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Abstract—Although neurohumoral antagonism has successfully reduced heart failure morbidity and mortality, the residual disability and death rate remains unacceptably high. Though abnormalities of myocardial metabolism are associated with heart failure, recent data suggest that heart failure may itself promote metabolic changes such as insulin resistance, in part through neurohumoral activation. A detrimental self-perpetuating cycle (heart failure → altered metabolism → heart failure) that promotes the progression of heart failure may thus be postulated. Accordingly, we review the cellular mechanisms and pathophysiology of altered metabolism and insulin resistance in heart failure. It is hypothesized that the ensuing detrimental myocardial energetic perturbations result from neurohumoral activation, increased adverse free fatty acid metabolism, decreased protective glucose metabolism, and in some cases insulin resistance. The result is depletion of myocardial ATP, phosphocreatine, and creatine kinase with decreased efficiency of mechanical work. On the basis of the mechanisms outlined, appropriate therapies to mitigate aberrant metabolism include intense neurohumoral antagonism, limitation of diuretics, correction of hypokalemia, exercise, and diet. We also discuss more novel mechanistic-based therapies to ameliorate metabolism and insulin resistance in heart failure. For example, metabolic modulators may optimize myocardial substrate utilization to improve cardiac function and exercise performance beyond standard care. The ultimate success of metabolic-based therapy will be manifest by its capacity further to lessen the residual mortality in heart failure. (***Circulation*****. 2007;116:434-448.)**

Key Words: fatty acids ■ glucose ■ heart failure ■ insulin resistance

Despite significant therapeutic advances, heart failure (HF) remains a leading cause of morbidity and mortality in developed[1] and increasingly in developing countries,[2] with a 5-year mortality rate of ≈50%, which rivals or exceeds that of many cancers.[3] This unacceptably high residual mortality and morbidity has mandated a reevaluation of cardiac biology with the aim to identify novel therapeutic strategies for HF. Because the daily turnover of ATP (≈6 to 35 kg) is very many times that of the myocardial ATP pool, and even the healthy heart only extracts ≈25% of energy derivable from substrates,[4] it is not surprising that even subtle variations in the efficiency of energy generation or utilization may have a profound cumulative impact on cellular energy levels.[5] Thus cardiac energetics in particular and metabolism in general represent promising targets for HF therapy.[6]

Correspondingly, numerous studies have identified decreased cardiac energy levels and flux as a consistent feature of HF.[6,7] These observations have been reinforced by genomic studies[8] and have focused considerable attention on metabolic modulation as a therapy for HF.[6] Specifically, altered myocardial carbohydrate metabolism and the related state of myocardial insulin resistance (IR), in which given concentrations of insulin produce an attenuated glucose response,[9] have attracted much interest as potential determinants of abnormal myocardial energetics. Even the earliest metabolic studies in diabetic patients by Bing and colleagues showed decreased myocardial glucose and increased fatty acid extraction.[10] These excess fatty acids may adversely affect the myocardium[11] and in HF may be associated with uncoupled respiration.[12] However, the details of metabolic aberrations in HF are often indirect, preliminary, and sometimes conflicting. With the aid of recent clinical and molecular data, we will assess the hypothesis that the hyperadrenergic state of HF initiates an adverse metabolic vicious cycle,[13] whereby aberrant metabolism and in some cases IR further detrimentally affect HF (Figure 1).[13] After a critical review of the epidemiology and mechanisms of whether and how cardiac IR contributes to the more established role of myocardial metabolism in HF, we evaluate existing and novel metabolic and energetic therapies for HF.

Does Insulin Resistance Have a Role in the Pathogenesis of Heart Failure?

Is There an Epidemiological Relationship Between IR and HF?

A robust association exists between type 2 diabetes mellitus (T2DM), the ultimate manifestation of IR, and HF.[14] The

The present article is the third in a series on the topic of "Targeting Metabolism as a Therapeutic Approach for Cardiovascular Diseases."

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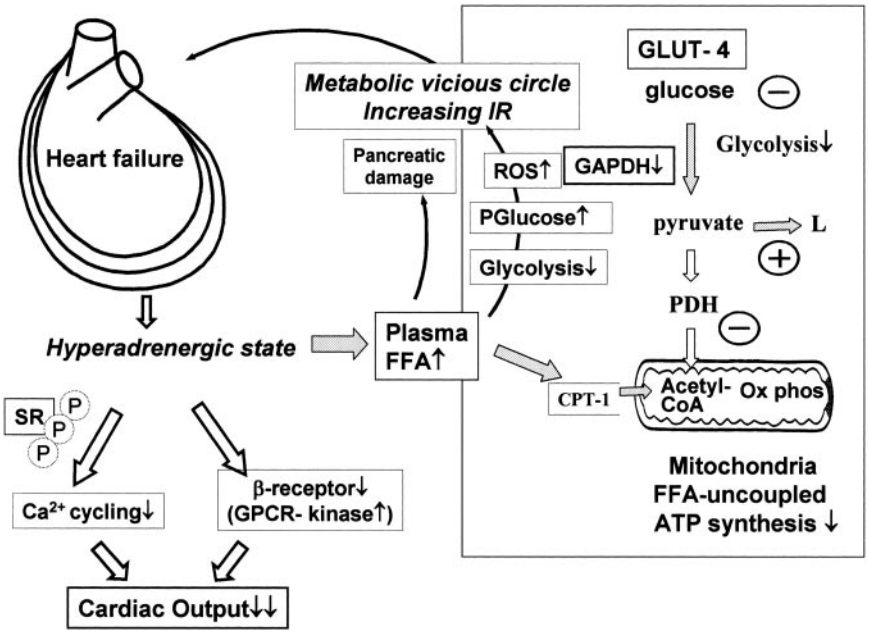

Figure 1. Proposed concept of metabolic vicious circle in HF with aberrant metabolism and increasing IR as a consequence of the hyperadrenergic state and increased plasma FFAs. FFAs inhibit glycolysis and glucose uptake by the heart and skeletal muscle, so that plasma glucose (PGlucose) increases (right) to promote formation of reactive oxygen species (ROS) that may inhibit glyceraldehyde-3-phosphate dehydrogenase (GAPDH). Multifactorial pancreatic damage, such as that mediated by FFA, together with hyperglycemia, causes IR. Plasma FFA taken up by the heart is activated and transported by carnitine palmitoyltransferase-1 (CPT-1) (Figure 4) into the mitochondria to uncouple respiration with oxygen wastage. These metabolic defects are added to other cellular consequences of the hyperadrenergic state, namely hyperphosphorylation of the sarcoplasmic reticulum and inhibition of the β-adrenergic receptor by increased G-protein–coupled receptor kinase (GPCR-kinase). Acetyl-CoA indicates acetyl coenzyme A; Ox phos, oxidative phosphorylation; P, hyperphosphorylation; and PDH, pyruvate dehydrogenase. Modified from Opie[13] with permission from Elsevier. Copyright 2006.

