Forgotten but Not Gone: The Rediscovery of Fatty Heart, the Most Common Unrecognized Disease in America

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Abstract—Until 60 years ago, fatty heart was an accepted clinical entity. Since then, its very existence has been questioned, despite the fact that 2 of 3 Americans are now obese or overweight and obesity has been shown to be correlated with cardiac functional abnormalities. In 2000, a syndrome of “lipotoxic cardiomyopathy” resembling earlier pathologic descriptions of fatty human hearts was described in rodents, and fatty infiltration of cardiomyocytes was subsequently reported in patients with congestive failure. Now, magnetic resonance spectroscopy has been adapted to permit routine noninvasive screening for fatty heart. The use of this technique in human volunteers indicates that cardiomyocyte fat correlates well with body mass index and is elevated in uncomplicated obesity. It is more severe when glucose tolerance becomes abnormal or diabetes is present. It is associated with impaired diastolic filling, even in seemingly asymptomatic obese volunteers. Because fatty heart can be readily prevented by lifestyle modification and pharmacologic interventions that reduce caloric intake and increase fatty acid oxidation, it seems important to recognize its existence so as to intervene as early as possible. (Circ Res. 2007;101:759-767.)

Key Words: magnetic resonance spectroscopy ■ lipotoxic cardiomyopathy ■ fatty heart ■ obesity

Fatty heart, or “cor adiposum,” had been known to clinicians for more than 300 years,1 before it vanished from the American diagnostic vocabulary some 60 years ago. Its disappearance from clinical consciousness followed a widespread skepticism that the condition actually existed. Ironically, even today, when obesity, the disorder most often associated with fatty heart, has reached pandemic proportions in America, fatty heart is almost never diagnosed.

In 2000, a form of fatty heart called “lipotoxic cardiomyopathy” was described in congenitally obese Zucker diabetic fatty (ZDF) rats.2 The morphological appearance of the ZDF cardiomyocytes resembled the earliest descriptions of “fatty degeneration” in human cardiomyocytes made by Corvisart in 1812,3 by Laennec in 1838,4 and by Virchow in 1858,5 the first to distinguish between fat on the surface of the heart muscle and fatty degeneration with fatty droplets within the sarcolemma. Similar results were found 169 years later in cardiac tissue of an obese human using modern pathology techniques (Figure 1).6 Since then, cardiologists have begun to reexamine lipotoxic heart disease as a clinical entity7,8 and to explore the relationship...
between obesity and cardiac function,9,10 aided by the availability of modern noninvasive technologies.11–13

**Current Status of Fatty Heart**

Obesity has long been considered to be an indirect cause of heart disease. Obese individuals typically present with a number of traditional Framingham risk factors (eg, hypertension, dyslipidemia, and diabetes), predisposing them to myocardial infarction,14 which can progress to ischemic cardiomyopathy. The hemodynamic hallmarks of obesity, increased heart rate and stroke volume,15 are thought to be a compensatory adaptation to increased adipose tissue mass at the expense of left ventricular remodeling, which can progress to nonischemic dilated cardiomyopathy.9,10

The concept of fatty heart was revised in the last decade of the 20th century by Alpert and colleagues.16–19 Using echocardiographic techniques, they studied left ventricular mass and function in morbidly obese subjects whose body weight was twice the ideal. They found left ventricular hypertrophy and impaired systolic and diastolic function. In individuals with increased left ventricular mass, exercise produced no increase in left ventricular ejection fraction, ie, when the left ventricular mass reached a certain level, reserve function for exercise was nonexistent. These studies also demonstrated a direct link between duration of obesity and the severity of myocardial disease: the longer the duration of morbid obesity, the greater the left ventricular mass and the worse the impairment of left ventricular systolic function and diastolic filling. A decade later, Sharma et al identified fatty infiltration of myocardial cells in patients with congestive heart failure and severe metabolic dysregulation.20 Their findings were very similar to those described by Zhou et al in obese rodents.2

Despite the foregoing evidence, clinical awareness of fatty heart remains close to nonexistent. Most cardiologists still doubt that this disorder really exists in humans.8 The purpose of this review is to consider new evidence that fatty heart could well be a common cause of cardiac morbidity and mortality in obese humans and that it can be prevented and arrested by available interventions.

