Clinical Management of Catecholaminergic Polymorphic Ventricular Tachycardia: The Role of Left Cardiac Sympathetic Denervation

Running title: De Ferrari et al.; LCSD and CPVT

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Abstract

**Background**—Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) is a genetic disorder causing life-threatening arrhythmias whenever sympathetic activity increases. B-blockers are the mainstay of therapy; when they fail, implantable cardioverter defibrillators (ICDs) are used but often cause multiple shocks. Preliminary results with flecainide appear encouraging. We proposed left cardiac sympathetic denervation (LCSD) as useful additional therapy, but evidence remains anecdotal.

**Methods and Results**—We report on 63 CPVT patients who underwent LCSD as secondary (n=54) or primary (n=9) prevention. The median post-LCSD follow-up was 37 months. The 9 asymptomatic patients remained free of major cardiac events (MCEs). Of the 54 patients with prior MCEs either on (n=38) or off (n=16) optimal medical therapy (OMT), 13 (24%) had at least 1 recurrence: none had an aborted cardiac arrest, 2 had syncope only, 10 had ≥1 appropriate ICD discharge and one died suddenly. The 1- and 2-year cumulative event-free survivals were 87% and 81%. The percentage of patients with MCEs despite OMT (n=38) was reduced from 100% to 32% (p<0.001) following LCSD and, among 29 patients with a pre-surgical ICD, the rate of shocks dropped by 93%, from 3.6 to 0.6 shocks/person/year (p<0.001). Patients with an incomplete LCSD (n=7) were more likely to suffer MCEs post-LCSD (71% vs 17%, p<0.01) than those with a complete LCSD.

**Conclusions**—LCSD is an effective anti-fibrillatory intervention for patients with CPVT. Whenever syncope occurs despite OMT, LCSD could be considered as the next step rather than an ICD and could complement ICDs in patients with recurrent shocks.

**Key Words:** arrhythmia, beta-blocker, death, sudden, genetics, nervous system, sympathetic
Introduction

Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) is a clinically important and potentially lethal genetic disorder characterized by exercise/stress-induced ventricular arrhythmias including ventricular tachycardia and fibrillation (VT-VF)\(^1\)\(^\text{-}^4\). The principal autosomal dominant form is caused by mutations in the \(R\text{YR2}\)-encoded cardiac ryanodine receptor while the rare autosomal recessive form stems from homozygous or compound heterozygous mutations in the \(C\text{ASQ2}\)-encoded calsequestrin 2 gene (\(C\text{ASQ2}\)), which both result in a net increase in intracellular, diastolic calcium during sympathetic activation\(^5\)\(^\text{-}^9\). CPVT manifests primarily in children and adolescents, and the ECG at rest is normal.

\[\text{B-blockers are effective in most patients}^3 \text{ but when breakthrough events occur or when patients continue to manifest VT on exercise, clinical management becomes complex.}\]

Furthermore, implantable cardioverter-defibrillators (ICDs), often useful in other arrhythmogenic disorders, can actually become part of the problem. Indeed, ICDs have not prevented sudden death in several patients, often because of exhausted therapies following arrhythmic storms or inappropriate discharges triggered by supraventricular tachycardias\(^10\),\(^11\). Recently, preliminary data have suggested the potential value of combination drug therapy involving \(\beta\)-blockers and flecainide, but definitive evidence is still lacking\(^12\),\(^13\).

In 2008, we demonstrated that left cardiac sympathetic denervation (LCSD) had been quite effective in 3 CPVT patients who continued to suffer VF and aborted cardiac arrest (ACA) despite full-dose \(\beta\)-blockers\(^14\). Our report was followed by others\(^15\)\(^\text{-}^18\) but, because of small numbers and limited follow-up, the most recent guidelines, while regarding LCSD as promising, still maintain that “its place in the management of CPVT remains to be proven” and relegate it to Class IIb status\(^19\). We felt the responsibility of following up on the initial study\(^14\) and of
quantifying the efficacy of LCSD in an international study involving a sufficiently large number of CPVT patients to allow a definitive assessment of its role.

