1. Introduction

Heart failure (HF) is a pathophysiologic state in which an abnormal cardiac function leads to a failure of the heart to pump blood at an adequate rate to meet the requirements of the metabolizing tissues. In the face of decreasing myocardial function, the renin–angiotensin–aldosterone system and the sympathetic nervous system (SNS) are activated in order for adequate organ perfusion to be maintained. Persistent neurohormonal activation with increased afterload and fluid retention, although compensative in the beginning, turns from an adaptive to maladaptive response leading to a vicious circle and further progression of the disease. In addition to haemodynamic effects, reactive hyperadrenergic state increases circulating plasma free fatty acids (FFAs), which leads to impaired glucose metabolism and insulin resistance.

2. Insulin resistance in chronic HF

Insulin resistance is a common and noteworthy co-morbidity in patients with chronic HF. Some data but not all suggest that whole body insulin resistance in HF is accompanied by myocardial insulin resistance. Patients with diabetes have a considerably increased lifetime risk of congestive HF incidence independently of established risk factors including diabetes. Furthermore, insulin resistance is an independent risk factor for developing ischaemic and also maybe non-ischaemic HF such as idiopathic dilated cardiomyopathy (DCM). In a large community-based sample of elderly men, insulin resistance predicted congestive HF incidence independently of established risk factors including diabetes.

2.1 Mechanisms

The development of insulin resistance in the HF patient is likely multifactorial and these morbidities worsen one another. One of the key pathophysiologic mechanisms is chronically increased SNS activity that can lead to decreased insulin responsiveness, glucose utilization, and beta-cell insulin secretion by increasing serum FFA levels and oxidative stress and by decreasing skeletal muscle blood flow. In addition, loss of skeletal muscle mass and sedentary lifestyle of the HF patient might reduce insulin sensitivity. Medical therapy may also alter insulin sensitivity in HF patients. Both angiotensin-converting enzyme-inhibitors and angiotensin receptor blockers have been reported to significantly reduce the incidence of new-onset diabetes in large clinical trials of patients with HF. In some studies, beta-blockers have been shown to increase insulin sensitivity at the whole body level in patients with HF.

The clinical significance of insulin resistance in patients with chronic HF is that it represents potentially reversible metabolic derangements in these individuals. At a myocardial level, in fact, treatment of impaired glucose tolerance has been shown to actually reverse systolic dysfunction in animal models. In patients with diabetes, improved glycaemic control can prevent the development of systolic dysfunction. Importantly, insulin resistance has been shown to be an independent risk factor for mortality in chronic HF.

2.2 Obesity

Obesity is a known risk factor for HF as well as one of the strongest predisposing features for insulin resistance. However, in patients with HF, low body mass index (BMI) has been shown to be associated with increased mortality that is partly mediated by adiponectin levels. It might be suggested that the U-shaped association between BMI and mortality, which is known to exist in healthy subjects, shifts to the right in chronic HF, resulting in a higher optimal BMI with regard to survival.
3. Myocardial metabolism in the healthy heart

The heart can utilize several substrates, the major ones being FFAs and glucose, while lactate, ketone bodies, and amino acids are less important sources of energy. The intermediary metabolism transforms these fuels to acetyl-CoA, which enters the citrate cycle to produce NADH and eventually H₂O, CO₂, and ATP by oxidative phosphorylation. Myocardial metabolism can be regulated by both acute and chronic mechanisms, with or without modulation of gene expression. The regulation of the myocardial metabolism is closely linked to arterial substrate and hormone concentrations, coronary perfusion and oxygen availability, and inotropic state and the nutritional status (fast/fed) of the tissue. Importantly, regulation of myocardial glucose and FFA metabolism does not occur independently, and several studies have demonstrated a ‘cross-talk’ between the utilization of these substrates originally described by Randle et al. Substrate preference is also dependent on age; during foetal stages, the heart relies mainly on glycolysis, whereas shortly after birth and in the normal adult heart FFAs (~70%) are the main substrate. Again with aging, there is a decline in myocardial FFA metabolism suggesting an increase in the relative contribution of glucose to myocardial substrate metabolism in the elderly.

The rate of fatty acid uptake by the heart is primarily determined by the concentration of non-esterified fatty acids in the plasma. Thus with fasting, when insulin is low and catecholamines are high, the plasma FFA concentration is high, resulting in a high rate of FFA uptake and oxidation by the heart. After a carbohydrate-rich meal, insulin secretion into the bloodstream increases muscle glucose uptake and oxidation by the heart, whereas shortly after birth and in the normal adult heart FFAs (~70%) are the main substrate. Again with aging, there is a decline in myocardial FFA metabolism suggesting an increase in the relative contribution of glucose to myocardial substrate metabolism in the elderly.

