Dietary Fat and Heart Failure: Moving From Lipotoxicity to Lipoprotection


Abstract: There is growing evidence suggesting that dietary fat intake affects the development and progression of heart failure. Studies in rodents show that in the absence of obesity, replacing refined carbohydrate with fat can attenuate or prevent ventricular expansion and contractile dysfunction in response to hypertension, infarction, or genetic cardiomyopathy. Relatively low intake of n-3 polyunsaturated fatty acids from marine sources alters cardiac membrane phospholipid fatty acid composition, decreases the onset of new heart failure, and slows the progression of established heart failure. This effect is associated with decreased inflammation and improved resistance to mitochondrial permeability transition. High intake of saturated, monounsaturated, or n-6 polyunsaturated fatty acids has also shown beneficial effects in rodent studies. The underlying mechanisms are complex, and a more thorough understanding is needed of the effects on cardiac phospholipids, lipid metabolites, and metabolic flux in the normal and failing heart. In summary, manipulation of dietary fat intake shows promise in the prevention and treatment of heart failure. Clinical studies generally support high intake of n-3 polyunsaturated fatty acids from marine sources to prevent and treat heart failure. Additional clinical and animals studies are needed to determine the optimal diet in terms of saturated, monounsaturated, and n-6 polyunsaturated fatty acids intake for this vulnerable patient population. (Circ Res. 2012;110:764-776.)

Key Words: heart failure ■ lipids ■ mitochondria ■ nutrition ■ polyunsaturated fatty acids

Dietary lipids are important regulators of cardiac function through their role in membrane phospholipids, as signaling molecules and ligands for nuclear receptors, and as the predominant oxidative substrate for cardiac mitochondria. While much attention has been paid to the clinical effects of dietary fats on the incidence of coronary heart disease (CHD), the effects on the development and progression of heart failure (HF) has been largely ignored. Recent studies in rodent models of HF suggest the novel concept that a diet high in fat and low in carbohydrate (CHO) prevents the development and progression of HF in comparison with low-fat/high-CHO diets.1–10 The idea of replacing dietary CHO with fat to prevent HF may seem counterintuitive; however, it is largely in line with current thinking regarding dietary fat and prevention of CHD.11–13

There is a clear need to develop recommendations for dietary macronutrients for people who are “at risk” for the development of HF (eg, patients with CHD, hypertension, left ventricular hypertrophy [LVH], diabetes), and for patients with established HF. Current HF treatment guidelines provide no specific recommendations for fat intake and recommend HF patients follow the dietary guidelines for prevention of CHD.14–16 CHD guidelines recently underwent major changes. Results from epidemiological studies prompted a re-evaluation of the idea that low fat intake prevents CHD, as it was observed that the incidence of CHD was not related to the intake of fat,11,17,18 nor was it affected by a 25% reduction in fat intake.18 Furthermore, reduced risk of CHD was observed in people with a high intake of unsaturated fatty acids11,17,19,20; while high intake of rapidly absorbed CHO (eg, sugar, white flour) was associated with increased risk.11,21 Thus, there has been a major shift in the paradigm for preventing CHD, away from reducing fat intake with little attention to the amount and type of CHO, to the current recommendation of a diet high in unsaturated fats and low in sugars and overly refined CHO.13 This concept extends to the prevention of obesity, for which decreased relative intake of rapidly absorbed CHO and increased consumption of unsaturated fat is associated with less weight gain.22

The purpose of this review is to present the current understanding of the effects of dietary fats on the development and progression of HF. Much emphasis has recently been placed on the effect of obesity on the development and progression of HF.23,24 The obesity epidemic appears to be mainly due to greater intake in highly processed CHO and total energy, and is not the consequence of greater fat intake per se.22 Thus, in this review we will focus on the impact of dietary fat intake on HF in the absence of major diet-induced obesity.
changes in body mass. The specific effects of saturated, monounsaturated, and n-3 and n-6 polyunsaturated fatty acids (PUFA) will be addressed, as well as the more general consequences of replacing sugar and other refined CHO with fat. Because of the paucity of clinical and large animal data, evidence will be primarily derived from studies in rodents.

**Effects of Dietary Fat on Development and Progression of HF**

Despite aggressive diagnosis and treatment, HF remains a major clinical problem and a huge burden on the US health care system. While current medical therapies can prevent new onset HF and can slow the progression once HF is established, the prognosis remains poor even for optimally treated patients, and new therapeutic approaches are needed. The concept of developing optimal diets for prevention and treatment of HF is particularly attractive, as any beneficial effects should be additive or synergistic with current treatments with drugs and devices. At present there is limited information regarding the effects of dietary macronutrient composition and HF. Population-based studies showed that the incidence of HF is significantly reduced in people who adhere to the Dietary Approaches to Stop Hypertension (DASH) diet, which emphasizes low saturated fat intake and high consumption of PUFA, complex CHO, fruits, and vegetables.25,26 On the other hand, analysis of the dietary patterns of HF patients in the United States reveals a generally poor diet that likely contributes to disease progression and the underlying pathophysiology.27