Methods

Study population

The study population consists of 63 patients with CPVT from 53 families who underwent LCSD between 1988 and 2014 at 11 centers worldwide: 6 in Europe, 2 in the USA, 1 each in Canada, Israel, and Australia. De-identified baseline and follow-up information were obtained by the coordinating center in Pavia using web-based forms. The diagnosis of CPVT was clinically based and/or genetically confirmed by the identification of a pathogenic CPVT-associated mutation in the proband and family members. The clinical features of these patients were overall similar to those described by Hayashi et al in their 101 CPVT patients\textsuperscript{3}, the only difference being that all events occurred earlier in our population, as expected by the much greater presence of severely symptomatic patients.

Patients were considered “symptomatic” if they had suffered at least one major cardiac event (MCE), i.e. either arrhythmic syncope, ACA, or ICD appropriate discharges (ICD-ADs). Electrical storms were defined as the occurrence of 3 or more separate episodes of sustained ventricular VT/VF in 24 hours in patients without ICD, or 3 or more non-consecutive ICD shocks within 24-hours in patients with an ICD. An “end-of-treatment” condition was a series of consecutive ICD shocks leading to device therapy exhaustion.

All therapies, including drugs, ICD and LCSD, were prescribed at the discretion of each patient’s physician. \(\beta\)-blockers and/or flecainide at the maximum tolerated dose represented optimal medical treatment (OMT). Based on the “intention to treat” principle, MCEs after LCSD
which occurred following potentially detrimental changes in therapy and MCEs occurring during a brief period of non-compliance were nevertheless included in the event count.

Early follow-up for a few patients has been reported\textsuperscript{14-18}.

**Surgery**

The interventions were performed over a 26-year period (from 1988 to 2014). Complete LCSD required resection of the lower half of the left stellate ganglion (T1) together with the thoracic ganglia T2-T4. This surgical denervation provides adequate cardiac denervation with no or minimal Horner’s syndrome because most of the sympathetic fibers directed to the ocular region usually cross the upper portion of the left stellate ganglion and thus are spared. Whenever T1 or T4 were not ablated, denervation was considered incomplete. The main surgical approaches used were the thoracoscopic\textsuperscript{16}, the transaxillary\textsuperscript{17}, and the supraclavicular approach\textsuperscript{20}.

Written informed consent was obtained for all patients according to local rules.

**Statistical Analysis**

Continuous data are presented as median with both the 25\textsuperscript{th} and 75\textsuperscript{th} percentiles which define the interquartile range (IQR). Absolute and relative frequencies were reported for categorical variables and compared by Fisher exact test. Non-parametric McNemar and Wilcoxon signed rank tests for correlated samples were used to analyze the effect of LCSD on morbidity and on cardiac event count, respectively. To account for varying observation times, the incidence rate of MCEs both pre- and post-LCSD was computed by dividing the total number of cardiac events by the total amount of follow-up duration of all patients and expressed as the average number (and 95\% CI) of MCEs per patient/year of follow-up. To assess the effect of LCSD on the rate of events, while controlling for sex and age at surgery (<\textgtrless=15 years), a negative binominal regression model was fitted, given the skewness in the frequency of MCEs, using generalized estimating
equations. Robust standard errors were computed to account for intra-patient correlation over time. The “incidence rate ratio” (IRR), together with its 95% CI, was reported to measure the impact of LCSD on event counts over time. Both the rates of any event (syncope, ACA, ICD-ADs) as well as appropriate discharges (ICD-ADs) only in patients with an ICD implanted were considered as end-points. Pre- and post-operative event-free survival was described by Kaplan-Meier cumulative estimates. Two-sided p-values <0.05 were considered statistically significant.

SPSS Statistics version 21 (IBM Co, Armonk, NY) was used for computation.

