Chapter 17
Myocardial Metabolic Abnormalities and Cardiac Dysfunction

Petra C. Kienesberger

Abstract To sustain contractile function, the myocardium has a very high and continuous demand for ATP, which it generates from a variety of carbon sources, including fatty acids, glucose, ketone bodies, pyruvate, and lactate. In the healthy adult heart, most of the ATP is generated via mitochondrial oxidation of fatty acids (50–70 %), and the balance between fatty acid oxidation and other forms of ATP production, such as glucose oxidation and glycolysis, is tightly regulated. In fact, dysregulation or inflexibility of myocardial energy metabolism has been linked to a number of major cardiac diseases including myocardial hypertrophy, heart failure, ischemic heart disease, and obesity and diabetes mellitus-associated cardiomyopathy. Deranged cardiac energy metabolism and impaired cardiac energetics have been suggested to contribute to these pathophysiological states, rendering metabolic modulators an attractive option for the management of various forms of heart disease. This chapter summarizes our current understanding of the role of cardiac energy metabolism in the development and progression of heart failure, pressure overload-induced hypertrophy, and obesity-related cardiomyopathy. In addition, potential therapies to restore metabolic balance and efficiency in the heart and ameliorate cardiac dysfunction are outlined.

Keywords Cardiac metabolism • Cardiac energetics • Heart failure • Cardiomyopathy • Hypertrophy • Obesity • Lipotoxicity

17.1 Introduction

To generate sufficient ATP for contractile function, cardiomyocytes transport energy substrates, mainly fatty acids and glucose, from the circulation across the sarcolemmal membrane. Fatty acids are presented to the cardiomyocytes in the form of "free" fatty acids conjugated to serum albumin or triacylglycerol (TAG)-rich

P.C. Kienesberger, PhD
Department of Biochemistry and Molecular Biology, Dalhousie University, Dalhousie Medicine New Brunswick, Saint John, New Brunswick E2L 4L5, Canada
e-mail: pkienesb@dal.ca

G. Jagadeesh et al. (eds.), *Pathophysiology and Pharmacotherapy of Cardiovascular Disease*, DOI 10.1007/978-3-319-15961-4_17

very-low-density lipoproteins and chylomicrons [1, 2]. TAGs in lipoproteins are hydrolyzed to fatty acids by lipoprotein lipase in the coronary lumen [3, 4]. Fatty acids then enter cardiomyocytes mainly via transport proteins or carriers including fatty acid translocase (FAT/CD36), plasma membrane fatty acid-binding protein (FABPpm), and fatty acid transport protein 1/6 (FATP1/6) [5–9]. Fatty acid carriers can translocate to the sarcolemma to increase fatty acid uptake into cardiomyocytes [5]. For example, FAT/CD36, which is believed to facilitate approximately 50 % of fatty acid uptake into cardiomyocytes and controls 40–60 % of myocardial fatty acid oxidation in the working mouse heart [9–12], can translocate to the sarcolemma following insulin stimulation, activation of AMP-activated protein kinase (AMPK), and contraction [5]. Upon transport across the sarcolemma, fatty acids are subsequently converted to fatty acyl-coenzyme A esters (fatty acyl-CoA) by long-chain acyl-CoA synthetases (ACSL) in an ATP-dependent manner [1, 13]. This metabolic step traps fatty acids within cardiomyocytes and activates them so that they can be metabolized [13].

In order to be transported across the mitochondrial membrane, fatty acyl-CoAs need to be converted to acylcarnitines by carnitine palmitoyltransferase 1 (CPT1) and are then transferred across the inner mitochondrial membrane via carnitine:acylcarnitine translocase, which exchanges carnitine for acylcarnitine [2]. Upon conversion of acylcarnitine back to long-chain acyl-CoA by CPT2 in the mitochondrial matrix, fatty acids enter β-oxidation, which is catalyzed by the sequential enzymatic action of acyl-CoA dehydrogenase, enoyl-CoA hydratase, hydroxyacyl-CoA dehydrogenase, and 3-ketoacyl-CoA thiolase. This shortens the fatty acyl moiety by two carbons in each cycle and produces reducing equivalents in the form of flavin adenine dinucleotide ($FADH_2$) and nicotinamide adenine dinucleotide (NADH) [14]. The β-oxidation of unsaturated fatty acids, which represent the majority of fatty acids in circulation that enter the cardiomyocyte, involves additional enzymes, 2,4-dienoyl-CoA reductase and enoyl-CoA isomerase, to convert *cis* double bonds to *trans* double bonds [15]. It should be noted that saturated and unsaturated fatty acids are oxidized at comparable rates in the rodent and human heart [16, 17]. Enzymes involved in β-oxidation are under a high degree of transcriptional control by peroxisome proliferator-activated receptor (PPAR) α and β/δ, as well as PPARγ coactivator (PGC) 1α and 1β [18, 19]. The reducing equivalents (NADH and $FADH_2$) generated via β-oxidation and subsequent delivery of acetyl-CoA to the tricarboxylic acid cycle are then converted to ATP through oxidative phosphorylation at the inner mitochondrial membrane. Since ATP cannot cross the mitochondrial membrane, creatine kinase transfers the high-energy phosphate bond in ATP to creatine, which is taken up from the circulation via a creatine transporter [20]. This leads to the formation of phosphocreatine and adenosine diphosphate (ADP) [21]. Phosphocreatine, which is smaller than ATP, can diffuse from the mitochondria to myofibrils, the contractile apparatus of cardiomyocytes [21]. The myofibrillar creatine kinase converts phosphocreatine back to ATP to power contractions and the free creatine diffuses back to the mitochondria [21]. The creatine kinase system functions as an important energy buffer in the myocardium [21]. When energy demand is higher than energy supply, the phosphocreatine pool decreases to

maintain ATP levels [21]. This is an early adaptation to myocardial energy deficiency. Also, under these conditions, ADP levels rise, which can impair a variety of intracellular processes and lead to defective contractile function [21].

Similar to fatty acids, glucose is transported into the cardiomyocyte via proteins embedded in the sarcolemma. Glucose uptake is mediated mainly by two glucose transporters, Glut1 and Glut4 [22]. Glucose transport via Glut1 is insulin independent and accounts for basal glucose uptake. Glut1 expression is reduced following birth but can increase again in pathophysiological states including cardiac hypertrophy [22] (Chap. 16). In contrast to Glut1, the insulin-sensitive glucose transporter Glut4 is abundantly expressed in the adult heart [23]. Glut4 translocation from storage vesicles to the sarcolemma is stimulated by insulin and by contractions [23]. Upon uptake into the cell, glucose is phosphorylated by hexokinase, which commits glucose to further metabolism [24]. Glucose-6-phosphate is then catabolized through glycolysis, and the resulting pyruvate is shuttled into mitochondria, converted to acetyl-CoA, and subjected to oxidation for ATP production. Glucose that is not immediately directed towards glycolysis and mitochondrial oxidation can be converted to glycogen for temporary storage [24]. The following sections outline how energy metabolism is altered in cardiac pathophysiology and highlight potential therapeutic avenues which could be pursued to restore energetic balance in the diseased heart.

