Good and bad consequences of altered fatty acid metabolism in heart failure: evidence from mouse models

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REVIEW

Good and bad consequences of altered fatty acid metabolism in heart failure: evidence from mouse models

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Abstract The shift in substrate preference away from fatty acid oxidation (FAO) towards increased glucose utilization in heart failure has long been interpreted as an oxygen-sparing mechanism. Inhibition of FAO has therefore evolved as an accepted approach to treat heart failure. However, recent data indicate that increased reliance on glucose might be detrimental rather than beneficial for the failing heart. This review discusses new insights into metabolic adaptations in heart failure. A particular focus lies on data obtained from mouse models with modulations of cardiac FA metabolism at different levels of the FA metabolic pathway and how these differently affect cardiac function. Based on studies in which these mouse models were exposed to ischaemic and non-ischaemic heart failure, we discuss whether and when modulations in FA metabolism are protective against heart failure.

Keywords Heart failure • Energy metabolism • Genetically altered mice • Metabolic shift

1. Introduction: metabolic switch upon heart failure

The heart has sustained high energy demands in order to pump sufficient blood through the body. This pump function is dependent on the contractility of the ventricular cardiomyocytes. To allow contraction, ATP is required for the myofibrillar shortening as well as for the excitation–contraction (EC) coupling of contraction, which is dependent on ATP-requirements of the sarcoplasmic calcium pump (SERCA). Hence, a decrease in ATP production in cardiomyocytes will cause a decrease in Ca^{2+} gradients across the sarcolemmal and sarcoplasmic membranes, together with elevated cytoplasmic Ca^{2+} levels, as is commonly observed in human heart failure.[1] For its energy production, the healthy adult heart primarily relies on the oxidation of fatty acids (FA) (~60–90%) and to a lesser extent glucose (~10–40%), lactate, and ketone bodies.[2] It is able to shift its substrate preference according to physiological and pathological challenges. An increase in cardiac workload, such as in heart failure conditions, leads to a higher energy demand. In this case, increased cardiac ATP production and cardiac efficiency to use the ATP for contractile function are important to maintain heart function.[3] It is generally accepted that the transition process towards heart failure is accompanied by a shift in cardiac substrate preference, with a greater reliance on glucose as substrate and a concomitant suppression of fatty acid oxidation (FAO).[2,3] The metabolic shift towards glucose utlilization has long been interpreted as an oxygen-sparing mechanism of the heart, and hence inhibition of FAO has evolved as an established approach to treat heart failure patients.[2,3]

Hearts of obese and/or diabetic patients rely almost exclusively on FAO and are suggested to have lost the ability to switch between substrates. Compared with glucose, FA are oxygen-inefficient energy substrates. Moreover, FA can induce mitochondrial uncoupling, leading to less efficient ATP production.[4] Given the increased risk of heart failure in type 2 diabetic and obese patients, it is indeed tempting to hypothesize that high FAO has deleterious effects on the heart. However, long-chain FAO is 3–4 times more efficient in producing ATP per substrate molecule compared with glucose oxidation. Therefore, a substantial increase in glucose oxidation is necessary to compensate for a loss in energy production, even in case of a small decrease in FAO. This suggests that the shift away from FAO might not be beneficial for the heart, and that inhibition of FAO might not always be the best strategy for heart failure treatment.

This review discusses new insights on the role of altered cardiac FA metabolism in ischaemic and non-ischaemic heart failure. We review how modulation of different aspects of cardiac FA metabolism in

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(genetic) mouse models affects cardiac function. We start with alterations downstream of the FA metabolic pathway, at the level of FAO, and then move upstream towards modulations of mitochondrial FA uptake, cellular FA uptake, and eventually to the level of FA supply from the circulation. Based on studies in which (genetic) mouse models of altered FA metabolism were exposed to heart failure conditions, we discuss whether and when modulations in FA metabolism are protective during ischaemic and non-ischaemic heart failure.

2. Cardiac metabolic adaptations

2.1 Ischaemic heart failure

During myocardial ischaemia, the limited oxygen supply suppresses aerobic glucose oxidation and FAO. In this condition, the oxygen-sensing pathway centred on the hypoxia inducible factor (HIF) is switched on, which induces transcriptional up-regulation of glycolytic enzymes.[5] As a result, cardiac substrate metabolism shifts from FAO to glycolysis, which is marked by translocation of the FA transporter FAT/CD36 away from the sarcolemma, translocation of glucose transporter-4 (GLUT4) toward the sarcolemma, and a decrease in glycogen content.[6] As ischaemia is associated with increased FA availability and suppressed FAO, the translocation of FAT/CD36 away from the sarcolemma prevents the accumulation of myocardial lipids.[6] It is important to note, however, that during mild-to-moderate ischaemia, FAO remains the main contributor of the residual oxidative metabolism.[7,8] The increase in glycolysis without a concomitant increase in glucose oxidation results in an accumulation of potentially harmful catabolites like lactate and protons, causing intracellular acidosis and intracellular Na^+ and Ca^{2+} overload.[9] This reduces the efficiency of the heart to convert energy into contractile work, because more energy is needed to restore ion homeostasis.

In the heart during post-ischaemic reperfusion, when oxygen levels are restored, anaerobic glycolysis (and also glucose oxidation) is reduced and becomes even lower than before ischaemia.[6,10] However, sarcolemmal GLUT4 levels remain increased, which is associated with replenishment of glycogen stores.[6] FAO is recovered to (or even exceeds) pre-ischaemic levels, while sarcolemmal FAT/CD36 remains low, leading to a reduced myocardial triglyceride (TG) content.[6] The stimulation of FAO has been thought to be contributed by 5′ AMP-activated protein kinase (AMPK) activation, which phophorylates and inhibits acetyl-CoA carboxylase-2 (ACC2).[11] The inhibition of ACC2 lowers the production of malonyl-CoA, which releases its inhibition on carnitine palmitoyltransferase-1 (CPT1) and its consequent inhibition on mitochondrial FA import. However, it has recently been shown that this AMPK–ACC signalling might not play an obligate role in regulation of myocardial FAO, and that other mechanisms, perhaps via up-regulated uncoupling protein-3 (UCP3) expression, may contribute to maintained FAO rates in the post-ischaemic heart. Either way, an increase in FAO during post-ischaemic reperfusion might negatively impact myocardial efficiency and function,[12] as it further suppresses glucose oxidation rates (via the Randle cycle), and thus uncouples glucose oxidation from glycolysis, aggravating the intracellular acidosis and disturbed ion homeostasis.

