Clinical Management of Catecholaminergic Polymorphic Ventricular Tachycardia

The Role of Left Cardiac Sympathetic Denervation

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Background—Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a genetic disorder causing life-threatening arrhythmias whenever sympathetic activity increases. β-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 63 patients with CPVT 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. Of the 54 patients with prior major cardiac events either on (n=38) or off (n=16) optimal medical therapy, 13 (24%) had at least 1 recurrence: 0 patients had an aborted cardiac arrest, 2 patients had syncope only, 10 patients had ≥1 appropriate ICD discharges, and 1 patient died suddenly. The 1- and 2-year cumulative event-free survival rates were 87% and 81%. The percentage of patients with major cardiac events despite optimal medical therapy (n=38) was reduced from 100% to 32% (P<0.001) after LCSD, and among 29 patients with a presurgical ICD, the rate of shocks dropped by 93% from 3.6 to 0.6 shocks per person per year (P<0.001). Patients with an incomplete LCSD (n=7) were more likely to experience major cardiac events after LCSD (71% versus 17%; P<0.01) than those with a complete LCSD.

Conclusions—LCSD is an effective antifibrillatory intervention for patients with CPVT. Whenever syncope occurs despite optimal medical therapy, LCSD could be considered the next step rather than an ICD and could complement ICDs in patients with recurrent shocks. **(*Circulation*. 2015;131:2185-2193. DOI: 10.1161/CIRCULATIONAHA.115.015731.)**

Key Words: adrenergic beta-antagonists ■ arrhythmias, cardiac ■ death, sudden ■ genetics ■ sympathetic nervous system

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Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a clinically important and potentially lethal genetic disorder characterized by exercise- or stress-induced ventricular arrhythmias, including ventricular tachycardia and fibrillation.[1–4] The principal autosomal-dominant form is caused by mutations in the *RYR2*-encoded cardiac ryanodine receptor, whereas the rare autosomal-recessive form stems from homozygous or compound heterozygous mutations in the *CASQ2*-encoded calsequestrin 2 gene (*CASQ2*), both of which result in a net increase in intracellular diastolic calcium during sympathetic activation.[5–9] CPVT manifests primarily in children and adolescents, and the ECG at rest is normal.

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β-Blockers are effective in most patients,[3] but when breakthrough events occur or when patients continue to manifest ventricular tachycardia 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 after arrhythmic storms or inappropriate discharges triggered by supraventricular tachycardias.[10,11] Recently, preliminary data have suggested the potential value of combination drug therapy involving β-blockers and flecainide, but definitive evidence is still lacking.[12,13]

In 2008, we demonstrated that left cardiac sympathetic denervation (LCSD) was quite effective in 3 patients with CPVT who continued to experience ventricular fibrillation and aborted cardiac arrest (ACA) despite full-dose β-blockers.[14] Our report was followed by others,[15–18] 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 patients with CPVT 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 United States, and 1 each in Canada, Israel, and Australia. Deidentified baseline and follow-up information was obtained by the coordinating center in Pavia using Web-based forms. The diagnosis of CPVT was clinically based 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 similar overall to those described by Hayashi et al[3] in their 101 patients with CPVT; the only difference was 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 experienced at least 1 major cardiac event (MCE), that is, arrhythmic syncope, ACA, or ICD appropriate discharges (ICD-ADs). Electrical storms were defined as the occurrence of ≥3 separate episodes of sustained ventricular tachycardia and/or fibrillation in 24 hours in patients without ICD or ≥3 nonconsecutive 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. β-Blockers or flecainide at the maximum tolerated dose represented optimal medical therapy (OMT). On the basis of the intention-to-treat principle, MCEs after LCSD that occurred after potentially detrimental changes in therapy and MCEs that occurred during brief periods of noncompliance were nevertheless included in the event count.

