

## The Adrenergic-Fatty Acid Load in Heart Failure

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The hypothesis proposed is that heart failure (HF) is associated with a reactive hyperadrenergic state that increases circulating plasma free fatty acids (FFAs), which leads to impaired glucose metabolism and insulin resistance. We propose that increased FFA-induced mitochondrial uncoupling and substantial oxygen wastage is closely associated with the generation of reactive oxygen species, inflammatory markers, and the development of insulin resistance. The therapeutic aims of metabolic therapy are as follows: 1) to decrease hyperadrenergic drive; 2) to inhibit lipotoxicity and glucotoxicity; and 3) to increase glucose uptake by muscle. These aims are achieved, respectively, by the following: 1) the use of beta-adrenergic blockade and all measures that relieve the mechanical load on the heart; 2) the use of drugs that inhibit fatty acid oxidation (trimetazidine, perhexiline), although without clinical evidence that the heart is their major site of action in HF; and 3) increase of the transport of glucose into the cells by exercise and metformin. Of these measures, only data concerning the reduction of mortality as the result of exercise are available. Of all the other measures, there are substantial positive data on the **use of trimetazidine that demonstrate metabolic and clinical benefit with almost no side effects**, but data from a large outcome trial are lacking. Our data suggest a major extracardiac site of trimetazidine action. Ranolazine, which inhibits the late sodium inward current, requires testing in human HF. Insulin to reduce hyperglycemia and FFAs is untested in HF, with incretins such as glucagon-like peptide-1 on the horizon. Other future therapies may include malonyl-coenzyme A regulators to inhibit fatty acid oxidation, fish oil omega-3, and activators of protein kinase C-epsilon. (J Am Coll Cardiol 2009;54:1637-46) © 2009 by the American College of Cardiology Foundation

Heart failure (HF) may be regarded as failure of myocardial contraction and/or relaxation that is accompanied by a neurohumoral reaction, the therapy of which has been strikingly successful and has led to the routine use of angiotensin-converting enzyme inhibitors and beta-blockers. Fluid overload is alleviated by the use of diuretics. These standard therapies indirectly improve the metabolism of the heart by decreasing pre-load, afterload, and heart rate, all of which diminish the mechanical workload, thereby reducing the myocardial oxygen demand and lessening the requirement for mitochondrial production of adenosine triphosphate (ATP).

In addition, there are specific major metabolic abnormalities, both cardiac and extracardiac, that are susceptible to metabolically based therapy (1). We propose that the core of these abnormalities lies in the compensatory hyperadrenergic state that develops in HF (2) with elevation of blood free fatty acid (FFA) levels (3), derived from adipose tissue (4-6). These excess circulating FFAs block the uptake of glucose by muscle (7), thereby increasing gluconeogenesis, which in turn may promote hyperglycemia if insulin secre-

tion is limited (8). These changes in glucose metabolism, when combined with the high FFA and the resultant stimulation of the inflammatory system (6), could constitute a pattern of metabolic dysregulation that is a major step on the route to insulin resistance (1). Excess FFA also can cause abnormalities of mitochondrial function, including excessive mitochondrial metabolism with the formation of reactive oxygen species (ROS), oxygen wastage (9-11), and increased mitochondrial and cytosolic calcium and sodium, all of which may further impair myocardial function with expected adverse effects on the already-failing heart (12). Thus, a process starting as HF due to standard causes with its compensatory hyperadrenergic and FFA responses may induce a wide variety of metabolic changes that, together with increasing insulin resistance, may deteriorate into a secondary insulin-resistant cardiomyopathy (1). The aim of metabolic therapy is to inhibit or delay this adverse sequence. In this paper we briefly review normal and abnormal glucose-fatty acid interactions that lead to the adverse metabolic effects of high FFA concentration and to insulin resistance. We then outline procedures whereby less-adverse fatty acid metabolism and a more favorable carbohydrate metabolism and decreased oxygen wastage (Fig. 1) can be achieved in patients with HF. However, it is not just a case of lessening circulating FFA and thereby improving myocardial function, as shown by the adverse effects of rapid

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**Abbreviations and Acronyms**

- AMPK** = adenosine monophosphate-activated kinase
- ATP** = adenosine triphosphate
- CoA** = coenzyme A
- FAO** = free fatty acid oxidation
- FFA** = free fatty acid
- GLUT** = glucose transporter
- HF** = heart failure
- LV** = left ventricular
- NE** = norepinephrine
- PKC** = protein kinase C
- PPAR** = peroxisome proliferator-activated receptor
- ROS** = reactive oxygen species
- TMZ** = trimetazidine
- UCP** = uncoupling protein

FFA reduction (13), but rather of taking into account the action of inhibitors of free fatty acid oxidation (FAO) on extracardiac sites such as skeletal muscle (14). Furthermore, hyperglycemia also needs to be controlled.

**Substrate Competition in the Heart**

**Randle's glucose-fatty acid cycle.** The heart relies almost exclusively on aerobic oxidation of substrates to generate ATP, which is required to maintain its cellular and contractile functions. A keen interest in the substrate supply in human HF dates back more than 50 years to the pioneering work of Blain et al. (15). The primary substrates metabolized by the myocardium are FFAs, glucose, lactate, and, to a lesser extent, amino acids (16,17). The myocardial substrate usage varies considerably throughout

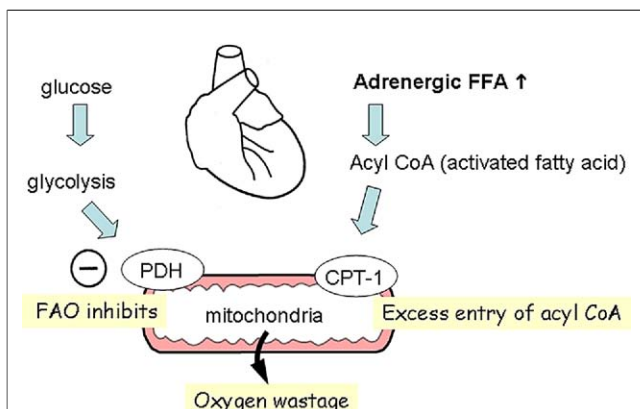
the day, depending on substrate availability, nutritional status, and exercise level. This variation forms the basis of the glucose-fatty acid cycle as first proposed by Randle et al. (4) in isolated heart and diaphragm muscle and later confirmed by Nuutila et al. (18) in the human heart and skeletal muscle. In the fasted state, when blood levels of FFAs are elevated, assuming that coronary flow and oxygen

supply are normal, FFAs are the major source of energy (~70%), for the myocardium ATP is formed by oxidative metabolism of FFAs, which inhibits glycolysis and glucose oxidation at several sites but chiefly at the level of pyruvate dehydrogenase (17), so that the decreased amount of glucose taken up is converted to glycogen (4,7,16). In the case of glucose, the contribution to the energy needs of the heart might vary from 10% after a fat meal to 70% after a carbohydrate meal. Lactate concentrations, when high as during heart perfusion or exercise, inhibit the uptake of FFAs and the oxidation of glucose (19-21). Triglyceride, after conversion to FFA by lipoprotein lipase, can account for 50% of the myocardial oxidative metabolism after an intravenous lipid load or post-prandial lipemia (22).

With this background, the excessive beta-adrenergic-driven excess mobilization of FFA in HF is likely to switch off glucose oxidation to obliterate most or all of the diurnal glucose-fatty acid cycling. Stated differently, we postulate that advanced HF would inhibit the physiological functioning of the Randle cycle. Of note, genetically induced myocardial lipid overload leads to cardiomyopathy (23). Conversely, cardiac-specific increased glucose uptake induced by overexpression of a glucose transporter prevents pressure-induced HF (24).

