Epidemiology and clinical aspects of sudden cardiac death in the young
van der Werf, C.

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Summary
In Japanese, a “pokkuri” death refers to a good death without long illness. Every year, thousands of elderly people pray for a “pokkuri” death, preferably during sleep or a sudden cardiac death (SCD), in the Kichiden-ji Temple in Nara Prefecture, so they are not a burden on their families during their final days. Kichiden-ji Temple was established in 987 by a monk whose mother had passed away peacefully wearing clothes that he had prayed over. As time passed, a new Japanese tradition took shape, and now elderly people visit Kichiden-ji to pray for a discrete and quick passing. Conversely, the sudden death of a young individual is a tremendous tragedy for the victim’s next of kin. Scientists around the world are continuously searching for new methods to prevent these tragic events. In this light, this thesis describes general issues of SCD in young individuals as well as specific aspects of two inherited arrhythmia syndromes, catecholaminergic polymorphic ventricular tachycardia (CPVT) and long-QT syndrome (LQTS), which can cause SCD.

PART 1: SUDDEN CARDIAC DEATH IN THE YOUNG

In Chapter 2, we review the incidence and causes of sudden death in apparently healthy young individuals. Inherited cardiac diseases play an important role in these events, which has implications for living relatives. We comment on several strategies that may prevent these cases or additional deaths within the family of a young SCD victim. We propose that more attention should be directed towards performance of autopsy, and cardiologic and genetic evaluation of relatives when the presence of an inherited cardiac disease cannot be excluded.

To evaluate current health care in these cases in the Netherlands and the most (cost-) effective strategy to improve health care we designed the CAREFUL (The yield of CARdiogenetic scrEening in First-degree relatives of sudden cardiac and UnexpLained death victims <45 years) study, as detailed in Chapter 3. The primary results of the CAREFUL study are presented in Chapter 4. Of the 390 cases of sudden death due to natural causes that were registered among individuals aged 1 to 45 years in four regions of the Netherlands, autopsy was performed in 169 (43%). While we considered cardiogenetic evaluation of the victim’s relatives indicated in 296 cases (76%), only 25 families (8%) attended a cardiogenetics clinic. An inherited cardiac disease was diagnosed in a quarter of these families. Two interventions that were executed to improve this usual care: in one region a central 24/7 study telephone number and a website were introduced to provide detailed information to physicians on the importance and practicalities of performing a detailed assessment of the cause of death including autopsy and possible genetic factors, whereas first line health care professionals were informed on these aspects by a letter and educational meetings in another region. These interventions did not result in a significant improvement of autopsy rates or the proportion of families attending a cardiogenetics clinic.

To identify possible factors that hamper the initiation of evaluation focused on inherited cardiac diseases after the sudden death of young individuals, we performed a focus group study among general practitioners and coroners (Chapter 5). The participants specified several logistic and emotional bottlenecks concerning the request for permission to have a clinical autopsy performed, for example financial barriers, indistinct responsibilities, lack of knowledge and reluctance to discuss autopsy with emotional next of kin. The initiation of family evaluation may be hampered by insufficient knowledge among general practitioners, insufficient information supply by the pathologist who performed the autopsy and anxiety and insufficient motivation among relatives.
Because cardiogenetic evaluation among apparently healthy first-degree relatives of young SCD victims may have potential drawbacks, similar to every screening program, we explored the experiences with and attitudes towards cardiogenetic evaluation among ten individuals that were evaluated, as detailed in Chapter 6. In this qualitative study, participants indicated that medical professionals did not play an important role in informing and referring them to a cardiogenetics clinic. All participants indicated that they would have appreciated a more directive approach from medical professionals, because the mourning process hampered their own information seeking and decision making. The most important motivations to attend a cardiogenetics clinic were a need for understanding the cause of death and the motivation to prevent another SCD event within the family. The multidisciplinary cardiogenetic evaluation itself was well appreciated, although minor organisational amendments were suggested.

The study presented in Chapter 7, in which we describe the incidence, causes, and outcomes of pediatric out-of-hospital cardiac arrest (OHCA), was performed because of a paucity of complete studies on this topic. By combining cases of pediatric OHCA in the Amsterdam Resuscitation Studies (ARREST) and in the coroners’ databases, we obtained comprehensive, prospectively collected, population-based data. The incidence of all-cause pediatric OHCA, including non-natural causes, was 9.0 per 100,000 pediatric person-years. Presumed cardiac causes amounted to 90 of 233 cases (39%). Of 51 resuscitated patients, 12 (24%) survived. Ten survivors had a neurologically intact outcome.

