Cardiovascular Complications of Anorexia Nervosa: A Systematic Review

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ABSTRACT

Objective: Anorexia nervosa portends the highest mortality among psychiatric diseases, despite primarily being a disease of adolescents and younger adults. Although some of this mortality risk is attributable to suicide, many deaths are likely cardiovascular in etiology. Recent studies suggest that adverse myocardial structural changes occur in this condition, which could underlie the increased mortality. Given limited prevalence of severe anorexia there is a paucity of clinical and autopsy data to discern an exact cause of death.

Methods: Given this background we conducted a systematic review of the medical literature to provide a contemporary summary of the pathobiologic sequelae of severe anorexia nervosa on the cardiovascular system. We sought to elucidate the impact of anorexia nervosa in four cardiovascular domains: structural, repolarization/conduction, hemodynamic, and peripheral vascular.

Results: A number of cardiac abnormalities associated with anorexia nervosa have been described in the literature, including pericardial and valvular pathology, changes in left ventricular mass and function, conduction abnormalities, bradycardia, hypotension, and dysregulation in peripheral vascular contractility. Despite the prevalent theory that malignant arrhythmias are implicated as a cause of sudden death in this disorder, data to support this causal relationship are lacking.

Discussion: It is reasonable to obtain routine electrocardiography and measurements of orthostatic vital signs in patients presenting with anorexia nervosa. Echocardiography is generally not indicated unless prompted by clinical signs of disease. Admission to an inpatient unit with telemetry monitoring is recommended for patients with severe sinus bradycardia or junction rhythm, marked prolongation of the corrected QT interval, or syncope.

Keywords: anorexia nervosa; cardiovascular; myocardial fibrosis; repolarization; conduction; hemodynamic; peripheral vascular

Resumen

Objetivo: La Anorexia Nervosa presagia la más alta mortalidad entre las enfermedades psiquiátricas, a pesar de ser primordialmente una enfermedad de adolescentes y adultos jóvenes. Aunque algo de este riesgo de mortalidad es atribuible al suicidio, muchas otras muertes son aparentemente de etiología cardiovascular. Estudios recientes sugieren que en esta condición ocurren cambios adversos en la estructura miocárdica, la cual podría ser la base del incremento en la mortalidad. Dada la limitada prevalencia de anorexia severa, hay escasez de datos clínicos y de autopsia, como para discernir una causa exacta de muerte.

Método: Dado este contexto, realizamos una revisión sistemática de la literatura médica para proveer un resumen actualizado de las secuelas patológico-biológicas de anorexia severa en el sistema cardiovascular. Buscamos elucidar el impacto de anorexia nervosa en 4 campos cardiovasculares: estructural, repolarización/conducción, hemodinámico y vascular periférico.

Resultados: Un número de anormalidades cardíacas asociadas con anorexia

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nervosa han sido descritas en la literatura, incluyendo patología pericárdica y valvular, cambios en la masa y función ventricular izquierda, anormalidades en la conducción, bradicardia, hipotensión y desregulación en la contractilidad vascular periférica. A pesar de la teoría prevalente de que las arritmias malignas están implicadas como causa de muerte súbita en esta enfermedad, los datos que apoyen esta relación causal son pocos.

Discusión: Es razonable solicitar de rutina un electrocardiograma y registro de cambios ortostáticos en los signos vitales en pacientes con anorexia nervosa. El ecocardiograma generalmente no está indicado a menos que los signos clínicos lo apoyen. La admisión a la unidad hospitalaria con monitoreo telemétrico, está recomendada para pacientes con severa bradicardia sinusal o alteraciones del ritmo, marcada prolongación del intervalo QT corregido o síncope.

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Cardiovascular Complications of Anorexia Nervosa: A Systematic Review

Weight loss and malnutrition are among the defining criteria of anorexia nervosa (AN). As a result of these, there are a litany of medical complications which are inextricably connected to the outcome of patients with this disorder. While general medical complications likely contribute to the excessive mortality rate of anorexia nervosa, those specifically related to the cardiovascular system have historically been considered the causal substrate for the poor prognosis of this disease. Herein, we have performed a systematic review of the known cardiovascular complications of anorexia nervosa in order to help define optimal clinical evaluation of the cardiac manifestations which may arise during treatment. Where possible, evidence-based recommendations are provided which may represent reasonable care standards applied by the authors for this patient population. Given the absence of randomized trials or comparative effectiveness research in this field, most clinical recommendations reflect authors' expert opinions. This review is intended to be comprehensive insofar as it pertains to expected cardiac clinical manifestations of anorexia nervosa.

