ESC European Society of Cardiology

Cardiovascular Research (2023) **119**, 1905–1914
https://doi.org/10.1093/cvr/cvad100

INVITED REVIEW

Cardiac lipid metabolism, mitochondrial function, and heart failure

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Received 14 October 2022; revised 31 January 2023; accepted 1 March 2023; online publish-ahead-of-print 1 July 2023

Abstract

A fine balance between uptake, storage, and the use of high energy fuels, like lipids, is crucial in the homeostasis of different metabolic tissues. Nowhere is this balance more important and more precarious than in the heart. This highly energy-demanding muscle normally oxidizes almost all the available substrates to generate energy, with fatty acids being the preferred source under physiological conditions.

In patients with cardiomyopathies and heart failure, changes in the main energetic substrate are observed; these hearts often prefer to utilize glucose rather than oxidizing fatty acids. An imbalance between uptake and oxidation of fatty acid can result in cellular lipid accumulation and cytotoxicity. In this review, we will focus on the sources and uptake pathways used to direct fatty acids to cardiomyocytes. We will then discuss the intracellular machinery used to either store or oxidize these lipids and explain how disruptions in homeostasis can lead to mitochondrial dysfunction and heart failure. Moreover, we will also discuss the role of cholesterol accumulation in cardiomyocytes. Our discussion will attempt to weave *in vitro* experiments and *in vivo* data from mice and humans and use several human diseases to illustrate metabolism gone haywire as a cause of or accomplice to cardiac dysfunction.

Keywords Lipids • Lipoprotein • Cholesterol • Heart failure

1. Introduction

Heart failure (HF) is a clinical syndrome characterized by structural, functional, and metabolic alterations of the heart that it is not able to pump enough blood to prevent lung congestion and to support oxygen and nutrient demand of peripheral tissues. In some situations, the heart increases ventricular wall thickness to compensate for the reduced contractility and this initially maintains heart ejection fraction (EF). With time, anatomical adaptations cannot compensate for the impaired function finally affecting EF. Several factors contribute to HF worsening; among these are myocardial infarction, arrhythmia, pneumonia, hypertension, and likely ventricular fibrosis.

Depending on the reduction or preservation of EF, HF patients are clustered in different classes from reduced (HFrEF with HF <40%), to mildly reduced (HFmrEF with HF 40–49%), and to preserved EF (HFpEF ≥50%).[1] All three HF groups have comparable morbidity and mortality. HFpEF is often observed in patients with diabetes,[2] in contrast to HFrEF, which often develops as a consequence of ischaemic heart disease, hypertension, or valvular disease. At the molecular level, impaired mitochondrial function was suggested to contribute to HFpEF development.[3] Why should diabetic hearts have a mitochondrial defect? The heart is one of the most metabolic tissues in the body and mainly uses fatty acids to fuel oxidative phosphorylation and energy production.[4] During HF, the heart has the capacity to switch its substrate preference and can utilize more glucose as a source of energy. Although fatty acid oxidation (FAO) remains the most important source of adenosine triphosphate (ATP) even in HF, a mismatch between lipid uptake and lipid utilization within cardiomyocytes may develop resulting in increased intracellular lipid accumulation, mainly of triglycerides (TGs), diacylglycerols (DAGs), and ceramides as well as cholesterol and its derivatives.[5,6] Ceramides and DAGs are proposed as cardiotoxic mediators involved in insulin resistance and mitochondrial dysfunction, a process that could lead to cardiac fibrosis and cardiomyocyte death.[7] Also, the accumulation of cholesterol and particularly free cholesterol within cellular membranes associates with cardiomyocyte cytotoxicity as it increases both cell and organelle rigidity, and also affects membrane permeability to antioxidant agents, proton flux, and mitochondrial dynamism.[8] Cytoplasmic and membrane content of these lipids is a balance involving their sequestration within lipid droplets (LDs), a haven to allow non-toxic storage of hydrophobic lipids such as TGs and cholesteryl esters.

The aim of this review is to discuss how lipid metabolism within cardiomyocytes is tightly regulated to avoid lipotoxicity and mitochondrial dysfunction. Alterations in this balance compromise heart lipid homeostasis and likely explain the relationships of obesity and diabetes with human

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HF. Readers are referred to other reviews that have focused on the role of endothelial cells in cardiac metabolism.[9,10]

2. Cardiac metabolism

The human heart consumes kilograms of ATP per day to sustain basal metabolism and normal contraction that is essential to support systemic and pulmonary blood pressure. Oxidative metabolism in mitochondria accounts for 95%[11] of the total energy produced in the heart, while 5% comes from anaerobic glycolysis. Changes in substrate availability and uptake, such as is the case in diabetes and other metabolic disorders, impact cardiac energy production and mitochondrial function, including calcium homeostasis and flux,[12] ROS production,[13] and the initiation of a pro-apoptotic cascade. Notably, increased glucose metabolism is sometimes followed by reduced FAO. This is the consequence of increased production of malonyl CoA that acts as an allosteric inhibitor of carnitine palmitoyl transferase in several cells[14] including cardiomyocytes,[15] thus limiting the transfer of fatty acids into mitochondria.

The heart is characterized by a high metabolic flexibility that allows it to alter its energetic substrates. In pathological conditions like HF, the heart lose its metabolic flexibility and ability to optimally produce energy.[16–18] This metabolic deficiency, in turn, impacts cardiomyocyte biology and mitochondrial function. Indeed, mitochondrial dynamics change with cardiomyopathies and specifically the balance between fusion and fission is altered.[19] Inhibition of inner mitochondrial membrane fusion[20] promotes apoptosis and the development of HF, while increased mitochondrial fusion protects from the development of pressure-induced HF.[21] Mitochondrial dynamics are associated not only with metabolic modelling of cardiac tissue but also with a major modification in oxidative pathways. Overexpression of inner membrane fusion protein can modulate ROS production reducing cardiac oxidative stress.[22] Heart substrate utilization modulates cardiac lipid homeostasis, the regulation of fatty acid uptake, storage, and oxidation[23] and as discussed below can affect heart function exclusive of changes in ATP production.