4. Myocardial metabolism in chronic HF

It is well established that metabolism is altered in the failing myocyte. In general, the failing heart is characterized as an ‘engine out of fuel’ since the phosphocreatine-to-ATP (PCr-ATP) ratio is clearly reduced when compared with the healthy heart. Importantly, a reduced PCr-ATP ratio may be associated with a worse prognosis in patients with idiopathic DCM (mortality 40% in patients with a reduced PCr-ATP ratio vs. 11% in those with a normal PCr-ATP ratio). However, studies on the myocardial substrate (glucose and FFA) metabolism in both experimental and human HF have yielded contradictory results.

4.1 Experimental models of HF

In experimental models of HF, the metabolic status of the myocardium varies depending on the haemodynamic state (compensated/decompensated) and the severity of the HF. In addition, myocardial insulin resistance characterizing end-stage HF modifies myocardial substrate preference further. Studies using direct non-invasive or indirect invasive methods suggest that in a well-compensated state of chronic HF myocardial metabolism is quite normal. However, in decompensated pacing-induced end-stage HF, myocardial glucose oxidation is the primary source for ATP production and less energy is derived from oxidation of FFAs. Another study confirmed reduced myocardial FFA uptake in advanced severe DCM in spite of increased levels of serum FFAs and norepinephrine. The afore-mentioned study also demonstrated development of insulin signalling abnormalities leading to decreased myocardial glucose uptake (both basal and insulin stimulated). Furthermore, reduced myocardial uptake of glucose and FFA was accompanied by reduced ATP levels in the myocardium. In summary, experimental models suggest that end-stage HF is an energy depletion state characterized by decreased FFA metabolism as well as insulin resistance, leading also to impaired myocardial glucose uptake.

4.2 Studies in humans

When compared with healthy controls, patients with HF have increased plasma norepinephrine and FFA levels, which is thought to reflect stress hormone-induced lipolysis. The change in plasma substrate levels is associated with increased FFA oxidation and decreased glucose oxidation both at the myocardial and whole body levels measured by indirect calorimetry. Enhanced FFA and decreased glucose uptake in HF patients [mean ejection fraction 24%, both ischaemic and non-ischaemic HF patients included] when compared with values previously published in healthy volunteers was confirmed also by a positron emission tomography (PET) study using fluoro-thia-heptadecanoid acid ([18F]FTHA) and fluorodeoxyglucose ([18F]FDG) as tracers. In contrast, another PET study using [13C]glucose and [13C]palmitate as tracers showed that in non-ischaemic HF myocardial glucose metabolism is increased, whereas that of FFA is decreased. Moreover, regional ischaemia may switch cardiac metabolism to enhanced glucose use also in non-ischaemic HF. According to experimental studies and a human PET study by Davila-Roman et al., we showed decreased myocardial FFA uptake (reduced by 14%) but an unchanged beta-oxidation rate constant in patients with idiopathic DCM and mean ejection fraction of 33% when compared with healthy controls. In our study, ejection fraction was inversely related with serum FFA levels and myocardial FFA uptake, suggesting that the severity of left ventricular dysfunction modulates cardiac substrate supply and metabolism equally to the metabolism at the whole body level.

In summary, the serum level of FFAs seems to be one of the main determinants of substrate metabolism both at the myocardial and whole body levels in patients with chronic HF. Increased serum FFA levels may reflect stress hormone-induced lipolysis and the accompanying stimulation of serum and myocardial FFA oxidation via mass action.

4.3 Expression and function of metabolic proteins in chronic HF

Ex vivo analyses of cardiac tissue have demonstrated that an altered substrate metabolism in end-stage HF is accompanied by several changes in the expression and activity of the key enzymes of both FFA and glucose metabolism. In mild to moderate HF, the expression and activity of metabolic enzymes [carnitine palmitoyl transferase I (CPT-1) and pyruvate dehydrogenase (PDH)] are unchanged, further suggesting that metabolic myocyte abnormalities are a late phenomenon in HF. In experimental models, impaired myocardial FFA metabolism is accompanied by a down-regulation of the
protein expression of medium-chain acyl-CoA dehydrogenase (MCAD) and retinoid X receptor alpha (RXR-a), and of the activity of MCAD and CPT-1.\textsuperscript{38,48} Similarly, the analysis of human end-stage failing cardiac tissue demonstrated reduced messenger RNA for long-chain acyl-CoA dehydrogenase\textsuperscript{49} and MCAD,\textsuperscript{49,50} and decreased protein levels of MCAD\textsuperscript{49} as well as reduced activity of CPT-1b\textsuperscript{50} and CPT-II.\textsuperscript{51}

