Clinical and genetic spectrum of hereditary cardiac arrhythmia syndromes

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Left Cardiac Sympathetic Denervation for Catecholaminergic Polymorphic Ventricular Tachycardia

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Summary
Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a potentially lethal disease characterized by adrenergically-mediated ventricular arrhythmias manifesting especially in children and teen-agers. ß-blockers are the cornerstone of therapy, but some patients are not fully protected and receive an implantable cardioverter defibrillator (ICD). Given the nature of CPVT, ICD shocks may trigger new arrhythmias leading to multiple shocks. We describe the remarkable long term efficacy of surgical left cardiac sympathetic denervation in three young adults with CPVT, all symptomatic prior to and symptom-free after the procedure.

Introduction
Catecholaminergic polymorphic ventricular tachycardia (CPVT), first recognized in the 1970’s, is a genetic disorder caused by mutations in genes involved in the calcium homeostasis of cardiac cells. Following initial observations that linked CPVT to chromosome 1, two disease-causing genes were identified: the Ryanodine receptor gene (hRyR2) and the cardiac calsequestrin gene (CASQ2). CPVT presents with life-threatening ventricular arrhythmias, usually polymorphic ventricular tachycardia (VT) or ventricular fibrillation (VF), especially in conditions of increased sympathetic activity including physical exercise or emotional stress. It often becomes manifest at young age and the first event may be lethal.

The management of CPVT is difficult. Most patients are protected by ß-adrenergic blocking agents but many continue to have symptoms and/or documented exercise-induced VTs. The current views hold that for these patients the only additional therapy available is the implantable cardioverter defibrillator (ICD). However, as even modest exercise initiates fast VTs that trigger ICD shocks the quality of life of these patients is often diminished. In addition, ICD’s do not protect all patients and physicians sometimes resort to the extreme measure of cardiac transplantation.

We present evidence that left cardiac sympathetic denervation (LCSD), an antifibrillatory intervention that largely prevents norepinephrine release in the heart, might reduce these adrenergically-mediated life-threatening arrhythmias. We also propose that LCSD may represent a novel and effective treatment for those young CPVT patients who are not fully protected by ß-blockers.

Clinical Cases
Patient 1 carries a de novo hRyR2 missense mutation, F4511L, absent in his relatives and in 117 controls. Since age 10 he had frequent syncope and at age 17 an episode of polymorphic VT was documented during a bicycle exercise stress testing at 50 watts. Despite pro-
pranolol (240mg) he had a cardiac arrest due to VF after an emotional encounter. In 1988, at age 18, he underwent LCSD. During the following 19 years he remained asymptomatic although non-sustained VT can still be induced by exercise but only at 120 watts and above. Patient 2 carries the hRyR2 mutation, E4076K, absent in 100 controls and strongly segregating within the family, characterized by adrenergically-dependent symptoms and premature sudden death under typical circumstances. She became symptomatic at age 10 and remained symptomatic despite full dose β-blockade (2.5mg/kg metoprolol, i.e.100mg) and continued to have VT during exercise. Her family members were successfully treated with β-blockers. Because of the negative impact of these exercise-induced arrhythmias on her quality of life, in 2005, at age 17, she underwent LCSD. During the next 24 months she remained asymptomatic and ventricular arrhythmias appear only at higher workloads. Figure 1 shows recordings from a stress test prior to and immediately after LCSD. The total arrhythmia burden (ventricular extrasystoles per minute) in all available exercise stress tests in this patient (all on the same dose of metoprolol) is shown in figure 2. In the left panels frequent extrasystoles (> 50/min) were seen at respectively 686, 450 and 183 days prior to surgery. The right panels were obtained 2, 12 and 236 days after surgery. There is a clear reduction in the number of extrasystoles which after the procedure do not exceed 20/min
at peak exercise. Note that the exercise test also lasts longer in the test at 236 days post surgery.

Patient 3 carries the hRyR2 G3946S mutation. Since age 11 this boy suffered many episodes of syncope with documented exercise-related polymorphic VT. An ICD was implanted in 1995. Despite treatment with high doses of propranolol and mexiletine he received numerous shocks including 5 consecutive appropriate shocks. For this reason he underwent LCSD in 1998. He was discharged on the same pharmacological therapy. During the subsequent 9 years he has remained fully asymptomatic and without any ICD discharge.

LCSD is performed in 35-40 minutes, following an incision at the base of the neck, by an extrapleural approach without opening the chest. The lower part of the stellate ganglion is ablated together with the second and third thoracic ganglia; the fourth ganglion is cathe-

Figure 2: The arrhythmia burden during all exercise tests prior to and following LCSD. The number of ventricular extrasystoles/min (VE/min) and heart rate are shown against time of exercise (HF (spm) = Heart rate (beats per minute). The vertical lines in all panels indicate the end of exercise (left line) and the end of the test (right line). In the left panels frequent extrasystoles (> 50/min) were seen at respectively 686, 450 and 183 days prior to surgery. The right panels were obtained 2, 12 and 236 days after surgery. There is a clear reduction in the number of extrasystoles which do not exceed 20/min after the procedure. Note that the exercise test also lasts longer in the test at 236 days.
ized. Preserving the upper half of the stellate ganglion prevents the occurrence of Horner’s syndrome.

