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Insulin Resistance and Cardiomyopathy

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1. Introduction

During the past two decades, a striking increase in the number of people with metabolic syndrome has taken place worldwide. With the increased risk worldwide of not only type 2 diabetes mellitus (T2DM), but also of cardiovascular disease from the metabolic syndrome, there is an urgent need for strategies to prevent the emerging global epidemic (1-4). Insulin-mediated glucose metabolism varies widely in healthy human beings, and the more insulin resistant an individual, the more insulin they must secrete in order to prevent the development of T2DM. However, the combination of insulin resistance and compensatory hyperinsulinemia increases the likelihood that an individual will be hypertensive, and have a dyslipidemia characterized by a high plasma triglyceride (TG) and low high-density lipoprotein cholesterol (HDL-C) concentration. Given the rapid increase in the number of clinical syndromes and abnormalities associated with insulin resistance/hyperinsulinemia, it is reasonable to suggest, that the cluster of these changes related to the defect in insulin action be included within the term, insulin resistant syndrome.

Under physiological conditions, insulin in the heart is for the regulation of the substrate employed in the contraction/ relaxation cycle and cell growth (5-9). Decreased insulin sensitivity reduces cardiac performance leading to left ventricular hypertrophy, diastolic dysfunction, and heart failure (10-12). Several mechanisms are known to contribute to the myocardial dysfunction including, reduced energy production due to decreased mitochondrial respiration and pyruvate dehydrogenase activity, oxidative stress, defective cardiac contractility, and intracellular Ca^{2+} regulatory proteins such as myosin, titin, sarcoendoplasmic reticulum Ca^{2+}-ATPase (SERCA), phospholamban, and Na^{+}-Ca^{2+} exchanger (13, 14). The high incidence of cardiac problems in patients with metabolic syndrome warrants a more stringent clinical management. Although a wide variety of pharmacological targets and agents have been discovered, the clinical management of cardiovascular risk associated with metabolic syndrome is still dismal.

2. Diabetic cardiomyopathy

It has been reported that diabetic patients suffer from heart failure with normal coronary arteries and with no other obvious aetiology for heart failure (3, 4). This phenomenon has led to the use of the term "diabetic cardiomyopathy" (DCM). The term now includes diabetic individuals with diastolic dysfunction, the prevalence of which may be as high as

60% in well-controlled T2DM individuals (12, 15). Thereby, subclinical left ventricular dysfunction may be a very common feature in diabetes, in addition to the increased prevalence of coronary heart disease (16-21). In experimental rodent models, myocardial contractile dysfunction independent of coronary artery disease has also been demonstrated in db/db, ob/ob, and Zucker rodent models, supporting the existence of an obesity-related cardiomyopathy and a diabetic cardiomyopathy (3, 22). In addition, mice with a selective cardiomyocyte only deletion of the insulin receptor (CIRKO mice) have reduced insulin-stimulated glucose uptake and also have a modest decrease in contractile function, thereby implicating insulin resistance as a contributing factor in the development of contractile dysfunction in the metabolic syndrome (23, 24).

3. Metabolic disturbances and cardiomyopathy

It is well recognized that insulin regulates the critical steps in intermediary metabolism of many tissues (including skeletal muscle, adipose tissue, and liver) and consequently maintains metabolic homeostasis within the body. However, many other tissues including the heart also express insulin receptors and their important functions may be regulated by insulin. Insulin resistance is an important risk factor for the development of hypertension, atherosclerotic heart disease, left ventricular hypertrophy and dysfunction, and heart failure. It reflects a disturbance of insulin-mediated glucose metabolism and can potentially worsen metabolic efficiency of both skeletal and cardiac muscle. Recently, the relationship between insulin resistance and cardiac contractile dysfunction has been investigated by generating a new insulin resistant animal rat model on a high cholesterol-fructose (HCF) diet. The HCF diet-induced insulin resistance not only occurred in metabolic-response tissues but also in the heart as well. These results indicate cardiac insulin resistance-associated metabolic alterations may consequently lead to the development of cardiomyopathy and contractile dysfunction (25).

Diabetes causes metabolic dysregulation and contains numerous risk factors which are associated with cardiomyopathy and heart failure. Extensive cellular and molecular studies have elucidated putative process of metabolic disturbances in the pathogenesis of cardiac dysfunction in diabetes (Table.1) (26). The metabolic disturbances in the development of cardiomyopathy are listed below.

3.1 Increased triglycerides (TG) and nonesterified fatty acids (NEFAs)

Hyperlipidemia is one of the features of obesity induced T2DM. When circulating NEFAs are greater than the oxidative capacity of the heart, NEFAs are stored as intramyocardial triglycerides. Both NEFAs and TG contribute to cardiac lipotoxicity and worsened heart failure (27-32). High levels of circulating NEFAs promote insulin resistance by impairment of insulin-Akt activation and compensatory hyperinsulinemia (27, 33-36). NEFAs also induce the activation of atypical protein kinase C (PKC)θ, which is a serine/threonine kinase that phosphorylates and subsequently activates IκB kinase. Then IκB kinase phosphorylates insulin receptor substrate-1 (IRS-1) serine residues which inhibit the ability of IRS-1 to bind to SH2 domains of the p85 regulatory subunit of phosphatidylinositol 3-kinase (PI3K), and consequently impair insulin signal transduction (36). NEFAs not only trigger the development of cardiac insulin resistance but also lead to the development of myocardial contractile dysfunction. NEFAs can

directly alter myocardial contractility by increasing NEFA flux into the myocardium. A recent study suggests that increasing the entry of fatty acyl coenzyme A (CoA) into the cardiomyocytes may modulate the K_{ATP} channel opening during the contractile state of the myocardium (37). Activation of K_{ATP} channel contributes to shortening of the action potential and decreases trans-sarcolemmal calcium flux and subsequent myocardial contractility (37).

