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Insulin Resistance and Heart Failure: Molecular Mechanisms

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Abstract

Insulin resistance and associated reductions in cardiac insulin metabolic signaling is emerging as a major factor for the development of heart failure and assumes more importance because of an epidemic increase in obesity and the cardiorenal metabolic syndrome and our aging population. Major factors contributing to the development of cardiac insulin resistance are oxidative stress, hyperglycemia, hyperlipidemia, dysregulated secretion of adipokines/cytokines and inappropriate activation of renin-angiotensin II-aldosterone system (RAAS) and the sympathetic nervous system. The effects of cardiac insulin resistance are exacerbated by metabolic, endocrine and cytokine alterations associated with systemic insulin resistance. The aggregate of these various alterations leads to an insulin resistant phenotype with metabolic inflexibility, impaired calcium handling, mitochondrial dysfunction and oxidative stress, dysregulated myocardial-endothelial interactions resulting in energy deficiency, impaired diastolic dysfunction, myocardial cell death and cardiac fibrosis. Therefore, understanding the molecular mechanisms linking insulin resistance and heart failure may help to design new and more effective mechanism-based drugs to improve myocardial and systemic insulin resistance.

Keywords

Cardiac insulin resistance; cardiorenal metabolic syndrome

Heart failure (HF) is a major cause of morbidity and mortality in the Western world. HF is present in more than 5 million people in the United States, accounting for nearly 40 billion US dollars in annual health care costs (1). Coronary heart disease (CHD), diabetes, hypertension, and cardio renal syndrome (CRS) are the major factors causing HF (1, 2). CRS is a constellation of metabolic disorders including obesity, hypertension, insulin resistance, and myocardial and renal abnormalities. CRS increases the risk for the

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development of type 2 diabetes mellitus (T2DM) and renal and cardiovascular disease (CVD) CHD and HF (3). At least 25% of US adults have been diagnosed with the CRS. The incidence of CRS is increasing at an alarming rate due to a rise in the aging population and epidemic increase in overnutrition and sedentary lifestyle. Epidemiological studies indicate that more than 60% of American adults are overweight and over 40% Americans older than 60 years have CRS. In addition, childhood-adult obesity is also emerging as a global health problem that predisposes to CRS and T2DM (1–4).

1. The Chicken and the Egg: Insulin Resistance and Heart Failure

Insulin resistance contributing to cardiomyopathy

A strong association exists between insulin resistance and HF. Insulin resistance predicted the development of HF in several clinical studies (5). Although association of insulin resistance to heart failure may be attributed to associated conditions such as CRS, hypertension, and coronary heart disease, the recognition of HF in association with diabetes in the absence of CHD and hypertension (diabetic cardiomyopathy), and obesity in the absence of diabetes, hypertension and coronary heart disease (obesity cardiomyopathy) raises the intriguing hypothesis that insulin resistance alone has profound adverse effects on cardiac function (6, 7). Although moderate alcohol consumption is considered beneficial for cardiovascular risk, heavy alcohol consumption is associated with the development of insulin resistance and cardiac dysfunction (alcoholic cardiomyopathy) (8). The causal association between insulin resistance and cardiac dysfunction is seen in the development of insulin resistance by both genetic and environmental factors (9). Transgenic mice with cardiomyocyte-specific deletion of IR (CIRKO) or insulin receptor substrate (CIRSKO) have reduced insulin-stimulated glucose uptake and also have impairment in cardiac function. Moreover glucose transporter 4 (GLUT4) KO mice also develop cardiac dysfunction thereby implicating insulin resistance as a contributing factor in the development of contractile dysfunction in the CRS (10–12).

Heart failure contributing to insulin resistance

The presence of HF may predict the development of insulin resistance and the risk of T2DM in HF is 18% to 22% higher per 10 years than in treated hypertension. 28% of elderly HF patients developed diabetes mellitus over a period of 3 years and in multivariate analysis, congestive heart failure predicted development of type 2 diabetes. HF patients may have both systemic and cardiac insulin resistance. Insulin resistance is also seen after myocardial infarction (13–15).

