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MODELS OF INSULIN RESISTANCE AND HEART FAILURE

Mauricio Velez, M.D., Smita Kohli, M.D., and Hani N. Sabbah, Ph.D.

Department of Medicine, Division of Cardiovascular Medicine, Henry Ford Hospital, Detroit, Michigan

Abstract

The incidence of heart failure (HF) and diabetes mellitus is rapidly increasing and is associated with poor prognosis. In spite of the advances in therapy, HF remains a major health problem with high morbidity and mortality. When HF and diabetes coexist, clinical outcomes are significantly worse. The relationship between these two conditions has been studied in various experimental models. However, the mechanisms for this interrelationship are complex, incompletely understood, and have become a matter of considerable clinical and research interest. There are only few animal models that manifest both HF and diabetes. However, the translation of results from these models to human disease is limited and new models are needed to expand our current understanding of this clinical interaction. In this review, we discuss mechanisms of insulin signaling and insulin resistance, the clinical association between insulin resistance and HF and its proposed pathophysiologic mechanisms. Finally, we discuss available animal models of insulin resistance and HF and propose requirements for future new models.

Keywords

Congestive Heart Failure; Animal models of human disease; Diabetes mellitus; Insulin resistance; Heart failure

Background

Heart failure (HF) is a major health problem in the United States. Approximately 6 million Americans suffer from HF, with 700,000 new cases diagnosed every year. The likelihood of having HF increases with age reaching 10 per 1,000 population in individuals older than 65 years of age [1]. Improvements in the treatment of the many forms of cardiovascular disease have led to a steady rise in the incidence and number of hospital admissions for HF over time, exceeding 1 million hospitalizations annually in the United States with approximately 300,000 deaths linked to HF every year [1]. Advances in HF therapy have translated into significant reductions in the likelihood of death from the disease. The introduction of angiotensin converting enzyme inhibitors, angiotensin receptor blockers, beta-adrenergic receptor blockers, aldosterone blockers, hydralazine and isosorbide dinitrate, implantable cardioverter defibrillators and cardiac resynchronization therapy, all have contributed to reductions in HF-related mortality in the order of 20–40% [2–8]. However, in spite of these advances, 5-year mortality from HF remains at about 50% in both men and women [9].

Address for Correspondence: Hani N. Sabbah, PhD, Director, Cardiovascular Research, Henry Ford Hospital, 2799 West Grand Boulevard, Detroit, Michigan 48202, Office Phone: (313) 916-7360, Office Fax: (313) 916-3001, hsabbah1@hfhs.org.

Conflicts of Interest:

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Co-morbid conditions have a significant impact on HF clinical status and outcomes. Conditions such as chronic kidney disease, anemia, sleep apnea, depression and diabetes contribute to worsening HF symptoms and increasing HF-related hospitalizations and mortality [10]. Among these, diabetes has emerged as a major risk factor that may have an etiologic role and that greatly worsens HF clinical status and outcomes. Data from the Centers for Disease Control and Prevention fact sheet estimate that nearly 24 million Americans have diabetes, and that estimated 57 million Americans aged 20 years or older have so-called pre-diabetes [11]. Racial minorities tend to be disproportionately affected, with African-Americans being almost twice as likely to be affected as Whites [11]. The problem is further complicated by the rising epidemic of childhood obesity that will likely result in a dramatic increase in the prevalence of type 2 diabetes (T2DM) [12].

Type 2 diabetes is closely associated with HF. A review of HF clinical trial populations shows that T2DM is a very common co-morbidity with a mean prevalence of 30% [13]. In studies with larger proportions of African-Americans, the prevalence of T2DM can be as high as 40% [8,13]. This is of critical importance as HF clinical status and prognosis are worse when T2DM is present. The pathophysiologic mechanisms that underlie this clinical association are not yet fully understood and research into this relationship has been ongoing at both the basic and clinical levels. Several animal models of insulin resistance and HF have been developed to facilitate opportunities to explore the adverse impact of insulin resistance on clinical outcomes in patients with HF. Understanding the relationship between insulin resistance and HF could also provide needed therapeutic opportunities. In this review article, we will discuss known mechanisms of insulin signaling and insulin resistance, the clinical association between this condition and HF and its proposed pathophysiologic mechanisms, and will discuss available animal models of insulin resistance and HF.

Insulin Signaling

Insulin resistance is closely associated with over-nutrition and obesity, but other factors such as chronic inflammation and stress responses may also be important etiologic contributors [14]. Insulin resistance manifests as metabolic syndrome and T2DM both of which are characterized by impaired insulin signaling and relative non-autoimmune insulin deficiency resulting in hyperglycemia. Environmental and genetic factors are known to increase individual susceptibility to developing an insulin resistance phenotype [15]. Hyperglycemia becomes evident when insulin function is impaired in the liver, skeletal muscle and adipose tissue. As the diabetic phenotype develops, pancreatic islet cells progressively lose their ability to secrete all the insulin that is needed and glucose production is increased due to increased hepatic gluconeogenesis [16]. However, the processes that culminate in these clinical manifestations likely evolve over the course of decades [15].