HFrEF is characterized by a marked increase in anaerobic glucose metabolism that is associated with an increased glycolytic flux with lactate and pyruvate accumulation.[24] Proton accumulation in the cytosol is therefore associated with increased acidosis that contributes to worsening cardiac contraction via inhibiting contractile proteins and intracellular Ca^{2+} flux.[24] This alteration in ionic homeostasis further aggravates the energy deficient status of HF and the reduced ATP production. A major metabolic derangement in HFpEF, which is mainly associated with obesity, is insulin resistance.[25,26]

Both HFrEF and HFpEF have a significant reduction in aerobic glycolysis. However, the lack of an appropriate animal model of HFpEF has hindered metabolic studies of this disease.[24,25] In addition to FAO, anaerobic glycolysis contributes 5–30% of the energy generated by the healthy heart.[27] As with changes in FAO, changes in glucose uptake and oxidation can occur in a failing heart.[28] Indeed, studies have shown that increased glycolytic uptake observed in some models of HF leads to an increased pentose phosphate pathway flux, which is a modulator of both cardiac redox state and cell proliferation.[29] This metabolic imbalance between glucose uptake and glucose oxidation in the failing heart is out of the scope of the review.

3. Lipid uptake in the heart

TGs, cholesterol, phospholipids, and a number of other lipids primarily circulate as components of lipoproteins. The basic lipoprotein structure with hydrophobic lipids such as TGs and cholesteryl esters in the core and amphipathic molecules such as phospholipids and proteins in the surface coat allows these particles to interact with cell surface receptors and to modulate enzymes involved in their metabolism. Chylomicrons, lipoproteins created from dietary lipids, mediate transport of fatty acids and fat-soluble vitamins from the gut. Very low-density lipoproteins (VLDL) and low-density lipoproteins (LDL) transfer lipids from the liver to peripheral tissues such as heart, skeletal muscle and adipose.

A second lipid delivery system operates to allow inter-organ movement of fatty acids and fat-soluble vitamins. Blood fatty acid levels are highly regulated by insulin, which inhibits the actions of intracellular lipases within adipocytes. During fasting and with defective insulin actions, as occurs with diabetes, adipocytes release non-esterified fatty acids (NEFAs) that associate with albumin. In a parallel process, retinoids (vitamin A) and tocopherols (vitamin E) associate with specific proteins that allow their movement from the liver to peripheral tissues.

Oxidation of fatty acids produces approximately 10-fold more ATP per molecule compared to glucose. Thus, not surprisingly high energy-requiring organs such as the heart and kidney primarily utilize circulating lipids for energy. The heart obtains fatty acids from three sources: NEFAs, chylomicrons, and VLDL (*Figure 1*). As early as the 1960s, studies of arterial venous differences across the human heart showed the importance of uptake of esterified fatty acids, i.e. lipoprotein-derived fatty acids,[5] as a primary fuel for heart energy. The heart lipolyzes and acquires lipids from both chylomicrons and VLDL. A more recent and comprehensive analysis of metabolites in the heart of fasting humans undergoing cardiac catheterization confirmed the uptake and almost total utilization of fatty acids. In some HF patients, fatty acid uptake decreases while the use of ketones and lactate increases.[30] Surprisingly, this study found little heart consumption of glucose in hearts from normal subject or patients with HF and did not identify greater glucose uptake with HF following 2-deoxy glucose administration.

The heart is one of the most active sites of uptake of NEFAs. Non-specific transfer of NEFAs across cell membranes would lead to NEFA uptake into all tissues as a function of their size or blood supply. Rather the high rates of uptake into heart and brown adipose must reflect a receptor-mediated process (discussed in more detail in Abumrad *et al.*[10]). NEFA uptake in the heart requires several steps: uptake and movement across the endothelial barrier, transfer from endothelial to subendothelial cells, and lipid uptake into cardiomyocytes. *In vivo*, both processes are mediated by the fatty acid transporter CD36.[31,32] Genetic deletion of CD36 reduces intramyocellular lipid accumulation in LDs[33] and CD36 overexpression increases heart lipid uptake and oxidation.[34] Although studies failed to show defective heart NEFA uptake by cardiomyocyte-specific CD36 knockout mice under acute experimental design,[31] others have noted a reduction in FAO in *ex vivo* working heart preparations from cardiomyocyte-specific inducible CD36 knockout mice.[35] Thus, it is likely that cardiomyocyte and endothelial cell CD36 mediate parallel or different stages of a single NEFA uptake pathway. CD36 is a peroxisomal proliferator-activated receptor (PPAR) downstream target; marked overexpression of either PPARα[36] or PPARγ[37] increased CD36 expression, which likely creates lipotoxicity due to more NEFA uptake. Indeed, knockout of CD36 protected PPARα transgenic mice from HF.[38]

In agreement with the studies of substrate extraction across the heart, loss of lipoprotein lipase (LpL) in the heart reduces heart uptake of both chylomicron and VLDL TGs.[39] LpL is primarily synthesized by cardiomyocytes but functions on the luminal surface of capillary endothelial cells where it is anchored to glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1. As reviewed elsewhere,[40,41] LpL activity is regulated by the size and apoprotein composition of TG-rich lipoproteins and its inhibitory proteins, angiopoietin-like proteins (Angptls) 3, 4, and 8. How LpL leaves the cardiomyocyte to begin its journey to the endothelial cells is unclear. One option is that LpL release from cardiomyocyte or matrix heparan sulphate proteoglycans requires the actions of a heparinase, which is regulated by hyperglycaemia and blood flow.[42,43]

Loss of LpL and reduced lipid uptake is, under non-stressed conditions, balanced by a greater uptake of glucose. When greater energy uptake is required during stress, LpL knockout hearts develop greater HF with transaortic coarctation[44] and hypertension.[45] Overexpression of the LpL inhibitor angiopoietin-like protein 4 (Angptl4) leads to a similar phenotype.[46] Cardiomyocyte transgenic expression of GLUT1, which allows greater uptake of glucose, corrects many of the defects found in heart LpL knockout mice.[47] These findings suggest that heart LpL knockout causes heart impairment due to defective substrate for ATP production. It should be noted that humans with LpL deficiency do not have heart dysfunction, perhaps because the energetic needs of a mouse heart, which

