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Review:

Metabolic remodeling in chronic heart failure

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Abstract: Although the management of chronic heart failure (CHF) has made enormous progress over the past decades, CHF is still a tremendous medical and societal burden. Metabolic remodeling might play a crucial role in the pathophysiology of CHF. The characteristics and mechanisms of metabolic remodeling remained unclear, and the main hypothesis might include the changes in the availability of metabolic substrate and the decline of metabolic capability. In the early phases of the disease, metabolism shifts toward carbohydrate utilization from fatty acids (FAs) oxidation. Along with the progress of the disease, the increasing level of the hyperadrenergic state and insulin resistance cause the changes that shift back to a greater FA uptake and oxidation. In addition, a growing body of experimental and clinical evidence suggests that the improvement in the metabolic capability is likely to be more significant than the selection of the substrate.

Key words: Chronic heart failure (CHF), Metabolic remodeling, Metabolic substrate, Metabolic capability
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1 Introduction

Chronic heart failure (CHF) is a complex clinical syndrome resulted from any structural or functional cardiac disorder that impairs the systolic and/or diastolic ability of the ventricle. Approximately 1%–2% of the adult population in developed countries suffer from CHF, with the prevalence rising to ≥10% among persons 70 years of age or older (McMurray *et al.*, 2012). CHF is a tremendous medical and societal burden. For the USA alone, the total annual cost of treatment for CHF is approximately USD28 billion. The number will continue to increase considering an aging population and the improved treatment of CHF (Neubauer, 2007).

The past decades have witnessed considerable progress in the treatment of CHF. The angiotensin-converting-enzyme inhibitors (ACEIs) (Hunt *et al.*, 2009; McMurray *et al.*, 2012), β receptor blockers (Hunt *et al.*, 2009; McMurray *et al.*, 2012), aldosterone antagonists (Pitt *et al.*, 2003; Zannad *et al.*, 2011), and resynchronization therapy (RCT) (Cleland *et al.*, 2005) have been wildly used in clinical applications and achieve remarkable outcomes. Nonetheless, CHF is still associated with an annual mortality rate of 10% (Neubauer, 2007). Further exploration of the mechanisms of CHF and its corresponding interference is still one of the primary tasks in cardiology. A growing body of evidence suggests that metabolic remodeling might play a crucial role in the pathophysiology of CHF.

2 Mechanism of chronic heart failure (CHF)

2.1 Neurohormone and ventricular remodeling

The classical mechanism of CHF includes neurohormone and ventricular remodeling. The portfolio of neurohormonal mechanisms that have been described thus far includes activation of the adrenergic nervous system and the renin-angiotensin system (RAS), which are responsible for maintaining cardiac output through increased retention of salt and water,

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peripheral arterial vasoconstriction, and increased contractility, and activation of the inflammatory mediators. The overexpression of the portfolios of biologically active molecules contributes to the disease's progression by virtue of the deleterious effects exerted on the heart and circulation. Ventricular remodeling is a significant pathophysiology in CHF, which consists of three levels: (1) organic remodeling (Kemp and Conte, 2012) that means the changes in the left ventricular (LV) mass, volume, shape, and composition of the heart; (2) cellular remodeling (Opie *et al.*, 2006; Kehat and Molkentin, 2010) that means myocyte hypertrophy, alteration in the contractile properties of the myocyte, progressive necrosis, apoptosis, and autophagic cell death; (3) subcellular remodeling (Shah and Mann, 2011) that means the varying degrees of changes in biochemical compositions and molecular structures of various subcellular organelles, such as extracellular matrix, sarcolemma, sarcoplasmic reticulum, myofibrils, mitochondria, energetic metabolism, and nucleus (Dhalla *et al.*, 2009).

2.2 Metabolic remodeling

Decherd and Visscher (1934) proposed the concept of energy-starvation, which stated that varying degrees of decrease in the creatinine (Cr), adenosine triphosphate (ATP), and phosphocreatine (PCr) exist in failing myocardium. The hypothesis was put forward in late years by some recent studies (Ventura-Clapier *et al.*, 2004; Neubauer, 2007; Doenst and Abel, 2011; Azevedo *et al.*, 2013).

Recently, some novel pharmaceuticals, e.g., ghrelin (Ledderose *et al.*, 2011) and allopurinol (Hirsch *et al.*, 2012; Opie, 2012) have been used to treat CHF by improving the metabolism of myocardia. The most significant changes among metabolic remodeling are the availability of metabolic substrate and the decline of metabolic capability.

3 Availability of metabolic substrate

3.1 Energy metabolism in the normal heart

In the normal heart, this requirement of energy metabolism is met by the daily synthesis of approximately 30 kg of ATP (Ashrafian and Frenneaux, 2007; Murray *et al.*, 2007). Exogenous substrates, such as fatty acids (FAs), glucose, pyruvate, lactate, and ketone bodies, generate energy through oxidative phosphorylation. The utilization of various substrates was influenced by the concentration of substrates (Ardehali *et al.*, 2012), the supply of oxygen (Sabbah *et al.*, 2000; Giordano, 2005), the workload of the heart, and the systemic level of hormone (Tuunanen *et al.*, 2006a), etc. Approximately 60%–70% of the ATP requirement is met by the catabolism of FAs via β-oxidation, the tricarboxylic acid cycle, and oxidative phosphorylation in the mitochondria (Rosca and Hoppel, 2010). During the postprandial period and during exercise, the relative contribution of glucose catabolism increases and produces approximately 10%–40% of ATP (Abozguia *et al.*, 2006). About 60%–70% of ATP hydrolysis fuels contractile shortening, and the remaining 30%–40% is primarily used for ion pumps (Nagoshi *et al.*, 2011). The metabolisms of FAs and glucose are highly coupled in myocytes, with an increase in FAs metabolism causing a decrease in glucose metabolism, and vice versa. This high coupling was termed as "Randle cycle" in Randle *et al.* (1963).