Animal studies that investigate high fat/low CHO intake should be evaluated with caution, as diet-induced obesity is frequently a confounding factor. Diet-induced obesity in mice and rats can be generated in select strains using a diet that is relatively high in fat (usually 40% to 50% of total energy intake compared to 10% to 15% in the typical commercial rodent chows) combined with high sugar (≈20% to 30% sucrose). Obesity has complex effects on the heart largely mediated through changes in circulating hormones, impaired vascular function and altered autonomic regulation of the cardiovascular system.23,28,29 Further, there is an “obesity paradox” in HF, where obese people have 2 to 3 times greater risk for developing HF than normal weight individuals,30 but once they are diagnosed they have improved survival and less hospitalization than nonobese HF patients.23,24 This complex topic is outside the scope of the current discussion, and had been addressed in recent reviews.23,24 Here we will address the effects of dietary lipid in HF in the absence of obesity. Recent studies from our laboratory and others suggest that in the absence of obesity, replacing CHO in the diet with fat can attenuate or prevent the development and progression of HF in response to hypertension or myocardial infarction (Table).2–7 Feeding a high-fat/low-CHO diet to normal healthy rats and mice generally has no adverse effects on the heart if there is not concomitant obesity.31–35 Studies with obesity resulting from high-fat feeding show either no adverse effects on the heart or mild LVH and contractile dysfunction associated with hypertension and elevated leptin.35,40–43 Classic studies in transgenic mice and leptin deficient Zucker fatty rats demonstrate that when myocardial fatty acid uptake or esterification is elevated to supraphysiological levels, it can result in accumulation of intracellular triglycerides and lipid intermediates associated with cardiac contractile dysfunction, cardiomyocyte hypertrophy, apoptosis, and HF.44–51 The clinical relevance of these observations in terms of dietary fat intake and the development and progression of HF in humans is limited, as the underlying causes of lipotoxicity in these genetic models are not directly relevant to conditions in the healthy or failing human heart.