Despite an enhanced myocardial glucose metabolism, there was a paradoxical down-regulation of the glucose oxidation pathway in experimental end-stage HF.\textsuperscript{48} Messenger RNA of all genes encoding for proteins involved in the carbohydrate metabolism [GLUT-1, GLUT-4, glyceraldehyde-phosphate dehydrogenase, PDH E2 unit, phosphoinositide-dependent kinase (PDK-4)] were down-regulated, although myocardial protein expression of GLUT-1 and GLUT-4 and the translocation of GLUT-4 to the plasma membrane were not altered when compared with control non-failing hearts. Accordingly, Razeghi et al.\textsuperscript{50} showed reduction in gene expression of glucose metabolism enzymes [GLUT-1, GLUT-4, pyruvate dehydrogenase kinase2,4 (PDK-2, PDK-4)] in human failing hearts.

Thus, ex vivo analysis suggests that all metabolic enzymes are down-regulated in the failing heart\textsuperscript{48,50} that reverts to a foetal metabolic gene profile mainly by repressing adult metabolic genes rather than re-inducing foetal isogenes.\textsuperscript{50} Therefore, the increase in glucose oxidation observed in the failing heart in vivo could be principally due to impaired oxidation of the competing substrate FFA through mechanisms originally described by Randle et al.\textsuperscript{26} It is important to note, however, that a decrease in expression of the fatty acid beta-oxidation pathway does not necessarily result in a decrease in flux through the pathway and, conversely, a large increase in flux through the beta-oxidation pathway in the heart does not require an increase in the expression and maximal activity of these enzymes.\textsuperscript{52}

### 4.4 Inherited ‘metabolic’ cardiomyopathies

The recognition that inherited defects in the myocardial long-chain fatty acid metabolism and premature cardiomyopathy are linked by a cause–effect relationship provides the strongest evidence that in some types of cardiomyopathies metabolic abnormality leads to myocardial dysfunction rather than vice versa.\textsuperscript{53} Defects have been identified at nearly every step of the fatty acid oxidation pathway. The most common defect is located in the acyl-CoA dehydrogenase family which catalyses the initial reactions in mitochondrial beta-oxidation. Bergmann et al.\textsuperscript{54} characterized the myocardial FFA metabolism in patients with defects in enzymes of FFA oxidation (acyl-CoA dehydrogenase and 3-hydroxyacyl-CoA dehydrogenase deficiencies). These patients had diminished palmitate oxidation, and more palmitate was shunted into the slow turnover compartment (esterification to triglycerides). Patients with carnitine deficiency had normal palmitate metabolism and relative to left ventricle oxidative metabolism have been demonstrated in HF patients with both mild\textsuperscript{5} and severe \textsuperscript{61} disease states. Thus, the imbalance between right and left ventricular oxidative metabolism is considered one of the earliest signs of energetically unfavourable situation in the failing heart.\textsuperscript{57,60}

As with the healthy heart, myocardial efficiency is directly associated with ejection parameters and inversely related to afterload in patients with idiopathic DCM.\textsuperscript{58} However, in contrast to the healthy heart, the severely failing heart is not able to respond with an increase in efficiency to increasing preload.\textsuperscript{58} In addition to changes in circulating substrates.\textsuperscript{55} The term lipotoxicity refers to an altered fatty acid metabolism, intra-myocardial lipid overload and contractile dysfunction, a phenomenon that has been associated with insulin-resistant states and links the altered myocardial metabolism to cardiac dysfunction pathophysiologically. The cardiomyocyte has a limited capacity for triglyceride storage, accumulation of intra-myocardial triglycerides can occur either because of an increase in fatty acid uptake or an impairment of fatty acid oxidation. Metabolic dysregulation in lipid overloaded hearts may induce reduced myocardial glucose uptake.

Compared with healthy controls, patients with ischaemic HF had reduced myocardial glucose uptake during euglycaemic hyperinsulinaemia, and this correlated with whole body and skeletal muscle glucose uptake.\textsuperscript{5} In contrast, in patients with idiopathic DCM, myocardial glucose uptake during euglycaemic hyperinsulinaemia was similar to that of healthy volunteers despite mild insulin resistance as evidenced by slightly elevated blood glucose and insulin levels when compared with controls.\textsuperscript{3} Furthermore, in diabetic and/or obese patients with severe end-stage idiopathic DCM (mean ejection fraction 19%) referred for cardiac transplantation, there was a significant accumulation of intra-myocardial lipids.\textsuperscript{56} Similar accumulation was not present in non-obese and non-diabetic patients with HF, suggesting that impaired fatty acid oxidation alone does not result in the accumulation of intra-myocardial lipids.\textsuperscript{56}

