Risk stratification and genetics in catecholaminergic polymorphic ventricular tachycardia

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CHAPTER 15

English Summary

ENGLISH SUMMARY

The overarching objective of this thesis was to develop effective strategies for rationalizing therapies based on an individual's risk profile, thereby reducing morbidity and preventing sudden cardiac death (SCD) in patients with catecholaminergic polymorphic ventricular tachycardia (CPVT).

The specific aims of this work were to: (1) define risk of SCD in different subgroups of patients with CPVT and elucidate factors that contribute to risk; (2) explore effective treatment strategies to reduce morbidity and prevent SCD; and (3) explore the role of genetics in patients with CPVT.

To achieve these aims, we established an international CPVT registry to correlate phenotype with genotype, to generate a risk prediction model for clinical use and to enable identification of relevant new genes. The conclusions and perspectives from this work are summarized below.

(I) Risk stratification

The first part of this thesis focuses on the identification of factors that contribute to the risk of SCD in patients with CPVT. Chapter 1 provides a review of the clinical characteristics, genetics, and diagnostic and therapeutic strategies of CPVT and describes recent advances and some of the current challenges.

In chapter 2 we present a risk prediction model for patients with RYR2-mediated CPVT using clinical parameters. In this retrospective multinational cohort study we found that predictors of arrhythmic evens (AEs) were syncope or sudden cardiac arrest (SCA) prior to diagnosis, age at diagnosis, ventricular arrhythmia severity, and resting heart rate adjusted for age and sex. Patients with predicted 5-year risk of AE <5%, 5-20% and >20% had 5-year observed AE incidences of 0.8% (95% CI, 0.0%-1.9%), 15.4% (95% CI, 11.3%-19.4%), and 28.8% (95% CI, 20.6%-36.2%), respectively. This risk model accurately distinguished CPVT patients at high and low risk for future CPVT-triggered syncopal episodes and potentially lethal CPVT-triggered life-threatening arrhythmic events (AEs).

In chapter 3 we studied the effect of pregnancy on the incidence of AEs in women with CPVT. In a combined Dutch and Canadian retrospective series of 96 CPVT mothers with a total of 228 pregnancies we found pregnancy and postpartum

event rates of 1.71 and 2.85 events per 100 patient-years, respectively. The combined event rate during the pregnancy and postpartum period was 2.14 events per 100 patient-years, which is similar to the non-pregnant event rate (1.46 events per 100 patient-years). Pregnancy and postpartum cardiac events included syncope (5%), and one aborted cardiac arrest (1%), all occurring in patients who were not taking β-blockers. Even though the current data represent the largest set of data regarding pregnancy in patients with CPVT, more studies are needed to determine the exact risk of AEs in patients diagnosed with CPVT.

Since the cardiac RyR2 receptor is not only expressed in the heart but also in the brain, in chapter 4 we sought to investigate the prevalence of intellectual disability (ID) and other neurodevelopmental disorders (NDDs) in RyR2-associated CPVT and to study the characteristics of these patients. We found that intellectual disability is more prevalent among these patients (8%) compared to the general population (1%-3%). In addition, this subgroup of CPVT patients has a (more) malignant cardiac phenotype with marked supraventricular and ventricular arrhythmias. Most of the RYR2 mutations associated with ID that we found in this study clustered in the central domain. Functional studies revealed a markedly enhanced response of RyR2 to activation by caffeine, especially at low concentrations of caffeine and such mutations may thus be associated with a more severe functional impact on RyR2 function compared with those associated with only a cardiac phenotype.

Due to the well documented influences of the autonomic nervous system on arrhythmogenesis and cardiac electrical stability, there is a strong rationale to assess autonomic reflexes in inherited arrhythmia disorders such as CPVT. In chapter 5 we explored the role of the autonomic nervous system, by investigating heart rate reduction immediately after exercise. We found that CPVT patients with a larger heart rate reduction following exercise are more likely to be symptomatic and have complex ventricular arrhythmias during the first exercise test off antiarrhythmic drugs. From a clinical perspective these results may, for example, suggest that in asymptomatic genotype-positive relatives, the presence of a strong vagal tone (which is responsible for a fast reduction in heart rate immediately after exercise) in the absence of ventricular arrhythmias during the first exercise stress test could be an argument to be more aggressive with β-blocker therapy than in those without strong vagal activation post-exercise.

In chapter 6 we explored the role of blood pressure (BP) on the occurrence of ventricular arrhythmias in mice and in patients with CPVT. In a retrospective study we analyzed the data from the exercise stress test in CPVT patients. We found that risk reduction of complex ventricular arrhythmias by β-blocker therapy was significantly related to the degree of reduction in diastolic BP during peak exercise. We subsequently tested the effect of BP in a CPVT mouse model and found that treatment with the vasodilators hydralazine or minoxidil prevented stress-induced ventricular arrhythmias in CPVT mice. Conversely, treatment with the vasoconstrictor phenylephrine increased BP and worsened the CPVT phenotype.