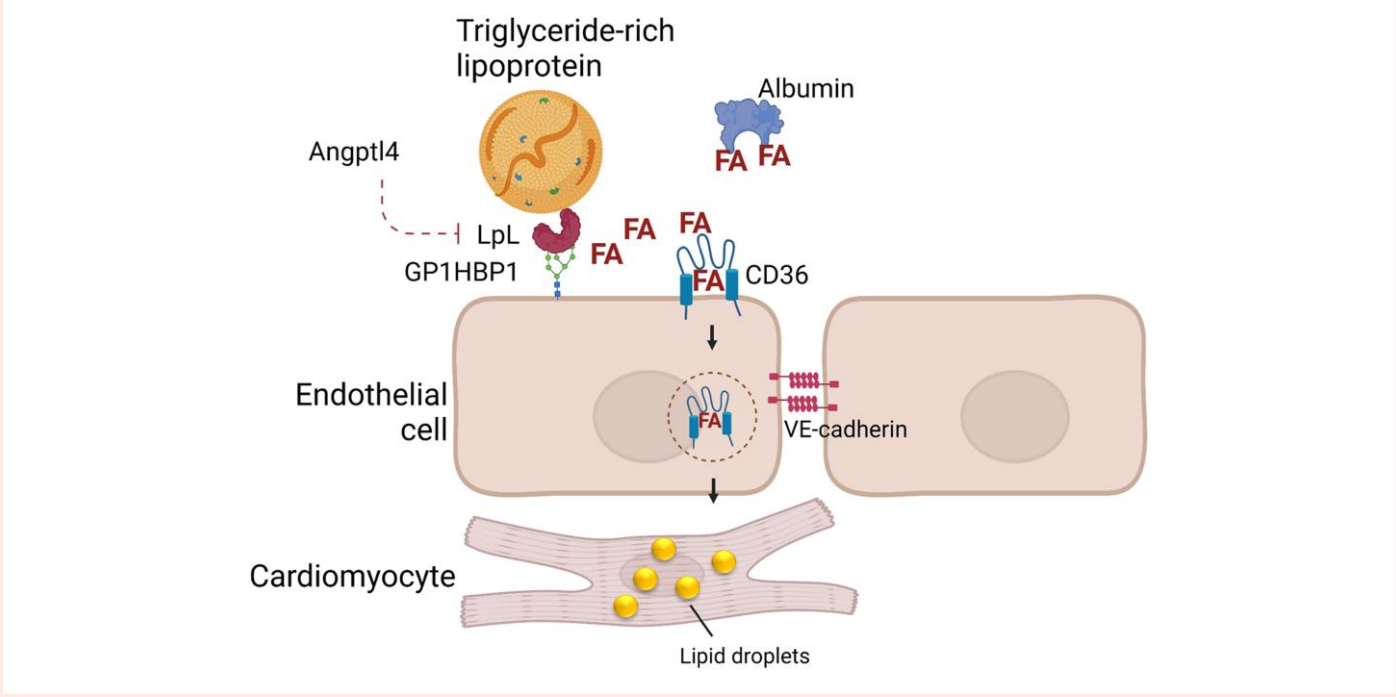

Figure 1 Uptake of circulating lipids. The heart obtains fatty acids (FAs) from circulating triglyceride-rich lipoproteins (chylomicrons and VLDL) and albumin-bound non-esterified FAs. Lipoprotein lipase (LpL) catalyses hydrolysis of triglyceride-rich lipoproteins at the endothelial cell surface. FA uptake by the heart requires transport across the endothelial cell barrier, which is mediated by the scavenger receptor CD36. Genetic deletion of CD36 or LpL or overexpression of the LpL inhibitor angiopoietin-like protein 4 (Angptl4) leads to defective lipid uptake and heart dysfunction.

beats ~8–10 times more frequently than that of humans, are greater,[48] thus unmasking a defect in substrate delivery.

An indication of the central role of lipid use for heart function is illustrated by obesity, a condition associated with greater FAO.[49] With high fat diets, the heart rapidly becomes insulin-resistant,[50] but knockout of insulin signalling leads to a relatively minor phenotype.[51] Cardiac-specific GLUT1 knockout mice have a 50% reduction in glucose uptake and use. By increasing FAO, these mice do not have an increased propensity to HF.[52] GLUT1 transgenic mice also have normal heart function on chow, although they develop HF when fed high fat diets.[53] Thus, factors that augment both fatty acid and glucose metabolic pathways are not benign. This hypothesis that increasing glucose uptake into the heart in the setting of greater fatty acid uptake was proposed as a cause of diabetic cardiomyopathy and led to a correct prediction that unlike insulin sensitizers, sodium glucose co-transporter inhibitors would reduce HF in patients with diabetes.[54]

4. Cardiomyocyte lipid oxidation

PPARs are the central regulators of heart fatty acid metabolism. Of this family of transcription factors, PPARα is most highly expressed in cardiomyocytes and controls the expression of downstream genes associated with FAO and lipid uptake. Notably, PPARα knockout mice have normal heart function,[55] likely reflecting the ability of the heart to adjust to different substrates. In contrast, transgenic expression of PPARα leads to HF associated with cardiac LD accumulation despite greater FAO.[36] This implies that the transcription factor causes a mismatch between lipid uptake and oxidation. A similar mismatch occurs when aryl hydrocarbon nuclear translocator (HIF1β) is knocked out in the heart.[56] PPARγ overexpression also leads to greater heart LDs and HF.[56]

The transcription activation of PPARs is mediated by different factors and among them Kruppel-like factor (KLF) 5, which binds to the PPARα promoter.[57] Another member of this family of transcription factors, KLF4 regulates mitochondrial biogenesis,[58] while KLF15 directly associates with PPARα.[59] Genetic deletion of each of these KLFs leads to defective FAO and some degree of heart dysfunction.