Framingham Study drew attention to the increased incidence (T2DM:control) of HF in diabetic men (2.4:1) and women (5:1) independent of age, coronary disease, hypertension, and body mass index.[15] Although the risk of HF was exaggerated in the young, the prevalence of HF in elderly diabetic patients was as high as 30%.[14] Other studies have shown that even a 1% increase in hemoglobin A1c enhances the risk of development of HF by 15%,[16,17] that glucose is an independent predictor of hospitalization for HF[18] and that stress-induced increased plasma glucose levels are associated with the risk development of HF.[19] T2DM predisposes severe presentations of HF and predicts HF mortality; ≈25% of stable compared with >33% of patients with decompensated HF manifest T2DM.[20,21] In 1187 men prospectively assessed over 9 years, IR predicted the development of HF. One standard deviation decrease in insulin sensitivity increased the risk of HF by approximately one third.[22]

This association may to a great extent be attributed to the confounding prevalence of hypertension, hyperglycemia, and associated free radical generation,[23] microvascular dysfunction, and ischemic heart disease in IR states.[24] However, although a tendentious diagnosis, the recognition of human diabetic cardiomyopathy as an entity characterized by the absence of coronary heart disease and hypertension but with ventricular and often diastolic dysfunction raises the hypothesis that IR, as a component of diabetic metabolism, could confer a detrimental metabolic effect on the myocardium.[24–31]

Can IR Cause Cardiomyopathy?

A striking manifestation of the potentially causative relationship between IR and HF is the high prevalence of dilated cardiomyopathy and HF in clinical syndromes of IR. For example, Alström syndrome, a disorder that affects only 300 patients worldwide and is associated with severe IR, results in a potentially fatal cardiomyopathy in ≈60% of cases.[32] Other genetic disorders such as Bardet-Biedl syndrome manifest obesity, IR, and cardiomyopathy.[33] It might be argued that, in addition to their common feature of IR, these syndromes may contribute to cardiomyopathy through other mechanisms[34]; importantly, however, as a corollary, in IR mice that develop genetic T2DM (*db/db*), IR is also associated with progressive cardiomyopathic changes.[35]

Does HF Lead to IR?

Although evidence is increasing that IR predisposes to HF,[24–31] preliminary evidence also suggests that HF may reciprocally predispose to IR and T2DM. Glucose abnormalities are overrepresented in HF as they are identified in 43% of HF patients, and these abnormalities correlate with increasing levels of circulating norepinephrine and with decreasing functional status.[36] Studies that apply the euglycemic-hyperinsulinemic clamp to patients with HF support these snapshot observations; irrespective of the inciting cause, HF is associated with systemic IR that itself predicts increased mortality.[37] It is important not to assume that systemic and myocardial IR invariably coexist; for example, T2DM patients with apparently normal ventricular function manifest a competent myocardial insulin response that contrasts with increased systemic IR.[38,39] By contrast in HF, both systemic and myocardial IR may increase. This proposal is based on positron emission tomographic (PET) observations that the HF myocardium has reduced glucose uptake in favor of fatty acid uptake[40] in most[41,42] but not all studies. HF predicts the development of T2DM in a graded way.[43] In 7.7 years of follow-up, T2DM developed in 13% of New York Heart Association (NYHA) class I, 15% of NYHA class II, and 20% of NYHA class III HF patients.[44] The risk of T2DM in HF is 18% to 22% higher per 10 years than in treated hypertension.[20]

PET studies remain necessarily indirect because of their capacity to quantify myocardial substrate uptake rather than the related but dissociable details of substrate utilization.[4]

With these limitations acknowledged, myocardial glucose uptake measured by PET appears to be lower in diabetic (0.34 μmol · min^{-1} · g^{-1}) than in nondiabetic patients (0.47 μmol · min^{-1} · g^{-1}) with coronary artery disease and HF.[45] Both are lower than historical control subjects (0.61 μmol · min^{-1} · g^{-1}). This implies that HF, particularly in the context of coronary disease, is associated with myocardial IR. As a corollary, preliminary evidence suggests that glucagon-like peptide 1, which increases plasma insulin levels and decreases glucose levels and thus mitigates IR, also ameliorates HF.[46]

Limitations

An explicit weakness of epidemiological studies is their inability to fully account for confounders such as traditional risk factors, reverse causation (whereby underlying preexisting IR was unmasked by advancing HF) or for diuretic-induced diabetes (the worse the HF, the greater the need for diuretics). The above studies cannot therefore be regarded as mechanistic but are hypothesis generating. Whereas the clinical and laboratory evidence presented here and elsewhere supports a contributory role for T2DM and probably IR in HF,[24–31] a reciprocal causal relation whereby HF also promotes IR remains largely associative and hence more speculative.[47] Nevertheless, the role of HF in the promotion of IR is mechanistically supported in a canine model of cardiomyopathy that develops systemic and myocardial IR.[48] More studies are clearly needed.

The Role of Myocardial Metabolism in Relating Insulin Resistance to Heart Failure

A number of compatible proposals to explain the associations between altered metabolism, IR, and HF include: (a) activation of the neurohumoral system, which includes the sympathetic nervous system (SNS) and the renin-angiotensin-aldosterone system (Figure 2)[20,49]; (b) inflammation as exemplified by increased tumor necrosis factor α levels and its soluble receptors[50]; (c) alterations in skeletal muscle function and mass as a result of reduced physical activity; (d) endothelial dysfunction; (e) increased adipokines such as adiponectin and leptin[51]; and (f) pharmacological exacerbation of IR (eg, by diuretics). Of these, (a) remains the best investigated and probably most robust contributor to altered metabolism in HF.

Adrenergic Mechanisms That Underlie Altered Myocardial Metabolism and IR in HF

Neurohumoral homeostasis is maladaptively activated in response to a chronic reduction in cardiac output as characterized by persistent activation of the SNS and the interlinked renin-angiotensin-aldosterone system.[52] In addition to this increased catecholamine secretion, reduced cardiac catecholamine reuptake can be observed.[53] Increased catecholamines have directly detrimental effects on the heart, which cause marked enzyme loss as an index of diffuse myocardial damage, and substantial oxygen-wastage even in the absence of free fatty acids (FFA) in the perfusate.[54] Furthermore, norepinephrine promotes both coronary vasoconstriction[20] and increased plasma FFA levels,[55] which further promote oxygen-wastage (Figure 3).[56] Infusion studies in volunteers support a role for increased norepinephrine levels in HF as a cause of elevated plasma FFA.[57] In turn, FFAs reciprocally augment SNS activity, at least in normal controls.[58] In human skeletal muscle, a dose-response relationship exists between plasma FFA[27,59,60,61] and defects in insulin signaling.[62] This may in part be caused by FFA-mediated activation of protein kinase C-β, which phosphorylates insulin receptors and results in reduced capillary opening and reduced myocyte glucose import.[63,64] Acute decreases in FFA levels in humans increase glucose uptake and decrease IR.[57] Importantly, IR can contribute to this aberrant metabolism; independent of other risk factors for cardiac dysfunction, a study of IR obese young women represents strong evidence that IR per se can increase cardiac FFA metabolism and decrease myocardial contractile efficiency.[27,60] According to this schema, because myocyte FFA metabolism is proportional to plasma FFAs, myocardial FFA metabolism should increase in HF (a frequent though not consistent finding).[41,65]