**FFA-induced oxygen wastage.** It is known that FAO is less energy efficient than glucose, requiring 11% to 12% more oxygen for a given amount of ATP produced (16). In addition, it is important to note that the amount of ATP synthesized per mole of oxygen consumed is dependent on the coupling of proton influx and ATP production in the mitochondria. Thus, with high levels of circulating FFA, the actual amount of ATP produced by FAO may be much lower than expected (11). Thus, when FAO is driven by marked elevation of FFAs by lipid infusions given to dogs, the myocardial oxygen uptake increased by about 20%, whereas with high degrees of adrenergic activation by norepinephrine (NE) infusions, the metabolic component of the myocardial oxygen uptake can be calculated to be about 50% (Table 1) (9,10,25-28). Of much interest, this large increase in the myocardial oxygen uptake could largely be reversed by the administration of high-dose intravenous glucose (10), strongly suggesting that there was FFA-induced oxygen wastage.

These data are compatible with the hypothesis that high circulating FFA levels have adverse mitochondrial effects, including substantial oxygen wastage (Fig. 2). Nonetheless, caution is required because the FFA-induced increases were extreme. In the human atrial myocardium from the failing human heart, the activity of uncoupling protein (UCP)-2 and -3 is substantially increased at high levels of plasma FFA, whereas the glucose transporter (GLUT)-4 decreases in activity (29). In diabetic mice high plasma FFA levels are associated with increased UCP-3 levels (30). There are several proposed molecular mechanisms for uncoupling (17). Thus, increased levels of UCPs can be linked to oxygen wastage induced by excessive circulating levels of FFAs (Fig. 2), even though UCPs basically have a physio-



**Figure 1 FFA Effects on Mitochondria**

High circulating levels of free fatty acid (FFA), activated within the muscle cell to fatty acid-coenzyme A (CoA), enter the mitochondria by the action of carnitine palmitoyl transferase (CPT)-1, thereby inhibiting the action of pyruvate dehydrogenase (PDH), blocking protective glycolysis that supplies cytosolic adenosine triphosphate used for ion pumps, and decreasing glucose uptake by muscle. Excess activated FFA increases the formation of reactive oxygen species. For oxygen wastage, see Figure 2. FAO = free fatty acid oxidation.

**Table 1** Effect of FFA on MVO<sub>2</sub>

Ref. #	Measure	Preparation	Intervention	Change
25	MVO <sub>2</sub> (unloaded)	In situ pig heart, coronary sinus catheterization	Infusion of intralipid heparin versus GIK	MVO <sub>2</sub> increase of 48%
9	MVO <sub>2</sub>	In situ dog heart	Infusion of intralipid heparin	MVO <sub>2</sub> increase by 26%
10	MVO <sub>2</sub>	In situ dog heart	Infusion of Iso ± glucose	MVO <sub>2</sub> increase by 91% after Iso, down to 45% after glucose; FFA-induced increase of ~50%
26	MVO <sub>2</sub>	Isolated working perfused rat heart	Epi 10 <sup>-6</sup> mol/l added to glucose perfusate	MVO <sub>2</sub> increased by 72% by Epi; reduced to 34% after nicotinic acid
27	MVO <sub>2</sub>	Isolated working perfused rat heart	Energy metabolism changed from carbohydrate to palmitate oxidation	MVO <sub>2</sub> increased by about 30%
28	Myocardial efficiency of work	Open chest pig	Infused glucose to 12 mmol/l	Efficiency of work increased by 32%

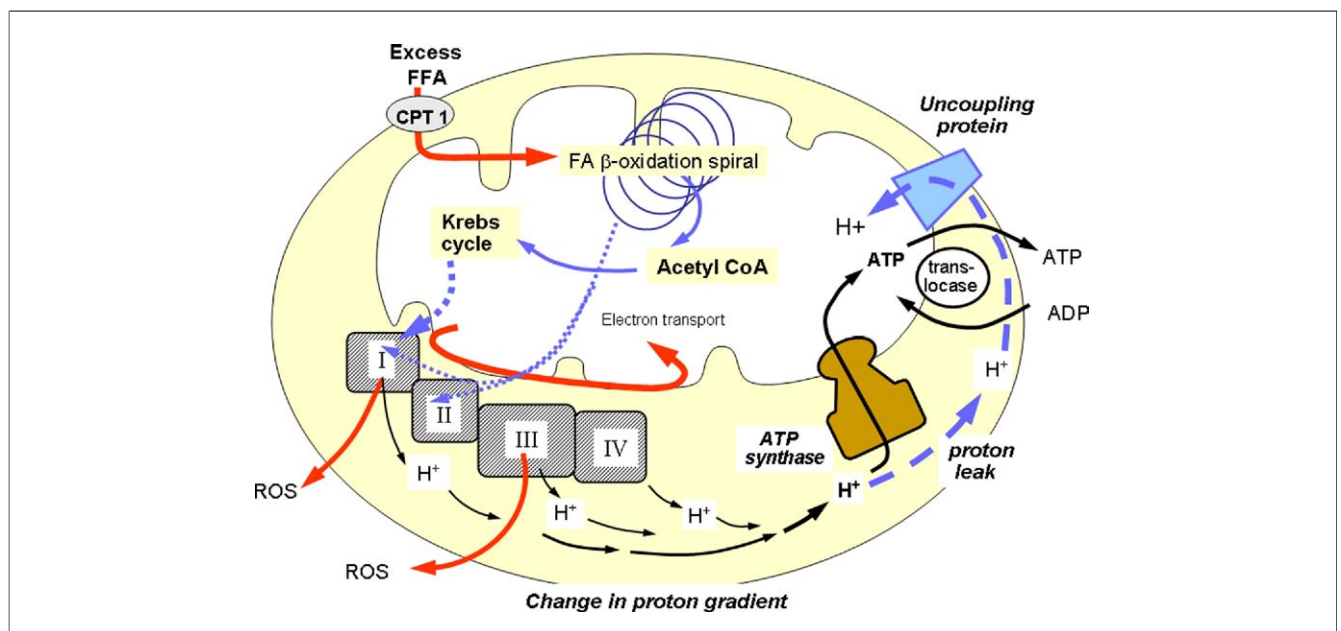
Epi = epinephrine; FFA = free fatty acid; GIK = glucose, insulin, potassium; Iso = isoproterenol; MVO<sub>2</sub> = myocardial oxygen uptake.

logical role (31). Our proposal is that similar changes occur in the hyperadrenergic state in HF to worsen HF by producing a metabolic vicious circle (32). However, it should be appreciated that the relationship between mitochondrial oxidation of activated fatty acids and uncoupling is extremely complex (33). On the one hand, an increased supply and oxidation of activated fatty acids promotes ROS formation to exaggerate mitochondrial dysfunction. Such ROS are derived from FFA-driven mitochondrial sources at complexes I and III (Fig. 2) (34). Furthermore, incomplete FAO may lead to intramitochondrial accumulation of acyl-coenzyme A (CoA), which damages mitochondria (35). On the other hand, mitochondrial UCPs can export activated fatty acids to decrease the degree of uncoupling of respiration and hence to decrease lipotoxicity. Presumably, in HF

the hyperadrenergic state and the associated excess FFA supply override any self-protective mechanisms.