TRIGGERS	MEDIATORS	EFFECTORS	TARGETS
NEFA	↑ Acyl CoA	↑ K^+_{ATP} CHANNEL	↓ ACTIVATOR Ca^{++}
	↑ ATYPICAL PKC ↑ PTEN	↓ Akt-1 ACTIVATION	INSULIN RESISTANCE
	↑ TNF α	↑ CERAMIDE	MYOCYTE APOPTOSIS
HYPERGLYCEMIA	↑ ROS → ↑ PARP ↓ ↓ GAPDH	↑ PKC	CALCIUM HOMEOSTASIS
		↑ HEXOAMINE	CONTRACTILE PROTEINS
		↑ POLYOL FLUX	
		↑ AGE	MATRIX PROTEINS
HYPERINSULINEMIA INSULIN RESISTANCE	PI3K/Akt-1	↓ GSK-3 β ↑ mTOR	MYOCYTE HYPERTROPHY
	↑ MAP KINASE	↑ Ras/ ↑ Rho	↑ PROTEIN SYNTHESIS

Table 1. The relationship between diabetic metabolic disturbances (triggers) and the mediators, effectors, and intracellular targets that lead to a diabetic cardiomyopathic phenotype. (Modified from Poornima IG, Parikh P, Shannon RP. Diabetic cardiomyopathy: the search for a unifying hypothesis. *Circ Res*. 2006; 98: 596-605.)

3.2 Hyperglycemia

Hyperglycemia leads to increasing glucose oxidation. Brownlee and colleagues have elucidated that hyperglycemia generates reactive oxygen species (ROS) and consequently mediates tissue injury (38, 39). In fact, mitochondria generate high levels of ROS which lead to damage of DNA and inhibit the activity of glyceraldehyde phosphate dehydrogenase (GAPDH) (39, 40). On the other hand, hyperglycemia also shifts the glucose glycolytic pathway into alternative pathways that are considered mediators of hyperglycemia induced cellular injury (26). The damage resulting from hyperglycemia includes elevation of advanced glycation end products (AGEs), hexosamine and polyol pathway, activation of beta 2 isoform PKC and alteration of myocardial structure and function (41-47). In addition, it has been suggested that hyperglycemia is linked to altering the expression and function of both the ryanodine receptor (RyR) and sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA), and this alteration may contribute to impair myocardial systolic and diastolic function (26).

3.3 Insulin resistance and hyperinsulinemia

Insulin resistance is prevalent in chronic heart failure patients with idiopathic dilated cardiomyopathy (12, 48). Furthermore, insulin resistance is a primary etiology factor in the development of nonischemic heart failure (HF) (49). The cardiac insulin action and how insulin resistance leads to the development of cardiomyopathy are discussed in detail below.

4. The cardiac action of insulin

The heart is an energy-consuming organ that requires a constant supply of fuel and oxygen in order to maintain its intracellular ATP level, which is essential for the uninterrupted myocardial contraction/relaxation cycle. Oxidation of fatty acids supplies approximately 70% of the heart's energy needs, while glucose and lactate may account for up to 30% of total ATP production. The energy requirements of the heart could be covered for a short period by the breakdown of intracellular stored glycogen and lipid droplets, but a longer duration would rely on the uptake of exogenous glucose and long chain fatty acid (LCFA). Circulating insulin and increased contractile activity are the two major signals responsible for acute increases in cardiac substrate uptake, enabled by inducing transporter translocation from intracellular stores to the sarcolemma (Fig.1) (5).

Under normal physiological conditions, the main role of insulin on the heart is the regulation of substrate utilization. Insulin regulates cardiac metabolism by modulating glucose and fatty acid transport, glycolysis, glycogen synthesis, lipid metabolism, protein synthesis, growth, contractility, and apoptosis in the cardiomyocytes (5). The actions of insulin are mediated by binding to specific cell surface receptors (insulin receptor, InsR). Each cardiomyocyte is expressed at levels of about 10,000 to 100,000 receptors of InsR. The InsR is a tetrameric enzyme comprising two extracellular α-subunits and two transmembrane β-subunits (5). The binding of insulin to the extracellular domain of InsR triggers the activation of intrinsic tyrosine kinase activity of the β-subunits of the receptor. This leads to an autotransphosphorylation of the receptor where one β-subunit phosphorylates the other on several tyrosine residues. Once activated and phosphorylated, InsR binds via its phosphotyrosine residues and phosphorylates a series of downstream elements, including the insulin receptor substrate (IRS) family and Shc (5, 50). This recruitment and activation lead to the activation of two main pathways, the phosphatidylinositol 3-kinase (PI3K) and the

mitogen-activated protein kinase (MAPK) pathway respectively. PI3K is considered to be the main player of the metabolic action of insulin, whereas the MAPK pathway is principally involved in cell growth and differentiation in the heart (Fig.2) (50, 51).