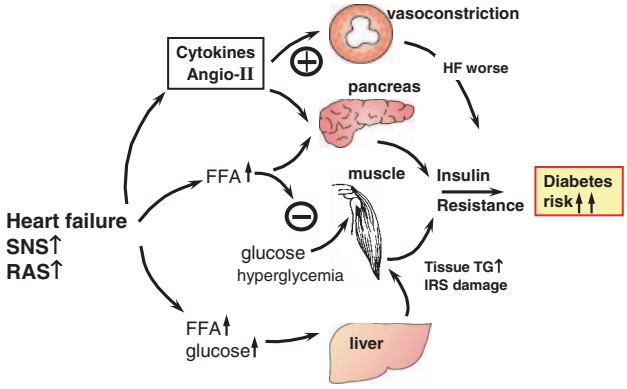

Figure 2. HF invokes compensatory SNS and renin-angiotensin-aldosterone system activation, which increases blood FFAs and thereby inhibits the uptake of glucose by muscle and damages the pancreas. Plasma glucose rises and elicits an insulin response that is, however, not adequate to overcome the hyperglycemia because of pancreatic damage mediated by cytokines such as tumor necrosis factor α, angiotensin II, and FFA. The net effect is aberrant metabolism and IR. Increased plasma FFA and glucose predispose to increased hepatic synthesis of triglycerides and increased blood levels of angiotensin II, which in turn increase tissue triglyceride levels and in the pancreas promote damage to the insulin receptor substrate-1 to thereby magnify IR. Angiotensin-II also promotes vasoconstriction, which worsens HF and therefore perpetuates the vicious circle shown in Figure 1. Angio-II indicates angiotensin II; IRS, insulin receptor substrate-1; and TG, triglycerides. Modified from Opie[49] with permission from Stanford Writers and the University of Cape Town Press. Copyright 2006.

Locally increased cardiac SNS activity in HF is also important. With use of PET with a norepinephrine analog and ^{18}F-fluorodeoxyglucose, myocardial segments with left ventricular (LV) dysfunction have reduced presynaptic norepinephrine reuptake and myocardial glucose uptake in relation to less impaired myocardial segments in the same patients.[66] Thus, after control for confounding variables, altered metabolism and IR directly relate to local SNS activity.

Thus, activation of the SNS by both catecholamines and the renin-angiotensin-aldosterone system both centrally and peripherally,[52] directly and through increased plasma FFA, is

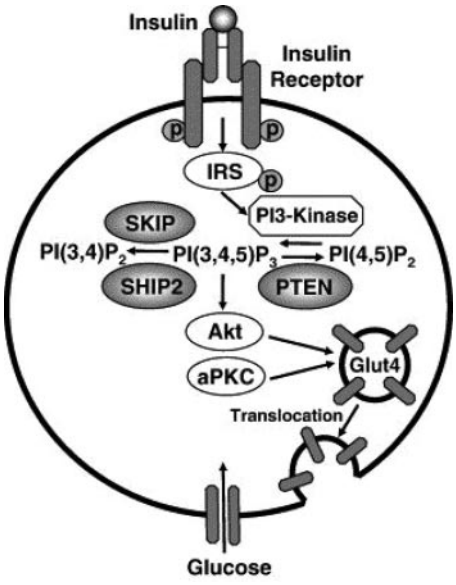

Figure 3. Insulin signaling in the heart. Although little definitive evidence exists to explain the alterations of insulin signaling in heart failure per se, limited data from canine models of HF coupled with an extensive knowledge of insulin signaling pathways in skeletal muscle permit a preliminary understanding of the aberrations in the insulin signaling pathways in HF. In skeletal muscle, insulin promotes translocation of glucose transporter (Glut)-4 to increase inward transport of glucose, which acts via insulin receptor substrate (IRS), phosphotidyl-inositol-3 kinase (P13), atypical protein C (aPKC), and protein kinase B (PKB), also called Akt. The insulin-responsive Glut-4–rich vesicles move to the sarcolemma to promote inward transport of glucose. Whereas in advanced severe dilated cardiomyopathy the proximal signaling cascade was unaltered, a marked decrease took place in serine (Ser473) phosphorylation of Akt-1. A corresponding significant decrease in Glut-4 translocation in severe dilated cardiomyopathy contributes to IR. Levels of the phosphatase PTEN (phosphatase and tensin homolog deleted on chromosome ten) were also increased in the myocardium of dogs with severe dilated cardiomyopathy consistent with the impaired Ser473 phosphorylation of Akt-1. PTEN is known to inhibit phosphorylation of Akt-1. Lipid phosphatases, src homology 2 domain containing inositol 5′-phosphatase 2 (SHIP2) and skeletal muscle and kidney-enriched inositol phosphatase (SKIP) hydrolyze $PI(3,4,5)P_3$ to $PI(3,4)P_2$, and PTEN hydrolyzes $PI(3,4,5)P_3$ to $PI(4,5)P_2$. Adapted from Sasaoka et al,[56] with permission from Elsevier. Copyright 2006.

associated with systemic and cardiac IR.[49] As a corollary, IR in HF appears to correlate well with markers of SNS activation, both in patients and in canine models of HF.[49,55] The assertion that SNS activation alters myocardial metabolism in HF is predominantly based on correlative or indirect observations. To prove causation, rather than association between plasma SNS, FFA, and IR in HF, would require enhanced suppression of SNS to reduce cardiac metabolism of FFA, cardiac IR, and would ultimately ameliorate HF prognosis.

How FFA Alters Insulin Signaling

At least in skeletal muscle, plasma FFA-induced IR is associated with increased triglyceride, increased cellular FFAs, increased cytoplasmic fatty acid metabolites such as diacylglycerol, and activation of protein kinase C and nuclear factor-kappa-B.[67] FFA metabolism also increases in response to the nuclear receptor peroxisome proliferator activator receptor α (PPAR-α).[68] Which of these are pertinent and proximate rather than downstream to IR?

Although a robust association exists between muscular triglyceride content and IR,[67] it is unclear whether the lipid species that mediates IR is triglyceride or intracellular fatty acid and its metabolites. The mobilization of FFA from triglyceride is determined by adiposome triglyceride lipase. In adiposome triglyceride lipase–null mice, despite the lack of triglyceride, the reduced availability of lipase-derived FFAs increased glucose utilization and decreased cardiac IR.[69] Thus, at least in transgenic mice, FFAs and their intracellular derivatives rather than triglycerides appear to be critical in the mediation of cardiac IR either by alteration of insulin signaling[28] or by direct competition with glucose metabolism. Accumulation of intramuscular fatty acyl coenzyme A (acyl CoA), a FFA that is activated after uptake, then inhibits intracellular muscle insulin signaling, which thereby limits glucose uptake (Figure 3).[67]

Consequences of Metabolic Disturbances in Heart Failure

Accordingly, one of the most profound consequences of contractile dysfunction and SNS activation in HF is altered metabolism. The pertinence of the ensuing energy deficiency in HF has recently been underlined by extensive advances in noninvasive imaging technology.[4,6,7] In this section, the energy changes that occur in HF in vivo are detailed, the contribution of altered substrate utilization to this energy deficiency is discussed, and how the cardiac transcriptional milieu contributes to these changes is reviewed. The limitations of energetic and utilization studies are discussed in detail. Ultimately, these mechanistic insights will set the scene on how to affect HF with metabolic therapy.