Results

Table 1 shows the baseline characteristics of the 63 CPVT patients. In 7 patients, all symptomatic and with a diagnosis based on accepted criteria, genetic screening was not performed or the results were not available. Among the remaining 56 patients, successful CPVT genotyping was obtained in 50 (89%): 43 were CPVT1 secondary to RYR2 mutations, 5 were CPVT2 secondary to either CASQ2 heterozygous (n=1) or homozygous (n=4) mutations, and 2 were carrying mutations in both RYR2 and CASQ2. The median observation time from first MCE to LCSD was 4 years (IQR 2-7 years) and 3 years (IQR 0.5-6 years) from formal CPVT diagnosis to LCSD.

Clinical History Before LCSD

No Cardiac Events

Nine (14%) asymptomatic patients, all CPVT1, underwent LCSD. In 8 of them, a positive family history for SCD and/or syncope was present, three also had minor documented ventricular arrhythmia (NSVT in 1 case, PVC's and bidirectional couplets in another, non-sustained broad complex tachycardia in the third) on therapy and two were intolerant to β-blockers due to
symptomatic sinus bradycardia.

Cardiac events
Fifty-four patients were symptomatic before LCSD and most of them (n=38, 70%) continued to experience MCEs despite OMT. The median age at onset was 8.5 (IQR 6-11) years and by age 15, 96% of these symptomatic patients had already had a first MCE (Figure 1). “Syncope only” occurred in 21 patients while 33 had ACA (n=18) and/or ICD-AD (n=23), usually in addition to one or more syncopal episodes. Electrical storms (n=14) and end-of-treatment conditions (n=4) also occurred.

Medical Therapy
Most patients (61/63, 97%) were on β-blockers at the maximum tolerated dose at the time of LCSD. Other antiarrhythmic drugs, mostly flecainide (n=13) and mexiletine (n=5), were used in addition to β-blockers in 26 patients (41%, Table 1). Two siblings were on flecainide monotherapy, without β-blockers, because of sinus bradycardia.

Among the 54 symptomatic patients there were non-significant differences (79% vs 62%, p=0.24) when comparing the recurrences in patients receiving either nadolol or propranolol (22/28) vs other β-blockers (16/26).

ICD
An ICD was implanted in 37/63 patients (59%) at a median age of 11 (IQR 9-14.5) years: 32 at a median time of 41 (IQR 15-66) months before LCSD, 2 simultaneously with LCSD, and 3 following LCSD. In 14/37 ICD implanted patients (38%), the indication was secondary prevention after at least 1 ACA. Among the remaining 23 patients (62%) who received an ICD as primary prevention, a family history of SCD, and/or recurrence of arrhythmic events despite OMT were considered markers of high risk. During a median post-implant follow-up time of 7 (IQR 3-10)
years, there was a total of 17 device-related complications in 12/37 patients (32%), including 1 sepsis, 1 endocarditis, and 1 deep venous thrombosis. The majority (10/17, 59%) were cases of lead malfunctioning/fracture. In addition, 7 (19%) patients had a total of 10 generator replacements due to end-of-battery-life.

Of the 32 patients implanted before LCSD, 23 (72%) received at least 1 ICD-AD. A median of 7 (IQR 0-21) ICD-ADs were recorded over 3.5 (IQR 1.3-5.5) years from ICD implant to LCSD, representing a mean annual rate of 3.8 shocks per patient (95% CI 3.4-4.1). Electrical storms were observed in 12/32 patients (37%) and at least one end-of-treatment condition was reported in 4 (12%) patients. A total number of 73 inappropriate shocks, mostly elicited by supraventricular arrhythmias, occurred in 7 patients (22%), 6 of them also experiencing ICD-ADs.

**LCSD Surgery**

The main indication for LCSD was the occurrence of breakthrough events while on OMT, and this occurred in 38 patients (60%). Among these patients, 25 (66%) had syncope, 7 (18%) had ACA, and 23 (61%) experienced ≥1 ICD-ADs. LCSD was performed as additional protection in the remaining 25 subjects, including the 9 asymptomatic patients. Median age at LCSD was 15 years (IQR 11-17) with no difference between symptomatic and asymptomatic patients. The approaches were mostly thoracoscopic (45, 71%) and supraclavicular (13, 21%), and LCSD was complete (from T1 to T4) in the majority of patients (n=56, 89%). In 7 patients (11%), only a partial denervation was performed: T1 was spared in 6 patients and T4 in 1. There was only 1 serious adverse event: 1 VF during surgery.

