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Unraveling the causes of arrhythmias in very-long chain acyl-CoA (VLCAD) deficiency through the combined use of non-targeted lipidomic and molecular analyses in a mouse model

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Introduction: VLCAD catalyses the first reaction of mitochondrial fatty acids (FA) β-oxidation. Inherited VLCAD deficiency predisposes to severe neonatal arrhythmias whose pathophysiology is not fully understood. We hypothesized that VLCAD deficiency disrupts cardiac lipid homeostasis, which could contribute to arrhythmia.
Methods: Our study model is the VLCAD null mouse (VLCAD-/-), which is known to develop a prolonged QT interval and ventricular arrhythmias. Mice were fed a chow or high fat (HF) diet, the latter being known to worsen the cardiac phenotype in VLCAD deficiency. Non-targeted lipidomic profiling of heart tissues was achieved using liquid chromatography-mass spectrometry (LC-QTOF). The expression of genes or proteins involved in polyunsaturated FA synthesis, phospholipid (PL) remodeling, endoplasmic reticulum (ER) stress and calcium handling were assessed using RT-qPCR or Western blotting.
Results: Compared to their littermate counterparts, VLCAD-/- mouse hearts displayed alterations in the FA composition of PL characterized by an increase in arachidonic acid and a decrease in docosahexaenoic acid, a profile that was worsened with the HF diet. These changes in PL composition were associated with diet-dependent increased expression of gene or protein markers for (1) PL remodeling, especially the calcium-dependent phospholipase A2 and the lysophosphatidylcholine-acyltransferase 2, (2) ER stress, namely CHOP and GRP78, and (3) calcium handling, namely SERCA2a and phospholamban (PLB). In contrast, the phosphorylated form of PLB (Ser16) and RyR2 (Ser2808) was decreased.
Conclusions: Altogether, results from this study highlight perturbations in PL remodeling in VLCAD-/- mouse hearts, which are associated with ER stress and alterations in proteins involved in calcium handling and exacerbated by a HF diet. These perturbations represent novel potential mechanisms, which could contribute to the pathogenesis of arrhythmias in VLCAD-/- mice as well as in humans.