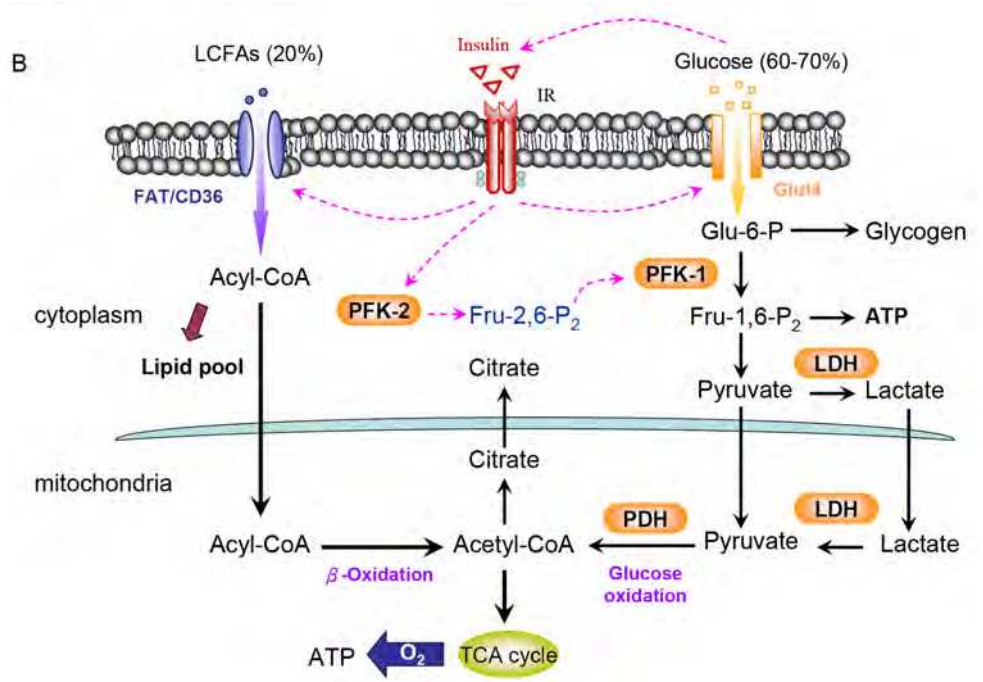

Fig. 1. Cardiac metabolism under control (A) and insulin (B) conditions. Under control conditions, ATP production comes from fatty acids and glucose oxidation. Fatty acid is the privileged substrate used by the heart, the β-oxidation inhibiting glucose oxidation via the Randle cycle. When glucose and insulin plasma levels increase, glucose becomes the main energy-providing substrate. Indeed, insulin induces Glut4 translocation and PFK-2 activation, leading to the concomitant stimulation of glucose uptake and glycolysis. (Modified from Bertrand L, Horman S, Beauloye C, Vanoverschelde JL. Insulin signalling in the heart. *Cardiovasc Res*. 2008; 79: 238-248.)

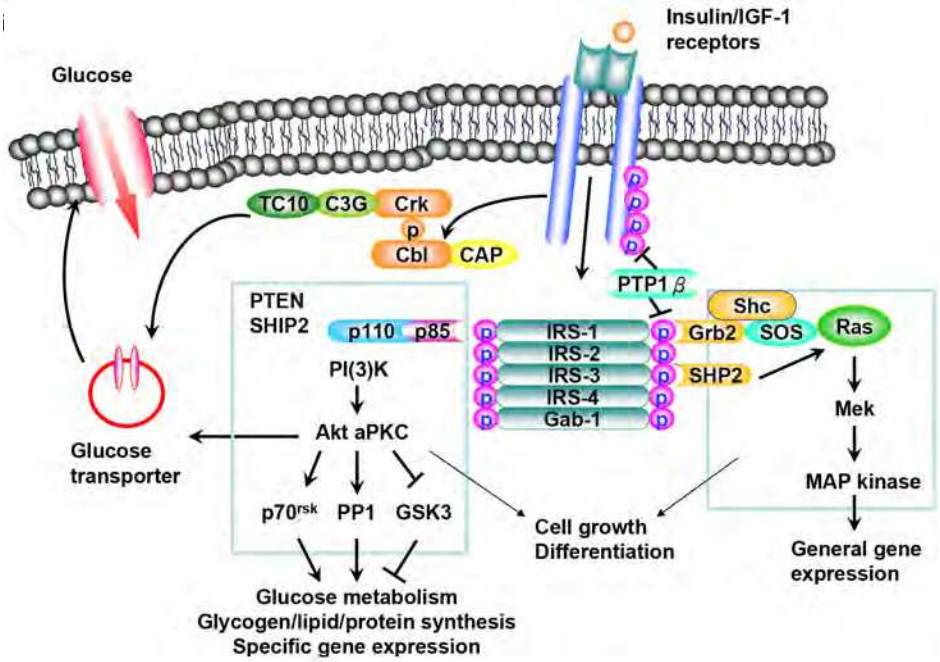

Fig. 2. Signal transduction in insulin action. The insulin receptor is a tyrosine kinase that undergoes autophosphorylation, and catalyses the phosphorylation of cellular proteins such as members of the IRS family, Shc, and Cbl. These pathways act in a concerted fashion to coordinate the regulation of vesicle trafficking, protein synthesis, enzyme activation and inactivation, and gene expression, which results in the regulation of glucose, lipid, and protein metabolism. (Modified from Saltiel AR, Kahn CR. Insulin signalling and the regulation of glucose and lipid metabolism. *Nature*. 2001; 414: 799-806.)

Insulin mediation of glucose uptake depends on the presence of glucose transporters (Gluts) at the plasma membrane. Glut1 and Glut4 are the two glucose transporters expressed in the heart; however, Glut4 is considered to be the main contributor for the insulin stimulated glucose uptake (52, 53). The role of the PI3K/PKB/Akt-signalling in the insulin-stimulated Glut4 translocation has been well established (54). Insulin not only stimulates glucose uptake, it also induces LCFA uptake in cardiomyocytes (55, 56). Insulin stimulates LCFA uptake by translocation of LCFA transporter (FAT/CD36) to the plasma membrane in the cardiomyocytes (57, 58).

