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Pericardial Effusions in Adolescent Girls With Anorexia Nervosa: Clinical Course and Risk Factors

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The aim of this study was to evaluate cardiac, biochemical and endocrine differences between female adolescents with anorexia nervosa (AN) with and without pericardial effusions. We studied 128 female adolescents (9.8–17.7 years) with anorexia nervosa (AN) diagnosed according to DSM-IV (American Psychiatric Association, 1994) criteria. They all underwent an echocardiographic evaluation. In 29 patients (22.2 %) a pericardial effusion (ranging between ≥ 0.35–2.5 cm) was noted. None of the patients

were clinically symptomatic. After 3 months of refeeding, the effusions disappeared in 18/29 patients while in 7/29 patients a pericardial effusion > 0.3 cm persisted. Risk factors for development of effusions were a BMI ≤ 13,5 kg/m, weight loss ≥ 25% and IGF-1-level ≤100 ng/ml. Pericardial effusions are common in adolescent AN patients. They are mostly asymptomatic not requiring any intervention and spontaneously regress with refeeding. They are more common in the patients with the most significant weight loss.

INTRODUCTION

Eating disorders, especially anorexia nervosa (AN), are occurring with increased incidence in young adolescent girls. Anexoria Nervosa is a potentially life-threatening disorder associated with significant morbidity but also mortality. About one third of the mortality is cardiac-related as cardiac complications are an important feature of this disorder (Isner et al., 1985). Cardiac abnormalities which have been described include thinning of the left ventricular walls, reduced left ventricular mass index, sinus bradycardia, significant QTc- prolongation (long-QT syndrome), mitral valve prolapse (with or without mitral regurgitation) and pericardial effusions. Most of the cardiac mortality is ascribed to the QTc prolongation and the risk for cardiac arrhythmia. Pericardial effusions have been reported in this population but the information on the incidence and clinical significance are relatively sparse (Frölich et al., 2001; Inagaki et al., 2003; Polli et al., 2006; Ramaciotti et al., 2003) Moreover there are no data regarding clinical or biochemical risk factors for pericardial effusions. Also data regarding the effect of treatment on pericardial effusions are limited. The purpose of the present study was to look at the incidence, clinical significance and the identification of clinical and biochemical risk factors for pericardial effusions in a large group of young adolescent girls diagnosed with anorexia. Moreover the effect of a refeeding strategy on pericardial effusions was studied.

PATIENTS AND METHODS

This study has a prospective design as all patients with AN admitted to our Eating Disorder Unit are scheduled to undergo an echocardiographic evaluation at admission and during follow-up (after 6 months and 1 year). In total 128 adolescent girls (9.8–17.7 years old), who were referred between September 2002 and April 2007 with the diagnosis of AN were included in the current study. The diagnosis was based on the *DMS-IV* criteria (American Psychiatric Association, 1994) was confirmed by two physicians including a child psychiatrist and a paediatric nutritionist. None of the patients had a

family history of cardiac diseases or of any systemic disease involving the cardiovascular system.

At admission all patients underwent a complete clinical examination by the same paediatric specialist in Adolescent Medicine. Blood samples were obtained for: blood urea nitrogen, creatinine, electrolytes, albumin, thyroid hormone, insulin growth factor 1, vitamin A D E C B serum levels, folic acid and minerals including iron, selenium, zinc and copper. Body mass index (kg/m^2) was calculated and curves and centiles were used as reported by Rolland-Cachera et al. (1991) All subjects underwent a two-dimensional Doppler echocardiocardiography (Vivid 7 GE, Horten, Norway) and a 12 lead electrocardiogram. On the ECG, QT intervals were manually measured in lead II and corrected for heart rate using the Bazett's (1920) formula ($QTc = QT/\sqrt{RR}$). QTc was also measured in the other leads and dispersion of the QTc-intervals was defined as the difference between the maximum and minimum QTc interval.

