with combined end point of ICD shock and death was advanced NYHA class [Log Rank (Mantel -Cox) p = 0.023], as shown in Figure 5.

There was no significant change in the LVEF at one year after CSD. In 5 patients the frequency of VT remained the same after CSD and thus they were taken up for catheter ablation. Of these, 2 patients had a significant decrease in VT episodes. Three other patients continued to have episodes of VT and requirement of ICD shocks. One of these patients diedduring follow-up because of VT storm.

Device interrogation data and follow-up: Many of our patients on subsequent follow-up had shown runs of non-sustained VTs and VTs terminated by ATP. However, we did not analyse this data in detail for our current study. All the patients were thoroughly followed up through clinic visits, telephonic interviews, telemetry with periodic ICD interrogation. The anti-arrhythmic drugs were later stepped down according to clinical status and VT burden.

Complications: Several patients developed sinus bradycardia and fall in blood pressure (BP) intraoperatively. The average heart rate prior to CSD was 88+-19/min, which reduced to 64+-8/min at the time of discharge after the surgery. The systolic and diastolic BP fell peri-operatively from 122+-12/78+-8 mm of Hg to 106+-9/62+-9 mm of Hg respectively. In 13 (20%) patients there was severe fall in BP during the postoperative period, requiring inotropes even after 48 hours of CSD. These include the 4 patients who died in the index hospitalization. Bradycardia (HR less than 60) in the post-operative period persisted in 6 (9.2%) patients. One patients developed left sided Horner's syndrome and another developed loss of sweating on left forehead. Another patient developed persistent transudative pleural effusion of undetermined etiology. None of our patients developed hemodynamically significant pneumothorax or hemothorax.

Discussion: In the largest data from India we describe here the long-term outcome of CSD in patients with refractory VT or VT storm, mostly with structural heart disease and severe LV dysfunction.. There has been a very significant fall in the frequency of ICD discharges after the CSD. Also, freedom from shock at 2 year was 70.8%.

ICD shocks have been shown to have a negative impact on morbidity, mortality and quality of life and every effort should be made to reduce shocks without affecting its efficacy (3, 15, 16). In our study, there was a 92% fall in requirement of shock after CSD. In the latest published systematic review of CSD by Shah et al, in 173 patients from 13 studies, the efficacy of procedure ranged from 58 to 100% (14). Vaseghi et al showed a 88% reduction in ICD shocks and freedom from shock, death or heart transplant of 50% at 1 year. In three previous reports with a total of 26 patients, 17 (65%) were responders (17-19). Bourke et al in their study had observed response in 4 (45%) out the 9 patients (<45%) who had undergone unilateral left sympathectomy (20). Another report by Vaseghi et al. has shown 90% reduction in shock after CSD and shock free survival of 48% for bilateral CSD over one year (21).

The overall survival of our cohort was 54/65 (83%) over a follow-up period of 28+-24 months. Previous studies on patients with VT storm have shown a mortality ranging from 33 to 53 % over a period of 5 years

(22-24). The better survival in our data may be attributed to younger age of patient, significant proportion with non-ischemic cardiomyopathy and the lesser duration of follow-up compared to these previous studies. Afinding which is interesting is that only one patient on follow-up died because of arrhythmic cause. This suggests that CSD by decreasing the incidence of arrhythmia and shocks may shift the mortality towards non arrhythmic causes such as progressive heart failure. This is in accordance to the finding by Hohnloser et al. who demonstrated mortality shift from arrhythmic caused to heart failure after prophylactic use of ICD (25).

