Anorexia nervosa and cardiovascular disease: a narrative review

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ABSTRACT

Anorexia nervosa (AN) is an eating disorder with one of the highest mortality rates among mental illnesses. Cardiovascular complications seem to account for more than half of all deaths. The aim of this review is to summarize the cardiac manifestations of AN and provide guidance for their diagnosis and management. Structural alterations, electrocardiogram abnormalities and hemodynamic changes are the most common cardiovascular manifestations in AN. High clinical suspicion and vigilance are of great importance, as cardiovascular complications in AN are potentially fatal. Avoidance of drugs with cardiovascular side effects is also crucial, while nutritional rehabilitation can stabilize and even reverse overt cardiovascular alterations.

KEYWORDS

Anorexia nervosa, cardiovascular disease, structural alterations, bradycardia, repolarization, hemodynamic.

Introduction

Anorexia nervosa (AN) is a psychological and potentially life-threatening eating disorder with a poorly understood etiology. It is mainly characterized by an abnormally low body mass index (BMI), severe self-induced malnutrition, an excessive fear of gaining body weight, and a distorted body image [1]. Increased physical activity, depression, stress thoughts, emotional disorders and amenorrhea often coexist. On the basis of their dietary behavior, patients are classically divided in two types of AN: (i) the "binge-eating/purging type", when food intake is followed by purging behaviors, such as self-induced vomiting, and (ii) the "restricting type", when food intake is kept strictly low [2,3].

The etiology of AN is believed to be multifactorial, involving genetic, environmental, psychological, sociological and cultural factors [4,5]. The average prevalence of AN has been reported to be 0.3% [6], with an increased number of diagnosed cases since 2013, when the diagnostic criteria for AN in the fifth edition of the "Diagnostic and Statistical Manual of Mental Disorders" (DSM-V) were revised. Among psychiatric disorders, AN has the highest mortality rate, which reaches 0.3-0.5% [7-9]. It mainly affects young women aged 15-19 years in Western societies [10]. The mortality rate is 5.1 deaths per 1000 person-years [11]. At least one third of these deaths are estimated to be of cardiovascular etiology, mainly sudden cardiac death [12,13]. The literature describes a large number of cardiac abnormalities associated with AN, including pathological changes in the myocardium, valvular disorders, conduction diseases, hemodynamic alterations, abnormal lipid profile and pericardial effusion. Cardiovascular complications worsen the prognosis of AN, and thus their management constitutes a major challenge for physicians. The aim of this paper is to review the cardiac manifestations of AN and provide suggestions for their diagnosis and management.

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Methods

This review is based on an extensive search in the "PubMed" database utilizing MEDLINE and the Cochrane Library. During the search, the term "anorexia nervosa" was used in combination with the terms "structural abnormalities", "cardiac mass", "cardiac chamber diameters", "ejection fraction", "valvular abnormalities", "myocardial fibrosis", "pericardial effusion", "bradycardia", "ventricular repolarization", "long QT", "QT prolongation", "QT dispersion", "heart rate", "blood pressure" and "ventricular function". We also assessed references of review articles for other relevant literature. Non-English articles were excluded. This review discusses a total of 67 references.

Structural alterations

A large number of cardiac structural abnormalities associated with AN have been described in the literature over the last two decades, including low cardiac mass, decreased cardiac chamber diameters, reduced left ventricular ejection fraction (LVEF), valvular abnormalities (such as mitral valve prolapse), myocardial fibrosis and pericardial effusion.

Several studies using Doppler echocardiography provide essential clinical information about left ventricular (LV) mass and cardiac chambers. A cross-sectional study, which assessed

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cardiac function in 13 patients with AN, showed that lower BMI is correlated with decreased LV mass index (LVMI; r = 0.74, p = 0.040) as well as with smaller LVMI (r = 0.74, p = 0.004) [14]. Similar results were obtained by Escudero et al. in a large case-control study of 95 female adolescents with AN and 58 healthy controls. They showed that LV dimensions, LV wall thickness, LVMI and left atrium dimensions were decreased by 5%, 10%, 20% and 8%, respectively, in females with AN (p<0.05). They also found that the most malnourished AN patients (with a BMI≤10th percentile) were at higher risk than those with a BMI>10th percentile [15]. Another case-control study, which investigated ultrasound findings in females with eating disorders, confirmed the relationship between AN and reduced LVMI and dimensions (p<0.01) [16]. Older studies evaluating cardiovascular alterations also revealed significantly lower LVMI in patients with AN compared with healthy individuals [17-20]. Indeed, lower LVMI values are associated with LV remodeling in patients with purging-type AN. These results were derived from "two-dimensional speckle tracking echocardiographic-derived strain imaging", an emerging method for assessing LV structure and function in newly diagnosed patients before the onset of clinical symptoms of cardiac dysfunction [21].