3.2 Fetal metabolic phenotype

In CHF, the recognition concerning substrate utilization has not reached a consensus. One prevalent view supported by experimental (Recchia *et al.*, 1998) and most clinical (Dávila-Román *et al.*, 2002; de las Fuentes *et al.*, 2003) studies is the "reversion to the fetal metabolic phenotype" (Rajabi *et al.*, 2007; Turer *et al.*, 2010). The essence of reversion is a shift from a FAs metabolism to a glucose metabolism in failing myocardia, which is analogous to the metabolic behavior of the fetal heart. In utero, where oxygen tension is low and insulin levels are relatively high, glucose metabolism is the predominate source of myocardial fuel (Turer *et al.*, 2010). In addition, the reversion might involve the expression of some fetal genes (Finck and Kelly, 2006; Dillon *et al.*, 2012).

3.2.1 Features and mechanisms of the decline of FAs metabolism

The decline of FAs metabolism could be explained by some hypothesis. FAs provide the highest energy (ATP) yield per molecule of FAs through β-oxidation (Nagoshi *et al.*, 2011). However, glucose metabolism has a greater efficiency in producing high

energy phosphates (Rosano *et al.*, 2008; Nagoshi *et al.*, 2011). In other words, for an equivalent amount of ATP synthesized, the FA oxidation requires approximately 10%–15% more oxygen compared to that of the glucose oxidation (Abozguia *et al.*, 2009). Consequently, the improvement of metabolic efficiency by the shift is considered to be adaptive (Nagoshi *et al.*, 2011). Its mechanism may include:

1. The number and size of mitochondria are decreased, and their functions are impaired (Turer *et al.*, 2010).

2. Depression of some genes (Razeghi *et al.*, 2001) encoding the FAs metabolism and down-regulation of their corresponding transcription factors (Huss and Kelly, 2005). Some of them widely studied are: (1) the peroxisome proliferator-activated receptor (PPAR) family (Finck and Kelly, 2006; Dillon *et al.*, 2012), which comprises three isoforms, PPARα, PPARβ, and PPARγ. All three isoforms affect the cardiac lipid metabolism, but the primary regulator appears to be PPARα (Karbowska *et al.*, 2003), which controls the expression of enzymes directly involved in FA oxidation (Neubauer, 2007). Deletion of PPARα in mice results in decreased FA oxidation and increased glucose oxidation in the heart (Arany *et al.*, 2005). (2) PPARγ coativator-1 (PGC-1) proteins family (Rowe *et al.*, 2010). PGC-1 enhances the activity of transcription by binding with PPAR. Three important members of PGC-1 are PGC-1α (Sihag *et al.*, 2009), PGC-1β, and PGC-1-related coactivator (PRC). Sihag *et al.* (2009) observed a significant decrease of PGC-1α in human failing hearts. Deletion of PGC-1α and/or PGC-1β results in decreased expression of proteins in oxidative phosphorylation, and increased expression of foetal metabolicgenes (Lai *et al.*, 2008). (3) The retinoid X receptor-α(RXRα) (Lionetti *et al.*, 2011). In fact, PPARα/RXRα/PGC-1α forms as a heterotrimer, the transcriptional activation complex. When activated by long-chain FAs, the heterotrimer is able to bind specific responsive elements regulating the expression of genes that encode enzymes involved in FA oxidation (Lionetti *et al.*, 2011).

Carnitine palmitoyltransferase type 1 (CPT-1) and medium chain acyl-CoA dehydrogenase (MCAD) were noteworthy enzymes. The former is a key rate-limiting enzyme responsible for transferring acyl-CoA into mitochondria (Martin *et al.*, 2000). The latter is one of the enzymes of FA β-oxidation. Some studies reported in heart failure models the decline of the protein levels of PPARα/RXRα/PGC-1α (Karbowska *et al.*, 2003; Sarma *et al.*, 2012), as well as the suppressed expression of CPT-1 (Sihag *et al.*, 2009; Karamanlidis *et al.*, 2010) and/or MCAD (Riehle and Abel, 2012). These changes in the cellular and molecular levels were considered as potential mechanisms for the decline of FAs metabolism (Fig. 1).

3.2.2 Mechanisms of incline of glucose metabolism

The incline of glucose metabolism is supposed to be a reaction to the decrease of FA oxidation. Its mechanism involved adenosine monophosphate-activated protein kinase (AMPK) (Beauloye *et al.*, 2011) that is considered as the 'fuel gauge' of the cell, sensing states of low energy and activating practically all energy-producing processes (Doenst and Abel, 2011). Impaired myocardial energetics resulted from the decrease of FA oxidation triggers AMPK, which promotes the translocation of the glucose transporters (GLUTs) onto the plasma membrane and enhances glucose uptake (Kolwicz and Tian, 2011). In addition, AMPK stimulates phosphofructokinase 2 (PFK2), which generates fructose-2,6-diphosphate acting as a potent allosteric stimulant of the rate-limiting enzyme, PFK1 (Marsin *et al.*, 2000). This partially explains that inclined glucose metabolism mainly manifests in other catabolic pathways (e.g., glycolysis) instead of glucose oxidation (Kolwicz and Tian, 2011) (Fig. 1).