Early follow-up for a few patients has been reported.[14–18]

Surgery

The interventions were performed over a 26-year period (1988–2014). Complete LCSD required resection of the lower half of the left stellate ganglion (T1), together with the thoracic ganglia T2 through T4. This surgical denervation provides adequate cardiac denervation with no or minimal Horner 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 was not ablated, denervation was considered incomplete. The main surgical approaches used were the thoracoscopic,[16] the transaxillary,[17] and the supraclavicular approach.[20]

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

Statistical Analysis

Continuous data are presented as median with the 25th and 75th percentiles, which define the interquartile range (IQR). Absolute and relative frequencies were reported for categorical variables and compared by the Fisher exact test. Nonparametric 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 before and after 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% confidence interval [CI]) of MCEs per patient per year of follow-up. To assess the effect of LCSD on the rate of events, while controlling for sex and age at surgery (<15 or ≥15 years), a negative binomial regression model was fitted, given the skewness in the frequency of MCEs, using generalized estimating equations. Robust standard errors were computed to account for intrapatient correlation over time. The incidence rate ratio, 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) and appropriate discharges (ICD-ADs) only in patients with an ICD implanted were considered end points. Preoperative and postoperative event-free survival was described by Kaplan–Meier cumulative estimates. Two-sided values of $P<0.05$ 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 patients with CPVT. In 7 patients, all symptomatic and with a diagnosis based on accepted criteria,[2,3] 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 from formal CPVT diagnosis to LCSD was 3 years (IQR, 0.5–6 years).

Clinical History Before LCSD

No Cardiac Events

Nine asymptomatic patients (14%), all CPVT1, underwent LCSD. In 8 patients, a positive family history for sudden cardiac

Table 1. Baseline Characteristics of the Study Population

CPVT patients, n	63
Families, n	53
FH for SCD, n (%)	18 (34)
Male sex, n (%)	32 (51)
Genotype unknown/not evaluated, n (%)	7 (11)
RYR2/CASQ2 negative	6 (10)
Genotype positive	50 (79)
RYR2 heterozygous	43 (86)
RYR2+*CASQ2* double-mutation carriers	2 (4)
CASQ2 homozygous	4 (8)
CASQ2 heterozygous	1 (2)
Symptomatic before LCSD, n (%)	54 (86)
≥1 syncope	46 (85)
≥1 ACA	18 (33)
≥1 ICD-AD	23 (43)
≥1 electrical storm	14 (26)
≥1 end-of-treatment condition	5 (9)
Age at first symptom, median (IQR), y	8.5 (6–11)
Age at diagnosis, median (IQR), y	9 (7–14)
Medical therapy before LCSD, n (%)	63 (100)
β-Blockers and daily dose, mg/kg	61 (97)
Nadolol 1.2±0.7	22 (35)
Atenolol 1.9±0.9	16 (25)
Metoprolol 1.9±0.9	10 (16)
Propranolol 3.9±1.2	9 (14)
Labetalol 6, 10	2 (3)
Bisoprolol 0.2, 0.3	2 (3)
Flecainide and daily dose, mg/kg 3.1±1.9	15 (24)
Other AADs and daily dose, mg/kg	13 (21)
Mexiletine 5.4±0.9	5 (8)
Verapamil 2.8±1.1	5 (8)
Amiodarone 4, 5	2 (3)
Dronedarone 13	1 (2)
ICD implantation	32 (51)
Observation time before LCSD, median (IQR), y	
From first symptom	4 (2–7)
From diagnosis	3 (0.5–6)

For drugs, daily doses are presented as mean±SD. For those therapeutic subgroups with ≤2 patients, individual values are provided. AAD indicates antiarrhythmic drug; ACA, aborted cardiac arrest; FH, family history; ICD, implantable cardioverter-defibrillator; ICD-AD, implantable cardioverter-defibrillator appropriate discharge; IQR, interquartile range; LCSD, left cardiac sympathetic denervation; and SCD, sudden cardiac death.

death or syncope was present. Three patients also had minor documented ventricular arrhythmia (nonsustained ventricular tachycardia in 1 case, premature ventricular contractions and bidirectional couplets in another, nonsustained broad-complex tachycardia in the third) on therapy, and 2 were intolerant of β-blockers because of 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 years (IQR, 6–11 years), and by 15 years of age, 96% of these symptomatic patients had already had a first MCE (Figure 1). Syncope only occurred in 21 patients, whereas 33 had ACA (n=18) and/or ICD-AD (n=23), usually in addition to ≥1 syncopal episodes. Electrical storms (n=14) and end-of-treatment conditions (n=4) also occurred.