Since a major cause of HF is chronic hypertension and resultant LVH, we investigated the effects of replacing much of the CHO in the diet with fat in hypertensive rats. We were surprised to observe improved LV contractile function and attenuation of LVH and/or remodeling in hypertensive rats fed a high-fat diet in comparison with normal low-fat chow.2–4 We initially speculated that a high-fat diet would accelerate pathological processes when the heart is subjected to conditions known to result in HF. Our first studies were performed in the Dahl salt-sensitive rat, a model that develops hypertension with salt feeding, and displays progressive LVH, a modest increase in LV end-systolic and diastolic volumes, and recapitulates much of the pathophysiology of the highly prevalent clinical condition of HF with preserved ejection fraction.52 We compared the effects of a high saturated fat chow (60% of energy from fat, mainly from cocoa butter) to a standard low-fat/high-CHO rat chow (10% of energy from fat) on the development of hypertension-induced HF.2–3 All chows had 20% of the energy from protein. After 12 weeks of hypertension on the diets there were no differences in body mass or the degree of hypertension.5 In the low-fat/high-CHO/high salt group, hypertension increased LV mass and end systolic and diastolic volume (Figure 1). As expected, the cardiac activity for the mitochondrial fatty acid oxidation enzyme medium chain acyl-CoA dehydrogenase (MCAD) and Krebs cycle enzyme citrate synthase were reduced in the hypertensive rats fed a low-fat diet in comparison with nonhypertensive animals on low-fat chow (Figure 1).3 This was prevented by the high-fat chow,
<table>
<thead>
<tr>
<th>Diet Comparison</th>
<th>Species</th>
<th>Model</th>
<th>Duration</th>
<th>Primary Outcome</th>
<th>Reference No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-fat diet studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60% fat vs 12% fat</td>
<td>Rats</td>
<td>Salt-induced hypertension</td>
<td>6 weeks</td>
<td>High-fat diet attenuated LVH and improved contractile function.</td>
<td>2</td>
</tr>
<tr>
<td>60% fat vs 10% fat diet</td>
<td>Rats</td>
<td>Salt-induced hypertension</td>
<td>12 weeks</td>
<td>High-fat diet attenuated LVH and improved contractile function.</td>
<td>3</td>
</tr>
<tr>
<td>60% fat vs 10% fat diet</td>
<td>Rats</td>
<td>Salt-induced hypertension</td>
<td>13 weeks</td>
<td>High-fat diet prolonged survival.</td>
<td>4</td>
</tr>
<tr>
<td>60% fat vs 10% fat diet</td>
<td>Rats</td>
<td>Salt-induced hypertension</td>
<td>8 weeks</td>
<td>High-fat diet prolonged survival.</td>
<td>5</td>
</tr>
<tr>
<td>60% fat vs 14% fat diet</td>
<td>Rats</td>
<td>Coronary artery ligation</td>
<td>8 weeks</td>
<td>High-fat intake decreased LV fractional shortening, but increased peak dP/dt.</td>
<td>1</td>
</tr>
<tr>
<td>60% fat vs 14% fat diet</td>
<td>Rats</td>
<td>Coronary artery ligation</td>
<td>8 weeks</td>
<td>High-fat diet increased LV contractile function.</td>
<td>9</td>
</tr>
<tr>
<td>42% fat (high linoleate or mixed fats) vs 12% fat diet</td>
<td>Rats</td>
<td>Genetic hypertension</td>
<td>~6 months</td>
<td>Both high-fat diets prevented LV dilation, and the high linoleic acid diet prolonged survival.</td>
<td>8</td>
</tr>
<tr>
<td>58% fat diet (mainly saturated fat) vs 10% fat diet</td>
<td>Rats</td>
<td>Aortic constriction</td>
<td>8 weeks</td>
<td>High-fat diet increased contractile function.</td>
<td>6</td>
</tr>
<tr>
<td>60% fat vs 10% fat diet</td>
<td>Rats</td>
<td>Aortic constriction</td>
<td>8 weeks</td>
<td>High-fat diet had no effect on LV mass, function, or chamber volume.</td>
<td>118</td>
</tr>
<tr>
<td>45% fat diet (either saturated+monounsaturated fat or PUFA) vs 12% fat diet</td>
<td>Hamsters</td>
<td>δ sarcoglycan cardiomyopathy</td>
<td>&gt;1 year</td>
<td>High saturated+monounsaturated fat diet prolonged survival in comparison with low-fat or high-PUFA diets.</td>
<td>7</td>
</tr>
<tr>
<td>60% fat vs 10% fat diet</td>
<td>Mice</td>
<td>Aortic constriction</td>
<td>16 weeks</td>
<td>High-fat diet had no effect on LV mass, function, or chamber volume.</td>
<td>38</td>
</tr>
<tr>
<td>60% fat vs 10% fat diet</td>
<td>Rats</td>
<td>Aortic constriction</td>
<td>4 weeks</td>
<td>High-fat diet increased LVH, worsened LV dilation, and worsened contractile dysfunction.</td>
<td>53</td>
</tr>
<tr>
<td>n-3 PUFA studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Observational epidemiological analysis</td>
<td>Humans</td>
<td>At-risk population</td>
<td>12 years</td>
<td>Intake of DHA+EPA inversely related to risk for new onset HF.</td>
<td>127</td>
</tr>
<tr>
<td>DHA+EPA (5.4 g/d) vs placebo</td>
<td>Humans</td>
<td>Advanced HF patients</td>
<td>18 weeks</td>
<td>DHA+EPA decreased TNFα.</td>
<td>135</td>
</tr>
<tr>
<td>DHA+EPA (0.9 g/d) vs placebo</td>
<td>Humans</td>
<td>HF patients</td>
<td>3.9 years</td>
<td>DHA+EPA decreased risk of death and admission to hospital for cardiovascular events by 8% vs placebo.</td>
<td>125</td>
</tr>
<tr>
<td>DHA+EPA (1.6 g/d) vs placebo</td>
<td>Humans</td>
<td>Nonischemic dilated HF</td>
<td>12 months</td>
<td>n-3 PUFA increased EF by 10.4%.</td>
<td>124</td>
</tr>
<tr>
<td>DHA+EPA (0.9 g or 3.6 g/d) vs placebo</td>
<td>Humans</td>
<td>Nonischemic dilated HF</td>
<td>3 months</td>
<td>Dose-dependent increase in LV ejection fraction.</td>
<td>126</td>
</tr>
<tr>
<td>High α linolenic acid/low n-6 PUFA diet vs standard low n-3 PUFA diet</td>
<td>Hamsters</td>
<td>δ sarcoglycan cardiomyopathy</td>
<td>&gt;1 year</td>
<td>High α linolenic acid prolonged survival.</td>
<td>55</td>
</tr>
<tr>
<td>DHA+EPA (2.8% of energy intake) vs standard low n-3 PUFA diet</td>
<td>Rats</td>
<td>Aortic constriction</td>
<td>12 weeks</td>
<td>DHA+EPA prevented LVH and LV dilation.</td>
<td>131</td>
</tr>
<tr>
<td>DHA+EPA or α linolenic acid dose response vs standard low n-3 PUFA diet</td>
<td>Rats</td>
<td>Aortic constriction</td>
<td>12 weeks</td>
<td>DHA+EPA prevented LV dilation and increased systemic inflammation, but α linolenic acid did not.</td>
<td>130</td>
</tr>
<tr>
<td>DHA, EPA, or DHA+EPA (2.3% energy intake) vs standard low n-3 PUFA diet</td>
<td>Rats</td>
<td>Aortic constriction</td>
<td>17 weeks</td>
<td>No effect on LV function or mass with moderate LVH, but increased resistance to Ca2+-induced MPTP.</td>
<td>106</td>
</tr>
<tr>
<td>DHA+EPA (2.3% of energy intake) vs standard low n3 PUFA diet</td>
<td>Rats</td>
<td>Aortic constriction</td>
<td>8 weeks</td>
<td>DHA+EPA prevented LVH and inflammation.</td>
<td>118</td>
</tr>
</tbody>
</table>