To summarize, during myocardial ischaemia, a shift away from FAO towards anaerobic glycolysis assists in the ATP production, as limited oxygen supply suppresses aerobic respiration. Upon reperfusion, FAO returns to pre-ischaemic levels. Uncoupling between glycolysis and glucose oxidation during ischaemia and reperfusion may lead to accumulation of harmful catabolites, causing intracellular acidosis and disturbed ion homeostasis.[9,10,13] This has been associated with reduced cardiac efficiency to use ATP to maintain contractile function, which contributed to the development of heart failure after an ischaemic insult.[10,13] As an increase in glucose oxidation would reduce the accumulation of harmful catabolites, a shift away from FA towards glucose oxidation would be beneficial to maintain cardiac efficiency and function (Section 4.1).

2.2 Non-ischaemic heart failure

Together with ischaemia, (non-ischaemic) pressure overload belongs to the most common causes of heart failure in patients. In the majority of animal studies, data point to the existence of a switch to glucose metabolism during the development of non-ischaemic heart failure. In mice with transverse aortic constriction (TAC)-induced pressure overload, it was demonstrated that myocardial glucose uptake and utilization rates were increased as early as 1 day after TAC, and that they were further increased at 7 days after TAC.[14] Supporting this observation, other studies have shown increased glycolysis and suppressed FAO at 4–8 weeks after TAC.[15–17] The increase in glucose utilization was associated with increased insulin-independent GLUT1 and decreased insulin-dependent GLUT4 transporters,[18] as observed in the fetal heart. Increased glucose utilization and reduced FAO were also observed in other animal models of heart failure, such as in rats with abdominal aortic constriction (AAC)-induced pressure overload,[19] volume overload,[20] and hypertension-induced heart failure,[21] rabbits with hypertension-induced heart failure,[22] and dogs with ventricular pacing-induced heart failure.[23,24] A few studies, however, do not support the existence of a switch towards glucose metabolism in non-ischaemic heart failure,[25–27] and it remains to be seen whether such shift would be beneficial.

3. Animal models of altered FA metabolism

The long-chain FA metabolic pathway is a multi-step process resulting in the breakdown of FA for energy production (*Figure 1*). Numerous genetic and non-genetic mouse models exist with interferences at different levels of the FA metabolic pathway (*Table 1*). They are extremely useful to study the effect of altered FA metabolism on cardiac function. In this section, we discuss the findings in these mouse models, starting with modulations downstream of the FA metabolic pathway, at the level of FAO, after which we move upstream, to conclude with modulations at the level of FA supply from the circulation.

3.1 Modulation of FAO

Identification of patients with inherited acyl-CoA dehydrogenase deficiencies has led to the development of several mouse models with FAO defects. Very long-chain acyl-CoA dehydrogenase (VLCAD) knockout (KO) mice developed cardiomyopathy and presented with abnormal cardiac electrophysiological changes, which was associated with myocardial TG accumulation (in case of whole-body KO)[59,60,74] and chronic energy deficiency.[61,62] The cardiac phenotype of VLCAD-KO mice was relatively mild, which can likely be explained by the overlapping substrate specificity of long-chain acyl-CoA dehydrogenase (LCAD).[63,75] In LCAD-KO mice, a compensatory increase in myocardial glucose utilization was observed.[64] Upon fasting, which normally results in an increased reliance on FAO, myocardial glucose uptake was not decreased and pyruvate dehydrogenase (PDH) activity was much less decreased in

