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Abstract
Anorexia nervosa, one of the more frequent and severe eating disorders, is a chronic psychiatric disease with potentially serious somatic consequences. This behavioral symptomatology leads to weight loss, undernutrition, and more or less severe—potentially life-threatening—somatic complications including respiratory, hepatic, digestive and cardiac features, electrolyte disturbances, endocrine and bone impairment, immunodepression, and related opportunistic infections. In this review, the authors report an overview of cardiac diseases in this disease.

Keywords Anorexia nervosa · Heart · QT interval · Echocardiography · Mortality

Introduction

Anorexia nervosa, one of the more frequent and severe eating disorders, is a chronic psychiatric disease with potentially serious somatic consequences [1]. Its prevalence varies between 0.9 and 3% in women and between 0.16 and 0.3% in men [2]. Anorexia nervosa (AN) is characterized by an emotional and cognitive incapacity to maintain a normal weight and by an active fight against the sensation of hunger [3]. This behavioral symptomatology leads to important weight loss, undernutrition, and more or less severe—potentially life-threatening—somatic complications including respiratory, hepatic, digestive and cardiac features, electrolyte disturbances, endocrine and bone impairment, immunodepression, and related opportunistic infections [1]. In this review, we report an overview of cardiac complications reported in patients with AN.

Heart complications in AN

Among medical complications described during AN, cardiac features are frequent, reaching 80% in some studies [4, 5]. These complications range from morphological cardiac abnormalities to electrical abnormalities with a potential risk of sudden death [6–10]. Cardiac abnormalities may involve the myocardium, the pericardium, the mitral valve, and the conduction system. Cardiac histological studies reported vacuolar degeneration, myocardium attenuation, and moderate interstitial fibrosis, without inflammation or necrosis [11]. In clinic, it has been reported left ventricular (LV) dysfunction, cardiac hypotrophy, mitral valve prolapse, pericardial effusion [4, 12], and QT long prolongation. In this context, electrocardiogram (ECG) and Doppler echocardiography should be routinely performed in patients with AN.

Electrocardiogram

Electrocardiogram should be systematically performed in all patients with AN especially in purgative forms (laxatives and more rarely diuretic abuses, vomiting…) with a particular focus on QT duration and heart rate. Indeed, ECG abnormalities are frequent in this disease and include bradycardia, increased QT interval, increased QT dispersion, QRS amplitude reduction, T wave, and ST non-specific abnormalities [13–16]. The most common finding is bradycardia, affecting 36% of patients, in the study by Dec et al. [17] and 95% in the study by Palla et al. [13], depending of the severity of underweight and malnutrition. Bradycardia may be in relation with

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hypothermia and seems to be a compensatory mechanism in the context of prolonged starvation [18]. Another explication of bradycardia may be an increase of the vagal tone and a decrease of sympathetic tone [7, 18]. Kollai et al. [19] reported a higher cardiac vagal tone in patients with AN with a significant correlation between cardiac vagal tone and percent weight loss (r 0.69, p 0.017). Significant conduction block are rare. Indeed, rare cases of second-degree atrioventricular block (Mobitz Type I), as well as junctional rhythm escape and sinus node dysfunction, have been reported in the literature [20–22].

Clinicians should mainly focus on QTc interval and QT dispersion in patients with AN. The QT dispersion represents the difference between the maximum and the minimum QTc across a 12-lead ECG and is considered higher when more than 60 ms. An increase of the QT interval and the QT interval dispersion are classically in relation with a regional difference in myocardial excitability recovery, and can expose the patient to arrhythmia [23, 24]. A low body mass index (BMI) and a rapid weight loss have been reported to be associated with QTc interval prolongation and dispersion [12]. Also, the reduction of LV mass has been reported to be associated with an increase of QT interval and QT dispersion ($r = -0.69$, $p < 0.01$) [25]. QT interval dispersion is negatively associated with resting metabolic rate [26].

Doppler echocardiography

The aim of the Doppler echocardiography is to assess cardiac function, hemodynamic status, and to search for the presence of pericardial effusion and mitral regurgitation.

Myocardium

With starvation that leads to a reduced weight, patients develop usually a reduction of cardiac mass [27]. Echocardiography performed in malnourished AN patients found reduction of LV wall thickness and LV mass. The decrease of LV mass can reach 30–50% [28].The reduction of LV dimensions and LV mass are classically associated with low energy intakes, BMI, and low T3 hormone level [12, 28, 29].

In parallel with cardiac morphological impairment, hemodynamically, patients with AN disclosed reduced cardiac output and hypotension [5, 12, 30–32]. De Simone et al. [4] reported reduction of the left ventricular mid-wall shortening, associated with reduced cardiac output in starving patients.

