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Review

# The Role of Adipose Triglyceride Lipase and Cytosolic Lipolysis in Cardiac Function and Heart Failure

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**Heart failure is one of the leading causes of death worldwide. New therapeutic concepts are urgently required to lower the burden of heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF), the two major forms of heart failure. Lipolytic processes are induced during the development of heart failure and occur in adipose tissue and multiple organs, including the heart. Increasing evidence suggests that cellular lipolysis, in particular, adipose triglyceride lipase (ATGL) activity, has an important function in cardiac (patho)physiology. This review summarizes the crucial role of cellular lipolysis for normal cardiac function and for the development of HFrEF and HFpEF. We discuss the most relevant pre-clinical studies and elaborate on the cardiac consequences of non-myocardial and myocardial lipolysis modulation. Finally, we critically analyze the therapeutic importance of pharmacological ATGL inhibition as a potential treatment option for HFrEF and/or HFpEF in the future.**

Chronic heart failure (HF) is still one of the leading causes of death worldwide.[1–4] Despite extensive (non-) pharmacological therapies, the 5-year mortality rate of up to 75% remains very high and resembles the rate observed in various types of cancer.[4] Therefore, new therapeutic concepts are required to lower the burden of this disease.[3,5]

According to recent guidelines, HF has been defined as a complex clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood.[3,5] HF is characterized by typical symptoms (e.g., dyspnea, fatigue) that may be accompanied by clinical signs such as elevated jugular venous pressure, pulmonary crackles, and peripheral edema.[3,5] The two major types include HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF).[3,5] In HFrEF, patients present with an EF below 40%, whereas in HFpEF an EF $\geq$50% is preserved and diastolic dysfunction occurs.[3]

Considering the pathogenesis of both forms, major differences are noticeable. HFrEF is commonly evoked by intrinsic cardiac damage and a loss of functional myocardium caused, for example, by myocardial infarction, ischemia, or genetic defects.[6–8] This leads to ventricular remodeling, dilatation, and a reduction in EF.[6,7] HFpEF is likely to be caused by extracardiac comorbidities such as hypertension, obesity, metabolic syndrome, or diabetes.[7–9] These comorbidities drive the pathophysiology of the disease by low-grade systemic inflammation, which impairs cardiac nitric oxide bioavailability, ultimately leading to increased cardiomyocyte stiffness, extracellular matrix deposition, fibrosis, and impaired diastolic filling.[10,11] The different underlying pathophysiological processes have resulted in the development of disparate preclinical models for HFrEF versus HFpEF.[12,13] All of these models exhibit certain limitations and do not reflect the complete clinical pictures of HFrEF or HFpEF. When discussing the role of lipolysis in HF, we name the applied HFrEF or HFpEF model, where appropriate.

The prevalence of HF is strongly age dependent. While only 1%–2% of the total adult population is affected, this number increases to $\geq$10% in individuals aged 70 years or older.[3,14–17] The latest reports show that among patients with chronic HF, one-third suffer from HFrEF and approximately two-thirds from HFpEF.[18] Despite recent advances in management, the prognosis of patients with HF is still very poor and resembles that of common cancers.[4,19]

Targeting metabolic processes in the heart may represent a promising way to develop new therapeutic approaches for HF.[20] Normal cardiac function relies on the continuous supply of the main energy substrates glucose, fatty acids (FAs), ketone bodies, or lactate.[21] Quantitatively, FAs provide >70% of "fuel" for the heart.[22] Exogenous non-esterified FAs, as cardiac energy fuel, are derived either from adipose tissue triacylglycerol (TAG) mobilization or from the hydrolysis of TAGs from TAG-rich lipoproteins by lipoprotein lipase.[23] During fasting, the liver additionally converts adipose tissue-derived FAs to ketone bodies, which, after their secretion, represent an additional energy substrate for cardiomyocytes.[21] In cardiomyocytes, exogenously delivered FAs can be immediately oxidized or reesterified to TAGs for transient storage and release upon later demand.

The enzymatic pathway to release FAs from stored TAGs in adipocytes and non-adipocytes (e.g., cardiomyocytes) is called lipolysis. Intracellular lipolysis occurs in two variants, cytosolic lipolysis and lysosomal lipolysis, depending on whether lipolytic enzymes act at neutral or acidic pH, respectively.[24] In adipocytes and cardiomyocytes, neutral lipolysis is predominant and the main topic of this review. The major enzymes catalyzing cytosolic lipolysis are adipose triglyceride lipase (ATGL), hormone-sensitive lipase (HSL), and monoacylglycerol lipase (MGL), which sequentially hydrolyze TAGs, diacylglycerols, and monoacylglycerols to eventually generate glycerol and FAs as the end products of lipolysis.[24]

During the development of HF lipolysis is induced in multiple organs, including the heart and adipose tissue.[25,26] Increasing evidence suggests that ATGL activity and cytosolic lipolysis both in cardiac muscle and adipose tissue affect cardiac function and HF development.[27–30] Recent data obtained from experiments with mutant mouse lines overexpressing or lacking ATGL, or with the application of the recently developed small-molecule ATGL inhibitor Atglistatin,[31] suggest that the inhibition of ATGL in adipose tissue or the activation of ATGL in cardiomyocytes represents potential pharmacological targets for the management of HF.[29,32] This review summarizes the current evidence for a role of ATGL in the regulation of cardiac function and the pathogenesis of HF. We briefly summarize the molecular basics of lipolysis and discuss the most relevant pre-clinical studies, elaborating on the cardiac consequences of myocardial and non-myocardial ATGL modulation. We further review the clinical evidence for the significance of lipolysis in HF. Finally, we critically analyze the therapeutic potential of pharmacological ATGL inhibition as a new treatment option for HF.