The autonomic nervous system extensively affects the normal function of human heart, and has an important role in initiation and maintenance of cardiac arrhythmia (26). Studies in the past have documented the role of sympathetic excitation in ventricular tachycardia (27,28). CSD recently has been a hot topic of discussion for management of ventricular arrhythmia storm. The largest evidence in favour of this has been the study by Vaseghi M, et al. where they studied the effect of CSD in 121 patients with structural heart disease and VT storm (13). This was an international collaborative study from 5 international centres of which our centre was one. The 2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death recommended CSD as one of the therapies for refractory VT storm if other treatment modalities (medication and catheter ablation) are either ineffective or non-tolerable (1). However, our cohort differs considerable from the Vaseghi M, et al. study as only 21% of our patient had a previous VT ablation procedure as compared to 64% in the previous study. The reasons for this difference were possibly: i) In our study, 58.5% of patients had pleomorphic VT, where the results of ablation are suboptimal; ii) More than 50% of our patients did not have an ischemic etiology, where again ablation results are inferior; iii) Our centre has experienced surgical teams adept at performing CSD, even at times during ongoing VT and iv) Cost constraints did not permit us to undertake expensive electroanatomic ablation procedures where we did not expect good results. Our study is also a retrospective analysis which spans over a period 10 years and as the knowledge and experience evolved,with time we often subjected our patient upfront for CSD prior to attempting a VT ablation. Given the significant benefit we have experienced with CSD, we suggests this therapy can be considered early in the line of management of refractory VT or VT storm.

In the current contemporary practice of cardiology, CSD is used mostly for secondary prevention in LQTS and CPVT where it has been a class I recommendation by theguidelines(1). The mechanism of benefit of CSD is because of complete disruption of sympathetic control on the heart (11,29,30). Isolated stellate ganglion stimulation(unilateral or bilateral) may cause increase in dispersion of repolarization (31). Animal experiments in the past suggested that while dispersion of repolarization decreases with an associated increase in ventricular fibrillation threshold with left stellate ganglion resection, right stellate ganglion resection had either no effect or causes increase in QT dispersion (32). ,CSD decreases the dispersion of repolarization and increases the threshold of VT inducibility as shown in porcine heart model (11). This provided the rationale for unilateral left CSD in LQTS. Though this approach worked well for LQTS and CPVT, it was unknown if could it be extrapolated to other VT etiologies, especially with myocardial scars. The right and left sympathetic nerves subtend to non-overlapping areas of the myocardium or scar (33). Recent study in humans have also shown that sympathetic stimulation increases the dispersion of repolarization in patients with prior myocardial infarction (MI) (34). Hence we postulate that unilateral left CSD may not be of benefit if the arrhythmogenic region is supplied predominantly by the right-sided sympathetic nerves. In fact, canine experiments have demonstrated that right CSD reduces the incidence of ventricular arrhythmias, particularly those arising from the right border of anterior infarct or ischemia. (35). Other animal experiments have shown that myocardial infarction is associated with bilateral sympathetic ganglionic and neuronal hypertrophy (36). Furthermore, right-sided sympathetic nerves may hypertrophy and provide ramifications to the area subtended by the left-sided sympathetic nerves, partly nullifying the effects of isolated left CSD. These observations support the role of bilateral over unilateral CSD for ventricular arrhythmias related to myocardial scars. Concordant to these observations in one study, recurrent arrhythmias in 3 cases after a unilateral left CSD were suppressed with a subsequent right CSD (19). Furthermore, the data of Vaseghi et al also showed that only left side sympathectomy was associated with poorer ICD shock-free and

5

transplant free survival (13) as compared to bilateral CSD. Since patients with channelopathies have usually a structurally normal heart and thus there may not be significant neural remodelling as a compensatory phenomenon, making unilateral left CSD effective. But in patients with structural heart disease as the neural remodelling is significant, bilateral CSD should always be preferred.

We observed 4 (6 %) deaths and 6 (9 %) patients requiring prolonged hemodynamic support after the CSD. In the systematic review by Shah et al the cumulative complication rate was 28%. Whether to attribute the four deaths in our study to the procedure is a matter of debate as these patients were very sick, all having severe LV dysfunction and refractory VT, and thus the CSD was tried as a last desperate measure. The study of Vaseghi et al showed NYHA class, unilateral (left sided) sympathectomy and VT with longer cycle length to be the predictor of recurrence of VT (13). However, in our study we could not relate any of the studied parameters to have an effect on recurrence of VT or failure of the CSD.

