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Too Much or Not Enough of a Good Thing? Cardiac Glucolipotoxicity versus Lipoprotection

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POINT: Cardiac Glucolipotoxicity (Dr. Taegtmeyer)

We live in an age of insatiable appetite for calorie dense food [1]. For many people the excess consumption of fuel inevitably results in a vicious cycle of metabolic dysregulation and multiple deleterious changes of cellular functions in vital organs. Angelina Jolie got it right with her tattoo “*Quod me nutrit me destruit*”; (Latin for: What nourishes me destroys me) [2]: Excess fuel supply destroys the heart [3]. No wonder, also, that in the United States the geographic spread of obesity and type 2 diabetes is almost exactly mirrored by a decline in life expectancy, suggesting a connection between overnutrition on the one hand (“*Quod me nutrit*”), and premature death and disability from cardiovascular disease on the other hand (“*me destruit*”).

Chronic overconsumption of sugar and fat elevates plasma levels of insulin, leptin, free fatty acids and triglycerides, even in the absences of diabetes, and exposes the heart to toxic anabolic stimuli and excessive oxidative substrates. Although we have proposed that cardiac insulin resistance may be an early adaptive response to diet-induced obesity, there is increasing evidence that the blunted ability of the heart to oxidize fat and carbohydrates results in the accumulation of non-oxidative metabolic intermediates and reactive oxygen-species[4]. The evidence presents itself most strikingly in genetic animal models of fuel toxicity[3]. The same footprints of dysregulated fuel metabolism can be observed in patients with obesity and/or type 2 diabetes and heart failure [5]. Several years ago Roger Unger and his group called the deleterious consequences of lipid overload in the heart “cardiac lipotoxicity”[6]. The state of knowledge concerning cardiac lipotoxicity has recently been reviewed[7]. At about the same time that lipotoxicity entered our thinking evidence grew for protein glycosylation via the hexosamine biosynthetic pathway[8,9], and for reactive oxygen species generation via NADPH oxidase and the pentose phosphate pathway[10]. We

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Disclosures

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therefore extended the concept of lipotoxicity to include the adverse effects of excessive glucose and subsequent generation of toxic sugar metabolites, and proposed the term “cardiac glucolipotoxicity”[11].

What is the basis for the toxic fuel imbalance in the heart? The normal postnatal heart is rich in mitochondria and prefers fat for oxidative ATP production[12]. However, like the body as a whole, the heart is an omnivore and keeps substrate metabolism in a delicate balance by which fatty acids suppress the oxidation of glucose, while glucose suppresses the oxidation of fatty acids[13]. In other words: the rate of ATP turnover is almost precisely matched by the rate of substrate uptake, CO₂ production and O₂ consumption. Depending on the prevailing metabolic milieu the heart adapts its metabolic machinery to convert the chemical energy contained in a multitude of oxidizable substrates to the energy needs of contraction.

In the failing heart the rate of ATP turnover declines while the rate of substrate uptake may not decrease proportionally. Here, a vicious cycle is created by the imbalance between substrate availability to the cell and substrate oxidation in the cell with the resultant accumulation of non-oxidative intermediates of glucose and fatty acid metabolism. When fatty acid uptake exceeds the capacity to oxidize fat the ensuing lipid overload results in elevated triglycerides stores and accumulation of lipid metabolites, particularly ceramides, greater oxidative stress and endoplasmic reticulum stress[3], and lipid mediated alterations in membrane function. This lipotoxicity is characterized by increased evidence for programmed cell death, contractile dysfunction, and progression to frank heart failure. This deleterious sequence of events may be rescued by lipid lower interventions or weight loss[6]. If unchecked, the consequences of excess fuel supply to the heart are a veritable metabolic disaster zone reflected in the build-up of reactive oxygen species and of substrate metabolites, first and foremost those of glucose and of long-chain fatty acid metabolism[14]. Inevitably these metabolites become signals or ligands for signal transduction pathways in the cell or for the activation or inactivation of transcription factors that regulate whole gene programs. The issue is much bigger though: How do we know whether metabolic dysregulation is the cause or consequence of contractile dysfunction? Most genetic models of altered myocardial metabolism seem to support the concept of the former. In short, fat is bad for the heart and dysregulated myocardial fat metabolism has major implications on contractile function as numerous animal models have shown.

Besides accumulation of lipid intermediates [15]there is also protein glycosylation, specifically the glycosylation of transcription factors and of proteins of Ca²⁺ metabolism, most likely due to O-glycosylation of transcription factors. Here we have implied a “spillover” effect from the glycolytic pathway into the hexosamine biosynthetic pathway[16]. The underlying assumption is that, according to Randle’s hypothesis[13], glucose oxidation is inhibited by the elevated fatty acids to greater extent than glucose uptake. This directs glucose 6-phosphate into non-glycolytic pathways.