Insulin also promotes protein synthesis by phosphorylation and dephosphorylation of several translational factors and ribosomal proteins through PI3K/AKT/mTOR pathway (59, 60). Activation of mTOR mainly regulates two translational factors which are 4E-binding protein-1 (4E-BP1) and the p70 ribosomal S6 protein kinase (p70S6K). Additionally, PKB/AKT also regulates GSK-3 and the forkhead transcription factor (FOXO) family, participating in the modulation of protein translation and promoting the atrogene transcriptional program (61). In addition to affecting energy metabolism, Akt activation also modulates several cellular functions which inhibit apoptosis, stimulate

myocyte hypertrophy/fibrosis, and enhance nitric oxide production. Therefore, an absent insulin response can lead to less nitric oxide production, more apoptosis, and alterations in myocardial structure (62-65). Fig.3 elucidates the multiple biological functions of PKB/Akt (63).

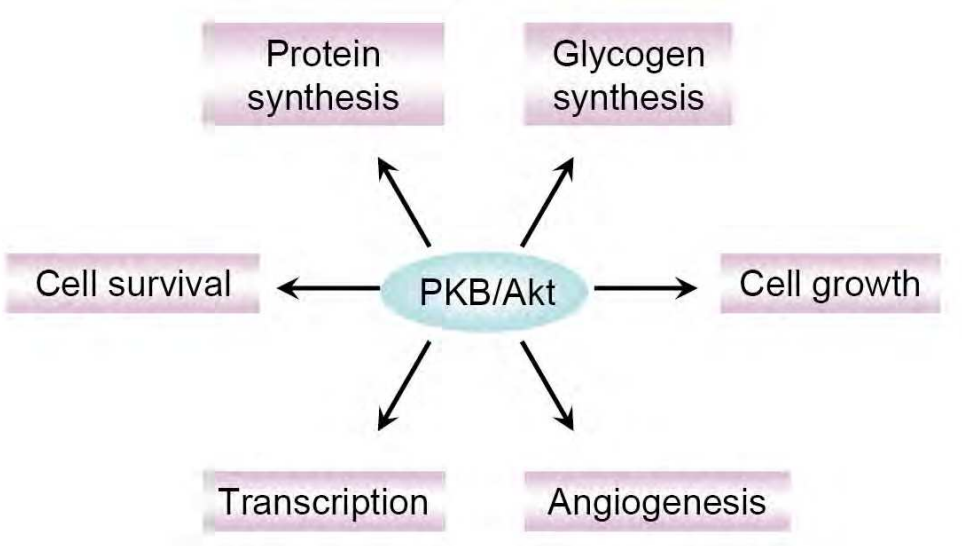

Fig. 3. Central role of protein kinase B (PKB)/Akt in multiple cellular responses. PKB/Akt control numerous of key cellular events. (Modified from Brazil DP, Hemmings BA. Ten years of protein kinase B signalling: a hard Akt to follow. *Trends Biochem Sci*. 2001; 26: 657-664.)

5. Insulin resistance induced cardiomyopathy

Insulin resistance describes an impaired biological response to insulin, and in the early stages, the plasma insulin level is increased. Although the increased insulin level may compensate for resistance to some biological actions of insulin, it may result in overexpression of actions in tissues that retain normal or slightly impaired sensitivity to insulin. In general, insulin resistance can be due to a prereceptor, receptor, or postreceptor abnormality (66). The insulin resistance induced cardiomyopathy may contain the following features.

5.1 Hypertension

Clinical studies reveal that insulin resistance and hyperinsulinemia is related to hypertension (67, 68). Mechanisms for the development of hypertension in insulin resistance and hyperinsulinemia include activation of the sympathetic nervous system, renal sodium retention, transmembrane cation transport alteration, growth-promoting effects of vascular smooth muscle cells, and vascular hyperreactivity (66, 69, 70). Fig. 4 is a schematic representation of the hypothetical relationships between obesity, insulin resistance, and hypertension (70).

