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REVIEW

Short QT syndrome. Update on a recent entity

Le syndrome du QT court : aspects actuels d'une entité récente

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Summary The short QT syndrome, a recently discovered ion channel disorder, combines shortened repolarization, a predisposition to atrial and ventricular fibrillatory arrhythmias, and a risk of sudden death. Few cases have been reported, but the prevalence may be underestimated. This syndrome might account for some cases of unexplained ventricular fibrillation in patients with otherwise healthy hearts. Patients have abnormally short QT intervals and refractory periods, and atrial/ventricular fibrillation can be triggered during investigations. Gain-of-function mutations have been detected in three genes encoding potassium channels. Treatment is based on defibrillator implantation, sometimes as a preventive measure. Quinidine may be beneficial in certain cases.

MOTS CLÉS
Intervalle QT ;

Résumé Nouvelle canalopathie de découverte récente, le syndrome du QT court associe raccourcissement de la repolarisation et propension aux arythmies fibrillatoires atriales et ventriculaires pouvant mener à la mort subite. À ce jour seul un nombre très limité de cas

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Syndrome du QT ;
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Fibrillation
ventriculaire
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Mort subite ;
Canalopathie

a pu être répertorié, mais une sous-estimation de la prévalence réelle est possible, ce syndrome pouvant expliquer un certain nombre de fibrillations ventriculaires inexpliquées sur cœur par ailleurs sain. Les patients présentent des intervalles QT et des périodes réfractaires anormalement courts, et des fibrillations atriales ou ventriculaires sont déclenchables lors des explorations. À ce jour des mutations sur trois gênes codant pour les canaux potassiques et entraînant des gains de fonction ont été découvertes. Le traitement actuel repose sur l'implantation d'un défibrillateur, qui sera même proposé parfois à titre prophylactique. Une alternative médicamenteuse pourrait être représentée par la quinidine dans certains cas.

Introduction

Each year in the United States and Europe, several hundred thousand people are victims of sudden death (SD). The immediate cause is usually ventricular fibrillation (VF) [1,2]. While most patients have a known or unknown underlying arrhythmogenic cardiopathy at the time of the event, the heart is considered ''healthy'' in 5 to 10% of cases [1,3], meaning that no morphological anomalies are detected with the methods routinely used in clinical practice [3,4]. Over the last two decades a number of etiologies have been identified, corresponding to apparently pure electrical disorders related to hereditary disorders affecting certain ion channels that generate cellular action potentials. These ion channel disorders disrupt cardiac rhythms and are capable, when combined with certain environmental factors, of causing malignant ventricular arrhythmias and SD. These disorders comprise, in chronological order of their discovery, long QT syndrome, catecholaminergic polymorphic ventricular tachycardia, and Brugada's syndrome. But some cases of VF in patients with apparently healthy hearts do not correspond to any of these electro-clinical syndromes and are considered ''idiopathic'', reflecting our limited knowledge in this area [4]. Some cases are probably associated with early repolarization, as recently reported.

A few years ago another entity was discovered — associating shortened repolarization with a risk of SD by VF — further reducing the proportion of ''idiopathic'' cases of VF.

Historical background

QT prolongation has long been known to increase the risk of SD and overall cardiac mortality among patients with a variety of underlying etiologies. However, it is only in the early 1990s that Holter recordings of more than 6500 patients suggested that a shorter than normal QT interval could be detrimental: the risk of SD at two years was more than doubled in patients with a mean QT_C below 400 ms or above 440 ms [5]. The princeps description of three familial cases of extremely short QT associated with paroxysmal atrial fibrillation (AF), plus an isolated case with syncope and SD, was reported in 2000 by Ihor Gussak et al. [6]. These authors were the first to postulate the existence of a new syndrome combining consistent shortening of repolarization and electrical instability. Then in 2003, Gaita et al. published a more thorough description of two unrelated families with a history of SD spanning several generations. They found that seven members of these families had a consistently short QT interval associated with syncope, palpitations, AF and documented episodes of VF [7]. These patients had short atrial and ventricular refractory periods, and VF could be induced in most of them. Other cases have since been reported, [8—14] retrospectively validating the existence of this new syndrome of cardiac rhythm disorder.