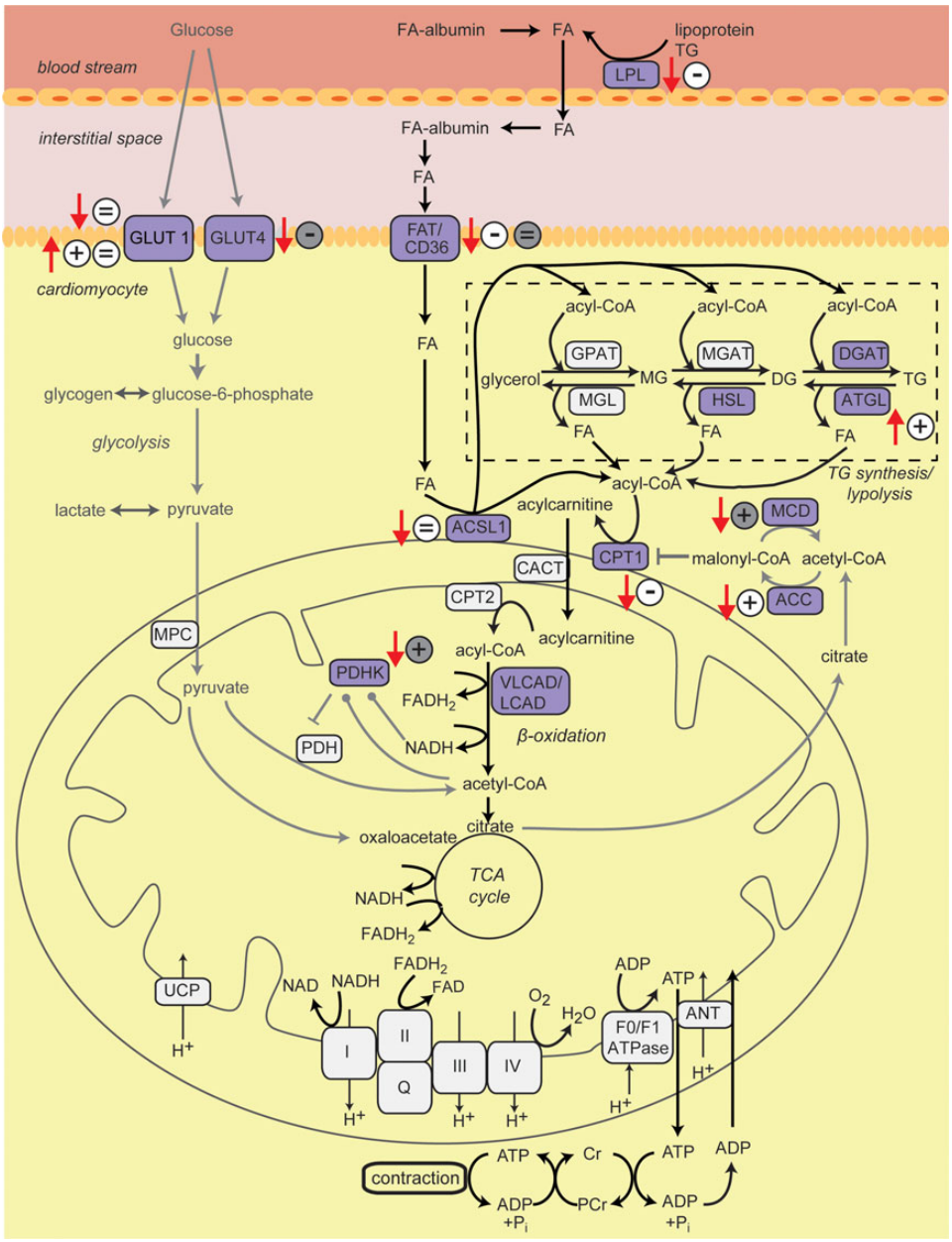

Figure 1 Cardiac long-chain fatty acids (FA) and glucose metabolic pathways. The proteins that are highlighted in purple have been overexpressed or knocked out in the mouse models discussed in this review. The effects of up-regulation (↑) or down-regulation (↓) of these proteins on cardiac function upon ischaemic (closed grey circle) or non-ischaemic (open circle) heart failure are indicated as improved/preserved (+), exacerbated dysfunction (−), or no effect (=). In plasma, FA are available as 'free' (unesterified) FA bound to albumin, or FA esterified in lipoprotein triglyceride (TG). FA in the lipoprotein TG are made available via hydrolysis by lipoprotein lipase (LPL). Mediated by FAT/CD36, FA are transported into the myocardium. In the myocardium, FA are converted into acyl-CoA by long-chain acyl-CoA synthetase-1 (ACSL1), which can either be stored as TG or imported into mitochondria for oxidation. The stored TG can be made available for oxidation by hydrolysis of TG into diglyceride (DG) by adipose triglyceride lipase (ATGL), and subsequently into monoglyceride (MG) by hormone-sensitive lipase (HSL) and glycerol by monoglyceride lipase (MGL). Each of these steps releases FA, which are converted into acyl-CoA. For oxidation, acyl-CoA is imported into the mitochondria. Carnitine palmitoyltransferase (CPT) 1 converts acyl-CoA into acylcarnitine, which then crosses the outer mitochondrial membrane. Acylcarnitine is then transported across the inner mitochondrial membrane by carnitine–acylcarnitine translocase (CACT). Acylcarnitine is converted back into acyl-CoA by CPT2. CPT1 activity is inhibited by malonyl-CoA, which is formed via carboxylation of acetyl-CoA by acetyl-CoA carboxylase (ACC). In the mitochondria, acyl-CoA undergoes β-oxidation, which produces NADH, $FADH_2$, and acetyl-CoA. NADH and acetyl-CoA can stimulate pyruvate dehydrogenase kinase (PDHK), which in turn inhibits pyruvate dehydrogenase (PDH) and subsequently glucose oxidation. Together with acetyl-CoA produced through the glucose metabolism pathway (shown in grey), acetyl-CoA from FA ß-oxidation is converted to citrate, which could either diffuse out of the mitochondria and (indirectly) inhibit CPT1, or enter the tricarboxylic acid (TCA) cycle. The TCA cycle produces NADH and $FADH_2$. The NADH and $FADH_2$ then enter the electron transport chain (ETC) complexes (I–IV), after which ATP is produced by F0/F1 ATPase. The coupling between ETC and ATP production can be reduced by uncoupling proteins (UCP) and adenine nucleotide translocase (ANT). ANT transports ATP out of the mitochondria, after which it is further transported to the utilization site (e.g. the contractile proteins) via the creatine kinase shuttle.

Table 1 Mouse models of altered cardiac substrate metabolism

Mouse models	References	Cellular FA uptake	Cardiac lipid content	Lipotoxicity	FAO	Glucose oxidation	Cardiac energetics	Cardiac function, normal condition	Cardiac function[a]	
									Upon ischaemic HF	Upon non-ischaemic HF
FA supply										
HFD	28–38	↑	↑/=	↑	↑	↓/=	↓/=	↑/=/↓	↑/=/↓	=/↑
LPL-KO	39–42	↓	↓	n.a.	↓	↑	↓	↓/=	n.a.	↓
Increased FA supply via HFD affects cardiac function variably depending on the feeding period and composition. Additionally, HFD has potential beneficial effects in non-ischaemic heart failure. On the other hand, lower FA supply exacerbates cardiac dysfunction upon non-ischaemic HF.										
Cellular FA import										
FATP1-OE	43	↑	↑/=	↑	↑	↓	n.a.	↓	n.a.	n.a.
ACSL1-OE	44,45	↑	↑	↑	↑	↑	n.a.	↓	n.a.	n.a.
FAT/CD36-KO	46–48	↓	↓	↓	↓	↑	=	=	=/↓	↓
ACSL1-KO	49,50	↓	=	=	↓	↑	=	↓	n.a.	=
Both increased and reduced cellular FA uptake are associated with reduced cardiac function. Upon non-ischaemic HF, reduced cellular FA uptake exacerbates cardiac dysfunction.										
TG synthesis/lipolysis										
DGAT1-OE	44,51	↑	↑	↓/↑	↑	↓	n.a.	=/↓	n.a.	n.a.
ATGL-OE	52–54	↓	↓	=	↓	↑	=	↑	n.a.	↑
ATGL-KO	55–57	↓	↑	↑	↓	↓	↓	↓	n.a.	n.a.
Increased TG synthesis or reduced TG lipolysis decrease cardiac function, while increased TG lipolysis increases cardiac function. Increased TG lipolysis can protect the heart upon non-ischaemic HF.										
Mitochondrial FA import										
ACC2-KO	17	=	=	=	↑	↓	=	=	n.a.	↑
MCD-KO	10,13,28,58	↑	=	=	=/↓	=/↑	=/↓	=/↓	↑	n.a.
CPT1b-KO	27	=	=	=	=	=	n.a.	=	n.a.	↓
Up- or down-regulation of mitochondrial FA import do not seem to affect cardiac function. An increase in mitochondrial FA import or a reduced inhibition thereof results in maintained cardiac function upon non-ischaemic HF, while reduced mitochondrial FA import results in exacerbated dysfunction upon non-ischaemic HF.										
FAO										
VLCAD-KO	59–63	n.a.	↑	↑	=/↓	=/↓	↓	=/↓	n.a.	n.a.
LCAD-KO	64,65	n.a.	↑	↑	n.a.	=	=	=	n.a.	n.a.
Reduced expression of proteins involved in FAO does not affect cardiac function consistently.										
Transcriptional control of FAO enzymes										
PGC1α-OE	15	n.a.	n.a.	n.a.	↑	↓	=	=	n.a.	=
PPARα-OE	66,67	↑	=	↑	↑	↓	n.a.	↓	↓	n.a.
PGC1α-KO	68–70	=	=	n.a.	↓	↑	↓	=	n.a.	↓
PPARα-KO	71	↑	n.a.	n.a.	↓	↑	=	=	n.a.	n.a.