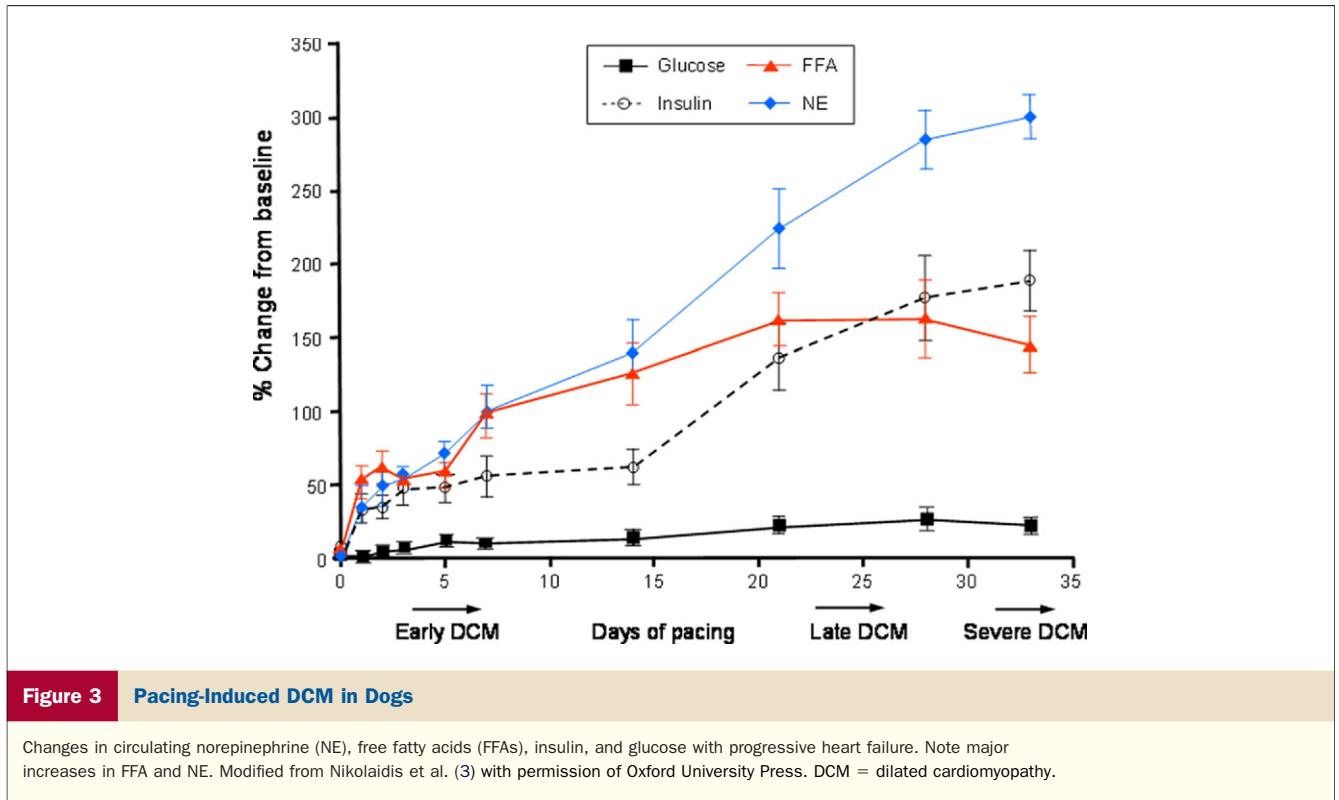
### Reduction in FFA Metabolism as Therapy for HF

**Stop it at the start: inhibit excess adrenergic activity.** Increased plasma NE levels in patients with HF were first described by Chidsey et al. (36) in 1962. The degree of elevation is closely related to the severity of the HF (2), with very high NE levels found in advanced untreated HF (3,37), compatible with the proposal that NE release is a compensatory phenomenon to sustain the decreasing blood pressure as cardiac failure progresses. The increased plasma levels of NE reflect both reduced clearance and markedly increased NE spillover from the heart and kidneys, so that there must



**Figure 2** Mitochondrial Sources of ROS

As protons are passed along the electron transport chain, reactive oxygen species (ROS) are formed at complexes I and III. FFA-induced proton leakage passes through uncoupling proteins, which divert protons from ATP formation and, hence, waste oxygen. Modified, with permission, from Opie (16). Figure copyright of L. H. Opie. ADP = adenosine diphosphate; ATP = adenosine triphosphate; FA = fatty acid; other abbreviations as in Figure 1.



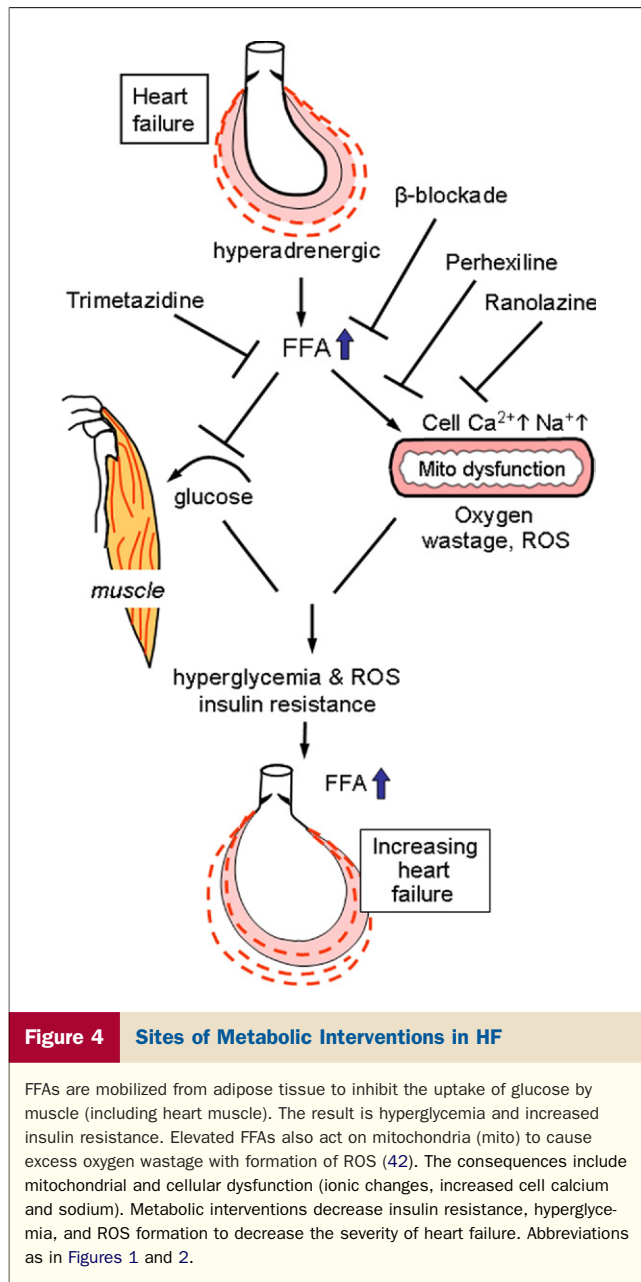
be increased sympathetic neural discharge (38). In a dog model of chronic HF, as the plasma NE increased, so did plasma FFA, insulin, and glucose (3), indicating the adrenergic-induced development of insulin resistance (Fig. 3). The basic remedy is to fix the cause, which is to counter the failing myocardium by any unloading step, including diuresis and renin-angiotensin inhibition. Improved mechanical function by cardiac resynchronization also should decrease plasma NE and FFA levels.

**Beta-blockade indirectly inhibits FFA metabolism.** Long-term therapy with beta-adrenergic receptor antagonists is known to improve left ventricular (LV) function and survival in patients with HF (Fig. 4) (39–42). Noninvasive studies (40,41) in which the authors used beta-blocker therapy demonstrated a significant decrease in oxidative metabolism and improved myocardial efficiency in HF patients after the intervention period. These improvements in myocardial energetics suggest that beta-blocking agents have an energy-sparing effect in HF patients that may be due to a switch in myocardial substrate preference away from FAO toward carbohydrate oxidation (40,43). Furthermore, after 3 months of treatment with metoprolol, LV function and myocardial efficiency improved as carbohydrate use increased (44). With another beta-blocker, carvedilol, also administered for 3 months, myocardial FFA uptake was decreased by 57% in patients with New York Heart Association functional class III HF (41). In 8 of the 9 patients, myocardial glucose uptake increased, although this finding was not statistically significant. Beta-blockade also reduced the rate of myocardial oxidative metabolism as

measured with  $^{11}\text{C}$ -acetate and positron emission tomography (40).

More recently, in the only prospective metabolic study (45) that directly compared carvedilol with metoprolol, 11 patients with HF were treated for 4 months with either agent with similar hemodynamic responses. Metabolically, only carvedilol shifted substrate use from FFA to lactate extraction. These metabolic differences between carvedilol and metoprolol may help to explain why carvedilol was better at reducing the rate of mortality in a large definitive trial on patients with HF (46).

