EFFECT OF WEIGHT LOSS ON MYOCARDIAL LIPID CONTENT AND CARDIAC INDICES IN THE OBESE

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ABSTRACT.

Study purpose: The incidence of overweight and obesity has increased in the United States with substantial impact on morbidity and mortality. In addition to its association with hypertension, diabetes, and coronary artery disease, obesity has more recently been linked to osteoporosis, sleep apnea, cancer, and congestive heart failure. Studies have shown that obesity increases the risk of heart failure, independent of other associated risk factors. However, the mechanism for this phenomenon is incompletely understood. In animals and humans, body mass index is correlated with myocardial lipid content. Elevated myocardial lipid content is associated with remodeling and systolic dysfunction and, in rodent models, with the development of heart failure. The purpose of this study is to determine whether weight loss in obese humans leads to a reduction in myocardial lipid content and to examine how weight loss affects indices of systolic and diastolic function.

Study subjects and method of recruitment: This study will enroll 50 obese females, with initial body mass index between 30 and 35, and age between 25 and 45. Exclusion criteria will include smoking, pregnancy, obesity of duration less than one year, excess alcohol consumption, illicit drug use, dyslipidemia, valvular or ischemic heart disease, pulmonary hypertension, known heart failure, inability to walk for 6 minutes, ejection fraction <45%, diastolic dysfunction, left ventricular hypertrophy, hypertension, diabetes, and use of cardioactive medications. Subjects will be recruited from the Columbia University Medical Center Adult Internal Medicine Clinic. Fliers will be distributed to all physicians in the clinic outlining the study and asking that they offer any patients thought to meet the study criteria the opportunity to be evaluated for enrollment in the study.

Study procedures: Patients who meet the study criteria will be invited to participate. They will be admitted to the Columbia University Irving Center for Clinical Research, where they will stay for the duration of the study. Subjects will have their caloric requirement calculated to maintain their initial body weights and will then be placed on a diet to maintain this weight for 4 weeks. Following the maintenance phase, subjects will be placed on an 800 calorie/day diet until they lose 10% of their initial weight, after which they will be placed on a diet to maintain this weight loss over 4 weeks. Each subject will have a transthoracic echocardiogram, exercise nuclear stress test, and cardiac magnetic resonance spectroscopy done prior to the weight loss phase and following the weight loss and maintenance phase.

Issues: The anticipated duration of the study is 10-12 weeks for each patient. The study requires that subjects stay as inpatients for the duration of the study. They will be compensated with a monetary payment. Subjects will need to provide informed consent, which will include demonstrating an understanding that this is a research study designed to further scientific knowledge, with no therapeutic intention.

A. Study purpose and rationale:

Overweight and obesity have reached epidemic proportions in the United States. Obesity has had a significant impact on morbidity and mortality. The adverse health consequences of obesity are typically thought to result from diabetes, hypertension, dyslipidemia, and coronary artery disease, a constellation of conditions termed the metabolic syndrome (Kopelman, 2000). Obesity has also been linked to osteoporosis, gallstones, sleep apnea, cancer, and congestive heart failure (CHF). CHF is one of the leading causes of medical cost as well as morbidity and mortality in this country. Identification and management of risk factors are critical for managing this debilitating disease.

Analysis of a large cohort from the Framingham Heart Study showed that increased BMI increases the risk of heart failure, even after accounting for known associated risk factors (Kenchaiah, 2002). Using a Cox proportional hazards model, this study showed that following adjustment for established risk factors, the risk of heart failure increased by 5% in men and 7% in women for each increment of 1 in body mass index (BMI). The mechanism for this phenomenon is incompletely understood.

