KARDIO LIST 2008;3(12):127.

Stručni rad UDK 616.127=164.42=111 Professional paper

Sindrom kratkog QT intervala

Short QT syndrome

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SAŽETAK: *Napretkom molekularne biologije otkrivaju se uzroci nagle srčane smrti (NSS) u bolesnika s morfološki normalnim miokardom. Termin kanalopatije uvodi se za bolesti kao što su Long QT sindrom, Brugada sindrom etc. Kao novi entitet u ovom području javlja se Short QT sindrom (SQTS). Prvi puta opisan 2000. godine uključuje pet različitih varijacija bolesti za koje su odgovorne različite mutacije na kalijskim i kalcijskim kanalima kardiomiocita. Svima je zajedničko autosomno dominantno nasljeđivanje, tipične EKG promjene sa konstantno kratkim QT intervalom (<340 ms), varijabilna klinička prezentacija koja uključuje visok rizik za naglu srčanu smrt, kratke efektivne atrijske i ventrikulske refraktorne intervale te laku inducibilnost ventirkulske i atrijske fibrilacije na elektrofiziološkoj studiji. Patofiziološku osnovu nastanka aritmija čini elektrofiziološka heterogenost miokarda koja uz različito skraćivanje QT intervala u "M" zoni miokarda čini podlogu za "reentry" mehanizam nastanka tahakardija. Zadovoljavajuća farmakoterapija za SQTS još nije otkrivena, stoga je terapija izbora implantacija ICD-a. Kao dodatak ICD-u ili kao osnovna terapija kod pojedinaca kojima iz različitih razloga nije implantiran ICD može biti kinidin, koji se jedini pokazao relativno uspješnim u prevenciji malignih aritmija. Na SQTS trebamo misliti kod diferencijalne dijagnoze "lone AF", sinkope, abortirane NSS ili pozitivne obiteljske anamneze na navedene bolesti.*

KLJUČNE RIJEČI: *kanalopatije, short-QT, nagla srčana smrt, implantabilni kardioverter defibrilator*

ABSTRACT: *With the advance of molecular biology, the causes of sudden cardiac death (SCD) in patients with morphologically normal myocardium are revealed. The term channelopathy has been introduced for diseases such as Long QT syndrome, Brugada syndrome, etc. A new entity appearing in this area is Short QT syndrome. It was first described in 2000 and included five different variations of the disease for which various mutations on the potassium and calcium channels of the cardiomyocytes are responsible. All the cases have in common autosomal dominant inheritance, typical ECG changes with constant short QT intervals (<340ms), a variable clinical presentation which includes a high risk for SCD, short effective atrial and ventricular refractory intervals and easy inducibility of ventricular and atrial fibrillation in electrophysiological study. The pathological foundation for the occurrence of arrhythmia comprises electrophysiological heterogeneous of myocardium which with various shortening of the QT interval in the M zone of the myocardium comprises the foundation for a re-entry of the mechanism for the occurrence of tachycardia. An appropriate pharmacotherapy for SQTS has no been yet discovered, therefore the choice of treatment remains an ICD implantation. As an addition to the ICD or as a fundamental treatment for individuals who possess various reasons for not implanting an ICD, the quinidine is to be considered, which has solely shown to be relatively successful in the prevention of malignant arrhythmia. For SQTS we should consider differential diagnoses for lone AF, syncope, aborted SCD or positive family history for the stated diseases.*

KEYWORDS: *channelopathy, short-QT, sudden cardiac death, implantable cardioverter defibrillator*

Nagla srčana smrt (NSS) predominantno se javlja u pojedinaca sa strukturalnom bolešću srca. No, u oko 10 do 20% slučajeva NSS-a nije moguće indentificirati strukturalnu srčanu bolest[1]. Opisano je više bolesti koje i bez vidljive morfološke srčane patologije mogu uzrokovati NSS (Long QT sindrom, Brugada sindrom, kateholaminergička polimorfna VT). Napretkom molekularne genetike ovim bolestima određena je etiologija, te su pronađene mutacije odgovorne za maligne aritmije. Unatoč ovim spoznajama još uvijek postoji veliki broj nerazjašnjenih NSS uz strukturalno normalan miokard.