Diagnosis

The frequency of the QT interval should be between 60 and 85 per min [15] in the lead (often V2) in which the amplitude of the T wave is largest and where the return to the isoelectric line is clearest, from the beginning of the QRS to the junction between the tangent of the maximal descending slope of the T wave and the isoelectric line [16]. QT and QT_C values of 300 ms or less were noted in these initial descriptions of highly selected patients [6,7], associated with a, tall, sharp, fine, positive and symmetrical T wave, especially in the precordial leads (V2 to V4); the ST segment was virtually absent [15,17] and, consequently, the interval between the end of the T wave and the following P wave was prolonged (Fig. 1 and 2). In a review of the first 15 reported cases, the QT_C was found to be below 320 ms, and this value thus became the diagnostic cutoff [18]. In the 29 patients studied to date, the QT interval has always been below 320 ms and the QT_C always below 340 ms, with an acuminate and symmetrical T wave in most cases [16] (Table 1). In some published cases, however, the QT was as high as 340 ms and the QT_C even higher [10,11]. If the upper normal limit of the QT interval is now well known, the lower limit has received far less attention. It can be defined as the mean minus two standard deviations of the QT interval in a normal population. Values of 330 ms (310 ms in children) for the QT [19] and between 360 and 380 ms for the QT_C have been proposed [20]. QT or QT_C intervals below these values can therefore be considered abnormally short. Indeed, other studies show that 99% of the normal population have a QT_C interval greater than 360 ms (men) or greater than 370 ms (women) [21,22] (Table 1). As in this syndrome, the QT interval shows little shortening as heart rate increases [15,17], QT correction with Bazett's formula

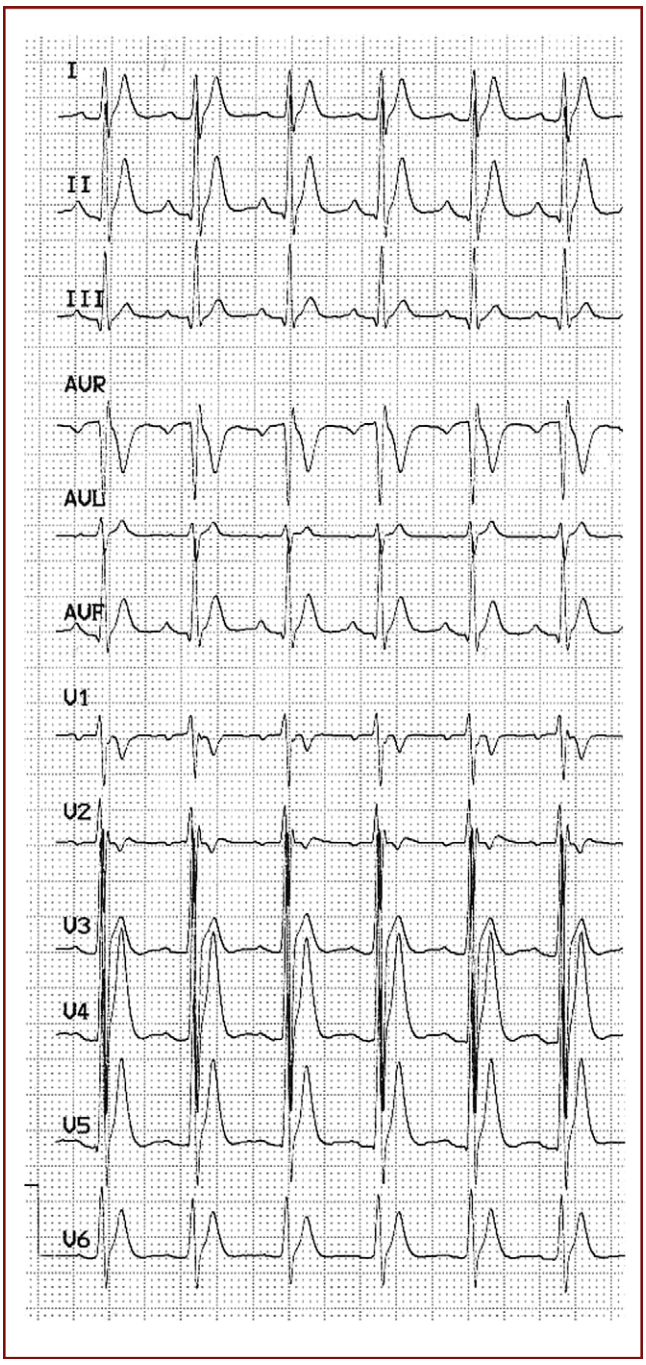

Figure 1. ECG pattern in a patient with a short QT interval. The ST segment is reduced and the T wave is tall and sharp, especially in the precordial leads. The QT is 240 ms. Owing to the high frequency, correction with Bazett's formula is inappropriate. The QT represents 78% of the QT predicted at this frequency with Rautaharju's formula (see text).