2. Insulin signaling and its regulation in the heart and vasculature

Insulin signaling in the heart and vasculature

Insulin signaling occurs through two different pathways: phosphatidylinositol 3 kinase (PI3-kinase)/protein kinase B (Akt) signaling pathway eliciting mainly metabolic responses and the mitogen-activated protein kinase (MAPK) signaling pathway eliciting growth factor-like responses (16, 17). In this path-selective signaling (Fig. 1), activation of ligand-activated insulin receptor phosphorylates insulin receptor substrate 1 (IRS-1). Phosphorylation of tyrosine residues on IRS-1 results in the engagement of Src homology 2 (SH2) domain-binding motifs for SH2 domain signaling molecules, including PI3-kinase and growth factor receptor bound protein 2 (GRB2). When SH2 domains of the p85 regulatory subunit of PI3-kinase bind to the tyrosine-phosphorylated motifs on IRS-1, this activates the pre-associated p110 catalytic subunit to generate phosphatidylinositol, 3,4,5, (PI(3,4,5) triphosphate (P3). This molecule then binds to the pleckstrin homology domain in 3-phosphoinositide – dependent protein kinase-1 (PDK-1), resulting in its phosphorylation and the activation of

other downstream kinases including Akt and atypical protein kinase C (PKC) isoforms, which mediate a number of actions including GLUT-4 translocation to the membrane, leading to glucose uptake in myocardial tissue and skeletal muscle, nitric oxide (NO) - mediated coronary vasodilation, metabolic flexibility, and energy homeostasis (16, 17). MAPK signaling pathway involves tyrosine-phosphorylated IRS-1 or Src homology 2 - and collagen homologous region containing protein (Shc) binding to the SH2 domain of GRB2 which results in the activation of the pre-associated GTP exchange factor son-of-sevenless (SOS) and GTP-binding protein rat-sarcoma (RAS), which phosphorylates/activates extracellular signal-regulated kinase (ERK) 1/2. These signaling pathways contribute to growth and remodeling responses and the resultant -myocardial hypertrophy, cardiac fibrosis, impaired myocardial-endothelial signaling and death of myocardial and endothelial cells. The regulation of phosphorylation by protein tyrosine phosphatases or lipid phosphatases provides a negative regulation loop (16–18).

Regulation of insulin signaling

The major converging point in the insulin signaling pathway contributing to insulin resistance is the docking proteinIRS-1. The phosphorylation of serine residues of IRS-1 by several kinases, including protein kinase C (PKC), C-Jun N-terminal kinase (JNK), mammalian target of rapamycin (mTOR) and ribosomal p70 S6 kinase 1 (S6K1), is the major mechanism for regulation of IRS-1 function (16–18). Phosphorylation of serine residues of IRS-1 attenuates IRS-1 tyrosine phosphorylation, its association with the p85 subunit of PI-3 kinase, and triggers its proteasome –dependent degradation. Proteasome degradation can occur by a suppressor of cytokine signaling (SOCS)-3 mediated but phosphorylation-independent mechanism. Inappropriate activation of tyrosine or lipid phosphatases, Akt, FOXO transcription factors, AMP- activated protein kinase (AMPK) signaling inhibiting mTOR/S6 kinase, regulation of IRS-1 expression and IRS-1 signaling components by micro-RNA, and increased expression of tribbles homolog protein 3 (TRIB3) modulating IRS-1 tyrosine phosphorylation and Akt activation also contribute to impaired insulin signaling and insulin resistance (16,18–21)

3. Molecular mechanisms of cardiac insulin resistance

The development of cardiac insulin resistance may occur independently of systemic insulin resistance, but systemic insulin resistance significantly contributes to cardiac insulin resistance secondary to increased circulating levels of nutrients, oxidative stress, and alterations in neurohumoral and cytokine balance (Fig. 1).