Insulin exerts its physiologic effect through a signaling pathway involving kinase Akt (protein kinase B) that ultimately causes translocation of glucose transporter 4 (GLUT4)-containing vesicles to cell membranes [17]. Once insulin binds its receptor, the insulin receptor autophosphorylates and this, in turn, causes phosphorylation of insulin receptor substrate proteins (IRS). Of these IRS proteins, IRS1 is the key mediator of insulin-stimulated glucose uptake and anabolic pathways in skeletal myocytes and adipocytes. IRS2 carries out similar functions in hepatocytes [18]. Phosphorylated IRS proteins associate with phosphatidylinositol 3-kinase (PI3K). This event triggers a cascade of events that ends with the phosphorylation of Akt. Phosphorylated Akt (p-Akt) causes translocation of GLUT4 to the cell membrane through the action of small GTPase RAB10 protein [17]. The translocation of GLUT4 to the membrane allows glucose entry into cells [19–22]. In the liver, p-Akt mediates multiple insulin effects via p-Akt including upregulation of glycogen synthesis, inhibition of gluconeogenesis, and stimulation of cell growth through activation of

mammalian target of rapamycin (mTOR). In skeletal muscle, insulin action causes glycogenesis. In adipose tissue, insulin is a major determinant of lipid transport and storage [19,23,24].

Dietary fats enter the circulation as triglyceride-containing chylomicrons. Since chylomicrons are not water soluble, they must be associated with soluble lipoproteins to be transported in the circulation. In the post-prandial state, when insulin levels are high, the activity of lipoprotein lipase is increased with a subsequent release of free fatty acids from circulating lipoproteins. Free fatty acids are captured into adipocytes by acylation-stimulating protein. Once in the adipocyte, they are re-packaged into triglycerides by diacylglycerol transferase [25]. In the fasted state, when insulin levels are low, adipose tissue lipolysis is enhanced by hormone-sensitive lipase with the consequent release of free fatty acids. Insulin stimulates lipoprotein lipase and inhibits hormone-sensitive lipase in the post-prandial state [19,20] (Figure 1). In addition to insulin, other hormones have effects on lipid transport: Leptin and adiponectin increase insulin sensitivity and reduce plasma free fatty acids and triglycerides, while resistin and retinol-binding protein-4 reduce insulin sensitivity [26,27].

Mechanisms of Insulin Resistance

Overnutrition is a major cause of insulin resistance. Insulin resistance due to overnutrition has been best characterized in the liver. Increased food intake impairs fatty acid oxidation with redirection of long-chain acyl coenzyme As (CoAs) to pathways that favor the synthesis of diacylglycerol, ceramide and triglycerides [28,29]. This is thought to be mediated by increases in the concentration of malonyl CoA by insulin [30]. In addition, insulin inhibits the expression of beta-oxidation enzymes in the hepatocyte. Accumulation of fat leads to liver steatosis, imbalance in free fatty acid availability, and impairment in the oxidative capacity of mitochondria ultimately causing mitochondrial dysfunction and further accumulation of fats in the cell [15]. Excessive concentrations of diacylglycerol also interfere with the phosphorylation of IRS proteins and activation of PI3K. This effect is mediated by serine kinases in the protein kinase C family that phosphorylate IRS proteins at serine residues impeding their ability to activate insulin signaling through PI3K. This effect impairs insulin signaling and prevents GLUT4 translocation [31]. In adipose tissue, this interference with insulin signaling results in reduced lipoprotein lipase function and increased activity of hormone-sensitive lipase leading to further increases in circulating free fatty acids [19,20,22] (Figure 2).

Insulin Resistance and Heart Failure: Clinical Association

Multiple observations have identified an increase in the risk of insulin resistance with HF. Data from the Framingham Heart Study show that men and women with T2DM are 4–5 times more likely to develop HF, even when the presence of coronary artery and valvular heart disease are taken into account. This increased risk was mainly observed in individuals treated with insulin, immediately suggesting that worsening insulin resistance may play a role in increasing HF risk [32]. This observation was confirmed in subsequent studies that showed that worsening features of insulin resistance also increase the risk of incident HF. In an analysis of the United Kingdom Prospective Diabetes Study, an increase of 2.5 kg/m² in body mass index resulted in a 12% increase in HF risk. Additionally, for every 1% increase in hemoglobin A1c, HF risk increased by 32% [33,34]. In a community-based cohort study of 2,300 Swedish men aged 50 years who were free of hypertension, coronary artery disease and valvular disease, the presence of metabolic syndrome was associated with a 3-fold increase in the likelihood of developing HF over 20 years of follow up [35]. Also, as the

number of features of the metabolic syndrome increases, left ventricular remodeling tends to be more severe [36].