**Mechanisms of Steatosis, Lipotoxicity, and Lipoapoptosis**

**Mechanisms**

When the caloric intake exceeds the caloric expenditure, the caloric surplus is normally stored in adipocytes in the form of triacylglycerol (TG), with little or no spillover into nonadipose tissues (such as the pancreas, the liver, and the myocardium). This stockpile of energy can sustain life during famines, which until recently constituted the major obstacle to survival on this planet, with its variable food supply. However, during the 20th century, famines have been replaced in the Western world by unremitting overnutrition, imposing on the adipocytes a challenge unprecedented in biologic history. Once the adipocytes have expanded to a maximum level, plasma free fatty acid (FFA) levels in obese individuals increase, followed by progressive ectopic accumulation of lipids in nonadipose tissues, including the myocardium.

The consequences of myocardial steatosis have been studied in several rodent models. Lipid overaccumulation in cardiomyocytes can theoretically result from increased fatty acid (FA) uptake, decreased FA oxidation, or a combination of both. However, in rodent and human obesity, decreased FA oxidation has not been demonstrated in the heart and is unlikely to be a primary factor. In fact, Peterson et al report an increase in FA oxidation and a decrease in efficiency in the heart of obese women.21

**Rodent Models of Cardiac Steatosis**

A commonly used model of fatty heart is the ZDF rat. In the ZDF rat, a loss-of-function mutation in the leptin receptor (Lepr)22 in the hypothalamic centers that regulate feeding behavior results in increased food intake, whereas in peripheral tissues, such as the pancreatic islets, it results in markedly increased lipogenesis.23 Consequently, the combination of increased caloric influx and a generalized increase in lipogenesis in tissues causes an accelerated steatosis in cardiomyocytes and other organs, implying that a key function of hyperleptinemia is to prevent ectopic lipid accumulation.24 Steatosis of the myocardium is associated with left ventricular hypertrophy and dysfunction that ultimately progresses to

![Figure 1. Oil red O staining for lipids of hearts from an obese (body mass index, 42) and a nonobese human (body mass index, 28). Adapted by permission of the Federation of American Societies for Experimental Biology.6](http://circres.ahajournals.org/Downloaded-from)
lipotoxic cardiomyopathy (Figure 2). Myocardial steatosis and lipotoxic cardiomyopathy in this model can be prevented by thiazolidinedione treatment initiated at an early age. Myocardial steatosis and dysfunction have also been reported in ob/ob and db/db mice.\textsuperscript{25,26} Another useful model of ectopic lipid deposition can be created by organ-specific expression of a transgene that increases fatty acid uptake. Cardiac steatosis has been created in otherwise healthy nonobese mice by cardiac-specific expression of a lipogenic transgene, long-chain acyl coenzyme A (CoA) synthetase (ACS).\textsuperscript{27} Although there is no systemic caloric mismatch in these mice, the increased influx of FFAs into cardiomyocytes causes local, myocardial accumulation of TG. This is followed by lipotoxic cardiomyopathy with cardiac hypertrophy, lipoapoptosis, left ventricular dysfunction, and premature death.\textsuperscript{27} These changes are believed to result entirely from increased FA influx without any other known metabolic defect. The entire phenotype can be prevented by early intervention with a lipid-lowering hormone, leptin, which increases FA oxidation and reduces cardiac TG content from 2.45 mg/g in the hearts of the untreated transgenic mice to 1.35 mg/g in the hearts of the “leptinized” transgenic mice.\textsuperscript{28} The cardiac TG content of normal mice is 1.6 mg/g. The gross appearance and microscopic and electron microscopic sections of typical hearts are shown in Figure 3A through 3C and electrocardiograms in Figure 3D.