Overnutrition

Increased levels of circulating free fatty acids (FFA) and triglycerides caused by peripheral insulin resistance or overnutrition accumulate in the myocardial cells by increased uptake. The consequences are increased accumulation of lipid molecules such as diacylglycerol (DAG), fatty acids and ceramide that contribute to insulin resistance through activation of kinases resulting in increased serine phosphorylation of IRS-1. In addition hyperglycemia induces oxidative stress which in turn activates redox-sensitive kinases and increases phosphorylation of IRS-1. Hyperglycemia-induced oxidation also causes activation of protein kinase C and up-regulation of intra-cardiac angiotensin II (Ang II) signaling. Excess glucose and amino acids also activate mTOR/S6K1. Hyperinsulinemia alone causes insulin resistance and further augments insulin resistance induced by high glucose and palmitic acid (16–22).

Adipokines

The central feature of abdominal obesity may predispose to the development of the other characteristics of the CRS and its complications, which may develop later (16–18). In addition to increased release of FFAs, dysregulated adipocyte function and macrophage activation results in increased secretion of cytokines such as tumor necrosis factor (TNF)-α and interleukin 6 (IL-6), and adipokines such as resistin while decreasing the secretion of adiponectin. TNF-α and IL-6 cause insulin resistance through activation of MAPK, PKC, mTOR/S6K1 and SOCS-3 mediated proteasomal degradation of IRS-1. Resistin induces insulin resistance and inflammation whereas adiponectin improves insulin resistance (3, 12, 16, 17, 23–25).

Activation of renin-angiotensin II-aldosterone (RAAS) and sympathetic nervous systems (SNS)

Activation of RAAS and SNS is not only seen in early stages of heart failure associated with insulin resistance but also in chronic heart failure or myocardial infraction (24- 27). In addition to the synthesis of aldosterone by Ang II, the mechanisms contributing to the link between aldosterone and insulin resistance include triggering of aldosterone release from adrenals by cytokines including TNF α, IL-6 and release of a lipid factor from adipose tissue. Both aldosterone and Ang II can activate the membrane-bound NADPH oxidase enzyme complex in vascular smooth muscle cells, heart and skeletal muscle tissue, which results in the generation of reactive oxygen species (ROS). Positive cross-talk between Ang II and aldosterone for the non- genomic effects results in potentiating effects on ROS production. ROS production leads, in turn, to activation of redox-sensitive kinases such as protein S6 kinase, protein kinase C isoenzymes, and mitogen –activated protein kinases; thereby causing serine phosphorylation of IRS-1 leading to insulin resistance. Recent studies are suggestive of cross-talk between RAAS and mammalian target of rapamycin complex I (mTORC1)/S6K1 activation mediated by the angiotensin type-2 receptor (AT2R), and therefore the possible existence of an adaptive role of mTOR-AT2R signaling loop (28). Although abnormal activation of sympathetic system is another component of insulin resistance and heart failure, it is often related to activation of RAAS (26, 27).

Mitochondrial oxidative stress and ER stress

Mitochondria are the major sources of cellular ROS and this occurs (1) secondary to cytosolic oxidative stress involving NADPH oxidase or xanthine oxidase, (2) dysregulation of mitochondrial electron transport, (3) increased expression of mitochondrial NADPH oxidase 4 (NOX4) and (4) altered protein lysine acetylation (27, 28). Mitochondrial oxidative stress has been shown to compromise insulin signaling through serine phosphorylation of IRS-1 (27, 28). The endoplasmic reticulum (ER) stress contributes to mitochondrial oxidative stress and insulin resistance. Although the mechanism of ER stress-induced insulin resistance is not yet clearly known, activation of stress-activated MAP kinase JNK has been proposed as one of the signaling pathways linking ER stress and insulin resistance (28, 29).

