



Hancox, J. (2018). Primary carnitine deficiency as a potential cause of short QT syndrome. *Cardiovascular Research and Medicine*, 2(1), 10-12.

Publisher's PDF, also known as Version of record

License (if available):
CC BY

[Link to publication record in Explore Bristol Research](#)
PDF-document

This is the final published version of the article (version of record). It first appeared online via GAP at http://globalaccesspub.com/open_access/primary_carnitine_deficiency_as_a_potential_cause_of_short_qt_syndrome_CRM . Please refer to any applicable terms of use of the publisher.

University of Bristol - Explore Bristol Research

General rights

This document is made available in accordance with publisher policies. Please cite only the published version using the reference above. Full terms of use are available:
<http://www.bristol.ac.uk/pure/about/ebr-terms>

Mini Review

Primary carnitine deficiency as a potential cause of short QT syndrome

Jules C Hancox*

School of Physiology, Pharmacology and Neuroscience, Medical Sciences Building, University Walk, Bristol, United Kingdom

Abstract

Congenital forms of short QT syndrome (SQTS) are associated with QT interval abbreviation on the electrocardiogram, with atrial and ventricular arrhythmias and with an increased risk of sudden death. Whilst mutations in a number of ion channel and transporter genes have been identified in SQTS patients, often the underlying basis of the condition is not identified. This article briefly surveys evidence that primary carnitine deficiency (PCD), which arises from mutations in the *SLC22A5* gene, may be a cause of SQTS. Experimental evidence linking carnitine deficiency with accelerated repolarization is also discussed and a case made for the imperative for further work to understand underlying mechanisms of low-carnitine induced repolarization abbreviation.

Keywords: Carnitine; OCTN2; hERG; Primary carnitine deficiency; PCD; QT interval; *SLC22A5*; short QT syndrome; SQTS

A brief introduction to the short QT syndrome

Congenital short QT syndrome (SQTS) is a rare condition characterized by abbreviated rate-corrected QT (QTc) intervals on the electrocardiogram, often accompanied by tall T waves, and by poor rate adaptation of the QT interval [1-3]. It is associated with an increased incidence of atrial and ventricular arrhythmias and with an increased risk of sudden death [1-3]. European Society of Cardiology guidelines suggest a diagnosis of SQTS with a QTc interval of ≤ 340 ms [4]. QTc intervals exceeding this value but of ≤ 360 ms may be indicative of SQTS if there is evidence of one or more of: a familial history of SQTS or sudden death below age 40, survival from ventricular tachycardia (VT) or fibrillation (VF) in the absence of structural heart disease⁴, or presence of a confirmed pathogenic mutation [4]. Thus far, eight distinct genetic SQTS variants have been identified that are associated with mutations to ion channels or transporters [3]. However, a relatively low proportion of patients who undergo genotyping (approximately 1 in 4 tested [5]) yield a mutation in an identified SQTS candidate gene, indicating that there is still much to discover about the underlying basis of QTc interval abbreviation in this condition. This brief article highlights why primary carnitine deficiency (PCD) should be evaluated as a potential cause of SQTS where examination of other genetic candidates proves negative.

An introduction to primary carnitine deficiency

Carnitine is a naturally occurring amino-acid obtained in the diet from meat and dairy produce and also produced endogenously in the liver and kidneys. L-carnitine is highly polar and is a critical metabolic cofactor, driving carnitine palmitoyltransferase I (CPTI), which is a rate-limiting step in the uptake into mitochondria and oxidation of long chain fatty acids (LCFAs) [6-10]. LCFAs are important energy sources in muscular tissue but cannot freely diffuse across the inner mitochondrial

membrane [10]. Deficiency of carnitine therefore inhibits mitochondrial oxidation of LCFAs, leading to lipid accumulation in the cell cytosol. Active uptake of L-carnitine into the heart is controlled by the organic cation transporter 2 (OCTN2) encoded by the *SLC22A5* gene [11,12].