Continued

Table I *Continued*

Mouse models	References	Cellular FA uptake	Cardiac lipid content	Lipotoxicity	FAO	Glucose oxidation	Cardiac energetics	Cardiac function, normal condition	Cardiac function[a]	
									Upon ischaemic HF	Upon non-ischaemic HF
Increased or reduced PPARα and PGC1α expression do not affect cardiac function at normal condition; however, reduced PGC1α expression exacerbates cardiac dysfunction upon non-ischaemic HF.										
Glucose pathway										
PDHK-KO	58	n.a.	n.a.	n.a.	=	=	n.a.	=	↑	n.a.
GLUT1-OE	16,18	n.a.	n.a.	=	=	↑	=	=	n.a.	=/↑
GLUT1-KO	108	n.a.	n.a.	=	↑	↓	=	=	n.a.	=
GLUT4-KO	72,73	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	=/↓	↓	n.a.
Changes in proteins involved in glucose metabolism do not affect cardiac function at normal condition. However, an increase in glucose metabolism is associated with improved function upon ischaemic and non-ischaemic heart failure.										

Data on glucose oxidation, cellular FA uptake, or FAO are from perfused heart setups or gene/protein expression measurements. Lipotoxicity is indicated by the presence of myocardial lipid intermediates, or lipid-associated fibrosis, apoptosis, or oxidative stress. Highlighted in grey are summarizing conclusions on the effects of alterations at the different metabolic regulatory sites on cardiac function.
↑, increased; ↓, decreased; =, unchanged compared with controls; n.a., data not available; AAC, abdominal aortic constriction; ACC, acetyl-CoA carboxylase; ACSL, long-chain acyl-CoA synthase; ATGL, adipose triglyceride lipase; ATP, adenosine triphosphate; CPT, carnitine palmitoyltransferase; DGAT, diglyceride acyltransferase; FA, fatty acid; FAO, fatty acid oxidation; FAT/CD, fatty acid translocase/cluster of differentiation; FATP, fatty acid transport protein; GLUT, glucose transporter; HF, heart failure; HFD, high-fat diet; I/R, ischaemia/reperfusion; KO, knockout; LPL, lipoprotein lipase; MCD, malonyl-CoA decarboxylase; OE, overexpression; PDHK, pyruvate dehydrogenase kinase; PGC1α, Peroxisome proliferator-activated receptor-γ cofactor 1α; PPARα, Peroxisome proliferator-activated receptor-α; TAC, transverse aortic constriction.
[a]Cardiac function when compared with cardiac function in wild-type mice upon ischaemic and non-ischaemic heart failure condition.

hearts of LCAD-KO mice compared with controls,[64] most likely in an attempt to maintain cardiac energy levels. However, due to hypoglycaemia, the sustained myocardial glucose uptake and PDH activity appeared ineffective to maintain metabolic homeostasis, resulting in reduced *in vivo* cardiac energy status and function in fasted LCAD-KO mice.[64] This cardiac dysfunction in fasted LCAD-KO mice was further accompanied by increased accumulation of myocardial TG,[65] which indicates the onset of lipotoxicity. To summarize, a reduction in FAO without sufficient compensation by increased glucose oxidation leads to cardiac dysfunction.

3.2 Modulation of FA import into mitochondria

With FA as a major source of energy in the healthy heart, one may speculate that reduced mitochondrial FA import may deprive the heart of energy and ultimately lead to cardiac dysfunction. Indeed, reducing mitochondrial FA import through homozygous deletions of CPT1a and CPT1b, the liver and muscle isoforms of CPT1, respectively, was shown to be embryonically lethal[76,77] or lead to increased mortality[78] (depending on gene targeting approach). Mice with heterozygous deletion of CPT1b, however, do survive, and interestingly do not display altered cardiac metabolic or functional phenotypes under normal conditions.[27] In line with this, inhibition of cardiac CPT1 activity by ~50% in rodents via supplementation of the CPT1 inhibitor etomoxir, did not affect long-chain FA uptake and FAO.[79] Together, these findings indicate that CPT1 is necessary but not rate limiting for regulation of cardiac FAO.[80]

Mitochondrial FA import could also be reduced by increasing malonyl-CoA levels, which consequently inhibits CPT1 activity. Deletion of malonyl-CoA decarboxylase (MCD) in mice resulted in increased malonyl-CoA levels.[10] Surprisingly, gene expression of CPT1b in MCD-KO mice was increased, together with an increase in other peroxisome proliferator-activated receptor α (PPARα) responsive genes, which led to maintained FAO, glucose oxidation, and cardiac function.[10] However, in contrast to wild-type mice, high-fat diet (HFD) feeding did not increase FAO in MCD-KO mice, which prevented accumulation of metabolic intermediates of incomplete FAO, resulting in protection against HFD-induced cardiac dysfunction.[28] Another study recently reported that deletion of MCD did, however, result in cardiac dysfunction during the peri-weaning period, when the heart is highly dependent on FA as a substrate.[81] Interestingly, the early cardiac dysfunction was shown to resolve with age.[81]

Opposite to the attempts to reduce mitochondrial FA import as discussed earlier, several mouse models have been developed with increased mitochondrial FA import. Cardiac-specific deletion of ACC2 in mice resulted in decreased malonyl-CoA levels and increased FAO.[17] In diet-induced obesity[28] and diabetes,[82] increased FAO has been associated with the accumulation of myocardial lipid intermediates and cardiac dysfunction. However, in ACC2-KO mice myocardial lipid intermediates were not increased, indicating that FA supply and oxidation are in balance. This resulted in preserved cardiac function and energetics in these mice, even until 1 year of age.[17]

In conclusion, increased FA import into mitochondria does not seem to be harmful as long as import and oxidation are balanced. It is important to note that attempts to lower mitochondrial FA import did not result in reduced FAO, which may highlight the importance of FAO in maintaining cardiac function.