(Continued)
consistent with better maintenance of mitochondrial content and function with a high-fat diet. With the low-fat diet there was a large induction of the mRNA for atrial natriuretic peptide and fetal myosin (classic markers of HF) that was blunted by the high-fat diet. In a follow-up study, survival was prolonged by the high-fat diet in comparison with various low-fat/high-CHO diets. 4

The cardioprotective effects of a high-fat diet observed in hypertensive Dahl salt-sensitive rats could be an anomaly unique to the Dahl rat model; thus we performed similar studies with pressure overload induced by aortic banding. Again we found that the high-fat diet significantly prevented the increase in LV end-diastolic and systolic volumes in comparison with a high-CHO diet. 5 Similar studies in mice with aortic constriction have found either no effect on LV mass or function but better maintenance of the activity of mitochondrial oxidative enzymes, 38,39 or greater LV mass and worse function, 53 suggesting that there are major species differences (Table). Studies in rats with HF induced by myocardial infarction found a neutral effect on LV remodeling and function with a high-fat diet; however, this was confounded by the development of obesity. 37 Chicco et al showed that feeding a high-fat diet enriched with either the n-6 PUFA linoleic acid from safflower oil or a mixture of

<table>
<thead>
<tr>
<th>Diet Comparison</th>
<th>Species</th>
<th>Model</th>
<th>Duration</th>
<th>Primary Outcome</th>
<th>Reference No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>DHA+EPA (1.5% of chow by mass) vs standard low n-3 PUFA diet</td>
<td>Rats</td>
<td>Aortic constriction</td>
<td>15 weeks</td>
<td>DHA+EPA improved ex vivo cardiac mechanical function and efficiency.</td>
<td>134</td>
</tr>
<tr>
<td>DHA+EPA (2.3% of energy intake) vs standard low n-3 PUFA diet</td>
<td>Rats</td>
<td>Myocardial infarction</td>
<td>12 weeks</td>
<td>No effect on LV function or mass, but increased resistance to Ca²⁺-induced MPTP.</td>
<td>104</td>
</tr>
<tr>
<td>DHA+EPA (2.3% of energy intake) vs standard low n-3 PUFA diet</td>
<td>Mice</td>
<td>Aortic constriction</td>
<td>6 weeks</td>
<td>DHA+EPA prevented LV dilation.</td>
<td>132</td>
</tr>
<tr>
<td>Menhaden oil (DHA+EPA at 1% of total energy intake) vs standard low n3 PUFA diet</td>
<td>Mice</td>
<td>Aortic constriction</td>
<td>4 weeks</td>
<td>DHA+EPA prevented contractile dysfunction and myocardial fibrosis.</td>
<td>129</td>
</tr>
</tbody>
</table>

Studies in which body mass was increased >10% were excluded. LV, left ventricular; LVH, left-ventricular hypertrophy; PUFA, polyunsaturated fatty acids; DHA, docosahexaenoic acid; EPA, eicosahexaenoic acid; HF, heart failure; MPTP, mitochondrial permeability transition pore.

Figure 1. A high-fat diet prevents expansion of the LV chamber (top panel) and down-regulation of the mRNA and activity of the fatty acid β-oxidation enzyme medium chain acyl-CoA dehydrogenase and the Krebs cycle enzyme citrate synthase in rat LV myocardium in Dahl salt-sensitive hypertensive rats. From Okere et al. 3
saturated and monounsaturated fat from lard to spontaneously hypertensive HF (SHHF) rats prevented the expansion of LV chamber size. Interestingly, the high-fat diet made from lard did not affect mortality in comparison with the standard diet, but the high linoleic acid diet significantly prolonged survival. This suggests that a high-fat/low-CHO diet enriched with linoleic acid may be optimal in advanced HF. However, one must keep in mind that this genetic HF model involves idiopathic hypertension and a defect in the myocardial fatty acid transport protein CD36, and thus likely has limited application to human HF.

In contrast, we and others have found very different results in a genetic hamster model of dilated HF caused by genetic δ-sarcoglycan deficiency. High intake of the n-3 PUFA α-linolenate (18:3n3; commonly found in canola and flaxseed oils) combined with a low intake of linoleate (18:2n6) prolonged survival in comparison with a diet rich in 18:2n6. We recently used a similar hamster model to compare the effects of 2 high-fat diets (45% of energy from fat): one high n-3 PUFA and n-6 PUFA, and the other high in saturated and monounsaturated fat. There was only a modest 10% increase in body mass with the 2 high-fat diets, but surprisingly, consumption of the high saturated and monounsaturated fat diet prolonged life in comparison with either the standard low-fat diet or the high-PUFA group was not different from the low-fat diet (260 days), but was shorter than high-fat diet with saturated and monounsaturated fat (P<0.01). Dietary treatment started at 6 weeks of age. The high-fat diets contained 45% of total energy from fat and the low-fat diet 12%. The fatty acid content is expressed as percentage of total energy in the diet. From Galvao et al.

Several mechanisms could possibly be responsible for the beneficial effects of high-fat diets in these diverse animal models of HF. In the following sections we will discuss the potential underlying mechanisms responsible for the effects of dietary fatty acids on cardiac structure and function in the normal heart and the failing heart.