Godine 1957. prvi puta je opisan sindrom dugog QT intervala[2]. Od tada je pronađeno više bolesti koje točkastom mutacijom jednog gena mijenjaju strukturu određenih ionskih kanala na kardiomiocitu (kanalopatije) što čini bazu za aritmije. 1993. analizom Holtera uočeno je da uz dugi QT interval i kratki QT interval povećava rizik od NSS-a. Čak 35% slučajeva neobjašnjene VF povezano je s QT intervalima oko 360 ms[3].

Tek je 2000. godine prvi puta opisan kratki QT interval povezan sa paroksizmalnom fibrilacijom atrija (FA) u 17-godišnje pacijentice (QTc 225 ms). Majka i sestra također

Sudden cardiac death (SCD) predominantly affects individuals with a structural heart disease. However, in around 10-20% of cases of SCD, it is not possible to identify a structural heart disease[1]. Various diseases are described which without obvious morphological cardiac pathology may cause SCD (Long QT syndrome, Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia). With the advancement of molecular genetics, such diseases have a determined etiology, and mutations have been discovered responsible for malignant arrhythmia. However, despite all such discoveries, there is still a large number of unexplained SCD with structurally normal myocardium.

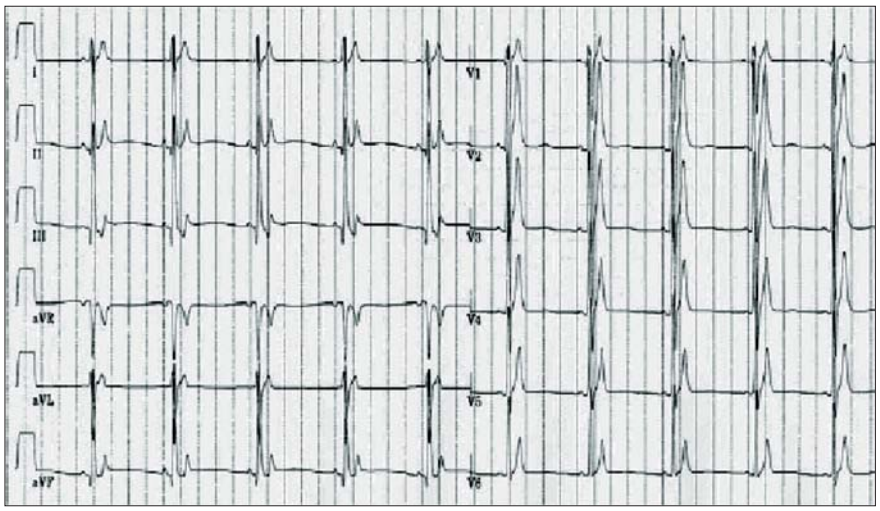
In 1957 for the first time, the Long QT interval syndrome[2] was identified. Since then, numerous diseases have been discovered which with a point mutation of a single gene change the structure of certain ionic channels on the cardiomyocyte (channelopathy) which constitutes the basis for arrhythmia. In 1993, Holter's analysis discovered that along with a long QT interval and short QT interval, there is an increased risk for SCD. Almost 35% of unexplained cases of VF are related to QT intervals of around 360ms[3].

In 2000, for the first time the short QT interval was described to be related to the paroxysmal atrial fibrillation

su imale perzistentni kratki QT interval, no bez aritmija. Do danas je opisano 40-tak slučajeva SQTS (Short QT syndrome), a definicija same bolesti još je u nastajanju. Glavne karakteristike SQTS su: autosomno dominantno nasljeđivanje, korigirani QT interval <340 ms po Bazzetu (**slika 1**), povišen rizik od NSS-a u bilo kojoj dobi, javljanje AF ili atrijske undulacije u mladosti te kratki efektivni atrijski i ventrikulski refrakterni periodi zabilježeni na elektrofiziološkoj studiji (EPS). Do sada je opisano pet genetskih mutacija (tri za kalijske i dvije za kalcijske kanale) povezane sa kratkim QT intervalom. Patofiziološku podlogu za aritmije u pacijenata sa kratkim QT intervalom čini značajna transmuralna disperzija dužine repolarizacije. Poznato je da miokard nije elektofiziološki uniforman i da postoje tri različita tipa stanica (epikard, "M" zona i endokard) sa heterogenim elektrofiziološkim profilom. Različito skraćivanje efektivnog refrakternog perioda u "M" zoni miokarda čini pogodan supstrat za "reentry" mehanizam tahikardije. Ovakvo skraćivanje QT intervala najprominentnije je kod manjih frekvencija, tako da je najvulnerabilniji period za javljanje aritmija odmor i spavanje[4].

