Lipotoxicity in the mechanisms of Arrhythmias

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Very-low-density lipoprotein (VLDL) is the only lipoprotein secreted from the liver, where hepatic triglycerides, cholesterol, and other lipids are assembled with variable apolipoproteins, including B100, C, and E. In some diseases, such as metabolic syndrome and hepatic steatosis, VLDL particles are enlarged, assembled with altered apolipoproteins, and exhibit abundant negative charge over the particle surface. These changes render VLDL a pathogenic mediator turning from the naive lipid payload. In addition, the metabolism of VLDL is dynamic and can be largely changed by nutritional conditions such as fasting, meal intake, fructose consumption, lifestyle, exercise, and gut microbiome. We found that postprandial VLDL, rather than fasting VLDL, determines the development of atrial myopathy.

The pathogenic effects of VLDL in atrial myopathy and abnormal cardiac electricity include direct cytotoxicity, excess lipid accumulation, abbreviated action potentials, modulated gap junctions, delayed conduction velocities, disturbed calcium regulation, and sarcomere protein derangement. In addition, we found that SK currents, which are mediated by calcium-regulatory potassium channels, became significant in the modulation of cardiac action potentials, determining arrhythmogenicity in high-fat feeding mice. These changes promote vulnerability to arrhythmias in the metabolic syndrome. We believe that cardio-toxic VLDL is an important residual pathogenic factor for cardiovascular diseases, particularly for the most common cardiac arrhythmia, atrial fibrillation.