Humans with severe defects in lipid oxidation display a clinical phenotype during childhood while less severe defects become clinically relevant during adulthood. Very long chain fatty acid dehydrogenase (VLCAD) deficiency impairs mitochondrial lipid oxidation, followed by altered muscle energy metabolism and eventually cardiomyopathy. VLCAD defects not associated with neonatal lethality as a consequence of severe hypoglycaemia often affect skeletal muscle more than cardiac muscle with marked increases in circulating creatine kinase at baseline and after exercise.[60] As discussed below, this and other defects in mitochondrial lipid uptake should also lead to intracellular lipid accumulation and, as expected, this was reported in mouse models of long chain[61] and very long chain acyl-CoA dehydrogenase deficiency.[62]

Although many studies show reduced FAO in the failing heart, recent data have reported that in HFpEF, heart FAO can increase while glucose use decreases[63] allowing greater ROS generation.[63–65]

5. Cardiac lipid accumulation

All mammalian cells generate LDs under the appropriate conditions. Although circulating lipids are the main energy source for the heart, myocardial TG storage within LDs is vital for cardiac lipid homeostasis. LDs constitute an accessible TG reserve that allows the heart to meet varying energy demands and compensate for the fluctuating availability of circulating fatty acids.[66] Hearts of wild-type mice on a chow diet develop LDs after an overnight fast,[67] as fatty acids are redistributed from adipose tissue. Increased LDs have been reported in pathological samples from humans with aortic stenosis and metabolic syndrome.[68] Also, a number of genetic modifications lead to pathological lipid accumulation; the most dramatic of

which is the loss of the intracellular TG degrading enzyme adipose TG lipase (ATGL) that leads to marked heart lipid accumulation and early death.[69] In humans, ATGL deficiency produces skeletal muscle and cardiac myopathy, i.e. neutral lipid storage disease. ATGL deficiency markedly down-regulates PPARα and reduces heart FAO; this defect in FAO can be corrected by pharmacologic activators.[70] Thus, ATGL lipolysis liberates PPAR agonists, but fatty acids do not necessarily need to traffic through LDs prior to their oxidation.[71] Similarly, cardiac-specific ATGL also decreased expression of PPARα downstream gene expression.[72] Surprisingly, deletion of neither LpL nor CD36 to block lipid uptake reduced ATGL-mediated cardiac toxicity.[73] *In vitro*, LD accumulation occurred in ATGL-deficient cardiomyocytes grown in lipid-free media due to induction of *de novo* lipogenesis.[73] These data suggest that several metabolic pathways might contribute to intracellular LD formation.

LD accumulation in the heart depends on three factors: the synthesis of core lipids, i.e. TG synthesis, the synthesis of amphipathic surface molecules, and TG hydrolysis. Because the normal heart performs limited *de novo* synthesis of fatty acids from carbohydrates, most LD TGs are derived from lipoproteins and NEFAs. The final step in TG synthesis is catalysed by diacylglycerol acyl transferases (DGATs), which esterify the third fatty acid chain onto the DAG background. There are two forms of DGAT, and both enzymes contribute to LD formation; a knockout of both enzymes is required to block LD production in adipocytes.[74] In the heart, loss of DGAT1 reduces LD production and increases heart levels of its substrate DAG.[75] DGAT1 knockout mice were reported to develop cardiac dysfunction[75]; a finding that was not reproduced in another mouse model with partial or inducible DGAT1 deletion.[76] DGAT1 deficiency also occurs in heart tissues from humans with advanced HF.[77] DGAT1 overexpression increases heart TG levels and reduces heart DAGs but does not lead to cardiac dysfunction.[78] Moreover, DGAT1 transgenic hearts have improved response to ischaemia/reperfusion,[79] presumably because cardiomyocytes have easier access to stored TG. Transgenic DGAT1 expression, which reduces both DAG and ceramides, also improves cardiac lipotoxicity in several experimental conditions. In contrast, inhibition of DGAT2 using a pharmacological approach prevented high fat diet-induced heart lipid accumulation and was well tolerated.[76] DAGs are therefore a principal TG metabolic intermediate that is crucially involved in the lipotoxicity of unused fatty acids that flux into the LDs.

The surface of LDs contains phospholipids and proteins. Smaller droplets have a greater surface to core ratio. Using an unbiased screen to assess LD characteristics in a drosophila cell line, the Farese/Walther laboratory found that enzymes mediating phospholipid synthesis regulated the size of LDs.[80] The major structural proteins of LDs are the members of the perilipin (Plin) family. Plins target to the LD surface and regulate TG storage and hydrolysis (*Figure* 2). Heart LD catabolism is largely under the regulation of Plin5, which is highly expressed in cardiac as well as other oxidative tissues. Plin5 interacts with central regulators of intracellular lipolysis, including hormone sensitive lipase (HSL), ATGL, and its co-activator CGI-58.[81] Plin5 binding to CGI-58 inhibits lipolysis by sequestering CGI-58 and precluding ATGL activation. PKA-mediated phosphorylation of Plin5 at serine 155 triggers the release of CGI-58 and its subsequent binding to and activation of ATGL.[82] Global knockout of Plin5 in mice results in heart LD depletion,[83] allowing cardiac lipids to directly route to oxidation rather than storage. Notably, Plin5 deficiency exacerbated myocardial infarct size, heart dysfunction, and mitochondria damage following ischaemia/reperfusion injury, likely due to increased oxidative stress.[84] Conversely, Plin5 overexpression in cardiomyocytes leads to severe TG accumulation akin to that found in ATGL-deficient mice. However, in contrast to ATGL-deficient mice, cardiac Plin5 overexpression does not negatively affect heart function or life span.[85]

A recent study by Kolleritsch *et al.*[86] aimed to understand the mechanisms protecting Plin5 transgenic mice from the development of heart dysfunction. Cardiomyocyte-specific overexpression of wild-type Plin5 or a Plin5-S155A mutant that lacks the PKA phosphorylation site led to cardiac steatosis with a marked increase in TG (22-fold), total cholesterol (6-fold), ceramides, and DAG, all of which can lead to cardiac stress and lipotoxicity.[87] However, both Plin5 and Plin5-S155A transgenic mice exhibited normal heart function and ATP production. Plin5 overexpression is associated with increased mitochondrial size,[85,88] and the authors observed the same in mitochondria from cardiomyocyte-specific Plin5-S155A transgenic mice. Cardiac overexpression of Plin5 markedly decreased the phosphorylation of mitochondrial fission factor, which is required for the recruitment of dynamin-related protein-1 (Drp1) to mitochondria and subsequent induction of mitochondrial fission. Mitochondria prepared from Plin5-S155A and Plin5 transgenic mice showed markedly reduced Drp1 protein levels compared to wild type, consistent with reduced mitochondrial fission. Elongated mitochondria are considered to be less vulnerable to oxidative stress and are metabolically more efficient.[89] Therefore, reduced mitochondrial fission may protect from the development of lipotoxic heart dysfunction.[86]

Another member of the Plin family, Plin2, has also been reported to participate in the regulation of heart LD metabolism. In mouse hearts, Plin2 was up-regulated during fasting-induced lipid accumulation,[90] and its cardiac overexpression induced severe LD accumulation, likely by preventing access of ATGL and HSL to the hydrophobic core. In this model, LD accumulation was resolved by overexpression of HSL.[91,92] Unlike global Plin5 knockout mice, Plin2-deficient mice also exhibited increased heart LD accumulation. Absence of Plin2 reduced levels of LC3B-II, phosphorylated AMPK, and co-localization of LDs with lysosomes, all indicative of impaired autophagy-mediated LD hydrolysis (lipophagy).[92] In contrast, Plin2 deficiency in the liver has been shown to reduce LD accumulation and stimulate lipophagy.[93,94] These tissue-specific effects highlight the importance of further research to elucidate the nature and role of cardiac LDs in heart disease.