Myocardial systolic function may also be affected, and this feature is classically reversible with weight recovery [7]. Majority of patients discloses normal LV ejection fraction (LVEF). However, using tissue Doppler Imaging (TDI) and 2-dimensional strain imaging, sub-myocardial systolic impairments have been reported in AN. Also, sub-myocardial LV diastolic impairment may be present. Galetta et al. [33], in a study that included 20 female patients (22.4 ± 4.3 years old), reported not only a decrease of left ventricular TDI basal peak systolic velocities, but also a decrease of LV diastolic velocities. In addition, the authors found an association between reduced cardiac tissular velocities and indexed LV mass ($r = 0.55$, $p < 0.02$) [33]. Escudero et al. [34] reported reduced diastolic peak TDI velocities in patients with AN. Eidem et al. [35] reported an increase of the myocardial performance index (0.49 ± 0.08 in patients vs 0.35 ± 0.03 in control group) in patients with AN whereas LVEF was in normal range. Overt cardiac failure symptoms are rare. Rarely, patients may present myocardial infarction [36]. Finally, Tako-Tsubo cardiomyopathy may rarely occur, due to possible increase of catecholamine levels, related to profound hypoglycemia [37, 38]. Table 1 summarizes echocardiographic finding in the literature [4, 6, 9, 12, 28, 33–35, 39–42]. The myocardial dysfunction may be associated with electrolytic disturbances. Indeed, with starvation, reduction of phosphate stores, calcium, and potassium especially in purgative subtype of AN, is classical and may be associated with impaired muscle contractility after several years of evolution of AN symptoms (chronic starvation leading to chronic underweight and chronic purgatives behaviors). Electrolytic abnormalities that include hypophosphatemia [43], hypomagnesemia [44], and hypokalemia can be associated with cardiac dysfunction. Moreover, selenium and thiamin deficiency have been reported to be associated with cardiac dysfunction [45].

Recently, magnetic resonance imaging merged as a radiological exam for the assessment of cardiac function in patients with AN. Magnetic resonance imaging is used to characterize myocardial function and fibrosis. In the study by Oflaz et al. [46], 23% of patients with AN disclosed myocardial fibrosis (late gadolinium enhancement). The clinical long-term impact of this feature will need future studies.

Pericardium

Pericardial effusion is frequent (Fig. 1), ranging from 20 to 70% [41, 47]. In a study that included 173 patients aged between 12 and 17 years, Kastner et al. [41] reported a prevalence of pericardial effusion at 34%. Cardiac tamponade have been reported in some published clinical cases, but this complication remains very rare [48, 49].The presence of pericardial effusion in AN

t1.1 **Table 1** Doppler-echocardiographic findings in patients with anorexia nervosa