4. Molecular mechanisms of heart failure in the context of insulin resistance

HF is associated with left ventricular (LV) hypertrophy with increases in wall thickness and LV mass index, myocardial cell death, dilated cardiomyopathy, extracellular fibrosis and functional abnormalities affecting diastolic and systolic function. The development of cardiac dysfunction results both from cardiovascular insulin resistance as well as peripheral and hepatic insulin resistance (5, 9, 14, 18, 22). The factors contributing to cardiac injury are

impaired calcium signaling, changes in substrate metabolism, mitochondrial dysfunction and oxidative stress, ER stress, and dysregulated myocardial–endothelial interactions. The consequences are impaired calcium handling and contractility, decreased cardiac energy efficiency, myocardial cell death and cardiac fibrosis (Fig. 2).

Impaired calcium handling

Intracellular calcium plays a critical role in modulating cardiac function.. Calcium-induced calcium release regulates myocardial contractility through activation of ion channels, activation of ryanodine receptor (Ryr) and activity of sodium/calcium exchanger (NCX). Myocardial relaxation mainly occurs though re-sequestration of Ca^{2+} in the sarcoplasmic reticulum by the activity of sarcoplasmic endoplasmic reticulum Ca^{2+} –ATPase 2a (SERCA 2a). Impaired diastolic function is the earliest cardiac dysfunction observed in CRS and T2DM. Abnormalities in the expression or activity of Ryr receptor, SERCA2a and NCX, and impaired uptake of calcium by the sarcoplasmic reticulum has been reported in CRS and diabetic cardiomyopathy. PI3-kinase/Akt signaling has been shown to regulate intracellular calcium thorough potentiation of L-type calcium channel function and up-regulation of SERCA2a expression and activity while cardiac insulin resistance blunts PI3-kinase/Akt signaling thereby contributing to impaired calcium handling (3, 6, 30–35).

Alterations in substrate metabolism and impaired cardiac efficiency

Early metabolic abnormalities in substrate metabolism—Decreased glucose oxidation mainly occurs due to decreased entry of glucose though GLUT-4 and increased fatty acid accumulation through inhibition of glucokinase and pyruvate dehydrogenase (3). Increased flux of fatty acids into myocardial cells caused by systemic/adipose tissue insulin resistance (IR) and IR-associated redistribution of cluster differentiation protein 36 (CD36) to plasma membrane results in increased fatty acid oxidation. Under these conditions, the expression of cardiac peroxisome proliferator activator receptor alpha (PPAR-α) is increased. Moreover, the PPARs are activated by ligands including fatty acids. Once activated, PPAR-α enhances the transcription of proteins controlling fatty acid uptake (lipoprotein lipase, CD36, and fatty acid-binding protein), and oxidation (medium and long-chain acyl CoA dehydrogenase and hydroxyl acyl CoA dehydrogenase). Since glucose is a more efficient substrate, cardiac metabolic switch from glucose metabolism to fatty acid oxidation decreases cardiac efficiency. This results in further metabolic stress to the failing heart. Prevention of altered substrate metabolism in db/db mice by perinatal expression of the GLUT-4 glucose transporter prevented cardiac dysfunction in db/db mice, which further favors the existence of a metabolic switch in insulin resistance associated with T2DM (34–35).

Late metabolic alterations in substrate metabolism and decompensated heart failure—As the disease progresses and myocardium assumes the phenotype of fetal gene program, the expression of genes regulating beta-oxidation of fatty acids is down-regulated, thereby further dampening the metabolic efficiency of the myocardium. Under these conditions, AMPK signaling is impaired, peroxisome proliferator activator receptor gamma co-activator (PGC)-1α is down-regulated and PPARα expression is decreased (33–35).