A similar model of cardiac steatosis was developed by overexpressing a lipoprotein lipase transgene in the myocardium. Ectopic accumulation of lipids in this model is also attributed to enhanced influx of FFAs hydrolyzed from circulating TGs.\textsuperscript{29}

Although it has no known counterpart in spontaneously occurring rodent or human lipotoxic heart disease, cardiac steatosis can also be created by a reduction in FA oxidation without an increase in FA influx. Such a model was engineered by knocking out peroxisome proliferator-activated receptor (PPAR)\textsubscript{α}, which upregulates at least 7 mitochondrial fatty-acid oxidizing enzymes,\textsuperscript{30,31} including mitochondrial carnitine palmitoyl transferase-1, peroxisomal acyl CoA oxidase, and uncoupling proteins (UCP1, -2, and -3).\textsuperscript{32} PPAR\textsubscript{α} knockout mice were unable to upregulate FA oxidation in response to carnitine palmitoyl transferase-1 inhibition.\textsuperscript{33} Surprisingly, cardiomyocyte-specific overexpression of PPAR\textsubscript{α} also causes myocardial lipid overaccumulation.\textsuperscript{34}

Figure 2. Mechanisms of cardiac lipotoxicity in ZDF rats showing triglyceride and ceramide content of their hearts, DNA laddering (an index of apoptosis), and the effect on myocardial contractility. Adapted by permission of the National Academy of Sciences.\textsuperscript{2}

Figure 3. Comparison of cardiac parameters in wild-type mice (left), (Untreated/ACS-tg) (middle), and ACS transgenic mice treated with AdCMV–leptin (Treated/ACS-tg) (right). A, Gross appearance of a representative heart from each group. The heart of an AdCMV–β-gal-treated mouse (ACS-β-gal) exhibits striking enlargement with a dilated left atrium, whereas that of an AdCMV-leptin-treated mouse (ACS-Lep) appears normal. B, Comparison of the myocardial histology of 10-week-old wild-type (a), untreated ACS transgenic (b), and treated ACS transgenic (c) mice. Hematoxylin/eosin stain showing myofiber disorganization, cardiomyocyte enlargement, and interstitial fibrosis (arrow) and inflammation in the untreated ACS transgenic heart. The heart of the ACS mouse appears normal (bar=40 μm). C, Electron microscopic appearance of myocardial cells of the 3 groups. Lipid vacuoles (arrows) are present in cardiomyocytes of the untreated ACS transgenic mice (b). None are noted in the other groups (bar=500 nm). D, A representative transthoracic echocardiogram from each of the 3 groups of mice. Adapted by permission of the National Academy of Sciences.\textsuperscript{28}
Presumably, this is through increased FA uptake, because the lipotoxic phenotype does not occur in the absence of the FA transporter, CD36.35

The similarity of the cardiac phenotypes in these different models of myocardial steatosis provides powerful support for the lipotoxic hypothesis, ie, that chronic nonoxidized surplus of FA injures normal cells irrespective of the mechanism of the surplus.

**Lipotoxicity and Lipoapoptosis**

Measurement of the ectopic TG content of an organ may provide a useful index of the degree of lipid overload, but neutral TGs are probably harmless to cells, and, at least initially, they may provide a protective buffer by diverting FFAs from deleterious pathways.36 Ultimately, however, hydrolysis of excessive TG stores expands the FFA pool and provides additional substrate for harmful FFA pathways. In cells of certain tissues, such as pancreatic islets, and possibly cardiomyocytes,2,27 the ceramide pathway seems to be an important destructive route, at least in the tissues of the leptin-insensitive ZDF rat.

Ceramide may be formed by hydrolysis of sphingomyelin,30,40 de novo synthesis via condensation of palmitoyl CoA and serine,41 glycosphingolipid breakdown, or conversion of other sphingolipids.42 De novo synthesis seemed to be the dominant mechanism in the pancreatic islets of ZDF rats. These islets exhibit increased expression of the mRNA of serine palmitoyl transferase,37,38,41 the enzyme that catalyzes the first step in de novo ceramide biosynthesis, the condensation of palmitoyl CoA and serine to form dihydrosphingosine (Figure 4), and incorporation of 3H-palmitate or 3H-serine into 3H-ceramide is increased,37 providing strong evidence for de novo ceramide synthesis. Ceramide also induces apoptosis in cardiomyocytes.43

