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ACUTE CORONARY SYNDROMES

Myocardial salvage with HDL infusion after infarction

> rHDL early in reperfusion results in myocyte salvage

A single dose of reconstituted HDL (rHDL) delivered after myocardial ischaemia enhances cardiac glucose uptake, reduces infarct size, and improves myocardial remodelling and functional recovery. These findings come from studies performed on mouse models of myocardial infarction and were published in *Science Translational Medicine*.

Controversy surrounds HDL therapeutics following the neutral results of several phase III trials that investigated the effects of chronic elevation of HDL-cholesterol levels with the use of inhibitors of cholesteryl ester transfer protein on atherosclerotic plaque regression and stablization. These trials revealed the importance of HDL particle function as well as particle number. In a different approach, Bronwyn Kingwell and colleagues from Melbourne, Australia, used an infusion of rHDL (a synthetic form of nascent HDL that combines apolipoprotein A-I with phospholipids) to increase the circulating pool of functional HDL after myocardial ischaemia.

Kingwell *et al.* used metabolically normal mice fed a standard chow diet and mice fed a high-fat diet to mimic a state of insulin resistance. Mice in both dietary groups had increased cardiac glucose uptake after a single dose of rHDL compared with an infusion of saline. Similarly, after 30 min of cardiac ischaemia produced by occlusion of the left anterior descending (LAD) coronary artery, mice in both dietary groups treated with rHDL had increased cardiac glucose uptake compared with mice that received saline. Treatment with rHDL was associated with increased cardiac output (increased ejection fraction and stroke volume) as well as reductions in infarct size and interstitial fibrosis in both dietary groups.

In rat primary neonatal ventricular cardiomyocytes, lipidated native human HDL increased glucose uptake and the basal rate of glycolysis compared with saline. Further experiments indicated that these effects were mediated by activation of the AKT–AS160 signalling pathway. Increased phosphorylation of this signalling pathway was confirmed following post-ischaemic delivery of rHDL into mice.

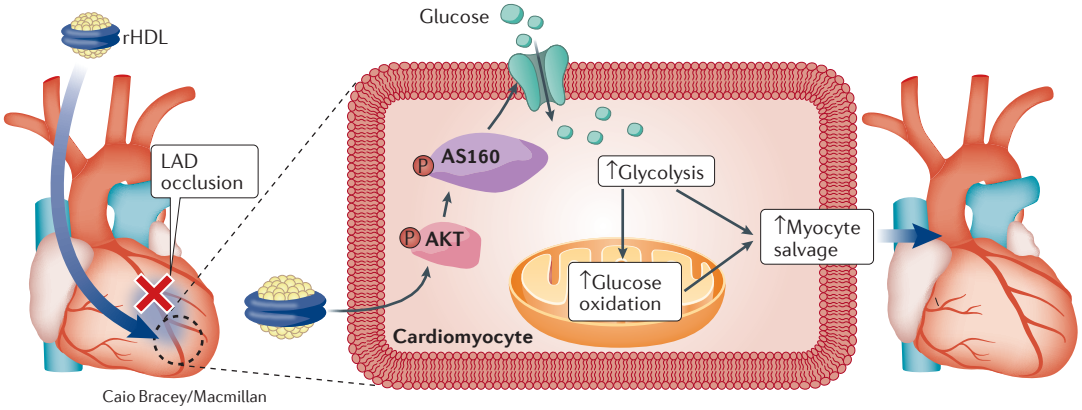
"We hypothesize that the metabolic support provided by the rHDL early in reperfusion results in myocyte salvage, and that this mechanism of action may protect the myocardium against cell damage, adverse remodelling, and subsequent cardiac dysfunction to maintain contractility and prevent progression to heart failure," summarizes Professor Kingwell.

"These results are relevant to therapeutic strategies for myocardial salvage after acute coronary syndromes and suggest that benefit may apply equally in the presence and absence of insulin resistance," conclude the investigators. "HDL infusion formulations are in clinical development and amenable for delivery in the context of primary percutaneous coronary intervention."

The researchers suggest that HDL-mediated enhancement of myocardial glucose metabolism might reduce the inflammatory response and oxidative stress associated with ischaemia. In addition, HDL might have direct antioxidative and anti-inflammatory effects that enhance myocardial salvage.

"Clinical studies will be required to determine whether these [preclinical] effects of HDL translate to humans," caution the researchers. "Whether concurrent administration of glucose with rHDL might be of additional clinical benefit is a further area of potential investigation."

Gregory B. Lim



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ORIGINAL ARTICLE Heywood, S. E. *et al.* High-density lipoprotein delivered after myocardial infarction increases cardiac glucose uptake and function in mice. *Sci. Transl. Med.* **9**, eaam6084 (2017)

FURTHER READING Rosenson, R. S. *et al.* HDL and atherosclerotic cardiovascular disease: genetic insights into complex biology. *Nat. Rev. Cardiol.* http://dx.doi.org/10.1038/nrcardio.2017.115 (2017)