Myocardial injury and superimposed insulin resistance—Another situation that has been increasingly recognized that makes clinical management challenging is the development of insulin resistance accompanied by activation of RAAS, SNS and oxidative stress after myocardial infarction or long-standing heart failure and ischemic heart disease. Under these conditions, the presence of insulin resistance abolishes the adaptation of myocardial switching to glucose oxidation necessary for the survival of the myocardium; resulting in increased myocardial cell death and poor outcome (9, 14, 15, 33–35).

Mitochondrial dysfunction, oxidative stress and endoplasmic reticular (ER) stress

Both reduced and increased myocardial mitochondrial biogenesis associated with altered mitochondrial dynamics (fission and fusion) have been observed in humans and animals with CRS coinciding with reduced ATP level and dysfunctional mitochondrial electron transport. The distinct findings are related either to the duration of the CRS or associated underlying disorders. Mitochondrial oxidative stress and ER stress also contribute to myocardial apoptosis (27, 28, 36, 37). The role of myocardial autophagy in cardiac dysfunction is not clear at present (38, 39).

Impaired cardiomyocyte –endothelial nitric oxide (NO) signaling

Endothelial dysfunction is an important link between insulin resistance and heart failure. Insulin resistance in endothelial cells results in impaired generation of NO or uncoupling of eNOS. This results in hypoxia and inhibition of angiogenesis leading to myocardial cell death. Endothelial insulin resistance also results in increased release of endothelin-1(ET-1) that causes cardiac hypertrophy and fibrosis (3, 6, 7, 40).

5. Targeting insulin resistance in heart failure

Life style interventions

The clinical significance of insulin resistance in patients with chronic heart failure often represents potentially reversible metabolic derangements in these individuals, especially at early stages of cardiac dysfunction. Life-style interventions such as reductions in caloric intake and alcohol intake and increased exercise appear to improve systemic and tissue insulin resistance. These measures target several insulin signaling cascades implicated in insulin resistance including suppression of TRIB3 expression thereby overcoming TRIB3-mediated insulin resistance (3, 5, 21, 41)

Insulin resistance

Apart from improving hepatic and peripheral insulin resistance, treatment of impaired glucose tolerance by metformin has been shown to actually reverse ventricular dysfunction in animal models. In insulin-resistant cardiomyocytes, metformin promotes translocation of glucose transporter 1 (GLUT-1) and GLUT-4 to the sarcolemma. It promotes glucose uptake in an AMPK-dependent manner and prevents high-glucose induced abnormalities in relaxation by reducing intracellular Ca transients. Metformin increases fatty acid oxidation (FAO) but effects on glucose metabolism and AMPK activation appear to maintain metabolic flexibility (9, 13, 42–43).

RAAS and SNS activation

Given the importance of insulin resistance as an independent risk factor for mortality in HF, the use of both angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) has been reported to significantly reduce the incidence of new onset diabetes in large trials of patients with HF. ACEIs and ARBs are not completely effective in improving insulin resistance or hypertension, and aldosterone escape often impedes their efficacy (26, 44, 45). The direct renin inhibitor aliskiren is a potent and selective inhibitor of renin (26), the enzyme considered to be the rate-limiting step in the RAAS (26, 44). Renin inhibition is associated with attenuation of Ang II levels and reduction in blood pressure (46, 47). MR antagonists (MRAs) also improve left ventricular function and clinical outcomes when they are taken in combination with ACEIs, ARBs and beta-blockers. However, some clinical studies linked MR antagonists to abnormal glucose homeostasis thereby suggestive of the complexity of MR receptor signaling (26, 44, 45). Non-selective beta blockers that do not worsen insulin sensitivity such as nebivolol and carvedilol appear to exert beneficial

effects in HF (48). Nebivolol also inhibits Ang II-induced activation of NADPH oxidase and ROS, thereby providing a rationale for having beneficial effects on insulin sensitivity (49).