3.3 Non-fetal metabolic phenotype

3.3.1 Characteristics of substrate utilization

It is crucial to recognize that the concept of fetal-metabolic phenotype has not been observed in all studies of CHF. Some other studies reported opposite results: up-regulation of FAs metabolism and down-regulation of glucose use in failing myocardium—the non-fetal metabolic phenotype (Paolisso *et al.*, 1994; Taylor *et al.*, 2001).

3.3.2 Potential causation

The phenomenon of a shift towards FAs metabolism might be associated with two general metabolic backgrounds in CHF: the hyperadrenergic state and insulin resistance. The compensatory

hyperadrenergic state that develops in CHF promotes the degradation of adipose tissue elevating the blood FA. These excess circulating FAs block the uptake of glucose by muscle (Opie and Knuuti, 2009). Excess FAs can also cause abnormalities of mitochondrial function, including excessive formation of reactive oxygen species (ROS) (Tsutsui *et al.*, 2011) and oxygen wastage (Opie and Knuuti, 2009). The high levels of plasma FAs activate uncoupling protein-2 and -3 (UCP-2 and -3) (Hesselink and Schrauwen, 2005) which descend the gradient of proton in the mitochondria and cause oxygen wastage (Fig. 2).

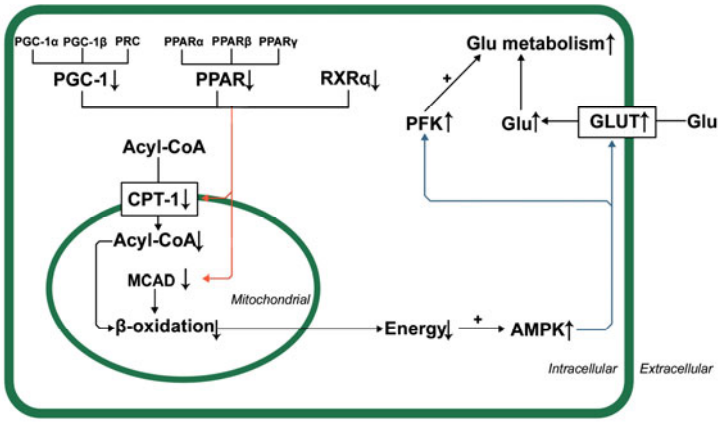
Insulin resistance is prevalent in CHF and its potential mechanisms (Petersen and Shulman, 2006; Tuunanen and Knuuti, 2011) contain: chronically increased sympathetic nervous system (SNS) activity which leads to decreased insulin secretion, insulin responsiveness, and skeletal muscle blood flow. In addition, loss of skeletal muscle mass and sedentary lifestyle of the CHF patient might reduce insulin sensitivity. No matter what the hyperadrenegic state or insulin resistance might cause descent of the glucose metabolism (Fig. 2).

4 Metabolic capability

Metabolic capability means changes in the energy-producing processes of the myocardium under conditions that directly or indirectly lead to CHF (Doenst and Abel, 2011). As mentioned above, in different conditions, such as various CHF etiologies, different clinical staging, and metabolic backgrounds, the characteristics and mechanisms of the availability of metabolic substrate are diverse. Nonetheless, the following ideas, which reflect the myocardial metabolic capability, have been proposed beyond the one-sided emphasis on the shift of substrate utilization in CHF.

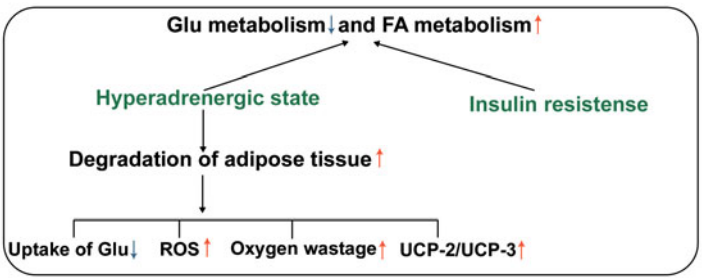
4.1 Metabolic extremes

Metabolism intervened by humans, either as fuel overabundance or absence, can cause lipotoxicity or glucotoxicity, both of which are adverse for the failing heart and lead to contractile dysfunction (Taegtmeyer and Ballal, 2006; Turer *et al.*, 2010). In other words, both glucose and FA oxidation are required for optimal function of the failing heart,



PPAR: peroxisome proliferator-activated receptor;
PGC-1: PPARγ coativator-1;
RXRα: retinoid X receptor-α;
CPT-1: carnitine palmitoyltransferase type 1;
MCAD: medium chain acyl-CoA dehydrogenase;
AMPK: adenosine monophosphate-activated protein kinase;
PFK: phosphofructokinase;
GLUT: glucose transporter;
Glu: glucose

