Assessment of Myocardial Damage by Cardiac MRI in Patients with Anorexia Nervosa

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ABSTRACT
Objective: Cardiac damage is a major complication of anorexia nervosa (AN). The present study evaluated the prevalence of myocardial damage in patients with AN by cardiac magnetic resonance imaging (CMR).

Method: This study was cross-sectional and observational. Forty consecutive female patients with a diagnosis of AN and 28 healthy female subjects were evaluated from January 2007 to 2011 at the Department of Psychiatry (University of Istanbul, Istanbul, Turkey). Following enrolment in the study, participants underwent a cardiac evaluation, a physical examination, a standard electrocardiogram (ECG), an echocardiography and a CMR.

Results: Body weight, body mass index and heart rate values were lower in patients with AN than in the control group. When compared with control groups, patients with AN showed reduced left ventricular mass with normal systolic function. Compared to control subjects, patients with AN had higher prevalence of pericardial effusion (30% in the AN group, 4% in the control group, \( p = .005 \)) and mitral valve prolapses (23% in the AN group, 4% in the control group, \( p = .03 \)). Myocardial fibrosis (detected as late gadolinium enhancement on CMR) was found in 23% of patients with AN. Myocardial fibrosis was not detected in any control subject (\( p = .007 \)).

Conclusion: A strong association was found between myocardial fibrosis and AN. Cardiac damage of myocardial fibrosis in asymptomatic patients with AN can be found by CMR examination.

Keywords: anorexia nervosa; myocardial damage; cardiac magnetic resonance imaging; sudden death; late gadolinium enhancement; echocardiography

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Introduction
Anorexia nervosa (AN) is a serious and complex disorder characterized by fear of weight gain, voluntary restriction of caloric intake, distorted self-image that can have devastating health consequences and amenorrhea. AN affects 0.3–0.7% of young women worldwide.1, 2 Cardiovascular complications are relatively common and have been reported in up to 80% of patients with AN, primarily in the form of bradycardia, hypotension, arrhythmias, reperfusion abnormalities, cardiac failure, silent pericardial effusion, and sudden death (SD).3–5 In addition recent study showed that anorexic patients with pericardial effusion had a significantly lower BMI than those without PE.6 However the data concerning the reversibility of cardiac abnormalities after refeeding are limited, recent studies observed a significant improvement in functional and structural abnormalities after treatment and weight recovery.6–9 In these studies, follow-up echocardiographic examination showed an increase in cardiac chambers, left ventricular mass and wall thickness and PE resolved with nutritional support. SD in patients with AN suggests that cardiac involvement may contribute to the high mortality rate. Several studies have shown that approximately 30% of deaths in patients with AN result from cardiac complications.10–12 For this reason, the ability to detect cardiac involvement during the asymptomatic period in patients with AN would be clinically relevant from diagnostic, therapeutic, and prognostic perspectives.

Research in recent years has focused on QT interval prolongation, changes in cardiac diameter and myocardial mass detected using echocardiography. However, echocardiographic studies on left ventricular (LV) function in patients with AN have yielded conflicting results.13, 14 Small myocardial scars are overlooked by nuclear scintigraphy and segmental wall motion abnormalities cannot be detected by echocardiography.
Cardiac magnetic resonance imaging (CMR) is considered the “gold standard” imaging technique for detection and quantification of myocardial damage such as transmural and subendocardial fibrosis.\textsuperscript{15}

The present study evaluated cardiac function and myocardial damage in patients with AN using standard echocardiography and CMR. To our knowledge, this is the first study to investigate silent cardiac involvement using CMR in patients with AN.