## Neutral Lipid Hydrolases and Their Regulation

In principle, cytosolic lipolysis occurs to some degree in all cell types and tissues. The highest lipolytic activities are observed in white and brown adipose tissue, followed by oxidative tissues such as cardiac muscle, skeletal muscle, and the liver. ATGL, HSL, and MGL are also highly expressed in white and brown adipose tissue and at lower levels in other metabolically important organs.[33] The catalytic domain of ATGL (patatin domain) is localized in the N-terminal part of the protein. The C-terminal part of the enzyme possesses a hydrophobic structure, which enables its binding to lipid droplets.[34,35] The activity of ATGL and concomitantly the initiation of TAG hydrolysis are markedly controlled by ATGL-specific cofactors, which bind to the patatin domain. Those cofactors include, among others, the co-activator CGI-58 (comparative gene identification-58, $\alpha/\beta$ hydrolase domain 5 (ABHD5),[36,37] the co-repressor G0S2 (G0/G1 switch gene 2),[38,39] and perilipins (PLINs).[40–42] HSL is the second lipolytic enzyme, predominantly catalyzing the breakdown of diacylglycerol (DAG) to monoacylglycerol (MAG) and FAs.[23,43] Unlike ATGL, HSL has a broad substrate specificity hydrolyzing TAGs, retinylesters, and cholesterylesters in addition to DAGs. Protein kinase A-dependent phosphorylation of HSL on several Ser residues affects its binding affinity to lipid droplets and significantly increases its lipolytic activity.[43–45] The final step in the lipolytic cascade is the hydrolysis of MAGs catalyzed by MGL.[43] In addition to its role in intracellular neutral lipolysis, MGL is involved in the catabolism of the important endocannabinoid, 2-arachidonylglycerol, which explains the high expression levels of MGL in the brain.[46] In addition to ATGL, HSL, and MGL, other enzymes may contribute to TAG hydrolysis in various tissues. They include members of the carboxylester and the a/b hydrolase domain families of hydrolases, and may contribute to neutral TAG and MAG hydrolysis, respectively.[47] Their quantitative contribution to bulk lipolysis is insufficiently understood.

Several hormones such as catecholamines and natriuretic peptides (atrial natriuretic peptide or brain natriuretic peptide), which control cardiac function and are dysregulated in HF, are also crucial regulators of lipolysis.[48–50] Catecholamines induce lipolysis by activating $\alpha$- and $\beta$-adrenergic receptors[48,50] (Figure 1). Adrenergic receptor-mediated stimulation of adenylyl cyclase leads to the formation of cyclic adenosine monophosphate and the subsequent activation of protein kinase A.[50] In adipose tissue, activated protein kinase A phosphorylates lipid droplet-bound PLIN1, CGI-58, and HSL.[50] This leads to the translocation of HSL to the surface of lipid droplets and the dissociation of CGI-58 from PLIN1. CGI-58 is then able to interact with ATGL to stimulate its enzymatic activity (Figure 1). The activation process of lipolysis may differ in oxidative tissues (e.g., muscle, liver) because they express PLIN2 and PLIN5 instead of PLIN1. Both represent a barrier for TAG hydrolysis because their cardiac-specific overexpression in mice causes lipid droplet accumulation and steatosis.[51,52] However, the molecular mechanism underlying this observation remains unclear. PLIN5 is able to bind ATGL, HSL, and CGI-58, and this interaction activates[40,53] or inhibits[54,55] lipolysis. In addition, PLIN5 links lipolysis to mitochondrial function by bridging lipid droplets to the mitochondrial membrane.[41]

In addition to catecholamines, atrial-, brain-, and C-type natriuretic peptides, also regulate lipolytic activity. Most studies focused on their regulation of HSL. Natriuretic peptides regulate lipolytic activity by binding to specific G-protein-coupled receptors: natriuretic peptide receptor A, B, and C. Both natriuretic peptide receptors A and B, when stimulated, induce cyclic guanosine monophosphate synthesis via guanylyl cyclase and trigger the activity of the protein kinase G[56,57] (Figure 1). When activated, protein kinase G phosphorylates and activates HSL and PLINs, subsequently inducing lipolytic activity. Although it has not been shown yet, it would be predicted that PLIN phosphorylation by protein kinase G enables ATGL activation by CGI-58 in a similar manner as PLIN1 phosphorylation by protein kinase A. In summary, lipolytic TAG breakdown in the cytoplasm of adipose and oxidative tissues such as the heart occurs in a highly coordinated fashion involving an enzymatic cascade with ATGL, HSL, and MGL. The activity of these enzymes is tightly controlled by multiple mechanisms, including the sympathetic nervous and natriuretic peptide systems, both of which are activated in HF.

## Cardiac and Non-cardiac Lipolysis in HF—Clinical Data

A common pathophysiological event in HFrEF and HFpEF comprises a chronic activation of the sympathetic nervous system.[58–62] Notably in HFrEF, sympathetic nervous system activation crucially determines outcomes.[59] In a compensatory manner, the adrenergic system is stimulated to maintain cardiac