3.3 Modulation of myocardial TG lipolysis/synthesis

Suppression of myocardial TG lipolysis in adipose triglyceride lipase (ATGL)-KO mice was shown to reduce PPARα expression and lead to lethal cardiomyopathy. This was associated with severely reduced FAO, excessive myocardial TG accumulation, and impaired mitochondrial function.[55] Accordingly, treatment of ATGL-KO mice with a PPARα agonist was able to fully restore cardiac performance.[55,83] Interestingly, unlike mice with whole-body deletion of ATGL,[55,56] mice with inducible deletion of cardiac-specific ATGL did not show reduced PPARα levels, but still FAO and cardiac function were reduced.[57] In this case, the lower FAO was not caused by lower expression of PPARα, but most likely was due to the decrease in FA liberated by TG hydrolysis and the suppression of cellular FA uptake by CD36.[57] Indeed, CD36-mediated FA uptake is known to be tightly coupled to both TG synthesis and lipolysis.[84,85]

While deletion of ATGL seems detrimental,[55–57] mice with ATGL overexpression had improved cardiac function, leading to better adaptation to high workload conditions compared with control mice.[52] Surprisingly, like in ATGL deficiency, ATGL overexpression resulted in reduced myocardial FA uptake and oxidation and reduced PPARα levels.[52] However, in contrast to ATGL-KO mice, ATGL-overexpressing mice showed reduced TG content, and the reduced FAO was compensated for by an increase in glucose oxidation. This shift in substrate reliance resulted in maintained absolute acetyl-CoA production rates, suggesting no impairment in ATP supply, and sufficient ATP production to maintain normal cardiac function.[52] Furthermore, ATGL overexpression was shown to protect the heart against diabetic and high-fat, high-sucrose (HFHS) diet-induced cardiomyopathy through the attenuation of cardiac steatosis and lower reliance on FA utilization compared with wild-type controls.[53,54] This lower reliance on FA utilization was associated with a blunted increase in PPARα and CD36 expression in ATGL-overexpressing mice compared with controls.[53,54]

Studies in ATGL-KO and overexpression models seem to support the hypothesis that reduced myocardial TG storage is associated with improved cardiac function. In agreement, hormone-sensitive lipase (HSL) overexpression reduced TG and diglyceride (DG) levels and, consequently, lipotoxicity,[86,87] and was able to decrease mortality rate in diabetic mice.[87] Interestingly, in mice overexpressing diacylglycerol transferase 1 (DGAT1) the enzyme catalysing the synthesis of TG from DG, increased myocardial TG content was not associated with reduced cardiac function. DGAT1 overexpression attenuated cardiac lipotoxicity by reducing toxic intermediates like DG and ceramides.[44] Findings from another independent study, however, suggest that the beneficial effects of DGAT1 overexpression are time-course dependent and that beyond 1 year of age DGAT1-overexpressing mice still develop severe cardiomyopathy and myocardial fibrosis.[51] Nevertheless, backcrossing DGAT1-overexpressing mice with a mouse model of lipotoxicity resulted in improved cardiac function and survival rate, which further supports the finding that DGAT1 overexpression during acute or subacute FA overload may be cardio-protective.[44] Other animal models with alterations in TG metabolism have been extensively reviewed in Kienesberger *et al.*[88]

To summarize, rather than the absolute size of myocardial TG storage it is the dynamics of TG metabolism that seems to play a role in the cardioprotection. Cardiac TG is an essential energy source. However, it is important that TG lipolysis and synthesis are tightly balanced. While sufficient TG lipolysis is needed to meet the energy demand, excessive TG lipolysis may lead to the production of harmful intermediates.

3.4 Modulation of cellular FA import

An increased cellular FA uptake without a concomitant increase in mitochondrial (FA) oxidative flux can lead to lipotoxicity.[88–90] In mice with cardiac overexpression of fatty acid transport protein-1 (FATP1)[43] or long-chain acyl-CoA synthetase-1 (ACSL1),[45] an imbalance between FA uptake and oxidation has indeed been shown to cause cardiac dysfunction. FATP1 overexpression resulted in increased FA uptake and FAO, but also in FA accumulation, indicating that mitochondrial FAO capacity is insufficient to oxidize excess FA during lipid overload.

Deletion of CD36 in mice resulted in reduced FAO and lower intramyocardial TG and DG, without compromised effects on cardiac function and energetics,[46,47] which is ascribed to a substantial compensatory increase in glucose oxidation.[46] Additionally, deletion of CD36 was able to attenuate HFD-induced increases in TG, DG, and ceramides.[47] Similar to CD36-deficient mice, whole-body and cardiac-specific ACSL1-deficient mice showed a remarkable decrease in FAO and myocellular lipids, with a concomitant increase in glucose and pyruvate oxidation. This resulted in hypertrophy and cardiac diastolic dysfunction, whereas systolic function was maintained.[49,50] Diastolic dysfunction, as observed in heart failure patients with preserved ejection fraction, is often associated with increased left-ventricular stiffness.[91] Left-ventricular stiffness is often accompanied with disturbed calcium handling. In ACSL1-deficient mice, however, SERCA2a levels and phosphorylation of phospholamban were not affected. Therefore, the cause of diastolic dysfunction in the ACSL1-deficient mice is not clear yet.

To conclude, increased cellular FA uptake can disturb the balance between FA import and FAO, and therefore lead to cardiac dysfunction. On the other hand, decreasing FA import in the setting of increased plasma FA levels, like upon HFD-feeding, may rescue cardiac function.