Ceramide has multiple actions that may contribute to lipid-induced demise of β-cells. It activates stress-activated protein kinases, such as jun kinase, and protein phosphatases, such as PP2A. PP2A inactivates protein kinase Cα44,45, Akt,46–48 and the antiapoptotic factor Bcl2.49,50 The down-regulation of the Akt/protein kinase B antiapoptotic pathway51 may be important in both cardiotoxicity52 and insulin resistance.53 There is evidence that ceramide may upregulate inducible NO synthase in islets54 and other cells.55–57 In islets, the apoptosis associated with inducible NO synthase upregulation can be inhibited by the inducible NO synthase inhibitors, aminoguanidine and nicotinamide.54 The damage to cells, including cardiomyocytes,57 from increased NO production may be mediated by the formation of peroxynitrite.58 In pancreatic islets, the lipid-induced increase in NO and the apoptosis are both blocked by inhibiting ceramide synthesis with fumonisin B1,37 and the same effect has been demonstrated in cardiomyocytes.59 Other reactive oxygen species may also be involved.56,60,61 In normal weanling rats fed a high-fat diet, impairment of cardiomyocytes function and mitochondria occurs without apoptosis.62

The fact that high levels of long-chain fatty acids and ceramide can give rise to both insulin resistance and apoptosis implies that insulin resistance interferes not only with insulin-mediated glucose regulation but also with insulin-mediated anti-apoptotic survival signals.63–65 (Interestingly, there appears to be a dichotomy between resistance to these actions of insulin and the lack of resistance to its lipopenic action, without which the lipid overload could not occur.66) This could be extremely important clinically, because prophylactic lipopenic intervention to reduce insulin resistance should also prevent organ damage.

Because cardiomyocytes are terminal cells that cannot be replaced, a continuous dropout of cardiomyocytes, at even a slow rate, will ultimately leave the heart less able to meet the increased workload required to perfuse the enlarging adipose tissue mass of the body during physical activity and, ultimately, even at rest. Thus, a low level of apoptosis of cardiac tissues can, more than time, substantially deplete the functional capacity of the heart. Remarkably, in obese ZDF rats, the early treatment with a thiazolidinedione, beginning at 7 weeks of age, reduced myocardial TG levels measured both biochemically and by morphometry of lipid droplets, lowered ceramide content, and prevented the loss of contractile function of the heart (Figure 2).2 Similarly, in the transgenic model of FA overload induced by cardiomyocyte-specific
ACS overexpression, lipotoxic cardiomyopathy was completely prevented by both leptin treatment (Figure 3) and α-lipoic acid therapy. Thus lipotoxic cardiomyopathy may be a completely preventable disorder.

Measurements of Myocardial Triglycerides in Humans Using Magnetic Resonance Spectroscopy

Given the shockingly high prevalence of obesity in humans, it is natural to wonder how much of the lipid excess in such patients has invaded their cardiomyocytes and whether cardiac steatosis impairs myocardial function as it does in rodents. Although morphological evidence of cardiomyocytes steatosis has been reported in an obese man (Figure 1), the most persuasive evidence proving that lipid overaccumulation occurs in human organs has been obtained noninvasively using magnetic resonance spectroscopy (MRS). The importance of in vivo myocardial triglyceride measurements has long been recognized. The technological advances of the past decade solved the major problems in studying myocardial steatosis in the beating human heart. Now, localized MRS provides a precise and reproducible tool for in vivo quantification of intracellular TG in human organs. MRS distinguishes between depots of TG in adipose tissue cells (fat surrounded by fat) and TG droplets stored in the cytosol of parenchymal cells (fat surrounded by cytosol).

The perpetual myocardial and respiratory motions greatly complicate the MRS procedure in the heart but can be minimized with a combination of cardiac and respiratory triggering applied during MRS signal acquisition. As described earlier, myocardial TG content in humans is assayed when the myocardium is contracted in end systole and when interaction of the heart and lungs is minimal (end exhalation). The experimental setup for myocardial TG evaluation by MRS is illustrated in Figure 5A.