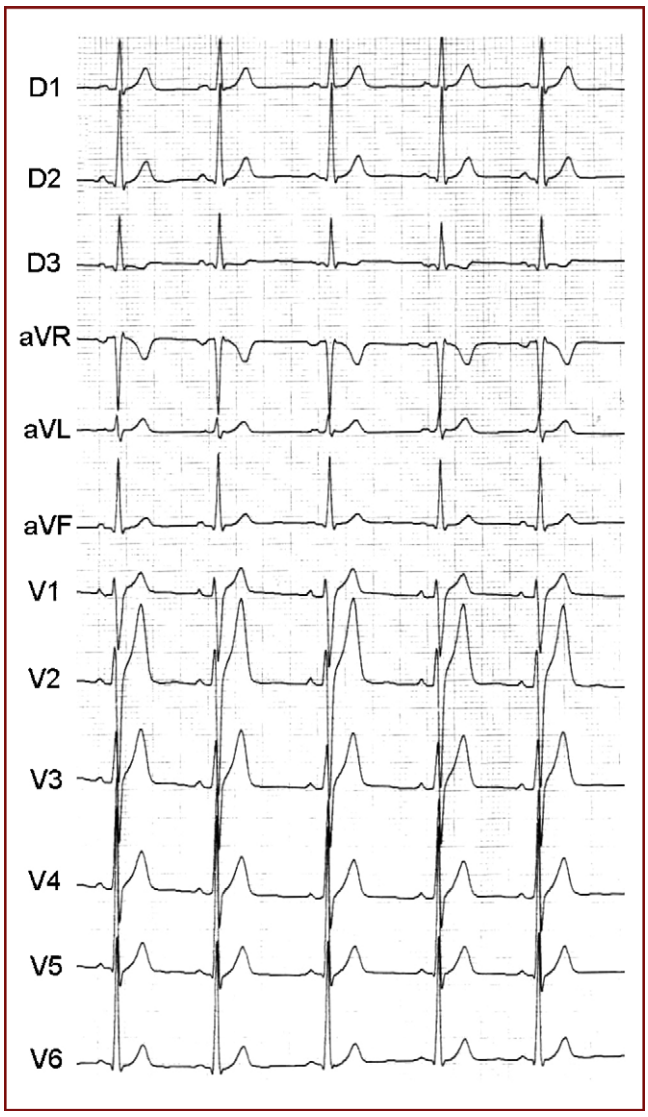

Figure 2. ECG pattern in another patient with a short QT interval from a different family. Here the QT interval appears at first glance to be less short than in the previous case (although measuring only 300 ms) but the T wave is tall and sharp and the segment between the end of the T wave and the following P wave is long. The corrected QT (Bazett's formula) is 335 ms. The QT represents 80% of the predicted QT at this frequency, using Rautaharju's formula (see text).

should probably only be used for frequencies below 80 or 85 per min [15], as the QT_C can appear falsely normal at higher cardiac rates [18]. Identification of this anomaly is therefore dependent on the frequency. When the frequency is consistently too rapid, the diagnosis can only be confirmed by ambulatory recordings during slower phases, or based on the poor adaptation of the QT interval to the frequency recorded on the Holter or during an exercise test [11,15,17,18]. One alternative is to use a formula based on ECG recordings of several thousand healthy subjects, thus allowing one to predict the ''normal'' value of the QT interval for a given frequency [23]. In this formula, the QT interval predicted by the frequency, $QT_P = 656/1 + \text{heart-rate}/100$, and a QT value below 88% of the QT_P represents the lower normal limit [23,24]. In early clinical reports, and in the 29 recently reported cases, the QT was below 80% of the QT_P [16,18]. Even if this formula is practical and insensitive to excessively low or high frequencies, it is too early to judge its sensitivity or specificity when used to diagnose or screen for the short QT syndrome. The morphology of the T wave can also be very useful, as ample

Table 1 Lower boundaries of the QT interval in the normal population, and successive cutoffs used to define a short QT.