Heart failure patients with T2DM have worse functional status and clinical outcomes when compared to non-diabetics as indicated by reduced peak oxygen consumption with exercise [37] and increased likelihood of mortality related to HF. Even worse outcomes have been observed in diabetics with ischemic cardiomyopathy [38,39]. While insulin resistance is commonly identified as a predisposing factor for HF, recent data suggest that HF may itself cause onset of insulin resistance and its progression [40,41]. In a study of ambulatory HF patients without a diagnosis of metabolic syndrome or T2DM, 63% of patients showed normal fasting glucose and insulin levels but abnormal responses to an oral glucose tolerance test, indicating that systemic insulin resistance is present in HF patients even when recognizable clinical features of insulin resistance are absent [42]. A retrospective study of diabetics with advanced HF who were treated with a left ventricular assist device suggested improvement in insulin sensitivity as a result of restoration of normal cardiac output [43]. This was supported by observed reductions in fasting blood glucose and HbA1c values, as well as reduced daily insulin requirements. Mean body weight increased after ventricular assist device implantation, suggesting that the observed improvements in insulin sensitivity were independent of weight, a typical component of the traditionally recognized insulin resistance phenotype [43]. These findings suggest that HF itself can worsen insulin resistance. This retrospective ventricular assist device study was followed up by another looking at a broader group of device recipients including a majority of non-diabetics at the time of implant. Prior to implantation, HF patients without clinical evidence of T2DM showed marked reductions in myocardial pAkt and phosphorylated forkhead box O (pFOXO), as well as reduced expression of GLUT4 and diacylglycerol transferase. These findings were associated with reduced concentrations of myocardial triglycerides and free fatty acids, and increased amounts of diacylglycerol and ceramide [44]. These observations provide further evidence of myocardial insulin resistance in HF patients in the absence of a clinically-evident insulin resistant phenotype. These pathologic findings improved dramatically or resolved after left ventricular assist device (LVAD) implantation, suggesting that correcting HF-related abnormalities can reverse the insulin resistance phenotype [44].

Insulin Resistance and Heart Failure: Proposed Mechanisms

Free fatty acid oxidation accounts for 60–90% of myocardial energy production, while glucose oxidation is responsible for the remaining 10–40%. Under conditions where oxygen supply and demand are matched, free fatty acid oxidation results in three times as much ATP production as compared to aerobic glycolysis, but this is achieved at a higher oxygen cost. When oxygen supply is compromised, glycolysis is more advantageous as glucose can be oxidized with lower oxygen cost, or even anaerobically, even though it results in lower amounts of ATP production per molecule of substrate [45]. Therefore, in pathologic states where there is increased myocardial oxygen consumption such as myocardial ischemia or HF, the heart preferentially oxidizes glucose for increased energetic efficiency [46]. This metabolic switch has been observed in the hearts of patients with non-ischemic cardiomyopathy, where there is an increased ratio of glucose to free fatty acid utilization as compared to controls with normal systolic function [47].

Type 2 diabetes, with its underlying impairment in insulin signaling, is associated with reduced rates of myocardial glucose uptake and extraction, indicating that the myocardium is affected by impaired insulin action just like other tissues [48]. Just as in the liver and skeletal muscle, insulin-stimulated glucose entry into the myocyte is dependent on GLUT4 translocation to the cell membrane [49]. In the setting of insulin resistance and HF, the expected metabolic switch from predominant fatty acid oxidation to glycolysis is abnormal

and the myocardium continues to rely on free fatty acid oxidation for energy production [50].

In order to be oxidized, fatty acids must enter the mitochondria. Access at the mitochondrial level is dependent on transport protein carnitine palmitoyltransferase 1 (CPT1). This enzyme allows transport of free fatty acids into mitochondria by transferring those attached to long-chain acyl CoA to long chain acyl-carnitine. However, in the setting of insulin resistance, CPT1 activity is inhibited by increased levels of malonyl CoA. This inhibition causes redirection of long-chain acyl CoA towards the synthesis of lipid storage molecules including triglycerides, diacylglycerol and ceramide [51]. Malonyl CoA is synthesized by acetyl CoA carboxylase, which is itself regulated through phosphorylation by AMP-dependent kinase. Inhibition of this carboxylase leads to increased free fatty acid oxidation and secondary suppression of glycolysis [52]. Proteins involved in fatty acid transport across the sarcolemma, such as CD36, and those responsible for cardiac lipolysis, such as adipose tissue triglyceride lipase and hormone-sensitive lipase, may also play a role in increasing free fatty acid availability [53–56].

The accumulation of lipid storage molecules and ceramide in the myocyte has toxic effects leading to ventricular dysfunction through ceramide-induced apoptosis, and through impaired mitochondrial function due to increased expression of peroxisome proliferator-activated receptor (PPAR)-regulated genes including uncoupling protein-3 and pyruvate dehydrogenase kinase-4 [57]. Increased levels of diacylglycerol result in further impairment of insulin signaling by inducing phosphorylation of IRS proteins via serine kinases [58]. These effects are accompanied by the development of ventricular remodeling similar to what is seen after pressure and volume overload or myocardial infarction [59]. These changes have been observed in humans in whom the predominance of free fatty acid oxidation over glucose in HF has been shown to be independent of coronary blood flow [60]. Whether these alterations in myocardial metabolism occur before or after the onset of clinically-evident insulin resistance is not entirely clear. As has been seen in animal models of insulin resistance and heart failure, increased myocardial oxygen consumption, abnormal free fatty acid oxidation, and decreased cardiac efficiency are detectable before hyperglycemia is apparent [61].