**Metabolic Effects of Substituting Fat for CHO**

It has become clear that increasing fat intake in exchange for CHO, particularly PUFA for sugars and rapidly absorbed starches, has favorable effects on plasma lipid profile, reduces insulin secretion, and lowers postprandial glyceremia and lipid storage. Dietary guidelines for over half a century have recommended consumption of a low saturated fat/high complex CHO diet to reduce coronary heart disease; however, over the last 40 years there has been greater consumption of fructose and rapidly absorbed CHO, and less intake of complex CHO and fat in industrialized countries. As noted above, clinical studies found no evidence for beneficial effects of low-fat/high-CHO diets in terms of the incidence of CHD. Low-fat/refined-high-CHO diets are associated with increased blood lipids, glucose, and insulin and elevated blood pressure in comparison with high-fat/low-refined-CHO/high-complex-CHO diets. Low-CHO diets are effective for reducing body weight, insulin resistance, and serum triglycerides and increasing high-density lipoprotein cholesterol in humans. In contrast, diets high in sucrose or fructose increase left ventricular dysfunction and mortality in comparison with either a low-CHO/high-fat or high-starch diet in hypertensive rats or mice with aortic constriction or salt-induced hypertension. Clinical studies find that elevated plasma insulin is associated with LVH. As illustrated in Figure 3, a high glycemic glucose load stimulates insulin secretion and activation of insulin-signaling pathways, stimulating protein synthesis and decreasing protein breakdown, which could induce LVH, fibrosis, reactive oxygen species, and apoptosis and drive the development of HF.
The effects of fat intake on blood lipids are very dependent on the fatty acid composition of the ingested lipid. Epidemiological studies find that intake of PUFA and vegetable oils are associated with reduced risk of CHD, as opposed to saturated and “trans fats” (long-chain unsaturated fatty acids with the double bond in the trans configuration). Recent meta-analyses found no relationship between saturated fat intake and cardiovascular disease. High intake of PUFA, particularly n-3 PUFA from marine sources at greater than 2 g/d, lowers plasma triglycerides. On the other hand, increased intake of trans fats increase plasma levels of low-density lipoprotein cholesterol. The effects of saturated fatty acids are complex and may vary on the basis of the type of saturated fat consumed. For example, stearic acid, in comparison with myristic and palmitic acids, is not hypercholesterolemic. Taken together, the evidence from epidemiological, clinical, and mechanistic studies is consistent, showing that an increase in fat intake, especially PUFA, in exchange for CHO will lower triglycerides without adverse effects on the cholesterol profile.

One potential cardiac effect of increasing fat intake in the absence of obesity is an increase in intracellular triglyceride in cardiomyocytes. Clinical studies using 1H NMR spectroscopy showed that obese individuals have accumulation of triglyceride stores in the myocardium, and speculated that this might contribute to development of HF. More recent clinical studies with this method showed that intracardiac triglyceride content is positively associated with LV ejection fraction in patients with hypertrophic cardiomyopathy and shows no association in dilated or ischemic cardiomyopathic patients. Furthermore, similar measurements in type II diabetic patients with either risk for, or established, cardiovascular disease found no association between myocardial triglyceride content and LV mass, chamber volume, or systolic or diastolic function. Taken together, there is no evidence to support the concept that accumulation of triglycerides at physiological levels either causes or predicts myocardial pathology or poor outcome.

Available data suggest that any increase in myocardial triglyceride stores induced by a high-fat diet in the absence of obesity is benign. We found that feeding a high saturated fat diet (60% of energy from fat) to rats for 8 weeks increased myocardial triglyceride stores by 35% in comparison with a low-fat diet but did not affect LV mass or function. Simultaneous inhibition of mitochondrial fatty acid oxidation with chronic oxefencine treatment increased triglyceride stores to 80% above levels with low-fat diet, but still had no effect on cardiac mass or function. There was also no effect on triglyceride levels when the same saturated fat diet was fed to hypertensive Dahl rats. Interestingly, there was no increase in cardiac triglyceride content when we fed a high-fat diet comprising the n-6 PUFA linoleic acid or the medium chain fatty acid octanoate ± oxefencine, illustrating that intracardiac triglyceride metabolism is dependent on fatty acid saturation and chain length. It is important to note that these relatively crude measures of myocardial triglyceride do not provide insight into how the lipid is stored. It has become increasingly clear that packaging of triglyceride into intracardiomyocyte lipid droplets plays an important role in cardiac fatty acid metabolism, and very likely prevents the toxic effects of lipid accumulation in the heart.