17.2 Myocardial Energy Starvation in Heart Failure

Heart failure is a multifactorial disorder that is fairly common – it affects more than 2 % of people in the United States, and 30–40 % of heart failure patients die within 1 year from the diagnosis [21]. Between 1979 and 2004, the United States was confronted with a threefold increase in heart failure hospitalizations, with more than 80 % of patients being at least 65 years old [25]. It is projected that the incidence of heart failure will increase in the future as the population continues to age. Despite the various causes of heart failure, which include hypertension, coronary artery disease, cardiomyopathy, and cardiac arrhythmias, impaired energy metabolism appears to be a fundamental characteristic that contributes to the progression of heart failure [21, 25] (Fig. 17.1) (Chaps. 1 and 3). This concept is not new as it was first described in 1939 by Herrmann and Decherd that the failing heart is essentially energy-starved [26], meaning that there are not enough energy equivalents (ATP and phosphocreatine) to sustain contractile function in end-stage heart failure. Interestingly, the efficacy of beta-blockers, angiotensin II blockers, or angiotensin-converting enzyme inhibitors in ameliorating heart failure is in part attributed to their effect in reducing cardiac energy demand and improving the metabolic balance [21] (Chaps. 8 and 18).

The derangement of cardiac energy metabolism in heart failure occurs at three stages – energy substrate utilization (uptake and oxidation), oxidative phosphorylation in mitochondria, and high-energy phosphate (ATP, phosphocreatine) metabolism, as was evidenced in the rodent and human heart [21]. Previous studies have

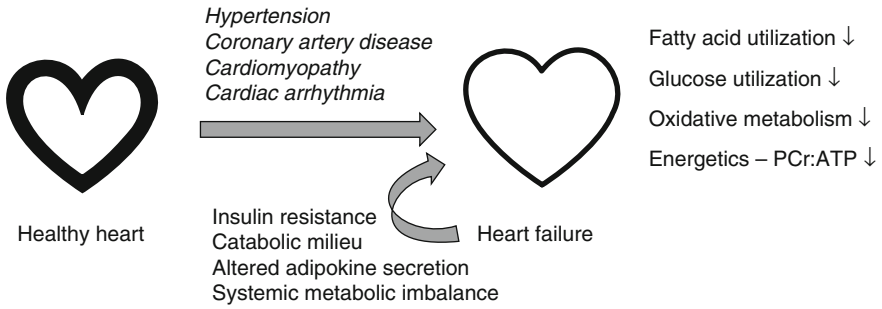

Fig. 17.1 Metabolic changes in advanced heart failure. Cardiovascular diseases such as hypertension, coronary artery disease, cardiomyopathy, and cardiac arrhythmia can lead to heart failure. In end-stage heart failure, typical metabolic changes are decreased fatty acid utilization, glucose utilization, and overall oxidative metabolism, resulting in impaired energetics. Effects of heart failure on systemic metabolism include insulin resistance, increased catabolism, and altered adipokine secretion, which contribute to the progression of heart failure and further impair myocardial energy metabolism. PCr:ATP is phosphocreatine:adenosine triphosphate

generally shown that while fatty acid utilization is not substantially altered in early stages of heart failure [27, 28], it drops substantially in advanced heart failure [29] (Fig. 17.1). Glucose utilization has been reported to increase in early stages of heart failure [30] and decrease along with the development of insulin resistance in advanced heart failure [21, 31–33] (Fig. 17.1). Since the systemic metabolic milieu is drastically altered in heart failure with commonly increased circulating fatty acids, glucose, and insulin, and catabolic over activity, these results need to be viewed with caution as it is difficult to distinguish between the inherent impairment of substrate metabolism in the myocardium and metabolic adaptations due to altered substrate availability [21, 25]. Impaired structure and function of mitochondria are also commonly observed in failing hearts [34, 35], leading to reduced oxidative phosphorylation, oxygen consumption, and ATP/phosphocreatine production.

In addition, the creatine kinase system is substantially altered in heart failure [21, 36, 37], which causes a drastic decline in ATP transfer and ATP starvation of myofibrils. Interestingly, ATP concentrations are sustained in a normal range in earlier stages of heart failure and only decline by approximately 30–40 % in advanced heart failure [21, 38–40]. However, the decline in intracellular creatine and phosphocreatine due to impaired creatine transporter function precedes and is greater than the decline in ATP concentrations (30–70 %), representing an early sign of deranged cardiac energetics in heart failure [36, 39, 41, 42]. Hence, phosphocreatine-to-ATP ratios are reduced in heart failure and correlate with heart failure classes according to the New York Heart Association [43] (Fig. 17.1). These changes in high-energy phosphate metabolism drastically limit the energetic reserve of the myocardium. For example, when failing hearts are challenged with high workload (e.g., by stimulation with catecholamines), free ADP increases to concentrations that are double compared to those in the healthy heart [44], thereby reducing the contractile reserve [21]. Given that impaired energy metabolism critically contributes

to heart failure development and/or progression, modulators that improve the energetic reserve of the heart may become attractive options for the treatment of heart failure.

At present, there is no approved therapy available that specifically targets energy metabolism in heart failure [25]. Experimental metabolic therapies that are aimed at improving metabolic balance and efficiency in the myocardium generally decrease fatty acid utilization and increase glucose oxidation [25]. For example, the piperazine derivative, trimetazidine, is an experimental drug that selectively inhibits mitochondrial long-chain 3-ketoacyl-CoA thiolase, thereby decreasing fatty acid oxidation and increasing glucose utilization via secondary activation of pyruvate dehydrogenase [45]. Trimetazidine restores coupling between glycolysis and glucose oxidation and leads to ATP production with less demand for oxygen [45]. While the results from clinical trials are promising [45–47], more clinical studies are required to demonstrate the efficacy of this drug in ameliorating heart failure and angina (Chap. 22).

Heart failure not only affects myocardial energy metabolism but whole body metabolism via endocrine communication of the heart with other organs [25, 48, 49]. For example, systemic insulin resistance is a characteristic feature of heart failure [48]. It develops in response to neurohormonal stimuli (catecholamines), inflammatory cytokine release, oxidative stress, and tissue hypoperfusion as a consequence of heart failure [25, 50]. Moreover, insulin resistance appears to predict severity of heart failure and reduced survival [25]. In addition, resistance to the anabolic hormone insulin, among other factors, leads to an overall catabolic environment that contributes to muscle cachexia in heart failure patients [25, 49]. Overstimulation of adipose tissue lipolysis via increased catecholamines, inflammatory cytokines, natriuretic peptides, and pressure overload also leads to a rise in circulating fatty acids and changes in adipokine secretion and thereby contributes to the systemic and cardiac metabolic imbalance in heart failure [25, 50, 51]. Therefore, therapies that target not only cardiac metabolism but whole body metabolism, for those individuals in heart failure, could hold promise in treating this debilitating disease (Chaps. 3 and 18).

17.3 Metabolic Remodeling in Myocardial Hypertrophy

Cardiac hypertrophy is an initially adaptive response to cellular stress leading to cardiomyocyte enlargement, increased protein synthesis, re-induction of the so-called fetal gene program, and heightened sarcomeric organization [52, 53]. Chronically, cardiac hypertrophy can become maladaptive and trigger heart failure and malignant arrhythmia due to perturbations of cellular calcium homeostasis and ionic currents [52, 53]. Significant morphological changes following long-term cardiac hypertrophy include increased rates of programmed cell death, fibrosis, and cardiac chamber dilatation [52, 53]. Common stressors that lead to hypertrophic remodeling in cardiomyocytes are pressure or volume overload, mutations of