Insulin resistance was a common feature in idiopathic DCM patients in our previous study\textsuperscript{57} although patients with overt diabetes were excluded. We found that the myocardial FFA beta-oxidation rate was associated with whole body insulin resistance; i.e. the greater was the extent of insulin resistance, the greater the rate of FFA beta-oxidation. Furthermore, myocardial FFA uptake was less reduced in patients with greater than median insulin resistance when compared with controls. Serum FFA or catecholamine levels in turn were not significantly associated with insulin resistance. Thus, in accordance with Buchanan et al.,\textsuperscript{55} we suggest that insulin resistance may interfere with myocardial substrate metabolism independently of FFA availability.

### 6. Myocardial efficiency in chronic HF

The finding of decreased myocardial forward work efficiency in the failing heart is a consistent\textsuperscript{34,59} and early finding.\textsuperscript{57,60} Although left ventricular oxidative metabolism appears to be similar in the mild-to-moderate\textsuperscript{5,45,57,61} and even reduced in the severe\textsuperscript{58} HF patients when compared with healthy controls, it is increased in relation to forward work power. In the dilated failing left ventricle, energy expenditure is shifted from useful forward work to overcoming increased wall stress. An increased absolute right ventricular metabolism and relative to left ventricle oxidative metabolism have been demonstrated in HF patients with both mild\textsuperscript{5} and severe\textsuperscript{61} disease states. Thus, the imbalance between right and left ventricle oxidative metabolism is considered one of the earliest signs of energetically unfavourable situation in the failing heart.\textsuperscript{57,60}
alterations in the haemodynamic, contractile, and anatomical properties of the failing myocardium, mechanisms contributing to mechanoenergic uncoupling in the failing heart include reactive oxygen species, abnormal substrate metabolism, and depleted energy stores. Markers of reactive oxygen species accumulate in the pericardial fluid and circulation of HF patients, indicating that HF is a state of oxidative stress. Oxidative stress and an abnormal metabolism in the failing heart are linked pathogenetically. Although ejection fraction was inversely related to myocardial FFA uptake, efficiency was not associated with FFA uptake or beta-oxidation rates. Thus, the main determinants of myocardial efficiency seem to be left ventricle dimension and function, while efficiency seems not overtly associated with substrate preference.

7. The effect of beta-blockers on cardiac metabolism in patients with HF

In addition to haemodynamic effects, metabolic modulation has been suggested to partially account for the positive effects of beta-blockers on HF patients. Three months of treatment with metoprolol has been shown to improve myocardial efficiency with or without a simultaneous increase in myocardial ejection parameters in patients with chronic HF. In the former study, the improvement in left ventricular efficiency during metoprolol treatment was associated with a decrease in myocardial FFA oxidation and an increase in carbohydrate oxidation when estimated indirectly from the transmyocardial respiratory quotient. It is suggested that the metabolic shift by beta-blockers results from inhibition of CPT-1 enzyme. Interestingly, after 3 months of treatment with metoprolol, myocardial triglyceride content was increased along with improved cardiac function, although increased triglyceride content in the heart has been associated with contractile dysfunction. Walfhaus et al. demonstrated that after 3 months of treatment with carvedilol, myocardial triglyceride content was increased along with improved cardiac function, although increased triglyceride content in the heart has been associated with contractile dysfunction. Interestingly, after 3 months of treatment with carvedilol, myocardial triglyceride content was increased along with improved cardiac function, although increased triglyceride content in the heart has been associated with contractile dysfunction. Walfhaus et al. demonstrated that after 3 months of treatment with carvedilol, myocardial triglyceride content was increased along with improved cardiac function, although increased triglyceride content in the heart has been associated with contractile dysfunction.

8. Metabolic modulation in HF

Metabolic modulation is linked to the fact that glucose is a more energy-efficient fuel than FFAs. A shift from predominant long-chain fatty acid utilization to glucose utilization will result in an increase in ATP production per unit of oxygen utilization. A metabolic switch from oxidation of FFAs towards that of glucose can be achieved by manipulating (i) circulating substrate levels (nicotinic acid and its derivatives such as acipimox, glucose-insulin-potassium infusion), (ii) FFA beta-oxidation inhibitors (trimetazidine, ranolazine), (iii) CPT-1 blockers (perhexiline, etomoxir), and (iv) dichloroacetate (direct carbohydrate oxidation activator).