To validate the MRS technique for measurements of myocardial TG to cross-sectional and interventional clinical studies, we conducted a series of initial testing experiments. First, we compared myocardial TG values obtained by MRS with those obtained by direct biochemical assessment in ex vivo and in vivo rodent studies and found that they correlated. Second, we demonstrated that in healthy individuals, myocardial TG levels measured by MRS were highly reproducible over hours, days, and months. These results clearly suggested that the method could serve as a clinical research tool in prospective intervention trials. Third, we showed that myocardial TG content increases progressively with body mass index. The relationship between body mass index and myocardial TG was continuous and without cutoff or deflection points, but the interindividual variability appeared high, suggesting that adiposity is not the sole determinant of TG deposition in human myocardium.

We also tested the impact of a single fatty meal on myocardial triglyceride levels. It does appear that a meal containing 50 g of fat does not alter myocardial TG contents measured 4 hours after meal consumption, despite persistent elevations of serum TG levels. On the other hand, 48 hours...
of fasting resulted in a dramatic elevation of myocardial TG levels\(^7\) that was transient, returning to normal when feeding resumed. We attributed this finding to increased myocardial uptake of FFAs released from adipose tissue during fasting and their subsequent esterification to TGs. It is important to distinguish this transient accumulation of myocardial TGs in nonobese persons during fasting-induced elevations in plasma FFAs, from the persistently elevated ectopic lipid content in the hearts of obese individuals. In obesity, the enlarged adipocyte mass coupled with resistance to the antilipolytic effects of insulin are the likely causes of the chronically elevated plasma FFA levels.

A shift in myocardial substrate utilization is another potential lipid-induced cause of functional impairment of the myocardium.\(^8\) A healthy heart selects the most efficient substrate for the energy production and is able to switch substrates for oxidation according to the availability of substrates and oxygen.\(^7\) This is often referred to as “a metabolic flexibility” of myocardial tissue.\(^7\) The mechanisms for substrate switching are complex and engage regulation of genes and hormones involved in fatty acids metabolism. A fatty heart, on the other hand, produces the energy mostly through the oxidation of FFAs, a process requiring high oxygen consumption. Moreover, fatty heart loses the ability to switch substrates between FFAs and glucose in cases of high glucose availability or oxygen deficiency. This defect in the fatty heart is postulated to lead to reduced myocardial contractility.\(^8\) Indeed, in our study of healthy individuals with various levels of obesity and with normal ejection fraction, the contractile function of myocardium measured by MRS was the lowest in individuals with the highest myocardial TG levels, as illustrated in Figure 5B (left).\(^1\) This observation suggests that high myocardial TG levels herald contractile dysfunction in humans. Interestingly, in the same group of individuals, we observed that persons with elevated myocardial triglyceride levels developed concentric hypertrophy of the left ventricle (Figure 5B, right).

**Cardiac Steatosis in Overweight Patients With and Without Impaired Glucose Tolerance and Type 2 Diabetes**

A growing body of research in obese rodents indicates that ectopic lipid deposition occurs in relative synchrony in nonadipose organs throughout the body, including skeletal muscle, heart, liver, and pancreas. In humans, intramuscular\(^76–78\) and intrahepatic\(^79–81\) lipid elevations are thought to be implicated in the insulin resistance associated with type 2 diabetes (T2D).\(^82\) It has been proposed that parallel lipid deposition in the pancreatic islets may also cause lipotoxic beta-cell loss and T2D.\(^83\)

To determine in humans the relationship between myocardial TG content and a clinical indicator of carbohydrate tolerance, we compared myocardial TG content in a cross-section of 134 individuals consisting of lean controls and obese persons with normal glucose tolerance, with impaired glucose tolerance, or with overt T2D.\(^84\) The study indicates that cardiac steatosis precedes impaired glucose tolerance and the onset of frank T2D (Figure 6A).