**Acute FFA reduction by acipimox.** If FFAs constitute such a serious problem in patients with HF, the logical step would be to reduce the FFA levels which, in turn, should improve glucose metabolism. We have undertaken 2 separate studies (13,14) to assess the ideal means of lowering FFAs. Acipimox, a nicotinic acid derivative, when given as an acute antilipolytic agent to patients with idiopathic cardiomyopathic HF, acutely decreased myocardial FFA uptake by more than 80% which, in those patients with healthy hearts, was accompanied by a decrease in oxidative metabolism, in keeping with the concept of FFA-induced oxygen wastage (13). However, in patients with failing hearts, acute FFA depletion did not down-regulate oxidative metabolism, and myocardial efficiency of work decreased. Thus, unexpectedly, these hearts were more dependent on FFA metabolism than normal hearts, which led to Taegtmeier and Ballal's (47) concept that metabolic extremes can cause lipotoxicity or glucotoxicity, both of which are adverse for the failing heart.



**Trimetazidine (TMZ) for HF.** Trimetazidine is a metabolically active antianginal widely used in Europe but not licensed in the U.S. It has multiple potentially cardioprotective mechanisms besides partial inhibition of FAO with increased glucose oxidation as found in isolated rat hearts (Online Table 1). In patients with type 2 diabetes and HF, a TMZ-induced increase in muscle glucose oxidation and decreased FAO (measured by citrate release) occurred in the forearm muscle (48).

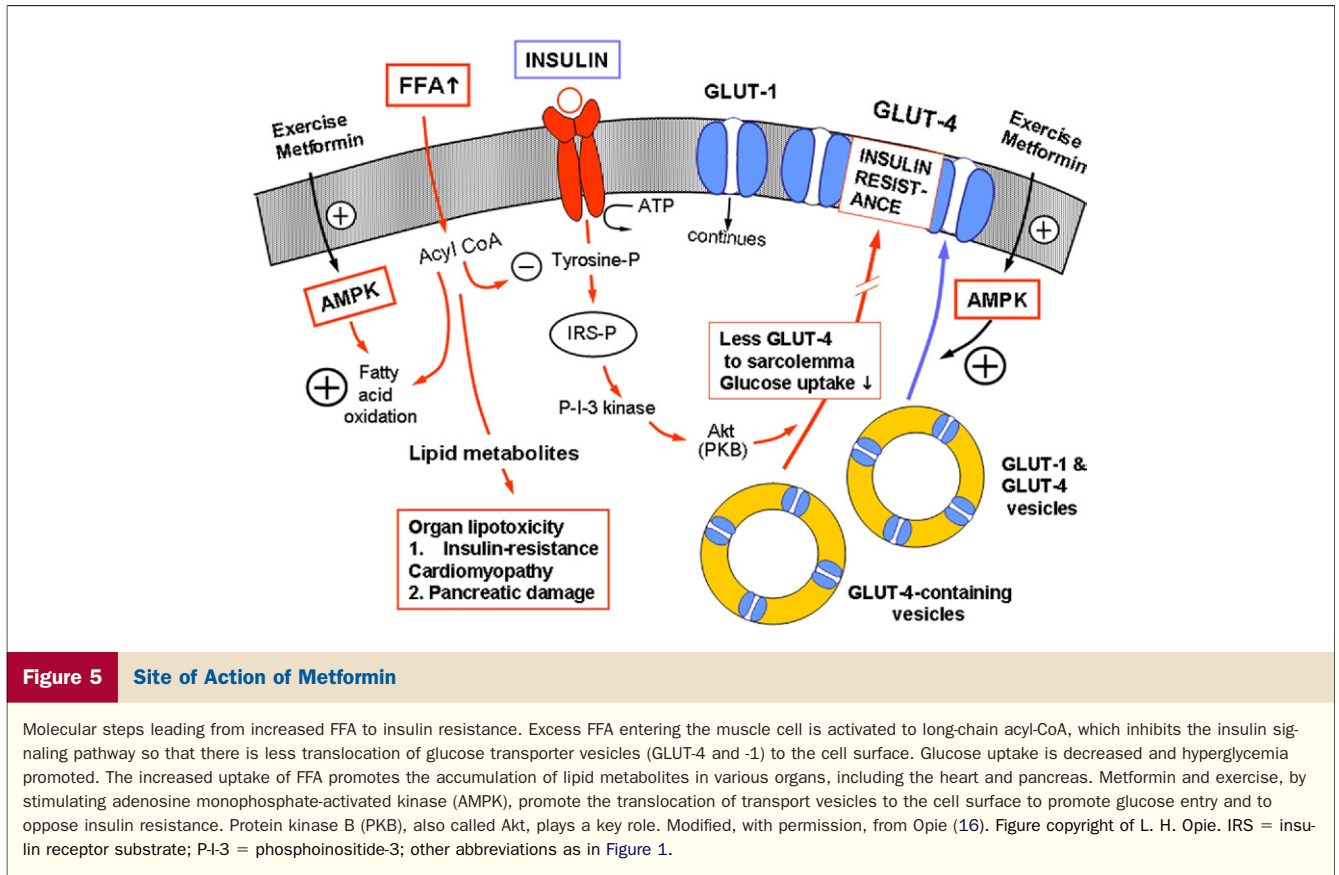
In our clinical studies with TMZ given for chronic HF, the hypothesis was that partial inhibition of myocardial FAO by the heart would result in improved mechanical function (14). Although the use of TMZ had previously been tested in patients with HF and found to be effective in 7 studies (12), there were no studies in which the authors

directly measured the postulated decrease in myocardial FAO (Online Appendix). Our study was the first to directly measure FAO by the heart and the first to study chronic HF caused by idiopathic dilated cardiomyopathy in patients without any overt clinical myocardial ischemia. When TMZ was given, the ejection fraction of patients with HF group increased modestly (14). However, myocardial fatty acid uptake was unchanged, and the rate of FAO decreased by only 10%, which we proposed was probably not the major site of TMZ action. Whole-body insulin resistance decreased, confirming the findings in patients with diabetic HF (48). For the first time in studies with TMZ we reported that fasting plasma high-density lipoprotein concentrations increased by 11%, presumably reflecting decreased insulin resistance (49). By virtue of its sphingosine-1-phosphate content, high-density lipoprotein has direct experimental cardioprotective effects (50). The change in ejection fraction induced by TMZ highly correlated with the beta-1 receptor occupancy, suggesting a synergistic interaction between the general metabolic changes achieved by TMZ and the degree of beta-1 receptor blockade already part of the therapy (14).

Hypothetically, decreased FFA and increased glucose oxidation in the failing human heart and skeletal muscle could decrease FFA- and hyperglycemia-associated oxidative stress. Of note, normalizing excess ROS counters pathways of hyperglycemic damage (51). However, no TMZ-induced effect on cardiac glucose oxidation in human HF has yet been measured.

**Perhexiline for HF.** Perhexiline is a partial inhibitor of FAO, inhibiting the mitochondrial uptake of FFA by the enzyme carnitine palmitoyl transferase-1 (Fig. 2). There is only 1 HF study (52) in which the authors reported the benefits of perhexiline in HF. When added to the previous therapy, while blood levels were monitored to avoid hepatotoxicity, the authors found that perhexiline improved peak exercise-induced oxygen uptake, enhanced the quality of life, and increased the LV ejection fraction (52). Perhexiline also normalized the post-exercise recovery of phosphocreatine in skeletal muscle. This study lends strong support to the concept that inhibition of FAO is beneficial in HF because of concordance with basic science studies and the unique mechanism of action on one mitochondrial enzyme, in contrast to the many diverse effects reported for TMZ. However, there are no direct measurements of perhexiline inhibition of cardiac FAO in human HF. Hepatotoxicity stopped a clinical trial with etoxomir, another inhibitor of carnitine palmitoyl transferase-1 (12).

**Ranolazine for HF.** Ranolazine, a compound that structurally resembles TMZ, originally was regarded as an agent with metabolic effects consonant with the benefits of a shift from fatty acid to glucose metabolism in ischemic rat hearts (53). In agreement with these metabolic changes in rodent hearts, there is improved glycemic control as shown by the persistent decrease in the HbA1c levels when ranolazine is



given to patients with chronic angina and diabetes (54) or to those with acute coronary syndrome (55).