**Clinical History After LCSD**

*LCSD and cardiac events in the study population*

**Figure 2** summarizes the post-LCSD outcome of the entire study population according to pre-
LCSD clinical characteristics. Overall, the percentage of patients with MCEs decreased from 86% (54/63) to 21% (13/63, p<0.001). This analysis included the 9 patients who were asymptomatic pre-LCSD and who remained completely event-free on continued OMT over an average observation time of 31 months. Including these patients in the analysis allowed to reveal potential proarrhythmic effects and mitigated the risk of a regression toward the mean phenomenon. However, since these asymptomatic patients clearly cannot provide information relative to the antiarrhythmic efficacy of LCSD, our analyses will focus hereafter on the 54 symptomatic patients.

These 54 patients with prior MCEs while either on OMT (n=38) or before institution of OMT (n=16) were observed for a median follow-up of 39 months (IQR 27-64). Their 1- and 2-year cumulative event-free survival was 87% and 81%, respectively (Figure 3). In total, MCEs recurred post-LCSD in 13/54 patients (24%); 1 of them, with a single ICD-AD during admitted non-compliance, belonged to the 16 patients with MCEs prior to OMT, whereas the remaining 12 were part of the 38 patients who had experienced breakthrough MCEs while on OMT. Among these 12 patients, there was one case of sudden death in a 15-year-old previously symptomatic adolescent male, who had been totally event-free for 8 months following LCSD and who died suddenly 2 days after having being switched from nadolol (no longer available in Russia) to metoprolol. He had an ICD, but unfortunately, his ICD could not be interrogated to confirm his rhythm status at the time of death. Figure 4 shows the overall effect of LCSD on the number of events in these 54 patients.

**LCSD in patients with MCEs despite OMT**

For the main efficacy analysis, we focused on the most seriously affected subgroup, the 38 patients who before LCSD continued to have MCEs despite OMT. The impact of LCSD on morbidity and on the incidence of cardiac events was equally remarkable in this high risk subset of non-responder
patients, as evident from the annual number of MCEs for each single patient (Figure 5). Table 2 shows that LCSD was associated with a remarkable reduction in both the percentage of symptomatic patients, from 100% to 32% (p<0.001), and in the mean annual rate of events per patient which dropped by 92% (p<0.001), from 3.4 (95% CI 3.2-3.7) to 0.5 (95% CI 0.4-0.6), while the median pre- and post-observation times were similar (51 months from institution of OMT to LCSD and 43 months post-LCSD follow-up, respectively).

We did consider some potential confounders: the burden of arrhythmic events prior to LCSD and changes in medical therapy. To address the first issue, we performed 2 different sensitivity analyses to evaluate the effect of LCSD on the event count. In the first, we excluded the 3 patients with an annual incidence rate >30 MCEs before LCSD (Fig. 5) and observed that the magnitude of the protective effect of LCSD was somewhat diminished but remained substantial and significant (a 78.5% reduction in the rate of MCEs when event rates after and before LCSD are compared, p<0.001). In the second, absolute numbers of MCEs >25 for a given patient were counted as 25 (n=9 patients). Also in this case, a remarkable reduction (88%) of MCEs post LCSD was observed.

We also considered that changes in medical therapy after LCSD might have contributed to its success rate. Table 3 shows that both the type and dose of β-blockers remained essentially the same after surgery. The only change was an increase in the number of patients receiving flecainide, from 9 pre- to 16 post-LCSD. Of these additional 7 patients, 2 received flecainide in absence of MCEs while 5 because of continued recurrences. In only one of these 5 patients flecainide was associated with suppression of arrhythmic events.

