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Obesity and Cardiac Function – The Role of Caloric Excess and its Reversal

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Abstract

Obesity is recognized as an independent and increasingly prevalent risk factor for cardiovascular morbidity and mortality. This stems in part from the contribution of obesity towards insulin resistance and diabetes, which associate with premature atherosclerosis, enhanced thrombogenicity and activation of systemic inflammatory programs with resultant cardiovascular dysfunction. This review will focus on the more direct mechanisms underpinning obesity-associated cardiac pathophysiology including the metabolic consequences of lipid accumulation in the myocardium and the consequences of direct systemic effects of lipid toxicity. Furthermore, there is growing recognition that metabolic intermediates, which may be perturbed with caloric excess, may play an important role in intracellular signal transduction and on the post-translational control of metabolic functioning within the heart. As strategies to reverse obesity appear to have ameliorative cardiac effects, surgical and therapeutic approaches to facilitate weight reduction this will also be discussed.

Introduction

The prevalence of both obesity and heart failure in the United States continue to rise with the latest figures showing that 69% of adults are either overweight or obese [1,2]. The increased risk of heart failure with obesity is well established [3,4], and much research has been undertaken to understand the pathophysiologic link between these conditions. At the same time obesity is a component of the insulin resistance syndrome (IRS), a syndrome characterized by increased insulin levels, hypertension, obesity and dyslipidemia [5]. This syndrome is also associated with increased cardiovascular risk, coronary artery disease, cardiac hypertrophy and heart failure [6–9] and IRS is predicted to reach worldwide epidemic rates with an expected prevalence of 300 million people by 2025 [10]. Yet, obesity itself may be a crucial player in the progression to cardiac dysfunction, and as such remains a potential target for intervention.

Characteristics of cardiac function in obesity with the development of heart failure

Heart failure is directly associated with obesity, as increases in incident heart failure are seen with increased body mass index (BMI) [3], and with the duration of obesity [11]. It may be

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expected, that as the multiple comorbidities prevalent in obesity are risk factors for atherosclerosis, that obesity is predominantly associated with ischemic cardiomyopathy [12]. However, many obese subjects with heart failure have non-ischemic dilated cardiomyopathy [13]. Additionally, isolated diastolic dysfunction is common in obese subjects, and systolic dysfunction is typically a late finding, or not seen at all [14,15]. While the pathophysiology continues to be debated, growing evidence supports both direct lipotoxic effect on cardiomyocytes and effects from systemic sequelae of obesity.

The clinical evolution of heart failure in obesity has long been recognized as representing an increase in left ventricular mass and volume [16]. An elevated circulating blood volume in obese subjects leads to larger stroke volumes and subsequent left ventricular dilatation. To compensate for the higher wall stress, eccentric hypertrophy develops. This hypertrophy may cause impaired diastolic relaxation and diastolic heart failure, or combined systolic and diastolic failure if the hypertrophy cannot match the output demands [4]. Evidence that fatty infiltration of myocardium is the cause of dysfunction is conflicting and cardiac dysfunction in obese subjects has also been linked to additional cellular and molecular alterations. This is illustrated where the left ventricular mass has been correlated with the degree of insulin resistance in non-diabetic, normotensive obese subjects [17] and where the elevated levels of cardiac and systemic markers of oxidative stress in obese subjects correlate closely with cardiovascular risk [18–20].

Direct cardiac lipotoxicity

In animal models where genetic manipulations have been employed to modulate lipid sensing, uptake and/or metabolism, and in response to prolonged excessive dietary fat, studies have begun to delineate the adverse effects of excess cardiac lipid accumulation. These studies have recently been reviewed [21,22] and find that the direct adverse cardiac effects of excessive lipid accumulation include: (i) a mismatch in lipid uptake and oxidation with the accumulation of toxic lipid intermediates (ceramide and diacylglycerol); (ii) toxic lipid intermediate induced disruption of insulin signaling, insulin resistance and the promotion of apoptosis [23]; (iii) excessive oxidative metabolism with increased redox stress and mitochondrial dysfunction [24]; (iv) lipid intermediate induced endoplasmic reticulum stress [25] and (v) the direct disruption of neutral lipid storage in the heart [26].

In humans, our understanding of the role of direct cardiac lipotoxicity and mechanisms of obesity associated cardiomyopathy are less precise. Nevertheless, subjects with obesity and heart failure have been found to have excess cardiac triglyceride content measured at the time of cardiac transplantation [27] and a modest correlation between plasma free fatty acid levels and reduced diastolic function is evident [28]. Additionally, patients undergoing insertion of a left-ventricular assist device for severe heart failure, show evidence of increased levels of toxic lipid intermediates, although whether the extent of toxic lipid intermediate levels correlated with BMI appear not to have been determined to date [29]. Concurrent positron emission tomography and echocardiographic studies have also shown that prolonged obesity in women modulates myocardial metabolism and diminishes myocardial mechanical efficiency [30].