Medical Therapy

Most patients (61 of 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 nonsignificant differences (79% versus 62%; P=0.24) in the comparison of recurrences in patients receiving either nadolol or propranolol (22 of 28) compared with other β-blockers (16 of 26).

ICD Implantation

An ICD was implanted in 37 of 63 patients (59%) at a median age of 11 years (IQR, 9–14.5 years): 32 at a median time of 41 months (IQR, 15–66 months) before LCSD, 2 simultaneously with LCSD, and 3 after LCSD. In 14 of 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 sudden cardiac death and/or recurrence of arrhythmic events despite OMT were considered markers of high risk. During a median postimplantation follow-up time of 7 years (IQR, 3–10 years), there was a total of 17 device-related complications in 12 of 37 patients (32%), including 1 sepsis, 1 endocarditis, and 1 deep venous thrombosis. The majority (10 of 17, 59%) were cases of lead malfunctioning or fracture. In addition, 7 patients (19%) had a total of 10 generator replacements after reaching the 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 years (IQR, 1.3–5.5 years) from ICD implantation 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 of 32 patients (37%), and at least 1 end-of-treatment condition was reported in 4 patients (12%). A total 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 years), 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–T4)

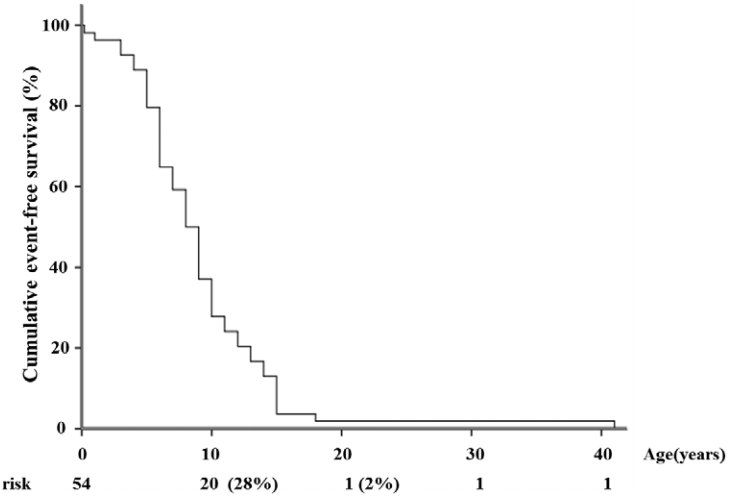

Figure 1. Kaplan–Meier curve of cumulative survival to a first major cardiac event before left cardiac sympathetic denervation in symptomatic patients with catecholaminergic polymorphic ventricular tachycardia. Numbers under the curve are patients at risk and percentage of event-free survival before surgery.

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, a ventricular fibrillation 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 of 63) to 21% (13 of 63; $P<0.001$). This analysis included the 9 patients who were asymptomatic before 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 us to reveal potential proarrhythmic effects and mitigated the risk of the phenomenon of regression toward the mean. However, because these asymptomatic patients clearly cannot provide information relative to the antiarrhythmic efficacy of LCSD, our analyses focus hereafter on the 54 symptomatic patients.

These 54 patients with prior MCEs either while on OMT (n=38) or before institution of OMT (n=16) were observed for a median follow-up of 39 months (IQR, 27–64 months). Their 1- and 2-year cumulative event-free survival was 87% and 81%, respectively (Figure 3). In total, MCEs recurred after LCSD in 13 of 54 patients (24%); 1 of them, with a single ICD-AD during admitted noncompliance, belonged to the 16 patients with MCEs before 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 1 case of sudden death in a 15-year-old previously symptomatic adolescent male patient who had been totally event