LCSD and ICD

Of the 32 patients with an ICD before intervention, 3 were not considered because either an
extremely short time between implant and LCSD or ICD removal due to sepsis or to the lack of interrogation data. The number of patients with ICD-ADs decreased from 22/29 (76%) to 10/29 (34%) following LCSD (p<0.01). Furthermore, the average post-LCSD rate of shocks significantly (p<0.001) dropped by 93%, from 3.6 (95%CI 3.2-3.9) to 0.6 (95%CI 0.5-0.7) shocks/person/year. Also, the number of patients experiencing electrical storms decreased markedly after LCSD from 11/29 (38%) to 4/29 (14%, p<0.05).

There were 21 symptomatic patients not implanted with an ICD prior to LCSD, including 11 who continued to have MCEs (3 ACA and 8 syncope) despite OMT. During 36 months of follow-up post LCSD, only 1/21 patient (5%) experienced syncope. Limiting this analysis to the 11 with MCEs on OMT, the post-LCSD percentage of patients with MCEs is 9% (1/11).

Extent of denervation and outcome

Among the 54 symptomatic patients, the 7 subjects with an incomplete denervation were much more likely to suffer recurrences of cardiac events post-surgery compared to those with a complete LCSD, [5/7 (71%) vs 8/47 (17%), p<0.01]). When the impact on outcome depending on the extent of denervation performed was evaluated among the 38 patients with MCEs while on OMT, the results were even more impressive (Figure 6) as recurrences post-LCSD occurred in 5/5 (100%) patients with an incomplete denervation vs 8/33 (24%) patients who received a complete LCSD (p<0.01).

Discussion

The present study provides evidence that LCSD plays a major role in the management of CPVT by markedly reducing the probability of life-threatening events, which unavoidably improves the quality of life of these young patients and of their families. Following the first report on the use
of LCSD in CPVT\textsuperscript{14}, we thought necessary to document whether or not LCSD should become a recommended treatment for CPVT patients with numbers adequate to draw definitive conclusions.

Given the rarity of CPVT and the fact that LCSD is a procedure performed in only a limited number of centers, the present data on 63 such patients are reassuring and objectively impressive. The results are based on a strong rationale\textsuperscript{21} and match those already observed in other arrhythmogenic conditions\textsuperscript{18, 22-24}. These findings should, therefore, importantly impact on the approach to the management of CPVT.

Our analysis focused on the 54 patients who had previously suffered life-threatening events and who clearly represent a high-risk group. Among these, 38 patients (70\%) continued to have recurrences despite OMT before LCSD, and 76\% of those implanted with an ICD continued to have ICD-ADs at the disquieting rate of 3.6 shocks/patient/year. LCSD had a clear impact on all cardiac events, as 76\% of the patients remained free of MCEs. The only patient who died during follow-up was the one who was switched suddenly from nadolol to metoprolol, despite the evidence of high risk for arrhythmic recurrences with this specific \(\beta\)-blocker in the long QT syndrome (LQTS)\textsuperscript{25}.

LCSD was associated with major reductions both in the number of patients with MCEs and in the actual number of MCEs. The impact of LCSD is clearly evident by the internal control analysis (\textbf{Figure 5}) where each patient served as his/her own control and which shows a 92\% reduction in MCEs. There was also a major reduction in the number of ICD-ADs; interestingly, this reduction (\(\approx\)93\%) is the same previously reported after LCSD for electrical storms in LQTS\textsuperscript{22}. We cannot exclude entirely the possibility that the observed 92\% reduction in MCEs is somewhat overestimating the protective effect of LCSD because of a natural variability in
arrhythmia frequency; however, the reduction in MCEs following LCSD remains very high even after the sensitivity analyses performed to decrease the impact of a few outliers. Also, the results were not influenced by changes in medical therapy as both doses and types of β-blockers remained substantially stable when comparing the pre- and post-LCSD periods.

The concept of “therapeutic dose” is confirmed also for LCSD. Indeed, the 7 patients with an incomplete denervation, mostly caused by sparing the lower half of the left stellate ganglion, had significantly more recurrences of arrhythmic events compared to patients who received what is considered the comprehensive LCSD (T2-T4 plus a lower-half stelllectomy). This finding, reported in LQTS patients as well\textsuperscript{22}, should mandate comprehensive LCSD and dissuade the execution of a suboptimal surgical procedure.