Some recent author data (56) question the role of inhibition of fatty acid oxidation as the major site of ranolazine action and rather suggest (57) that ranolazine inhibits the late sodium inward current. Because myocardial sodium overload occurs in the failing heart, it is not surprising that ranolazine, combined with enalapril or metoprolol, limits progressive LV dysfunction in dogs with moderate chronic HF (58). Sodium overload is responsible for a secondary calcium overload by the sodium/calcium exchange mechanism, compatible with the finding that ranolazine improves diastolic function in isolated myocardium from failing human hearts (57). In the latter study, there was direct evidence for inhibition of the late sodium current by ranolazine. However, there are no definitive studies on the effects of ranolazine in human HF.

### Mechanisms That Stimulate Adenosine Monophosphate-Activated Kinase (AMPK) Activity

AMPK is the cellular sensor that responds to situations of ATP breakdown, such as exercise. Because of the high ATP-to-adenosine monophosphate ratio in muscle cells, the breakdown of only a small amount of ATP considerably increases adenosine monophosphate levels to activate AMPK. When this enzyme is activated, it stimulates both the oxidation of FFA and the uptake of glucose (Fig. 5).

The mechanism whereby activation of AMPK increases fatty acid oxidation is complex. AMPK phosphorylates and activates the enzyme acetyl-CoA carboxylase, which in turn decreases malonyl-CoA activity, thereby lessening the normal inhibition that malonyl-CoA exerts on transport of activated long chain fatty acid into myocardial cells (17). The glucose effect results from increased migration of glucose-transporting vesicles (GLUT-1 and -4) to the sarcolemma to promote glucose uptake. Hypothetically, these effects could either benefit or harm patients with HF. Increased glucose uptake and oxidation would accord with the basic hypothesis proposed here, namely that promotion of glucose metabolism might be beneficial in patients with HF. Conversely, however, increased fatty acid oxidation would be expected to have adverse effects on mitochondrial ATP production (Fig. 2).

**Exercise.** Exercise in those with insulin resistance and pre-diabetes lessens the development of new diabetes (59). In relation to the therapy of HF, the protective glucose-mediated effects seem to dominate any adverse FFA-mediated effects. In HF, exercise training reduces insulin resistance (60) and increases skeletal and cardiac glucose uptake, probably by activating the insulin-insensitive GLUT-1 transporters (61,62). At least part of the benefit of exercise in HF patients, which includes mortality reduction (63), could be mediated by similar mechanisms. This postulate could explain why improved exercise tolerance in

patients with dilated cardiomyopathy already treated by beta-blockade was accompanied by enhanced forward work efficiency and decreased cardiac oxidative metabolism (64). **Metformin.** Besides stimulating AMPK to increase myocardial glucose uptake (Fig. 5), metformin decreases hepatic synthesis of fatty acids and of glucose (65,66). Experimentally, it has protective effects in experimental HF acting via AMPK (67,68). In patients with type 2 diabetes and HF, there were reduced deaths and hospital readmissions with metformin versus other glucose-lowering therapies (69). However, despite the stimulatory effect on AMPK, metformin could not further increase glucose uptake by skeletal muscle in exercising diabetic patients (70), suggesting that the exercise had already maximally stimulated muscle AMPK activity. In resting nonobese patients with type 2 diabetes, metformin considerably increases peripheral blood flow and uptake of glucose by muscle while decreasing blood FFA levels (71). Why do FFA levels decrease? One mechanism could be that metformin counters the direct toxic effect of FFA on human isolated pancreatic islets (72), which should decrease insulin resistance. Overall, prospective controlled trials with metformin in human HF are required.

**Adiponectin.** Adiponectin is an adipokine that interacts with and mimics some of the metabolic effects of insulin (73). Key among its intracellular reactions is activation of AMPK (73). Decreased adiponectin levels as found in diabetes, metabolic syndrome, and coronary artery disease may contribute to insulin resistance. Adiponectin counteracts the effects of increased FFA levels that promote endothelial dysfunction and insulin resistance (73), both hallmarks of HF. However, despite the activation of AMPK by adiponectin, there is no direct clinical evidence of a strong relationship between adiponectin and HF. In the Framingham Offspring Study (74), adiponectin was not associated with the development of new HF but, instead, resistin, another adipokine, was linked with HF. Of interest, epicardial fat is a newly identified source of adipokines, both pro- and anti-inflammatory (75), without as yet any direct relation to HF.

### Diet, Insulin, and Hyperglycemia

**Diet and HF.** As already explained, the human heart derives energy from glucose, fatty acids, and/or lactate depending upon substrate availability and nutritional status. In patients who are physically inactive, who are obese, and who have type 2 diabetes, circulating FFA and glucose levels often exceed the normal range, with risks of lipotoxicity and glucotoxicity possible (76). Emerging data (76) suggest that substrate excess leading to cardiac dysfunction and HF may be prevented or slowed by maintaining low body fat and high insulin sensitivity and by consuming a diet of low glycemic load that is high in monounsaturated and polyunsaturated fatty acids. At present, it is unclear whether this

new nutritional paradigm will be effective in the prevention or treatment of HF.

**Insulin to control FFA, glycemia, and inflammatory markers?** Besides the risk of FFA-induced deterioration of myocardial dysfunction in HF, a further risk is insulin resistance, which is highly prevalent in nondiabetic patients with HF (14,49) and sometimes severe enough to promote and cause the diabetic state (1). A striking feature of the response of the normal heart to injury is the reactivation of the fetal gene program that promotes glucose metabolism and lessens that of FFA. Gene-induced changes include decreased UCPs, thereby increasing the generation of ATP (1,77). Conversely, FFAs induce the transcription factor peroxisome proliferator-activated receptor (PPAR)-alpha that promotes FAO. When PPAR-alpha is pharmacologically activated, then the hypertrophied heart starts to fail (78), presumably as a result of excess FAO.

The inflammatory response is promoted both by hyperglycemia and high FFA levels (8,79). Superoxide production activates proinflammatory transcription factors and reduces the availability of nitric oxide (8,79). In diabetic patients, post-prandial hyperglycemia is associated with increased plasma C-reactive protein values (80). Thus, control of hyperglycemia and high FFA levels by insulin should be beneficial in HF both by metabolic effects and by dampening the inflammatory response.

**Can insulin benefit human HF?** Short-term animal studies link high FFA levels to substantial oxygen wastage in a variety of preparations, with evidence for the energetic benefit of glucose (Table 1). Yet, we still lack detailed human studies with insulin in HF, although the concept was proposed nearly 40 years ago (81). Regarding intensive glucose control for acutely ill patients, the newly available data (82,83) show harm rather than benefit, probably caused by episodes of dangerous hypoglycemia, thus supporting the view that the metabolic management of the acutely ill cardiac patient extends beyond control of hyperglycemia (84). We also stress the potential danger of an insulin-induced acute reduction in FFA metabolism (85), which could decrease cardiac efficiency and work as with acipimox (13). The present trend is to explore the use of incretins (see the next section).

**Rosiglitazone and pioglitazone: PPAR-gamma activators.** The thiazolidinediones, also called the “glitazones,” are drugs that activate the PPAR-gamma transcriptional system, thereby promoting the metabolism of glucose. These compounds also have anti-inflammatory effects and increase concentrations of adiponectin (86). Although known to increase myocardial glucose uptake in patients with type 2 diabetes (87,88), likely partly the result of reduction in circulating FFA concentrations, these agents also can precipitate fluid retention and hence HF. In the PROactive (PROspective Pioglitazone Clinical Trial In MacroVascular Events) trial, pioglitazone administered to patients with type 2 diabetes reduced serious cardiovascular events, including myocardial infarction and stroke, while substantially

increasing HF (89). Rosiglitazone given to pre-diabetic persons lessened the incidence of new diabetes, but the incidence of new HF increased (90). A proposed mechanism is that the PPAR- $\gamma$  activity acts on the distal nephron to promote sodium and fluid retention (91), which in the presence of lipid-induced incipient diastolic HF (92) can precipitate congestive HF (93) despite enhanced myocardial glucose uptake (87). Thus, a presumed beneficial event, increased glucose uptake by the heart (87,88), is overridden by the propensity to cause HF by renal sodium retention.