High-Energy Phosphates

Both the failing heart[6,7] and the IR myocardium are energy deficient. This precarious energy state is unsurprising when it is considered that even in the healthy heart only ≈25% of energy derivable from substrates is converted to useful external work.[4,70] This is further exacerbated by the astonishing requirement that the heart needs to generate up to ≈70 times its own weight in ATP everyday.[5] Robust biochemical evidence has existed for decades that the failing myocardium is energy deficient: the ratio of [ATP]/[ADP][Pi], based on the Gibbs law, determines the energy charge of the heart and hence the capacity to perform work. Early data from limited human myocardial biopsy specimens obtained during surgery or derived during cardiac transplantation demonstrated that the failing heart had ≈30% lower ATP level than controls.[6] Although this confirmed that the failing heart is indeed depleted of energy, extensive biochemical and later magnetic resonance spectroscopy studies have nevertheless failed to provide a compelling causal relation between such energy deficiency and HF.[6] Magnetic resonance spectroscopy has revolutionized the study of cardiac energy metabolism in that many studies have confirmed energy deficiency in HF (detailed in an excellent review by Neubauer)[7]; however, one criticism of both biopsy and magnetic resonance spectros-

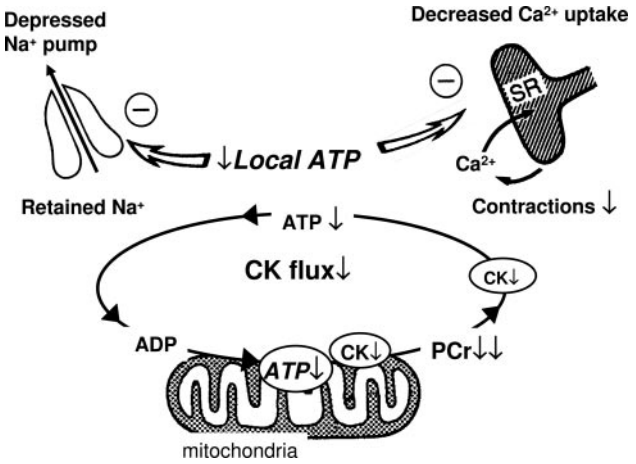

Figure 4. Multiple defects of energy transfer in HF. Note depressed activity of creatine kinase (CK) and depressed flux of PCr through CK. Hyperphosphorylation of the sarcoplasmic reticulum (SR) leads to decreased release of Na^+ from the SR, with decreased contractile force, augmented by deficits in the energy supply. Depressed Na^+ pump activity may sensitize to digoxin toxicity. Adapted from Opie.[72] Copyright 2004, Lionel H. Opie.

copy studies is the inability to study energetics in specific cardiac myocyte compartments. Because these techniques essentially measure the mean averaged level in the cardiac myocyte, the pertinence of profound and functionally important energy deficiency at the sarcomeres and ion pumps may be apparently diminished by lesser energy deficiency in other cell compartments. At present it is not possible to localize the degree and compartment of energy deficiency.[7]

Another aspect of altered energetics in HF relates to phosphocreatine (PCr), which provides a reserve supply of rapidly hydrolyzable ATP during periods of high energy demand and is part of the heart's energetic store. Because this PCr pool is readily interchangeable with ATP (under the influence of creatine kinase) and hence reflects cardiac energy levels, the PCr/ATP ratio is considered one of the best noninvasive markers of energy charge. In animal and human HF studies, PCr levels decrease by up to ≈70% irrespective of the etiology of HF.[6] Surprisingly, transgenic mice that overexpress the myocardial creatine kinase transporter developed substantial LV dysfunction. Although the mechanism of HF in these animals is not yet precisely defined, it is apparent that an increase in the total and compartmental creatine pools leads to ≈2-fold increase in ADP and lowers the energy of ATP hydrolysis. This exemplifies the principle that impairment of the energy control pathways in the heart leads to HF.[71]

Creatine Kinase Defects

Magnetic resonance spectroscopy studies that assessed the PCr/ATP ratio have confirmed the association between energetic deficiency and HF[6,7] and provide an independent predictor of both total and cardiovascular mortality in patients with dilated cardiomyopathy.[7,72] The recent development of high-speed magnetization transfer techniques has permitted studies of both the kinetics and thermodynamics of high-energy phosphate flux in the heart (Figure 4).[73] The PCr/ATP ratio falls by ≈30% in human hearts with both pressure-overload LV hypertrophy (LVH) and LVH with HF.[74] However, the flux of ATP and PCr through the creatine kinase system was reduced by 30% in LVH and by 65% in LVH with HF compared with controls; accordingly, it is impairment of energy flux that was especially detrimental.[74] Although these preliminary studies are not proof of causation, they underline the profound and specific energy defects in HF.

Substrate Metabolism

One of the main determinants of cardiac energetics is substrate utilization. Except in the postprandial period, the heart principally metabolizes FFAs (up to 70%).[65] Glucose and other carbohydrates such as lactate represent much of the remaining substrate. Mitochondrial oxidative phosphorylation represents the major source of energy (>95%). Being omnivorous renders the heart remarkably adept in the maintenance of its energy levels despite widely varying energy requirements, but this ability comes at a cost.[65] Fatty acid oxidation (FAO) requires greater oxygen for a given quantity of ATP synthesis than do carbohydrates. Thus, for the fully metabolized molecule of oleate, the major FFA taken up by the human heart, we calculate that 2.8 molecules of ATP are produced per oxygen atom utilized as opposed to 3.17 for carbohydrate. At first glance, this represents only a meager 11% increase in energy produced per oxygen (Table 1); the real difference may be greater.[54,75] In pigs, a switch from maximal glucose to maximal FFA utilization increased the oxygen requirement by ≈50%.[76] In dogs, the myocardial oxygen uptake on adrenergic challenge rose by 60%, of which approximately two thirds was mediated by FFA.[77] Hearts from IR obese mice had decreased metabolic efficiency, as manifested by a 27% increase in unloaded oxygen uptake.[78] Although these observations reflect unphysiological metabolic shifts, they may be relevant to the hyperadrenergic HF state, especially during an exercise-induced catecholamine surge that could provoke FFA-induced futile cycling and uncoupling (Figure 5). Proof of this supposition would require measurements of FAO and myocardial oxygen uptake in HF during exercise.