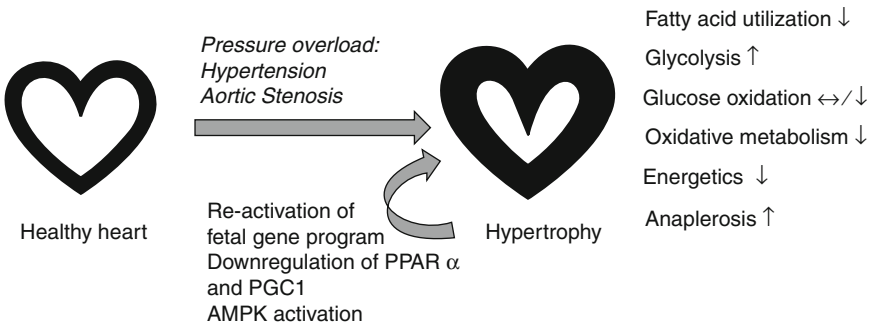

Fig. 17.2 Metabolic changes in pressure overload-induced cardiac hypertrophy. Pressure overload-induced hypertrophy, triggered by hypertension or aortic stenosis, is associated with a decrease in fatty acid oxidation and overall oxidative metabolism and energetics, while anaerobic glucose metabolism (glycolysis) is increased. Glycolysis is uncoupled from glucose oxidation, and excess pyruvate is shuttled towards alternative pathways, such as anaplerosis. The decrease in fatty acid utilization is mostly due to the reactivation of the fetal gene program and downregulation of transcriptional regulators of fatty acid oxidation and mitochondrial biogenesis and function. AMPK activation has been suggested to underlie the increase in glucose uptake and glycolysis in cardiac hypertrophy

sarcomeric or other proteins, and loss of contractile mass from prior infarction [52, 53]. The following section describes metabolic changes following pressure overload hypertrophy as this type of hypertrophy is increasingly common due to the increasing prevalence of hypertension (Chap. 16).

One of the metabolic hallmarks of pressure overload-induced cardiac hypertrophy is that cardiac energy metabolism reverts to a fetal-like profile, which is due to a decrease in fatty acid oxidation and increased reliance on carbohydrates for ATP production with an overall decrease in oxidative metabolism [54, 55] (Fig. 17.2). This substrate shift has been suggested to contribute to the progression of cardiac hypertrophy to overt heart failure [56], although it still remains elusive to what extent metabolic remodeling influences the development and progression of pressure overload-induced cardiac hypertrophy. The reduction in fatty acid oxidation is attributed to a decrease in the expression of genes involved in β-oxidation and oxidative phosphorylation [55]. A number of studies using animal models have shown that this is due to the downregulation of the transcriptional master regulators PPARα and PGC1 [55, 57–60] (Fig. 17.2). In addition, a reduction in membrane-bound fatty acid transporters and carnitine has also been observed in the hypertrophic heart [61–64]. The resulting energy insufficiency leads to the activation of the energy-sensing kinase, AMPK, which contributes to an increase in glucose uptake and glycolysis by promoting translocation of glucose transporters to the sarcolemma and stimulating the glycolytic enzyme, phosphofructokinase 2 [55, 65–67] (Fig. 17.2). Interestingly, the increase in glucose uptake is insulin-independent, and changes in glucose metabolism in the hypertrophic heart are not accompanied by marked changes in proteins involved in glucose transport or glycolysis [33, 55, 68]. In contrast to the increased glycolysis, many studies have reported that glucose

oxidation is either unchanged or decreased in the hypertrophied heart, suggesting that glucose oxidation and glycolysis are uncoupled in cardiac hypertrophy [55, 69–71] (Fig. 17.2). As a result of this uncoupling in glucose metabolism, lactate dehydrogenase, which converts pyruvate into lactate, is activated to process the excess pyruvate. Consequently, increased secretion of lactate from the hypertrophied myocardium has been reported [55, 72, 73].

The excess pyruvate can also be shuttled towards anaplerosis, which refers to metabolic processes that replenish tricarboxylic acid (TCA) cycle intermediates that are removed from the TCA cycle for biosynthetic pathways to produce glucose, fatty acids, and amino acids [74]. In this process, pyruvate is converted to oxaloacetate and malate through its carboxylation via pyruvate carboxylase and malic enzyme, respectively [74]. Consistent with this notion, an 80–90 % increase in anaplerotic flux has been reported in the hypertrophied heart [75, 76] (Fig. 17.2). Although pyruvate can replenish TCA cycle substrates via anaplerosis, it is an energetically costly process as it reduces the efficiency of ATP production from pyruvate [55]. Changes in other glucose metabolism pathways were also observed in the hypertrophied heart, including pentose-phosphate pathway [77–79] and hexosamine pathway [80, 81]. To date, it remains unclear whether and to what extent these "alternative" glucose metabolism pathways contribute to the pathophysiology of cardiac hypertrophy.

The increase in the reliance on glucose utilization in the hypertrophic heart appears to be an adaptive process, at least in earlier stages of hypertrophic remodeling. This notion is inferred from studies with mutant mice where the expression of glucose transporters has been altered. For example, mice overexpressing the insulin-independent glucose transporter Glut1, specifically in the heart, exhibit increased glucose uptake and glycolysis that is partially uncoupled from glucose oxidation, as well as decreased fatty acid oxidation [82]. Importantly, these mice were protected from pressure overload-induced cardiac dysfunction [82]. In contrast, mice with cardiac deficiency of the insulin-sensitive glucose transporter Glut4 exhibit reduced contractile function and cardiomyocyte hypertrophy [83]. Prevention of metabolic remodeling in pressure overload hypertrophy via cardiac-specific deletion of acetyl-CoA carboxylase 2, which produces the fatty acid oxidation inhibitor malonyl-CoA, attenuated cardiac hypertrophy, protected against fibrosis, and improved cardiac function [84]. These findings suggest that metabolic remodeling contributes to the pathophysiology of cardiac hypertrophy.

Interestingly, cardiac-specific overexpression of PGC1α and the associated increase in mitochondrial size did not protect from cardiac remodeling induced by transverse aortic constriction [85]. Instead, it led to a greater impairment in contractile function and increase in left ventricular chamber dimension [85]. These data suggest that attempts to stimulate master regulators of mitochondrial biogenesis and size in cardiac hypertrophy to improve oxidative metabolism may in fact worsen outcomes following pressure overload-induced hypertrophy. Dietary and pharmacological strategies have also been pursued to ameliorate outcomes in pressure overload-induced hypertrophy [54, 86, 87]. Interestingly, feeding rats with a diet low in carbohydrates and high in fat attenuated cardiac hypertrophy and remodeling [86]. In contrast, activation of fatty acid metabolism via PPARα agonist (WY-14643) treatment augmented pressure overload-induced contractile dysfunction,

despite the prevention of substrate switching [87]. Since these interventions drastically influence whole body metabolism in addition to cardiac metabolism, their direct effects on metabolism and function in the hypertrophic heart remain unclear.

17.4 Metabolic (Mal)adaptation of the Heart in Obesity

Obesity, defined as excess accumulation of body fat, and associated type 2 diabetes mellitus, is a significant risk factor for the development of heart failure [88, 89]. Although the onset of heart failure in obesity is likely multifactorial, obesity-associated cardiomyopathy appears to be a major initiating factor and contributes to the increased morbidity and mortality among obese individuals [88]. This is exemplified by the finding that even after correcting for hypertension and other common obesity-related risk factors, the presence of obesity still approximately doubles the risk of developing heart failure [90]. Chronic obesity commonly leads to systemic metabolic perturbances including insulin resistance and type 2 diabetes with concomitant hyperglycemia and hyperlipidemia. It has been hypothesized that this oversupply of energy substrates to the heart initially leads to adaptive changes and ultimately precipitates contractile dysfunction [90]. Specifically, the increased availability of fatty acids resulting in augmented fatty acid uptake, in conjunction with inadequate activation of fatty acid oxidation, gives rise to excess accumulation of toxic lipid metabolites in the myocardium and a general increase in cardiac fat content [88, 90]. High fatty acid oxidation rates in obesity, as have been observed in both animal models and humans, inhibit cardiac glucose utilization via substrate competition, hence contributing to decreases in glycolysis and glucose oxidation as well as insulin resistance [19, 91] (Fig. 17.3). These metabolic changes also lead to a decrease in mechanical efficiency [19, 91]. It has been suggested that the metabolic

