Long QT: Time to cut cholesterol?

Jin Li a,b, Flavien Charpentier c, Ange Maguy d,*

a Department of Cardiology, University Heart Center, University of Zurich, Zurich, Switzerland
b Center for Translational and Experimental Cardiology, Department of Cardiology, University Hospital Zurich, University of Zurich, Schlieren, Switzerland
c Nantes Universités, CNRS, INSERM, L’institut du thorax, F-44000 Nantes, France
d Department of Physiology, University of Bern, Bern, Switzerland

A prolonged QT interval on ECG should raise the suspicion of a long QT syndrome (LQTS).[1] LQTS may be inherited (gene variant) or acquired (drug-induced) and generally results from a cardiac ion channel dysfunction. Human ether-a-go-go related gene (hERG) is such a typically affected voltage-gated K+ channel. The concern is the abnormal delay in myocardial repolarization that predisposes patients to lethal arrhythmias called Torsade-de-pointes (TdP). Because patients are generally asymptomatic outside the actual arrhythmic episode, a diagnosis is often made after a cardiac event, such as syncope or sudden cardiac arrest/death. Pharmacotherapy (mainly beta- and sodium channel blockers), device (implantable cardioverter defibrillator) and/or left cardiac sympathetic denervation therapy are the mainstay of treatment of LQTS.[1] Most vitally, all patients are advised lifestyle adjustments.[1] Considerations usually revolve around competitive sports activities, avoidance of QT-prolonging drugs and dehydration, whereas diet recommendations have been kept to a minimum. While the arrhythmogenic effect of citrus fruit (hERG-inhibiting properties of the flavonoid naringenin) and quinine-containing beverages (hERG-inhibiting properties of the optical isomer of quinine) have been experimentally proven, energy drinks have raised concerns and public awareness of potentially life-threatening dietary triggers, especially for LQTS patients.[2]

With that in mind, anecdotal reports of QT prolongation and TdP following a ketogenic diet have drawn our attention. A ketogenic diet consists of a low-carbohydrate, but high-fat regimen. Intriguingly, a ketogenic diet can be the source of hypercholesterolemia.[3] Because little is known about the association between cholesterol and cardiac repolarization, we recorded action potentials on induced pluripotent stem cell-derived cardiomyocytes from a patient with congenital LQTS type 2 (p.A561P mutation in the KCNH2 gene) challenged with cholesterol. Impressively, cholesterol induced a 4-fold prolongation of action potential duration compared to baseline condition (P = 0.01, Fig. 1). Cholesterol is a major lipid component of the plasma membrane. Beyond its essential role in membrane plasticity, cholesterol also regulates ion channel function.[4,5] In the plasma membrane, cholesterol is unevenly distributed. It is suggested that cholesterol-rich membrane domains (lipid rafts) cluster ion channels to form functional entities.[4,5] hERG is an example of K+ channel that localizes in lipid rafts.[6] Moreover, cholesterol has been shown to inhibit hERG channel activity, which is manifested by a positive shift in voltage sensitivity of activation and acceleration of deactivation kinetics.[6,7] The underlying mechanism remains uncertain, but direct binding of cholesterol, membrane fluidity as well as interactions with other proteins assembled within raft domains have been described for other ion channels.[5]

Previous studies have suggested a link between hypercholesterolemia and QT prolongation.[8,9] This observation has prompted investigations on the impact of statins on cardiac repolarization. In fact, patients treated with atorvastatin or simvastatin have a shorter QT. However, a class effect cannot be attributed to HMG-CoA reductase inhibitors, as rosuvastatin has hERG-blocking properties and prolonged the QT interval in animal studies.[10–12] It remains speculative whether the beneficial effect of statins is the result of HDL cholesterol increase, which has been shown to correlate with QT shortening.[13,14] On the other hand, we now have in our cholesterol-lowering armamentarium next-generation PCSK9 inhibitors (monoclonal antibodies, small interfering RNA) that appear safe from the electrical point of view.

Our data highlights the need to implement more research in the cardiac safety of food products that are daily encountered by patients. Identifying dietary triggers will help us improve nutrition counseling and provide the best care for long QT patients.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

* Corresponding author at: Department of Physiology, University of Bern, Buehlerplatz 5, 3012 Bern, Switzerland.
E-mail address: ange.maguy@unibe.ch (A. Maguy).

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