Method

A systematic literature search on the cardiovascular manifestations of anorexia nervosa was conducted by a librarian (BH) between the dates of May 11 and May 14, 2015. Three databases were queried with no date restrictions applied: Ovid Medline (1946–2015), Embase (1947–2015), and Web of Science (1974–2015). Animal-only studies and non-English citations were excluded. The free-text phrase/subject heading "anorexia nervosa" (anorexia nervosa) was combined with 286 free-text search terms and their associated subject headings relating to heart structural abnormalities, heart diseases (heart or heart diseases), heart conduction/repolarization abnormalities (heart conduction system or arrhythmias, cardiac), hemodynamics (hemodynamics), and heart exam/imaging techniques (cardiac imaging techniques or diagnostic techniques, cardiovascular). Free-text search terms were harvested by searching all exploded MeSH and Embase Emtree terms additionally as free-text. Further terms were identified through MeSH and Emtree entry terms/synonym lists. An overview of the search strategy and literature screening process is depicted in Figure 1. Out of a total of 1,352 nonduplicate references generated, 1105 references were excluded based on title and abstract screening in accordance with the following criteria:

Studies not Primarily Pertaining to Anorexia Nervosa

Studies that focused solely on bulimia nervosa, given that the scope of this review is limited to anorexia nervosa and due to expected differences in cardiac structural and physiologic measures.

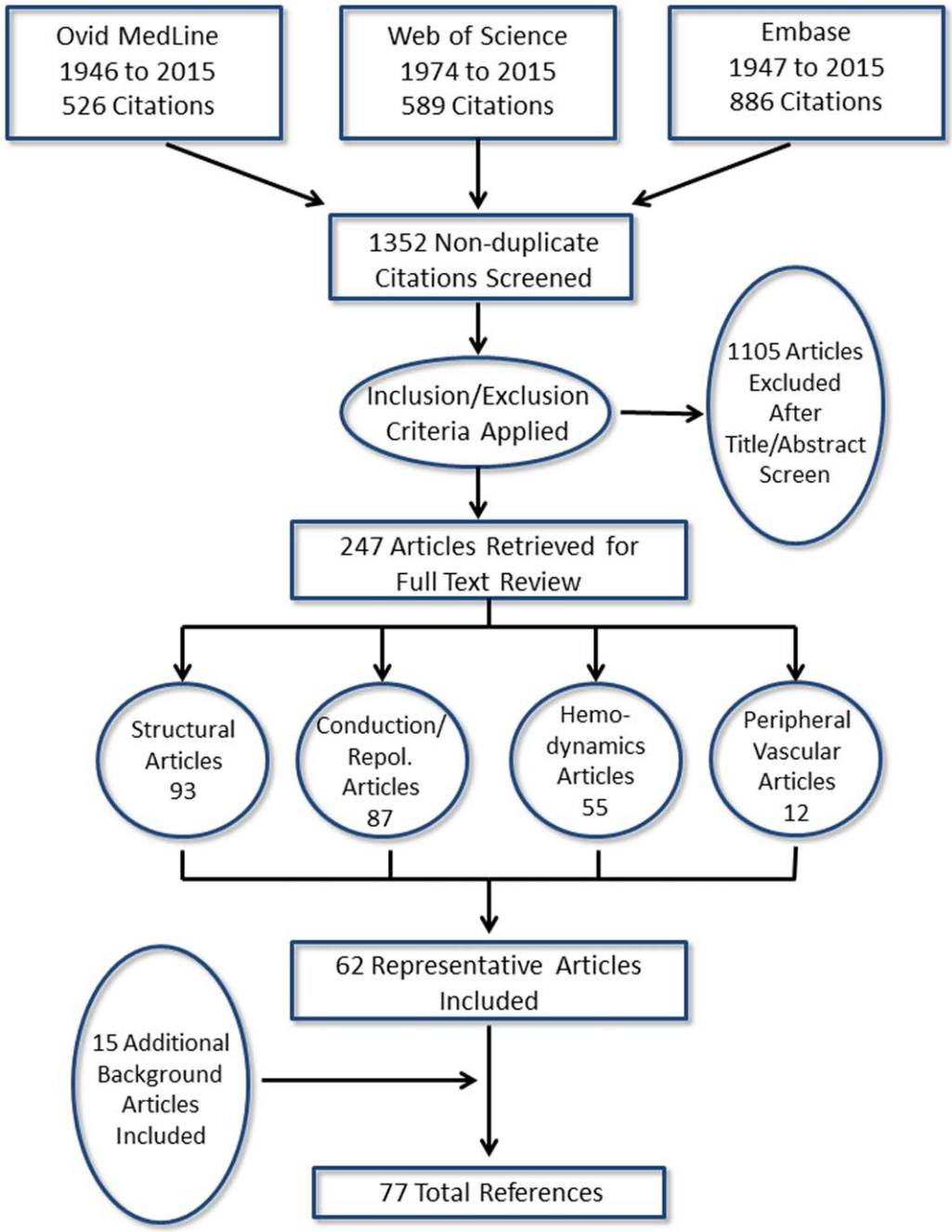
Studies that Primarily Focused on Psychiatric, Neurologic, or Neurocognitive Findings