Animal Models Insulin Resistance and Heart Failure

Several animal models of diabetes and HF have been developed (Table 1), with the majority of the models being described in rodents. Most models depict how an insulin resistance phenotype results in myocardial dysfunction and eventually HF. The emerging concept of HF causing an insulin resistant state has only been reproduced in a small number of models. In animal models where insulin resistance and T2DM are the initiating factor, these conditions have been typically induced in small laboratory animals with genetic modifications that may or may not require high fat feeding. Some models have also induced type 1 diabetes using pancreato-toxic agents. Models in which cardiac dysfunction was induced have used varied well-described methods including chronic pressure overload, myocardial infarction and rapid ventricular pacing.

Animal Models of Pancreatic Toxicity and Cardiac Dysfunction

The most commonly used technique of inducing type 1 diabetes is by injecting drugs such as alloxan (ALX) and streptozotocin (STZ), both of which are particularly toxic to the insulin-producing beta cells of the pancreas. Both drugs have been historically used in laboratory animals to induce and study the metabolic processes associated with type 1 diabetes and to conduct drug trials. These models have also been used to study cardiac dysfunction [21,62–64]. The consistency of induction of pronounced hyperglycemia with STZ allows this model

to be used without the necessity of glucose tolerance testing to reveal the presence of marginal glucose intolerance [65]. A combined model of diabetes and cardiac dysfunction based on STZ was described by Shiomi et al [66]. In their study, type 1 diabetes was induced in mice by a single intraperitoneal injection of STZ. Five days after the injection, tail vein blood glucose samples were used to ensure of the presence of diabetes. Two weeks after the STZ injection, myocardial infarction was induced by ligation of the left coronary artery. Four weeks after the injection, glucose levels in mice with both type 1 diabetes and myocardial infarction (T1DM + MI) were significantly higher than control mice or mice with myocardial infarction alone. Both LV dilation and dysfunction were evident in myocardial infarction mice at two weeks. These findings were more significant in the T1DM + MI group. Left ventricular end-diastolic pressure was significantly increased and maximum rate of rise in LV pressure (dP/dt max) was significantly decreased in T1DM + MI mice as compared to control or myocardial infarction alone. Interestingly, the infarct size did not change in T1DM + MI group suggesting that the exacerbation of the LV remodeling and dysfunction after MI was worsened by the presence of diabetes [66]. Additionally, T1DM + MI mice had poor survival. Other animal models of STZ-induced type 1 diabetes and cardiac dysfunction have shown that diastolic dysfunction precedes contractile abnormalities, similar to the myocardial dysfunction observed in humans [64]. In this study, significant hyperglycemia was detected within 3 days of the injection, but LV dilatation and systolic dysfunction were detected only after 35 days [64].

Although, relatively fast and easy to produce, a major disadvantage of using alloxan and STZ induced diabetes models for studying cardiac function is that some of the effects on the heart reported in STZ- and ALX-induced diabetes may be partly attributed to direct action of these compounds [67]. Further, the changes in these models primarily reflect the effect of insulin deficiency as seen in type 1 diabetes as opposed to the typical cardiac insulin resistance seen in T2DM which may limit the applicability of this model.

Animal Models of Overfeeding Leading to Diabetes and Cardiac Dysfunction

Both obesity and insulin resistance can be induced by nutritional modification of dietary fat and carbohydrates in animals. A high fat diet consisting of saturated fatty acids rather than polyunsaturated fatty acids leads to insulin resistance [68]. High fat diet models have been used alone and in conjunction with other models of HF or cardiac insulin resistance.

Ouwens and colleagues used male Wistar rats that were fed a high fat diet (containing 25 percent weight as fat, including more saturated fatty acids palmitate and oleate) [69]. Rats that were fed a high fat diet developed a T2DM phenotype with impaired glucose tolerance and marked structural abnormalities of cardiomyocytes when compared to rats that were fed low fat diet. Myocardial changes were accompanied by a two-fold rise in cardiac triglyceride content and mild cardiac hypertrophy. Additionally, cardiomyocytes from high fat diet-fed rats showed higher baseline contractile forces but a markedly diminished recovery after higher workloads. Also, a blunted force-augmentation response to high Ca^{2+} was observed in insulin-injected high fat diet-rat papillary muscles. Calcium-mediated cardiac force generation, PI3K activity, pAkt and glycogen synthase kinase concentrations were also decreased [69].