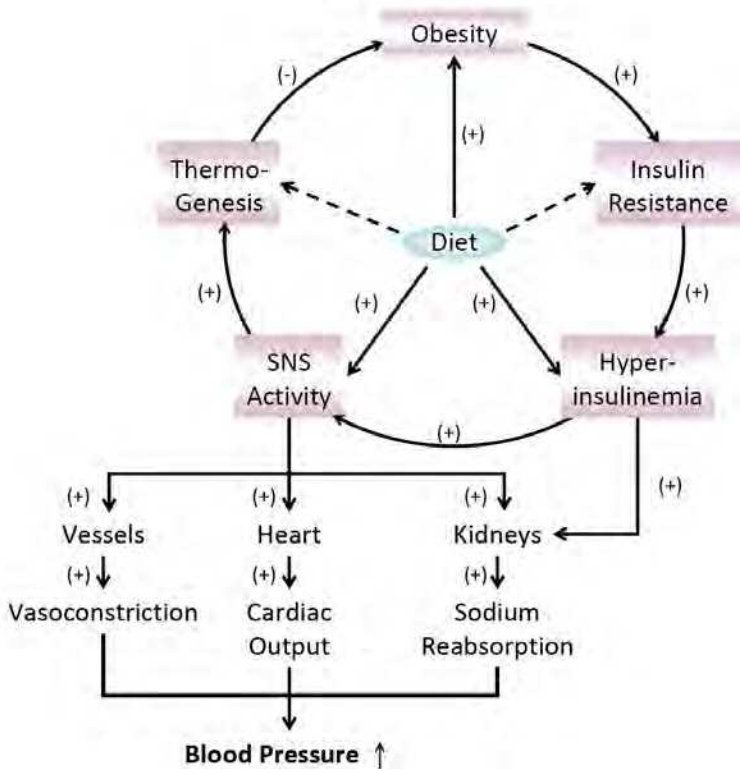

Fig. 4. Multiple role of insulin resistance to hypertension. Insulin resistance as a physiologic mechanism to restore energy balance, activate sympathetic stimulation, and leading to hypertension. The steady-state hyperinsulinemia, acting at the level of the kidney, and the consequent sympathetic stimulation of the vasculature, heart, and kidneys result in hypertension. Plus signs denote positive or stimulatory effects, the minus sign a negative or inhibitory effect, and the dotted line the direct effects of food on insulin resistance and metabolic rate. (Modified from Reaven GM, Lithell H, Landsberg L. Hypertension and associated metabolic abnormalities--the role of insulin resistance and the sympathoadrenal system. *N Engl J Med*. 1996; 334: 374-381.)

5.2 Ventricular hypertrophy

Previous studies have demonstrated that left ventricular hypertrophy and heart failure may be associated with insulin resistance (71-73). Insulin and insulin growth factor-1 (IGF-1) may exert a direct growth-promoting effect on cardiomyocytes (74, 75) and lead to cardiomyocyte hypertrophy. On the other hand, diabetes and insulin resistance are a disorder of metabolic regulation. Many acute metabolic changes alter the cellular signal transduction cascades and are believed to be involved in the adaptation of the heart to changes in its environment. PI3K, PKC and Ca^{2+}, all play a role in cardiac adaptation to regulate metabolism in the heart (76). Adrenergic activation induced hypertension may also stimulate pressure overload hypertrophy as an adaptation process (77).

5.3 Dilated cardiomyopathy and heart failure

Many studies have confirmed a strong correlation between nonischemic cardiomyopathy and diabetes, with a dramatically increased prevalence of diabetes in the dilated cardiomyopathy population (78). Additionally, abnormal glucose tolerance and insulin resistance in patients with idiopathic dilated cardiomyopathy (IDCM) has been described (49, 79). It is almost clear that insulin resistance itself is not enough to trigger dilated cardiomyopathy as the majority of patients with insulin resistance do not develop dilated cardiomyopathy. Insulin resistance is more likely to create an abnormal environment, rather than causing another stressor (e.g., pressure/volume overload, metabolic inbalance, energy defect or decreased perfusion). Insulin resistance makes the heart unable to maintain homeostasis of its energy and function, which may favor the development of cardiomyopathy and heart failure (45, 80, 81). Fig. 5 shows the relationships/mechanism between insulin resistance and heart failure (49).

5.4 Cardiac mitochondria abnormalities and ROS elevation

ROS is the one-electron reduction of O_2 to superoxide by nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, which contributes to ROS generation, especially in chronic pathological states (82, 83). Mitochondria provide another significant source of cardiomyocyte ROS, particularly under acute stress. Insulin resistance impaired mitochondrial biogenesis and oxidative phosphorylation, is associated with myocardial dysfunction (84). Insulin resistance-induced hyperglycemia also directly enhances ROS generation and protein damage which leads to mitochondrial apoptosis and degradation (84). In addition, activation of the renin angiotensin aldosterone system (RAAS) is associated with increasing oxidative stress (85). The oxidative stress can impair glucose transport/utilization as well as mitochondrial ATP generation and intracellular Ca^{2+} regulatory proteins. Abnormalities in Ca^{2+} signaling/flux and myofilament functions, contribute to the cardiomyopathy changes and defective cardiac contractile function (86-87). In the 1980s, Przyklenk K et al. demonstrated that superoxide dismutase (SOD) plus catalase improve myocardial contractile function in the canine model (88). A recent study also points out that cardiac overexpression of catalase rescues insulin resistance induced myocardial contractile dysfunction (89).

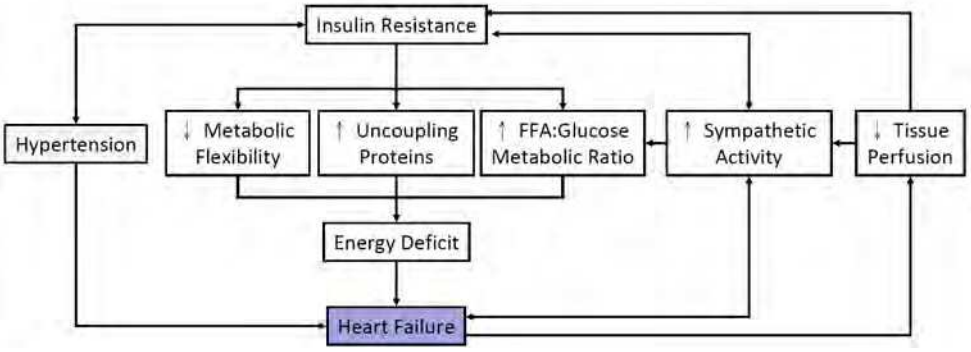

Fig. 5. Relationships/mechanism between insulin resistance to heart failure. (Modified from Witteles RM, Fowler MB. Insulin-resistant cardiomyopathy clinical evidence, mechanisms, and treatment options. *J Am Coll Cardiol*. 2008; 51: 93-102.)