Based on these exclusions, 247 references were reviewed as full text articles. This constituted 93 articles in the domain of structural complications, 87 in repolarization and conduction abnormalities, 55 in hemodynamic changes, and 12 in peripheral vascular abnormalities. We did not pre-specify critical appraisal criteria given the paucity of literature in this disorder and the absence of prospective randomized trials. We emphasized any longer term studies as having potentially more validity and relevance. Given the scope of the authors' clinical practice in treating patients ages 17 and older, emphasis was placed on studies pertaining to adolescents and adults, in keeping with their clinical expertise. Additional background articles not retrieved by the above search methods were reviewed and included at the discretion of the authors.

Cardiovascular Complications of Anorexia Nervosa

The energy deprivation and starvation associated with anorexia nervosa has profound consequences on the structure and function of the cardiovascular system. While some of the cardiovascular changes associated with this disease are mild and reversible, some may be

FIGURE 1. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]



life threatening. We examined the changes in cardiac structure, conduction and repolarization, hemodynamics, and the peripheral vascular system associated with severe caloric restriction. An overview of these changes is illustrated in Table 1.

Structural Complications

Pericardial Effusion. With the expansion of transthoracic echocardiography, pericardial effusion has increasingly been recognized among patients with anorexia nervosa. Although initially thought to be a rare finding, one study of 128 adolescent patients found that 22% of patients had pericardial effusion.[1] All patients were asymptomatic and most effusions had resolved on follow up echocardiography after refeeding. The etiology of pericardial effusion in AN is uncertain. One study observed that pericardial effusion remitted with weight gain and normalization of serum T3 levels.[2] This was corroborated by a more recent study of 173 adolescent patients with

TABLE 1. Cardiovascular complications of anorexia nervosa

Structural Complications
Pericardial effusion
Atherosclerotic vascular disease
Myocardial atrophy/decreased LV mass
Valvular prolapse
Myocardial fibrosis
Repolarization and Conduction Abnormalities
QT interval prolongation
Increased QT dispersion
Conduction delays
Junctional escape rhythms
Hemodynamic Changes
Sinus bradycardia
Hypotension
Orthostatic changes
Autonomic dysfunction/heart rate variability changes
Peripheral Vascular Abnormalities
Dysregulation of peripheral vasoconstriction/vasodilitation
Acrocyanosis
Arterial vasospasm

AN.[3] They found that 35% of patients had a pericardial effusion; in contrast no control patients had evidence of pericardial effusion. The presence of effusion was correlated with low body mass index (BMI) and low T3 syndrome. Importantly, resolution of effusion occurred in 88%. To our knowledge only one case in the literature describes the development of acute cardiac tamponade[4] in anorexia nervosa, though another case which required pericardiocentesis has been reported.[5] We conclude that pericardial effusion is generally a reversible, asymptomatic marker of disease severity. Nonetheless, echocardiography should be considered in those patients with severely reduced BMI, those with abnormal cardiothoracic ratio on chest X-ray, patients with unexplained hypotension, and any patient with pulsus paradoxus or elevated jugular venous pressure.

Atherosclerotic Vascular Disease. Although ischemic heart disease is not considered to be a significant cause of morbidity in anorexia nervosa, case reports do exist of acute coronary syndrome in this patient population. Abuzeid et al describe the case of a 39-year-old female who presented with severe chest pain and was found to have an ST segment elevation myocardial infarction requiring percutaneous coronary intervention to open a 100% occlusion in the proximal left anterior descending artery.[6] Similarly, Garcia-Rubira et al describe another 39-year-old female with a longstanding history of AN who had a non-ST-segment elevation myocardial infarction in the context of refeeding.[7] This patient, who had cardiovascular risk factors including tobacco abuse and elevated total and low density lipoprotein (LDL) cholesterol levels, developed severe chest pain on Day 44 of refeeding. An electrocardiogram revealed inferior ST depression and serum cardiac biomarkers were elevated. As this patient was relatively young it was postulated that the event may have related directly to refeeding that may reflect lipid fluctuations which triggered plaque rupture.