6. Mechanisms of fatty acid induced lipotoxicity

Lipid excess within the heart is detrimental for cardiomyocyte metabolism and function, and this is particularly relevant when some specific classes of lipids are accumulated.[95–98] Oleic acid, for example, is not deleterious and can counteract palmitate-induced cellular dysfunction.[99] On the contrary, palmitic acid is more cytotoxic[99]; perhaps due to a defect in its incorporation into TGs.[100] A number of possible reasons have been proposed to explain palmitic acid toxicity: (i) altered membrane flexibility, (ii) increased ceramide production, (iii) greater ROS generation,[101] and (iv) more palmitoylation of cellular proteins or nucleic acids.[102] One mechanism downstream of palmitic acid accumulation is increased expression of Plin2 that promotes the phosphorylation of the stress-activated-protein-kinase/Jun-amino-terminal-kinase, which is involved in cardiomyocyte apoptosis.[103]

Sphingolipids, including ceramides, and DAGs also act as lipotoxic mediators and contribute to cardiac lipotoxicity via several mechanisms.[103] Sphingolipids and ceramides modify cellular membrane organization and thus directly promote cardiomyocyte apoptosis—contributing to HFrEF—and also promote insulin resistance via inducing the dephosphorylation of Akt downstream of the insulin receptor.[104] These lipids also cause PKC and MAPK activation and ER and mitochondrial stress, contributing to both HFpEF and HFrEF.[105] A beneficial action of adiponectin, which is reduced in type 2 diabetes, is to induce ceramidase and alleviate ceramide-induced insulin resistance and cardiac toxicity.[106]

The activation of PKCα and the development of insulin resistance is also a common consequence of the accumulation of DAGs.[107] Sterols, as well as DAGs and ceramides, have been proposed as crucial player in cardiac lipotoxicity (see below).

7. Cholesterol, oxysterols, and mitochondrial function in the context of heart failure

Cholesterol is a crucial component of cellular membranes but can also modulate physical properties and membrane receptor activity. Cellular

