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Obese patients have an increased risk of arrhythmias and twice the risk of sudden cardiac death, which is often caused by ventricular tachycardias (VT). Cardiomyocytes from obese patients have increased lipid content, which is thought to contribute to the pathophysiology of arrhythmia. Furthermore, higher levels of serum fatty acids and higher saturated fat intake in the diet predict sudden cardiac death. This suggests that the arrhythmogenic effects of saturated fat can occur without obesity. **An unanswered question is: What are the molecular mechanisms causing arrhythmias during obesity and high-fat diet?**

The most common electrophysiologic abnormalities found in obese patients are increased frequency of ventricular ectopy and prolongation of the QT interval. We have previously shown that wild type (WT) mice with high-fat diet induced obesity (DIO) have long QT and increased ventricular ectopy, mimicking the abnormalities found in obese humans. Our preliminary data now show that a high saturated fat diet is sufficient to cause ventricular ectopy and prolong the QT interval, and to promote inducibility of VT/VF. Further, mice fed a diet with an equivalent amount of monounsaturated fat from olive oil do not have heart rhythm abnormalities. We discovered that a high saturated fat diet increases cardiac NAPDH oxidase 2 (NOX2) activity, whereas the olive oil high-fat diet does not. The NOX2 inhibitor apocynin, when given during a high saturated fat diet, prevents heart rhythm abnormalities. Additional experiments with isolated cardiac myocytes show that NOX2 is necessary for the oxidative stress and mitochondrial dysfunction caused by saturated fat. We will use both in vivo experiments and cardiomyocytes to determine the pathways linking cardiac lipid metabolism to arrhythmia. **Our central** hypothesis is that NOX2 activation causes the arrhythmogenic effect of saturated fat by causing sarcoplasmic reticulum calcium leak, which in turn promotes mitochondrial dysfunction.

We propose the following independent aims:
1. Determine if NOX2 activation causes arrhythmia during high fat diet, by using genetic gain and loss.
2. Determine how TLR4 signaling contributes to the arrhythmogenic effects of dietary saturated fat.
3. Determine if the mitochondrial abnormalities caused by NOX2 activation promote arrhythmia.