Cathecolaminergic ventricular tachycardia Treatment

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There are insufficient data for satisfactory risk stratification. Patients who have had an episode of VF and those who have sustained or are hemodynamically unstable VT whilst receiving β-blockers are considered at highest risk. Younger age at CPVT diagnosis is a predictor of future cardiac events (Hayashi et al., 2009). Invasive EP studies are not helpful (Priori et al., 2002). Genetic analysis does not yet contribute to risk stratification in clinically diagnosed patients.
Removal of triggers: Patients should be cautioned against virtually all forms of vigorous physical activity, (Maron et al., 2004). Therefore, the recommendations for patients with CPVT might be extrapolated from the LQTS guidelines, due to the similarity of the triggers in LQTS and CPVT.
All competitive sports are prohibited for symptomatic patients and asymptomatic patients with typically effort-induced ECG features. In genotype-positive, asymptomatic patients without any effort-induced ECG manifestation: recreational sports with only low intensity may be allowed (Ackerman et al., 2015).

A) Drugs
I.β-blockersarean effective pharmacological approach, unfortunately 30% of patients have recurrences with these drugs. β-blockers reduce arrhythmias, but in 30% of patients an implantable cardioverter defibrillator (ICD) may be required (Priori et al., 2002). ICD is necessary for prophylaxis of SCD because ≈30% of patients still experience Vts (N. Liu, Colombi, Raytcheva-Buono, Bloise, & Priori, 2007) that may arise in certain specific areas but the prognosis is poor. The onset of CPVT may be an indication for an ICD.The long acting β-blocker, nadolol (inexistent in Brazil) is preferred for prophylactic treatment of CPVT. Propranolol is also an effective medication; however, β-blockers cannot completely suppress the arrhythmic events in CPVT patients. Carvedilol is reported to inhibit the SOICR in an HEK 293 cell culture model. Among various β-blockers, only carvedilol inhibits RyR2 activity (Zhou et al., 2011). Thus, carvedilol may be an effective β-blocker for CPVT, but its β blocking effect may be weak in comparison to the other β-blockers. Therefore, the efficacy of carvedilol needs to be further investigated. Liu et al observed that RyR2-R2401H mutation in a Chinese patient with CPVT, and a high dose of metoprolol is the effective therapy option for CPVT related to RyR2 mutation (X. Liu et al., 2017).
II. Verapamil has also shown beneficial effects in some CPVT patients (Rosso et al., 2007; Swan et al., 2005). However, the long-term efficacy of verapamil is still controversial.
III. Flecainide reduced exercise-induced ventricular arrhythmias in patients with CPVT not controlled by conventional drug therapy (van der Werf et al., 2011). Watanabe discovered that flecainide directly inhibits RyR2 channels and prevents CPVT. (Watanabe et al., 2009), Among the Class I anti-arrhythmic medications, only flecainide and propafenone inhibit RyR2 activity (Hwang et al., 2011). However, recent report denies the direct suppression of RyR2 by flecainide (Bannister et al., 2015).That may suggest another mechanism of flecainide, such as inhibition of NCX. Flecainide was effective in patients with genotype-negative CPVT, suggesting that spontaneous Ca^{2+} release from ryanodine channels plays a role in arrhythmia susceptibility, similar to that in patients with genotype-positive CPVT (Watanabe et al., 2013). Flecainide can completely prevent ventricular arrhythmia during exercise and partially prevent recurrent ICD shocks in high-risk patients with CPVT2 (Khoury et al., 2013). Flecainide can be added for primary prevention of a SCA when β-blockers alone cannot control the onset of arrhythmias during TST (Napolitano, Priori, & Bloise, 1993). In a randomized clinical trial of patients with CPVT,

flecainide plus β-blocker significantly reduced ventricular ectopy during exercise compared with placebo plus β-blocker and β-blocker alone (Kannankeril et al., 2017). Flecainide suppresses cardiac tachyarrhythmias including paroxysmal AF, supraventricular tachycardia and arrhythmic LQTS, as well as the Ca^{2+}-mediated CPVT. The antiarrhythmic effects of flecainide that reduce triggering in CPVT models mediated by sarcoplasmic reticular Ca^{2+} release could arise from its primary actions on Na_V channels indirectly decreasing Ca^{2+} through a reduced Na^+ and/or direct open-state RyR2-Ca^{2+}channel antagonism. The consequent Ca^{2+} alterations could also modify AP propagation velocity and therefore the arrhythmic substrate through its actions on $Na_V1.5$ channel function. This is consistent with the paradoxical differences between flecainide actions upon Na^+currents, AP conduction and arrhythmogenesis under circumstances of normal and increased RyR2 function (Salvage et al., 2017). Flecainide proved to exhibit potential therapeutic efficacy in the Ca^{2+}- mediated CPVT. CPVT is predominantly associated with genetic abnormalities involving the cardiac ryanodine receptor type 2 sarcoplasmic reticular (SR) Ca2+ release channel (RYR2) and the SR binding protein calsequestrin type 2 (CASQ2) respectively. CPVT results in aberrant RYR2-mediated SR Ca^{2+} release precipitated by adrenergic stress. The leaky RyR2-Ca^{2+} release initiates delayed after depolarizations (DADs) that might trigger PVT. Initial findings that flecainide prevented ventricular arrhythmia in two patients with respective CASQ2 and RYR2 mutations in exercise stress tests suggested a mechanism involving reduced triggering activity (Watanabe et al., 2009). These clinical effects were corroborated by further case reports in which flecainide was added to prior conventional β-adrenergic antagonist therapy (Wanguemert-Perez et al., 2014).