The antiarrhythmic and antifibrillatory effect of LCSD in a variety of clinical conditions, and its mechanisms of action, have been reviewed recently\textsuperscript{21}. Critically important are the interruption of the localized release of norepinephrine at ventricular level which accentuates the arrhythmogenic ventricular dishomogeneity of repolarization\textsuperscript{26} and its direct antifibrillatory effect\textsuperscript{21}. Being a pre-ganglionic denervation, LCSD is not followed by reinnervation nor by post-denervation hypersensitivity\textsuperscript{28}. Alpha-adrenergic antagonism may contribute to the favorable effects of LCSD in agreement with experimental findings in a model of calsequestrin-dependent CPVT\textsuperscript{29}. Bilateral sympathectomy could be considered following only partial success with unilateral LCSD, to further reduce the release of norepinephrine at ventricular level and to better control heart rate\textsuperscript{30}.

The present data force a reassessment of the current clinical approach to CPVT patients. B-blockers (propranolol or nadolol) certainly should remain first-line therapy, being effective for the majority (two-thirds) of patients\textsuperscript{3}. Although reported as promising\textsuperscript{12,13,19}, the combination of
β-blocker and flecainide therapy still requires confirmation in an adequately large population of
CPVT patients experiencing recurrences on β-blocker monotherapy and implies life-long therapy
with a class I antiarrhythmic drug. Even though just a by-product of our study, the fact that in
only 1 of 14 patients with arrhythmias despite beta-blockade (n=9) and beta-blockade plus LCSD
(n=5) an arrhythmia suppression was observed following flecainide suggests modest independent
efficacy.

Among the 38 patients experiencing MCEs on OMT before LCSD, 9 (24%) were already
on combination drug therapy with β-blocker and flecainide (mean dose 3.8 mg/kg/day). Most of
them (6/9, 67%) became asymptomatic after LCSD. Finally, albeit ineffective in the single case
of death, the ICD usually saves lives but it does not represent an ideal solution for CPVT
patients. Indeed, ICD shocks, by causing pain and fear, increase catecholamine release and could
initiate electrical storms whereby the ICD actually causes the death (in the setting of an initial
inappropriate shock) or contributes to these tragic deaths rather than providing the intended
therapeutic solution\textsuperscript{10,11}. This potential unintended/undesired consequence is further compounded
by an extremely high rate of adverse events: the 7-year incidence of complications (32%) and of
generator replacements (19%) observed in our population is worrisome given the expected
duration of treatment exceeding 50 years in these young patients. Careful ICD programming is
necessary in CPVT because the effectiveness of appropriate shocks critically depends on the
arrhythmia mechanism, being effective usually only when the treated rhythm is VF\textsuperscript{31,32}. Thus,
CPVT patients with arrhythmic events despite β-blockers are in dire need of an effective adjunct
therapy. The present data conclusively indicate that LCSD represents a viable and effective
answer to this predicament. As a one-time, minimally invasive procedure, LCSD is an effective
anti-fibrillatory/antiarrhythmic intervention for patients with CPVT.
LCSD should always be considered in CPVT patients experiencing recurrent ICD shocks. The occurrence of major events post-LCSD in only 9% of the patients left without ICD despite life-threatening arrhythmias on OMT suggests that, in CPVT patients with syncope despite OMT, LCSD should be considered instead of proceeding directly to an ICD.

Limitations

We do not have a comparison group. In a disease such as CPVT, as it has been in the past the case for LQTS, a randomized clinical trial is simply not feasible for obvious reasons including ethical issues. The option to compare the present results with the outcome in our CPVT patients without LCSD is voided by the attendant selection bias because such a group would be at much lower risk as all our “high-risk” patients now undergo LCSD. Our observational study with “internal controls”, with numbers adequate for a rare disease and very similar observation times pre- and post-surgery should raise confidence in the data and is the best possible under the specific conditions of a life-threatening rare disease managed with a novel therapeutic strategy. Also, the appropriateness of the ICD shocks was assessed by the enrolling centers as we had not instituted a centralized blinded assessment for ICD interrogation. We did not deem necessary to obtain specific details for every patient as we were dealing with tertiary referral centers for arrhythmic patients with highly experienced electrophysiologists.-

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References:


10. Mohamed U, Gollob MH, Gow RM, Krahn A. Sudden cardiac death despite an implantable


20. Odero A, Bozzani A, De Ferrari GM, Schwartz PJ. Left cardiac sympathetic denervation for the prevention of life-threatening arrhythmias. the surgical supraclavicular approach to cervico-


Table 1. Baseline characteristics of the study population.