### Future Metabolic Therapies for HF

**Malonyl-CoA activity.** Carnitine palmitoyl transferase-1 is a key enzyme that not only is inhibited by perhexiline, but as the “gatekeeper” of mitochondrial fatty acid uptake, it is physiologically controlled by varying degrees of inhibition by malonyl-CoA. Physiologically, AMPK kinase indirectly regulates FAO by phosphorylation of acetyl-CoA carboxylase, which lowers malonyl-CoA levels (17). Thus, a novel approach to inhibit excess FFA uptake by mitochondria would be to increase the activity of malonyl-CoA by inhibiting the enzyme, breaking it down (malonyl-CoA decarboxylase) (94). The consequent metabolic shift away from fatty acid oxidation toward increased glucose oxidation should benefit the failing myocardium. Such compounds are now under development and may become ready for early clinical trials initially targeting ischemic/reperfusion injury.

**Omega-3 fatty acids.** High fish intake, correlating with levels of plasma omega-3 fatty acids, was associated with decreased incident HF in an elderly population study (95). Experimentally, rats treated by omega-3 polyunsaturated fatty acids in a dose range similar to that of humans taking such supplements were more resistant to the adverse effects of aortic banding with less ventricular dilation (96). The proposed mechanistic benefits are increased plasma adiponectin and decreased inflammatory markers. Preliminary human studies to treat HF metabolically by docosahexaenoic acid are planned.

**Protein kinase C (PKC)-epsilon.** Proteomic and metabolic analyses recently have shown that PKC- $\epsilon$  activity modulates cardiac glucose metabolism and lessens ischemic/reperfusion damage, whereas PKC- $\delta$  has the opposite effects (97). A selective inhibitor of PKC- $\delta$  has been given to patients with acute myocardial infarction. Testing in HF is awaited.

**Glucagon-like peptide-1.** This incretin increases myocardial glucose uptake with the advantage over insulin that it avoids hypoglycemia. In 12 patients with advanced HF, a 5-week infusion added to standard therapy improved LV ejection fraction, quality of life, and walking distance (98).

### Conclusions

Heart failure is associated with major metabolic changes that include the consequences of the hyperadrenergic state

with increased circulating plasma FFAs, impaired glucose metabolism, hyperglycemia, and increased insulin resistance. We have reviewed data supporting the hypothesis that cardiac and whole-body metabolic changes occur with the development of HF. Increased FFA-induced mitochondrial UCP activity is closely associated with the generation of ROS and inflammatory markers. Beta-blockade acts metabolically to decrease myocardial FFA uptake and increase work efficiency. Three antianginal drugs, TMZ, perhexiline, and ranolazine, all have data favoring their use or testing in HF, whether ischemic or nonischemic in origin. The metabolic effects of exercise are beneficial. However, care should be exercised when thiazolidinediones (glitazones) are given to patients with type 2 diabetes, despite positive effects on myocardial substrate metabolism. The detailed mechanisms whereby these different metabolic factors are linked to the development and therapy of HF are not yet elucidated.

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### REFERENCES

1. Witteles RM, Fowler MB. Insulin-resistant cardiomyopathy clinical evidence, mechanisms, and treatment options. *J Am Coll Cardiol* 2008;51:93–102.
2. Cohn JN, Levine TB, Olivari MT, et al. Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. *N Engl J Med* 1984;311:819–23.
3. Nikolaidis LA, Sturzu A, Stolarski C, Elahi D, Shen YT, Shannon RP. The development of myocardial insulin resistance in conscious dogs with advanced dilated cardiomyopathy. *Cardiovasc Res* 2004;61:297–306.
4. Randle PJ, Garland PB, Hales CN, Newsholme EA. The glucose fatty-acid cycle. Its role in insulin sensitivity and the metabolic disturbances of diabetes mellitus. *Lancet* 1963;1:785–9.
5. Lapointe A, Piché ME, Weisnagel SJ, Bergeron J, Lemieux S. Associations between circulating free fatty acids, visceral adipose tissue accumulation, and insulin sensitivity in postmenopausal women. *Metabolism* 2009;58:180–5.
6. Hajer GR, van Haeflten TW, Visseren FL. Adipose tissue dysfunction in obesity, diabetes, and vascular diseases. *Eur Heart J* 2008;29:2959–71.
7. Shipp J, Opie LH, Challoner DR. Fatty acid and glucose metabolism in the perfused heart. *Nature* 1961;189:1018–9.
8. Roden M, Stingl H, Chandramouli V, et al. Effects of free fatty acid elevation on postabsorptive endogenous glucose production and gluconeogenesis in humans. *Diabetes* 2000;49:701–7.
9. Mjos OD. Effect of free fatty acids on myocardial function and oxygen consumption in intact dogs. *J Clin Invest* 1971; 50:1386–9.
10. Mjos OD. Effect of inhibition of lipolysis on myocardial oxygen consumption in the presence of isoproterenol. *J Clin Invest* 1971;50:1869–73.
11. Essop F, Opie LH. Metabolic therapy for heart failure. *Eur Heart J* 2004;25:1765–8.
12. Ashrafian H, Frenneaux MP, Opie LH. Metabolic mechanisms in heart failure. *Circulation* 2007;116:434–48.
13. Tuunanen H, Engblom E, Naum A, et al. Free fatty acid depletion acutely decreases cardiac work and efficiency in cardiomyopathic heart failure. *Circulation* 2006;114:2130–7.
14. Tuunanen H, Engblom E, Naum A, et al. Trimetazidine, a metabolic modulator, has cardiac and extracardiac benefits in idiopathic dilated cardiomyopathy. *Circulation* 2008;118:1250–8.

