Weak spot for heart dysfunction discovered

Würzburg scientists identify missing mitochondrial calcium channel as trigger for arrhythmias and heart failure for the disease Barth syndrome

Patients with Barth syndrome may soon be able to breathe a sigh of relief. At the Comprehensive Heart Failure Center (DZHI) in Würzburg, Christoph Maack and his team have discovered that loss of the calcium channel in mitochondria is the reason for their cardiac dysfunction during physical exercise and likely also their higher risk for arrhythmias. Barth syndrome is caused by a mutation in the tafazzin gene, and tafazzin produces cardiolipin, an essential component of the mitochondrial membrane. The disease usually affects boys in early childhood and causes heart failure and arrhythmias. The scientists found out that due to the defect in cardiolipin, the channel required to import calcium into mitochondria is missing. Since calcium is the most important ion for the adaptation of energy production to increased demand, this defect explains the inability of Barth syndrome patients to increase their cardiac pumping capacity during physical activity and their predisposition to cardiac arrhythmias. These findings, which have now been published in the highly respected journal *Circulation* of the American Heart Association, are not only a ray of hope in the treatment of the rare Barth syndrome, but could also contribute to a better understanding and treatment of the more widespread heart failure with preserved pump function (HFpEF).

A normal healthy heart is pumping four to five litres of blood per minute into our body, and even up to 30 litres per minute during exertion. The heart of boys suffering from Barth syndrome beats faster during exercise, but the output cannot be increased accordingly. The consequence of this reduced functional reserve during exertion is shortness of breath and insufficient supply of the skeletal muscles with blood. In addition, the calcium defect predisposes to cardiac arrhythmias, which can lead to sudden death.

Less calcium = less energy in heart muscle cells

Cardiologist Christoph Maack and biologist Jan Dudek have been researching the disease mechanisms of Barth syndrome for many years. They found out that the impaired energy production of the heart muscle cells due to the defect of the tafazzin gene is related to the calcium balance. The reduced calcium uptake in the mitochondria, the power plants of the heart muscle cell, disturbs the activation of the so-called Krebs (or citrate) cycle. The Krebs cycle produces the coenzyme NADH, which provides electrons for the production of the energy-rich molecule adenosine triphosphate (ATP), and NADPH, which is required to detoxify oxygen free radicals.

Missing calcium channel depletes the stores

The researchers from the Department of Translational Research of the DZHI, in particular Edoardo Bertero, Alexander Nickel and Michael Kohlhaas, have now identified

the mechanism why cardiac output cannot be increased and arrhythmias occur more frequently in Barth syndrome hearts.

Formerly, it was assumed that the lack of cardiolipin mainly causes problems for the respiratory chain and that oxygen radicals damage the cells. Cardiolipin is also affected by oxidative stress in many other heart diseases. A deficiency of this phospholipid disrupts the respiratory chain, resulting in less ATP being produced. "Although we also found moderate disruption of the respiratory chain in our studies, we did not measure excessive levels of radicals," explains Edoardo Bertero, the study's first author. "Instead, we observed that the channel responsible for calcium import into the mitochondria, called the mitochondrial calcium uniporter, or MCU, was almost completely gone in mice with tafazzin knockdown. This is important for patients with Barth syndrome because it explains why their hearts are unable to increase their output during exercise; but also for general cardiac physiology because it reveals a previously unappreciated function of cardiolipin, namely the stabilisation of the MCU-protein complex."

New finding leads to better understanding of the Barth syndrome

Maack adds: "The gene and protein structure of the mitochondrial calcium channel has only been known for ten years. Barth syndrome is to our knowledge the first disease in which a relevant defect of the MCU in heart cells contributes to their dysfunction." With this discovery, the DZHI researchers provide an important therapeutic approach, possibly not only for the treatment of Barth syndrome, but also for other forms of heart failure with a preserved pump function, and in particular for other genetic cardiomyopathies. Maack urges that based on the new findings, drugs that increase the pumping power of the heart by increasing sodium may be less advantageous. This is the case for digitalis, which is still often used in patients with Barth syndrome. “Instead,” Maack adds, “the administration of SGLT2 inhibitors, drugs that improve outcome in patients with heart failure and a preserved pump function, could be more favourable.” Some studies suggested that SGLT2-inhibitors reduce the sodium levels in cardiac cells, which would positively affect mitochondrial calcium accumulation and Krebs cycle activation in Barth syndrome hearts, so that the heart can keep up better with increased stress. However, this is still an open field for future research.

