How High-Density Lipoprotein Fuels the Failing Heart

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Heart failure remains a major multifactorial health problem in the aging population. The causal cellular mechanisms are still incompletely understood, and further understanding of these mechanisms in heart failure is necessary to open up new perspectives for treatment and prevention. Distinct evidence suggests that cardiac energy metabolism in the failing heart is severely impaired. In fact, compromised cardiac energy metabolism might cause and worsen myocardial dysfunction. A growing body of evidence suggests that cellular energy sustenance in the diseased heart is crucial for understanding and treating cardiac dysfunction and thus needs to be investigated further. Nakajima et al now provide novel insights in the regulatory changes of cellular substrate use in the pathogenesis of heart failure.

Vast amounts of energy are required to fuel the perpetual pumping activity of the heart. Although the fetal heart predominantly generates ATP from carbohydrate oxidation, the adult human heart draws on free-fatty acids as the major substrate for energy supply. Approximately 60% to 90% of the ATP required is generated by β-oxidation of long chain fatty acids. The remaining 10% to 40% are obtained by oxidation of other substrates, such as glucose, lactate, and ketone bodies. So far, evidence has indicated that fatty acid demand in cardiac β-oxidation is covered by hydrolysis of intramyocardial triglyceride stores, dissociation of circulating albumin-bound fatty acid complexes derived from adipose tissue-lipolysis, and lipoprotein lipase (LPL)–mediated hydrolysis of triglyceride-rich very low–density lipoproteins.

β-oxidation of long chain fatty acids is severely impaired in heart failure. Nakajima et al now provide novel insights in the regulatory changes of cellular substrate use in the pathogenesis of heart failure.

In the failing heart, fatty acid use is impaired, resulting in a relative metabolic shift away from fatty acids to glucose oxidation in advanced heart failure. This condition might be owed to a more favorable ATP production to oxygen consumption ratio in glucose oxidation compared with β-oxidation. However, the distinct regulatory mechanisms that promote this change in substrate preference and whether they are cause or a consequence of heart failure is still not fully understood.

The present study by Nakajima et al introduces a novel player into the arena, namely endothelial lipase (EL). EL is a member of the triglyceride lipase family that is expressed in different tissues including the heart. Unlike other members of the triglyceride lipase family, EL primarily hydrolyzes fatty acids from high-density lipoprotein phospholipids, whereas triglyceride lipase activity is subordinate. Increased EL activity has been shown to be able to compensate for the absence of LPL in adipose tissue fatty acid uptake. Thus, Nakajima et al hypothesized that EL significantly contributes to cardiac fatty acid supply in conditions with increased energy demand or reduced LPL activity, such as in pressure overload-induced heart failure. A schematic overview is given in the Figure.

To evaluate the role of EL in the genesis of heart failure, Nakajima et al generated a murine model of pressure overload-induced cardiac hypertrophy and acute cardiac decoupling by means of ascending aortic banding in wild type (EL+/+) and EL-knock out (EL−/−) mice. In wild-type mice, acute pressure overload was followed by a significant increase in EL mRNA ≈ 1 day after aortic banding. At the same time there was a significant reduction of LPL mRNA. Both EL and LPL expression returned to a stable level ≈7 days after surgery, with a remaining slight increase in EL and decrease in LPL, respectively. Deletion of EL in EL−/− mice worsened pressure overload heart failure and congestion, suggesting that EL is essential in the regulation of cellular energy supply under failing conditions. The expression of genes facilitating cellular fatty acid uptake, fatty acid–binding protein CD36, and fatty acid transporter protein 6 remained unimpaired in both groups, after surgery. However, at the same time, EL−/− mice showed significantly lower expression of genes involved in mitochondrial fatty acid uptake and β-oxidation, carnitine-palmitoyltransferase 1, medium-chain acyl-dehydrogenase, citrate-synthase, and β-hydroxyacyl-CoA-dehydrogenase, after banding, compared with the wild type. Furthermore, EL−/− mice also showed substantially decreased myocardial ATP levels and increased cardiac triglyceride contents, after surgery, compared with EL-sufficient mice, suggesting that EL deficiency reduces cardiac lipid consumption by attenuating mitochondrial β-oxidation.

In line with this notion, EL overexpression in cardiomyocytes significantly enhanced genes involved in mitochondrial fatty acid use and cellular ATP levels. Together, these results indicate that cardiac fatty acid supply through EL is essential in the setting of pressure overload heart failure to maintain mitochondrial β-oxidation and ATP generation, and that increased expression of EL in the early phase of pressure overload heart failure seems to be a compensatory response to maintain vital metabolic functions of the heart. Thereby, inhibition of the process by deletion of EL causes impaired fatty acid flux, resulting in attenuation of ATP generation, cardiac lipid accumulation, and aggravation of heart failure.
In line with the observations of Nakajima et al., acute inhibition and chronic deletion of cardiac LPL, another member of the triglyceride lipase family, result in aggravation of arterial hypertension–induced heart failure, reduced uptake of lipoprotein triglycerides–derived fatty acids into the heart, and reduced expression of genes involved in mitochondrial fatty acid (FA) uptake (carnitine-palmitoyltransferase 1 [CPT-1]) and FA oxidation (medium-chain acyl-dehydrogenase [MCAD]), β-hydroxyacyl-CoA-dehydrogenase (β-HAD), and the tricarboxylic acid cycle (TCA: citrate-synthase [CS]), whereas cellular fatty acid uptake remains unimpaired. In this condition, cardiomyocyte ATP production decreases and intracardiac lipids accumulate, accelerating cardiac injury and heart failure. HDL indicates high-density lipoprotein; LC-FA, long chain fatty acids; LPL, lipoprotein lipase; PPAR, peroxisome proliferator–activated receptor; and VLDL, very low–density lipoproteins. Green arrows indicate increase/activation; and red arrows, reduction/inhibition.

In conclusion, Nakajima et al. present a novel concept for the generation of biochemical energy in the acutely failing heart. They found evidence that EL acquires a regulatory function, sustaining cardiac fatty acid availability and mitochondrial substrate oxidation and respiration. The mice develop severe cardiac insufficiency and lethal cardiomyopathy. In this setting, pharmacological PPAR-α agonism was able to reverse the mitochondrial dysfunction and to restore normal heart function. Possibly, reduced mitochondrial β-oxidation gene expression and ATP generation in the study of Nakajima et al. result from insufficient supply of PPAR-α activating long chain fatty acids. The relevance of this function of EL needs further investigation. Perhaps modulation of PPAR activity might be able to rescue the metabolic dysfunction induced by deletion of EL and to preserve cardiac function in pressure overload heart failure in this model. Moreover, it will be important to study specific effects of EL in reverse development of heart failure. Therefore, these observations cannot necessarily be transferred to chronic heart failure.

In this model, it will be important to also investigate the endocrine function of the heart and its control of systemic lipid metabolism via the secretion of natriuretic peptides. Finally, future studies need to address the role of EL in chronic heart failure. It is well known that heart failure commonly is a chronic condition that emerges gradually on the basis of multifactorial metabolic and vascular diseases, whereas aortic banding leads to rapid development of heart failure. Therefore, these observations cannot necessarily be transferred to chronic heart failure.

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Disclosures

None.

References

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