15. Blain JM, Schafer H, Siegel AL, Bing RJ. Studies on myocardial metabolism. VI. Myocardial metabolism in congestive failure. *Am J Med* 1956;20:820–33.
16. Opie LH, editor. *Heart Physiology, From Cell to Circulation*. 4th edition. Philadelphia, PA: Lippincott, Williams & Wilkins, 2004: 308–25, 331.
17. Stanley WC, Recchia FA, Lopaschuk GD. Myocardial substrate metabolism in the normal and failing heart. *Physiol Rev* 2005;85: 1093–129.
18. Nuutila P, Koivisto VA, Knuuti J, et al. Glucose-free fatty acid cycle operates in human heart and skeletal muscle in vivo. *J Clin Invest* 1992;89:1767–74.
19. Taegtmeyer H, Hems R, Krebs HA. Utilisation of energy-providing substrates in the isolated working rat heart. *Biochem J* 1980;186:701–11.
20. Kempainen J, Fujimoto T, Kalliokoski KK, Viljanen T, Nuutila P, Knuuti J. Myocardial and skeletal muscle glucose uptake during exercise in humans. *J Physiol* 2002;542:403–12.
21. Drake AJ, Haines JR, Noble MI. Preferential uptake of lactate by the normal myocardium in dogs. *Cardiovasc Res* 1980;14:65–72.
22. Carlson LA, Kaijser L, Rossner S, Wahlqvist ML. Myocardial metabolism of exogenous plasma triglycerides in resting man. Studies during alimentary lipaemia and intravenous infusion of a fat emulsion. *Acta Med Scand* 1973;193:233–45.
23. Yagyu H, Chen G, Yokoyama M, et al. Lipoprotein lipase (LpL) on the surface of cardiomyocytes increases lipid uptake and produces a cardiomyopathy. *J Clin Invest* 2003;111:419–26.
24. Liao R, Jain M, Cui L, et al. Cardiac-specific overexpression of GLUT1 prevents the development of heart failure attributable to pressure overload in mice. *Circulation* 2002;106:2125–31.
25. Korvald C, Elvenes OP, Myrmet T. Myocardial substrate metabolism influences left ventricular energetics in vivo. *Am J Physiol Heart Circ Physiol* 2000;278:H1345–51.
26. Opie LH, Thandroyen FT, Muller CA, Bricknell OL. Adrenaline-induced “oxygen-wastage” and enzyme release from working rat heart. Effects of calcium antagonism, beta-blockade, nicotinic acid and coronary artery ligation. *J Mol Cell Cardiol* 1979;11:1073–94.
27. Hütter JF, Schweickhardt C, Piper HM, Spieckermann PG. Inhibition of fatty acid oxidation and decrease of oxygen consumption of working rat heart by 4-bromocrotonic acid. *J Mol Cell Cardiol* 1984;16:105–8.
28. Chavez PN, Stanley WC, McElfresh TA, Huang H, Sterk JP, Chandler MP. Effect of hyperglycemia and fatty acid oxidation inhibition during aerobic conditions and demand-induced ischemia. *Am J Physiol Heart Circ Physiol* 2003;284:H1521–7.
29. Murray AJ, Anderson RE, Watson GC, Radda GK, Clarke K. Uncoupling proteins in human heart. *Lancet* 2004;364:1786–8.
30. Murray AJ, Panagia M, Hauton D, Gibbons GF, Clarke K. Plasma free fatty acids and peroxisome proliferator-activated receptor alpha in the control of myocardial uncoupling protein levels. *Diabetes* 2005;54: 3496–502.
31. Brand MD, Esteves TC. Physiological functions of the mitochondrial uncoupling proteins UCP2 and UCP3. *Cell Metab* 2005;2:85–93.
32. Opie LH. The metabolic vicious cycle in heart failure. *Lancet* 2004;364:1733–4.
33. Harmancey R, Wilson CR, Taegtmeyer H. Adaptation and maladaptation of the heart in obesity. *Hypertension* 2008;52:181–7.
34. Schonfeld P, Wojtczak L. Fatty acids as modulators of the cellular production of reactive oxygen species. *Free Radic Biol Med* 2008;45: 231–41.
35. Koves TR, Ussher JR, Noland RC, et al. Mitochondrial overload and incomplete fatty acid oxidation contribute to skeletal muscle insulin resistance. *Cell Metab* 2008;7:45–56.
36. Chidsey CA, Harrison DC, Braunwald E. Augmentation of the plasma norepinephrine response to exercise in patients with congestive failure. *N Engl J Med* 1962;267:650–4.
37. Anand IS, Ferrari R, Kalra GS, Wahi PL, Poole-Wilson PA, Harris PC. Edema of cardiac origin. Studies of body water and sodium, renal function, hemodynamic indexes, and plasma hormones in untreated congestive cardiac failure. *Circulation* 1989;80:299–305.
38. Hasking GJ, Esler MD, Jennings GL, Burton D, Johns JA, Korner PI. Norepinephrine spillover to plasma in patients with congestive heart failure: evidence of increased overall and cardiorenal sympathetic nervous activity. *Circulation* 1986;73:615–21.
39. Bristow MR.  $\beta$ -adrenergic receptor blockade in chronic heart failure. *Circulation* 2000;101:558–69.
40. Beanlands RSB, Nahmias C, Gordon E, et al. The effects of  $\beta_1$ -blockade on oxidative metabolism and the metabolic cost of ventricular work in patients with left ventricular dysfunction. *Circulation* 2000;102:2070–5.
41. Wallhaus TR, Taylor M, Degrado TR, et al. Myocardial free fatty acid and glucose use after carvedilol treatment in patients with congestive heart failure. *Circulation* 2001;103:2441–6.
42. Gambert S, Vergely C, Filomenko R, et al. Adverse effects of free fatty acid associated with increased oxidative stress in posts ischemic isolated rat hearts. *Mol Cell Biochem* 2006;283:147–52.
43. Chandler MP, Stanley WC, Morita H, et al. Short-term treatment with ranolazine improves mechanical efficiency in dogs with chronic heart failure. *Circ Res* 2002;91:278–80.
44. Eichhorn EJ, Heesch CM, Barnett JH, et al. Effect of metoprolol on myocardial function and energetics in patients with nonischemic dilated cardiomyopathy: a randomized, double-blind, placebo-controlled study. *J Am Coll Cardiol* 1994;24:1310–20.
45. Al-Hesayen A, Azevedo ER, Floras JS, Hollingshead S, Lopaschuk GD, Parker JD. Selective versus nonselective beta-adrenergic receptor blockade in chronic heart failure: differential effects on myocardial energy substrate utilization. *Eur J Heart Fail* 2005;7:618–23.
46. Poole-Wilson PA, Swedberg K, Cleland JG, et al. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): randomised controlled trial. *Lancet* 2003;362:7–13.
47. Taegtmeyer H, Ballal K. No low-fat diet for the failing heart? *Circulation* 2006;114:2092–3.
48. Monti LD, Setola E, Fragasso G, et al. Metabolic and endothelial effects of trimetazidine on forearm skeletal muscle in patients with type 2 diabetes and ischemic cardiomyopathy. *Am J Physiol Endocrinol Metab* 2006;290:E54–9.
49. AlZadjali MA, Godfrey V, Khan F, et al. Insulin resistance is highly prevalent and is associated with reduced exercise tolerance in nondiabetic patients with heart failure. *J Am Coll Cardiol* 2009;53:747–53.
50. Frias MA, James RW, Gerber-Wicht C, Lang U. Native and reconstituted HDL activate STAT3 in ventricular cardiomyocytes via ERK1/2: role of sphingosine-1-phosphate. *Cardiovasc Res* 2009;82: 313–23.
51. Nishikawa T, Edelstein D, Du XL, et al. Normalizing mitochondrial superoxide production blocks three pathways of hyperglycaemic damage. *Nature* 2000;404:787–90.
52. Lee L, Campbell R, Scheuermann-Freestone M, et al. Metabolic modulation with perhexiline in chronic heart failure: a randomized, controlled trial of short-term use of a novel treatment. *Circulation* 2005;112:3280–8.
53. McCormack JG, Barr RL, Wolff AA, Lopaschuk GD. Ranolazine stimulates glucose oxidation in normoxic, ischemic, and reperfused ischemic rat hearts. *Circulation* 1996;93:135–42.
54. Timmis AD, Chaitman BR, Crager M. Effects of ranolazine on exercise tolerance and HbA1c in patients with chronic angina and diabetes. *Eur Heart J* 2006;27:42–8.
55. Morrow DA, Scirica BM, Chaitman BR, et al. Evaluation of the glycometabolic effects of ranolazine in patients with and without diabetes mellitus in the MERLIN-TIMI 36 randomized controlled trial. *Circulation* 2009;119:2032–9.
56. Wang P, Fraser H, Lloyd SG, McVeigh JJ, Belardinelli L, Chatham JC. A comparison between ranolazine and CVT-4325, a novel inhibitor of fatty acid oxidation, on cardiac metabolism and left ventricular function in rat isolated perfused heart during ischemia and reperfusion. *J Pharmacol Exp Ther* 2007;321:213–20.
57. Sossalla S, Wagner S, Rasenack EC, et al. Ranolazine improves diastolic dysfunction in isolated myocardium from failing human hearts—role of late sodium current and intracellular ion accumulation. *J Mol Cell Cardiol* 2008;45:32–43.
58. Rastogi S, Sharov VG, Mishra S, et al. Ranolazine combined with enalapril or metoprolol prevents progressive LV dysfunction and remodeling in dogs with moderate heart failure. *Am J Physiol Heart Circ Physiol* 2008;295:H2149–55.
59. Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention and metformin. *N Engl J Med* 2002;346:393–403.