On the contrary, data on the association between AN and LV function are less conclusive. Most studies have failed to demonstrate a significant correlation between AN and LV function despite the decreased LVMI measured in individuals with AN [14,17-19,21,22]. Yet, Lelli et al. [16] and Romano et al. [20] showed that AN is significantly associated with lower ejection fraction (p<0.01 and p<0.007, respectively).

With regard to the valvular abnormalities occurring in AN, the most frequent is mitral valve prolapse. Echocardiographic studies in 95 and 40 young females with AN concluded that the incidence of mitral prolapse in these patients was 10% and 20%, respectively, [15,23] in comparison with the 2.4% in the general population calculated by the Framingham Heart Study [24]. Similar results were obtained in a cross-sectional study, where 9 out of 40 patients with AN and 1 of 28 members of the control group had mitral valve prolapse (RR=7.8, 95% CI: 1.03–65, p=0.03) [25]. Although this association has been known for a long time, it is still unclear whether it is secondary to decreased heart muscle dimensions or whether there is another underlying mechanism [26].

The widespread use of transthoracic echocardiography has led to an increase in the number of reports of pericardial effusion (PE) cases in AN. In general, the prevalence of PE in AN fluctuates within the range 8.5%-71.4% [19,22,27]. Kastner et al. showed that 34.7% of patients with AN presented with PE, in contrast to none of the control group (p<0.001) [28]. Another cross-sectional study showed that the risk of PE among females with AN was 11.5 times higher than in control individuals (p=0.005) [25]. Risk factors for the development of PE among AN patients seem to be a lower BMI and low T3 syndrome [27-29]. PE is generally mild, asymptomatic and regresses after weight restoration [27,28]. However, a few cases which required pericardiocentesis to prevent tamponade have been reported [30,31] and in two case-report studies PE progressed to tamponade requiring surgical intervention [32,33].

Myocardial fibrosis is another structural alteration affecting patients with AN. A recent case-report study, in which the postmortem heart of a patient with AN was examined histologically, revealed diffuse endocardial and interstitial fibrosis, as well as areas with myxoid material deposition and mast cells in the background [34]. An older case-report study confirms these histological findings, reporting myocyte attenuation and foci of fibrosis [35]. Nowadays, with the widespread use of cardiac MRI, subclinical cardiac involvement can be assessed. A cross-sectional study, among 40 AN females and 28 age-matched healthy controls, found signs of myocardial fibrosis, detected as late gadolinium enhancement, in 23% of patients with AN (p<0.007). The fibrosis involved the subendocardial region in three patients and the transmural one in six [25].

Electrocardiogram abnormalities

The most frequently described electrocardiogram (ECG) abnormalities are sinus bradycardia and impaired ventricular repolarization, which is most commonly manifested on the ECG as prolongation and increased dispersion of the heart rate-corrected QT (QTc) interval.

Sinus bradycardia is conventionally defined as a heart rate of less than 60 beats per minute with a normal P wave vector on the ECG, and it is the most common ECG abnormality among AN patients, with almost 40% found to be bradycardic [36]. Also, it has recently been found that sinus bradycardia affects more patients with the restricting, as opposed to the binge-eating/purging, type of AN: 48.4% vs 38.6%, respectively (p=0.03) [37]. Yahalom et al. found sinus bradycardia, assessed by 24-hour Holter monitoring, to be the most common clinical finding in AN and reported long periods (more than 180 minutes) of bradycardia with a mean lowest heart rate of 44 ± 6 bpm. Therefore, it is suggested that bradycardia can be used as a screening diagnostic tool in young adults, especially females with weight loss [38]. Bradycardia can be attributed to autonomic dysfunction and augmented vagal tone in patients with AN; these patients, though, seem to have enhanced baroreflex sensitivity and preserved sympathetic tone [39,40].

The heart rate for hospitalization of patients with AN ranges between <40 bpm 2 and <50 bpm.3 However, high clinical suspicion and vigilance are required for AN patients with resting tachycardia, too, as this may suggest underlying acute medical illness which does not manifest with obvious clinical features [41,42].