Studies of young obese women, without other comorbidities, have shown associations between systolic and diastolic indices and BMI. One large study of 82 obese women and 80 lean controls without hypertension, cardiovascular complaints, or pulmonary disease showed a statistically significant association between BMI and left ventricular (LV) mass (Crisostomo, 2001). Subsequent large studies demonstrated a close link between obesity and concentric LV remodeling as well as impaired systolic and diastolic dysfunction (Peterson, 2004; Wong, 2004). These and other clinical studies have pointed to the existence of an obesity cardiomyopathy, the pathophysiological basis of which is becoming increasingly well delineated (Alpert 2001a). The initial adaptation to excessive adipose tissue is increased blood volume and increased cardiac output, secondary to increased stroke volume. Systemic vascular resistance falls to allow for increased cardiac output. Increased cardiac output also leads to ventricular dilatation. Over time, left ventricular dilatation causes increased wall stress, leading to compensatory eccentric hypertrophy. At a certain point, remodeling can no longer accommodate increased wall stress, leading to left ventricular failure. LV failure increases the load on the right ventricle and, in concert with sleep apnea and obesity hypoventilation, can lead to RV failure. Obesity can also be associated with filling defects and the development of diastolic heart failure. At present, the best known way to arrest and manage this process involves weight loss and treatment of comorbid conditions (Alpert 2001b).

Available studies indicate that there is substantial heterogeneity in the progression of obesity cardiomyopathy. Identification of markers of preclinical disease may provide opportunities for treating at risk individuals before the process becomes irreversible. Obese individuals are well known to accumulate myocardial lipid, in the same manner as they develop hepatic steatosis. This was described as early as the 19th century by Laennec (Bedford, 1972). A subsequent body of work has suggested that myocardial lipid accumulation is toxic and may be crucial in the development of obesity cardiomyopathy (McGavock, 2006). A rodent model of obesity has been found to have increased myocardial triglyceride content along with eccentric LV remodeling and decreased systolic function (Zhou, 2000; Paradise, 1985). To dissect whether these findings are secondary to obesity or its sequellae, non-obese mouse models of myocardial lipid accumulation have been generated and shown to develop features of cardiomyopathy (Chiu, 2001; Cheng, 2004). In one such model, treatment with the hormone leptin can reverse the cardiac defects, supporting the hypothesis that leptin acts, in part, to prevent toxic lipid accumulation in peripheral tissues (Unger 2005).

Extension of these findings to humans had previously been limited to autopsy studies or has required biopsies, precluding the measurement of myocardial lipid content in a broad clinical setting. In the last several years, non-invasive magnetic resonance spectroscopy techniques have been developed to precisely and reproducibly quantitate myocardial lipid (Szczepaniak, 2001). Similar methods have been developed and validated for liver and muscle. This method was first applied using *ex vivo* heart tissue from obese and lean rats, in which quantitation as measured by fat/water percentage was significantly correlated with measures based on biochemical analyses ($r^2 = 0.94$, $p < 0.001$). Following this validation,

this method was then applied to humans, where epicardial and myocardial lipid could be distinguished by spectra. This method was found to be highly reproducible inter-subject as well as intra-subject over hours, days, and months. Use of this technique in human subjects over a wide range of BMI has demonstrated that even those of normal adiposity have detectable myocardial lipid (Szczepaniak, 2001). Moreover, BMI and myocardial lipid content follow a statistically significant linear correlation (Reingold, 2006). This group further showed that myocardial lipid content is significantly positively correlated with LV mass and concentricity index, and significantly negatively correlated with percentage systolic thickening (Szczepaniak, 2001). In a separate experiment using biopsy specimens, obese humans were found to have myocardial lipid content roughly five-fold that in lean controls as well as reduced expression of genes involved in contractile function (Sharma, 2004).

In aggregate, studies in animals and humans indicate a significant relationship between myocardial lipid content and BMI. Elevated myocardial lipid content is associated with remodeling, systolic dysfunction, molecular changes, and in rodents, with overt heart failure. This study has been developed to address whether weight loss in obese humans leads to a reduction in myocardial lipid content and, if so, whether this affects indices of systolic and diastolic function.

B. Study design and statistical analysis:

This study will prospectively enroll 50 obese females, with initial body mass index between 30 and 35 and age between 25 and 45. A detailed list of inclusion and exclusion criteria and means of recruitment are detailed below in sections (G) and (H). There will only be a single group of patients, analyzed before and after weight loss.