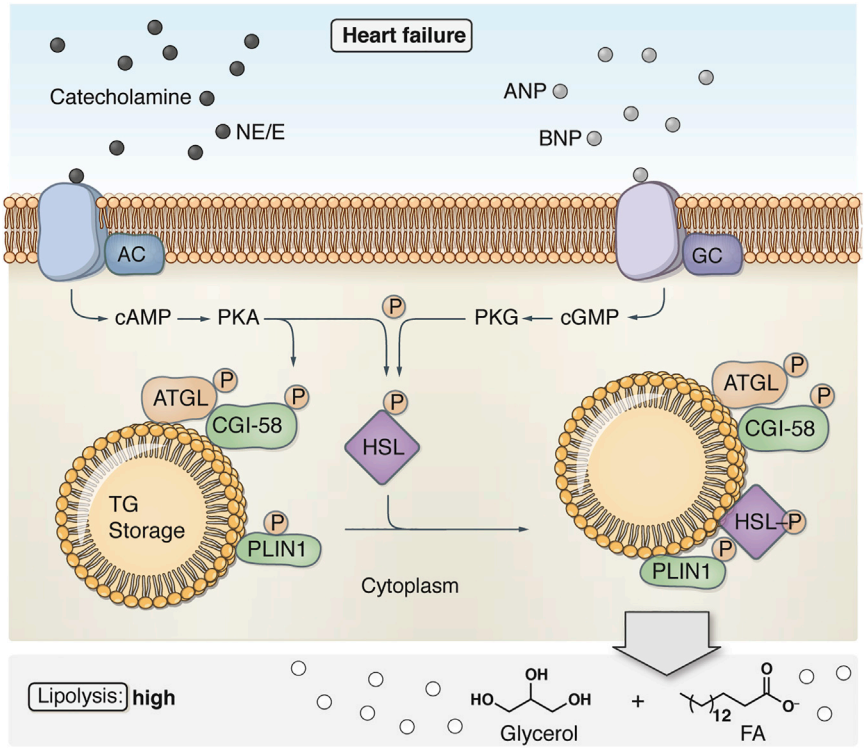


**Figure 1. Lipolytic Pathways in Adipocytes**

Heart failure induces high rates of lipolysis. Catecholamines (norepinephrine [NE] and epinephrine [E]) and natriuretic peptides (atrial natriuretic peptide [ANP] and brain natriuretic peptide [BNP]) induce lipolysis in adipocytes using two different signaling pathways. NE and E activats β-adrenergic receptors, which leads to the subsequent activation of adenylyl cyclase (AC), increased cyclic adenosine monophosphate (cAMP) production, and activation of protein kinase A (PKA). PKA mediates the phosphorylation and activation of adipose triglyceride lipase (ATGL) and comparative gene identification-58 (CGI-58), as well as hormone-sensitive lipase (HSL) and perilipin 1 (PLIN1). This leads to the formation of the ATGL-CGI-58 complexes on the lipid droplet and interaction between PLIN1 and HSL. ANP and BNP activate natriuretic peptide receptor-A, which leads to guanylyl cyclase (GC)-dependent cyclic guanosine monophosphate (cGMP) synthesis and triggers the activity of protein kinase G (PKG). When activated, PKG phosphorylates and activates HSL and PLIN1 in adipocytes, consequently inducing lipolytic activity in an ATGL-independent manner. FA, fatty acid.

output by increasing heart rate. However, this systemic chronic adrenergic drive does not only affect cardiac function but it also stimulates other processes such as non-cardiac lipolysis primarily in adipose tissue. In addition, lipolytic processes in adipose tissue during HF are further stimulated by high levels of natriuretic peptides[63] (Figure 2). HFrEF and HFpEF are often accompanied by insulin resistance and hyperinsulinemia.[64,65] Since insulin is a major regulator of lipolysis and lipogenesis, it is very likely that the impairment of insulin signaling contributes to non-cardiac lipolysis during HF.[66] In contrast, cardiac lipolysis, in particular in cardiomyocytes, seems to be attenuated, at least in the presence of distinct comorbidities such as diabetes or obesity.

### *Cardiac Lipolysis in HFrEF and HFpEF*

Cardiac lipid metabolism is subject to close-meshed control processes to respond in an adaptive and fast manner to changes in cardiac energy demand. As mentioned above, exogenously imported FAs can be either oxidized or stored in cardiomyocytes as TAGs. A precisely regulated balance between FA uptake, TAG synthesis, TAG hydrolysis, and FA oxidation is the prerequisite for effective cardiac FA and energy metabolism and proper heart function.[67] The imbalance of these processes, as commonly observed in obese and diabetic patients, leads to cardiac steatosis and cardiac dysfunction, likely resulting from non-cardiac and cardiac insulin resistance.[66] Sharma and colleagues described high intramyocardial lipid content in LV tissue sections from patients with advanced non-ischemic HFrEF, with the highest content detected in patients with HFrEF and diabetes.[68] Along this line, myocardial TAG content correlated inversely with regional systolic function in healthy volunteers using $^{1}$H-magnetic resonance spectroscopy.[69] Furthermore, prominent lipid droplets were also detected in the border zone of an acute myocardial infarct and in hypertrophic cardiomyopathies.[70,71] Two recent studies in HFpEF patients demonstrated significantly enhanced myocardial TAG accumulation compared to controls assessed by $^{1}$H-cardiac magnetic resonance spectroscopy.[72,73] In addition to TAG accumulation, increased abundance of toxic lipid species such as ceramides and DAGs have been described as important drivers of HF development.[67,74] These data support a link between increased cardiac lipid content and cardiac dysfunction in HFrEF and HFpEF.

Cardiac lipid accumulation can result either from increased TAG synthesis or defective TAG hydrolysis. The importance of impaired TAG hydrolysis in humans became evident in patients carrying mutations in the *patatin-like phospholipase domain containing protein 2* gene coding for ATGL.[75] These patients develop neutral lipid storage disease with myopathy. The majority of affected individuals present with cardiac steatosis, and 50% develop cardiomyopathy.[33] The degree of cardiac dysfunction in homozygous ATGL-deficient patients varies, but in many patients HF becomes so severe that they require heart transplantation.[33,76] It is unfortunate that most studies did not discriminate between HFrEF and HFpEF. However, in two studies with reported EF, two patients showed a rEF and two patients had a pEF.[77,78]

In summary, there is clinical evidence for cardiac lipid accumulation in HFrEF and HFpEF. Studies in patients with mutations in the human gene encoding ATGL suggest that impaired lipolysis may contribute to cardiac steatosis. However, whether reduced lipolysis and cardiac steatosis represents a more