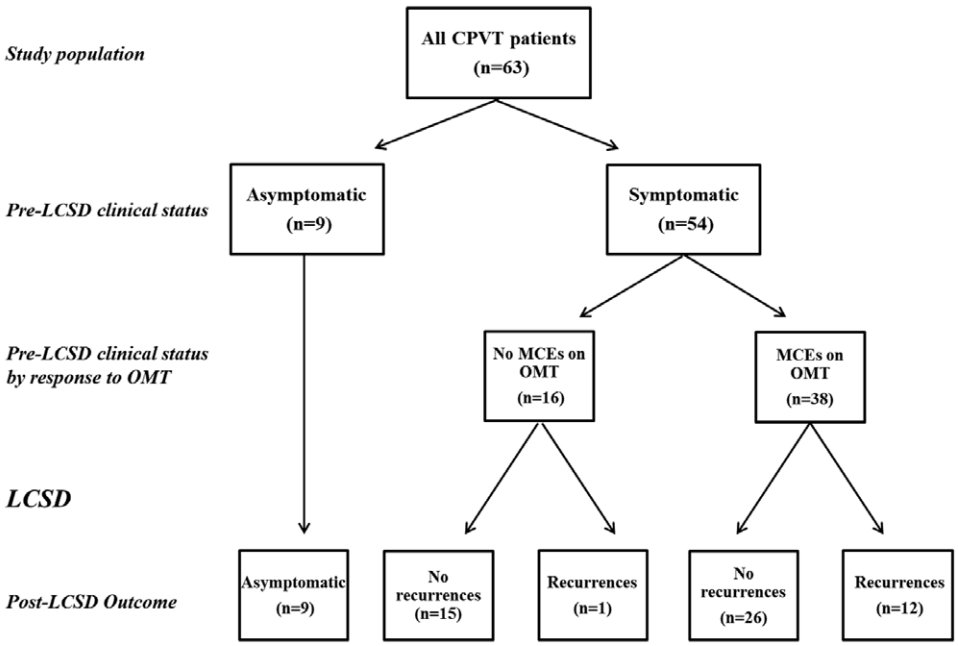

Figure 2. Flowchart of the study population showing the number of patients with catecholaminergic polymorphic ventricular tachycardia (CPVT) subdivided according to pre–left cardiac sympathetic denervation (LCSD) clinical and therapeutic status and by post-LCSD outcome. MCE indicates major cardiac events; and OMT, optimal medical treatment.

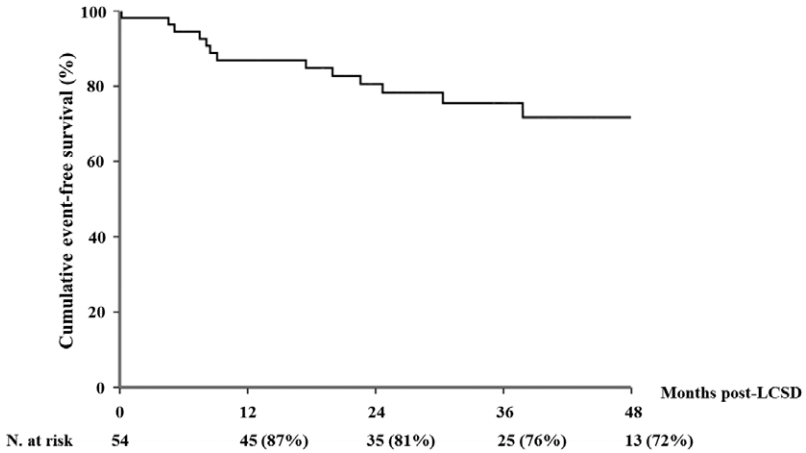

Figure 3. Kaplan–Meier curve of cumulative survival to a first major cardiac event after left cardiac sympathetic denervation (LCSD) in symptomatic patients with catecholaminergic polymorphic ventricular tachycardia. Numbers under the curve are patients at risk and percentage of event-free survival during follow-up.

free for 8 months after 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 nonresponder 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 both in 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), whereas the median preobservation and postobservation times were similar (51 months from institution of OMT to LCSD and 43 months after LCSD follow-up, respectively).

We considered some potential confounders: the burden of arrhythmic events before 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 (Figure 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). Additionally in this case, a remarkable reduction (88%) in MCEs after 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 before to 16 after LCSD. Of these additional 7 patients, 2 received flecainide in the absence of MCEs and 5 because of continued recurrences. Flecainide was associated with suppression of arrhythmic events in only 1 of these 5 patients.