3.5 Modulation of FA supply from blood

Increased FA availability usually leads to increased FA uptake and FAO in the heart.[29,92] We recently demonstrated that HFD feeding in mice increased mitochondrial FAO capacity. However, the increase in FAO could not match the FA supply and uptake, leading to myocardial TG accumulation and lipotoxicity-associated oxidative stress, fibrosis, impaired calcium homeostasis, and cardiac dysfunction.[30] Also other rodent studies have shown that HFD feeding led to accumulation of myocardial TG and lipid intermediates, and lipotoxicity-associated cardiac hypertrophy and/or dysfunction.[28,31–34] Especially, this TG accumulation occurred not only in the presence of increased FAO capacity, but also in the presence of increased FAO flux.[34] Chronically increased FA uptake due to increased sarcolemmal CD36 localization has been found the primary cause of lipid accumulation in hearts of HFD-fed rodents.[34,93]

Other than lipotoxicity, impaired cardiac energetics has been suggested as a cause for obesity-related cardiac dysfunction.[29,94] HFD feeding has been shown to lead to mitochondrial uncoupling and reduced cardiac efficiency.[29] In contrast, we showed that HFD feeding in mice did not result in impaired cardiac energetics *in vivo*.[30] This is in agreement with *ex vivo* isolated perfused heart data[95] that showed decreased contractile function, but unaffected myocardial PCr and ATP concentrations after HFD-feeding. Although detrimental effects of HFD feeding on the heart have clearly been shown, cardiac dysfunction was not always observed.[35–37] These differences in the effect of

HFD feeding on cardiac function are likely to be explained by differences in study design, such as diet composition, duration of the diet, species and gender, as well as the measurement techniques used (reviewed in Stanley *et al*[38]).

Given that lipoproteins are a major source of FA supply to the heart, ablation of cardiac LPL will lead to a marked impairment of this supply. Cardiac LPL ablation was associated with lower CD36 and FATP1 expression, lower myocardial uptake of FA liberated from lipoprotein-TG, and lower myocardial TG content.[39,40] Additionally, FAO was reduced in cardiac LPL-KO mice, which was accompanied by increased glucose oxidation, and cardiac hypertrophy and dysfunction.[40,41] Further stimulation of glucose utilization, by backcrossing cardiac LPL-KO mice with GLUT1-overexpressing mice, resulted in improved cardiac function and energetics. This suggests that cardiomyopathy in cardiac LPL-KO mice was rather due to defective energy production and not the reduced FA uptake *per se*.[42]

To summarize, increased FA supply from the blood can lead to an imbalance between cellular FA uptake and FAO, and consequently, lipotoxicity-associated cardiac dysfunction. On the other hand, decreased FA supply without sufficient compensation by increased glucose oxidation may also lead to cardiac dysfunction.

3.6 The effects of modulation of FA metabolism

Taken together, data from mouse models with alterations in FA metabolism show that detrimental effects seem to be caused by insufficient energy production in the heart, due to reduced FAO without a sufficient increase in glucose oxidation, or uncoupling of the electron transport chain from ATP production. Additionally, up-regulation of upstream components of the FA metabolic pathway that is not paralleled by concomitant increases downstream of the FA metabolic pathway can result in lipotoxicity and consequently lead to cardiac dysfunction.

4. Modulation of FA metabolism in heart failure

To examine whether and when modulations of FA metabolism are detrimental during the development of heart failure, we review the literature on mouse models of altered FA metabolism upon induction of ischaemic and non-ischaemic heart failure in the following section. The effects of modulation of FA metabolism in heart failure, collected from available studies using mouse models of altered cardiac substrate metabolism, are summarized in *Figure 1* and *Table 1*.

4.1 Ischaemic heart failure

Both during and after a cardiac ischaemic insult, a shift away from FA towards glucose utilization seems beneficial. The importance of glycolysis during ischaemia is particularly obvious in mice with GLUT4 deficiency, which have accelerated cardiac ATP depletion during ischaemia and delayed ATP recovery after ischaemia, together with profound cardiac dysfunction.[72] Mice with high FAO as a result of PPARα overexpression[66] or PPARα activation[96] showed exacerbated cardiac dysfunction after ischaemia–reperfusion, which was related to glycogen deposition, apoptosis, and oxidative stress, in addition to cardiac inefficiency due to glycolysis–glucose oxidation uncoupling. Furthermore, the detrimental effects of high reliance on FAO have been demonstrated in diabetic db/db mice, which have lower survival rates after ischaemia–reperfusion.[35,82,97] On the other hand, the hearts of FAT/CD36-KO mice, which displayed reduced FAO rate and increased glucose oxidation rate compared with wild-type, were not functionally or energetically compromised upon ischaemia/reperfusion.[46]

Data on cardiac substrate metabolism upon ischaemia largely originate from perfused heart studies, in which the whole heart is aerobically perfused, followed by no flow or low flow perfusion to reduce oxygen supply to the whole heart to mimic ischaemia.[6,46] During myocardial infarction, however, only a region of the heart is affected. As such, data from no flow or low flow perfused hearts may not fully represent the cardiac metabolic adaptation upon myocardial infarction. While upon myocardial infarction the cardiac metabolic adaptations may be different in the infarcted and the remote, viable zones, studies on these regional differences are currently lacking due to technical limitations. Nevertheless, studies suggest that an ischaemic assault in one region affects cardiac efficiency and cardiac function of the whole heart. Permanent coronary artery ligation (CAL) *in vivo* in mice, which caused 10% infarcted area in the heart, resulted in reduced global cardiac efficiency and cardiac mechanical function.[13] As an ischaemic assault increases the workload on the remaining viable myocytes, it is important that the heart has an increased cardiac energy production and efficiency. Indirect stimulation of glucose oxidation as a result of FAO suppression in MCD-KO mice[10,13,58] and direct stimulation of glucose oxidation in pyruvate dehydrogenase kinase-4 (PDHK4)-KO mice[58] were shown to decrease myocardial infarct size, reduce proton production, increase cardiac efficiency, and maintain cardiac function after ischaemia/reperfusion[10] or CAL.[13] Although upon CAL, ATP production rates in MCD-KO mice were lower than in wild-type mice, the cardiac function was better in MCD-KO mice than in wild-type mice, demonstrating improved coupling between glycolysis and glucose oxidation and improved cardiac efficiency to use ATP for cardiac work, rather than for maintaining ion homeostasis.[13] Furthermore, stimulating glucose oxidation by dichloroacetate (DCA) has also been shown to improve cardiac efficiency and cardiac function after ischaemia.[98] Indirect and direct stimulations of glucose oxidation therefore appear effective strategies in the treatment of ischaemic heart failure.[58,99]