A combined model of high fat diet and pressure overload has been proposed by Raher and colleagues [70] in which one group of mice was fed a high fat diet containing 60% saturated fat from lard for 9 days and another group was fed standard diet. The mice then underwent transverse aortic constriction to simulate chronic pressure overload. Myocardial insulin resistance in the high fat diet-fed mice was demonstrated by reduced myocardial glucose

uptake both in the basal state and in response to insulin. Although there was no effect on LV structure and function after 9 days of high fat feeding, transverse aortic constriction resulted in more pronounced LV remodeling, systolic and diastolic dysfunction in high fat diet-fed mice as compared to standard diet-fed mice. Furthermore, mice fed a short duration of high fat diet displayed coronary endothelial dysfunction, as indicated by a blunted response to acetylcholine [70].

Insulin resistance has also been generated by feeding sucrose to rats. Ventricular myocytes isolated from sucrose-fed rats demonstrate significantly longer periods of myocyte shortening and re-lengthening compared to starch fed-rats. These findings suggest systolic and diastolic abnormalities in rats fed simple versus complex carbohydrates [71,72]. Fructose, a monosaccharide obtained from fruits and a component of sucrose, has also been used to generate models of IR. Hwang et al [73] first reported in 1987 that fructose feeding in rats can lead to IR and hypertension. However, fructose-fed female rats are less susceptible to developing hypertension as compared to males [74]. Fructose feeding can increase hepatic glucose production [75] and increase the rate of de novo lipogenesis [76] that may partly explain the IR noted in this model.

Cardiac dysfunction has also been characterized in the Zucker diabetic fatty (ZDF) rat model. In 1961, a mutation designated “fatty” appeared spontaneously in a group of outbred rats giving rise to the Zucker fatty rat model [77]. The mutation occurred at the leptin receptor gene resulting in decreased affinity of leptin for its receptor, and is often referred to as *fa*. Leptin is responsible for satiety and eating behavior, such that rats that are homozygous for the mutation become hyperphagic and obese [78]. These fatty rats, although insulin resistant, do not become diabetic. The ZDF rat model was developed by inbreeding obese male *fa/fa* rats with diabetic traits [79]. Interestingly, the female ZDF rats do not develop spontaneous diabetes on normal chow diet but develop diabetes on a diabetogenic diet [80]. The hearts of these diabetic rats show reduced GLUT-4 expression [81] and upregulation of fatty acid transport [82]. The *fa/fa* rats are unable to increase their fatty acid oxidation in the presence of increased fatty acid availability leading to myocardial lipid accumulation and contractile dysfunction [83]. Both *fa/fa* and ZDF rats are unable to increase their PPAR- α activity in response to lipid accumulation. Loss of a functional PPAR- α gene results in lipid accumulation and contractile dysfunction of the heart with fasting [84]. This defect in the ability to increase fatty acid oxidation causes lipotoxic effects through deposition of intramyocardial triglycerides and increased production of ceramide leading to myocardial apoptosis [59].

The advantage of overfeeding is that these models may simulate human disease patterns more closely. Animal models of overfeeding causing insulin resistance clearly manifest cardiac abnormalities ranging from diastolic dysfunction to LV remodeling and systolic dysfunction as mentioned above. Additionally, these models have helped us in studying the early molecular changes in cardiac tissue, even before the onset of hyperglycemia. However, some of these models in which diabetes is superimposed onto a hyperlipidemic background face a major limitation due to their failure to differentiate the effects of hyperglycemia from those of hyperlipidemia.

Genetically-Engineered Animal Models of Insulin Resistance and Cardiac Dysfunction

The ability to manipulate gene expression in laboratory animals has enhanced our ability to study various disease processes including diabetic cardiomyopathy. Models of deletion and overexpression of proteins and receptors involved in insulin signaling have provided us with an opportunity to study the effects of IR on HF and vice versa. Amongst the various models

that have been developed by modifying myocardial insulin signaling, cardiomyocyte-selective insulin receptor knockout (CIRKO) mice have been extensively evaluated and validated. Cardiomyocyte insulin receptors are deleted shortly after birth in these mice resulting in reduced rates of glucose utilization, significant reduction in myocyte size, persistence of the fetal program, and metabolic features including glycolysis and decreased fatty acid oxidation that are characteristic of the immature heart [85]. Animals with the CIRKO mutation develop age-related LV dysfunction. In the presence of hemodynamic stress, these animals develop increased fibrosis, LV systolic dysfunction, and decreased capillary density in the myocardium [86]. In another study, after 4 weeks of pressure overload, the CIRKO hearts were more dilated and systolic function was reduced compared with wild-type hearts. Relative wall thickness is also reduced in banded CIRKO hearts, implying higher relative LV wall stress [87].

Two other mouse models are of interest. One is the Akita mouse model representing a spontaneous mutation leading to severe hyperglycemia, hypoinsulinemia and polydipsia [88]. Type 1 diabetic cardiomyopathy in this model is characterized by diastolic dysfunction associated with lipotoxic cardiomyopathy with preserved systolic function in the absence of interstitial fibrosis and hypertrophy [89]. The other transgenic diabetic mice is OVE 26 which is based on overexpression of a calmodulin minigene regulated by the rat insulin II promoter leading to islet cell destruction and an insulin deficient state [90]. These mice have been reported to develop diabetic cardiomyopathy [91]. Both these models depict type 1 DM and, as with the streptozotocin model, have limited applicability in studying the changes of cardiac IR which are more prominent with T2DM. Nonetheless, these two models can eliminate the potential confounding effect of drug administration as seen in the STZ and ALX model.