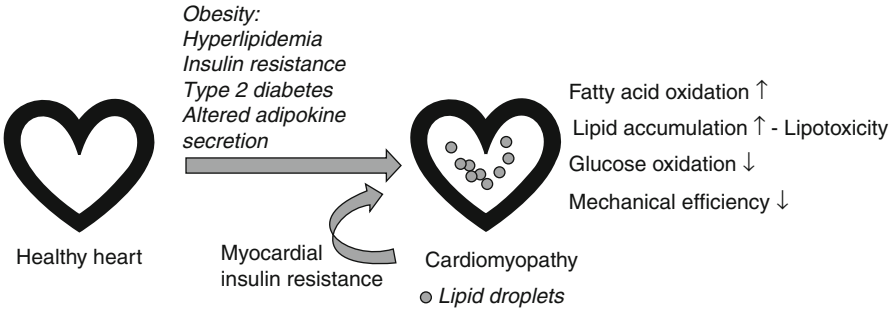

Fig. 17.3 Metabolic changes in obesity-associated cardiomyopathy. Obesity and obesity-associated systemic changes in energy metabolism (hyperlipidemia, insulin resistance, type 2 diabetes) and adipokine secretion lead to increased cardiac fatty acid oxidation, lipid accumulation, and lipotoxicity, which are paralleled by reduced glucose oxidation and mechanical efficiency. Myocardial insulin resistance further promotes metabolic dysregulation in the heart

remodeling of the myocardium observed in obesity not only precedes but contributes to overt functional and structural changes of the heart in obesity [90, 92].

Increased accumulation of toxic lipid metabolites, a process that is also termed as "lipotoxicity," has also been suggested to contribute to cardiac dysfunction during obesity [93–95] (Fig. 17.3). Examples for toxic lipid metabolites are long-chain acyl-CoAs, ceramides, diacylglycerols, and acylcarnitines [96]. Lipotoxicity may lead to cardiac dysfunction by means of activating apoptosis, impairing insulin signaling, promoting endoplasmic reticulum stress, activating protein kinase C and mitogen-activated protein kinase, as well as modulating PPAR signaling [96]. Studies using nonobese transgenic mice and obese-diabetic rat models show that accumulation of lipids in cardiomyocytes corresponds with a decrease in systolic and diastolic function and cardiac hypertrophy [4, 19, 93, 97–101]. However, the individual contribution of lipid subspecies to cardiac pathophysiology is unclear. Mechanisms for the lipotoxicity-induced insulin resistance in the heart have been suggested to involve diacylglycerol-mediated activation of protein kinase C, resulting in increased serine phosphorylation of insulin receptor substrate 1 and decreased activation of downstream insulin signaling mediators, such as phosphatidylinositol 3-kinase and Akt [19]. The implication of increased TAG accumulation in the obese heart is less understood, but it may impair cardiac function by fueling the production of "toxic" lipid species [1]. Myocardial TAG content positively correlates with body mass index, suggesting that cardiac TAG deposition increases gradually with increased adiposity [102]. Elevated myocardial TAG content was also observed in individuals with impaired glucose tolerance and type 2 diabetes [1, 103, 104]. Moreover, the increase in cardiac TAG accumulation preceded the development of overt cardiac dysfunction, suggesting a causal relationship between elevated TAG levels in the heart and obesity/type 2 diabetes-associated myocardial dysfunction [1, 103].

To date, drugs used to treat metabolic disturbances in obesity are mainly aimed at lowering circulating lipid levels and ameliorating insulin resistance. For example, there are two classes of PPAR agonists used to achieve this effect. These are ligands for PPARα and PPARγ, respectively. Both PPARα and PPARγ agonists lower circulating lipid levels either by increasing fat storage in adipocytes or increasing fatty acid oxidation in the muscle and liver [19]. Despite the beneficial systemic effect of PPARα and PPARγ agonists, their direct effect on the heart may not always be desirable. For example, cardiac-specific overexpression of PPARα induced a cardiac phenotype similar to diabetic cardiomyopathy [105]. Myocardial fatty acid oxidation rates were increased in these transgenic mice, while glucose uptake and oxidation were decreased, concomitant with the development of pathological cardiac hypertrophy, increased lipid accumulation, and cardiac dysfunction [105]. Similarly, cardiomyocyte-specific overexpression of PPARγ led to cardiac dysfunction in mice that was associated with increased myocardial lipid accumulation and expression of enzymes involved in fatty acid utilization [106]. In humans, PPARγ agonist treatment is also associated with peripheral edema and heart failure [106, 107]. These findings suggest that PPAR agonist treatment in obesity may have adverse effects on the heart by increasing cardiac lipid deposition. Interestingly, recent studies showed that inhibition of mitochondrial β-oxidation with trimetazidine,

which is widely used for the treatment of angina, can improve obesity-related cardiac dysfunction [108]. Trimetazidine not only improves contractile efficiency in obese humans but protects against obesity-induced systolic and diastolic dysfunction in mice without altering insulin sensitivity or exacerbating obesity-induced insulin resistance [108]. This suggests that trimetazidine, by improving the metabolic balance in the heart, may be a viable therapy for the treatment of obesity-related cardiomyopathy.

Metabolic disturbances in adipose tissue initiate obesity-associated morbidity and cardiovascular disease [109, 110]. Besides fueling the systemic and cardiac lipid oversupply in obesity, the hypertrophic obese adipose tissue also changes its secretory profile of hormones and cytokines, so-called adipokines, which promotes not only insulin resistance and inflammation but likely has a direct effect on cardiac energy metabolism [19, 90, 111] (Fig. 17.3). However, more studies are required to better understand the direct effects of changes in circulating adipokines such as adiponectin, leptin, resistin, and retinol-binding protein 4 on cardiac metabolism and function during obesity in both animal models and humans.

17.5 Concluding Remarks

Cardiac energy metabolism is tightly regulated to meet the high energy demands of myocardial contraction and to adapt to short-term fluctuations in energy substrate supply and workload. When challenged by chronic stressors, including pressure overload and obesity, myocardial energy metabolism can initially adapt to counter-regulate but is eventually locked into a dysregulated and inflexible state with a major shift in substrate utilization and/or cardiac energetics and efficiency. Many studies have shown that this impairment in cardiac energy metabolism can promote the development of heart failure with a significant drop in the heart's energetics and premature death. Since there is evidence that maladaptive changes in cardiac energy metabolism contribute at least in part to multiple forms of heart disease, drugs that aim to restore a balanced substrate utilization in the heart have the potential to become attractive options to treat these diseases and prevent their progression to overt heart failure.

References

1. Kienesberger PC, Pulinilkunnil T, Nagendran J, Dyck JR. Myocardial triacylglycerol metabolism. J Mol Cell Cardiol. 2013;55:101–10. PubMed PMID: 22789525, Epub 2012/07/14. eng.
2. Lopaschuk GD, Ussher JR, Folmes CD, Jaswal JS, Stanley WC. Myocardial fatty acid metabolism in health and disease. Physiol Rev. 2010;90(1):207–58. PubMed PMID: 20086077, Epub 2010/01/21. eng.
3. Pulinilkunnil T, Abrahani A, Varghese J, Chan N, Tang I, Ghosh S, et al. Evidence for rapid "metabolic switching" through lipoprotein lipase occupation of endothelial-binding sites. J Mol Cell Cardiol. 2003;35(9):1093–103. PubMed PMID: 12967632, Epub 2003/09/12. eng.