6. Animal models for diabetic or insulin resistant cardiomyopathy

The impairment of glucose uptake, glycolysis, and pyruvate oxidation has been observed in both, types 1 and type 2 diabetes. In addition, attenuation of insulin function augments lipolysis and increases FFA release from adipose tissue. These abnormalities play a crucial role in the development of cardiomyopathy. Recently, several diabetic and insulin resistant animal models which include chemical (STZ-diabetes), genetic defect (*ob/ob* and *db/db* mice and Zucker diabetic fatty rats), and western diets (high fat, high fructose, high cholesterol, and high choleserol with fructose diets) diabetic induced animals, have been used to elucidate the pathophysiological processes of insulin resistance related cardiomyopathy.

6.1 Type 1 diabetes model

Streptozotocin (STZ) is a chemical generating the production of ROS which damages the pancreas with loss of function and reduced insulin production, by triggering DNA fragmentation (90, 91). The STZ-diabetic animal model can be employed for assessing the mechanisms of insulin dependent non-obese diabetes and screening potential therapies for the treatment of this condition. The characteristics of STZ-diabetes-induced cardiomyopathy include the alteration of contractile protein synthesis, abnormality of diastolic pressure-volume relationships, impairment of cardiac contractility, and incomplete relaxation of the myocardium (92, 93-97). The STZ-induced diabetics have metabolic disturbances especially, an increased plasma free fatty acid concentration (98-100). Insulin treatment reverses STZ-diabetes-induced cardiomyopathy suggesting that insulin deficiency is the major reason leading to the development of diabetic cardiomyopathy but not due to a primary cardiotoxic effect of STZ (92, 101). Resveratrol (RSV), a natural antioxidant derived from grapes, has been suggested to improve cardiac contractile function in STZ-diabetic rats (102). Moreover, the angiotensin II blocker losartan, restores cardiomyocyte functional properties in STZ-diabetic rats (103).

6.2 *Ob/ob* and *db/db* mice model

Obesity is closely associated with insulin resistance and serves as a major risk factor for the development of T2DM. Leptin or leptin receptor gene deficiency mice (*ob/ob* and *db/db* mice) are commonly used animal models for the study of T2DM. The *ob/ob* and *db/db* mice exhibit an increase of hepatic lipogenesis and gluconeogenesis resulting in increased insulin secretion by the pancreas due to the hyperglycemia and hyperlipidemia, which begins a vicious cycle of insulin resistance. Recently, contractile dysfunction independent of coronary artery disease has also been demonstrated in db/db and ob/ob mice, supporting the existence of an obesity-related cardiomyopathy and a diabetic cardiomyopathy (104-108). These genetically defective mice show a decrease in glucose oxidation rates and an increase of FFA oxidation and myocardial oxygen consumption (MVO_2), resulting in impaired cardiac efficiency (106, 108). Moreover, *ob/ob* hearts show a decrease in mitochondrial oxidative capacity, an increase of fatty acid-induced mitochondrial uncoupling, and deleterious effects on global cellular Ca^{2+} homeostasis (109, 110). As observed in STZ-diabetic rats, *db/db* mice also have excessive ROS generation, which causes cardiomyocyte damage and augmentation of apoptosis (110, 111).

6.3 Zucker diabetic fatty rat (ZDF rat)

The Zucker rat (leptin receptor gene deficient) was bred to be a genetic model for research in obesity and hypertension, and T2DM. Obese Zucker rats exhibit hyperlipidemia,

hypercholesterolemia, and insulin resistance. The cardiac contractile functions and carbohydrate oxidation rates are reduced and fatty acid utilization is increased in the Zucker rat heart (28, 112-115). In contrast, several studies indicate that Zucker rats display insulin resistance without overt signs of diabetes (hyperglycemia and hyperlipidemia). These rats also show a normoglycemia phenomenon and absence of significant cardiac contractile dysfunction (116,117). Taken together, the genetic defect (leptin or leptin receptor)-induced cardiomyopathy may include several characteristics which contribute to impair myocardial contractility in diabetes mellitus. These are: (a) disturbance of substrate metabolism, (b) impairment of calcium homeostasis, (c) increased oxidative stress, (d) upregulation of the renin-angiotensin system, and (e) impairment of mitochondrial biogenesis and function (3).

6.4 Diet induced insulin resistance and cardiomyopathy

Based on previous reviews, it is widely accepted that disturbance of substrate metabolism is a key factor in the induction of insulin resistance and cardiomyopathy. Both genetic and environmental factors contribute to the development of metabolic abnormalities. Several experimental studies have demonstrated that the macronutrient composition of a diet is an important environmental determinant of the quality of insulin action (118, 119). High-fat and high-fructose intakes have been shown to contribute to conditions such as hyperlipidemia, glucose intolerance, hypertension, and atherosclerosis (120, 121). In addition, brief feeding of an excessive atherogenic diet (chow with 45% kcal from fat and 2% cholesterol) produces striking features of metabolic syndrome and coronary artery disease (122). High sugar intake is linked to an increased risk of heart disease. Simple sugars are the primary source of high triglycerides and very low-density lipoproteins (LDL), which are independent risk factors for atherosclerosis. Sugar lowers high-density lipoprotein (HDL) cholesterol and raises LDL cholesterol along with blood pressure. In addition, it has been suggested that fructose induced hyperuricemia results in endothelial dysfunction and insulin resistance, and might be a causal mechanism of the metabolic syndrome (123).