Substrate metabolism

Drugs modulating glucagon-like peptide 1 (GLP-1) signaling comprising GLP-1 mimetics or dipeptidyl peptidase (DPP)-4 inhibitors have been reported to be useful in controlling hyperglycemia by stimulating insulin secretion from the pancreas as well as enhancing myocardial glucose uptake via the translocation of GLUT-1 and GLUT-4 to the sarcolemma (9, 50). Chronic infusion of GLP-1 also improves left ventricular dysfunction, exercise tolerance and quality of life, in addition to improving cardiac insulin sensitivity. DPP-4 inhibitor sitagliptin improved left ventricular performance in response to stress and reduced post-ischemic stunning in patients with CHD and preserved left ventricular ejection fraction (LVEF). Linagliptin has also been shown to have cardiovascular (CV) benefits in patients with T2DM (9, 50, 51). Trimetazidine affects myocardial substrate use by inhibiting oxidative phosphorylation and by shifting the metabolism from free fatty acids to glucose oxidation though inhibition of long chain 3-ketoacyl CoA, the last enzyme in beta-oxidation. In small clinical studies, the drug showed small but statically significant improvement in decreasing fatty acid oxidation, improvement in ventricular function and decrease in insulin resistance in heart failure patients (13, 33, 52, 53).

Mitochondrial oxidative stress and ER stress

New compounds targeting mitochondrial oxidative stress and ER stress are being developed. In this regard, targeting mitochondrial production by synthetic Szezo-Schiller peptide S-31 prevented cardiac hypertrophy and fibrosis and improved left ventricular diastolic function in a model of Ang II and hypertension induced cardiomyopathy (54). FDA-approved drugs that have been shown to decrease ER stress also improve cardiac function in animal studies suggesting their potential use in suppression of insulin resistance in humans (55).

Summary

Insulin resistance is closely linked to HF. It is associated with major factors contributing to HF. In clinical situations, both conditions most often coexist, but the presence of insulin resistance contributes adversely to the progression of heart failure. The cardiovascular insulin resistance is also modulated by systemic insulin resistance. The signaling pathways contributing to insulin resistance converge mainly at IRS-1. In addition to glucotoxicity and lipotoxicity, dysregulation of neurohumoral and cytokine imbalance and oxidative stress are mainly responsible for cardiac insulin resistance and impaired cardiac function. Although targeting RAAS-SNS system has markedly improved clinical outcome, drugs targeting metabolic pathways, GLP-1 signaling, mitochondrial dysfunction and ER stress may show additional benefits based on underlying metabolic abnormality. Therefore, identifying mechanism-based new therapeutic targets to improve insulin resistance holds promise for better management of insulin resistance and heart failure.

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Key Points

1. Heart failure is increasing in parallel with aging and diabetes in westernized industrialized countries.
2. Insulin resistance is associated with diastolic dysfunction in the cardiorenal metabolic syndrome and type 2 diabetes.
3. Insulin metabolic signaling is important cardiac metabolic flexability and post ischemic reconditioning, and impairment in signaling compromises both processes.