LCSD and ICD

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

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

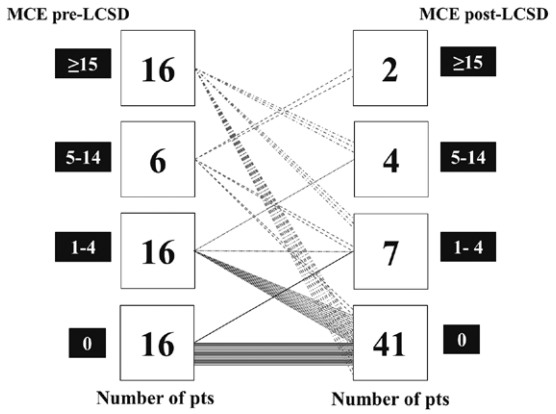

Figure 4. Effect of left cardiac sympathetic denervation (LCSD) on major cardiac events (MCEs) in the 54 symptomatic patients, including the 16 with no MCEs on optimal medical therapy (OMT) and the 38 with MCEs on OMT. The figure shows for each patient the number of MCEs before and after LCSD. Each line represents 1 patient. The numbers in the squares represent the patients; those outside the squares are clusters of MCEs of increasing frequency.

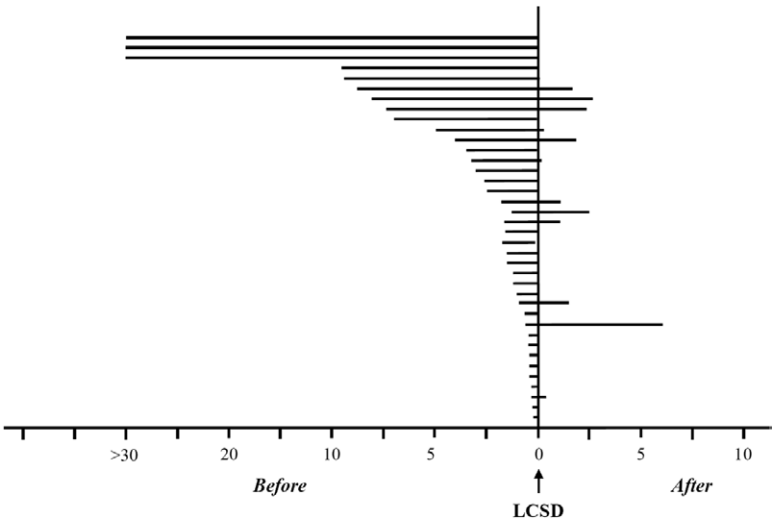

Figure 5. Incidence rate of major cardiac events (MCEs) before and after left cardiac sympathetic denervation (LCSD) for the 38 patients with catecholaminergic polymorphic ventricular tachycardia who continued to have symptoms despite optimal medical therapy (OMT). Each line on either side of the vertical line (time of LCSD) represents 1 patient and the corresponding number of MCEs per year occurring from the start of OMT to LCSD (**left**) and from LCSD to the last follow-up (**right**).

Extent of Denervation and Outcome

Among the 54 symptomatic patients, the 7 subjects with an incomplete denervation were much more likely to experience recurrences of cardiac events after surgery compared with those with a complete LCSD (5 of 7 [71%] versus 8 of 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): recurrences after LCSD occurred in 5 of 5 patients (100%) with an incomplete denervation versus 8 of 33 patients (24%) 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 their families. After the first report on the use of LCSD in CPVT,[14] we thought it necessary to document whether LCSD should become a recommended treatment for patients with CPVT 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[21] and match those already observed in other arrhythmogenic conditions.[18,22–24] These findings should therefore have an important impact on the approach to managing CPVT.