Other loss of function mutations pertaining to the insulin signaling pathway have also been generated and studied. PI3K lies downstream of many receptor tyrosine kinases including insulin and insulin-like growth factor-1 receptors, and plays a crucial role in many biological responses, such as membrane trafficking, cytoskeletal organization, cell growth and apoptosis [92]. Inactivation of PI3K by producing a dominant-negative PI3K (dnPI3K) transgenic mice [93] leads to diabetes and an enlarged heart with significant increases in myocyte size in response to stress [94,93]. Diabetic dnPI3K mice display an exaggerated cardiomyopathy phenotype compared with diabetic non-transgenic mice [95]. In contrast, diabetic mice with increased PI3K activity were protected against diastolic dysfunction, cardiomyocyte hypertrophy, fibrosis and apoptosis [95]. One of the most well characterized targets of PI3K is Akt [96], which itself has three isoforms, Akt1, 2 and 3. Of the three isoforms of Akt, targeted disruption of Akt2 in mice leads to increased cardiomyocyte apoptosis in the presence of ischemia [97], whereas cardiac myocytes from mice with Akt1 disruption develop an exacerbated form of cardiac hypertrophy in the presence of pressure overload due to transverse aortic constriction [98].

Leptin is a signaling molecule produced in adipocytes that increases insulin sensitivity and reduces plasma free fatty acid and triglyceride levels. Two mice models of leptin dysfunction, the leptin null (*ob/ob*) and the leptin receptor null (*db/db*), show well-characterized obesity, type 2 diabetes and cardiac dysfunction [61]. Leptin receptor null *db/db* mice exhibit initial cardiac hypercontractility followed by a decline in LV function that paralleled the earlier onset of hyperglycemia. These animals featured increased rates of myocardial free fatty acid oxidation and decreased rates of glucose oxidation that was evident even before the onset of hyperglycemia. These changes were exacerbated after hyperglycemia was evident. Leptin null *ob/ob* mouse hearts exhibit a fixed defect in glucose oxidation and fail to modulate glucose oxidation in response to insulin or to changes in the delivery of free fatty acids [99]. These models suggest that mitochondrial dysfunction could

contribute to lipotoxicity by further exacerbating the mismatch between fatty acid uptake and oxidation in the myocardium.

Another genetic model described by Goto and Kakizaki [100] exhibits common features of T2DM, namely fasting hyperglycemia, peripheral and hepatic IR and decreased insulin stimulated glucose uptake. This model is interesting as it is generated by selective breeding of normal Wistar rats with slight glucose intolerance over 30 generations and therefore, can closely mimic human adult onset T2DM. Furthermore, this is a non-obese model and can be used to study isolated effects of hyperglycemia without the confounding effects of hyperlipidemia. Brief hypoxia can impair both systolic and diastolic function in these rats [101].

Animal models of GLUT-4 deletion also show insulin resistance and marked cardiac hypertrophy even in the absence of overt T2DM as seen in GLUT-4 null mice [102]. Selective deletion of GLUT-4 from the heart results in the development of cardiac hypertrophy with preserved contractile function [103]. Taken together, these genetic models have shed light on the role of insulin signaling in the regulation of cardiac function and validate the hypothesis that myocardial insulin signaling is altered in insulin resistant states, and that these metabolic abnormalities play a significant role in the development of cardiomyopathy.

These genetically-modified models of insulin resistance manifest rapid progression of cardiomyopathy with myocardial metabolic abnormalities that lead to steatosis, worsening of myocardial insulin resistance and apoptosis. Although, they provide interesting insight into the role of insulin signaling in cardiac function, the progression or other features of the disease may not reflect human disease as closely as overfeeding models might.

Animal Models of Cardiac Dysfunction Leading to Insulin Resistance

We have described above models of insulin resistance and T2DM with associated cardiac dysfunction. However, the recognition that insulin resistance improves significantly after correction of HF with a ventricular assist device in humans with and without T2DM [44,43] has led to an emerging concept that HF itself may give origin to an insulin resistance phenotype. In fact, such observations have been made in two large animal models of experimental HF.

Nikolaidis and colleagues used a pacing-induced cardiomyopathy dog HF model to demonstrate the development of insulin resistance [104]. In this model, dilated cardiomyopathy was induced by rapid ventricular pacing for 5–6 weeks, and hemodynamic and metabolic measurements were performed. Serum glucose, insulin, norepinephrine and free fatty acids were measured before and after induction of HF. As LV function deteriorated and norepinephrine levels rose, plasma insulin levels increased providing evidence of systemic insulin resistance (Figure 3). These findings were associated with reduced activation of Akt1 and impaired GLUT-4 translocation in the myocardium, suggesting myocardial insulin resistance [104]. Similar findings of elevated glucose and insulin levels after induction of HF have been demonstrated in our own dog HF model [105]. In our model, experimental HF was induced by serial coronary micro-embolizations [106]. Hyperglycemia, hyperinsulinemia and insulin resistance were observed after the onset of HF (Figure 4).