Our observations also indicate that cardiac steatosis is associated with impaired left ventricular filling dynamics and accompanied by other components of the metabolic syndrome, including hepatic steatosis, in patients with impaired glucose tolerance and T2D (Figure 6B). Interestingly, we detected a significant relationship between myocardial TG and plasma FFA levels in this cohort. Namely, the area under the FFA curve during oral glucose tolerance test was predictive of myocardial TG levels. The correlation between plasma FFAs and myocardial TG was moderate in the fasting state \(r^2=0.12\) and was strongest at 60 minutes postprandially \(r^2=0.33\). This observation is consistent with observations showing that accumulation of TGs in the myocardium is related to FFA exposure and generalized ectopic fat excess.\(^85,86\) In ZDF rats, initiation of antilipotoxic treatment before any significant ectopic lipid accumulation completely prevented the cardiac dysfunction and all other associated pathology.\(^2\)

Thus far, the preliminary human research of fatty heart confirms findings from basic research in animals and suggests that myocardial TG levels may serve as an early biomarker for future lipid-induced myocardial dysfunction. Extrapolation of results from relatively small population samples to a general population is always hazardous. However, if the findings in the “healthy” obese group depicted in Figure 6 were representative of the American population at large, they would imply that at least 30% now have undiagnosed fatty heart with subtle functional impairment. Although it is hoped that this grim extrapolation is not valid, it would nevertheless be prudent to develop strategies to reduce this risk.

**Treatment Options and Patient Selection**

Maneuvers that reduce ectopic deposition of lipid appear to prevent lipotoxicity in rodent models of obesity. This in-
in vivo treatment of prediabetic fa/fa ZDF rats prevents both T2D88 and lipotoxic cardiomyopathy,2 although their use in humans cannot now be recommended.89 It seems imperative to begin the lifestyle modifications that prevent this form of heart disease in early childhood.

The Table provides a partial list of antilipotoxic interventions. It should be stressed that stringent lifestyle modification with regulation of caloric intake to reduce lipid influx, coupled with a rigorous exercise program to increase FFA oxidation, is the ideal intervention. Pharmacologic intervention should be considered only when hypocaloric diet and exercise do not achieve treatment goals of eliminating ectopic lipid deposition.

A chronic disease caused by an aberrant lifestyle almost certainly reflects patterns imprinted in early childhood. Optimal prevention of lipotoxic myocardial disease will undoubtedly require antisteatotic intervention early in life, just as optimal prevention of coronary artery disease requires early antihypercholesterolemic intervention.90

Avoidance of the large quantities of fat and carbohydrate during the early years of life, when food preferences are developed, will be essential. In addition, restoration of the normal hyperactivity of childhood, unlimited by immobilizing electronic devices, will be vital. Unless the next generation can be reared in the lifestyle that prevailed before the onset of our current obesity pandemic, there is little reason to believe that we can prevent further enhancement in the incidence of obesity, fatty heart, and the accompanying morbidities observed in rodent models.

Summary

In summary, technological advances have made it possible to estimate the TG content of the heart and other organs. It has become increasingly clear that in humans, as in rodents, a caloric surplus leads to obesity and, in time, to ectopic lipid deposition and lipid-induced organ damage. Cardiac steatosis is accompanied by functional loss; this is prevalent in the overweight and obese population and may culminate in lipotoxic cardiomyopathy. The current failure to recognize fatty heart as a common clinical entity precludes the early intervention that was effective in rodents in preventing lipotoxic cardiomyopathy.

Sources of Funding

L.S.S. was supported by NIH/National Heart, Lung, and Blood Institute K-25 award HL-68736 and American Diabetes Association Innovation award IN 27. The study was also partially supported by United States Public Health Service General Clinical Research Center grant M01-RR00663 from NIH/National Center for Research Resources–Clinical Research. L.O. was supported by the Swiss National Science Foundation. R.H.U. was supported by grants from the National Institute of Diabetes and Digestive and Kidney Diseases, the Department of Veterans Affairs Merit Review, and the Juvenile Diabetes Research Foundation.

Disclosures

None.

References


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Circ Res. 2007;101:759-767
doi: 10.1161/CIRCRESAHA.107.160457

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