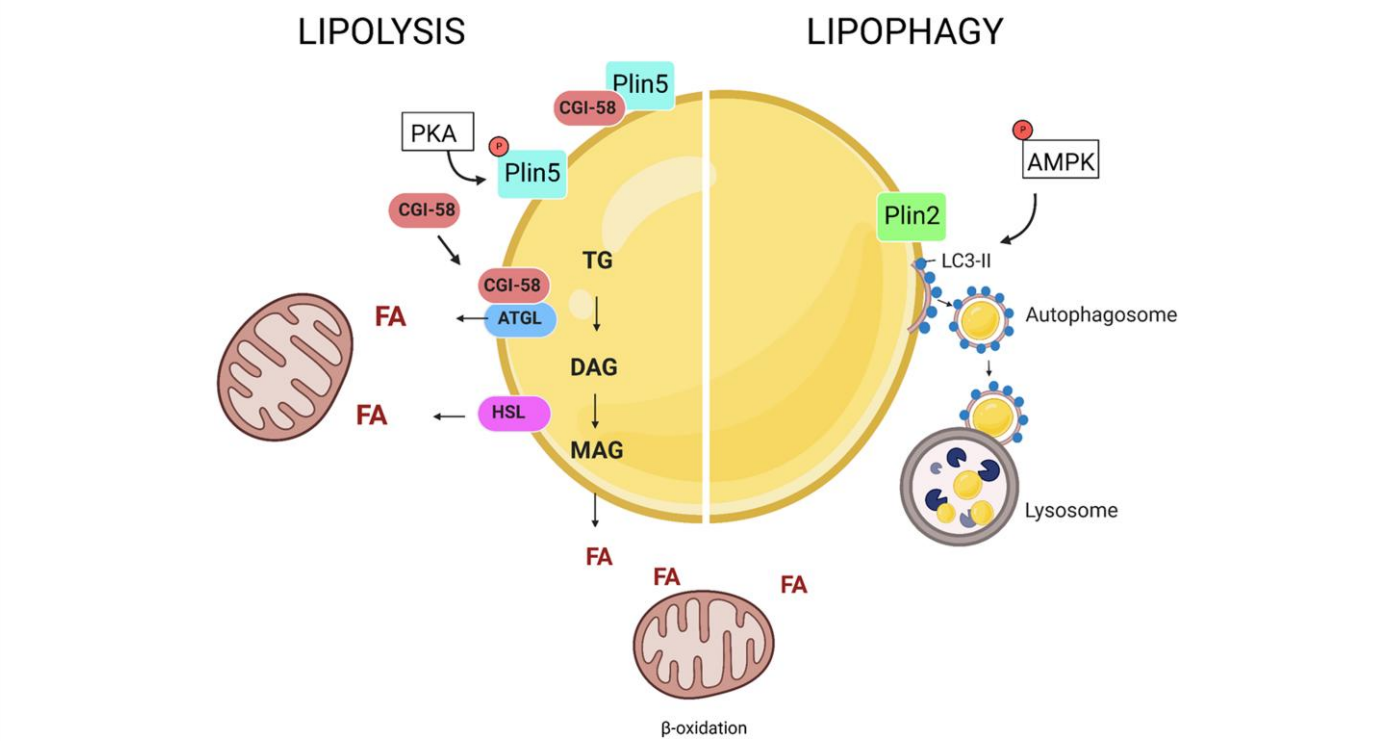

Figure 2 Cardiac lipid droplet hydrolysis. Cardiac lipid droplets provide a pool of fatty acids (FAs) to meet the varying energy requirements of the heart. Their hydrolysis is mediated by cytosolic triglyceride (TG) lipases—adipose TG lipase (ATGL) and hormone sensitive lipase (HSL) (left)—or acidic lysosomal lipases (lipophagy, right). Both processes are tightly regulated by members of the perilipin (Plin) family of lipid droplet proteins. Plin5 inhibits lipolysis by binding and sequestering ATGL co-activator CGI-58. Plin5 phosphorylation by PKA results in the release of CGI-58 and recruitment of ATGL, which catalyses the rate-limiting step of lipid droplet TG hydrolysis. Knockout of Plin5 results in lipid droplet depletion, whereas its overexpression induces severe lipid accumulation similar to that found in ATGL-deficient hearts. In addition, Plin2 has been reported to regulate cardiac lipophagy. Plin2 knockout results in heart lipid accumulation and reduced LC3-II, phosphorylated AMPK, and lipid droplet co-localization with lysosomes, all indicative of impaired lipophagy.

cholesterol needs can be fulfilled in two different ways: (i) through *de novo* synthesis or (ii) via uptake from circulating lipoproteins. *De novo* cholesterol synthesis via the mevalonate pathway is an energy-consuming pathway, which takes place part in the cytoplasm and part in the endoplasmic reticulum and requires elevated oxygen concentration for sterol branching where squalene is converted to cholesterol. Cholesterol biosynthesis occurs mainly in the liver and steroid hormone-synthesizing organs, i.e. adrenals and gonads. Cardiomyocyte cholesterol requirement is mainly fulfilled via uptake from lipoproteins. Cardiomyocyte-anchored LpL increases LDL uptake and cholesterol accumulation in the heart and promotes HF.[108] Whether HF is the direct consequence of increased fatty acid or LDL cholesterol accumulation is unclear. As the LDL receptor (LDLR) is expressed at very low levels in the heart, cholesterol uptake appears to be driven in an LDLR-independent manner. Notably early studies suggested that chylomicrons contribute to heart cholesterol delivery.[109] Another option is that cholesterol enters cardiomyocytes via either CD36 or the VLDL receptor (VLDLR), which can internalize remnant lipoproteins.[110] VLDLR was shown to be up-regulated under ischaemic conditions and to contribute to heart lipoprotein uptake and cardiac lipotoxicity.[110] Similarly, increased cardiac expression of CD36, as a consequence of PCSK9 deficiency, was associated with increased heart cholesterol content.[98]

Whether the increased flux of cholesterol into cardiomyocytes directly translates into cellular cytotoxicity is unknown, but it is reasonable to speculate that it could worsen lipotoxicity.[23] Once in the cell, cholesterol is distributed between cellular compartments through vesicular or non-vesicular transport.[111] While vesicular transport involves the direct transfer of cholesterol between membranes of different cellular compartments, non-vesicular transport is mediated by the steroidogenic acute regulatory protein (StAR), the prototype for the StAR-related lipid transfer family of transport proteins, which include also the ceramide transfer protein.[112] Within the cell, cholesterol can be found as free form, mainly localized in the membrane, or esterified within LDs. Cholesterol is highly toxic for cells, and excessive levels of free cholesterol can promote cell lipotoxicity.[8,113] To limit this possibility, cholesterol excess could be esterified by the action of acyl-CoA cholesterol acyltransferase.[114] Cardiomyocytes can esterify sterols within the cytoplasm to limit their cytotoxicity.[114]

Cellular cholesterol can also be oxidized. Oxysterols can be produced by both enzymatic processing and non-enzymatic oxidation via the addition of a second oxygen atom as a carbonyl, a hydroxyl, or an epoxide group.[115] Oxysterols generated by enzymatic reaction are 24α-hydroxycholesterol (24α-OH), 25-hydroxycholesterol (25-OH), and 27-hydroxycholesterol (27-OH). Oxysterols generated by non-enzymatic oxidation includes 7β-hydroxycholesterol (7β-OH) and 7-ketocholesterol (7-KC). Oxysterols are 1000-fold less abundant compared to cholesterol; nonetheless, they play an important role in cellular metabolism.[116] Cholesterol supplementation is associated with a worsening of cardiac functionality associated with an increased amount of enzymatic oxysterols like 25-OH and 27-OH as well as 7β-OH.[117] Oxysterols can be found as a main component of oxidized circulating LDL (Ox-LDL) as well as within the cells. Cellular oxysterol levels increase following cholesterol accumulation and are extremely cytotoxic. To prevent this, increased cellular oxysterol concentrations activate feedback mechanisms to dampen intracellular cholesterol biosynthesis via the inhibition of sterol-regulatory