The integrity of the mitochondrial membrane is central to the efficiency of energy generation. Uncoupling proteins (UCPs) and the adenine nucleotide translocator lower the proton gradient in that they allow protons to re-enter the mitochondrial matrix (leak) with the production of heat rather

TABLE 1. Effect on ATP-to-Oxygen Ratio of a Total Change From Glucose to FFA Utilization by Myocardium

Molecule	ATP Yield per Molecule	ATP Yield per Carbon Atom	ATP Yield per Oxygen Atom Taken Up, P/O Ratio	Relative Decreased ATP Production Efficiency per Unit Oxygen if Glucose Is Substituted by FFA, %
Glucose (C6)	38	6.33	3.17	0
Palmitate (C16)	129	8.06	2.80	11.7
Oleate (C18)	144	8.00	2.82	11.0

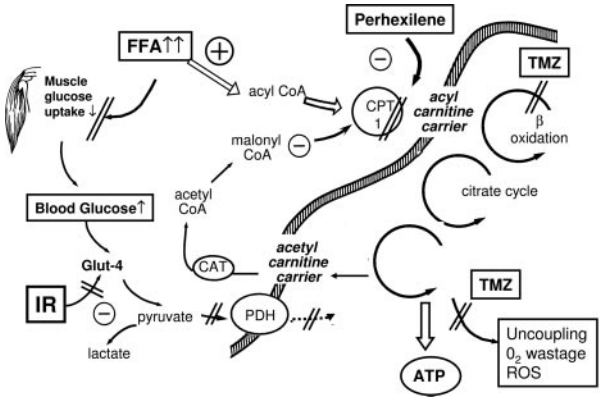

Figure 5. FFA metabolism in HF. Excessive circulating FFA leads to transfer of intracellular activated long-chain fatty acid (acyl CoA) with further facilitated transfer into mitochondria for oxidation. Carnitine palmityl CoA transferase (CPT-1) on the outer mitochondrial membrane forms long-chain acyl carnitine compounds (acyl carnitine), which are transferred into the mitochondrial space for oxidation in the fatty acid oxidation cycle that leads to the citrate cycle and electron transport chain. When this system is overloaded, as in HF, then excess reactive oxygen species (ROS) is produced with uncoupling, which occurs with oxygen wastage. Excess acetyl CoA is transported outward to form malonyl CoA, which inhibits CPT-1, but this system is overridden by high levels of FFA input as in HF. IR (left side) inhibits muscle glucose uptake of increasing blood glucose values and inhibition of GLUT-4. Note sites of inhibition by perhexiline and trimetazidine (TMZ). CAT indicates carnitine acyl translocase; PDH, pyruvate dehydrogenase. Adapted from Opie.[72] Copyright 2004, Lionel H. Opie.

than ATP.[79] High FFA levels activate PPAR-α and thereby increase FAO. Coupled with reactive oxygen species and lipid peroxidation products, PPAR-α and FAO increase both the expression and the activity of cardiac UCP expression. Not only does the latter cause proton leak through the mitochondrial membrane, but the extrusion of FFA out of the mitochondria matrix via UCP3, and their subsequent flip-flop re-entry, causes further energy loss.[65] Although only preliminary evidence exists for the role of UCPs in cardiac tissue, UCPs do appear to be upregulated in human HF.[12] The combination of increased UCP and other UCPs (eg, adenine nucleotide translocator) may render the myocardium inefficient when FFA is predominantly used as fuel. This sequence is at present best viewed as speculative but has preliminary support in the diabetic rodent heart.[80]

The precise nature of substrate utilization in cardiac health and disease is controversial; this is in part caused by the limitations of even the most sophisticated tools (eg, substrate labeling and assessment with carbon-13 nuclear magnetic resonance spectroscopy) and in part caused by the indirect nature of human studies.[4] These substrate studies should thus be interpreted judiciously. For example, in rodent LVH, a reduction in PPAR-α[81] may explain the observed reduced FFA metabolism. In the spontaneously hypertensive rat a defective FFA transporter (CD36) and reduced FFA utilization may reflect a model-specific defect rather than a general feature of LVH.[82] Nevertheless, in LVH a shift away from FFA metabolism to carbohydrate metabolism (such as anaplerosis) seems to occur.[83,84]

Although subject to the limitations and controversies of data from diverse animal models of HF, indirect studies, and heterogeneous clinical settings, HF as a state of SNS activation may result in increased plasma FFA and hence predispose to IR. Accordingly, in mild to moderate HF, the myocardium appears to utilize FFA as its predominant substrate.[65,85] Studies in skeletal muscle suggest that plasma FFAs inhibit glucose transport/phosphorylation as well as muscle glycogen synthesis and glucose oxidation[86]; similar mechanisms may explain the effect of FFA in the decrease in myocardial glucose metabolism.[87] Activated FFA as acyl CoA is transported into the mitochondria by the enzyme carnitine palmitoyl transferase-1 (Figure 5), which is subject to feedback inhibition by the acyl CoA breakdown product malonyl CoA that builds up during high rates of FAO. This negative feedback reduces FAO and further increases cytoplasmic FFA and acyl CoA metabolites. In advanced HF, this unfavorable metabolic profile is complicated by the downregulation of FAO as driven by reduced PPAR-α[49,88–90] and impaired mitochondrial oxidative capacity,[65] that results in metabolic inflexibility[91] and catastrophic energy deficiency, especially if FFA is abruptly reduced.[92] It is important to note that uncertainty exists with regard to the generalizability of substrate use findings; eg, some investigators have demonstrated increased PPAR-α and FAO in advanced HF.[42,93] Furthermore, it is unclear whether substrate alterations are adaptive and whether/when they become maladaptive. This uncertainty reflects a dearth of human studies that examine the prospective changes in substrate use and incapacity specifically to manipulate this utilization in the progression of HF. Nevertheless, it appears that early inhibition of inefficient FAO is a good target to improve metabolic profile and prognosis of HF.[65]

The Role of Transcription Factors in Metabolism Modulation in HF

Regulation of FAO is modulated by a variety of influences, such as an important gene transcriptional component, especially by the PPAR family of transcription factors. As mentioned above, PPARs, especially PPAR-α, and their co-activators are modified by lipid moieties and provide attractive targets for therapeutic intervention.[94] It is generally, although not universally, considered that PPAR-α is downregulated in advanced HF as noted above and that its pharmacological upregulation after pressure overload or ischemia hastens the development of HF.[94]