(AF) in a 17 year old female patient (QTc 225 ms). The mother and sister also possessed persistent short QT intervals, but without arrhythmia. Up until today, there have been a total of 40 or so such cases of SQTS (Short QT syndromes), while defining the disease remains ongoing. The main characteristics of SQTS are: autosomal dominant inheritance, altered QT interval <340 ms according to Bazzet (**picture 1**), increased risk of SCD at any age, occurrence of AF or atrial undulation in youth and short effective atrial and ventricular refractory periods recorded on the electrophysiological study (EPS). Up until now, a total of 5 genetic mutations (3 for potassium and 2 for calcium channels) relating to short QT intervals have been described. The pathophysiological foundation for arrhythmia in patients with short QT intervals constitutes a significant transmural dispersion of repolarization duration. It is known that myocardium is not electrophysiologically uniform and that there exist three types of typical cells (epicardial, M zone and endocardial) with a heterogeneous electrophysiological profile. Various shortening of the effective refractory period in the M zone of the myocardium offers an appropriate substrate for the re-entry of the tachycardia mechanism. Such shortening of the QT interval is the most prominent for smaller frequencies, so that the most vulnerable period for the occurrence of arrhythmia is during rest and sleep[4].

Picture 1. *12-lead ECG of a 16 year old youth with Short QT syndrome. QT = 248 ms, QTc = 252 ms.*



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Nazivlje sindroma određivano je prema redosljedu otkrivanja odgovornih mutacija, te razlikujemo tri, odnosno pet SQTS-a. Već smo spomenuli prvi otkriveni slučaj kratkog QT intervala (SQTS1) za koji je odgovorna "gain of function" mutacija na KCNH2 genu koji kodira I_{kr} kanal. Radi se od točkastoj mutaciji zamjene aspargina lizinom na 588. kodonu gena. Zamjena aspargina aspartatom na istom mjestu uzrokuje "loss of function" mutaciju, odnosno LQT 2. I_{kr} je također ciljno mjesto za vezanje antiaritmika i ostalih primarno nekardioloških lijekova koji uzrokuju produženje QT intervala[5]. SQTS 2 otkriven je 2004. godine u jednog 70-godišnjaka sa abortiranim NSS. Izmjeren QTc iznosio je 290 ms, a radi se također o točkastoj "gain of function" mutaciji na KCNO1 genu koji kodira I_{ks} kanal. Ovdje je odgovorna zamjena valina leucinom na 307. kodonu gena, a "loss of function" mutacija na ovom mjestu rezultira Long QT sindromom tip 1[6]. Već sljedeće godine je u jednoj obitelji opisan SQTS 3 s jedinstvenim EKG fenotipom (asimetrični T sa brzim silaznim dijelom). Odgo-

The name of the syndrome is determined by the order of discovering the responsible mutations, and we differentiate 3 or 5 SQTS. We have already mentioned the first discovered case of a short QT interval (SQTS1) for which the gain of function mutation is responsible on the KCNH2 gene coding the I_{kr} channel. It relates to point mutation replacing asparagine with lysine at the 588th codon gene. The replacement of asparagine with aspartate at the same location causes a loss of function mutation, that is LQT 2. I_{kr} is also the target location for linking antiarrhythmics and other primary non-cardiac agents which extend QT intervals[5]. SQTS 2 was discovered in 2004 in a 70 year old man with aborted SCD. The measured QTc amounted to 290 ms, and included a point gain of function mutation on the KCN01 gene which codes the I_{ks} channel. Here, the replacement of valine with leucine at the 307th codon gene was responsible, while the loss of function mutation at this

vorna mutacija je na KCNJ genu koji kodira I_{kl} kanal. Također se radi od "gain of function" mutaciji, a "loss of function" mutacija odgovorna je za Andersonov sindrom (LQT 7)[7]. Prošle godine otkrivene su dvije nove mutacije na L-tip kardijalnom kalcijskom kanalu kod pacijenata sa "Brugadoidnom" morfologijom EKG-a, kratkim QT intervalima i rizikom za NSS. Radi se o "loss of function" mutacijama CACNA1C i CACNB2 gena, a "gain of function" mutacija istog kanala odgovorna je za Timothyev sindrom (LQT 8). S obzirom da EKG fenotip odgovara i Brugada sindromu i SQT sindromu, još ne postoji konsenzus o nazivlju ova 2 entiteta (SQT 4 i 5 ili Brugada III i IV).