**Effects of Fat Intake on Cardiac Gene Expression PPARs**

Greater exposure of the heart to fatty acids—such as occurs with fasting, caloric restriction, or a high-fat/low-CHO diet—activates peroxisome proliferator activated receptors (PPAR) in cardiomyocytes and increases the expression of genes that encode proteins responsible for fatty acid import and oxidation. In the advanced stages of HF there is a down-regulation in fatty acid oxidation and increased glycolysis and glucose oxidation, which appears to be at least partially due to a decrease in the expression and activity of proteins involved in fatty acid metabolism. Fatty acids in cardiomyocytes activate PPARs, primarily PPARα and PPARβ/δ, which forms a heterodimer with retinoid X receptors and the cofactor PPARγ coactivator-1 and binds to specific PPAR response elements on nDNA. Thus, the PPAR system acts as a lipid sensor in the cell, increasing the capacity for fatty acid metabolism in response to greater exposure to fatty acids. The activity of PPARα decreases in response to hypertrophic growth in vitro, as reflected by a fall in the mRNA levels of genes regulated by PPARα. In vivo studies showed similar effects with advanced pressure overload–induced LVH and HF in mouse, rat, and dog models. Long-term pharmacological activation of PPARα, β/δ, or γ in rat and dog models of HF has neutral or mild positive effects on cardiac function or LV remodeling. A high-fat diet also activates PPARs in the heart, stimulates expression of key proteins involved in fatty acid oxidation, and may prevent the down-regulation of fatty acid oxidation and impairment in overall mitochondrial function that occurs in HF.

There is growing evidence that the composition of fatty acids in the diet affects both the extent and pattern of expression of PPAR regulated genes. High-fat diets comprising long-chain saturated fatty acids (16:0 and 18:0) or n-6 PUFA (18:2n6) both increased the mRNA levels for known PPAR-regulated genes in the rat heart; however, there were significant differences in the expression pattern. More controlled studies in isolated cardiomyocytes from adult rats showed that oleate (18:1) increased expression of PPARα-regulated genes, promoting fatty acid oxidation to a greater extent than did stearate (18:0), palmitate (16:0), or linoleate (18:2n6). This suggests that a diet high in oleate, which is the primary fatty acid in olive oil and the Mediterranean diet, may be more effective than are other fatty acids at activating PPARs and maintaining mitochondrial function in HF.

**Dietary Fat and Cardiac Phospholipids**

The amount and type of dietary fat affects the fatty acid composition of cardiac mitochondrial membrane phospholipids, which can impact mitochondrial function and could impact disease progression in HF. Similar to most cell types, the predominant phospholipids in mitochondrial membranes are phosphatidylethanolamine and phosphatidylcholine, each comprising 30% to 45% of total cardiac mitochondrial phospholipids. Mitochondrial membranes are...
unique because they contain high levels of cardiolipin (CL), a tetra-acyl phospholipid that occupies 10% to 20% of the total mass of mitochondrial PLs.107–112 CL is important for formation of contact sites between inner and outer mitochondrial membranes, for formation and maintenance of essential inner membrane proteins and respiratory complexes, and in mitochondrial apoptotic signaling pathways.112 Tetra-linoleoyl CL (L4CL) is the most predominant species of CL in cardiac mitochondria in humans, dogs, and rats (≈60% to 80% of total CL),110,112,113 but not mice (≈20%). Depletion of CL alters mitochondrial morphology and causes severe mitochondrial dysfunction. This is seen in Barth syndrome, a rare genetic disorder defined by a mutation in tafazzin, an essential enzyme for formation of functional CL.114,115 These patients have low levels of total CL and L4CL in myocardium, resulting in dilated cardiomyopathy.113 Reduction of L4CL has been observed in genetic and pressure overload–induced HF models in rats, and in myocardium from HF patients compared with nonfailing donor hearts, suggesting that loss of L4CL might contribute to the progression of HF.8,111,112,116 In contrast, dogs with established HF secondary to irreversible myocardial injury had severe mitochondrial respiratory dysfunction but normal mitochondrial CL content and L4CL levels.107,117 Other studies found no depletion of L4CL in humans and rats with HF.104,113 Furthermore, we recently found that a 60% depletion of L4CL induced by high saturated fat intake was not associated with worse LV dysfunction or pathology in rats subjected to aortic banding.118 Taken together, the well-documented impairment in mitochondrial respiratory function in advanced HF does not appear to be due to depletion of total CL or L4CL.

It has been suggested that diets rich in linoleic acid promote conversion to arachidonic acid and increase production of inflammatory prostanoids; however, the process of elongation and desaturation of linoleic acid to form arachidonic acid is tightly regulated.119 Thus, greater linoleic acid intake does not increase tissue phospholipid arachidonic acid content or systemic markers of inflammation, and clinical studies suggest that it reduces the risk for CHD.120 Linoleic acid is the primary fatty acid side chain in CL; however, there is no evidence to suggest that higher linoleic acid intake increases mitochondrial total CL or L4CL in normal healthy animals. On the other hand, in SHHF rats, which are depleted of total CL or L4CL, supplementation with a high linoleic acid diet increased total CL and L4CL in myocardium, prevented LV dilation, and extended survival, in comparison with a low-fat diet or a high-fat diet comprising saturated and monounsaturated fats.8 In cultured skin fibroblasts from Barth syndrome patients, treatment with linoleic acid increased L4CL,121 suggesting that supplementation with linoleic acid may be beneficial when L4CL is depleted.

