When a new disease entity is described, it is usually based on patients with obvious or severe manifestations of the disease. Indeed, the first substantial case series on catecholaminergic polymorphic ventricular tachycardia (CPVT), published by the Paris group of professors Coumel and Leenhardt in 1995, described a highly lethal condition in pediatric patients.¹ Twenty of 21 unrelated children (95%) had an history of syncopal events, and 3 (14%) experienced sudden cardiac death or aborted cardiac arrest during a mean follow-up of 7 years. In the same article, an analysis of all 21 untreated patients who had been published in the literature at the time revealed an impressive mortality rate of 48% before the age of 20 years.¹

Even since it has become clear that there is a wide spectrum of severity of CPVT. This became apparent when the genetic background of CPVT was unraveled and mutations in the cardiac ryanodine receptor gene (RYR2) were identified in the majority of patients with CPVT. At present, the entire CPVT patient population, which consists of patients with a clinical CPVT diagnosis or carriers of mutations in CPVT-associated genes,² can roughly be subdivided into the following major subpopulations: (1) young symptomatic patients (the patient with classic CPVT); (2) young patients with asymptomatic ventricular arrhythmias during cardiological examination (who are, for example, identified through cascade screening after identification of a CPVT-causing mutation in a relative); (3) carriers of a familial CPVT-causing mutation with no signs of CPVT (concealed mutation-carriers); and (4) older patients who are clinically diagnosed with CPVT (in whom coronary artery disease needs to be excluded, in whom the yield of genetic testing tends to be lower, and including patients in whom the clinical diagnosis is only established during adrenalin challenge testing³). Our current understanding from small observational studies is that all these subgroups have different clinical characteristics.

This issue contains the largest analysis on patients with classic CPVT to date.⁴

In this Pediatric and Congenital Electrophysiology Society (PACES) multicenter, retrospective cohort study, 226 children with CPVT from 27 pediatric centers were included. The lead investigators are to be applauded for uniting this impressive amount of centers and sampling this number of patients. In a rare disease like CPVT, it takes these kind of important efforts to study a reasonable number of patients to make meaningful observations.

In the PACES study, 170 children (75%) were probands and 176 (78%) were symptomatic before the diagnosis was made. This PACES study cohort has fundamentally different clinical characteristics than our Dutch cohort published in this Journal in 2012.³ Because we have been active in cascade screening for ≈20 years,⁵ our patients with CPVT are mainly proactively counseled presymptomatic (ie, asymptomatic) genotype-positive patients with or without phenotypic manifestations of the disease. Indeed, our cohort included 116 genotype-positive relatives from 15 families, of whom 40 (35%) were symptomatic and 50% showed a CPVT phenotype (on exercise).³

In the PACES cohort, in which the vast majority received some form of treatment, 6 fatal events (3%) occurred during a median follow-up of 3.5 years. This is in agreement with the 4-year mortality rate of 3.2% that we previously calculated in insufficiently controlled patients. Implantable cardioverter-defibrillators (ICDs) are to be restricted to patients presenting with aborted cardiac arrest before CPVT was diagnosed, and patients who do not respond to optimal medical therapy and in whom cardiac sympathetic denervation is not possible or not successful.² In the PACES study, 97% of patients received β-blockers. However, in 24% of these patients, β-blocker was discontinued during follow-up (mostly temporary), which puts patients with classic CPVT at high risk of arrhythmic events. Given the high rate of arrhythmic events on β-blocker monotherapy (31 syncopal events, 26 cardiac arrest events, and ≥1 treatment-failures in 42 patients with an ICD), the
use of flecainide and cardiac sympathetic denervation in only 23% and 8% of patients, respectively, is disappointingly low. Finally, ICDs were implanted in a high proportion (54%) and in 45% of these patients this was done for primary prophylaxis. ICDs are known to be potentially proarrhythmic in CPVT, so the use of ICDs in CPVT needs to be restricted to the patients outlined in the recommendations. At the time, we submitted our article on the efficacy of flecainide in CPVT reviewers asked for a randomized trial. In that light, it cannot be stressed enough that we equally lack a randomized trial with ICDs as a primary prophylaxis in patients with CPVT.

So, how lethal is catecholaminergic polymorphic ventricular tachycardia truly when one takes into consideration the PACES study and previous observations? The answer to this question is more complex and requires the following considerations.