4. Yagyu H, Chen G, Yokoyama M, Hirata K, Augustus A, Kako Y, et al. Lipoprotein lipase (LpL) on the surface of cardiomyocytes increases lipid uptake and produces a cardiomyopathy. J Clin Invest. 2003;111(3):419–26. PubMed PMID: 12569168, Pubmed Central PMCID: 151861, Epub 2003/02/06. eng.
5. Heather LC, Pates KM, Atherton HJ, Cole MA, Ball DR, Evans RD, et al. Differential translocation of the fatty acid transporter, FAT/CD36, and the glucose transporter, GLUT4, coordinates changes in cardiac substrate metabolism during ischemia and reperfusion. Circ Heart Fail. 2013;6(5):1058–66. PubMed PMID: 23940308.
6. Harmon CM, Luce P, Beth AH, Abumrad NA. Labeling of adipocyte membranes by sulfo-N-succinimidyl derivatives of long-chain fatty acids: inhibition of fatty acid transport. J Membr Biol. 1991;121(3):261–8. PubMed PMID: 1865490.
7. Sorrentino D, Stump D, Potter BJ, Robinson RB, White R, Kiang CL, et al. Oleate uptake by cardiac myocytes is carrier mediated and involves a 40-kD plasma membrane fatty acid binding protein similar to that in liver, adipose tissue, and gut. J Clin Invest. 1988;82(3):928–35. PubMed PMID: 3417874, Pubmed Central PMCID: 303604.
8. Schaffer JE, Lodish HF. Expression cloning and characterization of a novel adipocyte long chain fatty acid transport protein. Cell. 1994;79(3):427–36. PubMed PMID: 7954810.
9. Nagendran J, Pulinilkunnil T, Kienesberger PC, Sung MM, Fung D, Febbraio M, et al. Cardiomyocyte-specific ablation of CD36 improves post-ischemic functional recovery. J Mol Cell Cardiol. 2013;63C:180–8. PubMed PMID: 23948483, Epub 2013/08/21. Eng.
10. Brinkmann JF, Abumrad NA, Ibrahimi A, van der Vusse GJ, Glatz JF. New insights into long-chain fatty acid uptake by heart muscle: a crucial role for fatty acid translocase/CD36. Biochem J. 2002;367(Pt 3):561–70. PubMed PMID: 12088505, Pubmed Central PMCID: 1222912.
11. Ibrahimi A, Bonen A, Blinn WD, Hajri T, Li X, Zhong K, et al. Muscle-specific overexpression of FAT/CD36 enhances fatty acid oxidation by contracting muscle, reduces plasma triglycerides and fatty acids, and increases plasma glucose and insulin. J Biol Chem. 1999;274(38):26761–6. PubMed PMID: 10480880.
12. Webb T, Whittington J, Holland AJ, Soni S, Boer H, Clarke D, et al. CD36 expression and its relationship with obesity in blood cells from people with and without Prader-Willi syndrome. Clin Genet. 2006;69(1):26–32. PubMed PMID: 16451133.
13. Ellis JM, Mentock SM, Depetrillo MA, Koves TR, Sen S, Watkins SM, et al. Mouse cardiac acyl coenzyme a synthetase 1 deficiency impairs fatty acid oxidation and induces cardiac hypertrophy. Mol Cell Biol. 2011;31(6):1252–62. PubMed PMID: 21245374, Pubmed Central PMCID: 3067914, Epub 2011/01/20. eng.
14. Chegary M, Brinke H, Ruiter JP, Wijburg FA, Stoll MS, Minkler PE, et al. Mitochondrial long chain fatty acid beta-oxidation in man and mouse. Biochim Biophys Acta. 2009;1791(8):806–15. PubMed PMID: 19465148, Pubmed Central PMCID: 2763615.
15. Smeland TE, Nada M, Cuebas D, Schulz H. NADPH-dependent beta-oxidation of unsaturated fatty acids with double bonds extending from odd-numbered carbon atoms. Proc Natl Acad Sci U S A. 1992;89(15):6673–7. PubMed PMID: 1495956. Pubmed Central PMCID: 49565.
16. Saddik M, Lopaschuk GD. The fate of arachidonic acid and linoleic acid in isolated working rat hearts containing normal or elevated levels of coenzyme A. Biochim Biophys Acta. 1991;1086(2):217–24. PubMed PMID: 1932104.
17. Wisneski JA, Gertz EW, Neese RA, Mayr M. Myocardial metabolism of free fatty acids. Studies with 14C-labeled substrates in humans. J Clin Invest. 1987;79(2):359–66. PubMed PMID: 3805273, Pubmed Central PMCID: 424073.
18. Yang Q, Li Y. Roles of PPARs on regulating myocardial energy and lipid homeostasis. J Mol Med. 2007;85(7):697–706. PubMed PMID: 17356846.
19. Lopaschuk GD, Folmes CD, Stanley WC. Cardiac energy metabolism in obesity. Circ Res. 2007;101(4):335–47. PubMed PMID: 17702980.
20. Guimbal C, Kilimann MW. A Na(+)-dependent creatine transporter in rabbit brain, muscle, heart, and kidney. cDNA cloning and functional expression. J Biol Chem. 1993;268(12):8418–21. PubMed PMID: 8473283.

21. Neubauer S. The failing heart–an engine out of fuel. N Engl J Med. 2007;356(11):1140–51. PubMed PMID: 17360992, Epub 2007/03/16. eng.
22. Pereira RO, Wende AR, Olsen C, Soto J, Rawlings T, Zhu Y, et al. GLUT1 deficiency in cardiomyocytes does not accelerate the transition from compensated hypertrophy to heart failure. J Mol Cell Cardiol. 2014;72:95–103. PubMed PMID: 24583251, Pubmed Central PMCID: 4037364.
23. Abel ED. Glucose transport in the heart. Front Biosci J Virtual Libr. 2004;9:201–15. PubMed PMID: 14766360.
24. Depre C, Vanoverschelde JL, Taegtmeyer H. Glucose for the heart. Circulation. 1999;99(4):578–88. PubMed PMID: 9927407.
25. Doehner W, Frenneaux M, Anker SD. Metabolic impairment in heart failure: the myocardial and systemic perspective. J Am Coll Cardiol. 2014;64(13):1388–400. PubMed PMID: 25257642.
26. Herrmann G, Decherd GM. The chemical nature of heart failure. Ann Intern Med. 1939;12(8):1233–44.
27. Chandler MP, Kerner J, Huang H, Vazquez E, Reszko A, Martini WZ, et al. Moderate severity heart failure does not involve a downregulation of myocardial fatty acid oxidation. Am J Physiol Heart Circ Physiol. 2004;287(4):H1538–43. PubMed PMID: 15191896.
28. Stanley WC, Recchia FA, Lopaschuk GD. Myocardial substrate metabolism in the normal and failing heart. Physiol Rev. 2005;85(3):1093–129. PubMed PMID: 15987803, Epub 2005/07/01. eng.
29. Osorio JC, Stanley WC, Linke A, Castellari M, Diep QN, Panchal AR, et al. Impaired myocardial fatty acid oxidation and reduced protein expression of retinoid X receptor-alpha in pacing-induced heart failure. Circulation. 2002;106(5):606–12. PubMed PMID: 12147544, Epub 2002/07/31. eng.
30. Remondino A, Rosenblatt-Velin N, Montessuit C, Tardy I, Papageorgiou I, Dorsaz PA, et al. Altered expression of proteins of metabolic regulation during remodeling of the left ventricle after myocardial infarction. J Mol Cell Cardiol. 2000;32(11):2025–34. PubMed PMID: 11040106.
31. Taylor M, Wallhaus TR, Degrado TR, Russell DC, Stanko P, Nickles RJ, et al. An evaluation of myocardial fatty acid and glucose uptake using PET with [18F]fluoro-6-thia-heptadecanoic acid and [18F]FDG in patients with congestive heart failure. J Nucl Med: Off Publ Soc Nucl Med. 2001;42(1):55–62. PubMed PMID: 11197981.
32. Kalsi KK, Smolenski RT, Pritchard RD, Khaghani A, Seymour AM, Yacoub MH. Energetics and function of the failing human heart with dilated or hypertrophic cardiomyopathy. Eur J Clin Invest. 1999;29(6):469–77. PubMed PMID: 10354207.
33. Razeghi P, Young ME, Alcorn JL, Moravec CS, Frazier OH, Taegtmeyer H. Metabolic gene expression in fetal and failing human heart. Circulation. 2001;104(24):2923–31. PubMed PMID: 11739307.
34. Ide T, Tsutsui H, Hayashidani S, Kang D, Suematsu N, Nakamura K, et al. Mitochondrial DNA damage and dysfunction associated with oxidative stress in failing hearts after myocardial infarction. Circ Res. 2001;88(5):529–35. PubMed PMID: 11249877.
35. Marin-Garcia J, Goldenthal MJ, Moe GW. Abnormal cardiac and skeletal muscle mitochondrial function in pacing-induced cardiac failure. Cardiovasc Res. 2001;52(1):103–10. PubMed PMID: 11557238.
36. Nascimben L, Ingwall JS, Pauletto P, Friedrich J, Gwathmey JK, Saks V, et al. Creatine kinase system in failing and nonfailing human myocardium. Circulation. 1996;94(8):1894–901. PubMed PMID: 8873665.
37. De Sousa E, Veksler V, Minajeva A, Kaasik A, Mateo P, Mayoux E, et al. Subcellular creatine kinase alterations. Implications in heart failure. Circ Res. 1999;85(1):68–76. PubMed PMID: 10400912.
38. Starling RC, Hammer DF, Altschuld RA. Human myocardial ATP content and in vivo contractile function. Mol Cell Biochem. 1998;180(1–2):171–7. PubMed PMID: 9546644.
39. Beer M, Seyfarth T, Sandstede J, Landschutz W, Lipke C, Kostler H, et al. Absolute concentrations of high-energy phosphate metabolites in normal, hypertrophied, and failing human