There is growing evidence that cardiac phospholipid fatty acid composition is profoundly affected by high intake of marine n-3 PUFA, specifically docosahexaenoic acid (DHA; 22:6n3) and, to a lesser extent, eicosahexaenoic acid (EPA; 20:5n3).122,123 Human studies show rapid incorporation of DHA/EPA into myocardial phospholipids following initiation treatment at 6 g/d, with a proportional decrease in arachidonic acid (20:4n6), and a plateau in effect at approximately 4 weeks.122 Treatment with capsules containing DHA/EPA (0.9–3.6 g/d) has been shown to reduce mortality and hospitalization and improve LV function in patients with established HF (Table).124–126 In general, dietary intake of DHA and EPA is through oily fish; most people consume about 0.1 g/d, and a high dietary intake from fish is approximately 0.4 to 0.6 g/d.127,128 Epidemiology studies show that high intake of DHA+EPA (>0.4 g/d) is strongly associated with reduced risk for new onset HF.123,127

We and others found that intake of DHA+EPA at a dose equivalent to approximately ≥4 g/d in humans prevents LV remodeling and contractile dysfunction in rat and mouse models of pressure overload–induced HF.123,129–132 Dietary supplementation with fish oil containing DHA and EPA (70:30 ratio) increased DHA in cardiac phospholipids and prevented LV chamber expansion in response to aortic constriction in a dose-dependent manner (Figure 4).130
effect corresponded with a decrease in arachidonic acid in membrane phospholipids, and less systemic inflammation, as seen in lower urine thromboxane B2 and serum TNFα. In contrast, high intake of α-linolenic acid (18:3n3) from flaxseed oil did not increase DHA or EPA in cardiac membranes owing to a limited capacity for elongation and desaturation in heart, and did not improve cardiac function or exert anti-inflammatory effects. Furthermore, supplementation with DHA+EPA increased DHA and EPA in mitochondrial phospholipids and attenuated Ca2+-induced mitochondrial permeability transition pore (MPTP) opening in response to Ca2+-stress (Figure 5).104 Cardiac mitochondria in HF are more susceptible to MPTP opening, which causes mitochondria depolarization, uncoupling, and swelling. The loss of ATP production and release of cytochrome C can result in cell death via either apoptosis or necrosis; thus MPTP opening is a catastrophic event. We recently found resistance to MPTP opening was present only with DHA supplementation, not with EPA or α-linolenic acid.105,106 Furthermore, high intake of DHA prevented cardiac dysfunction and cardiomyocyte apoptosis in early-stage HF in rats,130 which could be due to less MPTP opening. Supplementation with DHA in rats has been shown to improve the mechanical function and efficiency of both postischemic133 and hypertrophied134 rat hearts when blood perfused ex vivo, suggesting that changes in membrane structure could improve mitochondrial coupling, efficiency of excitation–contraction coupling, or both.

Supplementation with n-3 PUFA has anti-inflammatory effects in both healthy populations and those with chronic inflammatory conditions, including HF.124,135 The anti-inflammatory actions of n-3PUFA may be through their actions on transcription factors to influence gene expression, or mediated through eicosanoids. In a typical Western diet, arachidonic acid is the predominant PUFA in cell membrane phospholipids, comprising 20% to 25% of total membrane fatty acids, and is the major substrate for eicosanoid synthesis. EPA is a substrate for both cyclooxygenase and 5-lipoxgenase, generating eicosanoids with a different structure in comparison with eicosanoids from arachidonic acid. In general, EPA forms weaker proinflammatory eicosanoids than arachidonic acid; therefore, manipulating n-3 to n-6 PUFA by diet alters the inflammatory environment.136 Development and progression of HF is associated with increased levels of inflammatory mediators such as eicosanoids and cytokines. Enhanced intake of DHA and EPA decreases arachidonic acid in inflammatory cells, which lowers production of prostaglandin PGE2, thromboxane A2, and leukotriene B4, while the increase in EPA increases production of anti-inflammatory eicosanoids such as prostaglandin PGE3, thromboxane A3, and leukotriene B5.123 EPA and DHA also generate potent anti-inflammatory eicosanoids, resolvins, in the COX-2 pathway.137 Supplementation with DHA+EPA blunted the increase in thromboxane B2 and 6-keto-prostaglandin F1 in rats with early HF,118,130 and reduced circulating levels of TNFα, IL-1, and IL-6.124,135,138,139 Decreased cytokine levels are mostly due to the effects of n-3 PUFAs on gene expression and transcription factors. Synthesis of cytokines is regulated by nuclear transcription factor kappa B (NF-kB), which is activated in HF.140 Taken together, high intake of DHA and EPA alters membrane phospholipids in a manner that suppresses inflammatory pathways that contribute to progression of HF.