A prolonged QT interval has long been considered a potential cause of increased risk of sudden death in AN patients due to its known association with polymorphic ventricular tachycardia, also known as torsade de pointes [43]. Older studies highlighted the relationship between AN and QTc prolongation [44-46]. In a recent study, the prevalence of QTc prolongation among patients with restrictive eating patterns during hospitalization was found to be 9.7%, and no association between prolonged QTc interval and electrolyte abnormalities was shown [47]. However, a meta-analysis, including 10 studies, failed to demonstrate prolonged QTc in patients with AN, although it showed longer, but within-normal-range, QTc intervals in

AN individuals compared with controls [48]. In line with this, a recent study by Padfield et al., in which exercise testing was used in order to unmask QT prolongation, demonstrated impaired repolarization reserve in AN patients in comparison with controls, but failed to reveal QT prolongation.49 Similar results were obtained by Frederiksen et al., namely no difference in mean QTc interval or risk of prolonged QTc between AN females and healthy controls [50]. Yet, it has to be stressed that prolonged QTc, reported in many cases, can be due to other confounding factors, such as antipsychotic drugs [51], commonly used in AN, or other concomitant provocative conditions, such as electrolyte abnormalities [52] and bradycardia [53].

QT dispersion, defined as the difference between the maximum and minimum QT interval in the 12-lead ECG, reflects inhomogeneity of myocardial repolarization and a risk of arrhythmia [54]. QT dispersion seems to be greater in patients with AN ($p<0.001$) compared with controls, but no correlation with BMI could be identified [46]. However, Krantz et al. reported that QT dispersion was markedly raised in patients with AN (66.67 ± 6.15 vs 26 ± 2.67, $p = 0.01$) especially in older patients with more chronic AN [55]. However, these changes in QT dispersion are likely to be reversed after weight restoration [56].

Other ECG findings reported in AN patients are QRS wave prolongation, PR interval prolongation, low voltage R wave in the V6 lead, sinus node dysfunction, conduction disorders and arrhythmia, and QRS wave right axis deviation [57,58].

Hemodynamic changes

Hemodynamic changes are commonly encountered in patients with AN. In a study of 214 patients with AN, heart rate was found to be less than 60 bpm in 43%, whereas, 17% had values less than 50 bpm. In addition, systolic blood pressure was less than 90 mmHg in 15% of the study population [36]. Orthostasis seems to be the commonest hemodynamic alteration encountered in AN patients. A study in 36 AN patients found a mean pulse rate of 54.4 bpm on hospital admission. Importantly, 60% and 15% of these patients had orthostatic pulse and blood pressure changes, respectively, while resolution of orthostasis was achieved after 21 days of re-feeding [59]. Both hypovolemia-induced orthostasis and starvation-related muscular atrophy significantly reduce venous return to the heart and increase the risk of dizziness and syncope; when these conditions are combined with bradycardia, the risk of such episodes is even greater.

Reduced ventricular mass is also a common finding in patients with AN, which, it has been suggested, might result in reduced ventricular function. Older studies, however, failed to provide such findings in patients with AN. On the contrary, more recent trials showed reduced cardiac function in patients with AN compared with patients with normal body weight. Specifically, a study assessing LVEF in AN patients before and after exercise noted that resting LVEF was normal before and after weight restoration. However, LV response to exercise was abnormal in all AN patients, and was normalized in all of them after 25-75% of weight restoration [60]. The reduction in muscle mass and wall thickness, along with a reduction in cardiac ejection fraction, seem to the main contributing factors resulting in cardiac dysfunction in the setting of AN [61]. Other potential factors involved in cardiac dysfunction include electrolyte abnormalities and hypoglycemia [62-64].

Conclusions

Prevention and management of cardiovascular complications should be part of the initial treatment of patients with AN. Potentially life-threatening clinical symptoms and signs, such as bradycardia, conduction abnormalities, prolonged QT interval, T-wave inversion, hypotension and dyspnea should be verified at each medical evaluation. Hospitalization for continuous monitoring and observation may be required [65]. During the re-feeding phase, frequent evaluation of plasma levels of electrolytes and minerals is highly recommended, so that potential arrhythmias can be prevented [66]. In patients considered to be at high risk of major adverse cardiac events, administration of drugs with major cardiovascular side effects should be avoided. Many commonly used drugs in psychiatry, such as common antidepressants and antipsychotics, can prolong the QTc interval and may increase the risk of sudden death [67].

Clinicians should be aware of the cardiovascular complications which often occur in patients with AN. Therefore, a meticulous evaluation and a close follow-up are recommended in all AN patients to avoid the development of overt cardiovascular disease. Importantly, correct re-feeding seems to stabilize and even reverse such complications. Therefore, timely management of reduced energy intake is of paramount importance in order to reduce the risk of AN-related morbidity and mortality.

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