Systemic effects of obesity on the heart

Nutrient excess is firmly linked to the derangement of cellular and molecular mediators of inflammation and immunity and the chronic nature of obesity produces a persistent low-grade activation of the innate immune system (reviewed [31]). The mechanisms underpinning cardiac inflammation have not been well established, although macrophage infiltration is evident in pathologic failing myocardial samples [29] and the systemic inflammatory markers correlate with heart failure risk in obese and diabetic subjects [32]. In

an animal model of cardiac lipotoxicity, macrophage infiltration and activation of inflammation in the heart preceded cardiac dysfunction and the depletion of macrophages reduced cardiac inflammation and improved contractile function [33]. Taken together, these studies support a pivotal interaction between cardiac lipotoxicity, inflammation and contractile function.

Angiotensin II is a potent cardiomyocyte growth factor and activation of the renin-angiotensin-aldosterone system (RAAS) as a component of the neurohumoral system to synthesize angiotensin II during heart failure contributes towards cardiomyocyte hypertrophy, cardiac fibroblast proliferation and fibrosis, myocardial apoptosis and cardiac dysfunction. Obesity itself, and/or in concert with increased insulin levels, upregulates the RAAS system with Angiotensin II production in both adipose tissue and in the liver [34,35], suggesting that this system may also be operational in the pathophysiology of obesity associated heart failure [36].

In addition to the extensively explored RAAS system numerous organs, including adipose tissue and skeletal muscle secrete circulatory factors, termed adipokines and myokines respectively, which function to sustain metabolic homeostatic programs. Obesity disrupts the balance and levels of these secreted factors and results in the augmentation of inflammation and insulin resistance (reviewed [37,38]). Delineation of the effects of these secreted mediators in the heart have not been well characterized, however, the disruption in adipose-associated leptin signaling does result in cardiac lipotoxicity and cardiac contractile dysfunction and the restoration of leptin can reverse these cardiac perturbations [39,40].

Studies on the effect of calorie restriction and weight loss on cardiac function

The distinct role of overnutrition in the development of cardiac diastolic and systolic dysfunction is challenging to differentiate from its effects on e.g. insulin resistance and hypertension. Nevertheless, the significant contribution of obesity to these cardiac perturbations would be further supported if the reversal of overnutrition rectifies cardiac pathology. This concept has historically been difficult to explore as the myriad of therapeutic approaches to ameliorate obesity had been disappointing. Nevertheless, recent surgical approaches (bariatric surgery) to reverse obesity have been remarkably successful [41–43] and as the number of patients subjecting themselves to this approach have increased, the capacity to investigate the cardiac effects of significant reduction in nutrient intake and concomitant weight loss are beginning to be explored.

In the mid 2000's, retrospective analysis of small bariatric surgical studies suggested that this therapy was both safe and could play a role in improving cardiac functional capacity in patients that were concurrently obese and had severe systolic heart failure [44,45]. An additional case study in two subjects mirrored these findings showing that bariatric surgery could sustain an improvement in cardiac function over a 2 year period [46]. Furthermore, a 10 year follow up study in obese subjects who underwent bariatric surgery show that the reduction in obesity is linked to a reduction in left ventricular cavity size, thickness and mass that appears to dissociate from a change in blood pressure [47]. Several additional studies have also shown improved left ventricular volume and diastolic function with weight loss following gastric bypass, while changes in left ventricular systolic function has been less consistent [48,49]. These cardiac parameters are often positively correlated with the degree of weight loss. Some have also shown benefit following surgical weight loss in exercise capacity as measured by oxygen consumption and performance duration [50]. Improvement in diastolic function was seen after six months of calorie restriction alone in non-obese individuals, perhaps an effect that might be mirrored in the obese [51]. These

effects may be more due to improved ventricular loading conditions than to changes in systemic or intramyocardial lipid state. To determine if weight loss and calorie restriction in humans with heart failure reverses the concurrent obesity and heart failure associated systemic perturbations, for example, in inflammation, oxidative stress and neurohumoral activation needs further clarification. Although, short-term caloric restriction in obese subjects has been shown to result in decreased circulating white blood cell ROS production with evidence of decreased oxidative damage [52] and a similar intervention has shown decreased levels of the inflammatory mediated tumor necrosis factor- α [53], although these data have not been universally found [54].

The role of metabolic intermediates, as mediators of caloric excess pathology

As described earlier, caloric excess predisposes to the development of insulin resistance, and the disruption in glucose handling itself may modify cardiac substrate utilization with increased preference for fatty acids and ketone bodies [55]. Prior to discussing how energy transduction pathway metabolic intermediates may, via posttranslational modifications, modulate metabolic function, I will briefly review the changes in energy substrate use as delineated in animal models and from heart failure patients with obesity and/or insulin resistance.

