After the occlusion of a coronary vessel in the heart, ischemia and subsequent infarction of cardiac tissue occurs because of an inadequate supply of blood, resulting in a deficiency of oxygen and glucose to the muscle cells. Within minutes, there are apparent changes in the ECG indicating cardiac cellular electric disorders, namely ST elevation myocardial infarction (MI). Because the processes postocclusion are complicated, the complex nature has been dissected into different facets in various in vitro studies. Solutions can be made to mimic ischemia and superfused over paced multicellular and single-cell preparations of cardiac tissues. Under these conditions, one can apply voltage clamp/Ca²⁺ imaging to define how specific biochemical changes that occur during this acute period affect ion channel behavior and signaling pathways. Single cells can be subjected to hypoxia, uncouplers of the mitochondrial oxidative chain, inhibitors of glycolysis, solutions containing a high concentration of K⁺ and low H⁺, and solutions deficient in glucose, amphiphiles, free radicals, catecholamines, as well as stretch. Professor Carmeliet¹ summarized these data in his 1999 review. This list is by no means complete and ignores the consequences of certain agents, for example, unabated reactive oxygen species that are potentiated by an ischemia-induced shift in anaerobic metabolism. This generates superoxide anion on reperfusion. Reactive oxygen species can modify protein structure and function in their isoforms and generate superoxide anion on reperfusion. Reactive oxygen species can modify protein structure and function in their isoforms, in ischemia in wild-type controls as well as in 2 validated dyslipidemic mouse models LDLr⁻/⁻ and ApoA1⁻/⁻. In these mice, ischemia occurs. In this study, the authors induced regional ischemia in wild-type controls as well as in 2 validated dyslipidemic mouse models LDLr⁻/⁻ and ApoA1⁻/⁻. In these mice, plasma low-density lipoprotein (LDL) and high-density lipoprotein and cell membrane cholesterol (increased) and sphingolipid (decreased) content were altered. They contend that the increased membrane cholesterol prolonged action potential duration and provided substrate protection against the expected acute ischemic reentrant arrhythmias (effects postulated to be similar to a class III drug).

Sarcolemmal cholesterol has been shown to modulate several ion channels⁴–⁶ so it is not surprising that these investigators found a 30% increase in L-type Ca²⁺ currents in these cells. This is unlike their findings of K⁺ (measured) and Na⁺ currents (not measured) where no effects were described. Others have noted that hypercholesterolemia (from diet) in rabbits reduces Iₚₛ by 38%.⁷ Although this change in Na⁺ current may not have altered action potential or ECG values in this murine study, it certainly would be a concern if cells in this type of substrate were exposed to a second hit on Na⁺ channels, such as the effects of flecainide in the epicardial border zone.⁸

Baartscheer et al's³ study provides interesting insight into the immediate protective effect of dyslipidemia on arrhythmia perpetuation induced with programmed ventricular stimulation of LDLr⁻/⁻ and ApoA1⁻/⁻ ex vivo hearts post coronary artery occlusion. The authors propose that patients with dyslipidemia may be protected from sustained ventricular arrhythmias because dyslipidemia prolongs the action potential duration. They suggest these effects may be akin to the therapeutic effects of fish oil. In the GISSI-Prevenzione trial,⁹ the consumption of fish oil in patients with a recent MI was studied by randomizing patients to usage of omega 3 polyunsaturated fatty acids. Polysaturated fatty acids are thought to prevent fatal arrhythmias by inhibiting both voltage-dependent Na⁺ and L-type Ca²⁺ channels in the cell membrane.³ However, they are also known to produce a 30% to 50% reduction in plasma triglycerides as well as help to improve cardiac end points because of their pleiotropic properties, which are anti-inflammatory and antioxidation.¹⁰ This is contrary to clinical studies that have shown that patients with dyslipidemia and obesity have increased oxidative stress, proinflammatory states, which would be proarrhythmic rather than antiarrhythmic.¹¹

Epidemiological studies have shown that obese patients have twice the risk of sudden cardiac death. A prolonged QT interval, frequent premature ventricular complexes and left ventricular hypertrophy are findings often found in patients who are obese. Obesity causes increased lipid accumulation within cardiomyocytes and is thought to contribute to development of heart failure and arrhythmia.¹¹,¹²

Baartscheer et al's³ study provides data to suggest that the protective effect of dyslipidemia on murine arrhythmia perpetuation does not carryover to protection against arrhythmia.