Unique Effects of Specific Fatty Acids
Toxic lipid products are formed when long-chain PUFA undergo peroxidation via reaction with oxygen or hydroxyl radicals within mitochondria, generating highly reactive toxic aldehydes.141,142 The main metabolite formed on peroxidation of n-6 PUFA is 4-hydroxy-2-nonenal (HNE), while n-3 PUFA generate 4-hydroxy-2-hexanal (HHE).143 HNE is highly reactive, and is increased in the myocardium following ischemic/reperfusion and in HF.144 It modifies key mitochondrial and contractile proteins and is associated with impaired oxidative phosphorylation and LV function.145 On the other hand, HHE is less reactive and does not exert the toxic effects observed with HNE.146 This has major implications for the impact of dietary lipids, because a high intake of n-3 PUFA, particularly DHA and EPA, will increase DHA and EPA in mitochondrial membranes in exchange for a decrease in n-6 PUFA (arachidonic acid and linoleic acid). This would result in a decrease in HNE and greater HHE, and thus less cytotoxicity for a given rate of lipid peroxidation. At present, there is no experimental evidence for this proposed beneficial effect of dietary supplementation with DHA or EPA in the heart.

Ceramides are lipid signaling sphingolipids implicated in the formation of ROS and apoptosis.44 Long-chain saturated fatty acids are the primary fatty acid moieties in cardiac ceramide, with palmitate and stearate each comprising approximately 40% and 30%, respectively, of the total ceramide pool in the rat heart.147,148 In vivo studies show that a high-fat diet with palmitate (60% of energy from fat) increased palmitoyl ceramide in normal rats and in animals with HF induced by myocardial infarction for 8 weeks, but was not associated with impaired cardiac function or pathology.31,32 Palmitoylceramide levels were elevated by 40% with 20 weeks of infarct-induced HF on a low-fat diet, but were not
increased in rats fed a high-fat/high-sugar diet (45% of total energy from fat).37 Taken together, there is no evidence to suggest that elevated cardiac ceramides contribute to the development of HF or that a high-fat diet triggers cardiac pathology through elevated ceramides.

Several studies have found that DHA and EPA supplementation increase adiponectin when given at pharmacological doses to mice, rats, and humans.131,149,150 Adiponectin is an anti-inflammatory adipokine secreted by white adipose tissue, and is negatively associated with obesity and systemic inflammation.151 Clinical studies find that circulating adiponectin levels are increased in advanced HF and are a positive predictor of worsening HF.152–154 On the other hand, the protective cardiovascular and anti-inflammatory effects of adiponectin in non-HF models of cardiovascular disease are well established,155 and the rise in adiponectin with worsening HF appears to be at least partially due to cachexia. Adiponectin gene expression is regulated by PPARγ, and incubation of adipocytes with EPA, DHA, or both increases adiponectin mRNA and synthesis, with a greater effect with DHA than with EPA.156

Clinical Implications and Future Directions

There is growing evidence that the development and progression of HF is affected by the composition of dietary fats and CHO. Studies in rodents suggest that in the absence of obesity, replacing refined CHO in the diet with fat can attenuate or prevent the development and progression of HF. While results from studies in rodent models of HF show that high intake of saturated, monounsaturated, or n-6 polyunsaturated fatty acids can exert beneficial effects on LV function, remodeling, and survival, the underlying mechanisms are complex, and there are clearly major differences among fatty acids. At present, there are more questions than answers, as illustrated in Figure 6. Does long-term consumption of long-chain saturated fatty acids increase ceramides and trigger cardiomyocyte loss? Is stearate better for the myocardium than is palmitate? Is oleate intake beneficial or neutral? The effects of n-6 PUFA, specifically linoleic acid, is particularly unclear, because high levels in membrane phospholipids could be detrimental owing to greater HNE formation.

Furthermore, the effects of dietary lipids in patients with HF and concurrent chronic ischemia heart disease are unknown (“ischemic cardiomyopathy”), because these HF patients may respond very differently than those with successful revascularization or no history of coronary disease.

On the other hand, it is becoming increasingly clear from clinical and animal studies that relatively low intake of n-3 PUFA from marine sources (approximately 0.4% to 2% of energy intake) alters cardiac membrane phospholipid fatty acid composition, decreases the onset of new HF, and slows the progression of established HF (Figure 6). This effect is associated with decreased inflammation and improved resistance to mitochondrial permeability transition. That said, there has yet to be a definitive clinical trial with an appropriately high dose (>3 g/d) or comparing DHA to EPA in established HF. Definitive information on the optimal dose and formulation of marine n-3 PUFA is not available; thus additional clinical trials are warranted.

In summary, manipulation of dietary fat intake shows promise in the prevention and treatment of HF. Clinical studies generally support high intake of n-3 PUFA from marine sources to prevent and treat HF. Additional clinical and animal studies are needed to determine the optimal diet in terms of the relative and absolute intake of saturated, monounsaturated, and n-3 and n-6 PUFA for this vulnerable patient population.

Sources of Funding

This work was supported by National Institutes of Health grants HL074237, HL101434, and HL072751.

Disclosures

None.

References


Dietary Fat and Heart Failure: Moving From Lipotoxicity to Lipoprotection

doi: 10.1161/CIRCRESAHA.111.253104
_Circulation Research_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2012 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/110/5/764

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation Research_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation Research_ is online at:
http://circres.ahajournals.org//subscriptions/