	QT interval	QT_C interval
Lower normal limit of the QT interval		
Moss AJ, 1993 [19], Luo S 1994 [20]	330 ms (children 310 ms)	360-380 ms
Vincent GM, 1992 [22]		360 ms (M) — 370 ms (F)
Definition of ''short QT''		
Gussak I, 2000 [5], Gaita F, 2003 [7]	<300 ms	<300 ms
Schimpf R, 2005 [18]	<320 ms	<320 ms
Giustetto C, 2006 [16]		<340 ms

and symmetrical T waves are observed in the right precordial leads in about 50% of cases [15,17]. Some patients also have a spontaneously variable QT interval, sometimes with transient normalization of repolarization, further hindering diagnosis and screening [14]. Before envisaging a diagnosis of the short QT syndrome, all causes of transient QT shortening must of course be ruled out, such as hyperkalemia, hypercalcemia, acidosis, digoxin therapy or overdose, fever, tachycardia, vagal or sympathetic hypertonia, and acute ischemia [7,15,18].

Epidemiology

A review of 29 cases has just been published, involving eight families plus men sporadic cases (21 men and eight women) [16]. Similar unpublished cases are known to other teams, and not all cases of short QT are included in this study, which comprises only cases associated with a personal or family history of SD. The recently updated European registry (Euroshort, rainer.schimpf@med.ma.uni-heidelberg.de) contains 51 cases (47 affected — 36 males — and four probably affected, 17 families, five sporadic cases, 10 with sudden death/aborted sudden death, nine with syncope, six with atrial fibrillation, three with palpitations (two with premature ventricular beats), 19 asymptomatic, mean age at clinical presentation 29 years old) (C. Giustetto and R. Schimpf) but not all published cases are included. It is likely that the prevalence of this syndrome is far higher, and that only the most severe cases are currently detected. The number of cases is likely to grow as cardiologists become more familiar with these ECG patterns and as better diagnostic tools are developed. In addition, in view of the lessons drawn from genetic studies of the long QT syndrome, and especially the existence of a subpopulation of subjects with relevant mutations but a normal phenotype [22], it is probable that the real prevalence is strongly underestimated, even though there is a good genotype-phenotype correlation, at least for some mutations (see below). However, recent epidemiological studies showed no cases of QT_C <335 ms among 12,012 healthy subjects [25], no QT_C <300 ms among 106,432 hospitalized subjects [26], and only 11 cases (0.1%) of QT_C <320 ms and 43 cases (0.4%) of QT_C <340 ms in a population of 10,822 middle-aged Finnish subjects [27], thus major forms therefore remain exceptional. These studies challenge the poor prognosis associated with a short QT interval, at least when the latter is found incidentally during routine screening of a large population [25,27]. Finally, it is also likely that a number of cases of ''idiopathic'' VF in fact correspond to a latent or borderline short QT syndrome. Indeed, the QT_C interval of men with VF of no apparent cause is significantly shorter than that of the normal population [21], and a QT interval less 300 ms is found retrospectively in 12% of survivors of ''idiopathic'' VF [28].

Clinical aspects

Mean age at diagnosis is about 30 years (4 to 80 years) [16]. Patients with a short QT interval can be totally asymptomatic (38%) [16] or suffer syncope (24%, first event in 14% of cases) [16] or palpitations (31%) [16] due to paroxysmal [6] or permanent AF [10], with a rapid [16] or slow ventricular rate [10,13] or ventricular premature beats (VPB) [16]. AF or flutter is documented in 24% of cases [16], at all ages, including children and adolescents, [6,16,18] and even in utero [13]. AF is therefore frequent in the short QT syndrome, and this means that the QT interval should always be measured in patients with AF and an otherwise healthy heart [17], particularly young patients and those with a positive family history. The vital risk is due to SD (31% of cases [16]), the most frequent manifestation; SD is also the first manifestation in most cases [16,18], and is secondary to VF in the few cases in which it could be documented [7,9,14,18,29,30]. VF or polymorphic ventricular tachycardia seems to be triggered by VPB with short coupling (180 to 300 ms [14,30]). Syncope and cardiocirculatory arrest can occur in the adrenergic phase [7,14] or at rest [11,30] and SD can sometimes even occur in both circumstances within a given family [17]. Sudden death has been reported at all ages (from the first months of life to more than 60 years [7,16]). Mean age at the time of SD or syncope is 35 ± 25 years (median 39 years), [17] and the risk of arrythmias therefore seems to persist for life. The prevalence of SD appears high in the few documented families, [15—17] but it is probably overestimated because of a recruitment bias (the first cases were detected because of this very high prevalence of SD) [15,17] and registration of patients with familial SD [16]. Late potentials are absent [7,11], heart rate variability appears normal [7], and Holter recording and effort tests show VPB (sometimes frequent) [7,8,11,14,16]. The QT interval is relatively constant, shortening only moderately on effort [7,11] and not lengthening during slow phases; the slope of the QT-heart rate correlation is weak [31] and values at maximal frequencies are near-normal [16]. The dispersion of the QT interval seems normal [7,11] or prolonged (>60 ms) [28] and