Fig. 1 Mechanism of fetal metabolic phenotype
The decline of FAs metabolism and the incline of glucose metabolism



ROS: reactive oxygen species;
UCP: uncoupling protein;
Glu: glucose

Fig. 2 Mechanism of non-fetal metabolic phenotype
The decline of glucose metabolism and the incline of FAs metabolism

which is supported by clinical studies of acipimox (a nicotinic acid derivatives with profound anti-lipolytic effects and can progressively decrease in the plasma level of FAs). Acipimox was hypothesized to enhance myocardium glucose metabolism and cardiac function by decreasing FAs metabolism (Tuunanen *et al.*, 2006b). However, this drug was found to be associated with a significant fall in cardiac work and efficiency. One possible explanation is the fact that although FA oxidation is reduced in the failing heart, it still represents a critical source of energy and its further inhibition by an aggressive pharmacological treatment would necessarily cause a functional derangement (Lionetti *et al.*, 2011).

4.2 Metabolic flexibility

The healthy heart considered as a substrate omnivore has an ability to respond to a changing workload, substrate availability, circulating hormones, coronary flow, and fuel metabolism by choosing the right substrate at the right moment (Murray *et al.*, 2007; Turer *et al.*, 2010; Ventura-Clapier *et al.*, 2011).

4.3 Metabolic inflexibility

Metabolic inflexibility means that the altered energy system of myocyte attenuates flexibility of the metabolism. Namely, failing myocyte lacks the metabolism ability to deal with hemodynamic stress (Yan *et al.*, 2009; Vadvalkar *et al.*, 2013).

4.4 Evidences from pharmacological treatment

4.4.1 Trimetazidine and L-carnitine

Trimetazidine, inhibitors of FAs β-oxidation, is a partial inhibitor of the terminal enzyme in β-oxidation long-chain 3-ketoacyl thiolase. Several studies have shown that trimetazidine is well tolerated in CHF patients. Results generally support either a trend or significant improvement in the LV ejection fraction concomitant with a reduction in constraction (Sisakian *et al.*, 2007; Zhang *et al.*, 2012).

In contrast, L-carnitine is a naturally occurring essential cofactor of FA metabolism and is synthesized endogenously or obtained from dietary sources. A systematic review and meta-analysis of 13 controlled trials (n=3629) was conducted to determine the effects of L-carnitine vs. placebo or control on mortality, CHF, etc. Compared with the placebo or control, L-carnitine can significantly reduce these outcome events (Dinicolantonio *et al.*, 2013). Obviously, substrate utilizations of the two drugs are just the opposite; however, they can also improve the prognosis of CHF, which in itself indicates that the choice of substrate may not be important. The critical issue could be the metabolic capability. The application of thiamin in CHF may provide some clues in this regard.

4.4.2 Thiamin

Thiamin plays an important role in the reaction of the central pathway for energy production. It is a catalyst in the reactions of pyruvate to acetyl CoA and α-ketoglutarate to succinyl CoA in the Krebs cycle and functions as a coenzyme with transketolase. A 2-carbon unit from α-ketose is transferred to an aldose by transketolase in the pentose phosphate pathway (Wooley, 2008). A cross-sectional study reported that 33% of hospitalized patients with CHF have erythrocyte thiamin pyrophosphate levels suggestive of thiamin deficiency (Hanninen *et al.*, 2006). It is possible that thiamin deficiency, by limiting the metabolic capability, might contribute to myocardial dysfunction. Previous thiamin supplementation trials in patients with CHF have reported significant improvements in the cardiac function (Azizi-Namini *et al.*, 2012). In addition to thiamin, there are many targets that can affect the metabolic capability. By interfering with them, we need to see whether we can improve these outcomes for the patients with CHF, which remains to be researched in the future.

In addition to thiamin, there are some indicators that have been proposed for evaluating or affecting the metabolic ability. In human heart failure caused by dilated cardiomyopathy (DCM), both PCr and ATP are significantly reduced (Beer *et al.*, 2002). Meanwhile, the myocardial PCr-to-ATP ratio, measured noninvasively with 31P-MR spectroscopy, offers significant independent prognostic information on cardiovascular mortality in patients with DCM (Neubauer *et al.*, 1997).

5 Conclusions

In the early phases of CHF, there is a shift

towards carbohydrate utilization from FA oxidation. Along with the progress of the disease, increasing levels of hyperadrenergic state and insulin resistance cause the opposite changes that shift back to greater FA uptake and oxidation, and lower glucose metabolism. In the advanced cases of severe CHF, there are obvious reductions in both FA oxidation and carbohydrate utilization (Neubauer, 2007; Rajabi *et al.*, 2007; van Bilsen *et al.*, 2009; Turer *et al.*, 2010; Tuunanen and Knuuti, 2011). However, improvements in the metabolic capability and efficiency are likely to be more significant than the selection of the substrate (Kolwicz and Tian, 2011; Lionetti *et al.*, 2011). Nevertheless, there are still fundamental gaps in knowledge including whether observed shifts in cardiac substrate utilization are adaptive or maladaptive, causal or an epiphenomenon of CHF, whether we can improve these outcomes for the patients with CHF by interfering with metabolic capability (Turer *et al.*, 2010). More studies, especially long-term large sample experiments, are warranted to clarify these observations.

Compliance with ethics guidelines

Jing WANG and Tao GUO declare that they have no conflict of interest.