Leptin deficient ob/ob mice, which develop profound obesity with insulin resistance/diabetes, have increased cardiac neutral lipid accumulation in parallel with the onset of diastolic dysfunction [56]. At the cardiac metabolic level these mice have reduced mitochondrial respiratory capacity, diminished pyruvate dehydrogenase activity and a restricted glucose-dependent oxidative capacity response to increased workload [57]. In response to the direct addition of fat as the fuel substrate, oxygen consumption is enhanced, but at the expense of cardiac efficiency with evidence supporting increased lipid-mediated mitochondrial uncoupling [57]. This phenotype has also been found in db/db (leptin receptor loss-of function mutation) mice, where the direct measurement of mitochondrial proton leak showed evidence of fatty acid induced mitochondrial uncoupling with perturbed leptin signaling [58]. Interestingly, this excess myocardial oxygen consumption was found to be exacerbated with higher levels of fat catabolized substrate for cardiac metabolism. This detrimental effect of the over-reliance on fat metabolism with progressive insulin resistance is also supported by the demonstration that overexpression of the glucose transporter GLUT4 which drives glucose oxidation rescues cardiac contractile function in db/db mice [59,60]. Additional animal models that support caloric overload mediated disruption of cardiac metabolic function include the Otsuka Long-Evans Tokushima Fatty rats which show disrupted left ventricular diastolic filling [61] and evidence that cardiac contractile dysfunction is accelerated and mortality increased in hypertensive rats when they are subject to a high carbohydrate-diet [62]. Moreover, high-fat feeding of Wistar rats also evokes cardiac contractile dysfunction, which appears to result from enhanced fatty acid uptake through CD36 and intramyocellular triacylglycerol accumulation [63]. This observation is further supported by a study showing that obese Zucker rats, fed on a high fat 'western diet', accumulate triglyceride in their hearts within a week of this dietary intervention in parallel with reduced cardiac contractile functioning. Interestingly in this model, longer term exposure to this diet promotes fatty acid oxidation which appeared to prevention of further deterioration in cardiac function or in progressive cardiac triglyceride accumulation [64]. This study also points out a role for genetic susceptibility in developing this dietary response, as Zucker lean control rats show a greater resistance to cardiac triglyceride accumulation and no adverse effects on the maintenance of cardiac power on this same high fat western diet [64].

Human subjects with diabetes or glucose intolerance similarly have increased cardiac steatosis as evident by ^1H -MRS [65]. Furthermore, the measurement of high-energy phosphates in diabetic and non-diabetic subjects without clinical coronary artery disease and normal echocardiographic studies indirectly suggest that diabetic subjects can develop diminished cardiac energetics prior to evidence of measureable cardiac dysfunction [66].

The concept that nutrient excess itself can be a primary modulator of metabolism has advanced significantly in the last decade or so, with the recognition that nutrient overload can modulate metabolic encoding gene expression and metabolic pathway protein activities via nutrient intermediate mediated posttranslational regulation (reviewed [67,68]). The most well characterized program is where the acetyl group derived from the metabolic intermediate acetyl-CoA modifies histones and non-histone proteins via acetylation of protein lysine residues. Excess glucose has been shown to increase acetyl-CoA levels with the subsequent acetylation of histones resulting in the induction of genes encoding glucose transport [69]. Additionally, the levels of glucose, fatty acids and amino acids have been shown to modulate the level of acetylation of mitochondrial metabolic enzymes which directly alter metabolic enzyme activity [70]. The nutrient-sensing regulatory proteins underpinning histone and non-histone protein acetylation are being actively explored and include the sirtuin family of deacetylases and multiple acetyl-transferase enzymes (reviewed [71,72]). The levels of these regulatory proteins are modified by caloric excess [73–75], and interestingly from the cardiovascular system perspective also regulated to enhance mitochondrial functioning in skeletal muscle in response to exercise [76,77]. Although not extensively explored in the context of caloric excess in the heart, Sirt1 regulates adaptation to sustain cardiac function under nutrient-deplete conditions [78] and the Sirt3 knockout mouse is more susceptible to pressure overload induced contractile dysfunction [79]. Also, pressure overload itself upregulates Sirt1, as a potential adaptive program to prevent adverse remodeling [80,81]. As this regulatory program is interrogated further, it may uncover pharmacological targets to modify metabolism and nutrient-overload mediated cardiac dysfunction.

More recently recognized modification via lysine-residue malonylation or succinylation may function to modulate metabolic pathways in a similar fashion [82,83]. However, these programs are only beginning to be explored and no data is currently available with respect to how these modifiers may regulate nutrient-level dependent cardiac function.

Conclusions

Caloric excess and obesity are increasingly prevalent and consequences of these nutrient-excess associated conditions confer direct (lipotoxicity and altered metabolism) and systemic (inflammation, cytokine and neurohormonal signaling) stressors on the heart as depicted in Figure 1. Surgical weight reduction strategies show promise in reversing this pathology and our understanding of how excess metabolic intermediates may disrupt cardiac metabolism may uncover novel targets to exploit in modulating obesity associated adverse cardiac metabolism and its role in adverse cardiac remodeling.

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Figure 1.
Schematic of direct cardiac and systemic effects of caloric excess on the heart.
Abbreviations: ER – endoplasmic reticulum, RAS – renin angiotensin system.