In addition to alterations in FAO under the influence of PPAR-α, human HF is associated with small aberrant mitochondria.[95] Besides uncoupling, other defects that contribute to energy deficiency in HF include a reduced expression of transcription factors that regulate mitochondrial biogenesis, especially PPAR-γ coactivator 1α (PGC-1α).[96–99] Not only is HF associated with decreased oxidative capacity, but with decreased PGC-1α, as well.[100] Mice hearts that lack PGC-1α are predisposed to develop HF in response to pressure overload and can be rescued by restitution of PGC-1α activity.[101] Thus PGC-1α, among other transcription factors, has a critical role in modification of the heart's response to metabolic stress. Induction of PGC-1α might therefore be

presumed to improve HF; indeed, "it will therefore be of great interest to develop small molecules with pharmaceutical potential that can increase PGC-1α activity in vivo".[101] However, profound cardiac induction of PGC-1α in some animal models results in cardiomyopathy, perhaps in part as a result of myofibrillar apparatus displacement by increased mitochondria.[102,103] Moreover, short-term induction of PGC-1α resulted in reversible contractile dysfunction.[103] Pertinently, PGC-1α expression in myoblast cell lines led to the mitochondrial uncoupling, which resulted in decreased ATP formation and heat production.[104]

The seeming paradox that HF results from models that either profoundly upregulate or downregulate the same metabolic mediator (eg, creatine kinase, PPAR-α, or PGC-1α), provides a salutary note that cardiac metabolism in health and disease is exquisitely balanced. As with all transgenic models, models of metabolic manipulation are prone to methodological and interpretative challenges.[105] For example, PPAR-α has been either greatly overexpressed in the heart by use of the powerful myosin heavy chain promoter or it has been knocked out. Both animal models develop systolic dysfunction and respond poorly to stress (the former's phenotype is greatly exacerbated by a high-fat diet).[94] Factors such as the transgenic construct (even the same promoter gene constructs respond differently in different models; eg, because of the differing site of transgene integration), the tissue specificity of transgene expression (ie, local or systemic), and the stresses imposed have a profound impact on the phenotype.[105] These animals do not behave physiologically; metabolic lessons derived from these transgenics to general HF should accordingly be generalized with due care.[94] Moreover, the impact of transcription factor modification in tissues other than the heart should be considered; eg, PPAR-α agonists exhibit limited effects on myocardial target genes; the peripheral actions of PPAR-α ligands may explain many resulting cardiac effects.[94]

Much remains unknown about the adaptive and maladaptive impact of transcription factor modification in HF; thus PGC-1α enhances mitochondrial biogenesis (presumed to be beneficial) but also enhances FAO and mitochondrial uncoupling through UCPs.[106] Depending on the degree and timing of activation and the tissues in which it is activated, PGC-1α activation may prove adaptive or maladaptive. Similarly, although FAO is generally considered undesirable in HF, FFAs yield more energy per unit of carbon than carbohydrates. It is conceivable that under some circumstances (eg, in the healthy heart) this increased energy density is desirable. Thus, when therapeutic inhibition of FAO, increased glucose metabolism, increased creatine transport, or enhanced PGC-1α is attempted, moderate rather than dramatic modifications in metabolic function should be sought.[106]

Role of Ketones in HF

HF has some metabolic similarities to starvation and to diabetes mellitus ("starvation in the midst of plenty"). In starvation, the liver converts plentiful FFA to the ketone bodies (KBs) acetoacetate and 3-hydroxybutyrate. HF promotes ketogenesis by the liver and increases plasma KBs.[107–109] Because KBs are converted rapidly and in a concentration-dependent manner to acetyl CoA by the heart, the 2-fold increased plasma KBs in HF suggests that HF mitochondria are replete with KB-derived acetyl CoA. This is rendered even more plausible by studies that suggest that KBs are the normal rodent heart's preferred substrate.[110–112] Experimentally, increased levels of KBs may block the citrate cycle to cause contractile dysfunction.[5] When added to myocytes, concurrent inhibition of glucose and FAO,[65] through inhibition of glycolysis and of AMP-activated protein kinase (AMPK), occurs (Figure 3). KBs could strangulate cardiac energy supplies, reduce glucose metabolism, alter signaling, and induce IR.[113] Manipulation of KB synthesis may represent one of the many noncardiac benefits of therapeutic metabolic modification. Hepatic carnitine palmitoyl transferase-1 represents the most regulated step in ketogenesis and its inhibition potentially increases myocardial energy supply (Figure 5).[114]

A Rational Metabolic Approach to Treatment of Heart Failure

To recapitulate, neurohumoral activation in HF thus results in increased FFA metabolism with some evidence for systemic and myocardial IR. These changes may have detrimental effects on myocardial energetics. A vicious cycle that involves IR (Figure 1) includes multiple therapeutic nodes that may be targeted in HF (Table 2 and Figures 3 and 5).

Neurohumoral Antagonism

Neurohumoral modification is the standard of care in HF.[115] Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers have significantly reduced the incidence of T2DM in patients with HF.[116,117] Of specific interest, enalapril prevented diabetes in those with IR (defined by a fasting plasma glucose $\geq$6.1 mmol/L) in a post hoc analysis.[116] Experimentally, these agents act by protection of β-pancreatic cells.[118,119] β-Blockers are pro-IR agents, with the exception of the α-β-blocker carvedilol.[20] Note that bisoprolol and nebivolol are still untested in relation to IR. In dogs with dilated cardiomyopathy, carvedilol but not metoprolol reduced circulating FFA, decreased myocardial FFA uptake, and increased glucose uptake.[120,121] This substrate switch was accompanied by increased stroke volume and decreased LV end-diastolic pressure. Similarly, carvedilol reduced myocardial FFA extraction between 20% and 60% in patients with HF.[120,121] Metoprolol, a cardioselective β-blocker, failed to decrease myocardial FFA uptake.[121] In another study, carvedilol decreased myocardial FFA use as assessed by PET while ejection fraction increased.[121] These metabolic effects of carvedilol may contribute to its remarkable clinical success in the therapy of HF.

Increasing Glucose Metabolism

Although insulin increases glucose utilization, the complications of long-term parenteral therapy and the risks of hypoglycemia render insulin an unattractive therapy. Nonetheless, as proof of principle, the application of glucose-insulin-potassium to patients with chronic ischemic cardiomyopathy lessened ventricular dysfunction.[122] AMPK is the cells' energy sensor and a critical metabolic regulator. It stimulates

TABLE 2. The Targets and Their Corresponding Therapeutic Agents for the Metabolic Modification of Insulin Resistance in Heart Failure

Target	Treatment
Inhibition of neurohumoral activation	ACE-inhibitors, angiotensin-II receptor blockers, aldosterone antagonists, and β-blockers (carvedilol)
	Pharmacological induction of vagus-like activity
Increasing glucose metabolism	Existing: exercise, metformin, insulin, glucagon-like peptide-1, dipeptidyl peptidase IV inhibitors
	Future: new AMP-activated protein kinase agonists and pyruvate derivatives
Reducing FA metabolism	Existing: exercise, insulin, glucagon-like peptide-1, dipeptidyl peptidase IV inhibitors, perhexiline, trimetazidine
Reducing IR	Glucagon-like peptide-1, dipeptidyl peptidase IV inhibitors, thiazolidenediones (glitazones) and biguanides (eg, metformin)
Increasing mitochondrial volume (total cellular energetic capacity)	Future: PPAR-γ coactivator-1α agonists, nitric oxide augmentation, cyclic guanosine monophosphate augmentation (eg, sildenafil and other type-5 phosphodiesterase inhibitors)
Reducing cellular energy demand	Existing: β-blockers, ranolazine and cardiac resynchronization therapy

While these agents have explicit and unequivocal metabolic benefits, a dearth of clinical trials exists in this area. None of these agents is yet indicated specifically for the treatment of insulin resistance in heart failure.