In all, these have generated special interest as they seem to closely mimic human observations of the effect of HF on insulin sensitivity and imply that insulin signaling is closely tied to abnormal hemodynamics or neurohormonal activation. These models may be the ones that most closely resemble human disease as they do not rely on genetic

modification. These models also raise the question of whether worse clinical profiles in HF with T2DM may be the result of more severe HF alone causing insulin resistance, rather than the effect of coexisting pathophysiologic processes that fuel each other. Considering that pacing-induced HF is reversible, this model may create another opportunity to study the effect of correcting HF on insulin sensitivity.

Conclusion

Insulin resistance has long been recognized as a risk factor for the development of HF. This is supported by multiple observations in a variety of animal models of insulin resistance and T2DM in which these phenotypes are associated with cardiac dysfunction. In this review, we have summarized the pathophysiology of insulin resistance and some of the existing animal models of diabetic cardiomyopathy.

The systemic metabolic abnormalities associated with insulin resistance result in impaired glucose uptake and lipid accumulation in multiple tissues including the liver and skeletal muscle. Hepatic insulin resistance has been extensively characterized and serves as a model to illustrate the abnormalities that exist in myocytes as well [15]. These manifestations can be achieved through multiple mechanisms, among which overfeeding may simulate human disease patterns more closely.

Increasing evidence suggests that HF itself can cause insulin resistance, as has been demonstrated in animal models of cardiomyopathy that show progressive worsening of insulin sensitivity after the creation of LV dysfunction. This occurrence has been well characterized in the rapid pacing HF dog model, with demonstration of features of systemic and myocardial insulin resistance. The coronary microembolization dog HF model also exhibits evidence of systemic insulin resistance manifested as hyperglycemia and hyperinsulinemia, however findings of myocardial insulin resistance are yet to be described.

Overall, the animal models discussed above illustrate different pathophysiologic mechanisms based on the methods used to cause insulin resistance or HF or both. With due consideration to potential advantages and disadvantages, these models have proven helpful in understanding some of the complex mechanisms that underlie the relationship between IR and HF. Since the pathogenesis of cardiac dysfunction in insulin resistance is likely multifactorial, it will be challenging to produce a model that will faithfully reproduce all the pathophysiological features of this syndrome.

The Animal Models of Diabetic Complications Consortium, with the support of the NIH, has established criteria for diabetic cardiomyopathy in mice [107]. Minimal criteria for characterization of this model include demonstration of LV dysfunction such as reduced LV ejection fraction and/or diastolic dysfunction, LV hypertrophy and interstitial fibrosis in the setting of diabetes. These criteria may be extended beyond the mouse model, and we would propose to consider the characterization of additional phenotypic features including reduced levels of insulin signaling factors such as pAkt, impaired GLUT-4 translocation, and demonstration of myocardial deposition of lipid storage molecules such as diacylglyceride and ceramide. Developing models that are known to have such molecular abnormalities may create further opportunities to analyze the signaling pathways involved and eventually develop therapies that take advantage of these clearly important yet unexplored pathogenic processes.

Animal research so far has focused on the myocardial implications of insulin resistance; however, it is increasingly evident that the insulin resistance phenotype associated with HF is associated with impaired insulin signaling in multiple tissues resulting in hyperglycemia in animal models. As research into myocardial insulin resistance progresses, focus should be

directed to the effect of HF on insulin signaling in other tissues. The systemic effects of sympathetic nervous system activation on insulin resistance have been long known [108,109]. Recognizing that adipose tissue lipases can respond to adrenergic stimulation is of particular interest considering that lipolysis results in increases in circulating free fatty acids that could potentially play a role in causing insulin resistance in other tissues including the heart. The effects of adipose tissue depletion on insulin resistance have been studied in other conditions associated cachexia such as malignant tumors [110]. Further understanding of the systemic mechanisms and effects of insulin resistance related to HF may give rise to opportunities to develop novel therapies for HF that go beyond already known pathophysiological mechanisms.

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Figure 1. Insulin signaling

A. Insulin signaling in the liver. Insulin exerts its effects through autophosphorylation of the insulin receptor and phosphorylation of IRS2. Activated IRS2 activates a PI3K pathway that leads to phosphorylation of Akt with downstream signaling resulting in translocation of GLUT4 to the cell membrane to allow glucose entry, increased glycogenogenesis, inhibition of gluconeogenesis by inhibiting transcription factors FOXO1, and promotion protein synthesis and cell growth through mTOR.