6.4.1 High fat diet (HFD)

With long term high fat intake, the response to a chronic high plasma concentration of long-chain fatty acids is that the heart is forced to increase the uptake of fatty acid. This switch in metabolic substrate uptake is accompanied by an increased presence of the fatty acid transporter FAT / CD36 at the cardiomyocyte sarcolemma. This shifts oxidation towards FA rather than glucose oxidation, and results in the development of cardiac insulin resistance and ultimately diabetic cardiomyopathy (124). It is unquestionable that chronic feeding with a high fat diet causes insulin resistance. The implication is that it decreases insulin-stimulated Akt phosphorylation, whereas cardiac basal Akt phosphorylation is elevated (124). HFD also causes cardiac lipotoxicity which may contribute to the development of diabetic cardiomyopathy (125). Additionally, hypertrophic growth and structural alterations in the context of disease is in the end maladaptive, because it will progress to, contractile dysfunction, decompensation and ultimately heart failure.

6.4.2 High fructose diet

High-fructose intake is shown to contribute to conditions such as hyperlipidemia, glucose intolerance, hypertension, and atherosclerosis (126). The preference of fructose in the lipogenesis pathway contributes to induce hyperlipidemia, in particular, a marked increase

of postprandial triglyceride (TG) concentration (Fig.6) (127-129). Fructose intake is associated with an increasing incidence of insulin resistance and insulin-resistant related hypertension and cardiomyopathy (130, 131). High fructose induced insulin resistance may manifest as alterations in insulin activated PI3K/Akt pathway leading to reduced, Glut4 translocation, glucose uptake, and cardiomyocyte growth and survival. Upregulation of lipid metabolism in fructose-fed rats increases ROS production and damages the cardiomyocyte. In addition, ROS-induced dephosphorylation of Akt at Serine473 residue has been reported to participate in the insulin resistance (132).

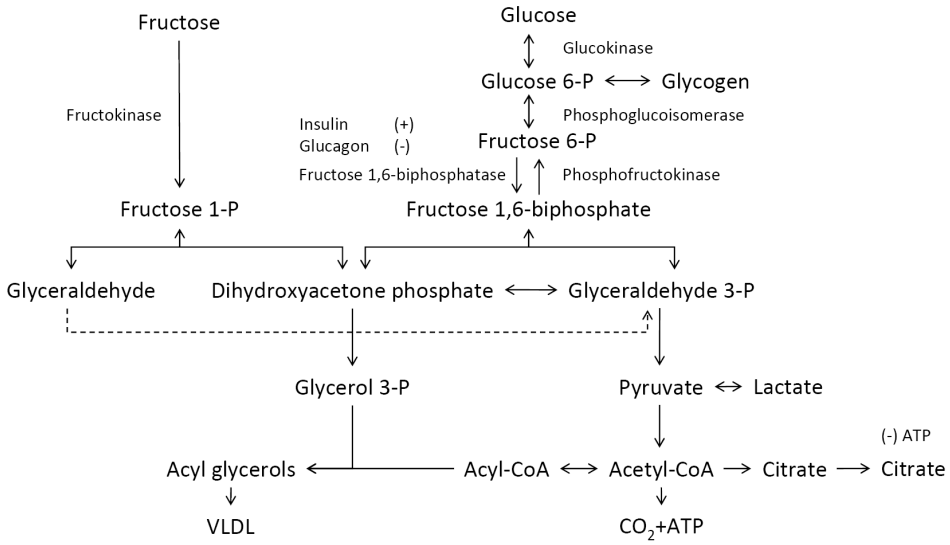

Fig. 6. Specific utilization of fructose and the glucose utilization in the liver. Hepatic fructose metabolism begins the phosphorylation by fructokinase. Fructose carbon enters the glycolytic pathway at the triose phosphate level. Thus, fructose bypasses the major control point by which glucose carbon enters glycolysis (phosphofructokinase), where glucose metabolism is limited by feedback inhibition by citrate and ATP. This allows fructose to serve as an unregulated source of both glycerol-3-phosphate and acetyl-CoA for hepatic lipogenesis. (Modified from Elliott SS, Keim NL, Stern JS, Teff K, Havel PJ. Fructose, weight gain, and the insulin resistance syndrome. *Am J Clin Nutr*. 2002; 76: 911-922.)

6.4.3 High cholesterol and fructose diet (HCF)

Brief feeding of an excessively atherogenic diet (chow with 45% kcal from fat and 2% cholesterol) produces striking features of metabolic syndrome and coronary artery disease (122). Numerous studies show that high cholesterol induces chronic inflammation. It is reported that the addition of a small amount of cholesterol to a western-type diet is associated with chronic systemic inflammation, as evidenced by an increase in atherosclerosis and circulating inflammatory protein levels (133, 134). Specifically, a study proposes the concept that, dietary cholesterol worsens adipose tissue macrophages independent of weight gain (133). This observation is consistent with the notion that adipose tissue inflammation and dysregulation of adipokines secretion contribute to the

development of systemic insulin resistance (135). Our laboratory study reveals that a high cholesterol-fructose (HCF) diet also induces insulin resistance not only in metabolic-responsive tissues (i.e. liver and muscle) but also in the heart as well (25). Insulin-stimulated cardiac glucose uptake was significantly reduced after 15 weeks of HCF feeding, and cardiac insulin resistance was associated with blunted Akt-mediated insulin signaling along with GLUT4 translocation. The basal FATP1 (fatty acid transporter 1) levels were increased in HCF rat hearts. The cardiac performance of the HCF rats showed a marked reduction (25). Our results indicate that high-cholesterol food and sugar-sweetened beverages that lead to maladaptive metabolic processes may interfere with the action of insulin and increase susceptibility for the development of cardiomyopathy (25).