<table>
<thead>
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<td>Age at first symptom, median (IQR), yrs</td>
<td>8.5 (6-11)</td>
</tr>
<tr>
<td>Age at diagnosis, median (IQR), yrs</td>
<td>9 (7-14)</td>
</tr>
<tr>
<td>Medical therapy before LCSD, n (%)</td>
<td>63 (100)</td>
</tr>
<tr>
<td>Daily dose (mg/Kg)</td>
<td></td>
</tr>
<tr>
<td>Beta-blockers</td>
<td></td>
</tr>
<tr>
<td>Nadolol</td>
<td>1.2 ± 0.7</td>
</tr>
<tr>
<td>Atenolol</td>
<td>1.9 ± 0.9</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>1.9 ± 0.9</td>
</tr>
<tr>
<td>Propranolol</td>
<td>3.9 ± 1.2</td>
</tr>
<tr>
<td>Labetalol</td>
<td>6; 10</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>0.2; 0.3</td>
</tr>
<tr>
<td>Flecainide</td>
<td>3.1 ± 1.9</td>
</tr>
<tr>
<td>Other AADs</td>
<td></td>
</tr>
<tr>
<td>Mexiletine</td>
<td>5 (8)</td>
</tr>
<tr>
<td>Verapamil</td>
<td>5.4 ± 0.9</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>2.8 ± 1.1</td>
</tr>
<tr>
<td>Dronedarone</td>
<td>4; 5</td>
</tr>
<tr>
<td>ICD Implant</td>
<td>13</td>
</tr>
<tr>
<td>Observation time before LCSD, median (IQR), yrs</td>
<td></td>
</tr>
<tr>
<td>from first symptom</td>
<td>4 (2-7)</td>
</tr>
<tr>
<td>from diagnosis</td>
<td>3 (0.5-6)</td>
</tr>
</tbody>
</table>

AAD = antiarrhythmic drugs; ACA = aborted cardiac arrest; FH = family history; ICD-AD = ICD appropriate discharge; LCSD = left cardiac sympathetic denervation; SCD = sudden cardiac death.

For drugs, daily doses in mg/kg are presented as mean±SD. For those therapeutic subgroups with ≤2 patients, individual values are provided.
Table 2. Effect of LCSD on event rate for the subset experiencing breakthrough major cardiac events (MCEs) while on optimal medical treatment (OMT).

<table>
<thead>
<tr>
<th></th>
<th>Number of pts with MCEs on OMT*</th>
<th>Median event count (IQR) §</th>
<th>Mean yearly event rates per patient (95%CI) ¶</th>
<th>IRR (95%CI)°</th>
<th>% change in expected count</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before LCSD</td>
<td>38/38</td>
<td>9(2-22)</td>
<td>3.4 (3.2-3.7)</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>After LCSD</td>
<td>12/38</td>
<td>0 (0-1)</td>
<td>0.5 (0.4-0.6)</td>
<td>0.08 (0.03-0.23)</td>
<td>-92%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Pre-and postoperative values were compared by means of McNemar test (p<0.001)

§Pre-and postoperative values were compared by means of Wilcoxon signed rank test (p>0.001)

¶Computed over a median observation time of 51 months (IQR 35-91) on OMT before LCSD and of 43 months (IQR 28-71) after LCSD.

°IRR=incidence rate ratio, estimate controlled for age at surgery (<15 years) and gender.
A ratio of 0.08 denotes a 92% reduction in the rate of MCEs when event rates after and before LCSD are compared.

Table 3. Types and daily doses of prescribed antiarrhythmic drugs pre- and post-LCSD in the 38 patients with MCEs despite OMT.