The primary endpoint of this study will be to determine whether weight loss causes a significant reduction in myocardial lipid content. Based on a previous study, the reported lipid contents vary over a roughly 3-fold interval (Szczepaniak, 2001). In a subsequent study, this group showed that this method could detect a statistically significant change of 311% with a standard deviation of 117% (Reingold, 2006). This 311% change is the only previously reported difference assessed with this technique. As the current protocol has the aim of detecting any meaningful difference and given that it is not clear, at this point, how much of a difference might be clinically meaningful, this study has been designed to detect a 50% difference. A power calculation done for a single group using a paired t-test indicates that 46 subjects will be needed to detect a 50% difference with a standard deviation of 117%, with an α of 0.05 and a β of 0.80. Given the possibility of subjects dropping out of the study, an attempt will be made to enroll 50 individuals. Secondary endpoints will include echocardiographic measurements such as ejection fraction, LV mass, concentricity index, systolic thickening, and E/A ratio.

C. Study procedure:

Patients who meet the study criteria will be invited to participate. Following the provision of informed consent, they will be admitted to the Columbia University Irving Center for Clinical Research, where they will stay for the duration of the study. Subjects will have their caloric requirement needed to maintain their initial body weights calculated and placed on a diet to maintain this weight for 4 weeks. Following the maintenance phase, subjects will be placed on an 800 calorie/day diet until they lose 10% of their initial weight, after which they will be placed on a diet to maintain this weight loss over 4 weeks. A similar paradigm has previously been reported by Rosenbaum *et al.* (2005) and is still being used in an ongoing IRB protocol by this group.

Each subject will have a transthoracic echocardiogram, exercise nuclear stress test, and cardiac magnetic resonance spectroscopy done prior to the weight loss phase and following the weight loss and maintenance phase. Myocardial lipid content as well as parameters of systolic and diastolic function will be compared pre- and post- weight loss. The echocardiograms, stress tests, and magnetic resonance

studies will each be read by the same, single operator who will be blinded to patient identification and clinical parameters.

The anticipated duration of the study is 10-12 weeks for each patient and the entire study of 50 patients could likely be completed within 1 year. The study requires that subjects stay as inpatients for the duration of the study. They will be compensated with a monetary payment. Other than the inconvenience of a prolonged inpatient stay and consumption of a liquid diet, this study does not make use of any interventions or tests that place participants at any risk. Subjects will need to provide informed consent, which will include demonstrating an understanding that this is a research study designed to further scientific knowledge, which has no therapeutic intention.

D. Study drugs

Not applicable.

E. Medical device

Not applicable.

F. Study questionnaires

Not applicable.

G. Study subjects

Inclusion criteria are female sex, BMI between 30 and 35, and age between 25 and 45. Exclusion criteria will include the following: smoking, pregnancy, obesity of duration less than one year, excess alcohol consumption (more than 3 units of alcohol per week), illicit drug use, dyslipidemia, valvular or ischemic heart disease, pulmonary hypertension, known heart failure, inability to walk for 6 minutes, ejection fraction <45%, diastolic dysfunction, left ventricular hypertrophy, hypertension, diabetes, and use of cardioactive medications.

H. Recruitment of subjects:

Subjects will be recruited from the Columbia University Medical Center Adult Internal Medicine Clinic. Fliers will be distributed to all physicians in the clinic outlining the study and asking that they offer any patients thought to meet the study criteria the opportunity to be evaluated for enrollment in the study. Patients interested in enrolling in the study will be screened by the study's director to ensure they meet eligibility criteria. If so, after providing informed consent, all patients who have not had a transthoracic echocardiogram and an exercise nuclear stress test in the past 6 months, will have these tests done with the understanding that they will not qualify for the study should they fulfill any of the above exclusion criteria.

I. Confidentiality of study data

All data will be coded and maintained in a secure location to ensure absolute confidentiality.

J. Potential conflict of interest

There are no conflicts of interest.

K. Location of the study

This study will be conducted in the Columbia University Medical Center Irving Center for Clinical Research.

L. Potential risks

This study does not have any foreseen risks. Patients may experience discomfort from prolonged hospitalization and consumption of an all liquid diet.

M. Potential benefits

The study director will explain to all participants that they may obtain no benefit from their enrollment in the study. Furthermore, this study makes no commitment that the weight loss achieved will be lasting. Potential benefits include advancing scientific knowledge, weight loss, and improved health.

N. Alternative therapies

Not applicable.

O. Compensation to subjects

Subjects will be compensated at 50 dollars daily to be received on a bi-weekly payment schedule.

P. Costs to subjects

Not applicable.

Q. Minors as research subjects

Not applicable.

R. Radiation or radioactive substances

Not applicable.

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