myocardium measured noninvasively with (31)P-SLOOP magnetic resonance spectroscopy. J Am Coll Cardiol. 2002;40(7):1267–74. PubMed PMID: 12383574.
40. Shen W, Asai K, Uechi M, Mathier MA, Shannon RP, Vatner SF, et al. Progressive loss of myocardial ATP due to a loss of total purines during the development of heart failure in dogs: a compensatory role for the parallel loss of creatine. Circulation. 1999;100(20):2113–8. PubMed PMID: 10562269.
41. Ten Hove M, Chan S, Lygate C, Monfared M, Boehm E, Hulbert K, et al. Mechanisms of creatine depletion in chronically failing rat heart. J Mol Cell Cardiol. 2005;38(2):309–13. PubMed PMID: 15698837.
42. Neubauer S, Remkes H, Spindler M, Horn M, Wiesmann F, Prestle J, et al. Downregulation of the Na(+)-creatine cotransporter in failing human myocardium and in experimental heart failure. Circulation. 1999;100(18):1847–50. PubMed PMID: 10545427.
43. Neubauer S, Krahe T, Schindler R, Horn M, Hillenbrand H, Entzeroth C, et al. 31P magnetic resonance spectroscopy in dilated cardiomyopathy and coronary artery disease. Altered cardiac high-energy phosphate metabolism in heart failure. Circulation. 1992;86(6):1810–8. PubMed PMID: 1451253.
44. Liu J, Wang C, Murakami Y, Gong G, Ishibashi Y, Prody C, et al. Mitochondrial ATPase and high-energy phosphates in failing hearts. Am J Physiol Heart Circ Physiol. 2001;281(3):H1319–26. PubMed PMID: 11514303.
45. Zhou X, Chen J. Is treatment with trimetazidine beneficial in patients with chronic heart failure? PLoS One. 2014;9(5):e94660. PubMed PMID: 24797235, Pubmed Central PMCID: 4010408.
46. Fragasso G, Palloshi A, Puccetti P, Silipigni C, Rossodivita A, Pala M, et al. A randomized clinical trial of trimetazidine, a partial free fatty acid oxidation inhibitor, in patients with heart failure. J Am Coll Cardiol. 2006;48(5):992–8. PubMed PMID: 16949492.
47. Fragasso G, Perseghin G, De Cobelli F, Esposito A, Palloshi A, Lattuada G, et al. Effects of metabolic modulation by trimetazidine on left ventricular function and phosphocreatine/adenosine triphosphate ratio in patients with heart failure. Eur Heart J. 2006;27(8):942–8. PubMed PMID: 16510466.
48. Uriel N, Gonzalez-Costello J, Mignatti A, Morrison KA, Nahumi N, Colombo PC, et al. Adrenergic activation, fuel substrate availability, and insulin resistance in patients with congestive heart failure. JACC Heart Fail. 2013;1(4):331–7. PubMed PMID: 24621937.
49. Szabo T, Postrach E, Mahler A, Kung T, Turhan G, von Haehling S, et al. Increased catabolic activity in adipose tissue of patients with chronic heart failure. Eur J Heart Fail. 2013;15(10):1131–7. PubMed PMID: 23696611.
50. Shimizu I, Yoshida Y, Katsuno T, Tateno K, Okada S, Moriya J, et al. p53-induced adipose tissue inflammation is critically involved in the development of insulin resistance in heart failure. Cell Metab. 2012;15(1):51–64. PubMed PMID: 22225876.
51. Szabo T, Scherbakov N, Sandek A, Kung T, von Haehling S, Lainscak M, et al. Plasma adiponectin in heart failure with and without cachexia: catabolic signal linking catabolism, symptomatic status, and prognosis. Nutr Metab Cardiovasc Dis. 2014;24(1):50–6. PubMed PMID: 23791298.
52. Frey N, Katus HA, Olson EN, Hill JA. Hypertrophy of the heart: a new therapeutic target? Circulation. 2004;109(13):1580–9. PubMed PMID: 15066961.
53. Heineke J, Molkentin JD. Regulation of cardiac hypertrophy by intracellular signalling pathways. Nat Rev Mol Cell Biol. 2006;7(8):589–600. PubMed PMID: 16936699.
54. Chatham JC, Young ME. Metabolic remodeling in the hypertrophic heart: fuel for thought. Circ Res. 2012;111(6):666–8. PubMed PMID: 22935530, Pubmed Central PMCID: 3462817.
55. Kolwicz Jr SC, Tian R. Glucose metabolism and cardiac hypertrophy. Cardiovasc Res. 2011;90(2):194–201. PubMed PMID: 21502371, Pubmed Central PMCID: 3078804, Epub 2011/04/20. eng.
56. Taegtmeyer H, Sen S, Vela D. Return to the fetal gene program: a suggested metabolic link to gene expression in the heart. Ann N Y Acad Sci. 2010;1188:191–8. PubMed PMID: 20201903, Pubmed Central PMCID: 3625436.