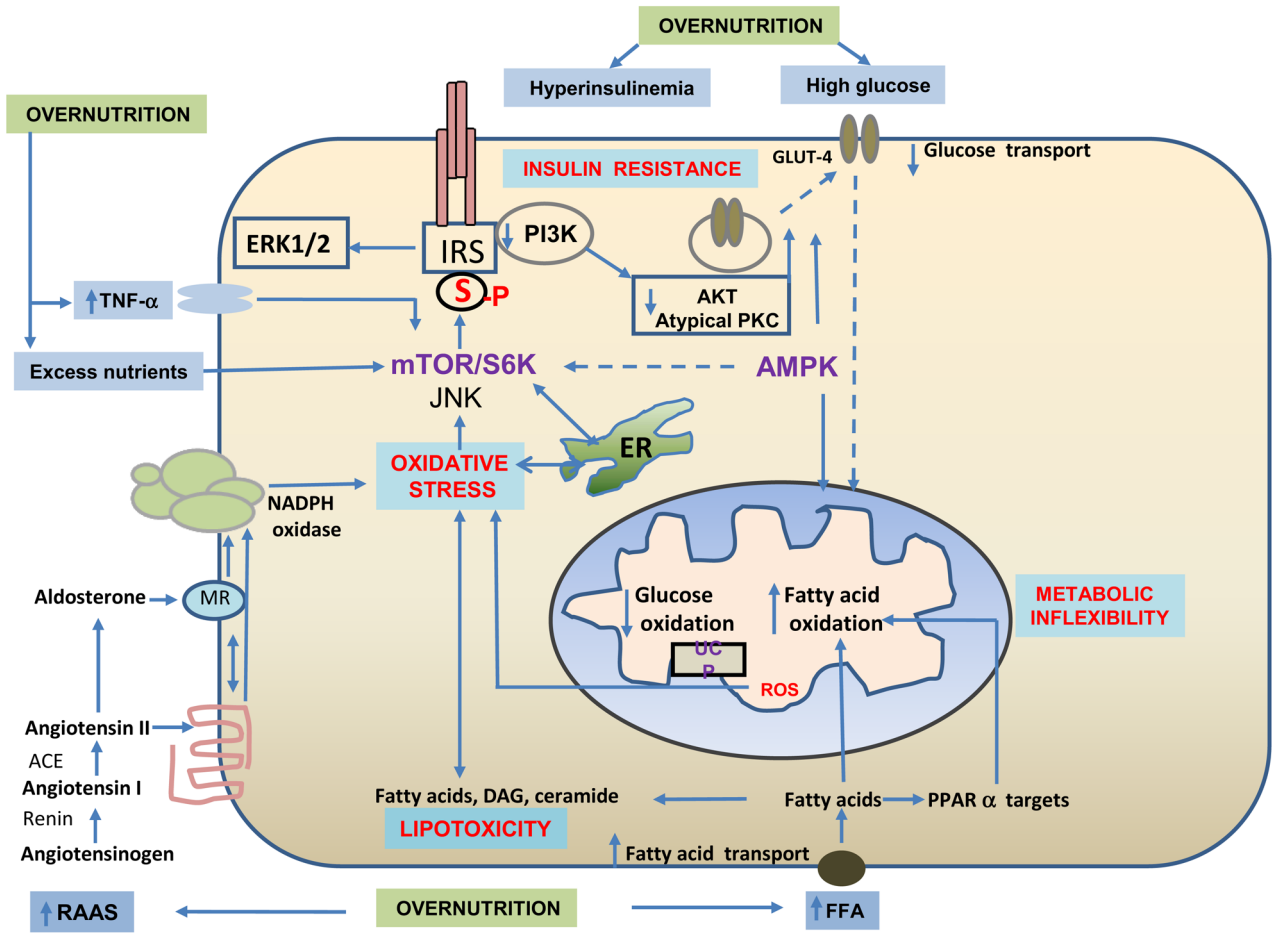

Figure 1. Overnutrition and impaired insulin metabolic signaling leading to cardiomyopathy

The major signaling pathway causing insulin resistance is the convergence of multiple stimuli leading to the activation of S6 kinase. Overnutrition results in increased levels of circulating fatty acids, amino acids and excess glucose that cause activation of mTOR/S6 kinase. Activation of RAAS results in oxidative stress due to activation of NADPH oxidase by Ang II and aldosterone. Oxidative stress induced activation of kinases including JNK and S6 kinase, results in serine phosphorylation of IRS-1 and inhibition of insulin metabolic signaling. Cytokine-induced insulin resistance also involves activation of S6 kinase. Oxidative stress and insulin resistance is also accompanied by impaired AMPK signaling which is a negative regulator of mTOR/S6 kinase. Persistent hyperactivation of mTOR/S6 kinase also leads to ER stress, oxidative stress and activation of JNK. Excess accumulation and enhanced oxidation of fatty acids concomitant with increased accumulation of lipid intermediates result in lipotoxicity and metabolic inflexibility. These four overnutrition-induced cellular events are further amplified by their feed-forward interactions.