Optimization of anti-arrhythmic drugs, sedation and general anesthesia wherever feasible, should be the initial steps in management of patients with VT storms. It is however easier said as such patients with a poor ventricular reserve, are often in CHF and cardiogenic shock and do not tolerate beta-blockers and general anesthesia. Thoracic epidural anesthesia may be used as a bridge to CSD if the surgery is not feasible immediately. TEA may also help the clinician to predict the candidates who are likely to benefit from CSD, although sympathetic blockade may not be as reliable with TEA as it is with surgical CSD. In our cohort two patient who did not respond to TEA, did better after CSD. Catheter ablation of VT including endocardial and epicardial approaches should be tried in suitable cases as still its recommendations are before CSD. We also postulate that as there could be existing reserves of catecholamine in the nerve endings even after CSD, the response to CSD could be delayed for some time and thus we waited for 2 weeks after CSD for interpretation of our results. We also inferred from our data that in some patients the effect of therapy may be delayed upto 3 months. Thus, a wait for the delayed effect may be required if the intervening period is not causing significant morbidity to the patient. Probably the CSD modifiesthe sympathetic discharge in such a way that the overall arrhythmia burden decreases and it also makes the arrhythmia more responsive to ATP or other non-shock related therapies of ICD.

In our cohort we had only 14 (21.5%) patients who underwent a EP study and an attempt of VT ablation prior to being considered for CSD. Out of these only 6 patients were from our centre and 8 had undergone an VT ablation at other centre. All these patients either had a failed attempt or had recurrence of VT prior to being referred to our centre for CSD. And after our initial experience with CSD, we started preferring CSD over catheter ablation and thus in 51 (78.5%) of our patients CSD was preferred over catheter ablation as strategy for VT storm or refractory VT.Thus, we propose that CSD may be used as one of the definitive therapies that may help stabilize patient with refractory VT or VT storm, allowing for a subsequent ablation if necessary. In the long term CSD may also reduce adverse myocardial remodelling in responders by reducing the VT burden, thereby stabilizing ventricular function. It also allows the physician to step down the anti-arrhythmic drugs. There always remain a question of what can be done further to these patient who do not respond to CSD and are not suitable for catheter ablation. Bradfield et al. suggested an incremental role of bilateral renal denervation in such patients (37). Though the study retrospectively evaluated only 10 such patients, the idea further strengthens the predominant role of sympathetic nervous system in maintenance of such arrhythmia. Indeed, improving the soil seems preferable than just tackling the seed!

Conclusion: Management of patients with refractory ventricular tachycardia and VT storms with structural heart disease and severe LV dysfunctionvery challenging. Catheter based ablation is also not feasible or effective in a significant proportion of these patients. Bilateral CSD has an important role to play in managing such patients. With more evidence gathering in favour of CSD, we suggest it should be considered as a viable therapeutic option in these patients.

References:

1. Sana M. Al-Khatib, William G. Stevenson, Michael J. Ackerman, William J.Bryant, David J. Callans, Anne B. Curtis et al. 2017 AHA/ACC/HRS Guideline for Management of Patients

With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death. J Am Coll Cardiol. 2018; 72 (14) e91-e220.

2. Herrmann C, von zur Muhen F, Schaumann A, et al. Standardized assessment of psychological well-being and quality-of-life in patients with implanted defibrillators. Pacing Clin Electrophysiol. 1997;20:95–103.

3. Poole JE, Johnson GW, Hellkamp AS, et al. Prognostic importance of defibrillator shocks in patients with heart failure. N Engl J Med 2008; 359:1009-17.

4. Vaseghi M, Shivkumar K. The role of the autonomic nervous system in sudden cardiac death. Prog Cardiovasc Dis. 2008;50:404-19.

5. Zipes DP, Rubart M. Neural modulation of cardiac arrhythmias and sudden cardiac death. Heart Rhythm. 2006;3:108-13.

6. 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.

