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Heart and anorexia nervosa

Abdallah Fayssoil^{1,2,3} · Jean Claude Melchior¹ · Mouna Hanachi¹

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.

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

71 Clinicians should mainly focus on QTc interval and
72 QT dispersion in patients with AN. The QT dispersion
73 represents the difference between the maximum and the
74 minimum QTc across a 12-lead ECG and is considered
75 higher when more than 60 ms. An increase of the QT
76 interval and the QT interval dispersion are classically in
77 relation with a regional difference in myocardial excit-
78 ability recovery, and can expose the patient to arrhyth-
79 mia [23, 24]. A low body mass index (BMI) and a
80 rapid weight loss have been reported to be associated
81 with QTc interval prolongation and dispersion [12].
82 Also, the reduction of LV mass has been reported to
83 be associated with an increase of QT interval and QT
84 dispersion (r = -0.69, p < 0.01) [25]. QT interval dis-
85 persion is negatively associated with resting metabolic
86 rate [26].

87 Doppler echocardiography

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

91 Myocardium

92 With starvation that leads to a reduced weight, patients
93 develop usually a reduction of cardiac mass [27].
94 Echocardiography performed in malnourished AN pa-
95 tients found reduction of LV wall thickness and LV
96 mass. The decrease of LV mass can reach 30–50%
97 [28]. The reduction of LV dimensions and LV mass are
98 classically associated with low energy intakes, BMI, and
99 low T3 hormone level [12, 28, 29].

100 In parallel with cardiac morphological impairment,
101 hemodynamically, patients with AN disclosed reduced
102 cardiac output and hypotension [5, 12, 30–32]. De
103 Simone et al. [4] reported reduction of the left ventric-
104 ular mid-wall shortening, associated with reduced cardi-
105 ac output in starving patients.

106 Myocardial systolic function may also be affected,
107 and this feature is classically reversible with weight

recovery [7]. Majority of patients discloses normal LV 108
ejection fraction (LVEF). However, using tissue Doppler 109
Imaging (TDI) and 2-dimensional strain imaging, sub- 110
myocardial systolic impairments have been reported in 111
AN. Also, sub-myocardial LV diastolic impairment may 112
be present. Galetta et al. [33], in a study that included 113
20 female patients (22.4 ± 4.3 years old), reported not 114
only a decrease of left ventricular TDI basal peak sys- 115
tolic velocities, but also a decrease of LV diastolic ve- 116
locities. In addition, the authors found an association 117
between reduced cardiac tissular velocities and indexed 118
LV mass (r = 0.55, p < 0.02) [33]. Escudero et al. [34] 119
reported reduced diastolic peak TDI velocities in pa- 120
tients with AN. Eidem et al. [35] reported an increase 121
of the myocardial performance index (0.49 ± 0.08 in pa- 122
tients vs 0.35 ± 0.03 in control group) in patients with 123
AN whereas LVEF was in normal range. Overt cardiac 124
failure symptoms are rare. Rarely, patients may present 125
myocardial infarction [36]. Finally, Tako-Tsubo cardio- 126
myopathy may rarely occur, due to possible increase of 127
catecholamine levels, related to profound hypoglycemia 128
[37, 38]. Table 1 summarizes echocardiographic finding 129
in the literature [4, 6, 9, 12, 28, 33–35, 39–42]. The 130
myocardial dysfunction may be associated with electro- 131
lytic disturbances. Indeed, with starvation, reduction of 132
phosphate stores, calcium, and potassium especially in 133
purgative subtype of AN, is classical and may be asso- 134
ciated with impaired muscle contractility after several 135
years of evolution of AN symptoms (chronic starvation 136
leading to chronic underweight and chronic purgatives 137
behaviors). Electrolytic abnormalities that include 138
hypophosphatemia [43], hypomagnesemia [44], and hy- 139
pokalemia can be associated with cardiac dysfunction. 140
Moreover, selenium and thiamin deficiency have been 141
reported to be associated with cardiac dysfunction [45]. 142

143 Recently, magnetic resonance imaging merged as a 144
radiological exam for the assessment of cardiac function 145
in patients with AN. Magnetic resonance imaging is 146
used to characterize myocardial function and fibrosis. 147
In the study by Oflaz et al. [46], 23% of patients with 148
AN disclosed myocardial fibrosis (late gadolinium en- 149
hancement). The clinical long-term impact of this fea- 150
ture will need future studies.