In an ideal world of biomedical research translational medicine takes observations from the bedside to the bench and then returns to the bedside with new insights gained at the bench. Why are we so rarely successful with this approach? The answer is difficult. With respect to diet and fuel overabundance it is recognized that, like animals, obese people have a shorter life expectancy and a higher incidence of heart failure than normal weight individuals[17]. Losing weight, in turn, extends life. Indeed, we observed in severely obese patients a complete reversal of impaired cardiac function, disappearance of insulin resistance, and disappearance of muscle triglycerides early after weight-loss surgery[18]. However our society as a whole still has not understood that losing weight extends life span.

Another point merits mentioning. In my general cardiology practice I have noted over the years that a number of patients I see are clinically obese, normotensive, euglycemic, and free of any detectable heart disease. These are metabolically normal obese individuals. How can this be possible? In order to test the hypothesis that different obesogenic diets affect the heart differently we fed rats two types of diets: a high fat diet (60% of calories from fat) and a Western diet (45% of calories from fat). Low fat diet served as control. Rats on high fat diet and Western diet gained the same amount of weight, but only hearts from animals fed Western diet, i.e., a diet rich in both fat and carbohydrate, showed evidence of impaired contractile function[19]. We are currently investigating the biochemical reasons for these remarkable differences. We have argued that fatty acids induce the expression of futile cycles in the heart that “burn off” excess fuel[19]. Dr. Stanley may come up with another explanation, but at least in one point we concur: Not all calories are created equal!

COUNTERPOINT: “Cardiac Lipoprotection” (Dr. Stanley)

I fully agree with Dr. Taegtmeyer that chronic exposure of the heart to an overabundance of circulating fuels (glucose, free fatty acids, triglycerides) and pro-growth hormones (insulin, leptin) accelerate the pathological processes in the myocardium that lead to cardiac hypertrophy and heart failure, as illustrated in the Figure. On the other hand, I take issue with the concept that increased cardiac fatty acid uptake and lipid accumulation and impaired mitochondrial capacity for lipid oxidation contributes to the development and progression of cardiac dysfunction and heart failure in humans. As outlined below, there is not a shred of evidence that lipid accumulation in the myocardium predicts poor cardiovascular outcomes. In the contrary, there is growing evidence for “cardiac lipoprotection” in response to a diet that is relatively high fat (>35% fat) but rich in ω -3 PUFA, low in saturated fat, sugar, and refined carbohydrates[20–22]

At present there is also no convincing evidence that the accumulation of lipids and lipid byproducts in the myocardium in humans or nontransgenic animals causes cardiac dysfunction or heart failure. Granted, studies comparing normal controls to genetic rodent models like the Zucker fatty rat or mice with overexpression or deletion of key proteins involved in fatty acid import or oxidation, suggest that a high cardiac fatty acid uptake and/or a low capacity for mitochondrial fatty acid oxidation results in cardiac lipid accumulation and dysfunction[23]. However, the defects that trigger this pathology have little relevance to the vast majority of human obesity or heart failure. Insight into clinical pathology can be gained by superimposing dietary manipulations (e.g. “western diets” high in both fat and sugar) in these genetic models to evaluate the effects of unbalanced nutrition or obesity on the development of cardiac pathological processes and heart failure. Numerous studies summarized in two recent reviews [23,24], find that feeding a western diet that generates obesity in these animals causes lipotoxic cardiomyopathy characterized by elevated cardiac triglyceride and ceramide content, apoptosis, fibrosis, hypertrophy, ventricular dilation and systolic dysfunction[23,24]. Unfortunately, most of the cited studies do not separate the effects of obesity from fat intake, and employ diets that are high in both sugar and saturated fat (see Figure, left side), not low in sugar, high in polyunsaturated fat, and with a neutral energy balance (Figure, right side).

The increase in clinical obesity and metabolic syndrome over the last 50 years are primarily the consequence of poor diet and lifestyle choices, and not the consequence of genetic predetermination. Thus one should use caution in extending results from rodents with cardiac lipid accumulation and subsequent pathology due to an abnormal genetic make-up to humans with unhealthy behavior (i.e. physical inactivity, gluttony, and consumption of highly processed carbohydrate). At present, there is no evidence to support the concept that people who eat a high fat diet that is low in saturated and trans fat are at greater risk for

coronary artery disease or heart failure[22], or that “lipotoxic cardiomyopathy” is even a clinical entity. Granted, there is growing evidence that obese and/or type 2 diabetic patients have greater cardiac triglyceride content than lean individuals [5,24], however a causal link has not been established between cardiac lipid stores and myocardial pathology in humans. It is important to keep in mind that these patients have plenty of hormonal, metabolic, dietary and behavioral characteristics that can result in cardiac abnormalities. At this point we need additional information from clinical studies to close the gap between animal models and patients, and determine if accelerated cardiac fatty acid uptake or triglyceride stores predict poor prognosis. One should keep an open mind on this issue. There is a well established “obesity paradox” in heart failure and acute myocardial infarction, where obese patients have significantly better survival than normal weight patients[25]. This suggests the counterintuitive possibility that elevated cardiac triglyceride content might be a marker of **better** prognosis, not worse outcome. There is great interest in this topic, as myocardial triglyceride content can be measured noninvasively in humans using proton NMR. It would be extremely useful if myocardial triglyceride content could predict prognosis or response to drug or lifestyle interventions. Elegant studies with this method have shown that myocardial triglyceride content is increased in patients with type II diabetes or obesity[24], and have confirmed animal studies showing that triglyceride content changes with normal physiological stresses like starvation and food restriction. Longitudinal studies with therapeutic interventions are needed using sensitive methods to determine if changes in fatty acid metabolism and triglyceride content predict changes in cardiac function and clinical outcomes.