This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Abozguia, K., Clarke, K., Lee, L., Frenneaux, M., 2006. Modification of myocardial substrate use as a therapy for heart failure. *Nat. Clin. Pract. Cardiovasc. Med.*, **3**(9): 490-498. [doi:10.1038/ncpcardio0583]

Abozguia, K., Shivu, G.N., Ahmed, I., Phan, T.T., Frenneaux, M.P., 2009. The heart metabolism: pathophysiological aspects in ischaemia and heart failure. *Curr. Pharm. Des.*, **15**(8):827-835. [doi:10.2174/138161209787582101]

Arany, Z., He, H., Lin, J., Hoyer, K., Handschin, C., Toka, O., Ahmad, F., Matsui, T., Chin, S., Wu, P.H., *et al.*, 2005. Transcriptional coactivator PGC-1α controls the energy state and contractile function of cardiac muscle. *Cell Metab.*, **1**(4):259-271. [doi:10.1016/j.cmet.2005.03.002]

Ardehali, H., Sabbah, H.N., Burke, M.A., Sarma, S., Liu, P.P., Cleland, J.G., Maggioni, A., Fonarow, G.C., Abel, E.D., Campia, U., *et al.*, 2012. Targeting myocardial substrate metabolism in heart failure: potential for new therapies. *Eur. J. Heart Fail.*, **14**(2):120-129. [doi:10.1093/eurjhf/hfr173]

Ashrafian, H., Frenneaux, M.P., 2007. Metabolic modulation in heart failure: the coming of age. *Cardiovasc. Drugs Ther.*, **21**(1):5-7. [doi:10.1007/s10557-007-6000-z]

Azevedo, P.S., Minicucci, M.F., Santos, P.P., Paiva, S.A., Zornoff, L.A., 2013. Energy metabolism in cardiac remodeling and heart failure. *Cardiol. Rev.*, **21**(3): 135-140. [doi:10.1097/CRD.0b013e318274956d]

Azizi-Namini, P., Ahmed, M., Yan, A.T., Keith, M., 2012. The role of B vitamins in the management of heart failure. *Nutr. Clin. Pract.*, **27**(3):363-374. [doi:10.1177/0884533612444539]

Beauloye, C., Bertrand, L., Horman, S., Hue, L., 2011. AMPK activation, a preventive therapeutic target in the transition from cardiac injury to heart failure. *Cardiovasc. Res.*, **90**(2):224-233. [doi:10.1093/cvr/cvr034]

Beer, M., Seyfarth, T., Sandstede, J., Landschutz, W., Lipke, C., Köstler, H., von Kienlin, M., Harre, K., Hahn, D., Neubauer, S., 2002. 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.*, **40**(7):1267-1274. [doi:10.1016/S0735-1097(02)02160-5]

Cleland, J.G.F., Daubert, J.C., Erdmann, E., Freemantle, N., Gras, D., Kappenberger, L., Tavazzi, L., 2005. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N. Engl. J. Med.*, **352**(15):1539-1549. [doi:10.1056/NEJMoa050496]

Dávila-Román, V.G., Vedala, G., Herrero, P., de las Fuentes, L., Rogers, J.G., Kelly, D.P., Gropler, R.J., 2002. Altered myocardial fatty acid and glucose metabolism in idiopathic dilated cardiomyopathy. *J. Am. Coll. Cardiol.*, **40**(2):271-277. [doi:10.1016/S0735-1097(02)01967-8]

Decherd, G., Visscher, M.B., 1934. Energy metabolism of the failing heart. *J. Exp. Med.*, **59**(2):195-199.

de las Fuentes, L., Herrero, P., Peterson, L.R., Kelly, D.P., Gropler, R.J., Dávila-Román, V.G., 2003. Myocardial fatty acid metabolism: independent predictor of left ventricular mass in hypertensive heart disease. *Hypertension*, **41**(1):83-87. [doi:10.1161/01.HYP.0000047668.48494.39]

Dhalla, N.S., Saini-Chohan, H.K., Rodriguez-Leyva, D., Elimban, V., Dent, M.R., Tappia, P.S., 2009. Subcellular remodelling may induce cardiac dysfunction in congestive heart failure. *Cardiovasc. Res.*, **81**(3):429-438. [doi:10.1093/cvr/cvn281]

Dillon, L.M., Rebelo, A.P., Moraes, C.T., 2012. The role of PGC-1 coactivators in aging skeletal muscle and heart. *IUBMB. Life*, **64**(3):231-241. [doi:10.1002/iub.608]

Dinicolantonio, J.J., Lavie, C.J., Fares, H., Menezes, A.R., O′Keefe, J.H., 2013. L-carnitine in the secondary prevention of cardiovascular disease: systematic review and meta-analysis. *Mayo Clin. Proc.*, **88**(6):544-551. [doi:10.1016/j.mayocp.2013.02.007]

Doenst, T., Abel, E.D., 2011. Spotlight on metabolic remodelling in heart failure. *Cardiovasc. Res.*, **90**(2): 191-193. [doi:10.1093/cvr/cvr077]

Finck, B.N., Kelly, D.P., 2006. PGC-1 coactivators: inducible regulators of energy metabolism in health and disease. *J. Clin. Invest.*, **116**(3):615-622. [doi:10.1172/JCI27794]