151 Pericardium

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

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

| t1.2 | 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 (<i>p</i> < 0.001) |
| t1.10 | | | | -Reduced LV mass indexed (g/m ²), 79.4 ± 13.1 in AN vs 106 ± 17.4 in controls (<i>p</i> < 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 (<i>p</i> 0.005) |
| t1.16 | | | | -CO (l/min), 2.84 ± 0.8 vs 3.92 ± 0.99 (<i>p</i> < 0.001) |
| t1.17 | | | | -LA (mm), 25 ± 3 vs 29 ± 3 (<i>p</i> < 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 (<i>p</i> < 0.0001) |
| t1.19 | | | | -Reduced mitral peak A wave velocity (cm/s), 33.7 ± 9.1 vs 45.3 ± 9.2 in control (<i>p</i> < 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, <i>r</i> = 0.55 (<i>p</i> < 0.02) for peak Sm septal and <i>r</i> = 0.49 (<i>p</i> < 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 (<i>p</i> 0.000) |
| t1.25 | | | | -LV mass index (g/m ²), 58.5 ± 10.6 vs 66.5 ± 12.6 at end follow up (<i>p</i> 0.000) |
| t1.26 | | | | -CO (l/min), 2.9 ± 0.3 vs 3.5 ± 0.4 at end follow up (<i>p</i> 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 (<i>p</i> < 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 (<i>p</i> 0.002) |
| t1.34 | | | | -Reduced LV dimensions, LVEDD (cm) at 4.31 ± 0.38 in AN vs 4.49 ± 0.46 in control (<i>p</i> 0.009) |
| t1.35 | | | | -Reduced LA size (cm), 2.83 ± 0.39 in AN vs 3.06 ± 0.34 in control (<i>p</i> 0.001) |
| t1.36 | | | | -Reduced CO (l/min), 3.04 ± 0.91 in AN vs 3.83 ± 0.93 in control (<i>p</i> < 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 (<i>p</i> 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

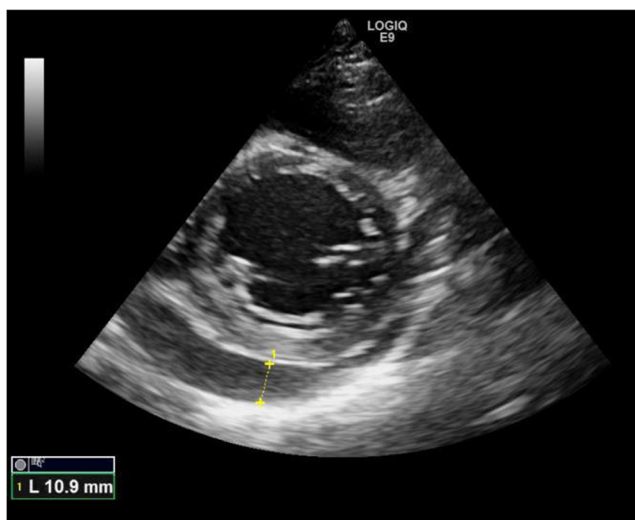
159 has been reported to be associated with low BMI and
 160 low T3 hormone levels [47]. Duration of illness and
 161 low BMI are reported to be predictive factors for peri-
 162 cardial effusion [41, 50].

Mitral valve

163

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

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 165



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

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

168 **Evolution of cardiac impairment with weight**
169 **recovery**

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

179 Also, the electrical abnormalities recover with
180 refeeding. Indeed, with weight restoration, the sympa-
181 thetic tone increases and the vagal tone decreases, provid-
182 ing normalization of heart rate [39, 52]. Kanbur
183 et al. [20] reported a Mobitz I disappear with weight
184 restoration in patients with AN with refeeding, it has
185 been reported a reduction of the QT dispersion in pa-
186 tients with AN [53]. Cooke et al. [54] reported a QT
187 interval prolongation recovery with refeeding in AN.
188 Mont et al. [39] reported a decrease of QT dispersion
189 and QT interval, as well as an increase of heart rate and
190 normalization of heart rate variability with refeeding.

191 However, clinicians have to be careful with refeeding in
192 patients with AN, because of the risk of refeeding syndrome
193 [55]. Congestive heart failure may occur during refeeding
194 syndrome [30], in addition with the classical increase of the
195 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, potas-
sium 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 psy-
chiatric 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 stan-
dardized 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 pa-
tients 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 at-
tempt, 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 hypoka-
lemia and/or hypophosphatemia) disorders, liver failure, hypo-
glycemic 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 disor-
ders, reported a six-fold increase in mortality, and suicide was
found to be the main cause of death. The other factors associ-
ated with mortality are the presence of recurrent hospital ad-
missions 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 pointes). Indeed, sudden death may be due to torsade de
pointes [69]. However, in patients with QT interval

246 prolongation, sudden death occurs particularly in case of ab-
 247 solute QT intervals more than 600 ms. Ventricular arrhythmia
 248 may occur particularly in a patient with severe hypokalemia.
 249 In the study by Facchini et al. [70], that included 29 patients
 250 with under nourished AN (BMI at 13.8 ± 1.5), three patients
 251 disclosed severe hypokalemia (< 2 mEq/l), and QTc was se-
 252 verely prolonged in 2 patients (QTc 600 ms and 650 ms). A
 253 ventricular arrhythmia occurred in one patient among the two
 254 patients with severe QTc prolongation. Finally, Rivaldi et al.
 255 [31] reported the following parameters as predictive factors
 256 for sudden death in patients with AN: chronic hypokalemia,
 257 chronic hypo-albuminemia < 3.6 g/100 ml, and chronic illness
 258 with duration > 10 years.

259 **Conclusion**

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

269 **Compliance with ethical standards**

Q6 270 **Conflict of interest** The authors declare that they have no conflicts of
 271 interest.

Q7 272 **References**

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