ATP-generating processes such as glycolysis and FAO. AMPK stimulants such as exercise and adiponectin are promising candidates to treat HF in that they increase glucose utilization.[123,124]

Insulin Sensitization

Metformin is an insulin sensitizer that works in part through AMPK and reduces the risk of new diabetes in patients with high fasting and postload plasma glucose concentrations, especially if combined with exercise.[125] A large Canadian observational study found that, in diabetic patients with HF, metformin but not sulfonylurea therapy was associated with reduced all-cause mortality.[24,126] However, despite calls by some authorities as a result of the perceived risk of acidosis, metformin is at present formally contraindicated in HF.[24] In the future, metformin could safely albeit cautiously be tested in HF.[24,127] Glucagon-like peptide, a parenteral insulin-sensitizer, improves myocardial glucose uptake and LV function in canine and human HF.[46,128]

PPAR-γ Agonists

On theoretical grounds, potent insulin-sensitizing agents such as rosiglitazone and pioglitazone might be expected to be particularly beneficial in HF. Yet, because of the capacity of PPAR-γ agonists to increase fluid accumulation, a risk that they might exacerbate HF is perceived. Accordingly, these agents have often been regarded as contraindicated or at least to be used with caution, even in diabetic patients with HF.[129] A retrospective series from the Cleveland Clinic concluded that diabetic individuals with prior HF who were given glitazones had less evidence of central fluid retention than nonusers.[130] PPAR-γ agonists increase fluid accumulation by an increase of renal tubular fluid retention; the consequent edema, at least in animals, can be mitigated with amiloride, a diuretic that selectively inhibits sodium reabsorption in the collecting duct.[131,132] Although studies such as the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) Study have suggested an increased incidence of HF that required hospitalization in patients treated with PPAR-γ agonists, no clear and centrally adjudicated definition of HF was provided.[133] In early HF at least, robust trial data would suggest that such fluid accumulation does not seem to correlate with deteriorating cardiac function.[134] Nonetheless, recent meta-analysis of 42 trials suggests that rosiglitazone given for T2DM has serious cardiovascular side effects.[135] Final judgment on the benefits or detriments of PPAR-γ agonists in HF may best be reserved until after the results of the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes (RECORD) trial, which is specifically designed to assess cardiovascular outcomes with rosiglitazone, are shared.[136] especially in the light of the improved LV function in a dog model of HF induced by mitral regurgitation.[137]

Decrease of Fatty Acid Metabolism by Fatty Acid Oxidation Inhibitors

Trimetazidine is the first agent shown to reduce myocardial FAO in humans (Tuunanen et al, unpublished data, 2007). The precise mechanism by which trimetazidine partially inhibits FAO remains controversial; some investigators advocate a selective inhibition of long-chain 3-ketoacyl CoA thiolase,[139] whereas other investigators reject this.[140] Trimetazidine has additional effects,[141] such as mitochondrial protection,[142] lessened proton production,[143] and endothelial protection.[144] Thus, although trimetazidine has in part delivered on the promise of metabolic modulation in human HF (Table 3),[138,145–155] it is unlikely to be marketed for HF because of patent issues.[156] A greater improvement in HF might be expected by perhexiline, a reversible carnitine palmitoyl transferase-1 inhibitor (Figure 5) that putatively reduces mitochondrial FFA transport.[157] Introduced in the 1970s as an effective antianginal agent, use of perhexiline diminished after unexplained cases of hepatic failure and neuropathy were caused by high plasma concentrations in poor perhexiline metabolizers.[158] The fact that these side effects are easily avoided by dose titration of plasma levels has led to its renaissance for refractory angina in Australia and New Zealand with restricted use in Europe.[159] In a randomized, double-blinded study of 56 optimally medicated HF patients over 8 weeks, perhexiline improved symptoms, peak exercise

TABLE 3. The Results of Clinical Trials With Partial Fatty Oxidation Inhibitors

Drug	Condition	No. of Patients Treated (Daily Dose)	Length of Treatment, Months	Outcome
Pooled trimetazidine studies[146–150]	Ischaemic LV dysfunction	95 placebo and 91 (20 mg × 3 trimetazidine)	6	Improved symptoms, exercise tolerance, and LVEF.
Trimetazidine[152]	All-cause LV dysfunction	12 (20 mg × 3 trimetazidine)	3	Improved symptoms, exercise, LVEF from 33% to 39% (placebo fell from 36% to 33%), and PCr/ATP ratio by 33%.
Trimetazidine[151]	All-cause LV dysfunction	27 placebo and 28 (20 mg × 3 times trimetazidine	13	Improved symptoms, exercise tolerance, and LVEF from 34 to 41% (placebo fell from 36 to 34%).
Trimetazidine[138]	Non-ischemic Cardiomyopathy	7 placebo and 12 (20 mg × 3 trimetazidine)	3	LVEF from 30.9% to 34.8% (placebo fell from 37.5% to 31.9%). Reduced FAO. Improved IR.
Etomoxir[153]	All-cause LV dysfunction	10 (80 mg etomoxir)	3	Improved symptoms and LVEF from 22% to 27%
Etomoxir[154]	All-cause LV dysfunction	121 placebo, 118 (40 mg) and 108 (80 mg) etomoxir.	6	No change in symptoms or EF. Increased incidence of hepatotoxicity
Perhexiline[145]	All-cause LV dysfunction	28 placebo and 28 (dose titrated) perhexiline	3	Improved symptoms, $M\dot{V}o_2$ (16.1 to 18.8 $mL \cdot kg^{-1} \cdot min^{-1}$, Minnesota quality of life score and LVEF fraction from 24% to 34%

Note: In this table some of the trimetazidine trials have been evaluated in combination.

oxygen uptake, and LV function (relative improvement of ≈40%).[145,160] Although these preliminary data are promising, prospective prognostic trials are needed to prove the capacity of perhexiline to improve HF. Moreover, although it is thought that perhexiline reduces myocardial FAO and improves glucose and lactate metabolism, this remains to be shown in patients.

Other Potential Therapies

Although as yet no agents exist that promote mitochondrial biogenesis, PGC-1α has generated interest.[101,161] The nitric oxide-cGMP–dependent pathway may also control mitochondrial biogenesis (Table 3).[162–164] If confirmed, the application of nitric oxide technology may ameliorate energy deficiency in HF. Indeed, phosphodiesterase 5 inhibitors such as sildenafil that increase cGMP have in preliminary studies improved LV function and exercise capacity in HF.[165,166]

Diuretics stimulate renin-angiotensin-aldosterone system and appear to promote IR[167]; they may adversely affect myocardial metabolism. In an observational study of HF patients, loop diuretic use was an independent predictor of mortality.[168] In a retrospective analysis, chronic diuretic therapy was associated with increased mortality.[169] Hence, unless prospective randomized trials prove otherwise, diuretics should be given for HF only when fluid retention is present. Potassium depletion, which predisposes to diabetes, must be avoided.