57. Akki A, Smith K, Seymour AM. Compensated cardiac hypertrophy is characterised by a decline in palmitate oxidation. Mol Cell Biochem. 2008;311(1–2):215–24. PubMed PMID: 18278440.
58. Arany Z, Novikov M, Chin S, Ma Y, Rosenzweig A, Spiegelman BM. Transverse aortic constriction leads to accelerated heart failure in mice lacking PPAR-gamma coactivator 1alpha. Proc Natl Acad Sci U S A. 2006;103(26):10086–91. PubMed PMID: 16775082, Pubmed Central PMCID: 1502510.
59. Barger PM, Brandt JM, Leone TC, Weinheimer CJ, Kelly DP. Deactivation of peroxisome proliferator-activated receptor-alpha during cardiac hypertrophic growth. J Clin Invest. 2000;105(12):1723–30. PubMed PMID: 10862787, Pubmed Central PMCID: 378509, Epub 2000/06/23. eng.
60. Sack MN, Disch DL, Rockman HA, Kelly DP. A role for Sp and nuclear receptor transcription factors in a cardiac hypertrophic growth program. Proc Natl Acad Sci U S A. 1997;94(12):6438–43. PubMed PMID: 9177236. Pubmed Central PMCID: 21068.
61. Aitman TJ, Glazier AM, Wallace CA, Cooper LD, Norsworthy PJ, Wahid FN, et al. Identification of Cd36 (Fat) as an insulin-resistance gene causing defective fatty acid and glucose metabolism in hypertensive rats. Nat Genet. 1999;21(1):76–83. PubMed PMID: 9916795.
62. Vork MM, Trigault N, Snoeckx LH, Glatz JF, van der Vusse GJ. Heterogeneous distribution of fatty acid-binding protein in the hearts of Wistar Kyoto and spontaneously hypertensive rats. J Mol Cell Cardiol. 1992;24(3):317–21. PubMed PMID: 1625352.
63. Christian B, El Alaoui-Talibi Z, Moravec M, Moravec J. Palmitate oxidation by the mitochondria from volume-overloaded rat hearts. Mol Cell Biochem. 1998;180(1–2):117–28. PubMed PMID: 9546638.
64. el Alaoui-Talibi Z, Landormy S, Loireau A, Moravec J. Fatty acid oxidation and mechanical performance of volume-overloaded rat hearts. Am J Physiol. 1992;262(4 Pt 2):H1068–74. PubMed PMID: 1533101.
65. Saeedi R, Saran VV, Wu SS, Kume ES, Paulson K, Chan AP, et al. AMP-activated protein kinase influences metabolic remodeling in H9c2 cells hypertrophied by arginine vasopressin. Am J Physiol Heart Circ Physiol. 2009;296(6):H1822–32. PubMed PMID: 19376807.
66. Nascimben L, Ingwall JS, Lorell BH, Pinz I, Schultz V, Tornheim K, et al. Mechanisms for increased glycolysis in the hypertrophied rat heart. Hypertension. 2004;44(5):662–7. PubMed PMID: 15466668.
67. Marsin AS, Bertrand L, Rider MH, Deprez J, Beauloye C, Vincent MF, et al. Phosphorylation and activation of heart PFK-2 by AMPK has a role in the stimulation of glycolysis during ischaemia. Curr Biol CB. 2000;10(20):1247–55. PubMed PMID: 11069105.
68. Allard MF, Wambolt RB, Longnus SL, Grist M, Lydell CP, Parsons HL, et al. Hypertrophied rat hearts are less responsive to the metabolic and functional effects of insulin. Am J Physiol Endocrinol Metab. 2000;279(3):E487–93. PubMed PMID: 10950814.
69. Allard MF, Schonekess BO, Henning SL, English DR, Lopaschuk GD. Contribution of oxidative metabolism and glycolysis to ATP production in hypertrophied hearts. Am J Physiol. 1994;267(2 Pt 2):H742–50. PubMed PMID: 8067430.
70. Wambolt RB, Lopaschuk GD, Brownsey RW, Allard MF. Dichloroacetate improves postischemic function of hypertrophied rat hearts. J Am Coll Cardiol. 2000;36(4):1378–85. PubMed PMID: 11028498.
71. El Alaoui-Talibi Z, Guendouz A, Moravec M, Moravec J. Control of oxidative metabolism in volume-overloaded rat hearts: effect of propionyl-L-carnitine. Am J Physiol. 1997;272(4 Pt 2):H1615–24. PubMed PMID: 9139943.
72. Taegtmeyer H, Overturf ML. Effects of moderate hypertension on cardiac function and metabolism in the rabbit. Hypertension. 1988;11(5):416–26. PubMed PMID: 3366475.
73. Smith SH, Kramer MF, Reis I, Bishop SP, Ingwall JS. Regional changes in creatine kinase and myocyte size in hypertensive and nonhypertensive cardiac hypertrophy. Circ Res. 1990;67(6):1334–44. PubMed PMID: 2147129.
74. Owen OE, Kalhan SC, Hanson RW. The key role of anaplerosis and cataplerosis for citric acid cycle function. J Biol Chem. 2002;277(34):30409–12. PubMed PMID: 12087111.

75. Pound KM, Sorokina N, Ballal K, Berkich DA, Fasano M, Lanoue KF, et al. Substrate-enzyme competition attenuates upregulated anaplerotic flux through malic enzyme in hypertrophied rat heart and restores triacylglyceride content: attenuating upregulated anaplerosis in hypertrophy. Circ Res. 2009;104(6):805–12. PubMed PMID: 19213957, Pubmed Central PMCID: 2908318, Epub 2009/02/14. eng.
76. Sorokina N, O'Donnell JM, McKinney RD, Pound KM, Woldegiorgis G, LaNoue KF, et al. Recruitment of compensatory pathways to sustain oxidative flux with reduced carnitine palmitoyltransferase I activity characterizes inefficiency in energy metabolism in hypertrophied hearts. Circulation. 2007;115(15):2033–41. PubMed PMID: 17404155, Epub 2007/04/04. eng.
77. Zimmer HG. Regulation of and intervention into the oxidative pentose phosphate pathway and adenine nucleotide metabolism in the heart. Mol Cell Biochem. 1996;160–161:101–9. PubMed PMID: 8901462.
78. Meerson FZ, Spiritchev VB, Pshennikova MG, Djachkova LV. The role of the pentose-phosphate pathway in adjustment of the heart to a high load and the development of myocardial hypertrophy. Experientia. 1967;23(7):530–2. PubMed PMID: 4228586.
79. Zimmer HG, Ibel H, Steinkopff G. Studies on the hexose monophosphate shunt in the myocardium during development of hypertrophy. Adv Myocardiol. 1980;1:487–92. PubMed PMID: 6156478.
80. Young ME, Yan J, Razeghi P, Cooksey RC, Guthrie PH, Stepkowski SM, et al. Proposed regulation of gene expression by glucose in rodent heart. Gene Regul Syst Biol. 2007;1:251–62. PubMed PMID: 19936093, Pubmed Central PMCID: 2759127.
81. Lunde IG, Aronsen JM, Kvaloy H, Qvigstad E, Sjaastad I, Tonnessen T, et al. Cardiac O-GlcNAc signaling is increased in hypertrophy and heart failure. Physiol Genomics. 2012;44(2):162–72. PubMed PMID: 22128088.
82. Liao R, Jain M, Cui L, D'Agostino J, Aiello F, Luptak I, et al. Cardiac-specific overexpression of GLUT1 prevents the development of heart failure attributable to pressure overload in mice. Circulation. 2002;106(16):2125–31. PubMed PMID: 12379584.
83. Domenighetti AA, Danes VR, Curl CL, Favaloro JM, Proietto J, Delbridge LM. Targeted GLUT-4 deficiency in the heart induces cardiomyocyte hypertrophy and impaired contractility linked with Ca(2+) and proton flux dysregulation. J Mol Cell Cardiol. 2010;48(4):663–72. PubMed PMID: 19962383.
84. Kolwicz Jr SC, Olson DP, Marney LC, Garcia-Menendez L, Synovec RE, Tian R. Cardiac-specific deletion of acetyl CoA carboxylase 2 prevents metabolic remodeling during pressure-overload hypertrophy. Circ Res. 2012;111(6):728–38. PubMed PMID: 22730442, Pubmed Central PMCID: 3434870.
85. Karamanlidis G, Garcia-Menendez L, Kolwicz Jr SC, Lee CF, Tian R. Promoting PGC-1alpha-driven mitochondrial biogenesis is detrimental in pressure-overloaded mouse hearts. Am J Physiol Heart Circ Physiol. 2014;307(9):H1307–16. PubMed PMID: 25172896. Pubmed Central PMCID: 4217009.
86. Okere IC, Young ME, McElfresh TA, Chess DJ, Sharov VG, Sabbah HN, et al. Low carbohydrate/high-fat diet attenuates cardiac hypertrophy, remodeling, and altered gene expression in hypertension. Hypertension. 2006;48(6):1116–23. PubMed PMID: 17060511.
87. Young ME, Laws FA, Goodwin GW, Taegtmeyer H. Reactivation of peroxisome proliferator-activated receptor alpha is associated with contractile dysfunction in hypertrophied rat heart. J Biol Chem. 2001;276(48):44390–5. PubMed PMID: 11574533.
88. Pulinilkunnil T, Kienesberger PC, Nagendran J, Sharma N, Young ME, Dyck JR. Cardiac-specific adipose triglyceride lipase overexpression protects from cardiac steatosis and dilated cardiomyopathy following diet-induced obesity. Int J Obes (Lond). 2013;38(2):205–15. PubMed PMID: 23817015, Epub 2013/07/03. Eng.
89. Kenchaiah S, Evans JC, Levy D, Wilson PW, Benjamin EJ, Larson MG, et al. Obesity and the risk of heart failure. N Engl J Med. 2002;347(5):305–13. PubMed PMID: 12151467, Epub 2002/08/02. eng.
90. Harmancey R, Wilson CR, Taegtmeyer H. Adaptation and maladaptation of the heart in obesity. Hypertension. 2008;52(2):181–7. PubMed PMID: 18574077, Epub 2008/06/25. eng.