I propose that the pathological conditions that result in cardiac glucolipotoxicity can be reversed or prevented by consuming a diet that is high in fat and low in carbohydrates (see Figure). There is growing evidence that high intake of refined carbohydrate is responsible for a positive energy balance, causing development of obesity, hypertension, dyslipidemia, and greater risk for coronary disease and heart failure[22]. Obesity triggers insulin resistance, hyperleptinemia, hypertension, increased plasma free fatty acids and triglycerides, and inflammation (see Figure). All this, combined with a diet rich in saturated fat and a high glycemic load, spells disaster for the heart, resulting in accumulation of toxic glucose and lipid intermediates in the myocardium, as noted by Dr. Taegtmeyer. This can cause cardiomyocyte apoptosis, fibrosis, cardiomyocyte hypertrophy, mitochondrial dysfunction, and impaired systolic and diastolic function, eventually progressing to heart failure. I propose that these conditions can be prevented or reversed by changing the diet to include only low glycemic carbohydrates, a high intake of ω -3 PUFA and unsaturated fat, low intake of saturated fats and elimination of trans fats, and a neutral energy balance through eating less and exercising more. Thus the increased energy intake from fat replaces the consumption of harmful “empty carbohydrates” from refined grains and processed sugars.

High intake of ω -3 PUFA, particularly docosahexaenoic acid and eicosahexanoic acid, prevents coronary artery disease and heart failure, which appears to be mediated through multiple effects including lowering plasma triglycerides, suppressing inflammation, anti-aggregatory effects, reducing fatal arrhythmias, and remodeling membrane phospholipids and improving mitochondrial function[21]. High fat diets in the absence of obesity prevent the development of left ventricular dysfunction and the decline in mitochondrial oxidative enzymes in hypertensive rats, which is associated with fatty acid ligand activation of PPAR α [20]. Moreover, high sugar diets accelerated development of LV dysfunction and death in hypertensive rats compared to a low sugar/high starch or a high fat diet[20]. Taken together, there is now a shift in the dietary lipid – heart paradigm, with emphasis on high intake of polyunsaturated fatty acids from fish and vegetable sources, and elimination of

intake of trans fats, saturated fats, and “empty carbohydrates” from refined grains and processed sugars[20,22].

Summary and Consensus (Taegtmeyer and Stanley)

More than 150 years ago Virchow first described “fatty degeneration (metamorphosis) of the heart” as “a real transformation of its substance, going on in the interior of the fibers”[26]. The same observation holds still true today (Figure, left panel). However, today we do know that the structural and functional changes of the heart are the results of complex derangements in the metabolism of energy providing substrates. Today we also know that the heart both adapts and maladapts to various metabolic stresses and that the adaptive responses (Figure, right panel) may be favorably manipulated by the provision of specific fatty acid substrates, ingestion of foods with a low glycemic index, and a prevention of obesity, which all work together to benefit the overall function of the heart.

Lastly, we wish to make a point to our many clinical colleagues: The metabolism of fats and sugars does not stop at the arterial wall. In addition to the vascular effects of metabolic dysregulation, there are profound independent effects on the myocardium that alter cardiac structure and function. We have provided evidence for both deleterious (maladaptive) and salutary (adaptive) effects of myocardial fatty acid metabolism (Figure). The main challenge for the immediate future is to identify the metabolic mechanisms and markers of cardiac glucolipotoxicity and to modulate them accordingly.

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Biographies

William C. Stanley, PhD is a Professor of Medicine (Cardiology) and Physiology at the University of Maryland School of Medicine in Baltimore. His research focuses on the regulation of myocardial energy metabolism during stress, with an emphasis on heart failure. Most recently his group is investigating the impact of dietary fatty acid and carbohydrate composition on the development and progression of heart failure. Specifically, they are addressing the mechanisms for the toxic effects of high sugar intake on the heart, and the potential role of reactive oxygen species formation via novel cytosolic pathways. Additional translational studies address the effects of dietary intake of ω -3 polyunsaturated fatty acids on mitochondrial function, inflammation and outcomes in heart failure. Lastly, they investigate the effects of dietary fatty acid composition on mitochondrial function and structure.

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Figure.

Schematic depiction of the toxic effects of fuel overabundance and obesity on the heart (left side; “cardiac glucolipotoxicity”), and the cardioprotective effects of high intake ω -3 polyunsaturated fatty acids (ω -3 PUFA), low intake of saturated fat and “empty carbohydrate”, and prevention of obesity (right side). Additional abbreviations: FFA, free fatty acids; LDL, low density lipoprotein cholesterol; HDL, high density lipoprotein cholesterol; CAD, coronary artery disease; LVH, left ventricular hypertrophy.