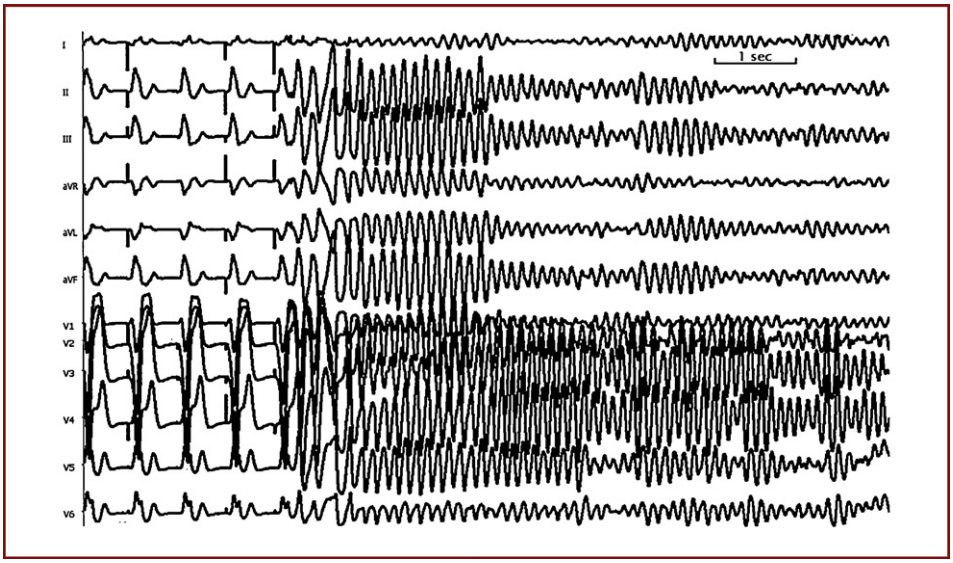

Figure 3. Triggering of ventricular fibrillation by programmed ventricular stimulation in the pulmonary infundibulum with two extrastimuli and short couplings (S1—S2 200 ms and S2—S3 150 ms).

the interval between the peak and the end of the T wave is lengthened [17,32]. Electrophysiological studies show short atrial and ventricular refractory periods (<180 ms), regardless of the genotype [7,11,15,16,18]. Suprahissien conduction disorders [11,13] and a low ventricular rate during AF that accelerates little on effort [10] have also been described. Episodes of sustained AF can be triggered by a single extrastimulus [15]. Programmed ventricular stimulation (two sites, two or three basic rates, up to three extrastimuli, with coupling intervals below 200 ms until the refractory period [16]) reproducibly triggers VF in two thirds of cases [16—18] (Fig. 3), whether or not the patient is symptomatic, and sometimes rapid monomorphic ventricular tachycardia [7]. Simple manipulation of the catheters in the right ventricle can frequently trigger VF, and this seems to be characteristic of the short QT syndrome [18]. Negative findings, especially in resuscitated VF patients [9] could be due to inadequately short couplings [16]. No underlying cardiopathies are found, of course, even after thorough investigations [16] including myocardial biopsy [9] or autopsy [7].