In addition to these potential refeeding-related lipid changes, general concern has existed for an elevated risk of vascular disease in anorexia nervosa due to the noted existence of elevated total cholesterol levels in patients with this disorder. This seemingly paradoxical finding was first described in the 1960s and despite being noted in multiple studies, conflicting opinions regarding this finding exists in the literature.[8,9] Some authors have proposed a mechanism of slowed removal of LDL-cholesterol contributing to elevated cholesterol levels, while other studies have concluded that any elevation in total cholesterol is solely reflective of favorably high levels of high density lipoprotein (HDL)-cholesterol.[10,11]

Despite these isolated case reports and conflicting data regarding lipid abnormalities, definitive data is lacking to support increased risk for atherosclerotic vascular disease in the anorexia nervosa population. One case control study of 18 females with anorexia nervosa and matched controls measured carotid intima-medial thickness and showed no difference between the two groups, implying lack of significant preclinical atherosclerotic disease at least by this surrogate marker.[12] However another study demonstrated an increase in aortic pulse wave velocity, a marker of increased arterial stiffness.[13] Despite conflicting findings with regard to preclinical markers of atherosclerotic risk, an absence of occlusive coronary artery disease found in an autopsy series of anorexia nervosa patients suggests that despite alterations in lipoprotein levels, ischemic heart disease is an unlikely cause of premature sudden death in this disorder.[14] Additional pre-mortem studies are needed to systematically characterize lipid abnormalities including LDL particle size and number, to confirm changes in arterial stiffness, and ultimately identify evidence of clinically relevant atherosclerotic disease. Given the lack of clear clinical significance of abnormal cholesterol levels, obtaining lipid panels in AN patients for screening purposes is unlikely to be helpful or necessary.

Myocardial Atrophy, Dysfunction, and Valvular Prolapse. Many patients with significant weight loss will develop left ventricular atrophy as reflected by a reduced left ventricular mass index with reductions in chamber dimensions including the left ventricle and left atrium.[15,16] This leads to subsequent annular laxity given reductions in chamber volumes that lead to mitral valve prolapse despite no intrinsic myxomatous valvular degeneration. Mitral valve prolapse has been shown to be present among 37% of 43 consecutive eating disorder patients who had two-dimensional echocardiography.[17] Despite multiple studies documenting mitral valve prolapse in anorexia nervosa, a causative association with

sudden cardiac death in both anorexia and the general populations remains speculative.

Overall, the most prominent cardiovascular structural abnormality detected by transthoracic echocardiography in anorexia nervosa is a substantial reduction in left ventricular myocardial mass. The degree of cardiac atrophy appears to relate to reductions in free T3 levels[18] which suggest a potential endocrinologic basis, though the association may be epiphenominal. Most studies suggest that left ventricular systolic function remains preserved though cardiac output may be diminished relative to control patients.[19] In addition, AN patients may manifest diastolic dysfunction as assessed by Doppler flow indices.[13] Similarly Galetta and colleagues noted reductions in tissue Doppler indices of myocardial diastolic performance.[20] This suggests that myocardial stiffness and chamber alterations could impact overall cardiac performance in the setting of starvation. In support of this possibility, a recent study demonstrated that patients with AN have preserved left ventricular systolic function but increased left ventricular sphericity index, a marker of poor cardiac performance due to abnormal geometry.[21] This study also observed that AN patients have asynchronous longitudinal strain with torsion which may suggest adverse cardiac remodeling. Despite these changes, an independent causal association between anorexia nervosa and systolic dysfunction cardiomyopathy has not been proven. Although refeeding syndrome is clearly associated with congestive heart failure, tachycardia, and arrhythmia, this is generally a reversible process.[22] Similarly, ingestion of ipecac has been associated with cardiomyopathy and in rare cases has been fatal.[23,24] Although cardiac transplantation and fatal cardiomyopathy have both been recently described in AN patients, the majority of individuals, even with severe AN, will have normal left ventricular ejection fraction on echocardiography despite the reduced LV mass.[25,26] Fortunately, reduced left ventricular mass is generally reversible with refeeding.[27] Nonetheless, it is possible that myocardial atrophy, a marker of disease severity, could lead to permanent, microscopic changes in the myocardium that place patients at risk for sudden cardiac death.

Routine echocardiography is not routinely indicated in the anorexia nervosa population. However, it should be prompted by clinical findings that would merit echocardiographic assessment in any patient, such as symptoms (syncope, orthopnea, dyspnea) physical exam findings (elevated jugular venous pressure, pulmonary and peripheral edema, gallop or a murmur suggestive of valvular pathology). Echocardiography may also be reasonable in patients with electrocardiographic abnormalities such as bundle branch block, ventricular hypertrophy, or pericarditis. A repeat echocardiogram should be performed in any patient with left ventricular systolic dysfunction after at least 3 months of optimal, guideline-directed medical therapy.[28] Among patients with clearly reversible left ventricular systolic dysfunction (e.g., Profound hypothyroidism or hyperthyroidism) or stress-cardiomyopathy.[29] repeat echocardiogram after metabolic status normalized and in 30–60 days after presentation respectively. Near normalization of ejection fraction is expected, and if not achieved cardiac consultation is warranted. In the presence of persistent focal segmental wall motion abnormalities evaluation for ischemic heart disease is reasonable in adult patients with anorexia nervosa. Finally, as mentioned previously echocardiography is indicated in all patients with suspected pericardial effusion.