Our analysis focused on the 54 patients who had previously experienced 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 per patient per year. LCSD had a clear impact on all cardiac events; 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 β-blocker in long-QT syndrome.[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 (Figure 5) in which each patient served as his/her own control that shows a 92% reduction in MCEs. There was also a major reduction in the number of ICD-ADs; interestingly, this reduction (≈93%) is the same previously reported after LCSD for electrical storms in long-QT syndrome.[22] We cannot entirely exclude 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,

Table 2. Effect of LCSD on Event Rate for the Subset Experiencing Breakthrough MCEs While on OMT

	Patients With MCEs on OMT, n*	Median Event Count (IQR)†	Mean Yearly Event Rates per Patient (95% CI)‡	IRR (95% CI)§	Change in Expected Count, %	*P* Value
Before LCSD	38/38	9 (2–22)	3.4 (3.2–3.7)	1		
After LCSD	12/38	0 (0–1)	0.5 (0.4–0.6)	0.08 (0.03–0.23)	–92	<0.001

A ratio of 0.08 denotes a 92% reduction in the rate of MCEs when event rates after and before LCSD are compared. CI indicates confidence interval; IQR, interquartile range; IRR, incidence rate ratio; LCSD, left cardiac sympathetic denervation; MCE, major cardiac events; and OMT, optimal medical treatment.

*Preoperative and postoperative values were compared by means of the McNemar test ($P<0.001$).

†Preoperative and postoperative values were compared by means of the Wilcoxon signed-rank test ($P<0.001$).

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

§IRR is controlled for age at surgery (<15/≥15 years) and sex.

Table 3. Types and Daily Doses of Prescribed Antiarrhythmic Drugs Before and After LCSD in the 38 Patients with MCEs Despite OMT

	Before LCSD		After LCSD	
	n	mg/kg*	n	mg/kg*
β-blockers				
Nadolol	13	1.4±0.9	15	1.4±0.8
Propranolol	9	3.9±1.2	8	4.0±1.1
Metoprolol	5	2.2±1.0	8	2.4±1.3
Atenolol	7	2.1±1.0	5	2.1±1.3
Labetalol	2	6, 10	1	10
Bisoprolol	2	0.2, 0.3	1	0.2
Flecainide in addition to β-blockers	9	4.0±1.8	16	3.5±1.6
Other AADs in addition to β-blockers				
Mexiletine	5	5.4±0.9	3	5.7±1.1
Verapamil	5	2.8±1.1	4	2.5±1.0
Dronedarone	1	13	0	
Amiodarone	2	4, 5	2	4, 5
Propafenone	0		1	9

Doses are expressed as mean±SD. For those therapeutic subgroups with ≤2 patients, individual values are provided. AAD indicates antiarrhythmic drug; LCSD, left cardiac sympathetic denervation; MCE, major cardiac events; and OMT, optimal medical treatment.

*Latest doses recorded in each of the 2 periods.

the reduction in MCEs after LCSD remains very high even after the sensitivity analyses performed to decrease the impact of a few outliers. In addition, the results were not influenced by changes in medical therapy because both doses and types of β-blockers remained substantially stable when the pre-LCSD and post-LCSD periods were compared.

The concept of a therapeutic dose is confirmed also for LCSD. Indeed, the 7 patients with an incomplete denervation, caused mostly by sparing the lower half of the left stellate ganglion, had significantly more recurrences of arrhythmic events compared with patients who received what is considered the comprehensive LCSD (T2–T4 plus a lower-half stellectomy). This finding, also reported in patients with long-QT syndrome,[22] should mandate comprehensive LCSD and dissuade the execution of a suboptimal surgical procedure.

The antiarrhythmic and antifibrillatory effects of LCSD in a variety of clinical conditions and its mechanisms of action have been reviewed recently.[21] The interruption of the localized release of norepinephrine at the ventricular level, which accentuates the arrhythmogenic ventricular dis-homogeneity of repolarization,[26] and its direct antifibrillatory effect are critically important.[27] Being a preganglionic denervation, LCSD is not followed by reinnervation or by postdenervation hypersensitivity.[28] α-Adrenergic antagonism may contribute to the favorable effects of LCSD, in agreement with experimental findings in a model of calsequestrin-dependent CPVT.[29] Bilateral sympathectomy could be considered after only partial success with unilateral LCSD to further reduce the release of norepinephrine at the ventricular level and to better control heart rate.[30]