Genetics

A few years after its initial description, like other hereditary cardiac arrhythmias, the short QT syndrome is already showing marked genetic heterogeneity. While mutations have been discovered in some families [15,17], none are found in most cases [16]. Five missense mutations on three genes coding for potassium channels, responsible for repolarization and already implicated in some cases of the long QT syndrome, have been found in familial and sporadic cases. Two different mutations have been found on HERG, leading to substitution of the same amino acid in IKr channels (SQT1) [12,29], two different mutations leading to substitutions in the KCNQ1 gene coding for IKs (SQT2); [9,13] and a mutation by substitution on the KCNJ2 gene, coding for IK1 (SQT3), [8] were identified between 2004 and 2005 (Table 2). These gain-of-function mutations of repolarizing potassium currents force the transmembrane potential to reach negative values more quickly and therefore contribute to earlier repolarization as well as a shortening of the action potential of myocardial cells and, therefore, of the QT interval in the whole heart [8,9,29]. Other gain-of-function mutations have been found on the same genes in familial AF cases with a normal QT interval [33—35]. In the first two families in which a HERG mutation was found (SQT1) [29], the mutation was present in all phenotypically affected subjects and absent in all the others [15,29]; as a result, in the light of current data, the genotype-phenotype correlation seems excellent, for these mutations at least. Transmission appears to occur in dominant mode, with marked penetrance in documented families due to the numerous SD affecting men and women across several generations [7,16]. There are also de novo mutations [13] and sporadic cases [16]. However, these mutations are not found in other cases or families, and when one compares the number of mutations already identified and the number of cases without mutations with the number of patients/families tested, the short QT syndrome seems to show marked genetic heterogeneity. For example, no mutations were found in six of the eight families described in the recent review, or in the two sporadic cases [16]. A genotype-phenotype relationship can already be proposed, even if systematic studies of a larger number of patients will be necessary to confirm these initial hypotheses [17]. ''Typical'' patterns with a sharp and symmetrical T wave seem to be present in case of SQT1 [7,12,16], while a less ample T wave with a normal aspect (although quite symmetrical and close to the QRS) is noted in SQT2 [9,13] and SQT3 is associated with an asymmetrical sharp T wave with a normal ascending slope but a very rapid descending slope and a slightly less short QT interval [8]. The T wave can be less characteristic in non genotyped forms and in forms with no identified mutations [16]. There is also marked phenotypic variability

Table 2 Current classification of the different genotyped forms of the short QT syndrome (SQT) according to the genetic defect and the affected ion current/channel.

	Gene	Current	Author	Mutation	Substitution	Pathophysiology
SQT1	HERG/KCNH2	IK_R	Brugada R 2004 [29] Hong K 2005 [12]	C1764A C1764G	N588K N588K	Defective inactivation [29]
SQT2	KCNQ1	IK_S	Bellocq C 2004 [9] Hong K 2005 [12]	G919C G421A	V307L V141M	Trafficking less sensible to IsK subunit regulation [9] Defective inactivation [12] Activation too fast and too early [8,18]
SQT3	KCNJ2	IK_1	Priori S 2005 [8]	G514A	D172N	Activation too early and too strong [8]

This classification will have to be regularly updated — an update may already be necessary with the recent discovery of three new mutations in the genes encoding the α (CACNA1C) and β (CACNA2B) subunits of the slow calcium channel I_{CaL} (loss of I_{CaL} function or trafficking disorder of the channel protein) in three patients with Brugada's syndrome and below-normal QT_C intervals (<360 ms) that normalize on quinidine; the authors propose to designate these new forms SQT4 and SQT5 [37].

with respect to symptoms and arrhythmias, whatever the genotype, with asymptomatic forms in SQT1 and SQT3; AF, syncope and/or SD in SQT1 and SQT2; and nocturnal seizures and palpitations in SQT3. This broad phenotypic variability is also found in families who have not been genotyped or in whom no mutations have been detected [14,16]. Furthermore, a given mutation can be associated with SD in one family and with only AF in another [12,29]. In the recent study of 29 patients, SD occurred in patients both with and without ample and symmetrical T waves [16].

Arrhythmogenic mechanism in the short QT syndrome

Cellular electrophysiology is physiologically variable because ion channels are heterogeneously distributed [36]. For example, in the ventricular wall, subendocardial cells, subepicardial cells and medio-ventricular cells (M cells) have appreciably different action potentials and electrophysiological properties [36]. The summit of the T wave is classically considered to mark the end of the repolarization phase in subepicardial cells, while cells with the longest action potential —M cells— have already completed their repolarization at the end of the T wave. The difference between the summit and the end of the T wave could reflect this transmural dispersion of repolarization and, thus, the potential electrical instability of the ventricle [18,36]. Temporal transmural dispersion of repolarization is seen in physiological conditions but is exacerbated in some pathological conditions such as the long QT syndrome and Brugada's syndrome [36]. This dispersion is also increased in the short QT syndrome, [32] favoring reentry phenomena that could be initiated by a PVB with very short coupling [18]; this has effectively been found in the rare cases of onset of spontaneous arrhythmia documented to date [14,30].