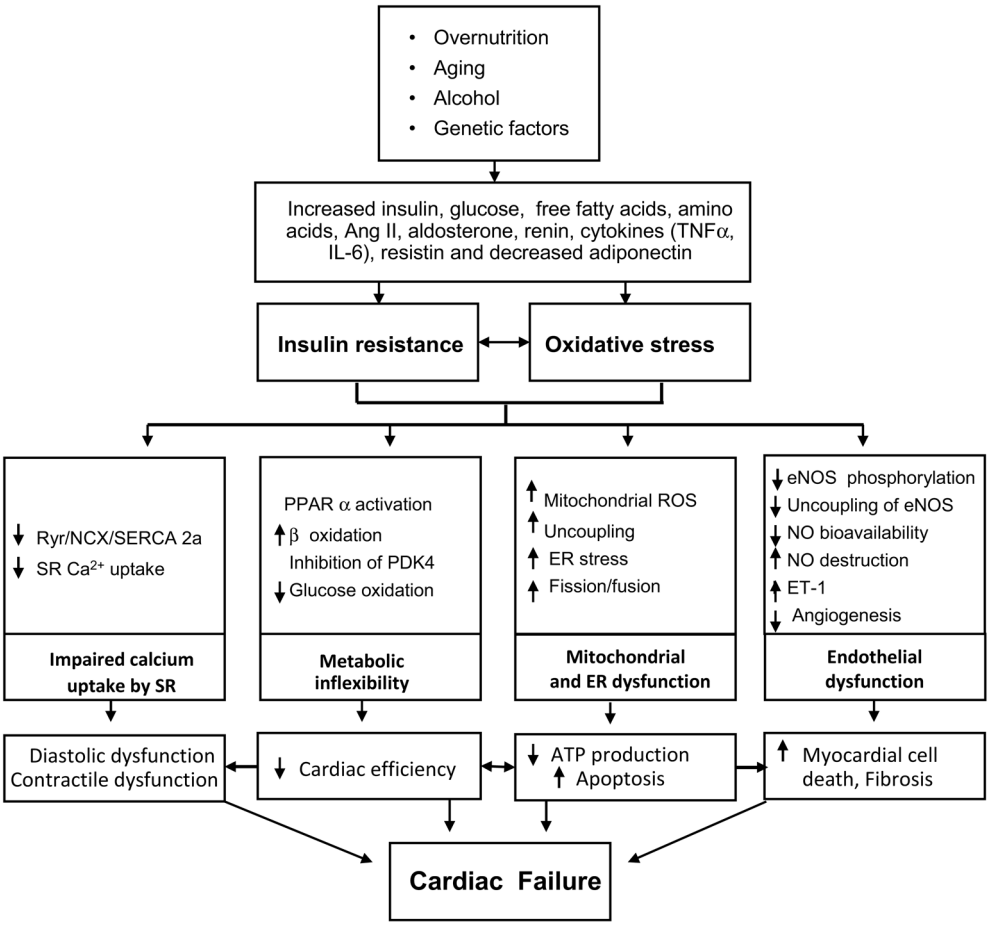

Figure 2. Molecular mechanisms of cardiac insulin resistance and consequences of impaired insulin signaling and overnutrition leading to cardiac dysfunction

The major consequences of insulin resistance and oxidative stress causing cardiac dysfunction are impaired calcium handling, metabolic inflexibility, mitochondrial and ER dysfunction, and endothelial dysfunction. These events contribute to cardiac inefficiency, myocardial cell death and cardiac fibrosis and diastolic dysfunction. The progression of cardiac injury leads to contractile dysfunction and cardiac failure.