Myocardial Fibrosis. In addition to reduction in LV mass in AN, one study suggested significant abnormal ultrasonic tissue characterization suggesting pathologic remodeling.[30] A more recent study demonstrated myocardial fibrosis/scar manifested by late gadolinium enhancement on cardiac magnetic resonance imaging (MRI) in nearly a quarter of anorexia nervosa patients compared with no patients in the control group.[31] This study corroborates older data suggesting regional myocardial contraction abnormalities in patients in the acute phase of eating disorders.[19] Although echocardiographic atrophy and fibrosis by MRI have been demonstrated, cardiac histologic abnormalities have been poorly characterized until very recently: a published autopsy report showed left ventricular atrophy with endocardial and interstitial fibrosis, focal myxoid material deposition with mast cells, and increased cytoplasmic lipofuscin.[32] These findings may suggest the presence of an important risk of sudden cardiac death that is independent of delayed repolarization. Although most cardiac structural abnormalities are reversible in this condition, the presence of myocardial scar suggests that malignant arrhythmias due to underlying structural heart disease remain a possible mechanism of increased mortality in this disease.

Repolarization and Conduction Abnormalities

QT-Interval Prolongation. Although the precise etiology behind an increased risk of sudden cardiac death in anorexia nervosa remains unclear, prolongation of the corrected QT interval (QTc) was long felt to be a potential cause because of its known association with torsade de pointes.[33,34] However, more recently it has been reported that anorexia nervosa may not inherently be associated with QTc prolongation; rather, when it is present on the surface electrocardiogram, it should result in a search for secondary causes such as aberrations in serum levels of electrolytes (hypokalemia, hypomagnesemia) or from medications known to prolong the QTc interval through blockade of the delayed rectifier potassium ion current.

Specifically, QTc prolongation has been reported in several older studies.[35–37] Two small studies also found the QTc interval to be longer in adolescent patients with anorexia nervosa than in healthy controls.[38,39] and similarly, in adult anorexia nervosa patients.[32,40] However, the association between anorexia and delayed repolarization this remains questionable due to limited sample size, varying degrees of anorexia nervosa severity and stages of weight restoration and patient types in previously evaluated cohorts. Also electrocardiographic data acquisition and interpretation are infrequently standardized. Yet, a meta-analysis of QTc intervals in patients with anorexia nervosa did demonstrate the presence of QTc interval prolongation in these patients.[41]

However, there are also numerous studies, comprised almost exclusively of females, which do not report QTc prolongation in anorexia nervosa. In a study of 19 adult patients hospitalized with severe anorexia nervosa, (mean BMI 12 kg m^{-2}) QTc intervals were not independently prolonged in the absence of contributing factors known to prolong the QTc interval.[42] Similarly, in a smaller study of adult patients with severe anorexia nervosa, the QTc interval did not differ from age-matched controls.[43] In a larger recent study of 100 less severely ill adult patients, QTc intervals were not noted to be longer in patients with anorexia nervosa versus controls.[44] Also, an older study of severely ill adult female patients with anorexia nervosa did not find QTc prolongation except in those with hypokalemia. Moreover after potassium levels were normalized, QTc interval was similar in duration to controls.[45] Thus, it is not accurate to summarily opine that QTc prolongation is an inherent abnormality specific to restrictive anorexia nervosa. Rather when found thorough search for abnormal electrolyte levels and for medications known to prolong QT intervals, should be undertaken.[46] There does not exist incontrovertible evidence of a causal association between anorexia nervosa and QTc interval prolongation.

However, regardless of the validity of the association between QTc interval prolongation with anorexia nervosa, patients presenting with QTc prolongation should be viewed with concern given the risk for torsade de pointes, a form of polymorphic ventricular tachycardia. Effort should be made to correct contributing electrolyte abnormalities and remove offending medications. Patients with a QTc of >500 ms should generally be admitted to an inpatient unit where continuous telemetry monitoring and serial electrocardiography can be performed. A QTc of >470 ms warrants surveillance with daily electrocardiograms.