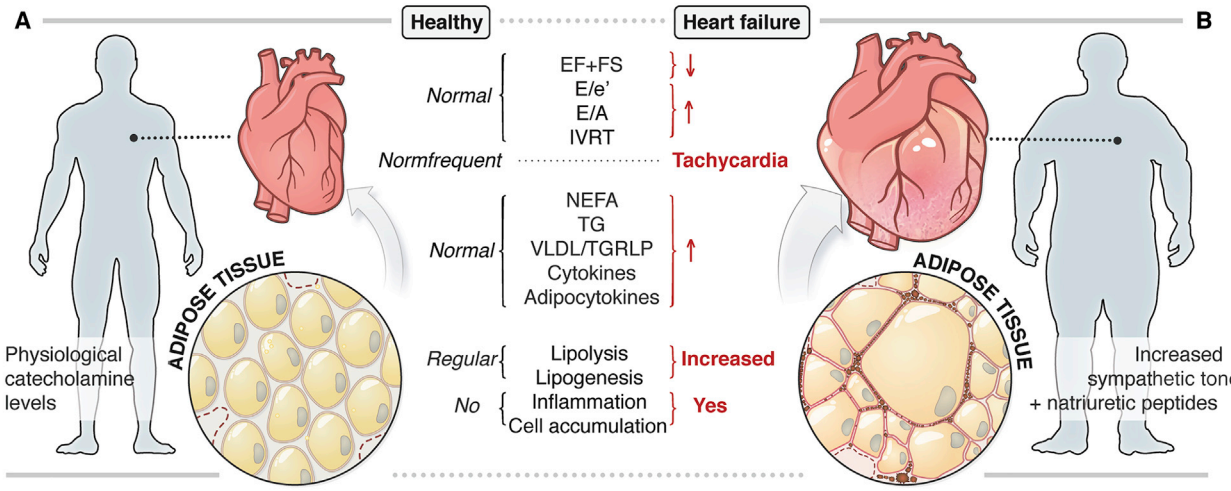


**Figure 2. Pathophysiological Changes in the Heart and Adipose Tissue during the Development of Chronic Heart Failure**

(A) Healthy state, with regular cardiac function (systolic and diastolic), normal circulating lipid and cytokine levels, and regular adipose tissue function.

(B) Heart failure, with increased sympathetic tone and natriuretic peptide levels, systolic and diastolic cardiac dysfunction, elevated circulating lipids and cytokines, and adipose tissue dysfunction.

e′, tissue Doppler-passive LV filling; EF, ejection fraction; E-wave, early passive LV filling; FS, fractional shortening; IVRT, isovolumic relaxation time; LV, left ventricular; NEFA, non-esterified fatty acid; TAG, triacylglycerol; TGRLP, triglyceride-rich lipoprotein; VLDL, very-low-density lipoprotein.

general mechanism of pathogenesis in HFrEF and HFpEF patients requires better validation.

### *Non-cardiac Lipolysis in HFrEF and HFpEF*

Non-cardiac lipolytic processes are markedly augmented in HF. More than 20 years ago, Lommi and colleagues identified significantly increased serum levels of free FAs in a small group of patients with HFrEF (n = 5) and HFpEF (n = 2) compared to controls (n = 7), indicating enhanced lipolysis in white adipose tissue.[25] Consistent with this observation, Polak and colleagues directly showed enhanced adipose tissue lipolysis in HFrEF patients by using local microdialysis.[26] Increased lipolytic rates in adipose tissue closely correlated with plasma atrial natriuretic peptide levels in HFrEF patients, suggesting the involvement of natriuretic peptides in this process.[79] These authors even hypothesize that enhanced adipose tissue lipolysis during HF results in adipose tissue wasting contributing to cardiac cachexia. Given the established interaction between insulin resistance and adipose tissue lipolysis, as well as the observation that HFrEF and HFpEF are often associated with insulin resistance, it appears very likely that systemic insulin signaling is involved in the regulation of lipolysis during HF.[65,66] The involvement of other lipolytic hormones, such as glucagon, in these processes is unknown. Despite documented cardiac actions of glucagon in HF,[80] the impact of this hormone on metabolic alterations, in particular on lipolysis, during HF has not been investigated.

Data on lipolytic activity in other non-adipose organs such as skeletal muscle are very limited. Twenty years ago, Tikunov and colleagues provided indirect evidence of stimulated lipolysis and FA oxidation in the diaphragmatic muscle by showing a significantly increased activity of β-hydroxyacyl-coenzyme A dehydrogenase in patients with advanced HFrEF (mean EF: 18% ± 8%).[81] In contrast, other groups demonstrated excess intracellular lipid accumulation in quadriceps biopsies from HFrEF patients and increased intramyocellular lipid content in tibialis anterior muscles studied by $^{1}$H-magnetic resonance spectroscopy, indicative of decreased TAG turnover.[82,83]

Robust evidence exists for an enhanced, non-cardiac systemic lipolysis during HF development (Figure 2), with most studies performed in HFrEF patients. Based on the available clinical data, it seems most likely that adipose tissue lipolysis is the strongest contributor to this process (Figure 2). However, despite the evidence of increased adipose tissue lipolysis in HF patients, the impact of this exacerbation for cardiac metabolism and function is incompletely understood. In contrast to non-cardiac lipolysis, cardiac lipolytic processes seem to be attenuated, resulting in cardiac lipid accumulation. These differences in cardiac versus non-cardiac lipolysis will likely play an important role in the development of lipolysis-based pharmacological interventions.

### *Adipogenesis and Lipogenesis and Cardiac Function*

In addition to lipolytic processes, adipogenesis and lipogenesis have been recently discussed as being involved in the pathogenesis of HF. Notably in obese patients with HFpEF, enhanced adipogenesis and lipogenesis in epicardial adipose tissue has been documented.[84] As a result of chronic systemic inflammation in obesity, adipogenesis is particularly stimulated in the epicardium.[84–86] The enlarged epicardial adipose tissue depot has been suggested to induce systemic inflammation in the myocardium, thereby aggravating cardiac inflammatory and fibrotic processes.[84,87,88] In addition, the amount of epicardial adipose tissue is associated with impaired myocardial microcirculation, a central feature of HFpEF.[89] Increased adipogenesis in