The present data force a reassessment of the current clinical approach to patients with CPVT. β-Blockers (propranolol or nadolol) certainly should remain the first-line therapy, being effective for the majority (two-thirds) of patients.[3] Although reported as promising,[12,13,19] the combination of β-blocker and flecainide therapy still requires confirmation in an adequately large population of patients with CPVT experiencing recurrences on β-blocker monotherapy and implies lifelong therapy with a Class I antiarrhythmic drug. Even though just a byproduct of our study, the fact that after flecainide an arrhythmia suppression was observed in only 1 of 14 patients with arrhythmias despite β-blockade (n=9) and β-blockade plus LCSD (n=5) suggests that this agent has a 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 $mg \cdot kg^{-1} \cdot d^{-1}$). Most of them (6 of 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 patients with CPVT. 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.[10,11] This potential unintended, undesired consequence is further compounded by an extremely high rate of adverse events. The 7-year incidences of complications (32%) and of generator replacements (19%) observed in our population are worrisome given that the expected duration of treatment exceeds 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, usually being effective only when the treated rhythm is ventricular fibrillation.[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 1-time, minimally invasive procedure, LCSD is an effective antifibrillatory/antiarrhythmic intervention for patients with CPVT.

LCSD should always be considered in patients with CPVT experiencing recurrent ICD shocks. The occurrence of major events after LCSD in only 9% of the patients left without ICD

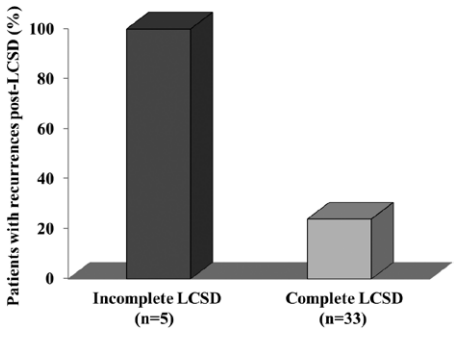

Figure 6. Percentages of recurrences in the 38 patients with major cardiac events on optimal medical therapy before left cardiac sympathetic denervation (LCSD) after either incomplete or complete LCSD.

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 was the case for long-QT syndrome, a randomized, clinical trial is simply not feasible for obvious reasons, including ethical issues. The option to compare the present results with the outcomes in our patients with CPVT without LCSD is voided by the attendant selection bias because such a group would be at much lower risk since 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 before and after 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. In addition, the appropriateness of the ICD shocks was assessed by the enrolling centers because we had not instituted a centralized blinded assessment for ICD interrogation. We did not deem it necessary to obtain specific details for every patient because we were dealing with tertiary referral centers for arrhythmic patients with highly experienced electrophysiologists.

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CLINICAL PERSPECTIVE

We have investigated the effects of left cardiac sympathetic denervation (LCSD) in 63 patients (54 symptomatic) with catecholaminergic polymorphic ventricular tachycardia. Patients who continue to have catecholaminergic polymorphic ventricular tachycardia–triggered ventricular tachyarrhythmias and syncope despite full-dose β-blockade represent a major clinical problem. Implantable cardioverter-defibrillators are not an ideal solution because shocks may trigger electrical storms and because both malfunction and adverse events are common in this young population (32% in 7 years among our cases). In addition, combination therapy with flecainide is often ineffective in the most severe cases. On the other hand, our data show that among the 38 patients with continued major cardiac events despite optimal medical therapy, LCSD was associated with an estimated 92% and 93% reduction in the rate of major cardiac events and of appropriate implantable cardioverter-defibrillator discharges, respectively. The few patients in whom an incomplete/suboptimal LCSD was performed were not protected from arrhythmias, thus confirming the importance of complete LCSD (from the lower half of the stellate ganglion to T4). The present data force a reassessment of the clinical approach to patients with catecholaminergic polymorphic ventricular tachycardia who are not fully protected by β-blockers. Unless a cardiac arrest has occurred, LCSD should be considered and implemented instead of proceeding directly to an implantable cardioverter-defibrillator. In very-high-risk patients, a rational strategy while continuing with β-blockers can include an implantable cardioverter-defibrillator, to serve as a safety net, and LCSD, to prevent major arrhythmic events. This approach would take care of both safety and quality of life for these predominantly young patients.

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