Giordano, F.J., 2005. Oxygen, oxidative stress, hypoxia, and heart failure. *J. Clin. Invest.*, **115**(3):500-508. [doi:10.1172/JCI24408]

Hanninen, S.A., Darling, P.B., Sole, M.J., Barr, A., Keith, M.E., 2006. The prevalence of thiamin deficiency in hospitalized patients with congestive heart failure. *J. Am. Coll. Cardiol.*, **47**(2):354-361. [doi:10.1016/j.jacc.2005.08.060]

Hesselink, M.K., Schrauwen, P., 2005. Uncoupling proteins in the failing human heart: friend or foe? *Lancet*, **365**(9457):385-386. [doi:10.1016/S0140-6736(05)17823-4]

Hirsch, G.A., Bottomley, P.A., Gerstenblith, G., Weiss, R.G., 2012. Allopurinol acutely increases adenosine triphospate energy delivery in failing human hearts. *J. Am. Coll. Cardiol.*, **59**(9):802-808. [doi:10.1016/j.jacc.2011.10.895]

Hunt, S.A., Abraham, W.T., Chin, M.H., Feldman, A.M., Francis, G.S., Ganiats, T.G., Jessup, M., Konstam, M.A., Mancini, D.M., Michl, K., *et al.*, 2009. 2009 focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines developed in collaboration with the International Society for Heart and Lung Transplantation. *J. Am. Coll. Cardiol.*, **53**(15):e1-e90. [doi:10.1016/j.jacc.2008.11.013]

Huss, J.M., Kelly, D.P., 2005. Mitochondrial energy metabolism in heart failure: a question of balance. *J. Clin. Invest.*, **115**(3):547-555. [doi:10.1172/JCI24405]

Karamanlidis, G., Nascimben, L., Couper, G.S., Shekar, P.S., del Monte, F., Tian, R., 2010. Defective DNA replication impairs mitochondrial biogenesis in human failing hearts. *Circ. Res.*, **106**(9):1541-1548. [doi:10.1161/circresaha.109.212753]

Karbowska, J., Kochan, Z., Smolenski, R.T., 2003. Peroxisome proliferator-activated receptor α is downregulated in the failing human heart. *Cell Mol. Biol. Lett.*, **8**(1):49-53.

Kehat, I., Molkentin, J.D., 2010. Molecular pathways underlying cardiac remodeling during pathophysiological stimulation. *Circulation*, **122**(25):2727-2735. [doi:10.1161/CIRCULATIONAHA.110.942268]

Kemp, C.D., Conte, J.V., 2012. The pathophysiology of heart failure. *Cardiovasc. Pathol.*, **21**(5):365-371. [doi:10.1016/j.carpath.2011.11.007]

Kolwicz, S.C.Jr., Tian, R., 2011. Glucose metabolism and cardiac hypertrophy. *Cardiovasc. Res.*, **90**(2):194-201. [doi:10.1093/cvr/cvr071]

Lai, L., Leone, T.C., Zechner, C., Schaeffer, P.J., Kelly, S.M., Flanagan, D.P., Medeiros, D.M., Kovacs, A., Kelly, D.P., 2008. Transcriptional coactivators PGC-1α and PGC-1β control overlapping programs required for perinatal maturation of the heart. *Genes. Dev.*, **22**(14):1948-1961. [doi:10.1101/gad.1661708]

Ledderose, C., Kreth, S., Beiras-Fernandez, A., 2011. Ghrelin, a novel peptide hormone in the regulation of energy balance and cardiovascular function. *Recent Pat. Endocr. Metab. Immune Drug Discov.*, **5**(1):1-6. [doi:10.2174/187221411794351897]

Lionetti, V., Stanley, W.C., Recchia, F.A., 2011. Modulating fatty acid oxidation in heart failure. *Cardiovasc. Res.*, **90**(2):202-209. [doi:10.1093/cvr/cvr038]

Marsin, A.S., Bertrand, L., Rider, M.H., Deprez, J., Beauloye, C., Vincent, M.F., van den Berghe, G., Carling, D., Hue, L., 2000. Phosphorylation and activation of heart PFK-2 by AMPK has a role in the stimulation of glycolysis during ischaemia. *Curr. Biol.*, **10**(20):1247-1255. [doi:10.1016/S0960-9822(00)00742-9]

Martin, M.A., Gomez, M.A., Guillen, F., Bornstein, B., Campos, Y., Rubio, J.C., de la Calzada, C.S., Arenas, J., 2000. Myocardial carnitine and carnitine palmitoyltransferase deficiencies in patients with severe heart failure. *Biochim. Biophys. Acta Mol. Basis Dis.*, **1502**(3):330-336. [doi:10.1016/S0925-4439(00)00061-2]

McMurray, J.J., Adamopoulos, S., Anker, S.D., Auricchio, A., Bohm, M., Dickstein, K., Falk, V., Filippatos, G., Fonseca, C., Gomez-Sanchez, M.A., *et al.*, 2012. ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012. *Eur. Heart J.*, **33**(14):1787-1847. [doi:10.1093/eurheartj/ehs104]

Murray, A.J., Edwards, L.M., Clarke, K., 2007. Mitochondria and heart failure. *Curr. Opin. Clin. Nutr. Metab. Care*, **10**(6):704-711. [doi:10.1097/MCO.0b013e3282f0ecbe]

Nagoshi, T., Yoshimura, M., Rosano, G.M., Lopaschuk, G.D., Mochizuki, S., 2011. Optimization of cardiac metabolism in heart failure. *Curr. Pharm. Des.*, **17**(35):3846-3853.