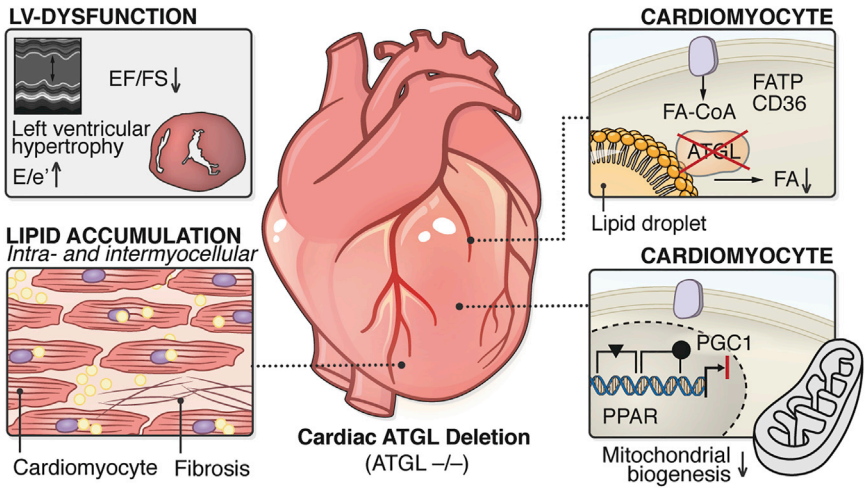


**Figure 3. Consequences of ATGL Deletion and Inhibition in the Heart**

Cardiac-specific deletion and inhibition of ATGL results in systolic and diastolic LV dysfunction, LV hypertrophy (upper left box), cardiac lipid accumulation (lower left box), reduced cardiomyocytic lipolysis with lower cellular FA levels (upper right box), decreased ligand (FA)-induced PPARα/δ activation/reduced PGC-1 expression, and reduced mitochondrial biogenesis/mitochondrial dysfunction (lower right box).

CD36, cluster of differentiation 36 (also known as fatty acid translocase); e′, tissue Doppler-passive LV filling; E-wave (early passive LV filling); EF, ejection fraction; FA-CoA, fatty acyl-CoA ester; FATP, fatty acid transport protein; FS, fractional shortening; LV, left ventricular; PGC1, PPARγ coactivator-1; PPAR, peroxisome proliferator-activated receptor.

atrial epicardial adipose tissue may be involved in the development of atrial fibrillation, a common arrhythmia in HFpEF and HFrEF.[90,91] These data indicate that, in addition to lipolysis, adipogenesis and lipogenesis are involved in the pathogenesis of HF. Adipogenic and lipogenic processes seem to be predominantly relevant in the epicardium and in the obese phenotype of HFpEF, whereas alterations of lipolysis likely occur in the myocardium and/or non-cardiac tissues.

## The Role of ATGL in HF

### *Cardiac ATGL in Cardiac Function and HF*

A series of preclinical studies using gain- or loss-of-function approaches investigated the role of ATGL in the heart and in different HF models. Cardiomyocyte-specific overexpression of ATGL reduces cardiac TAG content and improves systolic LV function.[92] Similar results were reported in diabetic and obese mice, in which the cardiomyocyte-specific overexpression of ATGL reduced intramyocardial TAG levels, reduced lipotoxicity, and improved systolic and diastolic functional parameters, including EF, E/A ratio, or isovolumic relaxation time.[93,94] ATGL deletion in mice led to an even more severe cardiac phenotype. Constitutive ATGL knockout mice showed massive lipid accumulation in the heart with a 20 times higher cardiac TAG content compared to wild-type (WT) mice[27] (Figure 3). TAGs were predominantly stored as intracellular lipid droplets in cardiomyocytes. Cardiac TAG accumulation in ATGL$^{-/-}$ mice was accompanied by a robust impairment of cardiac function with decreased LVEF in ATGL$^{-/-}$ mice, which resulted in a markedly higher mortality rate[27] (Figure 3). Further investigations revealed that defective lipolysis in ATGL$^{-/-}$ mice led to dysfunctional cardiac peroxisome proliferator-activated receptor (PPAR)α and PPARδ signaling, resulting in a reduced expression of cardiac PPARγ coactivator 1α and 1β and the respective target genes[28] (Figure 3). That in turn impaired mitochondrial function and oxidative phosphorylation in cardiac tissue, causing decreased substrate utilization, increased deposition of lipids, and cardiac dysfunction.[28] Defective PPARα signaling was restored by the administration of PPARα agonists in that model, which resulted in extended survival, arguing for a causative relation between impaired PPAR signaling and cardiac failure. Inducible cardiomyocyte-specific deletion of ATGL in mice corroborated the cardiac phenotype observed by constitutive deletion, including increased myocardial TAG content, cardiac hypertrophy, and impaired cardiac function.[95] Vice versa, the cardiac phenotype of the whole-body ATGL knockout mice could be rescued by a cardiomyocyte-specific overexpression of ATGL in ATGL$^{-/-}$ mice.[96] The restoration of cardiac lipolysis in these mice resulted in a complete reversion of cardiac TAG deposition, recovery of cardiac mitochondrial function, and prolonged lifespan. Thus, the cardiac phenotype in ATGL$^{-/-}$ mice exclusively results from the absence of cardiac ATGL and is not due to the lack of ATGL in other organs or defects in *in utero* development. These data show that cardiac ATGL is essential for normal cardiac and mitochondrial function, as well as for cardiac energy substrate metabolism (Figure 3). Thus, therapeutic interventions that lead to a complete inhibition of cardiac ATGL must be avoided.

### *Non-cardiac ATGL in Cardiac Function and HF*

A series of publications in recent years has investigated the importance of non-cardiac ATGL for cardiac function and for the development of HF. The main focus of these investigations was on the analysis of adipose tissue and its interaction with the heart (Figure 4).