7. Potential therapies in insulin resistant related cardiomyopathy

Insulin resistance is an important risk factor for the development of hypertension, atherosclerotic heart disease, left ventricular hypertrophy and dysfunction, and heart failure (136-138). It reflects a disturbance of glucose metabolism and can potentially worsen the metabolic efficiency of both skeletal and cardiac muscle. The exact mechanisms of cardiac insulin resistance leading to and progression of, left ventricular contractile dysfunction are not fully elucidated. Currently, the most promising potential medical therapies for insulin resistant cardiomyopathy can be divided into 2 broad categories which are, metabolic modulators and diabetic medications (Table.2)(49).

Medication	Mechanism	Other/Side-effects
Metabolic modulators		
Trimetazidine	↓ FFA metabolism	Not approved In U.S.
Perhexiline	↓ FFA metabolism	Not approved In U.S.,liver/neuro-toxicity
Ranolazine	↑ Glu metabolism	Might not be primary mechanism, ↑ QT interval
L-carnitine	↑ FFA/Glu metabolism	
Diabetic medications		
Insulin	↑ Ins	Hypoglycemia
Sulfonylureas	↑ Ins	Hypoglycemia
Metformin	↑ Ins sensitivity	Lactic acidosis (rare)
TZDs (glitazones)	↑ Ins sensitivity	Fluid retention/edema
GLP-1	↑ Ins/ ↑ Ins sensitivity	Very short half-life (1-2 min)
Exenatide	↑ Ins/ ↑ Ins sensitivity	Nausea/weight loss, subcutaneous injection
DPP-IV inhibitor	↑ Ins/ ↑ Ins sensitivity	

Table 2. Potential treatments for insulin resistant cardiomyopathy. (Modified from Witteles RM, Fowler MB. Insulin-resistant cardiomyopathy clinical evidence, mechanisms, and treatment options. *J Am Coll Cardiol*. 2008; 51: 93-102.)

1. Metabolic modulators which increase glucose metabolism, decrease FFA metabolism, and potentially enhance myocardial contractile efficiency are e.g. Trimetazidine, Perhexiline, Ranolazine, and L-carnitine.
2. Diabetic medications enhancing insulin sensitivity (TZDs) might theoretically be the most attractive therapies to improve insulin resistant related cardiomyopathy. These agents work on the activation of PPARγ, a transcription factor that promotes insulin sensitivity and decreases circulating FFA, and increases myocardial glucose uptake (139).

Moreover, several newly developed classes of antidiabetic medications have been discovered recently. Glucagon-like peptide 1(GLP1) treatment, results in promotion of post prandial insulin secretion and improvement of insulin sensitivity (140). GLP1 infusion improves left ventricular function, hemodynamic status, and cardiac efficiency (141). In addition, angiotensin converting enzyme inhibitors (ACEI), angiotensin II receptor blockers and statins all affect glucose metabolism (142-144); although combined therapy involving a diuretic agent and a calcium-channel blocker is required (145). Interestingly, a recent study shows that RSV and insulin combination treatment has preventive effects on diabetes-associated cardiovascular dysfunction. However, when a diabetic individual has suffered an acute heart attack the synergistic actions of combination treatment were nullified and the advantage of RSV was antagonized by insulin. This study provides valuable advice for using insulin and RSV in patients with diabetes and those diabetic individuals with ischemic heart disease (102).

8. Summary and conclusion

Insulin plays an important physiological role in coupling metabolic and cardiac homeostasis under healthy conditions. Loss of normal insulin action (insulin resistance) on the heart makes the heart unable to maintain homeostasis of its energy and function, which may favor the development of cardiomyopathy and heart failure. It is almost clear that insulin resistance itself is not enough to trigger dilated cardiomyopathy as the majority of patients with insulin resistance do not develop dilated cardiomyopathy. Insulin resistance is more likely to create an abnormal environment, rather than causing another stressor.

9. References

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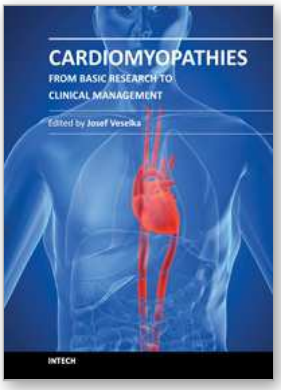

Cardiomyopathies - From Basic Research to Clinical Management
Edited by Prof. Josef Veselka

ISBN 978-953-307-834-2
Hard cover, 800 pages
Publisher InTech
Published online 15, February, 2012
Published in print edition February, 2012

Cardiomyopathy means "heart (cardio) muscle (myo) disease (pathy)". Currently, cardiomyopathies are defined as myocardial disorders in which the heart muscle is structurally and/or functionally abnormal in the absence of a coronary artery disease, hypertension, valvular heart disease or congenital heart disease sufficient to cause the observed myocardial abnormalities. This book provides a comprehensive, state-of-the-art review of the current knowledge of cardiomyopathies. Instead of following the classic interdisciplinary division, the entire cardiovascular system is presented as a functional unity, and the contributors explore pathophysiological mechanisms from different perspectives, including genetics, molecular biology, electrophysiology, invasive and non-invasive cardiology, imaging methods and surgery. In order to provide a balanced medical view, this book was edited by a clinical cardiologist.

How to reference
In order to correctly reference this scholarly work, feel free to copy and paste the following:

Jiung-Pang Huang and Li-Man Hung (2012). Insulin Resistance and Cardiomyopathy, Cardiomyopathies - From Basic Research to Clinical Management, Prof. Josef Veselka (Ed.), ISBN: 978-953-307-834-2, InTech, Available from: http://www.intechopen.com/books/cardiomyopathies-from-basic-research-to-clinical-management/insulin-resistance-and-cardiomyopathy

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