4.2 Non-ischaemic heart failure

Like in ischaemic heart failure conditions, the stimulation of glucose utilization has also been proved beneficial under heart failure conditions with sufficient oxygen supply. Data from mice overexpressing GLUT1 from birth showed that a substantial increase in glucose uptake and glycolytic rates can preserve cardiac function and energetics in pressure overload conditions.[18] However, it is worth noting that while the induction of GLUT1 overexpression just 2 days before induction of pressure overload was sufficient to increase glucose utilization, maintain mitochondrial function and ATP synthesis, and attenuate the adverse remodelling process, it failed to rescue cardiac function.[16] Data from GLUT1-overexpressing mice suggest that the shift towards glucose utilization upon pressure overload may be an adaptive mechanism to cope with the extra workload. However, during stressed conditions such as heart failure, the ability of the heart to sufficiently increase glucose uptake seems to be impaired.[25,100] This is further demonstrated in PPARγ-coactivator-1α (PGC1α)-KO mice[68] and PPARα-KO mice,[71] which have an increased reliance on carbohydrates as a substrate for oxidation as a compensation for their decreased FAO. Under normal conditions, hearts of these mice are able to sustain normal energy metabolism, however, during a high workload challenge, the hearts fail to sustain high contractile performance.[68,71] Interestingly, a further increase in glucose transport and utilization, by backcrossing the

PPARα-KO mice with GLUT1-overexpressing mice, corrected the decreased contractile and metabolic reserve in PPARα-KO mice.[71] This suggests that further stimulation of glucose oxidation can help to provide sufficient ATP levels required during high workload. In line with this, increased glucose oxidation, as compensation for decreased FAO in cardiac-specific ATGL-overexpressing mice, appeared sufficient to maintain myocardial energetics and prevent cardiac dysfunction upon TAC-induced pressure overload.[52]

The data above suggest that increased glucose utilization can be a sufficient mechanism to protect against pressure overload-induced cardiac dysfunction. Currently, inhibition of FAO has evolved as an established approach to treat heart failure patients. However, it can be questioned if inhibition of FAO without an accompanied increase in glucose oxidation is indeed beneficial for the pressure overload-challenged heart. Several mouse models with reduced FAO due to direct modulation of FA metabolism, such as CPT1b-KO,[27] CD36-KO,[47] PGC1α-KO,[69] and LPL-KO[40] mice, show exacerbated cardiac dysfunction upon pressure overload. In all of these models, the cardiac functional impairments seemed to be related to insufficient energy production in the heart and/or cardiac lipotoxicity. In CPT1b-KO mice, the exacerbated cardiac dysfunction upon TAC-induced pressure overload was associated with reduced FAO, increased TG content and ceramide formation, as well as increased myocardial fibrosis and apoptosis.[27] In cardiac LPL-deficient mice,[40] pressure overload resulted in more severe cardiac dysfunction as compared with wild-type mice, which was most likely due to the impaired FA supply and the associated

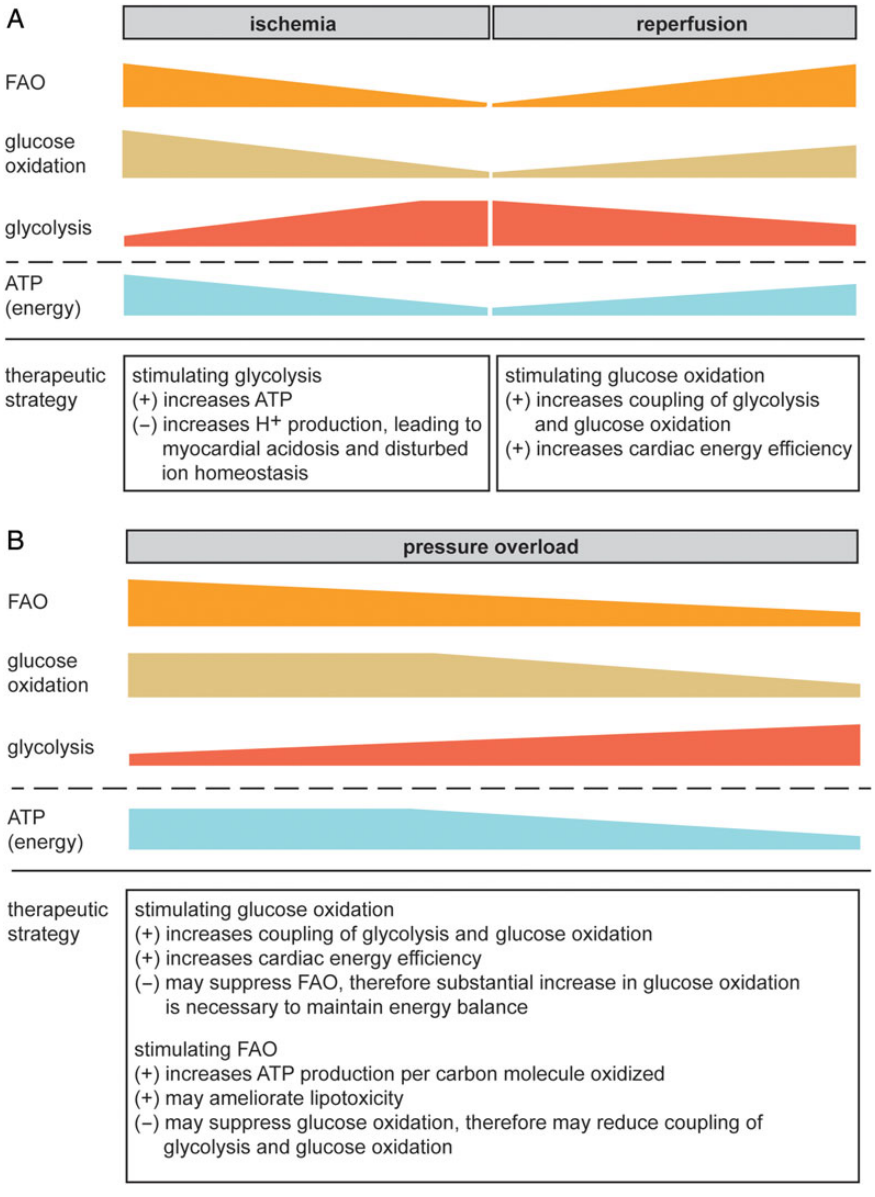

Figure 2 Summary of myocardial substrate contribution and potential therapeutic targets in (*A*) ischaemic and (*B*) non-ischaemic heart failure. The relative contributions of the major metabolic pathways (glucose oxidation, fatty acid oxidation, and glycolysis) to myocardial energy production change during heart failure development and progression. Therapeutic targets should aim at providing sufficient energy production. The probability of success of therapeutic strategies largely depends on the type and stage of heart failure.