91. Buchanan J, Mazumder PK, Hu P, Chakrabarti G, Roberts MW, Yun UJ, et al. Reduced cardiac efficiency and altered substrate metabolism precedes the onset of hyperglycemia and contractile dysfunction in two mouse models of insulin resistance and obesity. Endocrinology. 2005;146(12):5341–9. PubMed PMID: 16141388.
92. Abel ED, Litwin SE, Sweeney G. Cardiac remodeling in obesity. Physiol Rev. 2008;88(2):389–419. PubMed PMID: 18391168, Pubmed Central PMCID: 2915933, Epub 2008/04/09. eng.
93. Zhou YT, Grayburn P, Karim A, Shimabukuro M, Higa M, Baetens D, et al. Lipotoxic heart disease in obese rats: implications for human obesity. Proc Natl Acad Sci U S A. 2000;97(4):1784–9. PubMed PMID: 10677535. Pubmed Central PMCID: 26513. Epub 2000/03/04. eng.
94. Borradaile NM, Schaffer JE. Lipotoxicity in the heart. Curr Hypertens Rep. 2005;7(6):412–7. PubMed PMID: 16386196, Epub 2006/01/03. eng.
95. Goldberg IJ, Trent CM, Schulze PC. Lipid metabolism and toxicity in the heart. Cell Metab. 2012;15(6):805–12. PubMed PMID: 22682221, Pubmed Central PMCID: 3387529, Epub 2012/06/12. eng.
96. Drosatos K, Schulze PC. Cardiac lipotoxicity: molecular pathways and therapeutic implications. Curr Heart Fail Rep. 2013;10(2):109–21. PubMed PMID: 23508767, Pubmed Central PMCID: 3647019.
97. Chiu HC, Kovacs A, Blanton RM, Han X, Courtois M, Weinheimer CJ, et al. Transgenic expression of fatty acid transport protein 1 in the heart causes lipotoxic cardiomyopathy. Circ Res. 2005;96(2):225–33. PubMed PMID: 15618539, Epub 2004/12/25. eng.
98. Chiu HC, Kovacs A, Ford DA, Hsu FF, Garcia R, Herrero P, et al. A novel mouse model of lipotoxic cardiomyopathy. J Clin Invest. 2001;107(7):813–22. PubMed PMID: 11285300, Pubmed Central PMCID: 199569, Epub 2001/04/04. eng.
99. Lee Y, Naseem RH, Duplomb L, Park BH, Garry DJ, Richardson JA, et al. Hyperleptinemia prevents lipotoxic cardiomyopathy in acyl CoA synthase transgenic mice. Proc Natl Acad Sci U S A. 2004;101(37):13624–9. PubMed PMID: 15347805, Pubmed Central PMCID: 518804, Epub 2004/09/07. eng.
100. Carley AN, Severson DL. Fatty acid metabolism is enhanced in type 2 diabetic hearts. Biochim Biophys Acta. 2005;1734(2):112–26. PubMed PMID: 15904868.
101. Young ME, Guthrie PH, Razeghi P, Leighton B, Abbasi S, Patil S, et al. Impaired long-chain fatty acid oxidation and contractile dysfunction in the obese Zucker rat heart. Diabetes. 2002;51(8):2587–95. PubMed PMID: 12145175, Epub 2002/07/30. eng.
102. McGavock JM, Victor RG, Unger RH, Szczepaniak LS. Adiposity of the heart, revisited. Ann Intern Med. 2006;144(7):517–24. PubMed PMID: 16585666, Epub 2006/04/06. eng.
103. McGavock JM, Lingvay I, Zib I, Tillery T, Salas N, Unger R, et al. Cardiac steatosis in diabetes mellitus: a 1H-magnetic resonance spectroscopy study. Circulation. 2007;116(10):1170–5. PubMed PMID: 17698735, Epub 2007/08/19. eng.
104. Rijzewijk LJ, van der Meer RW, Smit JW, Diamant M, Bax JJ, Hammer S, et al. Myocardial steatosis is an independent predictor of diastolic dysfunction in type 2 diabetes mellitus. J Am Coll Cardiol. 2008;52(22):1793–9. PubMed PMID: 19022158, Epub 2008/11/22. eng.
105. Finck BN, Lehman JJ, Leone TC, Welch MJ, Bennett MJ, Kovacs A, et al. The cardiac phenotype induced by PPARalpha overexpression mimics that caused by diabetes mellitus. J Clin Invest. 2002;109(1):121–30. PubMed PMID: 11781357, Pubmed Central PMCID: 150824, Epub 2002/01/10. eng.
106. Son NH, Park TS, Yamashita H, Yokoyama M, Huggins LA, Okajima K, et al. Cardiomyocyte expression of PPARgamma leads to cardiac dysfunction in mice. J Clin Invest. 2007;117(10):2791–801. PubMed PMID: 17823655, Pubmed Central PMCID: 1964508.
107. Tang WH, Maroo A. PPARgamma agonists: safety issues in heart failure. Diabetes Obes Metab. 2007;9(4):447–54. PubMed PMID: 17587386.
108. Ussher JR, Fillmore N, Keung W, Mori J, Beker DL, Wagg CS, et al. Trimetazidine therapy prevents obesity-induced cardiomyopathy in mice. Can J Cardiol. 2014;30(8):940–4. PubMed PMID: 25064584.

109. Turer AT, Hill JA, Elmquist JK, Scherer PE. Adipose tissue biology and cardiomyopathy: translational implications. Circ Res. 2012;111(12):1565–77. PubMed PMID: 23223931, Pubmed Central PMCID: 3532954.
110. Sun K, Kusminski CM, Scherer PE. Adipose tissue remodeling and obesity. J Clin Invest. 2011;121(6):2094–101. PubMed PMID: 21633177, Pubmed Central PMCID: 3104761.
111. Nakamura K, Fuster JJ, Walsh K. Adipokines: a link between obesity and cardiovascular disease. J Cardiol. 2014;63(4):250–9. PubMed PMID: 24355497, Pubmed Central PMCID: 3989503.