60. Nishiyama Y, Minohara M, Ohe M, et al. Effect of physical training on insulin resistance in patients with chronic heart failure. *Circ J* 2006;70:864-7.
61. Kemppainen J, Tsuchida H, Stolen K, et al. Insulin signalling and resistance in patients with chronic heart failure. *J Physiol* 2003;550:305-15.
62. Stolen KQ, Kemppainen J, Kalliokoski KK, et al. Exercise training improves insulin-stimulated myocardial glucose uptake in patients with dilated cardiomyopathy. *J Nucl Cardiol* 2003;10:447-55.
63. Piepoli MF, Davos C, Francis DP, Coats AJ, ExTraMATCH Collaborative. Exercise training meta-analysis of trials in patients with chronic heart failure (ExTraMATCH). *BMJ* 2004;328:189.
64. Stolen KQ, Kemppainen J, Ukkonen H, et al. Exercise training improves biventricular oxidative metabolism and left ventricular efficiency in patients with dilated cardiomyopathy. *J Am Coll Cardiol* 2003;41:460-7.
65. He L, Sabet A, Djedjos S, et al. Metformin and insulin suppress hepatic gluconeogenesis through phosphorylation of CREB binding protein. *Cell* 2009;137:635-46.
66. Bailey CJ, Turner RC. Metformin. *N Engl J Med* 1996;334:574-9.
67. Gundewar S, Calvert JW, Jha S, et al. Activation of AMP-activated protein kinase by metformin improves left ventricular function and survival in heart failure. *Circ Res* 2009;104:403-11.
68. Sasaki H, Asanuma H, Fujita M, et al. Metformin prevents progression of heart failure in dogs: role of AMP-activated protein kinase. *Circulation* 2009;119:2568-77.
69. Eurich DT, McAlister FA, Blackburn DF, et al. Benefits and harms of antidiabetic agents in patients with diabetes and heart failure: systematic review. *Br Med J* 2007;335:497.
70. Hallsten K, Virtanen KA, Lonnqvist F, et al. Rosiglitazone but not metformin enhances insulin- and exercise-stimulated skeletal muscle glucose uptake in patients with newly diagnosed type 2 diabetes. *Diabetes* 2002;51:3479-85.
71. Magalhaes FO, Gouveia LM, Torquato MT, Paccola GM, Piccinato CE, Foss MC. Metformin increases blood flow and forearm glucose uptake in a group of non-obese type 2 diabetes patients. *Horm Metab Res* 2006;38:513-7.
72. Lupi R, Del Guerra S, Fierabracci V, et al. Lipotoxicity in human pancreatic islets and the protective effect of metformin. *Diabetes* 2002;51 Suppl 1:S134-7.
73. Han SH, Quon MJ, Kim JA, Koh KK. Adiponectin and cardiovascular disease: response to therapeutic interventions. *J Am Coll Cardiol* 2007;49:531-8.
74. Frankel DS, Vasan RS, D'Agostino RB Sr., et al. Resistin, adiponectin, and risk of heart failure the Framingham offspring study. *J Am Coll Cardiol* 2009;53:754-62.
75. Iacobellis G, Barbaro G. The double role of epicardial adipose tissue as pro- and anti-inflammatory organ. *Horm Metab Res* 2008;40:442-5.
76. Chess DJ, Stanley WC. Role of diet and fuel overabundance in the development and progression of heart failure. *Cardiovasc Res* 2008;79:269-78.
77. Depre C, Young ME, Ying J, et al. Streptozotocin-induced changes in cardiac gene expression in the absence of severe contractile dysfunction. *J Mol Cell Cardiol* 2000;32:985-96.
78. 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;276:44390-5.
79. Dandona P, Chaudhuri A, Ghanim H, Mohanty P. Insulin as an anti-inflammatory and antiatherogenic modulator. *J Am Coll Cardiol* 2009;53:S14-20.
80. Wolever TM, Gibbs AL, Mehling C, et al. The Canadian Trial of Carbohydrates in Diabetes (CCD), a 1-y controlled trial of low-glycemic-index dietary carbohydrate in type 2 diabetes: no effect on glycated hemoglobin but reduction in C-reactive protein. *Am J Clin Nutr* 2008;87:114-25.
81. Taylor SH, Majid PA. Insulin and the heart. *J Mol Cell Cardiol* 1971;2:293-317.
82. Griesdale DE, de Souza RJ, van Dam RM, et al. Intensive insulin therapy and mortality among critically ill patients: a meta-analysis including NICE-SUGAR study data. *CMAJ* 2009;180:821-7, discussion 799-800.
83. Finfer S, Chittock DR, Su SY, et al. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med* 2009;360:1283-97.
84. Opie LH. Metabolic management of acute myocardial infarction comes to the fore and extends beyond control of hyperglycemia. *Circulation* 2008;117:2172-7.
85. Stanley AW Jr., Moraski RE, Russell RO, et al. Effects of glucose-insulin-potassium on myocardial substrate availability and utilization in stable coronary artery disease. Studies on myocardial carbohydrate, lipid and oxygen arterial-coronary sinus differences in patients with coronary artery disease. *Am J Cardiol* 1975;36:929-37.
86. Ghanim H, Dhindsa S, Aljada A, Chaudhuri A, Viswanathan P, Dandona P. Low-dose rosiglitazone exerts an antiinflammatory effect with an increase in adiponectin independently of free fatty acid fall and insulin sensitization in obese type 2 diabetics. *J Clin Endocrinol Metab* 2006;91:3553-8.
87. Lautamaki R, Airaksinen KE, Seppanen M, et al. Rosiglitazone improves myocardial glucose uptake in patients with type 2 diabetes and coronary artery disease: a 16-week randomized, double-blind, placebo-controlled study. *Diabetes* 2005;54:2787-94.
88. van der Meer RW, Rijzewijk LJ, de Jong HW, et al. Pioglitazone improves cardiac function and alters myocardial substrate metabolism without affecting cardiac triglyceride accumulation and high-energy phosphate metabolism in patients with well-controlled type 2 diabetes mellitus. *Circulation* 2009;119:2069-77.
89. Yki-Jarvinen H. The PROactive study: some answers, many questions. *Lancet* 2005;366:1241-2.
90. DREAM Trial Investigators, Dagenais GR, Gerstein HC, Holman R, et al. Effects of ramipril and rosiglitazone on cardiovascular and renal outcomes in people with impaired glucose tolerance or impaired fasting glucose: results of the Diabetes REduction Assessment with ramipril and rosiglitazone Medication (DREAM) trial. *Diabetes Care* 2008;31:1007-14.
91. Zhang H, Zhang A, Kohan DE, Nelson RD, Gonzalez FJ, Yang T. Collecting duct-specific deletion of peroxisome proliferator-activated receptor gamma blocks thiazolidinedione-induced fluid retention. *Proc Natl Acad Sci U S A* 2005;102:9406-11.
92. McGavock JM, Lingway I, Zib I, et al. Cardiac steatosis in diabetes mellitus: a 1H-magnetic resonance spectroscopy study. *Circulation* 2007;116:1170-5.
93. Lago RM, Singh PP, Nesto RW. Congestive heart failure and cardiovascular death in patients with prediabetes and type 2 diabetes given thiazolidinediones: a meta-analysis of randomized clinical trials. *Lancet* 2007;370:1129-36.
94. Ussher JR, Lopaschuk GD. Targeting malonyl CoA inhibition of mitochondrial fatty acid uptake as an approach to treat cardiac ischemia/reperfusion. *Basic Res Cardiol* 2009;104:203-10.
95. Mozaffarian D, Bryson CL, Lemaitre RN, Burke GL, Siscovick DS. Fish intake and risk of incident heart failure. *J Am Coll Cardiol* 2005;45:2015-21.
96. Duda MK, O'Shea KM, Tintinu A, et al. Fish oil, but not flaxseed oil, decreases inflammation and prevents pressure overload-induced cardiac dysfunction. *Cardiovasc Res* 2009;81:319-27.
97. Mayr M, Liem D, Zhang J, et al. Proteomic and metabolomic analysis of cardioprotection: interplay between protein kinase C epsilon and delta in regulating glucose metabolism of murine hearts. *J Mol Cell Cardiol* 2009;46:268-77.
98. Sokos GG, Nikolaidis LA, Mankad S, Elahi D, Shannon RP. Glucagon-like peptide-1 infusion improves left ventricular ejection fraction and functional status in patients with chronic heart failure. *J Card Fail* 2006;12:694-9.

**Key Words:** adrenergic ■ fatty acids ■ oxygen wastage.

 **APPENDIX**

**For a table on the cardioprotective basic and clinical studies with TMZ and related references, please see the online version of this article.**