In each patient the voltage of T wave in V4 and the R wave in V6 was measured. Echocardiographic measurements of the left ventricular dimensions were performed based on M-mode measurements in the short axis at the level of the mitral leaflets. The standard Devereaux formula was used to calculate left ventricular mass (LVM) as recommended by the American Society of Echocardiography (Devereux & Reichek, 1977; Sahn et al., 1978). To account for linear growth and body mass, the measurements were corrected using the formula of de Simone et al. (left ventricular mass corrected = left ventricular mass /height $^{2.7}$; de Simone et al., 1992). The measurement of pericardial fluid was performed in systole and diastole. A pericardial effusion < 3 mm was considered a normal finding (Ramaciotti et al., 2003). An effusion larger than 3 mm in any part of the cardiac cycle, was considered to be abnormal.

Automated blood pressure measurements (Criticon Dynamap pro-100) were obtained on the right upper arm in a supine position after 5 minutes of rest and repeated three times with a 5 minute interval. Cuffs were adjusted for age and body size. Two cuffs were used: Ultra Check Blood Pressure Cuff Model U1826 Small Adult Range 18–26 cm for girls ≤ 10 years and the Dura Cuff Adult Cuff Johnson & Johnson Medical Inc. 23–33 cm for older girls (Arafat & Mattoo, 1999)

The study was approved by the Medical Ethical Committee from the institution and informed consent was obtained from all participants.

STATISTICAL ANALYSIS

Clinical, biochemical electrocardiographic and echocardiographic characteristics for patients with and without an effusion were compared. Variables were described as the mean ± standard deviation. Data were tested for normality by the Kolmogorov-Smirnov test. As normality could be demonstrated

for all variables the three groups were compared by a student's *t*-test. As the distribution of pericardial effusion size was skewed the measurements were log-transformed to obtain a normal distribution. The independent contribution of potential risk factors on the logarithm of pericardial effusion was then assessed by multiple linear regression analysis. The patients were divided into three groups (group 1: pericardial effusion ≤ 3 mm, $n = 99$ patients; group 2: minor pericardial effusion > 3–8 mm, $n = 19$ patients; group 3: moderate to large pericardial effusion > 8 mm $n = 10$ patients and data were compared using ANOVA with post-hoc correction. Data were analysed with the SPSS statistical software for Windows 13.0 (SPSSinc.). Differences were considered statistically significant if $p < .05$.

RESULTS

In total we identified a pericardial effusion (PE) in 29 of the 128 patients with AN (22.2%). In 19 patients the effusion was small (ranging 0.3–0.8 cm) while a moderate to large effusion (> 0.8cm) could be detected in 10 patients. None of the patients with PE had cardiovascular symptoms: no pericardial friction murmurs were detected on clinical examination. None of the patients had either clinical or echocardiographic signs of tamponade physiology. This explains why no interventions were required.

The clinical, biochemical, electrographic and echocardiographic characteristics of the patients with and without pericardial effusion were compared (Table 1). Regarding the clinical characteristics, the patients with an effusion were significantly younger but the difference was small (13.9 ± 1.1 year vs.14.6 ± 1.6 year). Patients with effusions had a significantly lower body mass index (BMI), lower left ventricular mass (LVM) and left ventricular mass index (LVMc), a lower heart rate (HR), and lower insulin growth factor-1 (IGF-1) levels. The blood urea nitrogen (BUN) was significantly higher in the group with effusions. All these clinical parameters indicated that patients with effusions were having more clinically severe weight loss and muscle wasting. Importantly no significant differences in systolic and diastolic blood pressure could be found. Also the electrocardiographic parameters including the voltage criteria and the QTc intervals were not significantly different between both groups. The ECG seems not to be predictive for the presence of pericardial effusions (Kossmann, 1953). Thyroid-stimulating hormone (TSH), free triiodothyronine (FT3) and free thyroxine (FT4) were not statistically significant between both groups. The euthyroid sick syndrome was found in 34.5 % of the patients in the pericardial effusion group versus 22.2 % in the group without effusion. In the non-effusion group one girl was diagnosed with hyperthyroidism due to Basedow-Graves disease.