Left cardiac sympathetic denervation (LCSD) and bilateral thoracoscopic sympathectomy and via a minimally invasive Video-Assisted Thoracoscopic Surgery (VATS-LCSD) Cardiac denervation was first undertaken by Estes and Izlar in 1961 for the treatment of ventricular arrhythmia (Nitter-Hauge & Storstein, 1973). With the advent of β-blocking drugs in 1964, the popularity of the procedure waned as a “medical sympathectomy” could be performed without the need for open surgery (Methangkool, Chua, Gopinath, Shivkumar, & Mahajan, 2014). Currently, cardiac denervationis indicated in the management of electrical storms and VT refractory to medical drugs, especially in the setting of LQTS (Schwartz et al., 2004) and CPVT VATS-LCSD is a safe and effective procedure for patients with hereditary VT syndrome, with no serious adverse events and with short hospital stay (Jang et al., 2017). Additionally,despite the anticipated side effects associated with VATS-LCSD, patients are satisfied with their surgery and indicate that they would recommend the surgery to another patient (Antiel et al., 2016).
VATS-LCSD is a surgical procedure that has been shown to have an antiarrhythmic and antifibrillatory effect. Evidence indicating its antiarrhythmic effect has been available for over 100 years. The procedure consists in removal of the lower half of the stellate ganglion and T2-T4 of the sympathetic ganglia and is carried out as either a unilateral or bilateral procedure. It can be safely performed via a minimally invasive VATS-LCSD approach resulting in significantly less morbidity and a shortened patient stay (McNamara et al., 2017).VATS-LCSD provides a valuable treatment option for patients with life-threatening channelopathies and cardiomyopathies. VATS-LCSD provides a critical adjunct to existing medical therapies and should be considered for all patients with life-threatening refractory arrhythmias especially those patients on maximal medical therapy. VATS-LCSD is reported to be a useful therapeutic method for suppressing ventricular arrhythmias in CPVT patients (De Ferrari et al., 2015; A. A. Wilde et al., 2008). In patients with uncontrollable VTs (electrical storm), VATS-LCSD is highly useful in controlling the events. The rate of complications involving Horner syndrome is very low if denervation is performed in the lower half of the T1 sympathetic ganglion through the T4 ganglion (De Ferrari et al., 2015). This approach is indicated in recurrent VTs for congenital LQTS and CPVT. There are studies suggesting an improvement in symptoms and survival for VATS-LCSD in a diverse range of underlying cardiac pathologies. Some evidence supports that bilateral cardiac sympathetic denervation may be more effective at preventing recurrent VT compared to left sided alone. Despite recent studies demonstrating promising results, rigorous clinical trials demonstrating the effectiveness and safety of VATS-LCSD surgery are lacking.

However, individuals with recurrent VT have a poor prognosis and a low quality of life, and surgical treatment may be justified in some individuals. Patients with recurrent VT, a multimodal approach should be used, including ICD, pharmacologic therapy, and catheter ablation. If VT persists after exhausting medical management, then VATS-LCSD may be considered. Future studies should focus on determining the impact of laterality on effectiveness and using novel imaging modalities to select patients most likely to benefit (Hong, Crawford, Tandri, & Mandal, 2017).

Main side effects of VATS-LCSD

- Dryness on left side (59%)
- A Harlequin-type (unilateral) facial flush (55%)
- Contralateral hyperhidrosis (39%)
- Differential hand temperatures (11%)
- Permanent (9%) and transient ptosis (11%)
- Thermoregulation difficulties (9%)
- A sensation of left arm paresthesia (7%)
- Sympathetic flight/fright response loss

The majority of the patients were satisfied postoperatively: (86%) were happy with the procedure, (75%) felt safer, (91%) recommended the procedure to others, and (91%) felt happy with their scar appearance (Waddell-Smith et al., 2015).

Summary of VATS-LCSD indications

1) When β-blockers are contraindicated or not tolerated:
a) when history of asthma is present,
b) when chronic obstructive pulmonary disease (COPD) is moderate to severe, i.e. with forced expiratory volume (FEV1) reduction <50% of the predicted value,
c) in patients on chronic bronchodilator treatment,
d) in chronic airflow limitation with evidence of ≥20% reversibility in airway obstruction in response to inhaled salbutamol. When FEV1 is >50% of the predicted value, β-blockers can be given, providing adequate control of stability of ventilatory conditions;

2) When syncope recurs despite maximum-dose β-blockade;

3) When ICD shocks recur;

4) When a patient remains at high risk of SCD despite being asymptomatic on β-blocker therapy (Schwartz, 2014).

When a cardiologist deals with a LQTS or CPVT patient at risk for SCD, it is no longer acceptable that the right to proper information about VATS-LCSD is denied (Schwartz, De Ferrari, & Pugliese, 2017).

ICD: Implantation of an ICD should be considered in patients in the absence of controlled optimal therapy (van der Werf, Zwinderman, & Wilde, 2012). However, implantation of an ICD in children still has several technical problems. Moreover, inappropriate or painful shocks may increase the risk of further ventricular arrhythmias, and electrical storms that may result in lethal events. The effectiveness of ICD shock therapy in CPVT depends on the mechanism of the rhythm treated. Shocks delivered to initiating triggered arrhythmias nearly always fail, whereas those for subsequent VF are usually effective.
ICD programming in these patients is exceptionally challenging (Roses-Noguer, Jarman, Clague, & Till, 2014).

Catheter ablation
Pulmonary vein isolation is reported to be effective in some CPVT patients with AF (Abe et al., 2014; Sumitomo et al., 2010). Purkinje cells are reported to be more arrhythmogenic than ventricular myocytes in a mutant knockout mouse model of CPVT (Kang et al., 2010). The onset of CPVT may be initiated from Purkinje cells. Successful catheter ablation has been reported at the site of Purkinje potentials or discrete prepotentials (Kaneshiro et al., 2012).