ONE
MINUTE
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BRIEF ANSWERS
TO SPECIFIC
CLINICAL
QUESTIONS

Q: Does a short QT interval increase the risk of cardiac death in healthy people?

A: In healthy people without symptoms, a short QT interval by itself does not necessarily increase the risk of sudden cardiac death and may in fact be a normal variant. However, it may warrant further investigation to determine if the patient is at risk.[1–3]

■ CORRECTING THE QT INTERVAL

The corrected QT interval (QTc) should be calculated. However, this should not be done when the patient is in tachycardia or bradycardia (using long-term electrocardiographic monitoring or beta-blockers if needed) to prevent the use of the Bazett formula at heart rates in which its correction is not linear and may lead to overestimation or underestimation of QTc values.[2] Furthermore, in patients with short QT syndrome, the physiologic abbreviation of the QT interval during tachycardia can be blunted (pseudonormalization of the QT interval) with failure to prolong the QT interval at slower heart rates, which contributes to the poor performance of correction formulas with heart rates above 100 beats/min or below 60 beats/min.

■ WHAT IS NORMAL?

The definition of the lower limit of the normal QT interval is a matter of debate. Mason et al[4] analyzed the electrocardiograms of 79,743 healthy people (including babies and children) and found that a QTc value 2 standard deviations below the mean was 350 ms in males and 360 ms in females. Many cardiac society guidelines deem that a QTc less than those values should be considered short, and a QTc interval less than 330 to 340 ms should be considered extremely short.[1,2,4,5]

> Most agree that a QTc < 330–340 ms is diagnostic of short QT syndrome

Applying the cutoff of 2 standard deviations, the prevalence of a short QT interval is around 2%.[4] Although this cutoff is sensitive, it takes in a large number of people who are not really at risk, and it does not necessarily predict arrhythmogenic potential.[6]

Proposed diagnostic criteria for short QT syndrome

The threshold of 360 ms is considered diagnostic of short QT syndrome if it is accompanied by 1 or more of the following:
- Pathogenic mutation
- Family history of short QT syndrome
- Family history of sudden death before age 40
- Survival of an episode of ventricular tachycardia-ventricular fibrillation (VT-VF) in the absence of heart disease.

Most experts agree that even without any of these factors, a QTc shorter than 330 to 340 ms is diagnostic of short QT syndrome, as such values are very rare in a healthy population.

■ DIFFERENTIAL DIAGNOSIS

Diagnosing short QT syndrome can be challenging, owing to the overlapping QT range of at-risk and healthy populations. Patients with short QT syndrome with normal QT interval have been reported, but in most cases, the QTc interval is less than 360 ms.

Assess for acquired causes first

Acquired causes of short QT interval should be considered first. Potential causes of nongenetic QT shortening include:
- **Hypercalcemia, hyperkalemia, acidosis, and hyperthermia**[7]
- **Drug effects**, eg, from digitalis,[8] nicorandil (through activation of adenosine triphosphate [ATP]-sensitive potassium

channels),[9] isavuconazole (through inhibition of L-type calcium channels),[10] and lamotrigine[9]

- **Effect of acetylcholine and increased vagal tone,** through activation of acetylcholine-sensitive potassium channels. This leads to deceleration-dependent shortening of the QT interval (ie, paradoxical QT interval shortening with a decrease in heart rate instead of lengthening)[11]
- **Effect of catecholamines,** through beta-adrenoceptor-induced activation of ATP-sensitive potassium channels[12]
- **Myocardial ischemia** through activation of ATP-sensitive potassium channels[12]
- **Ventricular fibrillation,** possibly related to increased intracellular calcium[13]
- **Androgen use.**[14]

Genetic causes

After considering possible acquired causes of short QT syndrome, the proposed diagnostic criteria discussed above should be satisfied before evaluating for a genetic cause.[1,2,6]

Short QT syndrome can be caused by a rare inherited genetic channelopathy associated with markedly shortened QT intervals and a structurally normal heart. Electrocardiography usually shows short or absent ST segments, tall and narrow T waves, marked shortening of the interval from the J point to the T peak (< 120 ms), and the signature sign of short QT intervals in the precordial leads.

Ion channel defects associated with short QT syndrome may be caused by mutations in potassium channels (KCNH2, KCNQ1, KCNJ2), calcium channels (CACNA1C, CACNB2, CACNA2D1), or carnitine channels (SLC22A5), leading to an abnormal acceleration of repolarization. This predisposes patients to the risk of reentry and hence atrial arrhythmias, ventricular arrhythmias, and sudden cardiac death. Often, patients with calcium channel mutations have a Brugada syndrome pattern on electrocardiography in addition to a short QT interval, either spontaneously or in response to a drug challenge with a class I antiarrhythmic agent.[15]

■ MANAGEMENT

A short QTc interval (330–360 ms) in isolation—ie, in the absence of pathogenic mutations, family history, or clinical history criteria proposed for the diagnosis of short QT syndrome—may not be associated with an increased risk of sudden cardiac death. Such patients are classified as having a low probability for the diagnosis of short QT syndrome and observation is recommended, providing that other acquired causes of short QT interval have been excluded.[1–3]