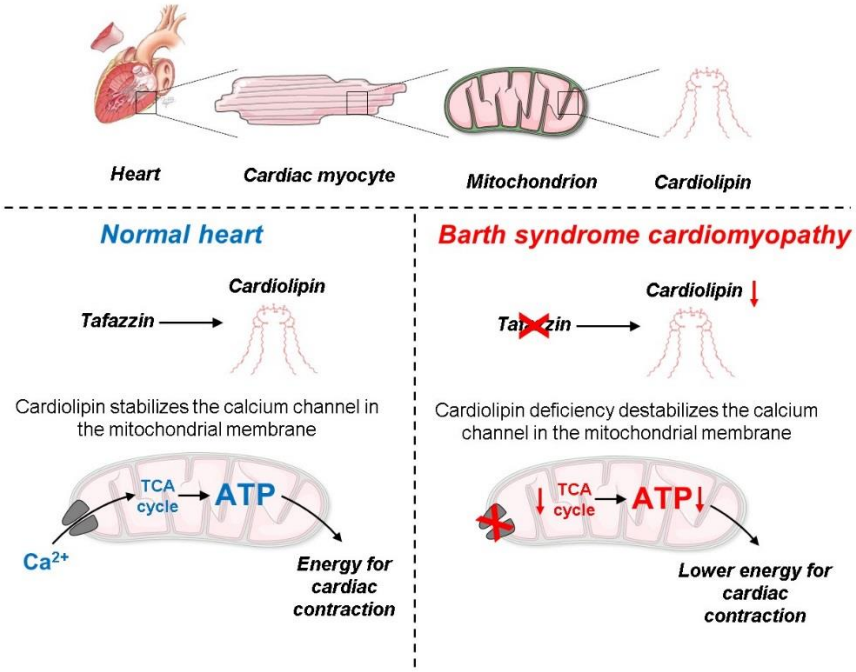
In the past, boys with Barth syndrome often did not live beyond the age of three. They died of heart failure or infections. With improved diagnosis and proper medical treatment and monitoring of all symptoms, quality of life and survival of these children is much better. "That's what motivates and encourages us. The disease is rare. There are about 300 known cases worldwide. However, we assume that the number of unreported cases is high. And what counts is the fate of every individual affected by Barth syndrome," Maack emphasises.

The research was conducted in close cooperation with numerous other groups in Homburg/Saar, Göttingen and Würzburg and funded by the German Heart Foundation (Margret Elisabeth Strauß program), the German Research Foundation (DFG), the Federal Ministry of Education and Research (BMBF), the European Research Council (ERC) and the Barth Syndrome Foundation (www.barthsyndrome.org).

Publication in AHA Journal Circulation: Loss of Mitochondrial Ca2+ Uniporter Limits Inotropic Reserve and Provides Trigger and Substrate for Arrhythmias in Barth Syndrome Cardiomyopathy

Edoardo Bertero, Alexander Nickel, Michael Kohlhaas, Mathias Hohl, Vasco Sequeira, Carolin Brune, Julia Schwemmlein, Marco Abeßer, Kai Schuh, Ilona Kutschka. Christopher Carlein, Kai Münker, Sarah Atighetchi, Andreas Müller, Andrey Kazakov, Reinhard Kappl, Karina von der Malsburg, Martin van der Laan, Anna-Florentine Schiuma, Michael Böhm, Ulrich Laufs, Markus Hoth, Peter Rehling, Michaela Kuhn ,Jan Dudek, Alexander von der Malsburg, Leticia Prates Roma and Christoph Maack

Originally published14 Oct 2021 https://doi.org/10.1161/CIRCULATIONAHA.121.053755



Comprehensive Heart Failure Center (CHFC)

The CHFC researches and treats the complex disease heart failure and its comorbidities in a comprehensive approach. Cutting edge science in an interdisciplinary setting especially between the CHFC and the University clinic Wuerzburg are essential. As nationwide unique centre the CHFC connects heart failure from basic science, clinical research and patient care in one building.

Universitätsklinikum Würzburg
Deutsches Zentrum für Herzinsuffizienz Würzburg DZHI
Am Schwarzenberg 15 Haus A15
D 97078 Würzburg Deutschland