7. Wilde AA, Bhuiyan ZA, Crotti L, Facchini M, De Ferrari GM, Paul T, et al. Left cardiac sympathetic denervation for catecholaminergic polymorphic ventricular tachycardia. N Engl J Med 2008; 358:2024-9.

8. De Ferrari GM, Dusi V, Spazzolini C, Bos JM, Abrams DJ, Berul CI, et al. Clinical Management of Catecholaminergic Polymorphic Ventricular Tachycardia: The Role of Left Cardiac Sympathetic Denervation. Circulation. 2015;131:2185-93.

9. Kumar S, Tedrow U, Stevenson W. Adjunctive interventional techniques when percutaneous catheter ablation for drug refractory ventricular arrhythmias fail: a contemporary review. Circ Arrhythm Electrophysiol. 2017; 10:e003676.

10. Shivkumar K, Ajijola OA, Anand I, et al. Clinical neurocardiology defining the value of neuroscience-based cardiovascular therapeutics. J Physiol. 2016; 594:3911-54.

11. Irie T, Yamakawa K, Hamon D, Nakamura K, Shivkumar K, Vaseghi M. Cardiac sympathetic innervation via middle cervical and stellate ganglia and antiarrhythmic mechanism of bilateral stellectomy. Am J Physiol Heart Circ Physiol 2017;312: H392-405.

12. Schwartz PJ, Stone HL. Left stellectomy in the prevention of ventricular fibrillation caused by acute myocardial ischemia in conscious dogs with anterior myocardial infarction. Circulation 1980; 62:1256-65.

13. Vaseghi M, et al. Cardiac sympathetic denervation for refractory ventricular arrhythmias. J Am Coll Cardiol. 2017; 69:3070-80.

14. Shah R, Assis F, Alugubelli N, Okada DR, Cardoso R, Shivkumar K, Tandri H. Cardiac sympathetic denervation for refractory ventricular arrhythmias in patients with structural heart disease: A systematic review. Heart Rhythm. 2019 Oct;16(10):1499-1505.

15. Tung R, Shivkumar K. Neuraxial modulation for treatment of VT storm. J Biomed Res. 2015; 29:56-60.

16. Moss AJ, Schuger C, Beck CA, et al., for the MADIT-RIT Trial Investigators. Reduction in inappropriate therapy and mortality through ICD programming. N Engl J Med 2012; 367:2275-83.

17. Nitter-Hauge S, Storstein O. Surgical treatment of recurrent ventricular tachycardia. Br Heart J. 1973; 35:1132-5.

18. Zipes DP, Festoff B, Schaal SF, Cox C, Sealy WC, Wallace AG. Treatment of ventricular arrhythmia by permanent atrial pacemaker and cardiac sympathectomy. Ann. Intern. Med. 1968; 68:591-7.

19. Ajijola OA, Lellouche N, Bourke T, Tung R, Ahn S, Mahajan A, et al. Bilateral cardiac sympathetic denervation for the management of electrical storm. J Am Coll Cardiol. 2012; 59:91-2.

20. Bourke T, Vaseghi M, Michowitz Y, Sankhla V, Shah M, Swapna N, et al. Neuraxial Modulation for Refractory Ventricular Arrhythmias: Value of Thoracic Epidural Anesthesia and Surgical Left Cardiac Sympathetic Denervation. Circulation. 2010 ; 121:2255-62.

21. Vaseghi M, Gima J, Kanaan C, Ajijola OA, Marmureanu A, Mahajan A, et al. Cardiac sympathetic denervation in patients with refractory ventricular arrhythmias or electrical storm: intermediate and

7

long-term follow-up. Heart Rhythm. 2014 Mar;11(3):360-6

22. Gatzoulis Konstantinos A, AndrikopoulosGeorge K, ApostolopoulosTheodoros, SotiropoulosElias, ZervopoulosGeorge, AntoniouJohn, BriliStella, StefanadisChristodoulos I. Electrical storm is an independent predictor of adverse long-term outcome in the era of implantable defibrillator therapy. Europace. 2005;7 (2):184–92.