In the Netherlands, the majority of young sudden death victims are not autopsied. In autopsied cases, the cause of death remains unexplained in approximately 20%. In Chapter 8 we further extend previous small-scale observations on the yield of cardiogenetic evaluation of relatives of young sudden unexplained death (SUD) victims, in whom autopsy was negative (46%) or was not performed (54%). In this large cohort of 140 SUD families, a certain or probable was made in 47 families (33%). In line with previous observations, inherited arrhythmia syndromes (LQTS, Brugada syndrome and CPVT) were most prevalent. The diagnostic yield significantly declined with increasing age of the SUD victim. Inherited arrhythmia syndromes were the most predominant diagnoses in the age group 1 to 15 years, whereas cardiomyopathies played a significant role in the older age groups, and premature coronary artery disease was generally diagnosed in the age group 30 to 50 years. In addition, we studied the yield of cardiologic examination in an unselected population of young aborted cardiac arrest (ACA) victims. Here, a diagnosis was made in 42 patients (61%), predominantly hypertrophic cardiomyopathy, myocardial infarction, LQTS, Brugada syndrome and arrhythmogenic cardiomyopathy.

Because it is unknown whether individuals from SUD families in which cardiogenetic evaluation revealed no abnormalities are at risk of manifest disease or cardiac events during follow-up, we carried out a follow-up study in diagnosis-negative families (Chapter 9). Overall, the risk of cardiac events during 6.6 years of follow-up in 417 first-degree relatives from 83 families was low, except for individuals from a family with obvious familial idiopathic ventricular fibrillation. Inherited cardiac disease was diagnosed in three families during follow-up. All affected individuals showed discrete non-diagnostic abnormalities at the initial examination or had not been part of the initial examination. Therefore, we conclude that a completely unremarkable cardiologic examination in adult first-degree relatives of a young SUD victim may be sufficient to exclude the presence of an inherited cardiac disease. In children, individuals with subtle abnormalities
at the initial examination and relatives from families with obvious familial idiopathic ventricular fibrillation this is not the case and repeated cardiologic examination is advised. In conclusion, the data presented in Part 1 indicate that first-degree relatives of young sudden death victims have a much higher prevalence of inherited cardiac diseases compared with the prevalence of these conditions in the general population. This may justify a standardized diagnostic procedure following the sudden death of a young individual, focused on indentifying the cause of death and relatives at increased risk of SCD, which is currently lacking in the Netherlands and many other countries. In the Netherlands, this would translate into approximately 500 autopsies and 375 families in which cardiogenetic evaluation would be indicated or, when limited to apparently healthy victims, approximately 200 autopsies and 150 families yearly. Very recently the Dutch government has introduced new regulations on adequate postmortem assessment of pediatric victims (<18 years), including an autopsy that may be imposed by a judge when other examinations have failed to indentify the cause of death. A possible solution would be to increase the upper age limit of this assessment to 40 or 50 years and include family evaluation, when indicated, in this assessment.

**PART 2: CATECHOLAMINERGIC POLYMORPHIC VENTRICULAR TACHYCARDIA**

In Part 2 we focus on one specific cause of SCD in the young: CPVT. Patients with this rare inherited arrhythmia syndrome display polymorphic ventricular tachyarrhythmias under conditions of emotional or physical stress, as reviewed in Chapter 10. β-blockers are the cornerstone of therapy in CPVT patients. In Chapter 10 we also analyzed the efficacy of β-blockers based on all CPVT patient series published before 2011. Eight-year near-fatal (including aborted cardiac arrest, appropriate implantable cardioverter-defibrillator discharges and SCD) and fatal event rates in CPVT patients treated with β-blockers were 14% and 6%, respectively. Finally, we review alternate treatment options and propose an optimal therapeutic approach.