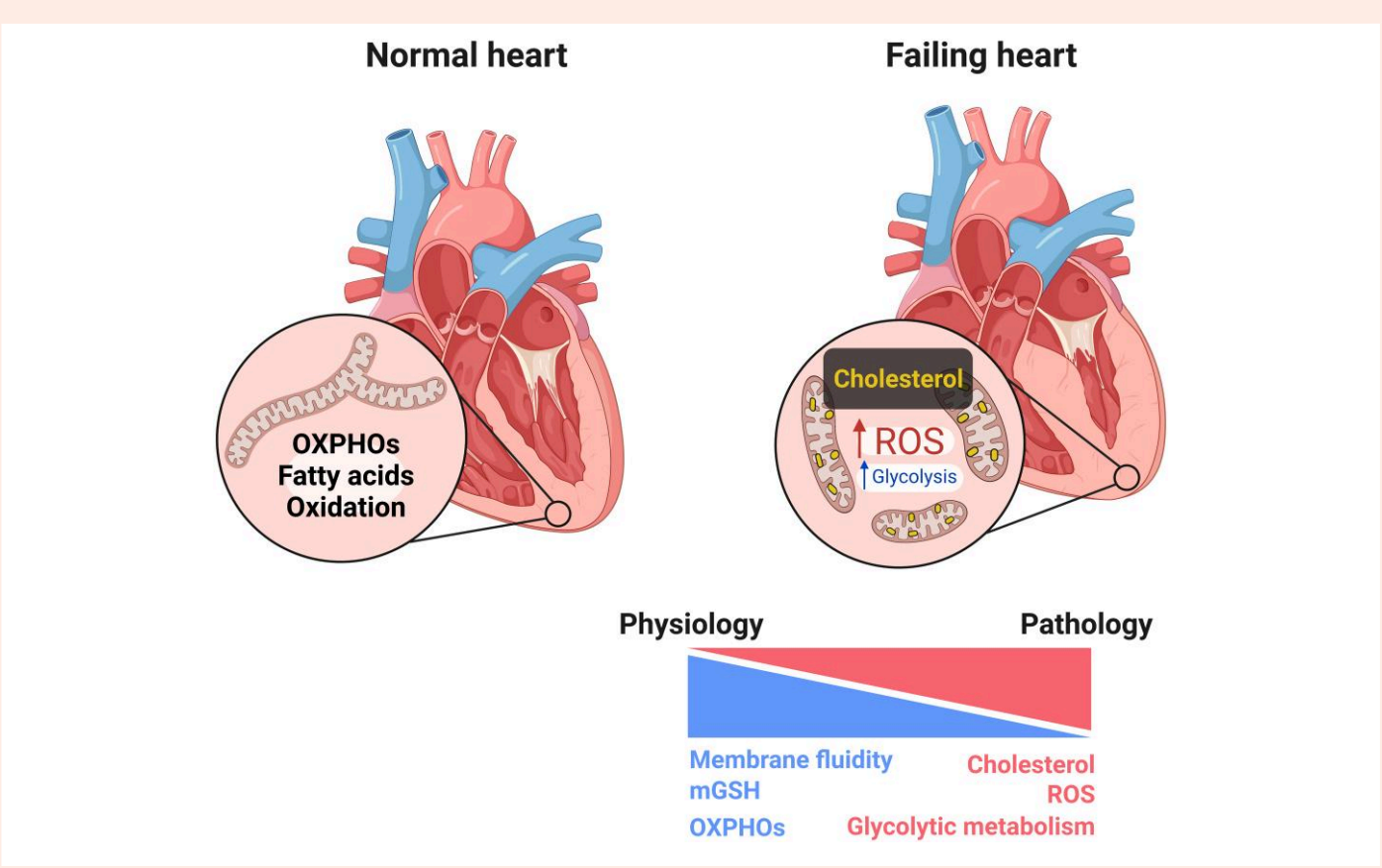

Figure 3 Metabolic impact of cardiac sterols. A normal/healthy heart mainly relies on fatty acid oxidation and mitochondrial oxidative phosphorylation (OXPHOs) for energy production. Failing heart has reduced OXPHOs and mitochondrial antioxidant pathways (mGSH) and greater reliance on glycolysis for ATP production. If lipid uptake is not reduced, sterols and other potentially toxic lipids can accumulate and trigger greater reactive oxygen species (ROS) production.

element binding proteins and also to promote cellular cholesterol efflux via the activation of liver X receptor-dependent pathways.

Oxysterols and in particular 7-KC have a direct effect on mitochondria promoting morphological changes leading to mitochondrial membrane rupture, increased cytochrome c release, altered membrane phospholipid content, and activation of autophagic processes.[118,119] Notably, 7KC seems to be able to promote cardiomyocyte ROS production through an ATF4-dependent pathway.[120] Further analyses show that oxysterols can rewire cardiomyocyte lipid metabolism.[114] *In vitro*, Ox-LDL increases the expression of brain natriuretic peptide in cardiomyocytes[121] and induces apoptosis via the modulation of calcium-sensing receptors.[122] Moreover, Ox-LDL stimulates PCSK9 in cardiomyocytes, reduces contractile capacity of cardiomyocytes, and increases cell death.[123]

Within the cell, mitochondria, although known to be cholesterol poor organelles (around 3–5% of the total cellular pool), are crucially involved in steroidogenesis and bile acids synthesis. In cardiomyocytes, mitochondrial cholesterol enrichment alters membrane organization, which negatively impacts the fluidity by altering the balance between lipid-ordered and disordered membrane phases.[124,125] Moreover, cholesterol impacts the spatial organization of membrane carriers, including that of the GSH transport system. Increased mitochondrial cholesterol levels negatively affect the mitochondrial pool of GSH (mGSH) and result in increased mitochondrial ROS production (*Figure 3*), which in turns could favour ceramide generation, cardiolipin peroxidation, and mitochondrial pore opening. These factors, together, contribute to the development of the fibrotic phenotype that is characteristic of hypertrophic hearts and promote cardiomyocyte metabolic reprogramming,[126,127] which can further promote mitochondrial ROS generation and oxidative stress.[128] Factors that increase the expression of lipid and lipoprotein receptors on cardiac tissue can promote cholesterol accumulation and LD generation. This in turn affects mitochondrial respiration leading to the development of the metabolic changes typical of HFpEF.[98] Indeed, mitochondrial function is altered during HF; this includes mitochondrial biogenesis, which is reduced as a consequence of decreased PGC1a expression,[129,130] and mitochondrial dynamism, which was also shown to be altered during HF with increased mitochondrial fission and reduced fusion.[20]

An open question is whether these intracellular mechanisms are affected by changes in systemic cholesterol levels. Notably, low circulating cholesterol levels are neutral or even deleterious in patients with HF leading to a worst outcome. Whether this is the consequence of the reduced availability of cholesterol-rich substrates to the heart is debated.[131] Alternatively, low cholesterol levels might reflect an underlying cachexia in very sick HF patients.