	Author	*N*	Age (years)	Cardiac findings
t1.3	ST. John Sutton MG et al. [28]	17	26	-Reduced LV mass
t1.4				-Reduced LV volumes
t1.5	De Simone G et al. [4]	21	22 ± 5	-Mitral motion abnormalities
t1.6				-Reduction LV dimension and mass
t1.7				-Reduced CO
t1.8				-Reduced LA dimension
t1.9	Eidem BW *et al* [35]	13	16.5 ± 1.9	-Increased MPI, 0.49 ± 0.08 in AN vs 0.35 ± 0.03 in controls ($p < 0.001$)
t1.10				-Reduced LV mass indexed (g/m^2). 79.4 ± 13.1 in AN vs 106 ± 17.4 in controls ($p < 0.01$)
t1.11	Romano C *et al.* [12]	91	20.5 ± 6.1	-Reduced LV dimension and LV wall thickness
t1.12				-Reduced LVEF et CO
t1.13	Mont L *et al.* [39]	31	15.7 ± 1.4	-Sinus bradycardia
t1.14				-Increase of LA dimension, LV mass and CO after refeeding (3 to 18 months later)
t1.15				-LV mass indexed (g/m^2), 59 ± 11 vs 67 ± 13 (p 0.005)
t1.16				-CO (l/min), 2.84 ± 0.8 vs 3.92 ± 0.99 ($p < 0.001$)
t1.17				-LA (mm), 25 ± 3 vs 29 ± 3 ($p < 0.01$)
t1.18	Galetta F *et al.* [33]	20	22.4 ± 4.3	-Reduced LV mass (g), 66.2 ± 8.3 vs 109.5 ± 9.8 in control ($p < 0.0001$)
t1.19				-Reduced mitral peak A wave velocity (cm/s), 33.7 ± 9.1 vs 45.3 ± 9.2 in control ($p < 0.01$)
t1.20				-Reduced peak Sm TDI velocity at basal septum and basal lateral wall of the LV
t1.21				-Significant association between peak Sm velocity and LV mass indexed, $r = 0.55$ ($p < 0.02$) for peak Sm septal and $r = 0.49$ ($p < 0.03$) for peak Sm lateral
t1.22	Olivares JL *et al.* [9]	40	From 12.1 to 18.5	-Reduced LV dimension, LV mass, and cardiac output
t1.23				-Improvement of cardiac abnormalities at end follow up (9 to 18 months):
t1.24				-LVEDD (mm), 41.3 ± 3.6 at baseline vs 43.7 ± 3.3 at end follow up (p 0.000)
t1.25				-LV mass index (g/m^2),58.5 ± 10.6 vs 66.5 ± 12.6 at end follow up (p 0.000)
t1.26				-CO (l/min), 2.9 ± 0.3 vs 3.5 ± 0.4 at end follow up (p 0.000)
t1.27	DiVasta AD et al. [40]	38	16.5 ± 2.2	-Sinus bradycardia: 26 (68%)
t1.28				-Reduced LV mass: 11 (31%)
t1.29	Kastner S et al. [41]	173	15.3 ± 1.4	-Pericardial effusion: 60 (34.7%)
t1.30				-Reduced LVEDD (mm), 41.1 ± 4.3 in AN vs 46.9 ± 3.7 in control ($p < 0.001$)
t1.31	Lelli L et al. [42]	14	28.4 ± 9.9	-Pericardial effusion, 4 (28.5%)
t1.32				-Mitral valve prolapse, 3 (21.4%)
t1.33	Escudero CA et al. [34]	95	15.5 ± 1.7	-Reduced LV mass index (g/m^2), 75.8 ± 17.5 in AN patients vs 85.9 ± 21.5 in control (p 0.002)
t1.34				-Reduced LV dimensions, LVEDD (cm) at 4.31 ± 0.38 in AN vs 4.49 ± 0.46 in control (p 0.009)
t1.35				-Reduced LA size (cm), 2.83 ± 0.39 in AN vs 3.06 ± 0.34 in control (p 0.001)
t1.36				-Reduced CO (l/min), 3.04 ± 0.91 in AN vs 3.83 ± 0.93 in control ($p < 0.001$)
t1.37				-Reduced diastolic peak TDI velocities
t1.38	Morris R et al. [6]	30	13(12–15)	-Reduced LV mass index in purging behaviors, 18 (16.2–23.4) vs 24.2 (21.2–28.7) in no purging behaviors (p 0.003)
t1.39				-Normal global longitudinal strain

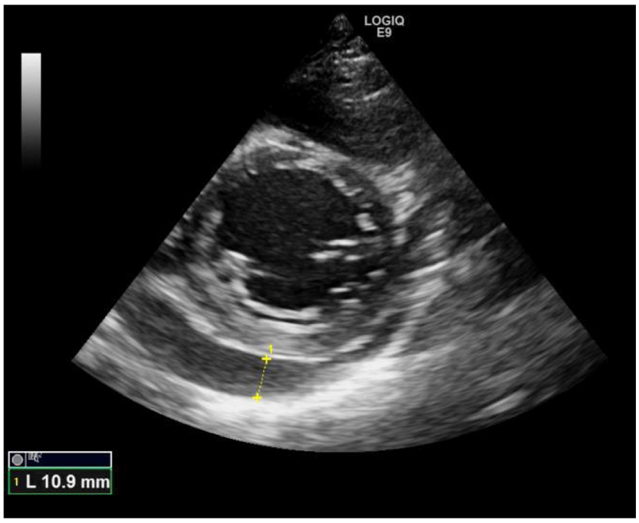
Data are expressed as mean ± SD or median (interquartile range) or number (percentage)

CO, cardiac output; *HR*, heart rate; *MPI*, myocardial performance index; *LV*, left ventricle; *LVEDD*, left ventricular end diastolic diameter; *LVEF*, left ventricular ejection fraction; *LA*, left atrium; *TDI*, tissue Doppler imaging; *MPI*, myocardial performance index; *N*, number of patients; *Ref*, reference

has been reported to be associated with low BMI and low T3 hormone levels [47]. Duration of illness and low BMI are reported to be predictive factors for pericardial effusion [41, 50].

Mitral valve

Mitral valve prolapse is frequent in patients with AN [25], with a higher prevalence, ranging from 33 to 60% [51],



Q4 **Fig. 1** Left ventricular two-dimensional echocardiogram from a parasternal short axis view showing a pericardial effusion in a patient with anorexia nervosa

without any association with BMI [46]. However, significant mitral regurgitation is rare.

Evolution of cardiac impairment with weight recovery

Cardiac abnormalities are generally reversible with weight recovery [39]. Left ventricular systolic dysfunction recovers with refeeding as well as LV dimensions. Gottdiener et al. [32] reported normalization of cardiac dimensions and LV mass with refeeding. Olivares et al. [9] reported an improvement of LV mass index, LV dimensions, and cardiac output, with weight restoration. Finally, with refeeding, pericardial effusion disappears. Kastner et al. [47] reported a remission of pericardial effusion in 88% of patients.