At present, pathogenic mutations in the gene encoding the cardiac ryanodine receptor (RYR2), which show an autosomal dominant inheritance pattern, are identified in approximately 60% of CPVT probands (the individual through whom the family was ascertained). Identification of a familial RYR2 mutation offers the opportunity to test the proband’s relatives for mutation carriership (so-called cascade screening). Importantly, this allows taking potentially life-saving preventive measures in RYR2 mutation-carriers, because even asymptomatic RYR2 mutation-carriers are known to be at risk of SCD. In Chapter 11 we report on disease penetrance, expression and prognosis of 116 relatives from 15 families carrying a RYR2 mutation who were identified by cascade screening. Half of these relatives showed phenotypic manifestations of CPVT, including 50% with ventricular tachycardia. The arrhythmic event rate in these mostly actively treated patients was low and none of the relatives died due to CPVT during a follow-up of over six years. In 2008, the accidental finding that the antiarrhythmic drug flecainide inhibited RyR2 calcium release channels, reduced spontaneous calcium release events and triggered beats and suppressed ventricular arrhythmias in a mouse model of CPVT was published. This paper included the successful results of flecainide in two severely affected patients from our center
in whom flecainide was initiated after the demonstration of favourable results in the CPVT mouse model. Subsequently, we initiated a worldwide collaborative study to evaluate the efficacy of flecainide in a larger number of difficult-to-treat mutation-positive CPVT patients. The results are presented in Chapter 12. We included 33 genotype-positive patients who received flecainide because of exercise-induced ventricular arrhythmias despite conventional therapy with β-blockers. Flecainide was associated with a reduction in ventricular arrhythmias during exercise testing in 76% of patients. During a median follow-up of 20 months none of the patients experienced an arrhythmic event, except for one patient who received ICD discharges for polymorphic ventricular arrhythmias, which were associated with a low serum flecainide level, suggesting noncompliance. In Chapter 13 we further explored the efficacy of flecainide in 12 genotype-negative CPVT patients. We observed a reduction in exercise-induced ventricular arrhythmias by a similar extent to genotype-positive CPVT patients. Despite the advances that have been made in elucidating the basic and clinical aspects of CPVT, many important questions have remained unanswered. This is, among others, a result of the low number of CPVT patients in the international centers with an interest in this condition. For example, prognostic parameters that allow clinicians to perform a thorough risk stratification have hitherto not been identified, resulting in a general therapeutic approach in every clinically of molecular genetically diagnosed CPVT patient instead of a personalized therapeutic approach. The launch of a prospective International CPVT Registry including a high number of patients, similar to the International LQTS Registry that was commenced in 1979 and has provided unique data on LQTS, is an important next step that we are currently undertaking.

**PART 3: LONG-QT SYNDROME**

Part 3 contains two studies aimed at improving the accuracy of the clinical diagnosis of LQTS, the most prevalent inherited arrhythmia syndrome. The clinical diagnosis of LQTS is relatively uncomplicated in patients with overt prolongation of the corrected QT-interval (QTc) on the resting electrocardiogram (ECG) and LQTS-related symptoms. However, the diagnosis is challenging in patients with borderline QT prolongation, in particular in the absence of a family history of established LQTS and when the results of molecular genetic testing are inconclusive. The discovery of the genetic background has provided the opportunity to perform diagnostic studies using the results of molecular genetic testing as the golden standard. As a result, we are now aware of the significant overlap in the QTc range between LQTS mutation-carriers and non-carriers. In Chapter 14 we studied the predictive value of exercise testing in asymptomatic relatives of probands with LQTS types 1 or 2. In the derivation cohort consisting of 69 relatives, a simple algorithm that incorporates resting and exercise-recovery QTc-interval yielded a sensitivity of 94% and specificity of 90% for detecting LQTS mutation-carriers. When applied to the validation cohort including 152 relatives, sensitivity was 92% and specificity was 82%. Importantly, the combined diagnostic algorithm also had an overall sensitivity of 93% for identifying mutation-positive probands in an independent cohort of 45 probands assessed for possible LQTS.

Another new diagnostic test for LQTS is the so-called “standing test”. During this easy bedside test, subjects rest for 10 minutes in the supine position as a baseline ECG is recorded. They are then asked to stand up quickly and remain standing still for 5 minutes during continuous ECG
recording. The second paper on the accuracy of this test is presented in Chapter 15. First, our previous findings on the abnormal response of the QT interval in response to standing in patients with LQTS were validated in a new cohort of 54 LQTS patients and 71 healthy volunteers. “QT stretching” (i.e., the abnormal QT-interval response to standing) yielded a sensitivity of 89% and a specificity of 87%. A new parameter, “QT stunning” (i.e., the abnormal persistence of QTc-interval prolongation as the heart rate slows back to baseline), had a sensitivity of 84% at a cut-off point of 90% sensitivity in the total cohort of 108 patients with LQTS and 112 healthy volunteers. Altogether, these studies may improve the accuracy of the clinical diagnosis of LQTS in patients with a borderline prolonged QTc-interval on their resting ECG. In addition, these tests may play a role in getting insight into the pathogenicity of variants that are indentified in the genes linked to the LQTS and, based on the presently available knowledge, are classified as variants of unknown significance.

**CONCLUSIONS**

This thesis presents a variety of clinical data and considerations to help preventing “pokkuri” deaths in young persons in the general population as well as in patients affected with CPVT and LQTS. The intriguing field of cardiogenetics has developed spectacularly in the last two decades and will undoubtedly continue to do so.