Management

With the exception of young children, the first 29 registered patients were all proposed an implanted defibrillator if they had unexplained syncope, a personal history of SD, or in case of induction of VF in an otherwise asymptomatic subject [16,18]. Fourteen patients have been implanted [16]. Despite a mean follow-up of 23 months (9—49) [16] we do not have enough experience to judge this approach. SD are sufficiently frequent in some registered families, and spontaneous VF was documented a few months after implantation in a non inducible subject with a positive family history, pointing to the existence of a risk that cannot be detected with current methods [18,30]. At present, however, none of the other implanted patients has had appropriate therapy or a severe arrhythmic event. The predictive value of programmed ventricular stimulation is poorly known but imperfect, with a sensitivity of about 50% [15,6,18,30]. Similarly, risk stratification based on the QT interval is probably unreliable, given the very different clinical histories of families with the same mutations and similar QT intervals [12,15,18,29]. In the largest population studied to date, neither the QT_C nor gender appeared to have

predictive value, but no firm conclusions can be drawn from data obtained in such a small number of patients [16]. In this specific setting, however, defibrillator use raises the possibility of overdetecting the ample early T wave, with a risk of double counting and, therefore, inappropriate treatment [36]. These cases of double counting are related to a reduction in the intracardiac R wave or to an increase in the amplitude of the T wave over time and are solved by reprogramming certain sophisticated detection parameters [15,18,36]. The use of truly bipolar leads, obtention of an ample R wave and a weak T wave after implantation, and regular monitoring of the relative amplitudes of the R and T waves can help to prevent these phenomena [36]. An alternative solution in these cases could be to administer drugs that lengthen the repolarization phase [15,18]. Class 3 antiarrhythmic drugs do not appear to be effective for this purpose, probably owing to a lesser sensitivity of mutated potassium channels to IK_R blockers such as ibutilide and sotalol, possibly because of a reduction in channel affinity for antiarrhythmic drugs due to a reduction in channel inactivation [24,29,31]. Amiodarone, a drug that blocks IK_R and IK_S, does not lengthen the QT interval [14], especially in case of HERG mutations (C. Giustetto, personal observation), but can prevent the recurrence of symptoms that are apparently dependent on adrenergic tone [14]. No such experience with beta-blockers has been reported. Class 1C drugs have also been tested. Flecainide slightly prolongs the QT interval and the refractory periods but does not always prevent inductibility [7,18,24], while propafenone has been successfully used for paroxysmal AF in some patients with the short QT syndrome and HERG mutations, without, however, modifying the duration of ventricular repolarization [12]. Only quinidine, in experimental and clinical studies, showed some efficacy within the strict framework of SQT1 with HERG mutations, by normalizing repolarization even during effort, lengthening the refractory periods, and preventing the induction of VF and the occurrence of spontaneous malignant arrhythmias during follow-up of the few patients in whom it was first tested then prescribed for long-term therapy (750 to 1000 mg/d) [10,24,31]. This appears to be due to its supplementary action on other repolarizing potassium currents (especially IK_S) or to increased affinity for IK_R when the canal is in the open conformation [24,31]. The sensitivity of IK_R to quinidine and/or the affinity of the channel for this anti-arrhythmic drug would appear to be less strongly modified by the mutation than in the case of sotalol [18,31]. The place of this adjuvant treatment is poorly documented, but it could be interesting in case of SQT1 (after confirming its efficacy by exercise testing and electrophysiological studies) [15], as well as for children, cases where defibrillator implantation is refused or contraindicated, treatment of AF, [18,24] and possibly in case of electrical storm. Ten patients have been treated with quinidine for a median of 29 months (21—36 months), with no symptomatic AF and no ventricular arrhythmias [16].

Conclusion

The recently described short QT syndrome combines shortening of repolarization and susceptibility to atrial and ventricular arrhythmias, with a risk of SD. It adds to the list of genetic electrical abnormalities responsible for ventricular fibrillation in patients with morphologically healthy hearts, and thereby reduces the proportion of cases of ventricular fibrillation that remain ''idiopathic''. If its current definition involves a marked shortening of the QT interval, it is very likely that less severe forms, with less short QT intervals, could explain some cases of ''idiopathic'' ventricular fibrillation. The lower normal limit of the QT interval remains to be defined for screening and prevention purposes, and new tools must be developed to diagnose borderline forms.

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