23. Nademanee K, TaylorR, BaileyW E, RiedersD E, KosarE M. Treating electrical storm: sympathetic blockade versus advanced cardiac life support-guided therapy. Circulation. 2000;102 (7):742–7.

24. Stuber Thomas, EigenmannChrista, DelacretazEtienne. Characteristics and relevance of clustering ventricular arrhythmias in defibrillator recipients. Pacing ClinElectrophysiol. 2005;28 (7):702–7.

25. Hohnloser SH, Kuck KH, Dorian P, et al., for the DINAMIT Investigators. Prophylactic use of an implantable cardioverter-defibrillator after acute myocardial infarction. N Engl J Med 2004;351:2481–8.

26. Gilmour R, et al. Life out of balance: the sympathetic nervous system and cardiac arrhythmias. Cardiovasc Res. 2001;51:625–6.

27. Porter B, et al. Autonomic modulation in patients with heart failure increases beat-to-beat variability of ventricular action potential duration. Front Physiol. 59. 2017;8:328.

28. Franciosi S, et al. The role of the autonomic nervous system in arrhythmias and sudden cardiac death. AutonNeurosci. 2017;205:1–11.

29. Malliani A, Recordati G, Schwartz PJ. Nervous activity of afferent cardiac sympathetic fibres with atrial and ventricular endings. J Physiol 1973;229: 457–69.

30. Schwartz PJ, Foreman RD, Stone HL, Brown AM. Effect of dorsal root section on the arrhythmias associated with coronary occlusion. Am J Physiol 1976;231:923–8.

31. Opthof T, Coronel R, Vermeulen JT, Verberne HJ, van Capelle FJ, Janse MJ. Dispersion of refractoriness in normal and ischaemic canine ventricle: effects of sympathetic stimulation. Cardiovasc Res 1993;27:1954–60.

32. Schwartz PJ, Foreman RD, Stone HL, Brown AM. Effect of dorsal root section on the arrhythmias associated with coronary occlusion. Am J Physiol 1976;231:923–8.

33. Puddu PE, Jouve R, Langlet F, Guillen JC, Lanti M, Reale A. Prevention of postischemic ventricular fibrillation late after right or left stellate ganglionectomy in dogs. Circulation. 1988; 77(4): 935–946.

34. Vaseghi M, Lux RL, Mahajan A, Shivkumar K. Sympathetic stimulation increases dispersion of repolarization in humans with myocardial infarction. Am J Physiol Heart Circ Physiol. 2012 May 1;302(9):H1838-46.

35. Martins JB. Autonomic control of ventricular tachycardia: sympathetic neural influence on spontaneous tachycardia 24 hours after coronary occlusion. Circulation. 1985; 72(4): 933– 942.

36. Ajijola OA, Shivkumar K. Neural remodeling and myocardial infarction: the stellate ganglion as a double agent. J. Am. Coll. Cardiol. 2012; 59(10): 962–964.

37. Bradfield JS, Hayase J, Liu K, Moriarty J, Kee ST, Do D, Ajijola OA, Vaseghi M, Gima J, Sorg J, Cote S, Pavez G, Buch E, Khakpour H, Krokhaleva Y, Macias C, Fujimura O, Boyle NG, ShivkumarK.Renal denervation as adjunctive therapy to cardiac sympathetic denervation for ablation refractory ventricular tachycardia. Heart Rhythm. 2020 Feb;17(2):220-227.

Table 1: Baseline characteristics of study population and their comparison between CSD responders and non-responders subgroups.