SQTS karakterizira velika klinička varijabilnost bolesti, tako da čak i u istoj obitelji manifestacije bolesti variraju od NSS, paroksizama FA, rekurentnih sinkopa i palpitacija pa do kompletnog izostanka simptoma. Nastupni simptom može biti u najranijoj dobi, SQTS je sigurno odgovoran za dio slučajeva Sindroma iznenadne dojenačke smrti. Na elektrofiziološkom ispitivanju zabilježeni su kratki atrijski i ventrikulski refraktorni periodi te se u 60% do 90% slučajeva mogla inducirati VF i FA. Kod razmatranja diferencijalne dijagnoze kratkog QT intervala moramo također misliti na hiperkalijemiju, hiperkalcemiju, acidozu, hipersaturaciju digitalisom i hipertermiju.

Zbog visokog rizika od NSS terapija izbora za SQTS je ugradnja ICD-a[8]. Više vrsta antiaritmika testirano je za SQTS1, no samo se kinidin (klasa 1A) pokazao adekvatan. On uspješno produžava QT interval i ukida inducibilnost VF na EPS. Farmakoterapija može služiti kao dodatak ugradnji ICD-a ili kao osnovna terapija kod djece i pacijenata koji odbiju ICD[9].

Zaključno, na SQTS treba misliti u evaluaciji sinkope, abortirane NSS, "lone AF", pozitivne obiteljske anamneze na NSS i sinkopu. Radi se o genetski heterogenoj kanalopatiji koju fenotipski karakteriziraju konstantno kratki QTc (<320 ms) i visok rizik za NSS, a terapija izbora je ugradnja ICD-a.

Received: 9th Oct 2008
Updated: 22nd Oct 2008
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location resulted in the Long QT syndrome type 1[6]. The following year, in a family, an SQTS 3 case was discovered with a unique ECG phenotype (asymmetrical T with quick descending section). The responsible mutation is at the KCNJ gene which codes the I_{kl} channel. Also, present is the gain of function mutation, while the loss of function mutation is responsible for Anderson's syndrome (LQT 7)[7]. Last year, two new mutations were revealed on the L-type cardiac calcium channel in a patient with Brugada morphology for the ECG, short QT intervals and a risk of SCD. It concerns the loss of function mutation CACNA1C and CACNB2 gene, while the gain of function mutation for the same channel is responsible for Timothy's syndrome (LQT 8). Considering that, the ECG phenotype equals the Brugada syndrome and SQT syndrome, there is still no consensus regarding the terminology of these two entities (SQT 4 and 5 or Brugada III and IV).

SQTS is characterized by a large clinical variability of the disease, so that even in the same family manifestations of disease vary from SCD, paroxysmal AF, recurrent syncopes and palpitations right up to a complete absence of symptoms. The occurring symptom may be in the earlier age, SQTS is surely responsible for some of the cases of the sudden infant death syndrome. Electrophysiological examination shows evidence of short artial and ventricular refractory periods and in up to 60-90% of cases it can induce VF and FA. When considering differential diagnoses of short QT intervals, we must also consider hyperkalemia, hypercalcemia, acidosis, hypersaturation with digitalis and hyperthermia.

Due to a high risk from SCD, the choice of therapy for SQTS is to incorporate an ICD[8]. Various types of antiarrhythmics have been tested for SQTS1, but only quinidine (Class 1A) proved to be effective. It successfully prolongs the QT interval and removes the inducibility of VF to EPS. Pharmacotherapy can serve as an addition to the incorporation of the ICD or as a basic therapy for children and patients refusing ICD[9].

To conclude, the SQTS is to be considered in the evaluation of the syncope, aborted SCD, lone AF, positive family history for SCD and syncope. It concerns a genetic heterogeneous channelopathy which is in terms of phenotype characterized by constantly short QTs (<320 ms) and a high risk for SCD, while the therapy of choice is implantation of the ICD.