The study of Baartscheer et al's³ in this issue focuses on the effects of changes in the lipid composition of the membrane and ion channel function before the acute effects of ischemia occur. In this study, the authors induced regional ischemia in wild-type controls as well as in 2 validated dyslipidemic mouse models LDLr⁻/⁻ and ApoA1⁻/⁻. In these mice, plasma low-density lipoprotein (LDL) and high-density lipoprotein and cell membrane cholesterol (increased) and sphingolipid (decreased) content were altered. They contend that the increased membrane cholesterol prolonged action potential duration and provided substrate protection against the expected acute ischemic reentrant arrhythmias (effects postulated to be similar to a class III drug).

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initiation (triggers) in the same hearts. After an MI, cells within the region of infarction are in different stages of depolarization. In the center of the ischemic zone, cells depolarize and die, whereas in the periphery, cells may be partially depolarized and, therefore, may be more excitable. During the acute time period post MI, the surge in catecholamines is thought to trigger ventricular arrhythmias through activation of endothelin-1. Thus, it is possible that these events still occur. Furthermore, in the presence of enhanced Ca2+ currents in the LDLr−/− and ApoA1−/− myocytes, delayed afterdepolarizations and early afterdepolarizations are more likely to occur.

The bigger question is whether the findings of Baartscheer et al. should be translated to the clinic. Should we suggest patients to EAT BACON after an MI to increase their serum and membrane cholesterol?

This would be counter to current recommendations for acute treatment of MI, which strive to provide a rapid lowering of LDL and thus total cholesterol levels. According to the 2013 American College of Cardiology/American Heart Association (ACCF/AHA) Guidelines, a class I indication is that all patients with an ST elevation MI should be initiated with intensive statin therapy as it has been shown to lower the risk of coronary heart disease death, recurrent MI, stroke, and the need for coronary revascularization. In the Pravastatin or Atorvastatin Evaluation and Infection Therapy—Thrombolysis in Myocardial Infarction 22 (PROVE-IT TIMI 22) trial, intensive statin therapy, compared with less intensive therapy, led to an additional lowering of nonfatal clinical end points in patients with acute coronary syndrome. Statin therapy after MI benefits additional clinical outcomes including all cause mortality, lower risks for stroke, urgent revascularization and repeat hospitalizations, even in patients with baseline LDL cholesterol levels of <70 mg/dL.15 Intensive statin therapy is thought to stabilize atherosclerotic plaque, which when ruptured leads to thrombosis of the coronary artery. Increasing serum lipids for the benefit of increasing action potential duration to achieve an antiarrhythmic effect may not be worth the risk of plaque instability and a worsening of atherosclerosis.

Hypercholesterolemia also reduces vasodilatory properties of blood vessels. Diet-induced hypercholesterolemia in a porcine model causes suppression of KATP current in isolated aortic endothelial and bone marrow–derived progenitor cells, thus affecting myocardial repair. This results in significant aortic endothelial and bone marrow–derived progenitor cells, delayed afterdepolarizations and early afterdepolarizations are more likely to occur.

Continued investigation is necessary to understand the long-term effects of increased membrane cholesterol after MI. Does sustained hypercholesterolemia affect the reverse remodeling processes that occur with time? This could be elucidated by feeding LDLr−/− and ApoA1−/− mice a high-fat diet for months post MI to determine whether the cardioprotective class III effect still exists in myocardial cells. However, it may be that the negative effects of the high-fat diet will outweigh the expected substrate effects. Dyslipidemia has vast acute and chronic clinical repercussions such as obesity, bone marrow progenitor cells depletion, which can impair infarct healing, as well as, impediment of vasodilation and metabolic abnormalities. These profound irregularities during an MI may overshadow any antiarrhythmic properties that may be derived from increased deposition of cholesterol in the cellular membrane.

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None.

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