The first study on adipose tissue-specific deletion of ATGL (ATGL$^{fl/fl}$-aP2-Cre) was published in 2011, with the primary focus on the metabolic phenotype of these mice.[97] Similar to ATGL$^{-/-}$ mice, ATGL$^{fl/fl}$-aP2-Cre mice had increased body weight due to the enlargement of adipose tissue depots, including brown adipose tissue.[97] However, despite increased adiposity, ATGL$^{fl/fl}$-aP2-Cre mice on a high-fat diet exhibited improved systemic glucose and insulin tolerance.[97] This may have resulted from the retention of lipids in fat depots and the subsequent protection of non-adipose organs, in particular, the liver, against lipid overload.[97] Consistent with this conclusion, the lack of ATGL in adipose tissue resulted in a reduction in FA release from fat, accompanied by lower circulating TAG and non-esterified FAs[97,98] (Figure 4). Schoiswohl and colleagues confirmed and extended these data by studying ATGL$^{fl/fl}$-Adipoq-Cre

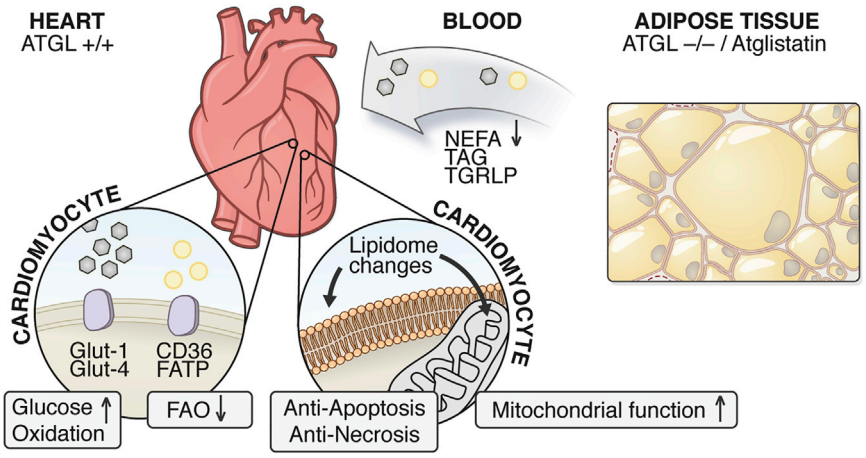


**Figure 4. Potential Cardioprotective Actions of ATGL Deletion and Inhibition in Adipose Tissue**

Adipose tissue-specific deletion and pharmacological inhibition (Atglistatin) of ATGL in the presence of normal cardiac ATGL expression level results in adipose tissue mass expansion with larger adipocytes (right box); reduced circulating NEFA, TAG, and TGRLP levels; enhanced cardiac glucose oxidation and decreased cardiac FAO; cardiac lipidomic changes, cardiomyocytic anti-apoptosis/ necrosis, improved mitochondrial function.

CD36, cluster of differentiation 36 (also known as fatty acid translocase); FAO, fatty acid oxidation; FATP, fatty acid transport protein; Glut1/2, glucose transporter 1/2; NEFA, non-esterified fatty acid; TAG, triacylglycerol; TGRLP: triglyceride-rich lipoprotein.

mice.[98] They also found reduced basal and stimulated adipose tissue lipolysis, improved systemic insulin and glucose metabolism, and improved hepatic insulin sensitivity as a result of diminished liver steatosis. In addition, the absence of adipose ATGL resulted in a marked reduction in hepatic inflammation. Apparently, adipose tissue-specific deficiency of ATGL results in lower circulating lipid levels and protects the liver against lipid overload and lipotoxicity, arguing for lipolysis-driven metabolic interorgan crosstalk.

To assess whether crosstalk also exists between adipose tissue and the heart, studies were first performed in ATGL$^{fl/fl}$-aP2-Cre mice under conditions of exercise-induced lipolysis.[99] When subjected to chronic exercise, mice with adipose-specific ATGL deletion had impaired adipose tissue lipolysis accompanied by the absence of exercise-induced FA appearance in the circulation and by diminished systemic lipid oxidation.[99] Similar results were found in ATGL$^{fl/fl}$-Adipoq-Cre mice challenged with exhaustive submaximal endurance training.[100] When we studied the cardiac response to exercise in these mice, positron emission tomography (PET) analysis revealed reduced cardiac FA uptake and instead enhanced glucose uptake. Notably, this substrate switch was associated with an attenuation of the cardiac hypertrophic response to exercise, highlighting the relevance of adipose tissue lipolysis in the regulation of cardiac metabolism and function.[99] Two recent studies investigating the impact of adipose tissue ATGL on cardiac function in an HFrEF model of pressure-induced cardiac failure by transverse aortic constriction (TAC) substantiated this conclusion.[29,30] Adipose tissue lipolysis is enhanced during the development of LV failure in the TAC model.[101] In mice with adipose tissue ATGL deletion, either in ATGL$^{fl/fl}$-aP2-Cre or ATGL$^{fl/fl}$-Adipoq-Cre mice, a marked improvement in systolic LV function during pressure overload was found.[29,30] The lack of ATGL in adipose tissue protected mice against pressure-induced cardiac hypertrophy, LV enlargement, and cardiac fibrosis, and almost completely preserved EF to levels observed in sham-operated mice.

### *Pharmacological Inhibition of ATGL*

In 2013, Rolf Breinbauer and colleagues succeeded in developing the first small-molecule inhibitor of ATGL, called Atglistatin.[31] Atglistatin is a potent, highly specific, and competitive inhibitor of ATGL that does not affect the activity of other TAG hydrolases such as HSL, MGL, pancreatic lipase, or lipoprotein lipase. In a high-fat diet-induced obesity mouse model, Atglistatin potently but transiently blocked white adipose tissue lipolysis, reduced plasma FA levels, improved insulin sensitivity and glucose tolerance, and led to a reduction in body weight, at least in part mediated by lower food intake and reduced intestinal fat absorption.[32] Bioavailability studies and tissue-specific lipolysis assay revealed that Atglistatin inhibits ATGL in white and brown adipose tissue but not in non-adipose tissues. Consistent with specifically targeting adipose ATGL, FA delivery to and TAG accumulation in non-adipose tissues such as heart, skeletal muscle, and liver decreased in Atglistatin-treated mice.[32] This finding inspired the Dyck laboratory to assess the effect of Atglistatin-mediated ATGL inhibition on heart function in a murine model of HFrEF.[29] Atglistatin treatment markedly improved LV systolic function, reduced LV hypertrophy, and prevented pulmonary congestion in pressure-mediated HF. The tissue-selective action of Atglistatin suggested that the beneficial actions of Atglistatin are mediated by its effects in white adipose tissue. It is unfortunate that Atglistatin does not inhibit human ATGL activity, disqualifying it for (pre-) clinical drug development.[31,32,102]