Primary carnitine deficiency (PCD; OMIM 212140) is a rare but potentially fatal genetic disorder characterised by low plasma carnitine levels and a deficiency of intracellular carnitine. It exists as an autosomal recessive disorder, due to mutations in the *SLC22A5* gene that encodes the high affinity, sodium-dependent carnitine transporter, OCTN2 (OMIM 603377), and is associated with metabolic crisis, hepatic encephalopathy and sudden death [10,13-15]. Carnitine levels in PCD are low intracellularly and plasma and high in urine (due to renal wasting). A cardiac manifestation of PCD is common (with one review reporting a $> 60\%$ exclusive cardiac manifestation [15]): patients develop a progressive cardiomyopathy, which is responsive to carnitine supplementation. Without diagnosis and treatment PCD patients develop lethal heart failure [10,15]. More than 100 disease causing mutations in *SLC22A5* have been identified [15], with variable correlation between genotype and phenotype, possibly due to a role for external influences in exacerbating or mitigating clinical phenotype [15,16].

Primary carnitine deficiency, arrhythmias and abbreviated repolarization

Cardiac arrhythmias have been described in both PCD patients and heterozygous carriers of *SLC22A5* mutations [10]. There is long-standing evidence that PCD leads to repolarization abnormalities. In 1981, T wave modification (tall, peaked T

***Corresponding author:** Jules C Hancox, School of Physiology, Pharmacology and Neuroscience, Medical Sciences Building, University Walk, Bristol, BS8 1TD United Kingdom, E-mail: jules.hancox@bristol.ac.uk

Received: July 18, 2018; **Accepted:** July 24, 2018; **Published:** July 27, 2018

waves) was first reported in a young female PCD patient with cardiomyopathy [17], with subsequent studies reporting similar T wave changes in children with PCT and reversibility of these with carnitine supplementation [18-20]. Retrospective analysis of these studies showed simultaneous presence of tall T waves with abbreviated QT intervals [10]. Tall, peaked T waves together with abbreviated rate corrected (QTc) intervals are also characteristic of the congenital short QT syndrome (SQTS; [1,3]). In 2016, Roussel and colleagues reported patients from 2 unrelated families presenting with abbreviated QTc intervals in concert with *SLC22A5* mutations [21]. The first patient was a 21 month-old boy with low plasma free carnitine and a QTc of 309 ms, tall peaked T waves and low daytime QT dynamics. He was found to have a W62X *SLC22A5* (premature stop codon) mutation inherited from his father and a R471C mutation from his mother. He also had mild dilated cardiomyopathy. The second patient was this boy's mother, who had undergone an episode of aborted sudden death due to ventricular fibrillation. She had an abbreviated QTc (340 ms) interval and increased T wave height. She had the same R471C mutation as transmitted to her son, with a complete deletion on the second allele of exon 2 of *SLC22A5* gene, and low plasma free carnitine [21]. Screening for mutations in known SQTS K⁺ channel genes was negative. The third patient was from a different family and, again, had an abbreviated QTc interval (282 ms) and tall T waves. All three patients responded to carnitine supplementation. A further, recent report is of an 11 year old girl, originally identified at age 2 to have dilated cardiomyopathy possibly secondary to myocarditis, and treated pharmacologically with ACE inhibitors, diuretics, beta-blockers and digitalis [22]. Examined again at the age of 10, she showed severe left ventricular dilatation, bradycardia, and an abbreviated QTc interval (265 ms) with tall peaked T waves. Her blood carnitine was low and she had a heterozygous p.R289* truncation mutant in *SLC22A5*. A second variant was not found, but fibroblast analysis confirmed impaired carnitine transport. Carnitine supplementation improved her cardiomyopathy and increased her QTc interval [22]. It has been suggested that carnitine deficiency be suspected in situations of abbreviated QTc interval and/or unexplained cardiac arrhythmias [21]. This may be particularly the case where short QT intervals are concurrent with dilated cardiomyopathy [22].

Evidence for causality?