Characteristics	Study population (N = 65)	Complete responders of CSD (N = 51)	Non-responders of CSD (N=14)	p value* (comparison between CSD responders and non-responders)
Age (mean ± SD)	50±18	49±17	53±20	0.307
Gender (Male:Female)	50:15	39:12	11:3	0.870

| Characteristics	Study population (N = 65)	Complete responders of CSD (N = 51)	Non-responders of CSD (N=14)	p value* (comparison between CSD responders and non-responders)
Hypertension	23 (35.4%)	16 (31.4%)	7(50%)	0.200
Etiology of VT (ICMP:NICMP)	30:35	22:29	8:6	0.356
Diabetes Mellitus	12(18.5%)	8 (15.7%)	4(28.6%)	0.291
Hyperlipidemia	15 (23.1%)	10 (19.6%)	5(35.7%)	0.209
Atrial Fibrillation	7 (10.8%)	5 (9.8%)	2(14.3%)	0.634
LVEF	0.28±0.13	0.29±0.13	0.24±0.12	0.136
NYHA status prior to CSD I II III IV	3 (4.6%) 20 (30.8%) 35 53.8%) 7 (10.8%)	5 (9.8%) 14(27.5%) 29(56.9%) 3(5.9%)	1 (7.1%) 0 (0%) 6 (42.9%) 7(50%)	**0.001**
Devices implanted prior to CSD No AICD AICD CRT-D	8(12.3%) 51(78.5%) 6 (9.2%)	7(13.7%) 40(78.4%) 4(7.8%)	1(7.1%) 11(78.6%) 2(14.3%)	0.356
Morphologies of VT Monomorphic Pleomorphic Polymorphic	19(29.2%) 38 (58.5%) 8 (12.3%)	16(31.4%) 28(54.9%) 7(13.7%)	3(21.4%) 10(71.4%) 1(7.1%)	0.305
Radiofrequency ablation attempted prior to CSD	14 (21.5%)	11(21.6%)	4 (28.6%)	0.585
Medications Amiodarone B Blockers	55(83.3%) 41(62.1%)	44 (86.3%) 33 (64.7%)	11(78.6%) 2(21.4%)	0.483 0.606
Type of CSD Unilateral (left) Bilateral	5 (7.7%) 60 (92.3%)	4(7.8%) 47(92.2%)	1(7.1%) 13(92.9%)	0.931

Table 2. Underlying substrates for refractory VT or VT storm.

| Etiology	N (%)
Coronary artery disease	30 (46.1%)
Idiopathic Dilated cardiomyopathy	10 (15.4%)
Old healed Myocarditis	13 (20%)
Arrhythmogenic right ventricular cardiomyopathy (ARVD)	3 (4.6%)
Rheumatic heart disease (RHD)	1 (1.5%)
Hypertrophic cardiomyopathy	2 (3.1%)
Sarcoidosis	2 (3.1%)
Catecholaminergic polymorphic VT	3 (4.6%)
Idiopathic VF	1 (1.5%)
Long QT syndrome	1 (1.5%)
Muscular dystrophy	1 (1.5%)

Table 3. Details of anti-arrhythmic drugs being received by patients prior to CSD

Medications	N (%)
Amiodarone, Beta Blocker	26 (40%)
Amiodarone, beta blocker, Sotalol	1 (1.5%)
Amiodarone, Beta blocker, Phenytoin	6 (9.2)
Amiodarone, Beta blocker, mexilitine	1 (1.5%
Amiodarone, Sotalol,	8 (12.3%)
Amiodarone, Sotalol, Phenytoin	3 (3.6%)
Amiodarone, Phenytoin	1 (1.5%)
Amiodarone, Flecainide	1 (1.5%)
Beta blocker	6 (9%)
Beta blocker, Sotalol	1 (1.5%)
Sotalol	2 (3.1%)