<table>
<thead>
<tr>
<th></th>
<th>Before LCSD</th>
<th>After LCSD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>mg/Kg</td>
</tr>
<tr>
<td><strong>Beta-blockers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nadolol</td>
<td>13</td>
<td>1.4±0.9</td>
</tr>
<tr>
<td>Propranolol</td>
<td>9</td>
<td>3.9±1.2</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>5</td>
<td>2.2±1.0</td>
</tr>
<tr>
<td>Atenolol</td>
<td>7</td>
<td>2.1±1.0</td>
</tr>
<tr>
<td>Labetalol</td>
<td>2</td>
<td>6; 10</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>2</td>
<td>0.2; 0.3</td>
</tr>
<tr>
<td>Flecainide in addition to BBs</td>
<td>9</td>
<td>4±1.8</td>
</tr>
<tr>
<td><strong>Other AADs in addition to BBs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mexiletine</td>
<td>5</td>
<td>5.4±0.9</td>
</tr>
<tr>
<td>Verapamil</td>
<td>5</td>
<td>2.8±1.1</td>
</tr>
<tr>
<td>Dronedarone</td>
<td>1</td>
<td>13</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>2</td>
<td>4; 5</td>
</tr>
<tr>
<td>Propafenone</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

*Doses are expressed as mean±SD; for those therapeutic subgroups with ≤2 patients, individual values are provided.

*Latest doses recorded in each of the two periods.
Figure Legends:

**Figure 1.** Kaplan-Meier curve of cumulative survival to a first MCE pre-LCSD in symptomatic CPVT patients. Numbers under curve are patients at risk and percentage of event-free survival before surgery.

**Figure 2.** Flowchart of the study population showing the number of CPVT patients sub-divided according to pre-LCSD clinical and therapeutic status and by post-LCSD outcome. Abbreviations: CPVT=Catecholaminergic Polymorphic Ventricular Tachycardia; LCSD=Left Cardiac Sympathetic Denervation; MCE=Major Cardiac Events; OMT=Optimal Medical Treatment.

**Figure 3.** Kaplan-Meier curve of cumulative survival to a first MCEs post–LCSD in symptomatic CPVT patients. Numbers under curve are patients at risk and percentage of event-free survival during follow-up.

**Figure 4.** Effect of LCSD on MCEs in the 54 symptomatic patients including the 16 with no MCEs on OMT in addition to the 38 with MCEs on OMT. The figure shows for each patient the number of MCEs, before and after LCSD. Each line represents one patient. The numbers in the squares represent the patients and those outside are clusters of MCEs of increasing frequency.

**Figure 5.** Incidence rate of MCEs before and after LCSD for the 38 CPVT patients who continued to have symptoms despite optimal medical therapy (OMT). Each line on either side of
the vertical line (time of LCSD) represents one patient and the corresponding number of MCEs per year occurring from start of OMT to LCSD (left) and from LCSD to last follow-up (right).

**Figure 6.** Percentages of recurrences in the 38 patients with MCEs on OMT pre-LCSD following either incomplete or complete LCSD.
Figure 1

Cumulative event-free survival (%)

Age (years)

N. at risk

54

20 (28%)

1 (2%)

1

1
**Study population**

All CPVT patients (n=63)

- **Pre-LCSD clinical status**
  - Asymptomatic (n=9)
  - Symptomatic (n=54)

  - **Pre-LCSD clinical status by response to OMT**
    - No MCEs on OMT (n=16)
    - MCEs on OMT (n=38)

- **LCSD**
  - Asymptomatic (n=9)
  - No recurrences (n=15)
  - Recurrences (n=1)
  - No recurrences (n=26)
  - Recurrences (n=12)

*Figure 2*
Figure 3
INCIDENCE OF MCEs PER YEAR BEFORE AND AFTER LCSD ON OMT (n=38)

Figure 5
Figure 6
Clinical Management of Catecholaminergic Polymorphic Ventricular Tachycardia: The Role of Left Cardiac Sympathetic Denervation


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