First, all CPVT patient series have survival bias. The PACES series, for example, included 2 cases in which CPVT was diagnosed by identifying a pathological RYR2 mutation postmortem. For that matter, this approach may be hazardous in terms of genetic testing, because if no further relatives are available to investigate (or being investigated), there is no way to proof a causal relationship between the identified genetic information and the outcome. Thirty-two patients had a family history suggestive of CPVT because of young relatives who had died suddenly. In these type of studies, every investor is forced to make arbitrary choices on the inclusion of individuals with fatal events with little information available that occurred long before CPVT was diagnosed within the family. Not including these fatalities that occurred in the past because of the lack of information is probably the right thing to do. Including only these fatal events and not other affected relatives from past generations who did not die prematurely and in whom CPVT mutation-carriership is unknown would cause the opposite effect of survival bias, ie, an overestimation of CPVT-related mortality. On the contrary, recent fatal events that sometimes directly led to the family being investigated and diagnosed with CPVT are sometimes included. This arbitrary line inevitably makes us study and observe the patients who (nearly) made it to the doctor’s office. A clear example of this issue is our large family carrying the R420W mutation in RYR2. Our current population of carriers of this mutation shows a relatively mild phenotype. However, the proband first came to our attention after the sudden death of 7 young relatives (of 10 family members who could potentially be affected). An unbiased way of studying the natural history of the disease is the family tree mortality ratio method. This method compares all-cause mortality of families with an inherited condition at a time when the disease was not known and patients were untreated with that in the general population. In the RYR2 R420W family, this standardized mortality ratio was increased only in the age group of 20 to 39 years. Thus, for this specific mutation, affected children did not excessively die when compared with their peers. These observations are obviously restricted to this particular family and may be different in families with other RYR2 mutations.

Second, reporting arrhythmic events during follow-up can be approached by 2 methods. In all studies on CPVT and most studies on the other inherited arrhythmia syndromes follow-up duration is counted starting from the moment of diagnosis. So, in these studies, we are looking at arrhythmic event rates in patients who were alive at baseline and, depending on the exact inherited arrhythmia syndrome but certainly in CPVT, were mostly actively treated. This method is clearly appropriate to gain insight into the prognosis of a newly diagnosed patient. In addition, these patients are usually well-characterized, which provides the opportunity to study these clinical and genetic characteristics as markers of risk for arrhythmic events.

In some studies, however, follow-up is counted from birth to the first arrhythmic event, even though most patients are actually diagnosed with the disease somewhere during follow-up. This method provides a better picture of natural course of a disease before therapy was started. However, the previously described difficulties in including or excluding fatal events from past generations also apply to this method. Although the prognostic value of constant factors (eg, age, sex, and mutation) can simply be studied, dynamic factors (presence of symptoms or other manifestations of the disease) that are recorded somewhere during follow-up may have been different earlier in life are cannot, therefore, reliably be studied. Interestingly, reports from the International Long-QT Syndrome Registry have consequently used a mixture of these 2 methods by counting follow-up from birth to the first arrhythmic event or a certain age (usually 40 years) and by entering dynamic factors (in particular, corrected QT-interval, symptoms, and therapeutic interventions) into the equation.

Third, most observations of arrhythmic event rates have been done in patients with classic CPVT treated with β-blockers and, since the past few years, flecainide. A significant proportion of these events, including those in the PACES study, can be attributed to nonadherence. On the basis of intention-to-treat principle, these events associated with nonadherence are also counted as treatment-failures. This tells us that β-blockers and also flecainide are in fact more effective than the data tell us, as long as the patients take their pills. In addition, it tells us that some patients who seem well-controlled on these medications and intuitively seem at lower risk of events than the severely affected patients are in fact critically dependent of their therapy. Thus, arrhythmic event rates in untreated patients with classic CPVT are probably significantly higher than current arrhythmia event rates on medication, as suggested by the first observations in untreated patients with CPVT.

In summary, a simple mortality rate in all patients known with CPVT today cannot be given and simply citing the extremely high mortality rate in untreated patients in the first articles on CPVT is an inappropriate representation of the truth. When dealing with a patient with CPVT, it is important to realize to which of the previously outlined subgroups this patient belongs. The PACES study nicely shows the efficacy and drawbacks of different treatment modalities and the prognosis of patients with classic CPVT, whereas our Dutch cohort is more informative when one is confronted with a patient identified through cascade screening. Our task for the future is to extend and unite all the local observations to study a large CPVT populations that represents all parts of the spectrum. This will enable us to develop a well-validated risk stratification tool to guide our therapeutic approach and protect the patients at high risk without overtreating those at low risk.
Disclosures

None.

References


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