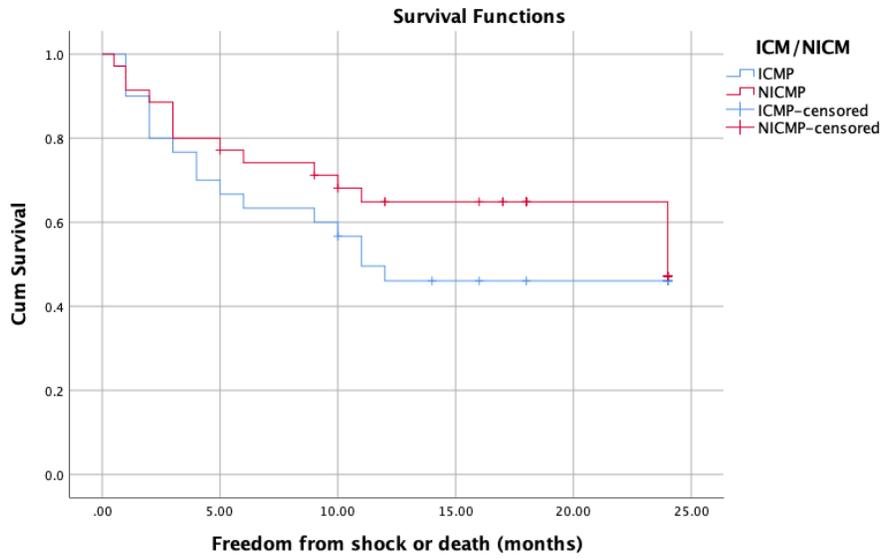**Graph 1.** KM curves of freedom from shock at 2 years
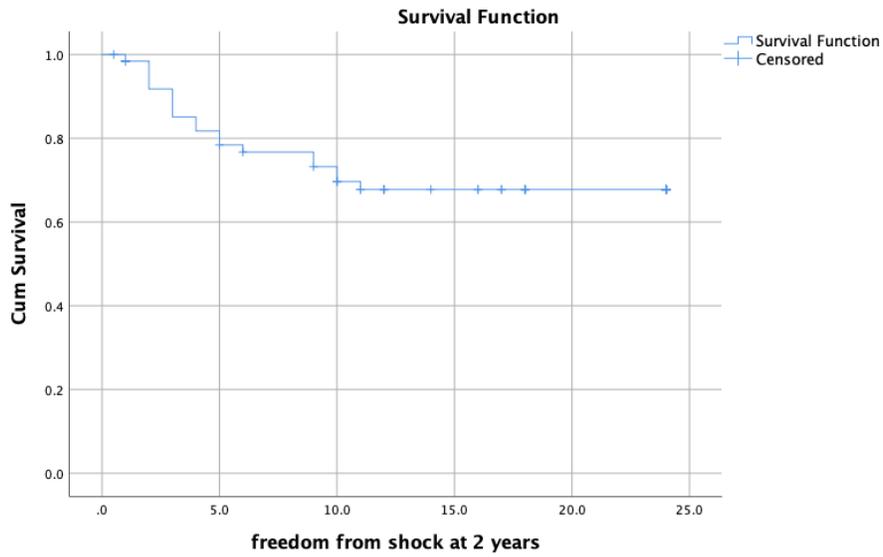
Graph 2. KM curve of freedom form death at2 years