\section*{Methods and Study Population}

The cross-sectional study consisted of 40 female patients with AN who were consecutively admitted to the Eating Disorders Program, Department of Psychiatry, Istanbul School of Medicine at Istanbul University between 2007 and 2011. All patients had been applied an psychiatric examination by two experienced psychiatrists and diagnosed with AN according to four criteria as defined in the \textit{Diagnostic and Statistical Manual of Mental Disorders} (Fourth Edition, Text Revision) (DSM-IV-TR): (1) refusal to maintain weight within a normal range for height and age (i.e., having <85\% of expected body weight); (2) fear of weight gain despite being underweight; (3) severe body image disturbance in which body image is the predominant measure of self-worth, with denial of the seriousness of the illness; (4) in postmenarcheal females, absence of the menstrual cycle, or amenorrhea (>3 cycles). There is no formal research interview for psychiatric examination; we applied the part of eating disorders of DSM-IV to the patients in a detailed manner.\textsuperscript{16} The control group consisted of 28 age-matched healthy females with a body mass index (BMI) range of 18–22 kg/m\textsuperscript{2}. Participants were recruited from a medical vocational high school and a school of medicine in Istanbul/Turkey. Controls were free of an eating disorders, assessed using the DSM-IV criteria for Anorexic and Bulimic eating disorders by two experienced psychiatrists. Following enrollment in the study, participants were applied a semistructured interview form including socio-demographic characteristics and they underwent a cardiac evaluation, a standard electrocardiogram (ECG), an echocardiography and a CMR. Biochemical analyses were performed on all participants. A glomerular filtration rate (GFR) was measured according to Cock Croft-Gault formula. All patients in the AN group were studied during the overt phase of the disease when BMI was <18 kg/m\textsuperscript{2}. Patients were excluded from study if they had any history of psychotic disorder, mental retardation, cognitive impairments, and history of cardiovascular disease, chronic disease or undergoing pharmacological treatment and abuse of alcohol and other substances. The study was approved by the ethics committee of Istanbul School of Medicine, Istanbul University. All patients provided written informed consent.

\section*{ECG}

ECGs were recorded using a standard resting 12-lead ECG at a paper speed of 25 mm/sn. Heart rate was calculated using the average RR interval. QT intervals were corrected using the Bazett formula (QTc). A QTc interval above 440 ms was considered to be prolonged.

\section*{Echocardiography}

Echocardiography was performed using the Vivid 7 echocardiography device (General Electrics, Milwaukee, WI) using a middle-range frequency (3–8 MHz) broadband transducer. We examined the motion of the mitral valve leaflets in the parasternal long axis view to identify billowing or prolapse. Diameters and ejection fraction were calculated according to American Society of Echocardiography guidelines. A pulsed Doppler transmitral flow velocity profile was obtained from the apical four-chamber view, and the sample volume was positioned just below the mitral valve leaflets. The following parameters were assessed: peak transmitral flow velocity in early diastole (peak E), peak transmitral flow velocity in late diastole (peak A), and E/A ratio.

\section*{CMR}

CMR was performed using a dedicated 1.5 T scanner (Siemens 1.5 T Symphony, Erlangen, Germany) with an eight-channel cardiac phased-array coil. IV end-systolic and end-diastolic volume and maximal wall thickness were traced and recorded from the short axis and long axis views of the standard ECG-gated steady state-free precision cine MRI sequence from the atrioventricular ring to the apex. Typical imaging parameters were slice thickness 6 mm, gap 4 mm, TE 1.3 ms, flip angle 10°, matrix 256 × 205, 160 time frames, and temporal resolution 28–38 ms. Volumes and mass were indexed to body surface area (BSA).

Myocardial fibrosis was evaluated using late gadolinium enhancement (LGE). Briefly, LGE images were acquired 15 min after administration of gadolinium-diethylenetriaminepentaacetate (Magnevist, Schering-AG, Berlin, Germany, 0.2 mmol/kg) in the short axis and long axis views using a T\textsubscript{1}-weighted fast low-angle shot, three-dimensional inversion-recovery pulse sequence. The physiological basis of the LGE of myocardial fibrosis is based upon the combination of an increased volume of distribution for the contrast agent and a prolonged washout related to the decreased capillary density within the myocardial fibrotic tissue. The increase in gadolinium concentration within fibrotic tissue causes T\textsubscript{1} shortening which appears as bright signal intensity in the CMR image based on conventional inversion-recovery gradient echo sequences. Thus the discrimination between scarred/fibrotic myocardium and normal myocardium relies on contrast concentration differences combined with the chosen setting of the inversion-recovery sequence parameters. These parameters are set to “null” the normal myocardial signal that will appear dark in the final image relative to the bright signal of the scarred/fibrotic myocardium. The extent of fibrosis in the LGE image was quantified, as previously described, and tree patterns were defined as: (1) absence of fibrosis when myocardial enhancement was not detected, (2) transmural...
enhancement, and (3) subendocardial enhancement. The CMR data were analyzed according to the AHA/ACC 17-segment model. All cardiac images were analyzed using an independent observer blinded to all the data.