8. Cardiac lipoprotein biosynthesis to overcome lipotoxicity

A poorly investigated aspect of physiology is the fact that cardiomyocytes, in addition to hepatocytes and enterocytes, have the possibility to synthesize lipoproteins. The importance of this pathway in normal cardiac physiology and in response to heart lipid overload is unclear. Cardiomyocytes synthesize apolipoprotein B (ApoB), the major structural protein of VLDL and LDL, and mitochondrial TG transfer protein (MTTP) is required for lipidation of the ApoB. While the intestine synthesizes lipoproteins

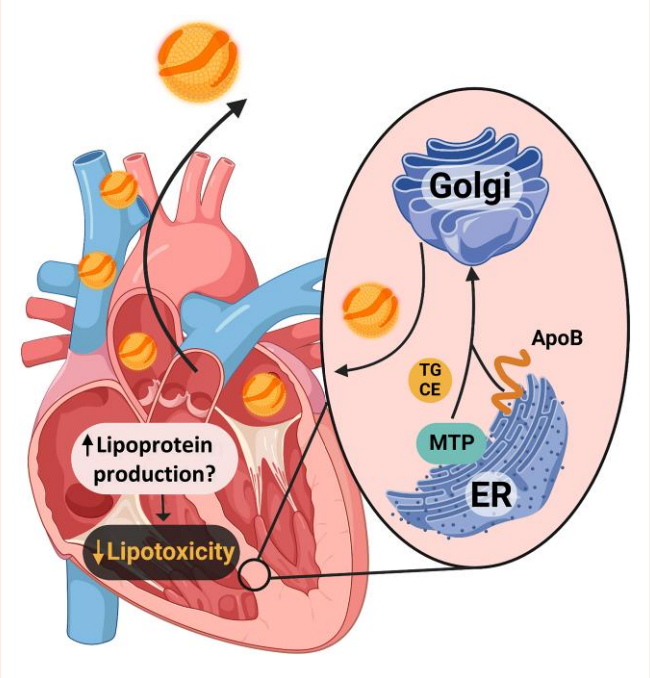

Figure 4 Cardiac lipoprotein production. The heart has the capacity to alleviate its burden of excess toxic lipids by oxidation, storage in lipid droplets, or secretion in lipoproteins. Akin to the liver and the intestine, the heart expresses both apolipoprotein B (ApoB) and microsomal triglyceride (TG) transfer protein (MTTP). This allows the packaging of intracellular cholesterol ester and TG in the endoplasmic reticulum into nascent lipoproteins. The nascent lipoprotein is then released into the bloodstream; cardiac lipotoxicity is reduced by this 'reverse lipid transport' process.

(chylomicrons) to route exogenous lipids to the blood stream and the liver produces VLDL to distribute lipids to different tissues, the biological reason for the heart to produce lipoproteins remains a mystery. The finding that the ApoB and MTP genes are expressed in both human and mouse hearts,[132] two species separated by more than 80 million years of mammalian evolution, suggests that the expression of these genes is important and might be an evolutionarily conserved mechanism involved in heart lipid metabolism. Notably, analysis of lipoprotein fractions has shown that the lipoproteins produced by the heart are LDL-like particles.[133] However, the relative contribution of this pathway in unloading lipids from the heart and therefore limiting lipotoxicity as compared to the mechanisms described above is still a matter of investigation (*Figure 4*).

Streptozotocin-treated diabetic mice have a dramatic increase in heart TG content, which is prevented by overexpression of apoB100.[134] This finding confirms that TG accumulation in the heart is important for the development of diabetic cardiomyopathy, and that lipoprotein generation by cardiomyocytes contributes to cardiac lipid metabolism. This is further supported by the observation that increased expression of MTTP and ApoB is observed under different disease conditions known to be related to cardiac lipotoxicity, including hypoxia[135] and obesity.[136] In humans, homozygosity for null mutations in the ApoB gene (homozygous hypobetalipoproteinemia) or in the MTTP gene (as in abetalipoproteinemia) dampens the secretion of ApoB-containing lipoproteins by the liver and intestine and results in the accumulation of cytosolic LDs in hepatocytes and enterocytes. Whether cardiac lipoprotein production is also affected in these patients is unknown; although there are no reports of heart LD accumulation in abetalipoproteinemia, there have been reports of cardiomyopathy and arrhythmias in these patients.[132] This finding, however, might also relate to the defects in delivery of fat-soluble vitamins, esp. retinoids. On the same line, the promotion of lipoprotein production (achieved in MTTP overexpressing heart) protects against lipotoxic cardiomyopathy.[137] Changes in MTTP activity (observed in carriers of different polymorphisms on the MTTP gene) affect cardiac remodelling and the risk of coronary heart disease independently of plasma lipoprotein levels.[138] These findings suggest a need for a deeper characterization of human carriers of MTTP loss of function mutations.

9. Conclusion

Although not usually viewed as an important organ in lipid metabolism, evidence has accumulated that defective lipolysis in the heart modifies circulating TG levels.[139,140] The heart is a major site of NEFA uptake, as lipids are the primary substrate for cardiac energy production. Metabolic alteration and imbalances in lipid oxidation can cause cardiac energy depletion and morphological alteration finally promoting the development of HF. Lipid uptake, storage, and metabolic regulation play also a central role during HF development. While many processes involved in lipid metabolism are altered prior to and during the development of HF, it is likely that abnormal accumulation of toxic lipids alters mitochondria function and creates a feed-forward process leading to reduced lipid oxidation not compensated by reduced lipid uptake. It has been suggested that during HF, the sympathetic system could drive a sustained adipose lipolysis with increased circulating NEFA levels that could exacerbate HF.[141] In support of this hypothesis, the inhibition of adipose NEFA release was shown to reduce catecholamine-induced heart failure.[142,143] While elevated plasma lipid levels are seen primarily as the key driver of atherosclerosis, these molecules do much more and serve as both the fuel and poison for the heart. Furthermore, from the evolutional point of view, the fact that the heart is one of the three organs in the body able to produce lipoproteins suggests that this mechanism is in place to limit lipid and cholesterol accumulation and to unload toxic lipids from cardiomyocytes.

Author's contributions

All authors have made equal intellectual contributions to the writing of this manuscript. All authors read and approved the final manuscript.

Conflict of interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

This manuscript was handled by Reviews Deputy Editor Ali J. Marian.

Funding

The authors of this work are supported by: Telethon Foundation (GGP19146 to G.D.N.); Progetti di Rilevante Interesse Nazionale (PRIN 2017 K55HLC to G.D.N.); Ricerca Finalizzata, Ministry of Health (RF-2019-12370896 to G.D.N.); PNRR, Centro Nazionale Di Ricerca 3 (Sviluppo Di Terapia Genica E Farmaci Con Tecnologia a RNA to G.D.N.) and PNRR Ecosistemi per L'Innovazione, (Multilayered Urban Sustainability Action to G.D.N.), and HL45095, 160891, and 151326 from the National Heart Blood and Lung Institute (I.J.G.). A.G.C. is supported by the American Heart Association Postdoctoral Fellowship.

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