reductions in FAO and myocardial ATP content.[101] Also PCG1α-KO mice, in which the suppression of cardiac FAO was associated with significant defects in their ATP balance,[70] showed accelerated pressure overload-induced heart failure.[69] Interestingly, when CD36-KO mice were fed a HFD, they were protected against TAC-induced cardiac dysfunction, which suggests a need for FA substrates during mechanical stress.[47]

Inhibition of FAO might thus not be beneficial when this results in impaired cardiac energetics. Increasing FA utilization might in fact be an alternative mechanism to treat pressure overload-induced heart failure. This was demonstrated in a mouse model of cardiac-specific ACC2 deficiency, which was shown to preserve high FAO, prevent a metabolic shift towards increased reliance on glycolysis, and better sustain myocardial energetics and function upon pressure overload.[17] However, maintaining the balance between FA supply/uptake and FAO is crucial when stimulating FA utilization, to prevent the accumulation of TG and lipid intermediates and the associated lipotoxicity.[17] Hence, strategies designed to up-regulate (CD36-mediated) FA uptake would be inadvisable in view of the danger of exceeding the FAO capacity. In addition, it is important that the increase in FAO is sufficient, not only to provide basal energy levels, but also to meet energy requirements during high workloads. This was shown in PGC1α-overexpressing and GLUT1-KO mice, which have high FAO, but which failed to maintain their cardiac energetics and function upon pressure overload.[15,108] Finally, maintaining coupling between glycolysis and glucose oxidation also needs to be taken into consideration, because reduced glucose oxidation may occur secondary to increased FAO.[3]

In summary, data show that increased FAO may be protective upon pressure overload. On the contrary, reduced FA supply, reduced cellular FA uptake, reduced mitochondrial FA import, and reduced expression of genes involved in transcriptional control of FAO can lead to exacerbated cardiac dysfunction upon pressure overload.

5. Summary and future outlook

The available data from mouse models with alterations in FA metabolism highlights the importance of FA as a substrate for the heart, and stresses the importance of maintaining the balance between FA supply and oxidation to maintain normal cardiac function. In humans, defects in at least 22 enzymes and specific transport proteins of FA metabolism have been shown to cause diseases,[102] in which many of these patients clinically present with signs of cardiac defects.[103]

To summarize the effect of FA modulation in mice, in the ischaemic heart (*Figure 2*), where oxygen supply is limited, a shift away from aerobic FAO towards anaerobic glycolysis seems necessary to assist in sufficient production of ATP. During ischaemia–reperfusion, a shift towards glucose oxidation seems favourable to prevent uncoupling between glycolysis and glucose oxidation. This uncoupling may lead to the accumulation of protons and lactate, which in turn lowers cardiac energetic efficiency because more energy is used to reduce the levels of these harmful metabolites. Therefore, reduced cardiac efficiency may contribute to the development of heart failure in the (post-)ischaemic heart. In this instance, an up-regulation of glucose oxidation would enhance glycolysis/glucose oxidation coupling, reduce the accumulation of protons and lactate, and consequently, increase cardiac efficiency.

In the non-ischaemic failing heart, particularly under pressure overload conditions, it seems that preserved energetics, rather than increased glucose oxidation and/or decreased FAO *per se*, is key for restoring cardiac function. A shift towards glucose utilization may be a rescue mechanism under stressed conditions; however, the increase in glucose utilization then needs to be sufficient to maintain the required energy levels. On the other hand, the shift towards glucose utilization may not be necessary and energetic compensation through high FAO can also be a successful strategy to protect the heart from failure. Current trends in heart failure treatment are based on stimulation of glucose utilization or inhibition of FA utilization. However, as demonstrated in mouse models of altered FA metabolism, the efficacy of inhibition of FA utilization in the treatment of non-ischaemic heart failure is as of yet not evident. Available data suggest that high FA utilization may actually be beneficial during the development of heart failure. These data are also in line with the 'obesity paradox' observed in obese heart failure patients. Despite the increased risk of obese patients to develop heart failure, obese heart failure patients actually have a better prognosis than non-obese heart failure patients.[104] In this case, the high FA metabolism in the obese heart may provide a degree of protection against the progression of heart failure, and may explain the better prognosis in these patients. Studies with HFD also show that increased FA utilization has potential in the prevention and treatment of heart failure.[38] Current findings therefore present exciting opportunities for stimulation of FA metabolism as a potential new strategy in non-ischaemic heart failure treatment. Next to the classical transcriptional regulation of FA metabolism, non-coding miRNAs are suggested to be potent post-transcriptional regulators of FA metabolism. Interestingly, miRNAs are also suggested as potential molecular targets in heart failure.[105–107] Furthermore, data on the role of other myocardial substrates, like ketone bodies, in heart failure are still limited, but may provide alternative metabolic targets.

Future research should focus on elucidating when and how alterations in myocardial substrate metabolism affect heart failure development and progression. The effect of these alterations on the excitation–contraction coupling machinery is also of relevance as excitation–contraction coupling is energy-dependent and plays an important role in cardiac function. Data that provide a comprehensive view of changes in cardiac metabolic adaptations during different stages of the development and progression of heart failure, as well as in different metabolic conditions (e.g. in obesity and diabetes), are currently lacking. Advancement in this field crucially depends on the development of non-invasive *in vivo* techniques, such as magnetic resonance imaging, magnetic resonance spectroscopy, and positron emission tomography, which allow longitudinal measurements of cardiac function and metabolism during the progression of heart failure within the same animal or patient.

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