QT Interval Dispersion. Another putative cardiac repolarization abnormality, which may be related to cardiac morbidity and mortality in anorexia nervosa, is QT interval dispersion. This inter-lead variability in QT intervals from 12-lead surface electrocardiography has been previously shown to correlate with an increased risk of arrhythmias after myocardial infarction and congestive heart failure.[47,48] QT dispersion is simply the difference between the longest raw QT interval and the shortest QT interval on the 12-lead tracing and values >100 ms portend substantial risk of adverse outcomes. Similarly in an aforementioned study which did not demonstrate prolonged QT intervals in female patients with moderately severe anorexia nervosa, QT dispersion was significantly greater in anorexia nervosa patients.[43] Moreover, QT dispersion correlated negatively with resting metabolic rate (RMR), and as refeeding progressed there was a substantial decrease in QT dispersion in both adult and adolescent patients with anorexia nervosa.[27,43] Two previous studies which involved adolescent patients with anorexia nervosa, also established the presence of increased QT dispersion in the acute phase of anorexia nervosa.[36,49] More recently a study of female patients with moderately severe anorexia nervosa, demonstrated increased QT variability versus controls, an abnormality of cardiac repolarization that may be more predictive of arrhythmia risk than QT dispersion.[47]

Junctional Escape Rhythms. Sinus bradycardia is a common and expected arrhythmia in anorexia nervosa. On rare occasions, likely as the bradycardia becomes more pronounced, a junctional escape rhythm may develop.[50,51] Of note in one of the two reports of junctional escape rhythm, it was extinguished with exercise, despite a prolonged duration of the junctional escape rhythm. Similarly there are rare singular cases of more complex sinoatrial block in anorexia nervosa, as well as paroxysmal supraventricular tachycardia.[52]

However, it is currently not definitive, which if any of the aforementioned cardiac rhythm abnormalities or of the structural–functional abnormalities found in anorexia nervosa, cause the clearly increased mortality rate associated with anorexia nervosa. This is because at the time of their ultimate demise there is generally no objective rerecorded rhythm data which can be connected with the death. While it is clear that atherosclerotic disease is not involved, it is not at all clear why these patients are consistently reported to have an elevated risk of sudden cardiac death and what the mechanism therein might be.

Hemodynamic Changes

Bradycardia, Hypotension, and Orthostasis. While junctional escape rhythm is rare, sinus bradycardia is a nearly universal finding in anorexia nervosa. This is particularly true in patients with very low body weight and advanced malnutrition. The prevalence of sinus bradycardia has been described in the literature in numerous case reports and multiple studies. It has been often noted

as the presenting sign prior to a diagnosis of anorexia nervosa, and the presence of bradycardia in the correct clinical setting should alert the provider to the possibility of an eating disorder.[53,54] In addition to thinness, low heart rate is likely the most consistent physical finding of anorexia nervosa patients. This finding has been widely theorized to reflect increased resting vagal tone as perhaps an adaptive response to attempt to conserve energy in the setting of decreased caloric intake.[22,49,55]

In addition to heart rate abnormalities, both systolic and diastolic blood pressure is also reduced in this population, and AN patients lack the normal circadian variations in blood pressure seen in health controls.[56] In a 2013 study by Yaholom et al. 22 out of the 23 patients with anorexia nervosa who were evaluated with a 24-h Holter monitor showed prolonged periods of bradycardia with mean lowest heart rates of 44 ± 6 beats per minute. In contrast, the mean lowest heart rate in age matched controls was 74 beats per minute.[57] The finding of sinus bradycardia in this population is so pervasive that unexpected elevations in heart rate to the normal range should be viewed with caution as they may represent signs of a secondary process, such as infection.[58]

While acute and sudden pseudonormalization of heart rate can be worrisome, the abnormally low resting heart rate and low blood pressures are expected to resolve slowly over time with refeeding. A 2002 study of 36 adolescent patients with anorexia nervosa admitted to a specialized eating disorder unit showed a mean heart rate of 54.4 ± 14.8 beats per minute. This mean heart rate increased to 70 beats per minute by Day 12 of hospitalization. However, orthostatic blood pressure changes persisted longer but resolved by the time the patients reached approximately 80% of their ideal body weight.[59] While patients with sinus bradycardia generally tolerate low heart rates well with minimal symptoms, when combined with orthostatic blood pressure changes and altered baroreceptor sensitivity, syncope can occur. A 2004 study of two patients with presyncopal symptoms showed that isometric exercise led to worsened bradycardia and asystolic pauses, as captured on Holter monitor.[60] These examples illustrate that although bradycardia and orthostasis are commonplace findings in this population, their potential consequences should not be underestimated.