To understand better what the consequences of carnitine deficiency are for cardiac repolarization, Roussel and colleagues made a mouse model of carnitine deficiency [21]. For this, they used a drug called MET-88 (3-(2,2,2-trimethylhydrazinium) propionate; also known as mildronate or meldonium) which inhibits OCTN2 and the L-carnitine biosynthesis enzyme γ -butyrobetaine hydroxylase [23]. Treatment of mice for 28 days with MET-88 decreased plasma carnitine levels, induced cardiac hypertrophy and induced a significant increase in mitochondrial content of left ventricular myocytes [21]. ECG analysis did not show differences in basal heart rate, PR interval or QRS duration. However, there was a decrease in QT interval in MET-88 treated mice. 70% of treated mice also developed spontaneous sustained ventricular tachycardia and 50% developed VF. Cellular electrophysiology experiments were not performed to elucidate which ion channels/conductances were modified in the MET88 model [21]. However, the authors noted the ability of LCFA to

regulate activities of different ion channels [21] and highlighted a possible role of the hERG/rapid delayed rectifier (I_{Kr}) current in mediating effects of carnitine deficiency as previous work had shown regulation of function of "hERG" (the channel underlying I_{Kr}) by long-chain acyl-carnitines [24].

The need for further experimental investigation

The available information, summarised in the foregoing text, appears to be sufficient to indicate a causal relationship between PCD and QTc interval shortening. It is worth noting, however, that PCT may also present atypically with QTc prolongation [25] and this highlights a need to understand more deeply the relationship between OCTN2 dysfunction and cardiac repolarization mechanisms. Roussel and colleagues recommended that Class III antiarrhythmic drugs be employed to test the role of potassium currents in their mouse model of carnitine-deficiency linked QT interval shortening [21]. The changes to repolarization seen in the mouse PCD model certainly warrant further exploration at the cellular electrophysiology level, in order to understand the underlying basis of altered repolarization. It seems unlikely, however, that changes to I_{Kr} would be an explanation for their observations [21]. This is because the comparatively abbreviated mouse ventricular action potential differs markedly from that in humans and other animals that possess action potentials with a high plateau phase, and mouse ventricular myocytes rely on other currents than I_{Kr} to drive repolarization [26]. Thus, the primary effects on repolarization in the murine MET-88 induced carnitine deficiency model are far more likely to be attributable to effects on other ionic conductances and this merits experimental exploration. Furthermore, given the importance of I_{Kr} to human ventricular repolarization [27,28] and the ability of LCFA to modulate hERG channel function [24], it seems imperative also to develop an experimental model of PCD, perhaps using MET-88 [21], that uses a species with ventricular repolarization mechanisms closer to those in humans. Such work is likely to provide novel insights into pathophysiological modulation of ventricular repolarization and may highlight novel intervention point(s) for abbreviated repolarization disorders.

Conflicts of Interest

None

Acknowledgements

The author was supported by a University of Bristol Research Fellowship.