10

Survival Function
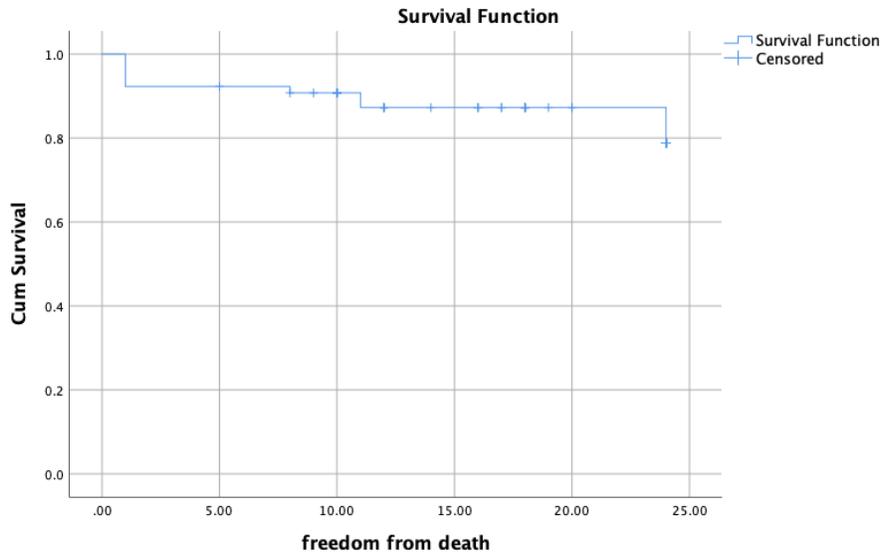
Graph 3. KM curve of freedom from shock/death at 2 years
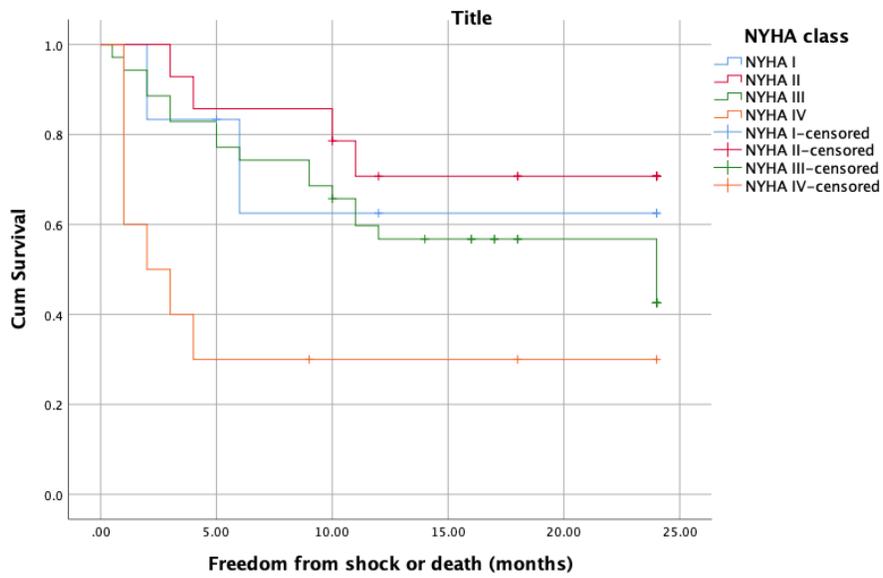
Survival Function
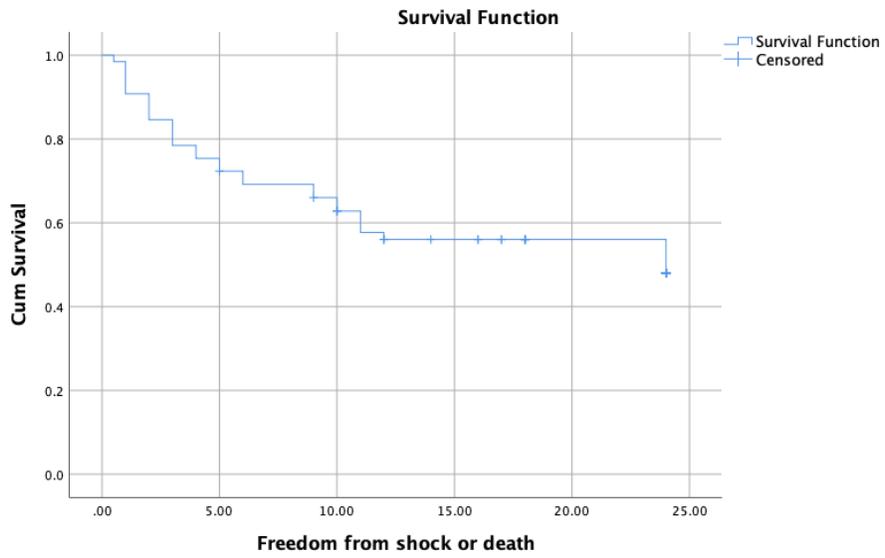
Graph 4. KM curve of freedom from shock at 2 years between ICMP and NICMP

11

Log Rank (Mantel -Cox) –P = 0.435

Graph 5. KM curve of freedom from shock or death at 2 years between different NYHA class.

Log Rank (Mantel -Cox) –P = 0.023