In some cases, the dramatic orthostatic and heart rate changes in seen in anorexia nervosa patients have similar features to the Postural Orthostatic Tachycardia Syndrome (POTS) described extensively in other populations. POTS is believed to represent a heterogeneous collection of pathophysiologic mechanisms, including impaired vasoconstriction, autonomic dysfunction, and impaired volume regulation.[61] While many of these processes exist in AN patients, and the existence of POTS in anorexia nervosa has been acknowledged in the field, it has not been formally discussed in the literature.

Any episode of unheralded syncope, particularly with evidence of trauma or generalized seizures in the setting of anorexia nervosa and severe malnutrition warrants immediate inpatient admission for telemetry monitoring. Both true syncope and seizures may the result of a malignant ventricular arrhythmia such as torsade de pointes or high grade atrioventricular block. It is reasonable to consider telemetry for patients with resting heart rates of <40 beats per minute and any patient with symptoms of palpitations, presyncope, or syncope. Obtaining screening orthostatic vital signs at the time of admission to a treatment facility is helpful as the presence of orthostatic changes can alert providers to the possibility of volume depletion which is reversible, as well as autonomic dysfunction and need for caution with rapid changes in position.

Autonomic Dysfunction. The autonomic nervous system dysfunction that leads to pervasive sinus bradycardia in anorexia nervosa patients has been attributed to excessive vagal tone. Autonomic dysfunction in anorexia nervosa has been evaluated by numerous studies generally using the surrogate marker of heart rate variability to measure autonomic activity. A 1994 study by Kollai et al compared vagal control of sinus node function in 11 adolescent girls with anorexia nervosa and 11 age matched controls. Vagal tone was measured as the change in R–R interval in response to complete cholinergic blockage via intravenous administration of atropine sulfate. Cardiac vagal tone was calculated to be 30% higher in AN patients compared to healthy controls and was directly correlated with weight loss.[62]

Heart rate variability has been widely acknowledged as a marker for estimating autonomic function.[63] The clinical significance of heart rate variability was first described in the 1960s when it was noted that interbeat interval variability was a harbinger of fetal distress, prior to appreciable heart rate changes.[64] Despite compelling studies in the late 1980s showing heart rate variability as an independent predictor of mortality following myocardial infarction, it has yet to gain a role in standardized clinical practice.[65,66] However, this potential association between changes in heart rate variability, autonomic dysfunction, and sudden cardiac death has prompted multiple studies in the anorexia nervosa literature.

Given the heterogeneous nature of these studies, and generally small sample sizes, definitive conclusions about the role of heart rate variability as a mortality predictor in anorexia nervosa have been difficult. A 2011 review by Mazurak et al. analyzed in detail 20 papers on heart rate variability in anorexia nervosa, ranging in date of publication from 1994 to 2009.[67] This review found that these studies had drawn three distinct conclusions regarding

the significance of the data recorded: The majority found an autonomic imbalance with parasympathetic dominance, other studies reported the opposite conclusion with results indicating sympathetic dominance, and a final group found no difference between patients and controls. These seemingly conflicting results speaks to the complexity of this disease process. Many of the studies included in this analysis did not differentiate between subtypes of anorexia nervosa, account for history of purging behavior, other psychiatric comorbidities, or duration of illness. All studies were relatively small, ranging from 8 to 48 participants, which contrasts sharply with the 808 patients studied by Kleiger et al. in the post-MI study.

The concept that the balance of autonomic function may change with disease duration has been explored in a number of ways, and it has been hypothesized that the balance of autonomic activity shifts from parasympathetic to sympathetic dominance as the patient moves from acute to chronic disease.[68,69] Recently, Nakai et al. conducted a cross sectional study of 14 female patients with anorexia nervosa and 22 age-matched healthy controls.[70] Heart rate variability was stratified against duration of illness in each patient. It was found that duration of illness negatively correlated with normalized high-frequency power but positively correlated with the low frequency to high frequency ratio, suggesting that as illness progresses there is lower vagal and higher sympathetic tone. Although the sample size of this study was also small, it illustrates an important distinction in the progression of autonomic dysfunction in this population. Failure to account for duration of illness could explain some of the seemingly contradictory results obtained in prior studies.

Despite numerous studies on the topic of autonomic dysfunction as measured by heart rate variability, definitive conclusions are lacking. However, based on examination and interpretation of the available data, it can be speculated that there is a shift in cardiac autonomic control with the progression of anorexia nervosa, from parasympathetic to sympathetic dominant. It could be further speculated that this change in autonomic regulation, combined with the structural and conduction changes discussed above, could be a contributor to sudden death.

Peripheral Vascular Abnormalities

While peripheral vascular disease is not known to be a major complication of anorexia nervosa, there are nevertheless known associated vascular abnormalities. As with many of the vital sign and hemodynamic abnormalities discussed, it is postulated that these changes are derangements in an adaptive response to starvation and energy deprivation, rather than a primary pathologic process. The peripheral vascular manifestations described relate to dysregulation of peripheral vasodilatation and vasocontraction, particularly in response to temperature.