References

1. Maury P, Extramiana F, Sbragia P, et al. (2008) Short QT syndrome. Update on a recent entity. Arch Cardiovasc Dis 101: 779-786. [PubMed]
2. Giustetto C, Di MF, Wolpert C, et al. (2006) Short QT syndrome: clinical findings and diagnostic-therapeutic implications. Eur Heart J 27: 2440-2447.
3. Hancox JC, Whittaker DG, Du C, et al. (2018) Emerging therapeutic targets in the short QT syndrome. Expert Opin Ther Targets 22: 439-451. [PubMed]
4. Priori SG, Blomstrom-Lundqvist C, Mazzanti A, et al. (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). *Eur Heart J* 36: 2793-2867.
5. Bjeerregaard P, Gussak I (2013) Short QT Syndrome. *Electrical Diseases of the Heart*. Gussak I, Antzelevitch C (Eds) London, Springer pp.569-581.
 6. Fritz IB, Yue KT (1964) Effects of carnitine on acetyl-CoA oxidation by heart muscle mitochondria. *Am J Physiol* 206: 531-535. [[PubMed](#)]
 7. Fritz IB, Kaplan E, Yue KT (1962) Specificity of carnitine action on fatty acid oxidation by heart muscle. *Am J Physiol* 202: 117-121. [[PubMed](#)]
 8. Bremer J (1983) Carnitine--metabolism and functions. *Physiol Rev* 63: 1420-1480. [[PubMed](#)]
 9. Sebastian D, Guitart M, Garcia-Martinez C, et al. (2009) Novel role of FATP1 in mitochondrial fatty acid oxidation in skeletal muscle cells. *J Lipid Res* 50: 1789-1799.
 10. Fu L, Huang M, Chen S (2013) Primary carnitine deficiency and cardiomyopathy. *Korean Circ J* 43: 785-792. [[PubMed](#)]
 11. Tamai I, Ohashi R, Nezu J, et al. (1998) Molecular and functional identification of sodium ion-dependent, high affinity human carnitine transporter OCTN2. *J Biol Chem* 273: 20378-20382.
 12. Iwata D, Kato Y, Wakayama T, et al. (2008) Involvement of carnitine/organic cation transporter OCTN2 (SLC22A5) in distribution of its substrate carnitine to the heart. *Drug Metab Pharmacokinet* 23: 207-215.
 13. Wang Y, Ye J, Ganapathy V, et al. (1999) Mutations in the organic cation/carnitine transporter OCTN2 in primary carnitine deficiency. *Proc Natl Acad Sci U S A* 96: 2356-2360.
 14. Scaglia F, Wang Y, Longo N (1999) Functional characterization of the carnitine transporter defective in primary carnitine deficiency. *Arch Biochem Biophys* 364: 99-106.
 15. Shibbani K, Fahed AC, Al-Shaar L, et al. (2014) Primary carnitine deficiency: novel mutations and insights into the cardiac phenotype. *Clin Genet* 85: 127-137.
 16. Lamhonwah AM, Olpin SE, Pollitt RJ, et al. (2002) Novel OCTN2 mutations: no genotype-phenotype correlations: early carnitine therapy prevents cardiomyopathy. *Am J Med Genet* 111: 271-284.
 17. Tripp ME, Katcher ML, Peters HA, et al. (1981) Systemic carnitine deficiency presenting as familial endocardial fibroelastosis: a treatable cardiomyopathy. *N Engl J Med* 305: 385-390.
 18. Waber LJ, Valle D, Neill C, et al. (1982) Carnitine deficiency presenting as familial cardiomyopathy: a treatable defect in carnitine transport. *J Pediatr* 101: 700-705.
 19. Matsuishi T, Hirata K, Terasawa K, et al. (1985) Successful carnitine treatment in two siblings having lipid storage myopathy with hypertrophic cardiomyopathy. *Neuropediatrics* 16:6-12.
 20. Tein I, De V, Bierman F, et al. (1990) Impaired skin fibroblast carnitine uptake in primary systemic carnitine deficiency manifested by childhood carnitine-responsive cardiomyopathy. *Pediatr Res* 28: 247-255.
 21. Roussel J, Labarthe F, Thireau J, et al. (2016) Carnitine deficiency induces a short QT syndrome. *Heart Rhythm* 13: 165-174.
 22. Perin F, Rodriguez-Vazquez Del Rey MDM, Carreras-Blesa C, et al. (2017) Dilated Cardiomyopathy With Short QT Interval Suggests Primary Carnitine Deficiency. *Rev Esp Cardiol Pii Nov* 30: S1885-5857.
 23. Dambrova M, Makrecka-Kuka M, Vilskersts R, et al. (2016) Pharmacological effects of meldonium: Biochemical mechanisms and biomarkers of cardiometabolic activity. *Pharmacol Res* 113: 771-780.
 24. Ferro F, Ouillé A, Tran TA, et al. (2012) Long-chain acylcarnitines regulate the hERG channel. *PLoS One* 7: e41686. [[PubMed](#)]
 25. De Biase I, Champaigne NL, Schroer R, et al. (2012) Primary Carnitine Deficiency Presents Atypically with Long QT Syndrome: A Case Report. *JIMD Rep* 2: 87-90.
 26. Nerbonne JM, Nichols CG, Schwarz TL, (2001) Genetic manipulation of cardiac K⁺ channel function in mice: what have we learned, and where do we go from here? *Circ Res* 89: 944-956. [[PubMed](#)]
 27. Sanguinetti MC, Tristani-Firouzi M (2006) hERG potassium channels and cardiac arrhythmia. *Nature* 23: 463-469.
 28. Hancox JC, McPate MJ, El Harchi A, et al. (2008) The hERG potassium channel and hERG screening for drug-induced torsades de pointes. *Pharmacology and Therapeutics* 119: 118-132.