B. Insulin signaling in skeletal muscle. Insulin binding causes autophosphorylation of the insulin receptor and phosphorylation of IRS1. Activated IRS1 leads to phosphorylation of

Akt via PI3K ultimately causing translocation of GLUT4 to the cell membrane to allow glucose entry. Glucose is then phosphorylated by hexokinase to being path to glycogenogenesis.

C. Insulin signaling in adipose tissue. Insulin signaling causes similar translocation of GLUT4 to the cell membrane. Insulin action also affects lipid transport. Insulin stimulates LPL in the post-prandial state to release FFA and DAG from circulating TG. FFAs are captured in the adipocyte by ASP and are re-packaged as TG by DGAT. Insulin prevents lipolysis by inhibiting HSL in the post-prandial state.

Abbreviations: IR: insulin receptor; IRS: Insulin receptor substrate protein; PI3K: phosphatidylinositol 3-kinase; pAkt: phosphorylated Akt; GLUT4: glucose transporter 4; FOXO1: Forkhead box protein O1; mTOR: mammalian target of rapamycin; UDP-glucose: uridine 5-diphosphate glucose; TG: triglyceride; FFA: free fatty acid; DAG: diacylglycerol; ASP: acylation-stimulating protein; DGAT: diacylglycerol acyltransferase; HSL: hormone-sensitive lipase.

Figure 2. Hepatic insulin resistance due to overnutrition

Over-nutrition increases levels of malonyl CoA resulting in inhibition of CPT1 activity and re-direction of long-chain acyl CoAs to synthesis of TG, DAG and ceramide causing phosphorylation of IRS protein by serine kinases resulting in further impairment of insulin signaling. Adapted with permission from Muoio, DM and Newgard, CB. *Nat Rev Mol Cell Biol* 2008;9:193–205 [15].

Abbreviations: FFA: free fatty acids; ACC: acyl CoA carboxylase; CPT1: carnitine-palmitoyltransferase 1; β -TCA: Tricarboxylic acid cycle; ETC: electron transport chain; DGAT: diacylglycerol acyl transferase; SPT1: serine palmitoyltransferase-1; GPAT1: glycerol-3-phosphate acyltransferase-1; TG: triglyceride; DAG: diacylglycerol; P: phosphate; PI3K: phosphatidylinositol 3-kinase; IRS: insulin receptor substrate protein; IR: insulin receptor.

Figure 3. Insulin resistance develops after rapid pacing-induced cardiomyopathy in dogs

As a result of rapid pacing in dogs, norepinephrine begins to increase. Parallel to that process, glucose, FFA and insulin levels increase as well, demonstrating progressive worsening on insulin resistance as cardiomyopathy develops. Nikolaidis LA et al. *Cardiovasc Res* 2004; 61: 297–306 [104]. Reproduced with permission by Oxford Journal Press.

Abbreviations: DCM: dilated cardiomyopathy; FFA: free fatty acids; NE: norepinephrine.

Figure 4. Insulin resistance develops after the onset of heart failure in dogs with coronary microembolization

After the onset of heart failure, dogs subjected to coronary microembolization develop hyperinsulinemia, hyperglycemia and, consequently, an increase in their HOMA-IR score. Abbreviations: HOMA-IR: homeostasis model assessment for insulin resistance.

Table 1

Animal models of insulin resistance and heart failure.

Model	Animal	Reference	Cardiac phenotype	Metabolic effects
Streptozotocin induced hyperglycemia and experimental MI	Mice	Shiomi et al [66]	LV dysfunction and LV dilation, increased fibrosis	Hyperglycemia
High fat diet model	Rats	Ouwens et al [54]	Cardiac hypertrophy, myocardial contractile dysfunction, elevated cardiac triglyceride content	Elevated triglycerides
High fat diet and pressure overload model	Mice	Raher and Thibault et al [70]	Increased LV remodeling, LV hypertrophy(LVH)	Systemic and myocardial insulin resistance, impaired glucose tolerance.
Zucker diabetic fatty rat model	Rats	Petersen et al [79]	Contractile dysfunction, elevated lipid deposition	Hyperglycemia, Insulin resistance, increased FFA
CIRKO model	Mice	Belke et al [85]	Age related LV dysfunction, increased fibrosis, decreased glucose utilization, reduction in myocyte size	Increased glycolysis, decreased fatty acid oxidation, insulin resistance
Leptin deficiency and leptin resistance model	Mice	Buchanan et al [61]	LV dysfunction, LVH, impaired insulin signaling	Hyperglycemia. Elevated FFA, TG and insulin
Pacing induced HF and insulin resistance	Dogs	Nikolaidis et al [104]	LV dysfunction	Hyperglycemia, hyperinsulinemia, insulin resistance and elevated FFA levels
Microembolization induced HF and insulin resistance	Dogs	Velez et al [105]	LV dysfunction	Hyperglycemia, hyperinsulinemia, insulin resistance

Abbreviations: HF= heart failure; MI= myocardial infarction; LV= left ventricular; CIRKO= cardiac insulin receptor knockout; LVH= left ventricular hypertrophy; FFA=free fatty acids; TG= triglyceride.