The underlying molecular mechanisms by which adipose tissue ATGL regulates cardiac function are incompletely understood. Cardiac energy substrate metabolism undergoes profound changes during the development of HF.[21] The healthy heart is able to use multiple energy substrates, including FAs, glucose, lactate, ketones, and amino acids, to maintain adequate ATP production.[21] It is well established that in HF, this metabolic flexibility is reduced and various metabolic substrate changes occur, one of which is the increase in cardiac glucose metabolism.[21] This increase has been considered beneficial in a hypoxic or failing heart since glucose has higher oxygen efficiency (ATP produced/oxygen consumed) for ATP synthesis compared to FAs. As pointed out earlier, ATGL deletion in adipose tissue reduces overall lipid oxidation and increases glucose metabolism.[97–99] Cardiac glucose uptake is increased and FA uptake is decreased in adipose tissue-specific ATGL-deficient mice.[99] Thus, changes in cardiac energy substrate availability, uptake, and metabolism may be a potential beneficial

mechanism in mice with ATGL blockade in fat (Figure 4). In addition to the beneficial regulation of cardiac energy substrate utilization, ATGL deletion in adipose tissue resulted in dramatic changes in the circulating lipid profile, which subsequently led to robust changes in cardiac lipid composition[30] (Figure 4). The most prominent alteration in cardiac lipid species was an upregulation of phosphatidylethanolamine (PE), along with a decreased phosphatidylcholine (PC):PE ratio in failing WT hearts, which was completely prevented by the perturbation of ATGL-mediated adipose tissue lipolysis.[30] The ratio of PC:PE has been identified as an important determinant of cell membrane integrity, and a decreased ratio is often associated with cell damage.[103] Thus, the maintenance of a physiological cardiac PC:PE ratio by ATGL inhibition in adipose tissue may result in the preservation of "healthier" cellular lipid membranes in cardiomyocytes. Whether these processes occur in plasma membranes or membranes of other subcellular organelles, such as mitochondria, requires further investigation.

The inhibition of adipose tissue ATGL activity improves cardiac function. The underlying mechanisms of the beneficial actions by adipose tissue ATGL inhibition in HF need to be fully elucidated, and it seems likely that they will involve changes in cardiac energy substrate utilization and/or alterations in cardiac membrane lipid composition.

## ATGL Cofactors and HF

ATGL activity is tightly regulated by multiple cofactors. In addition to the above-mentioned CGI-58, G0S2, and PLINs, a number of proteins additionally affect ATGL enzyme function, including hypoxia-inducible lipid droplet-associated protein, the ubiquitin-like domain containing protein-8, fat-specific protein-27, and pigment epithelium-derived factor.[24] Whether these factors are involved in cardiac lipolysis and metabolism, thereby affecting cardiac function, awaits further investigation.

Deletion of the ATGL coactivator CGI-58 exclusively in cardiomyocytes and skeletal muscle, using CGI-58$^{fl/fl}$-muscle-specific creatine kinase-Cre mice, resulted in a comparable although less severe cardiac phenotype as observed in cardiac ATGL-deficient mice, including impaired cardiac lipolysis, massive cardiac TAG accumulation, impaired FA oxidation, and decreased related gene expression levels, as well as reduced oxygen consumption rates.[104,105] In addition, LV systolic function was markedly impaired, accompanied by LV hypertrophy.[104,105] These functional alterations in the heart occurred in the presence of prominently higher ATGL protein levels, thus supporting the importance of CGI-58 as an activating cofactor of ATGL activity in the heart, at least in mice.[105] This crucial role of CGI-58 in cardiac lipolysis and function should be critically considered during future developments of ATGL-based therapies for cardiac disease. Whether forced changes in CGI-58 expression in adipose tissue affect cardiac function is unknown. Published studies that either overexpressed or knocked down CGI-58 in adipose tissue did not report cardiac function or a heart phenotype.[106–108]

G0S2 is a potent peptide inhibitor of the lipolytic activity of ATGL.[39] In consonance, mice overexpressing G0S2 under the control of α-myosin heavy-chain promoter specifically in the heart exhibit massive cardiac TAG accumulation, accompanied by significantly reduced cardiac TAG hydrolase activity.[109] However, the phenotype is less severe than in ATGL$^{-/-}$ mice. PPARα signaling and FA oxidation is normal in G0S2$^{-/-}$ mice, and the expression of inflammatory and pro-fibrotic genes is much lower than in ATGL$^{-/-}$ mice.[109] Echocardiographic analysis of cardiomyocyte-specific G0S2 transgenic mice demonstrated LV hypertrophy, including increased LV mass and wall thickening. However, normal fractional shortening in G0S2 transgenic mice indicated normal LV systolic function.[109] This is in sharp contrast to the pronounced impairment of LV systolic function in ATGL-deficient mice, and it suggests different cardiac responses, depending on manipulations of the enzyme or its co-regulators. Whether these differences involve the phospholipase activity of ATGL, as suspected by Kanno and colleagues,[110] requires further elucidation.