Neubauer, S., 2007. The failing heart—an engine out of fuel. *N. Engl. J. Med.*, **356**(11):1140-1151. [doi:10.1056/NEJMra063052]

Neubauer, S., Horn, M., Cramer, M., Harre, K., Newell, J.B., Peters, W., Pabst, T., Ertl, G., Hahn, D., Ingwall, J.S., *et al.*, 1997. Myocardial phosphocreatine-to-ATP ratio is a predictor of mortality in patients with dilated cardiomyopathy. *Circulation*, **96**(7):2190-2196. [doi:10.1161/01.CIR.96.7.2190]

Opie, L.H., 2012. Allopurinol for heart failure: novel mechanisms. *J. Am. Coll. Cardiol.*, **59**(9):809-812. [doi:10.1016/j.jacc.2011.09.072]

Opie, L.H., Knuuti, J., 2009. The adrenergic-fatty acid load in heart failure. *J. Am. Coll. Cardiol.*, **54**(18):1637-1646. [doi:10.1016/j.jacc.2009.07.024]

Opie, L.H., Commerford, P.J., Gersh, B.J., Pfeffer, M.A., 2006. Controversies in ventricular remodelling. *Lancet*, **367**(9507):356-367. [doi:10.1016/s0140-6736(06)68074-4]

Paolisso, G., Gambardella, A., Galzerano, D., D′Amore, A., Rubino, P., Verza, M., Teasuro, P., Varricchio, M., D′Onofrio, F., 1994. Total-body and myocardial substrate oxidation in congestive heart failure. *Metabolism*, **43**(2):174-179. [doi:10.1016/0026-0495(94)90241-0]

Petersen, K.F., Shulman, G.I., 2006. Etiology of insulin resistance. *Am. J. Med.*, **119**(5S1):S10-S16. [doi:10.1016/j.amjmed.2006.01.009]

Pitt, B., Remme, W., Zannad, F., Neaton, J., Martinez, F., Roniker, B., Bittman, R., Hurley, S., Kleiman, J., Gatlin, M., *et al.*, 2003. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N. Engl. J. Med.*, **348**(14):1309-1321. [doi:10.1056/NEJMoa030207]

Rajabi, M., Kassiotis, C., Razeghi, P., Taegtmeyer, H., 2007. Return to the fetal gene program protects the stressed

heart: a strong hypothesis. *Heart Fail. Rev*., **12**(3-4): 331-343. [doi:10.1007/s10741-007-9034-1]

Randle, P.J., Garland, P.B., Hales, C.N., Newsholme, E.A., 1963. The glucose fatty-acid cycle. Its role in insulin sensitivity and the metabolic disturbances of diabetes mellitus. *Lancet*, **281**(7285):785-789.

Razeghi, P., Young, M.E., Alcorn, J.L., Moravec, C.S., Frazier, O.H., Taegtmeyer, H., 2001. Metabolic gene expression in fetal and failing human heart. *Circulation*, **104**(24): 2923-2931. [doi:10.1161/hc4901.100526]

Recchia, F.A., McConnell, P.I., Bernstein, R.D., Vogel, T.R., Xu, X., Hintze, T.H., 1998. Reduced nitric oxide production and altered myocardial metabolism during the decompensation of pacing-induced heart failure in the conscious dog. *Circ. Res*., **83**(10):969-979. [doi:10.1161/01.RES.83.10.969]

Riehle, C., Abel, E.D., 2012. PGC-1 proteins and heart failure. *Trends Cardiovasc. Med*., **22**(4):98-105. [doi:10.1016/j.tcm.2012.07.003]

Rosano, G.M., Fini, M., Caminiti, G., Barbaro, G., 2008. Cardiac metabolism in myocardial ischemia. *Curr. Pharm. Des*., **14**(25):2551-2562. [doi:10.2174/138161208786071317]

Rosca, M.G., Hoppel, C.L., 2010. Mitochondria in heart failure. *Cardiovasc. Res*., **88**(1):40-50. [doi:10.1093/cvr/cvq240]

Rowe, G.C., Jiang, A., Arany, Z., 2010. PGC-1 coactivators in cardiac development and disease. *Circ. Res*., **107**(7): 825-838. [doi:10.1161/CIRCRESAHA.110.223818]

Sabbah, H.N., Sharov, V.G., Goldstein, S., 2000. Cell death, tissue hypoxia and the progression of heart failure. *Heart Fail. Rev*., **5**(2):131-138. [doi:10.1023/A:1009880720032]

Sarma, S., Ardehali, H., Gheorghiade, M., 2012. Enhancing the metabolic substrate: PPAR-α agonists in heart failure. *Heart Fail. Rev*., **17**(1):35-43. [doi:10.1007/s10741-010-9208-0]

Shah, A.M., Mann, D.L., 2011. In search of new therapeutic targets and strategies for heart failure: recent advances in basic science. *Lancet*, **378**(9792):704-712. [doi:10.1016/s0140-6736(11)60894-5]

Sihag, S., Cresci, S., Li, A.Y., Sucharov, C.C., Lehman, J.J., 2009. PGC-1α and ERRα target gene downregulation is a signature of the failing human heart. *J. Mol. Cell Cardiol.*, **46**(2):201-212. [doi:10.1016/j.yjmcc.2008.10.025]

Sisakian, H., Torgomyan, A., Barkhudaryan, A., 2007. The effect of trimetazidine on left ventricular systolic function and physical tolerance in patients with ischaemic cardiomyopathy. *Acta Cardiol.*, **62**(5):493-499.