For patients who satisfy the proposed diagnostic criteria for short QT syndrome, the optimal strategy of primary prevention is unclear. Placement of an implantable cardioverter-defibrillator (ICD) or prescribing quinidine or sotalol may be considered on an individual basis in patients without symptoms but with a strong family history of sudden cardiac death and evidence of short QTc in some of the victims; otherwise, observation is recommended.[1,2]

For patients with short QT syndrome who survived cardiac arrest or have spontaneous sustained VT with or without symptoms, ICD implantation is recommended.[1–3] Quinidine or sotalol should be considered in patients who qualify for an ICD but have a contraindication or refuse one.[1,3] Finally, isoproterenol infusion can be useful in short QT syndrome with VT-VF storm.[3]

Referral for electrophysiologic study is not recommended for sudden cardiac death risk stratification or arrhythmia risk prediction.[1,3]

In patients with short QT syndrome, genetic testing should be considered. Those determined to have a mutation causative for short QT syndrome should have genetic counseling, and first-degree relatives should undergo mutation-specific genetic testing.[3] ■

A cutoff of 360 ms does not necessarily predict arrhythmogenic potential

■ REFERENCES

1. **Priori SG, Blomstrom-Lundqvist C, Mazzanti A, et al; Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC)**. 2015 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC) Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). Europace 2015; 17(11):1601–1687. doi:10.1093/europace/euv319

2. **Priori SG, Wilde AA, Horie M, et al**. HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes: document endorsed by HRS, EHRA, and APHRS in May 2013 and by ACCF, AHA, PACES, and AEPC in June 2013. Heart Rhythm 2013; 10(12):1932–1963. doi:10.1016/j.hrthm.2013.05.014

3. **Al-Khatib SM, Stevenson WG, Ackerman MJ, et al**. 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol 2018; 72(14):e91–e220. doi:10.1016/j.jacc.2017.10.054

4. **Mason JW, Ramseth DJ, Chanter DO, Moon TE, Goodman DB, Mendzelevski B**. Electrocardiographic reference ranges derived from 79,743 ambulatory subjects. J Electrocardiol 2007; 40(3):228–234. doi:10.1016/j.jelectrocard.2006.09.003

5. **Giudicessi JR, Ackerman MJ**. Determinants of incomplete penetrance and variable expressivity in heritable cardiac arrhythmia syndromes. Transl Res 2013; 161(1):1–14. doi:10.1016/j.trsl.2012.08.005

6. **Khera S, Jacobson JT**. Short QT syndrome in current clinical practice. Cardiol Rev 2016; 24(4):190–193. doi:10.1097/CRD.0000000000000091

7. **Maury P, Extramiana F, Sbragia P, et al**. Short QT syndrome. Update on a recent entity. Arch Cardiovasc Dis 2008; 101(11–12):779–786. doi:10.1016/j.acvd.2008.08.009

8. **Cheng TO**. Digitalis administration: an underappreciated but common cause of short QT interval. Circulation 2004; 109(9):e152. doi:10.1161/01.CIR.0000118177.56908.5B

9. **Shah RR**. Drug-induced QT interval shortening: potential harbinger of proarrhythmia and regulatory perspectives. Br J Pharmacol 2010; 159(1):58–69. doi:10.1111/j.1476-5381.2009.00191.x

10. **Keirns J, Desai A, Kowalski D, et al**. QT interval shortening with isavuconazole: in vitro and in vivo effects on cardiac repolarization. Clin Pharmacol Ther 2017; 101(6):782–790. doi:10.1002/cpt.620

11. **Gussak I, Brugada P, Brugada J, et al**. Idiopathic short QT interval: a new clinical syndrome? Cardiology 2000; 94(2):99–102. doi:10.1159/000047299

12. **Tinker A, Aziz Q, Thomas A**. The role of ATP-sensitive potassium channels in cellular function and protection in the cardiovascular system. Br J Pharmacol 2014; 171(1):12–23. doi:10.1111/bph.12407

13. **Kontny F, Dale J**. Self-terminating idiopathic ventricular fibrillation presenting as syncope: a 40-year follow-up report. J Intern Med 1990; 227(3):211–213. doi:10.1111/j.1365-2796.1990.tb00145.x

14. **Hancox JC, Choisy SC, James AF**. Short QT interval linked to androgen misuse: wider significance and possible basis. Ann Noninvasive Electrocardiol 2009; 14(3):311–312. doi:10.1111/j.1542-474X.2009.00313.x

15. **Antzelevitch C, Pollevick GD, Cordeiro JM, et al**. Loss-of-function mutations in the cardiac calcium channel underlie a new clinical entity characterized by ST-segment elevation, short QT intervals, and sudden cardiac death. Circulation 2007; 115(4):442–449. doi:10.1161/CIRCULATIONAHA.106.668392

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