(II) Treatment

In the second part of this thesis we investigated the role of pharmacological therapies in the treatment of CPVT. The cornerstone of medical therapy are β-blockers. In the past years flecainide has been added to the therapeutic arsenal of CPVT. In chapter 7 we summarized current data of the efficacy of flecainide in CPVT and the current role of flecainide in the treatment of CPVT. Even though multiple clinical reports have shown that flecainide reduces the burden of ventricular arrhythmias in CPVT patients, the effect on the arrhythmic event rate has not fully been investigated. In chapter 8, we evaluated the effect of flecainide on arrhythmic events when added to optimal medical therapy in the setting of unchanged background medical therapy. This multicentre retrospective cohort study consisted of 247 CPVT patients. We found that adding flecainide to β-blockers was associated with a reduction in AEs in the overall cohort, symptomatic patients, and particularly in patients with breakthrough AEs on β-blocker therapy

In chapter 9 we present a case series of eight patients successfully maintained on flecainide monotherapy because of β-blocker intolerance. None of the patients experienced serious arrhythmia during follow-up, although β-blocker therapy was reinitiated in one patient after exercise testing revealed NSVT. β-Blockers remain the first-line therapy; however, where β-blocker therapy is not tolerated it may be safer to use flecainide monotherapy than no therapy at all.

In chapter 10, we studied the risk-benefit of implantable cardioverter-defibrillator (ICD) therapy in patients with previously undiagnosed and untreated CPVT who presented with SCA as their sentinel event, with an emphasis on the efficacy

and complications of ICDs during follow-up. The study population included 136 patients in whom guideline-directed therapy, including β-blockers, flecainide, and/or left cardiac sympathetic denervation was initiated after the SCA. An ICD was implanted in 79 patients (58.1%). After a median follow-up of 4.8 years, SCD had occurred in 3 patients (3.8%) with an ICD and none of the patients without an ICD (P = 0.1). SCD, SCA, or appropriate ICD shocks occurred in 37 patients (46.8%) with an ICD and 9 patients (15.8%) without an ICD (P < 0.0001). The composite outcome of SCD, SCA, appropriate ICD shocks, or syncope occurred in 38 patients (48.1%) with an ICD (10.1 events per 100 person-years) and 17 patients (29.8%) without an ICD (4.7 events per 100 person-years, P = 0.014). Inappropriate ICD shocks occurred in 19 patients (24.7%) and other device-related complications in 22 patients (28.9%). This data shows that ICD did not confer a survival benefit but only ICD-associated co-morbidities including device-attributable death.

(III) Genetics

The third part of this thesis focusses on the role genetics on the CPVT phenotype.

In chapter 11 we studied the genetic and functional determinants underlying a family that presented with a combined phenotype of ventricular arrhythmias with a likely adrenergic component, either in isolation or in combination with a mildly decreased cardiac function and early onset (<55 years) atrial fibrillation. In this family we identified a novel missense variant in SCN5A-(p.M1851V). Subsequent electrophysiological studies demonstrated a faster recovery from inactivation and a positive shift in voltage dependency of inactivation in SCN5A-p.M1851V channels leading to increased sodium channel availability and increased window current, explaining the phenotype in the family.

In chapter 12 we aimed to investigate the inheritance patterns, arrhythmic risk and molecular mechanisms of patients with a heterozygous CASQ2 mutation through an international multi-center collaboration. A total of 112 individuals, including 36 CPVT probands (24 homozygotes/compound heterozygotes and 12 heterozygotes) and 76 family members possessing at least one presumed pathogenic CASQ2 mutation, were identified. We observed that heterozygous CASQ2 mutations can sometimes manifest with a malignant arrhythmic phenotype, indicating that CASQ2 heterozygotes should undergo clinical evaluation for arrhythmic

risk. The mechanisms responsible for heterozygous CASQ2 mutations yielding a positive arrhythmic phenotype are likely multifactorial and may be intrinsic to the mutation itself for certain putative dominant acting variants, while in others there may be a vulnerable genomic background or environmental influences that sensitizes for the phenotype. However, the overall penetrance for most pathogenic heterozygous mutations appears low, suggesting that medical therapy for patients should primarily be guided by the clinical phenotype, rather than genotype alone. Future studies will be necessary to attempt to identify potential modifiers of an arrhythmic phenotype.

A relevant proportion of the RYR2 variants found in patients with a definite CPVT-phenotype are adjudicated as a variant of uncertain significance (VUS) when called with the ACMG variant calling criteria. In chapter 13 we included 233 CPVT patients from 2 centers (Mayo Clinic and Amsterdam University Medical Center), with definite phenotype and a RYR2 variant. Here, 47% of the RYR2 variants were classified as a VUS in accordance with current ACMG guidelines even though this study included many individuals with a clinically-definitive CPVT phenotype. Without significant co-segregation, paternity/maternity-confirmed de novo status, or cumbersome functional validation, it is very difficult for a novel RYR2 missense variant to achieve an ACMG label of pathogenic or likely pathogenic. Therefore, we studied if the incorporation of a CPVT-specific phenotype/clinical data into the existing ACMG variant classification framework could assist in the promotion or demotion of RYR2 VUS thereby significantly decreasing the current interpretative ambiguity associated with clinical CPVT genetic testing. With a newly developed CPVT diagnostic scorecard, the collective pre-test clinical probability of CPVT was determined in a standardized fashion. With the use of the combined ACMG criteria and our newly developed diagnostic card (“amended PE-ACMG standards”) the VUS rate dropped significantly in both the Mayo Clinic cohort and the Amsterdam University Medical Center cohort.

In conclusion, in this thesis we present data for rationalizing therapies based on an individual’s risk profile, thereby reducing morbidity and preventing SCD in patients with CPVT.