Cardiac resynchronization therapy lessens morbidity and mortality in advanced HF.[170] By reduction of the inefficiency of dyscoordinate ventricular contractions, cardiac resynchronization therapy increases glucose metabolism and reduces IR[171,172] to improve cardiac efficiency and cardiac energetics.[173–176] Statins lessen the incidence of new diabetes in patients with metabolic syndrome,[175] improve glucose tolerance,[177,178] and improve HF.[179] A plausible mechanism may be through activation of AMPK.[180] Even interventions that are seemingly unrelated to energetics, such as continuous positive airway pressure, may ameliorate energy efficiency.[181]

Exercise and Dietary Modification

Even when mobilization of insulin-sensitive glucose transporter (GLUT) 4 vesicles to the sarcolemma is indirectly blocked by high FFA, other vesicles are still sensitive to exercise (Figure 3).[182] In obese subjects, short-term exercise improves insulin-mediated perfusion of skeletal muscle and glucose delivery. In HF, exercise training reduces IR[183] consonant with its effect in the increase in skeletal and cardiac glucose uptake. The latter increase occurs in HF despite unchanged insulin signaling[184]; the likely mechanism is by stimulation of the insulin insensitive GLUT-1 transporters.[185]

Existing and Future Clinical Applications of Metabolic Modulation in HF

Existing Treatments

As reviewed herein, the association and possible causative role of aberrant metabolism in HF has only recently come to the foreground. Accordingly, no definitive data exist that show the incontrovertible benefit of any one therapy for the correction of abnormal metabolism. On the basis of the preceding discussion it appears that existing standard practice

with therapies that include high doses of an angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or both, as well as β-blockers with preferential use of the α-β-blocker carvedilol, may help restore metabolic normality. Unnecessary diuretics must be avoided except in fluid overload. In light of promising preliminary evidence, metformin should be tested in HF (some authorities propose a revocation of the current contraindication in HF), especially with exercise training. Although evidence exists to suggest that thiazolidinediones may not be deleterious in HF,[24,134] this contrasts with recent studies that suggest adverse cardiovascular outcomes in patients with T2DM[135,136] and an existing consensus statement from the American Heart Association and the American Diabetes Association that recommends caution in prescription of thiazolidinediones in those with NYHA class I and NYHA II HF and complete avoidance of thiazolidinediones in patients with NYHA class III and NYHA IV HF.[186] Increasing controversy surrounds the use of thiazolidinediones in T2DM patients and at present thiazolidinediones should be used in HF with great caution until the publication of appropriate trial evidence specific to HF. Finally, although not yet supported by definitive evidence, we propose that a specific goal in HF should be prevention and treatment of IR, preexisting and new T2DM as assessed, albeit relatively bluntly, by serial fasting plasma glucose and perhaps homeostasis model assessment values.[187] Although many questions remain with regard to the role of metabolism in HF (Table 4), a number of exciting future prospects promise to contribute to the amelioration of HF prognosis through metabolic modulation, subject to further research and trials.

TABLE 4. Questions Yet to be Definitively Answered Relating to the Metabolic Modification of Heart Failure

Neurohumoral activation	Does neurohormonal activation/inhibition modify substrate utilization, insulin resistance, or cardiac energetics?
Glucose metabolism	What are the changes in glucose uptake and glycolysis in HF?
	What is the optimal profile of glucose metabolism in HF?
	Does glucose oxidation match increased glycolysis in HF?
	If not; why not, and what happens to the resulting excess lactate?
FFA metabolism	What are the changes and optimal profile in FFA metabolism in HF?
	How do these changes in FFA metabolism relate to the transition from compensated to decompensated or advanced HF?
	What is evidence for FFA-induced uncoupling in HF?
	To what extent does varying cardiac and skeletal muscle FFA metabolism in HF (eg. during exercise-induced surges) affect cardiac function?
KBs	What are the contributions of KBs to normal and HF cardiac metabolism?
	Which KB species is particularly detrimental in HF?
IR	How and to what degree does IR predispose to HF and vice-versa?
	Would reversing IR in HF alter prognosis?
Energetics	How big a role does energy deficiency play in contractile deficiency in HF?
	Is amelioration of energy deficiency in HF clinically meaningful?
	Which cardiac compartments are particularly energy deficient and can they be specifically targeted for therapy?
Therapy	When and to what degree does FAO inhibition improve HF?
	Which other mechanisms explain HF alleviation with metabolic therapies?
	Which is the optimal agent(s) and when should it be given?
	Does glucose metabolism compensate for decreased FFA metabolism in HF?

Future Prospects

Insulin Sensitization

Whereas tight glycemic control, such optimal insulin dosing, is strongly advocated in diabetic patients, insulin is neither practical nor supported by evidence in nondiabetic HF patients. However, novel insulin-sensitizing agents developed for the treatment of diabetes and effective in amelioration of metabolic profile may also prove effective in HF. Glucagon-like peptide, a gut-derived incretin hormone, promotes insulin secretion and sensitization, was effective in preliminary HF trials, and will be further investigated.[46,128] Inhibitors of glucagon-like peptide degradation include dipeptidyl peptidase-4 inhibitors.[188] Augmented AMPK signaling (through exercise, metformin, and statins) promotes insulin sensitization. In animal models, adiponectin deficiency leads to HF, especially during pressure overload,[189] which may be mediated via impaired AMPK signaling and glucose metabolism.[190] Conversely, small-molecule AMPK agonists may improve HF.[123]

Substrate Modification

Improvements in cardiac substrate profile may reverse any existing IR of HF associated with improved cardiac energetics, LV function, and amelioration of the morbidity and mortality of HF. Further HF trials with promising metabolic modulators such as trimetazidine and perhexiline should be initiated to include IR and new diabetes as prespecified end points. In consideration of their provenance and well-understood chemistries, these agents are more likely to be more cost-effective for both the developed and developing world than novel therapies.

Kinase Modification

Although existing agents such as β-blockers and angiotensin-converting enzyme inhibitors have proven effective in HF, centrally acting sympatholytics such as moxonidine have failed, apparently inexplicably.[191] It is the α_2-adrenoreceptors through which these agents act that are dysregulated by increased expression and activity of G-protein–coupled receptor kinase 2 in the adrenal gland.[192] Inhibition of this

kinase and/or those that act on the β-adrenergic receptor may further decrease adrenergic activation to ameliorate metabolic abnormalities.[193]

Disclosures

Drs Frenneaux and Ashrafian have applied for a patent for the use of perhexiline in HF. Dr Frenneaux is on the clinical end points committee for 2 heart failure trials funded by Menarini (Seniors) and Beautiful (Servier). He has received support to attend international meetings from Novartis, Pfizer, AstraZeneca, and Servier. Dr Opie has given lectures for Servier, the manufacturer of trimetazidine.

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