8.1 Manipulation of circulating substrate levels

Recent studies assessing the effect of substrate supply manipulation on cardiac function in HF patients have yielded discouraging results. Wiggers et al. demonstrated that acute substrate availability modulation does not influence cardiac function in hibernating myocardium either at rest or after exercise. The study included substrate modulation either with insulin-glucose (high insulin, low FFA) and somatostatin-heparin (high FFA, low insulin). Furthermore, the same group showed that 28 days of treatment with acipimox tended to increase glucose and decrease lipid utilization rates at the whole body level and significantly changed the effect of insulin on substrate utilization. Acipimox had no effect on insulin sensitivity, global or regional myocardial function nor exercise capacity, or the cardiac index, or systemic vascular resistance. However, in that study myocardial substrate metabolism was not measured and, thus, the metabolic changes in the myocardium were not confirmed. Our previous study demonstrated that acute FFA deprivation by acipimox in patients with idiopathic DCM, in contrast to healthy controls, uncouples cardiac contractile function from oxidative metabolism so that myocardial efficiency deteriorates further. Although glucagon-like peptide-1 (GLP-1) improved the left ventricle ejection fraction in dogs with HF, 48 h of GLP-1 infusion had no cardiovascular effects in patients without diabetes but with compensated HF. Thus, these preliminary studies suggest that acute or short-term manipulation of substrate levels may not be a promising form of therapy in HF.

8.2 FFA beta-oxidation inhibition

Several small studies have shown an improvement in cardiac function both in ischaemic and non-ischaemic HF after trimetazidine use. Enhancement in cardiac function has been accompanied by improvement in exercise tolerance, NYHA class, and life quality as well as improvement in myocardial metabolism as evidenced by an increased myocardial PCr-ATP ratio. The largest study involving 200 patients with multi-vessel coronary artery disease and mildly impaired left ventricle function demonstrated surprisingly pronounced improvement in survival rates after 2 years of treatment with trimetazidine. Our recent PET study, including non-diabetic patients with idiopathic DCM, demonstrated improvement in the ejection fraction after 3
months of treatment with trimetazidine when compared with placebo. Trimetazidine had no effect on myocardial FFA uptake and only minor inhibitory effects on myocardial FFA oxidation, suggesting some other major mechanisms contributing towards the benefit. Rather, our data showed increased whole body insulin sensitivity in idiopathic DCM, as also found by Fragasso et al. 78 in diabetic ischaemic HF patients, thus hypothetically counteracting the myocardial damage of insulin resistance. Moreover, the positive effects of trimetazidine on left ventricular function were especially evident in patients with a high degree of beta-blockade, strongly suggesting an additive effect of these two modalities of therapy. Furthermore, Monti et al. 85 showed that improvement in the whole body insulin sensitivity by trimetazidine is accompanied by a metabolic shift from FFA to glucose oxidation in skeletal muscle during euglycaemic hyperinsulinaemia in diabetic HF patients. Additionally, there is some evidence that trimetazidine limits inflammatory response 76 and improves endothelial function 86 in HF patients.

8.3 CPT-1 blockers

Studies on the effects of CPT-1 blockers on HF patients have yielded conflicting results. A double-blind, placebo-controlled study demonstrated that 8 weeks of administration of perhexiline improves the ejection fraction, resting and peak dobutamine stress regional myocardial function, peak exercise oxygen consumption, and quality of life as well as normalizes skeletal muscle phosphocreatine recovery after exercise in both ischaemic and non-ischaemic HF patients. 87 Furthermore, a retrospective multi-centre database analysis in the UK revealed that perhexiline therapy is well tolerated and provides symptomatic relief in ~59% of patients with chronic HF and/or refractory angina. 88 However, a recent study, 89 including 36 patients with post-infarction HF showed that 1 year of administration of perhexiline has no impact on exercise capacity and does not improve the deformation of abnormal myocardial segments in these patients. In a small group of HF patients, etomoxir improved left ventricular function, 90 but due to the liver toxicity it is not candidate for further development of treatment of patients with HF. 91

9. Summary

In summary, abnormal cardiac substrate metabolism characterizes patients with HF and is at least partly linked with increased enhanced fatty acid availability. Whole body insulin resistance is a common co-morbidity in HF patients and also modulates cardiac metabolism in HF. Since myocardial metabolism is altered and seems to contribute to the disease pathogenesis, identifying the metabolic characteristics of HF patients is important. The concept that metabolic agents may optimize myocardial energy metabolism and allow more efficient production of energy from glucose than from FFAs is appealing. However, studies on the effects of metabolic modulation on patients with HF have yielded conflicting results. Larger clinical randomized, multi-centre studies are warranted to confirm the effects of these agents on patients with HF.

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