**Statistical Analysis**

Statistical analysis was performed with SPSS 19.0 for Windows (SPSS, Chicago, IL). Continuous data are expressed as the mean ± SD or median and range, and categorical data are expressed as percentages. The chi-square-test was used to assess differences between categorical variables among the groups. Student's t-test or Mann–Whitney U test was performed to compare unpaired samples. The results are presented as relative risks (RR) with the 95% (confidence interval (CI)). A p-value <.05 was considered statistically significant.

**Results**

**General Characteristics**

Weight, age, BMI, heart rate of the study participants are shown in Table 1. Body weight, BMI, heart rate values, GFR values and systolic–diastolic blood pressure values were lower in patients with AN than in the control group. The duration of the illness was 13 (range 1–120 months) months. Of the patients with AN, 31 were restricting and nine were purging. The use of ipecac was not reported by any of the patients. There were only four subjects with laxative use history in the remote past. Baseline potassium, sodium, magnesium, phosphorus, and calcium levels were within the normal range in all participants with no significant difference between groups (data not shown). In the baseline ECG evaluation, width of QRS, PR, and QT intervals were similar between groups (Supporting Information Appendix-Table 2).

**Echocardiography**

The echocardiographic measurements are shown in Table 1. Nine of 40 patients with AN and one subject in the control group had mitral valve prolapses (MVP), (RR = 7.8, 95% CI = 1.03–65, p = .03). We did not find color Doppler evidence of a moderate to severe mitral regurgitation jet in any participants. Echocardiography revealed silent mild to moderate pericardial effusion in 30% of the patients with AN and 4% of the control subjects (RR = 11.5, 95% CI = 1.4–95, p = .005). Statistical comparisons of anorexic patients with and without cardiac abnormalities showed that BMI, age, GFR and duration of illness were similar between the patients with and without cardiac abnormalities (Supporting Information Appendix-Table 3). The transmirtal E velocity, peak A velocity and E/A flow velocity ratio were similar between groups (Supporting Information Appendix-Table 2).

**CMR**

No adverse events occurred during cardiac imaging. CMR confirmed a normal LV ejection fraction in all study participants. Diastolic LV volume, systolic LV volume, wall thickness, and LV mass were significantly lower in the AN group, as compared to the control subjects (indexed to BSA), (Table 1).

**Myocardial Fibrosis**

LGE was detected in LV segments in nine patients (two segment involvement in two patients, one segment involvement in seven patients). The pattern of LGE was subendocardial in three and transmural in six patients. LGE was not detected in any control subject (p = .007). Statistical comparisons of anorexic patients with and without LGE showed that BMI, age, GFR and duration of illness were similar between the patients with LGE and without LGE (Supporting Information Appendix-Table 3).

**Discussion**

According to a recent meta-analysis, AN, at 5.1 deaths per 1,000 person-years, has the highest rate of mortality of any mental illness.17 Cardiac involvement in AN, an important predictor of mortality, may involve the myocardium, conduction system, vascular wall, or pericardium. Although up to 80% of patients with AN have been demonstrated to have cardiac involvement, none showed clinical manifestations.18 Thus, detection of cardiac involvement is critical for patients with AN. The purpose of the present study was to examine the clinical usefulness of routine CMR assessment for the early identification of subclinical myocardial damage in patients with AN.

Prior studies have demonstrated pericardial effusion in about 20–37% of adolescents with AN who required medical hospitalization for being severely underweight. In this study, echocardiography revealed silent
pericardial effusion in 30% of the patients vs. 4% of the controls ($p = .005$). Although we were unable to identify cause of pericardial effusion, our laboratory findings allowed us to rule out the inflammatory factors. MVP is frequent, with a prevalence of 0.6–2.4% in the general population\(^9\) and between 33 and 62% in patients with anorexia nervosa.\(^4\) The importance from MVP results from the association with arrhythmias and sudden death. In accordance with previous studies, we observed that MVP was more frequent among the patients with AN than the controls ($p = .03$). Several studies have shown that strict caloric deprivation has significant effects on cardiac structure and function.\(^4\) \(^8\) Our finding that diastolic and systolic LV volume, LV mass, and wall thickness were reduced in patients with AN. However, despite these structural changes, our findings, and those of several others, showed that LV systolic function was not impaired, as indicated by normal echocardiographic fractional shortening and ejection fraction, suggesting that the down-regulation of LV mass and wall thickness is not associated with abnormal LV function.\(^13\) \(^14\)