This condition was first described via a series of experiments performed by Freyschuss et al in 1978. In this study blood flow in the lower leg measured by venous occlusion plethysmography, arm blood pressure, and skin temperature measurements were taken in a group of sixteen patients with anorexia nervosa and 14 healthy controls. It was found that in the anorexia nervosa group calf blood flow was about 50–60% lower than the mean values observed in the control group, and skin temperatures were significantly higher in the control group. These results suggested a heat-conserving, selective peripheral vasoconstriction in the anorexia nervosa patients[71] Similar results have been replicated much more recently by Palova et al. who demonstrated not only that flow-mediated vasodilatation is decreased in patients with anorexia nervosa compared to healthy controls, but also that this abnormality improves following refeeding[72]

These findings collectively support the observation that acrocyanosis may occur in the setting of anorexia nervosa. Acrocyanosis is a rare disorder characterized by cyanotic changes and coldness most commonly of the hands but also occurring in the feet and distal parts of the face. The exact pathophysiologic mechanism is unknown, but is suspected to relate to vasospasm of the peripheral arterioles, with compensatory dilatation of the post capillary venules.[73] This is generally believed to be mainly a cosmetic problem, not associate with significant discomfort or risk for tissue damage. The cyanotic features are often most prominent in the cold and general resolve with warming of the skin. The increased prevalence of these findings in patients with anorexia nervosa has been noted anecdotally and also documented in a case series analysis of 155 patients with anorexia nervosa, which noted a strong correlation of this finding to more severe degrees of malnutrition.[74]

Although rare, more severe manifestations of peripheral vascular dysregulation, such as vasculopathy and Raynaud's phenomenon have been described in case reports.[75,76] In these reports an extensive serologic evaluation for known etiologies of Raynaud's phenomenon such as vasculitis or connective tissue disorders were negative. In 2000 Launay et al. describe the case of an 18-year-old female with anorexia nervosa and chronic acrocyanosis who developed severe vasospasm of the radial artery leading to digital necrosis following a radial arterial puncture for blood gas analysis.[77] Although an isolated case, and potentially influenced by other comorbid factors, this example should prompt providers to carefully consider the need for invasive vascular procedures in this tenuous patient population.

Discussion

Numerous studies have sought to examine and characterize the cardiovascular changes that occur with anorexia nervosa. It is well established that significant structural, conduction, repolarization, hemodynamic, and peripheral vascular changes occur in patients afflicted with this disorder. The potential for myocardial fibrosis to lead to repolarization changes in the setting of autonomic dysregulation and subsequent malignant arrhythmias and sudden cardiac death is a reasonable albeit speculative causal pathway to explain the high mortality of this disorder. However, this chain of events and mechanism of death as a primary cardiac event remain hypotheses unsupported by any conclusive data. Definitive data on best management practices for monitoring and screening patients are also lacking, and therefore clinicians must rely on expert opinion extrapolated from the available literature. Electrocardiography, telemetry, and echocardiography may be useful in managing selected patients with anorexia nervosa. In general, hospitalized patients with greater disease severity, advanced age, and multiple comorbidities should receive more careful monitoring. Further studies are needed to fully elucidate the impact of cardiovascular complications on the mortality associated with this disease, and to further guide best management practices.

Guidelines for Clinicians

- Routine echocardiography is unnecessary in the AN population, even among patients with very low body weights. However, it should be considered in patients who have clinical signs raising concern for either pericardial or valvular pathology, left ventricular dysfunction, or for those patients with electrocardiographic abnormalities.
- It is rarely clinically necessary to obtain screening blood lipid levels in patients with AN, given lack of evidence of atherosclerotic heart disease in AN.
- Routine screening of AN patients with an electrocardiogram is reasonable given known repolarization and conduction abnormalities associated with this disease. A patient presenting with a corrected QT interval of 500 ms or greater warrants inpatient admission for telemetry monitoring. Patients with a QTc of 470 ms or greater merit surveillance with daily ECGs. Prolonged QTc intervals should prompt immediate evaluation for electrolyte abnormalities or medication side effects, rather than summarily attributing it to AN.
- Patients with profound sinus bradycardia (heart rate <40 beats per minute) or junctional escape rhythm merit inpatient admission for telemetry monitoring.
- Resting bradycardia and hypotension are common among AN patients, particularly at lower body weights. It is helpful to obtain orthostatic vital signs with routine evaluation as their improvement correlates with weight restoration. While mild orthostasis is often well tolerated, an episode of syncope or presyncope is grounds for inpatient admission.

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