As pointed out above, PLINs are important regulators of ATGL. In particular, PLIN5 is highly expressed in the heart, and its impact on cardiac function has been studied in overexpression as well as deletion mouse models. Cardiomyocyte-specific overexpression of PLIN5 led to severe cardiac steatosis and reduced lipid droplet-associated hydrolase activity.[51] It appears that PLIN5 blocks ATGL activity by impeding the access of the enzyme to the lipid droplet surface, forming a lipolytic barrier.[51] This observation contradicts the finding that the binding of ATGL to PLIN5 is required for normal ATGL function[40] and highlights apparent mechanistic deficiencies in our understanding of cardiac lipolysis. Unlike ATGL deficiency, cardiac-specific PLIN5 overexpression did not affect diastolic or systolic cardiac function.[41] Cardiomyocyte morphology, however, was markedly different in PLIN5 overexpressing mice compared to ATGL$^{-/-}$ mice. While the deletion of ATGL led to a heterogenous pattern of lipid droplets, including giant and small droplets associated with an atrophic cellular architecture, PLIN5-overexpressing cardiomyocytes exhibited uniform hypertrophied lipid droplets tightly attached to mitochondria.[51] Mitochondrial respiration was maintained or only mildly impaired in PLIN5-overexpressing cardiomyocytes compared to a stronger defect in ATGL-deficient hearts.[28,41,111] The differences in cardiac function between PLIN5 transgenic- and ATGL-deficient hearts in the presence of similar cardiac TAG accumulation have been explained by the induction of the antioxidative pathway mediated by nuclear factor-E2-related factor 2 in PLIN5 mice.[41] In addition, recently, PLIN5 has been shown to protect mitochondrial function via the reduction of mitochondrial fission.[111] Consistent with the proposed barrier function, the constitutive deletion of PLIN5 strongly reduced cardiac TAG content. PLIN5 deficiency resulted in a significant reduction in systolic LV function under dobutamine stress.[112] The cause for this impact on cardiac function remains to be elucidated, but it may involve the proposed function of PLIN5 to "bridge" lipolysis with mitochondrial FA oxidation.[41,111]

## HSL and MGL in HF

In addition to ATGL, HSL and MGL complete the process of sequential intracellular neutral lipolysis. HSL expression in

cardiomyocytes was first described in the 1980s.[113–115] Subsequently, the role of HSL in the regulation of cardiac lipid metabolism was investigated by using genetic mouse models. Since severe cardiac defects were absent in these mice, a further detailed analysis of cardiac function was not performed in these studies. Transgenic mice with a heart-specific overexpression of HSL prevented fasting- and diabetes-induced cardiac lipid accumulation,[116,117] whereas constitutive deletion of HSL resulted in DAG accumulation in the heart.[118,119] HSL-deficient mice were protected against high-fat diet-induced cardiac insulin resistance, which may be linked to the lower cardiac TAG content.[119] To our knowledge, adipose tissue-specific HSL-deficient mice have not yet been phenotyped regarding cardiac function,[120] and it may be a worthwhile model to study. Similar to mice, no cardiac phenotype was reported in the few human individuals that are affected by HSL deficiency.[121,122]

Studies on the role of MGL in the heart are limited. Severson and Hee-Cheong described MGL activity in isolated rat cardiomyocytes in 1988.[123] Pharmacological inhibition of MGL with JZL184 resulted in enhanced cardiac inflammation after myocardial infarction associated with worsened cardiac function.[124] In this study, augmented cardiac inflammation and impairment of cardiac function by MGL inhibition was accompanied by increased levels of 2-arachidonoylglyerol pointing toward the role of MGL in endocannabinoid catabolism. However, data on cardiac function in murine models of MGL deficiency were not reported.[125,126] The available data are not sufficient for a definitive conclusion on the significance of cardiac and non-cardiac HSL and MGL in the development of HF.

## Future Therapeutic Options

Recent experimental evidence suggests that lipolysis and lipolysis-dependent metabolic processes are important for normal cardiac function and may, when dysfunctional, contribute to the pathogenesis of HFrEF and HFpEF. Therefore, lipolysis may represent a suitable target for the treatment of these diseases. In particular, the inhibition of ATGL in adipose tissue appears to be promising. However, its pharmacological inhibition requires unconditional organ specificity because ATGL blockade in non-adipose organs such as the heart is likely to exert deleterious side effects. Atglistatin fulfills this requirement by inhibiting ATGL predominantly in adipose tissue. However, the inhibitor acts only on murine and rat ATGL and does not target the human enzyme.[32] To address this limitation and to improve pharmacodynamic-pharmacokinetic properties, the search for potent and safe small-molecule inhibitors of human ATGL is actively pursued.[127–129] Nevertheless, the work so far has provided the proof-of-principle that pharmacological inhibition of ATGL in an organ-specific manner is possible and may be beneficial for the treatment of cardiac disease.

In contrast to the direct inhibition of ATGL by means of small-molecule inhibitors, other approaches to pharmacologically modulate ATGL-mediated lipolysis are conceivable. These alternative avenues include strategies to interfere with the interaction of ATGL with activating or inhibitory cofactors. Based on the identification of a core peptide from G0S2, Cerk and colleagues developed a synthetic peptide that inhibits ATGL activity in a non-competitive manner in the nanomolar range.[130] Along this line, CGI-58/ABDH5 has been targeted recently by synthetic ligands modifying the CGI-58/ABDH5-PLIN interaction and subsequently adipocyte and muscle lipolysis.[131] Although this study focused on the activation of lipolysis by endogenous and synthetic ABDH5 ligands, further development of this concept toward the inhibition of white adipose tissue lipolysis seems conceivable.

## Conclusions

Robust clinical evidence argues for an important role of lipolytic processes in the regulation of cardiac function and in the development of HF. Preclinical data have clearly shown that the modulation of ATGL activity strongly affects cardiac morphology and function, and, more important, that the inhibition of non-cardiac ATGL has been beneficial in pre-clinical heart failure models. Thus, in view of the urgent need for new treatment strategies for HFrEF and HfpEF, the development of pharmacological inhibitors that target human ATGL in adipose tissue seems to be a promising track to follow.

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## AUTHOR CONTRIBUTIONS

All of the authors wrote, edited, and reviewed the manuscript.

## DECLARATION OF INTERESTS

R.Z. holds a patent for Atglistatin.

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