**Discussion**

CPVT is a malignant disorder affecting young individuals and for which, in individual cases, current therapies are unsatisfactory. Adrenergic stimuli trigger difficult to treat life-threatening arrhythmias. β-adrenoreceptor blockade does not provide full protection, nor does ICD implantation. The latter is particularly ill-suited for CPVT because the pain and fear generated by the shocks may initiate arrhythmic storms with multiple shocks. LCSD may represent a viable solution for CPVT patients not fully protected by β-blockers as exemplified by the patients described here.

**Rationale for LCSD**

The arrhythmogenic mechanism in CPVT has been shown to involve catecholamine-induced activation of cAMP-dependent protein kinase A which phosphorylates several key Ca++ handling proteins including the ryanodine receptor 2 (RyR2). This increases calcium-activated calcium release from the sarcoplasmic reticulum. Mutant RyR2 channels show a gain-of-function effect resulting in excessive calcium release during sympathetic activation generating depolarizing membrane currents, delayed afterdepolarizations and cardiac arrhythmias. Hence, the two most critical steps in the arrhythmogenesis of CPVT are represented by increased catecholamines and by the attendant increased release of calcium. The therapeutic strategy presented here focuses on interfering with the release of norepinephrine at the myocardial level.

LCSD interrupts the major source of norepinephrine released in the heart and has multiple antiarrhythmic effects. It increases the threshold for VF and increases ventricular refractoriness. As LCSD is a preganglionic denervation, there is no reinnervation. Also, since LCSD does not reduce to zero the catecholamines content in the ventricles, it does not lead to post-denervation supersensitivity.

LCSD has been shown to be highly effective in a high-risk subgroup of post-myocardial infarction patients and in the long QT syndrome (LQTS) in which it has been shown, in a mean follow-up of 8 years, to reduce by 90% the major arrhythmic events among patients not protected by full-dose β-blocker therapy.

LCSD does not preclude an ICD implant when the strategy aims at having the ICD as a safety net and at LCSD plus β-blockers to minimize the risk of life-threatening arrhythmias.

**Management of CPVT**

β-blockers, universally regarded as the first-line therapy for CPVT, have been reported to
have a very high success rate by some\textsuperscript{8,22}, but not all\textsuperscript{9,23}, investigators. Recently, verapamil has successfully been added in 5 non-genotyped CPVT patients.\textsuperscript{24} Asymptomatic persistence of frequent ventricular premature beats during exercise does not justify a major change in therapy. The main clinical issue is what to do when patients continue to have frank syncope or sustained VT under stress. Current views\textsuperscript{10,25} recommend ICD implant for any CPVT patient who still presents arrhythmias despite maximally tolerated doses of β-blockers. Physicians, however, need to address what happens after the ICD implant. Given the nature of the disease, in CPVT patients appropriate ICD shocks may potentially be life-saving but also produce pain and fear, both resulting in a catecholamines release which might then initiate a new episode of VT/VF and a second shock, sometimes initiating a vicious cycle. Furthermore, as not infrequently inappropriate defibrillator shocks occur, they may also lead to arrhythmia storms and in this case the ICD actually becomes proarrhythmic. The apparent lack of alternatives for patients failing β-blockers has even led to a cardiac transplant for a 17 year old CPVT patient who suffered from “innumerable” ICD shocks. Interestingly, before the occurrence of reinnervation, his clinical condition improved markedly without arrhythmic episodes. Indeed, complete denervation may produce denervation supersensitivity (i.e. excessive responses to catecholamines) with serious unwarranted effects.

There are several significant advantages with LCSD. This is a therapy done once and forever, because preganglionic denervation precludes possible reinnervation. LQTS patients operated even more than 30 years ago have remained completely free of cardiac events\textsuperscript{21}. It overcomes the limitations of medical therapy represented by incomplete compliance, especially in teen-agers. It can well complement an ICD, when really necessary, because it will markedly decrease the probability of arrhythmic events while having in place a device likely to interrupt VF and to restore sinus rhythm.

One unifying point of these three cases is represented by the significant improvement in their quality of life, associated with the reduction of the adrenergically-mediated cardiac arrhythmias.

**Conclusion**

The ability to antagonize or to reduce cardiac sympathetic activity seems the cornerstone of successful therapeutic interventions in CPVT, with β-adrenoreceptor blockade as the standard treatment. Whenever β-blockers fail, the current trend is to implant an ICD. While ICD therapy may indeed effectively protect against life-threatening arrhythmias, in CPVT this treatment may trigger arrhythmic storms and multiple shocks with negative effects on the patients’ quality of life. The present report provides evidence that LCSD may represent a very effective alternative treatment, especially indicated for those patients who are not ad-
equately controlled by β-blockade. Data on a larger number of CPVT patients treated with LCSD are warranted to properly assess the impact of this physiologically-based treatment modality for CPVT.

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