Also, the electrical abnormalities recover with refeeding. Indeed, with weight restoration, the sympathetic tone increases and the vagal tone decreases, providing normalization of heart rate [39, 52]. Kanbur et al. [20] reported a Mobitz I disappear with weight restoration in patients with AN with refeeding, it has been reported a reduction of the QT dispersion in patients with AN [53]. Cooke et al. [54] reported a QT interval prolongation recovery with refeeding in AN. Mont et al. [39] reported a decrease of QT dispersion and QT interval, as well as an increase of heart rate and normalization of heart rate variability with refeeding.

However, clinicians have to be careful with refeeding in patients with AN, because of the risk of refeeding syndrome [55]. Congestive heart failure may occur during refeeding syndrome [30], in addition with the classical increase of the liver enzymes.

With refeeding, the patient shifts from an undernourished state to an artificial refeeding that is an anabolism statement; this phenomenon creates a significant metabolic modification with biochemical impairment due to insulin secretion, potassium cells intake. Hypophosphatemia is frequent in refeeding syndrome, as well as hypokalemia and hypomagnesemia in refeeding syndrome, and arrhythmia can occur in this situation [56].

Mortality, sudden death, and anorexia

Anorexia nervosa has the highest mortality rate among psychiatric disorders. In the study by Lowe et al. [57], which included 84 patients with a very long-term follow-up (21 years), the authors reported a standardized mortality rate at 9.8, and 51% of patients recover from illness. In a British study, long-term mortality (20 years) has been reported, reaching 4% and 13% in two centers [58]. In an Italian study [59], with an 8-year follow-up, mortality rate was 2.7%. In Denmark, in a study that included patients with AN between 1970 and 1993 [60], crude mortality was 8.4% with a standardized mortality ratio at 6.69. Sullivan et al. [61], in a meta-analysis that included 42 studies, reported a mortality rate at 5.6% per decade. In another meta-analysis that included patients with eating disorders from 36 studies, Arcelus et al. [62] reported a standardized mortality rate at 5.8. In a French study that included 601 patients with AN, Huas et al. [63] found a standardized mortality ratio at 10.6 and reported six factors associated with mortality: older age, history of suicide attempt, longer eating disorder duration, diuretic use, intensity of eating disorder symptoms, and BMI. Suicide and illness are the main causes of death [58].The other causes of death are cardiac failure, metabolic and electrolyte (notably by hypokalemia and/or hyphosphatemia) disorders, liver failure, hypoglycemic coma, sometimes gastric rupture in bulimia, and rarely cerebral hemorrhage [64–66].

However, half of deaths are due to suicide [66]. Patton et al. [67], in a study that included 460 patients with eating disorders, reported a six-fold increase in mortality, and suicide was found to be the main cause of death. The other factors associated with mortality are the presence of recurrent hospital admissions for eating disorders and the lowest weight at initial presentation.

Cardiac diseases account for at least 1/3 of all causes of deaths in patients with AN [68]. The QT dispersion has been reported to a risk factor for sudden cardiac death in patients with AN. In the study by Isner et al. [69] that included tree anorexia patients who died suddenly, the authors reported ECG and necropsy findings and documented ventricular tachyarrhythmia in 2 patients (among them, one with torsade de pointe). Indeed, sudden death may be due to torsade de pointes [69]. However, in patients with QT interval

prolongation, sudden death occurs particularly in case of absolute QT intervals more than 600 ms. Ventricular arrhythmia may occur particularly in a patient with severe hypokalemia. In the study by Facchini et al. [70], that included 29 patients with under nourished AN (BMI at 13.8 ± 1.5), three patients disclosed severe hypokalemia (< 2 mEq/l), and QTc was severely prolonged in 2 patients (QTc 600 ms and 650 ms). A ventricular arrhythmia occurred in one patient among the two patients with severe QTc prolongation. Finally, Rivaldi et al. [31] reported the following parameters as predictive factors for sudden death in patients with AN: chronic hypokalemia, chronic hypo-albuminemia < 3.6 g/100 ml, and chronic illness with duration > 10 years.

Conclusion

Anorexia nervosa is a psychiatric eating disorder with higher morbidity and mortality. Cardiac impairments are frequent complications that require systematic cardiac noninvasive explorations especially for severe AN patients. Their clinical nutritional care must be conducted carefully to avoid cardiac impairment. Doppler echocardiography should be performed particularly in patients with severe undernutrition and during refeeding to assess left ventricular function, hemodynamic status, and cardiac preload.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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