The multiple linear regression analysis showed that BMI and left ventricular mass (LVM) were the most relevant parameters related to the presence of a pericardial effusion (Table 2). When the patient population was divided

TABLE 1 Different Characteristics Between the Group With and Without Pericardial Effusion

Variables	Group with effusion ($n = 29$)	Group without effusion ($n = 99$)	*p*-value
Age, yr	13.9 ± 1.1	14.6 ± 1.6	.03
BMI, kg/m	13.6 ± 1.1	15.8 ± 1.6	<.001
Weight loss, %	25.0 ± 9.0	19.3 ± 7.9	.002
HR, bpm	56 ± 16	63 ± 17	.04
SBP, mm Hg	96 ± 14	97 ± 12	.76
DBP, mm Hg	59 ± 9.5	59 ± 9.0	.79
QT, msec	395 ± 41	385 ± 35	.23
QTc, msec	376 ± 34	380 ± 27	.53
QTc dispersion, msec	34 ± 21	39 ± 22	.22
V4 (T wave), mm	$2,52 \pm 1,62$	$2,71 \pm 1,44$	.55
V6 (R wave), mm	$9,29 \pm 3,59$	$9,48 \pm 3,30$	.97
LVM, g	75.5 ± 17.2	89.6 ± 19.5	.001
LVM/height $^{2.7}$, g/m$^{2.7}$	26.2 ± 5.7	30.3 ± 5.6	.001
TSH, μU/L	1.9 ± 1.1	1.6 ± 0.9	.06
FT4, pmol/L	11.6 ± 2.0	12.2 ± 3.1	.30
FT3, pmol/L	3.8 ± 1.3	4.6 ± 1.8	.25
IGF-1, ng/ml	103 ± 63	143 ± 73	.02
Zinc, μg/dl	86 ± 13	85 ± 22	.97
BUN, mg/dl	35 ± 9.3	30 ± 9.6	.02
Creatinine, mg/dl	0.8 ± 0.1	0.8 ± 0.1	.60
Sodium, meq/L	142 ± 3.5	143 ± 2.1	.25

Note. Data are expressed as mean ± SD. Significant difference (at .05 level) by student-t-test. BMI: body mass index, LVM: left ventricular mass, TSH: thyroid-stimulating hormone, FT4: free thyroxine, FT3: free triiodothyronine, IGF-1: insulin growth factor-1, BUN: blood urea nitrogen, SBP: systolic blood pressure, DBP: diastolic blood pressure, HR: heart rate.

TABLE 2 Determinants of (Logarithm of) Pericardial Effusion: Multiple Linear Regression on the Whole Patient Group ($n = 128$)

	Linear regression coefficient	Standard error	*p*-value
Intercept	2.810	0.260	<.001
BMI, kg/m	−0.157	0.020	<.001
Weight loss, %	−0.001	0.003	.72
LVM, g	0.004	0.002	.21
LVM/height $^{2.7}$, g/m $^{2.7}$	−0.008	0.005	.15
IGF-1, ng/ml	−0.001	<0.001	.13
BUN, mg/dl	<0.001	0.002	.94
HR, bpm	−0.001	0.001	.59

BMI: body mass index, LVM: left ventricular mass, IGF-1: insulin growth factor-1, BUN: blood urea nitrogen, HR: heart rate.

into three groups related to the size of the effusion (group 1: pericardial effusion ≤ 3 mm, $n = 99$ patients; group 2: minor pericardial effusion > 3–8 mm, $n = 19$ patients; group 3: moderate to large pericardial effusion > 8 mm $n = 10$ patients), we found that BMI, LVM, LVMc, HR, IGF-1 and BUN were significant different in group 3.

After 3 months refeeding with a weekly weight gain of 500 grams, the effusion disappeared in 18 of the 29 patients. In 7 patients a pericardial effusion of >3mm persisted but never caused hemodynamic compromise. Four of the 29 patients with a pericardial effusion discontinued their therapy and were lost for follow-up.