Stanley, W.C., Recchia, F.A., Lopaschuk, G.D., 2005. Myocardial substrate metabolism in the normal and failing heart. *Physiol. Rev*., **85**(3):1093-1129. [doi:10.1152/physrev.00006.2004]

Taegtmeyer, H., Ballal, K., 2006. No low-fat diet for the failing heart? *Circulation*, **114**(20):2092-2093. [doi:10.1161/CIRCULATIONAHA.106.659235]

Taylor, M., Wallhaus, T.R., Degrado, T.R., Russell, D.C., Stanko, P., Nickles, R.J., Stone, C.K., 2001. 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*., **42**(1):55-62.

Tsutsui, H., Kinugawa, S., Matsushima, S., 2011. Oxidative stress and heart failure. *Am. J. Physiol. Heart Circ. Physiol.*, **301**(6):H2181-H2190. [doi:10.1152/ajpheart.00554.2011]

Turer, A.T., Malloy, C.R., Newgard, C.B., Podgoreanu, M.V., 2010. Energetics and metabolism in the failing heart: important but poorly understood. *Curr. Opin. Clin. Nutr. Metab. Care*, **13**(4):458-465. [doi:10.1097/MCO.0b013e32833a55a5]

Tuunanen, H., Knuuti, J., 2011. Metabolic remodelling in human heart failure. *Cardiovasc. Res*., **90**(2):251-257. [doi:10.1093/cvr/cvr052]

Tuunanen, H., Engblom, E., Naum, A., Scheinin, M., Nagren, K., Airaksinen, J., Nuutila, P., Iozzo, P., Ukkonen, H., Knuuti, J., 2006a. Decreased myocardial free fatty acid uptake in patients with idiopathic dilated cardiomyopathy: evidence of relationship with insulin resistance and left ventricular dysfunction. *J. Card. Fail.*, **12**(8):644-652. [doi:10.1016/j.cardfail.2006.06.005]

Tuunanen, H., Engblom, E., Naum, A., Nagren, K., Hesse, B., Airaksinen, K.E., Nuutila, P., Iozzo, P., Ukkonen, H., Opie, L.H., *et al.*, 2006b. Free fatty acid depletion acutely decreases cardiac work and efficiency in cardiomyopathic heart failure. *Circulation*, **114**(20):2130-2137. [doi:10.1161/CIRCULATIONAHA.106.645184]

Vadvalkar, S.S., Baily, C.N., Matsuzaki, S., West, M., Tesiram, Y.A., Humphries, K.M., 2013. Metabolic inflexibility and protein lysine acetylation in heart mitochondria of a chronic model of type 1 diabetes. *Biochem. J*., **449**(1): 253-261. [doi:10.1042/BJ20121038]

van Bilsen, M., van Nieuwenhoven, F.A., van der Vusse, G.J., 2009. Metabolic remodelling of the failing heart: beneficial or detrimental? *Cardiovasc. Res*., **81**(3): 420-428. [doi:10.1093/cvr/cvn282]

Ventura-Clapier, R., Garnier, A., Veksler, V., 2004. Energy metabolism in heart failure. *J. Physiol.*, **555**(Pt1):1-13. [doi:10.1113/jphysiol.2003.055095]

Ventura-Clapier, R., Garnier, A., Veksler, V., Joubert, F., 2011. Bioenergetics of the failing heart. *Biochim. Biophys. Acta*, **1813**(7):1360-1372. [doi:10.1016/j.bbamcr.2010.09.006]

Wooley, J.A., 2008. Characteristics of thiamin and its relevance to the management of heart failure. *Nutr. Clin. Pract.*, **23**(5):487-493. [doi:10.1177/0884533608323430]

Yan, J., Young, M.E., Cui, L., Lopaschuk, G.D., Liao, R., Tian, R., 2009. Increased glucose uptake and oxidation in mouse hearts prevent high fatty acid oxidation but cause cardiac dysfunction in diet-induced obesity. *Circulation*, **119**(21):2818-2828. [doi:10.1161/CIRCULATIONAHA.108.832915]

Zannad, F., McMurray, J.J., Krum, H., van Veldhuisen, D.J., Swedberg, K., Shi, H., Vincent, J., Pocock, S.J., Pitt, B., Group, E.H.S., 2011. Eplerenone in patients with systolic heart failure and mild symptoms. *N. Engl. J. Med*., **364**(1):11-21. [doi:10.1056/NEJMoa1009492]

Zhang, L., Lu, Y., Jiang, H., Zhang, L., Sun, A., Zou, Y., Ge, J., 2012. Additional use of trimetazidine in patients with chronic heart failure: a meta-analysis. *J. Am. Coll. Cardiol.*, **59**(10):913-922. [doi:10.1016/j.jacc.2011.11.027]