Cardiovascular complications in AN are potentially fatal and present in the early stages of the disease. In addition, these complications are reversible in most cases; thus, early diagnosis of cardiac damage, prompt treatment, refeeding in a timely manner, and correct cardiac monitoring is essential. Among current imaging modalities, CMR is considered the reference standard for the assessment of myocardial damage (necrosis and scar).\(^15\) This technique offers high spatial resolution imaging of pathophysiological processes related to myocardial infarction,\(^20\) \(^21\) and nonischemic heart disease\(^22\) that was previously achievable only by postmortem histopathological evaluation. Although myocardial edema and fibrosis have been previously reported in postmortem trials, our study is the first cross-sectional study to investigate noninvasive assessment of myocardial fibrosis using CMR in patients with AN. We showed that myocardial fibrosis was present in nine (23%) patients with AN (detected as LGE on MRI). The factors underlying myocardial fibrosis in AN are not well understood and several mechanisms have been postulated. AN causes diminished protein synthesis, myofibrillar atrophy, interstitial edema, mitochondrial swelling, vagal hyperactivity, decreased glycogen content, and deficient selenium, thiamine, and magnesium.\(^24\) Postmortem examination of hearts from animals and humans that died from starvation have demonstrated marked histological abnormalities, including vacuolation and fragmentation of myofibrils, replacement fibrosis, widened interstitial spaces and marked loss of muscle fibers.\(^25\)

The clinical significance of myocardial fibrosis in patients with AN remains a matter of debate. Previous studies have shown that myocardial fibrosis was clinically relevant as a predictor of mortality, morbidity, and SD, independent of ventricular function in patients with ischemic and non-ischemic heart disease.\(^26\) \(^22\) A strong positive association between cardiac fibrosis and incidence of SD in the clinical setting and growing experimental evidence suggest an important causal role for cardiac fibrosis in the development of ventricular arrhythmias. Several experimental studies have demonstrated that cardiac myocardial fibrosis, detected using CMR, is an independent predictor of ventricular arrhythmias.\(^23\) Several possible mechanisms have been proposed to link myocardial fibrosis and increased SD. Recent experimental evidence in isolated whole-heart studies indicate that fibrosis may modulate the formation and propagation of cardiac after-potentials that lead to triggered activity causing ventricular arrhythmias.\(^26\) \(^27\) Furthermore, increased fibroblast density in myocardial fibrosis may promote heterocellular coupling between cardiomyocytes and myofibroblasts, causing ectopic pacemaker activity, as shown in recent studies of co-cultures of cardiac myocytes and myofibroblasts.\(^28\) Although recent studies show that angiotensin converting enzyme inhibitors, angiotensin receptor blockers and spironolactone may reduce myocardial fibrosis in patients with hypertension, there are no specific treatments for myocardial fibrosis.\(^29\) \(^30\) In our study, myocardial fibrosis, which was found in 23% of the patients with AN, was detected in the absence of clinical signs of myocardial ischemia and failure. In the light of the above mentioned facts, LGE may be a predictor of mortality and morbidity in patients with AN.

There are some limitations of LGE CMR as a cardiac assessment methodology for AN. First, being placed in the MRI scanner can induce significant claustrophobia in about 5% of patients.\(^31\) In patients with very fast heart rates, or frequent irregular beats, ECG gating can prove unreliable. In addition; MRI technology was extremely complex and expensive. Although LGE CMR is the most accurate method to measure myocardial replacement fibrosis, its sensitivity is limited for the assessment of diffuse interstitial fibrosis. In LGE-CMR, image contrast relies on the difference in signal intensity between fibrotic and “normal” myocardium, and such differences may not exist if the process is diffuse. New technique of extracellular volume mapping appears promising to complement LGE imaging in cases of more homogeneously diffuse myocardial disease states which affect the myocardial extracellular space.\(^32\) This technique is based on measurement of the longitudinal relaxation time constant ($T_1$) both precontrast and postcontrast, and are calibrated using the value of hematocrit. Additionally, anorexia can lead to severe electrolyte disturbances (hypokalemia, hypophosphatemia, etc.), renal failure and alterations in water metabolism (like hyponatremia and edema).\(^33\) LGE may be influenced by these factors in particular by myocardial edema. In addition, contrast agent use in patients with impaired renal function can result in contrast nephropathy.

The primary limitation of our study is the cross-sectional design, which hampers interpretation of the cause-effect relationship. Further studies including follow-up data may provide important prognostic information in patients with AN.
Conclusion
Detection of LGE using CMR in patients with AN who have a high rate of cardiac involvement may be an important tool for early detection of myocardial involvement. We believe that further study of CMR in patients with AN is warranted.

References