DISCUSSION

In our large series of patients with AN, we detected a high incidence of pericardial effusions at presentation (22.2%) the majority having a small effusion (0.3–0.8 mm) and a small number of patients having a moderate to large effusion (> 0.8 mm). None of the patients was clinically symptomatic and required pericardial drainage. The presence of pericardial effusions was associated with more significant weight loss (lower BMI) and more significant cardiac muscle wasting (lower myocardial mass index). Most effusions regressed when refeeding and all patients remained clinically asymptomatic during follow-up. ECG criteria were not helpful in identifying patients with a pericardial effusion who could only be identified using echocardiography.

There are relatively few data available on the incidence and clinical significance of pericardial effusions in children with AN. The reported incidence of pericardial effusions ranges between 15 and 17% (Frölich et al., 2001; Inagaki et al., 2003; Polli et al., 2006; Ramaciotti et al., 2003), which is lower than the 22.2% reported in our series. This could be related to the systematic screening performed in this cohort and also the relatively strict criteria used to define a pericardial effusion. None of our patients were showing signs of hemodynamic compromise caused by the effusion. None of the patients had significant hypotension or pulsus paradoxus and none of the patients showed echocardiographic evidence of cardiac tamponade, suggesting the clinically benign nature of these effusions. In only one case reported in the literature a pericardiocentesis was performed in a 15-year-old AN patient with some signs suggesting tamponade physiology (limited right ventricular diastolic collapse; Polli et al., 2006). This confirms that this is a benign finding in this patient group and that this should be considered a normal finding in this patient population especially in those with more significant weight loss and cardiac muscle wasting. Patients with effusions have significantly lower BMI, significantly more weight loss and lower left ventricular mass index. Also in the multiple regression analysis these parameters were associated with the size of the pericardial effusion with larger effusions in those patients with lower BMI and ventricular mass index. These findings differ from Frölich et al. (2001), who were able not to demonstrate a correlation between the extent of pericardial effusion and the BMI. Consistent with our finding that lower BMI was a significant risk factor, we found that patients with pericardial effusions have the lowest levels of

IGF-1 and the highest BUN levels. This also indicates that patients with pericardial effusions have more severe forms of starvation and are more of the restrictive type.

Thus the presence of pericardial effusions seems a parameter for disease severity. This is probably due to the fact that the effusion is caused by the reduction in pericardial fat and myocardial muscle wasting resulting in a pericardium space that has become too large relative to the heart size. The extra space is just filled by pericardial fluid. Other potential explanations have been mentioned in the literature. Especially associated hypothyroidism was mentioned as a potential mechanism. In our study there were no difference in FT3, FT4 and TSH levels between those with and without effusions, suggesting that lower thyroid hormone levels cannot explain the occurrence of effusions. A higher proportion of our patients with effusions had low FT3 levels and were diagnosed with the "euthyroid sick syndrome" but this is not considered part of the clinical syndrome of hypothyroidism associated with pericardial effusions. Another hypothesis is that protein synthesis could be affected by extreme starvation resulting in decreased albumin and total protein levels (Frölich et al., 2001; Inagaki et al., 2003). Our biochemical data could exclude this hypothesis as all patients had normal serum albumin and total protein levels.

Consistent with our hypothesis that the effusions reflect the loss of myocardial fat and muscle is the observation that successful refeeding results in the resolution of the pericardial effusions in the majority of patients. Our follow-up data also confirm the benign nature of the finding at presentation as the effusion regressed during follow-up in nearly all patients.

An interesting observation in the current study is that the presence of pericardial effusions is not associated with ECG abnormalities. Low voltages of the R wave in V6 and the T wave in V4 were present in both groups (Kossmann, 1953). Also no ST-segment abnormalities were noted to be present in our patient group. This means that diagnosis cannot be made using electrocardiography and that an echocardiography should be performed especially in those patients with significant weight loss (> 25%).

We conclude from this study that pericardial effusions are a common benign finding in patients with AN and do not result in hemodynamic compromise. They are associated with more significant weight loss and cardiac muscle wasting. They regress upon refeeding the patients.

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