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Review Article

Cardiac changes in anorexia nervosa

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Abstract *Introduction:* Anorexia nervosa is an eating disorder, which is associated with many different medical complications as a result of the weight loss and malnutrition that characterise this illness. It has the highest mortality rate of any psychiatric disorder. A large portion of deaths are attributable to the cardiac abnormalities that ensue as a result of the malnutrition associated with anorexia nervosa. In this review, the cardiac complications of anorexia nervosa will be discussed. *Methods:* A comprehensive literature review on cardiac changes in anorexia nervosa was carried out. *Results:* There are structural, functional, and rhythm-type changes that occur in patients with anorexia nervosa. These become progressively significant as ongoing weight loss occurs. *Conclusion:* Cardiac changes are inherent to anorexia nervosa and they become more life-threatening and serious as the anorexia nervosa becomes increasingly severe. Weight restoration and attention to these cardiac changes are crucial for a successful treatment outcome.

Keywords: Anorexia nervosa; cardiovascular; bradycardia; ventricular; malnutrition

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ANOREXIA NERVOSA HAS THE HIGHEST RATE OF mortality of any psychiatric disorder with 5.1 deaths per 1000 person years.[1] With up to 80% of patients with anorexia nervosa suffering from cardiovascular complications,[2–5] which in turn cause up to 30% of the mortality in anorexia nervosa,[6,7] a review of the current knowledge base of cardiac manifestations in anorexia nervosa is warranted and presented below.

Diagnostic criteria for anorexia nervosa include restriction of energy intake leading to significantly low body weight, failure to meet the expected weight gain or maintain normal developmental trajectory, in children and adolescents, intense fear of weight gain and disturbance in the experience of one's body weight or shape with undue influence of body weight or shape on self-evaluation, and persistent lack of recognition of the seriousness of current low body weight.[8] An individual's concern with his or her body or weight as well as changes in eating or exercise behaviours may precede meeting full diagnostic criteria by 6–12 months.[9] In addition, very young individuals may initially deny drive for thinness and fear of gaining weight,[10,11] clouding the diagnostic picture.

Anorexia nervosa commonly begins during adolescence or young adulthood; retrospective data support a median age of onset of 18 years[12] with a lifetime prevalence of 0.5–2%.[13] The course of anorexia nervosa is highly variable. Many individuals will experience remission within 5 years, but about half will develop a chronic, relapsing course.[14]

Structural and functional cardiac alterations

Changes in cardiac mass and chamber dimensions present early in anorexia nervosa[15] and have been well studied. Consistently, decreases in left ventricular mass[16–33] and left ventricular end-diastolic and left ventricular end-systolic dimensions[20,23,25,29–35] are found; however, some controversy remains regarding some other very specific dimension measures, with some authors finding changes in left ventricular wall thickness[16–33] or left ventricular posterior wall

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thickness[20,23,25,32–35] and intraventricular septal wall thickness[16,32] while others refute these findings.[29]

A postulated mechanism for the cardiac structural remodelling observed is vagal hyperactivity, seen as an attempt to conserve energy, leading to changes in both contractility and decreased pre-load, which then result in cardiac atrophy in compensation for the volume depletion.[30,31,36] On the other hand, De Simone et al[20] found that the loss of left ventricular mass in women with anorexia nervosa was not the same as that seen in underweight women without starvation. Moreover, Galetta et al[37] observed that decreased left ventricular mass has been associated with prolonged QT interval in women with anorexia nervosa but not in underweight women without starvation. Thus, the specific mechanisms of remodelling seen in anorexia nervosa are not yet fully understood.

Several associations have been found between starvation and cardiac remodelling, but conflict remains. Silvetti et al[16] found decreased left ventricular mass and cardiac chamber dimension to be associated with low body mass index, low caloric intake, low free triiodothyronine, and low sodium; however, Carlomagno et al more recently found elevated growth hormone levels and decreased insulin-like growth factor-1, in addition to the decreased free triiodothyronine, to be potential markers. After adjusting for the reduced haemodynamic load, they found that body mass index, amount of weight loss, afterload, and other routine laboratory markers of malnutrition did not predict the loss of left ventricular mass.[38]

Biological plausibility exists for these endocrine markers being associated with starvation-induced cardiovascular disease as elevated growth hormone levels, low insulin-like growth factor-1, and low free triiodothyronine are known predictors of short-term risk of organic complications in anorexia nervosa,[39] and improvement in left ventricular mass and normalisation of insulin-like growth factor-1 levels have been observed with weight restoration of adolescents with anorexia nervosa;[40] however, studies of supplementation with growth hormones and/or insulin-like growth factor-1 to stimulate appetite and muscle metabolism – instead of catabolism – have proved to be inconsistent.[41–43] Overall, cardiac remodelling is not predictable, not just associated with loss of weight or weight nadir, and not always seen along with standard malnutrition labs.[40]

The exact link between structural alterations and decreased cardiac function found in anorexia nervosa is not clear. Specific electrolyte, mineral, and other chemical deficiencies are known to impact contractility including hypomagnesaemia, hypophosphataemia, thiamine or selenium deficiency,[44–51] direct cardiac toxicity from syrup of ipecac,[52–59] thyrotoxicosis, alcohol abuse,[60] and potentially hypoglycaemia[61] and catecholamine overload.[60,62] Many of these same deficiencies and complications exist in patients struggling with restricting and/or purging subtypes of anorexia nervosa.

Reductions in cardiac output are due to decreases in stroke volume or heart rate reflected in the relationship expressed by the classic cardiac equation "cardiac output = stroke volume × heart rate". Cardiac output is lower in patients with anorexia nervosa[29–31] as is heart rate; however, debate remains regarding changes in stroke volume.

Some studies have used ejection fraction or fractional shortening to evaluate contractility and stroke volume and have shown decreases in patients with anorexia nervosa;[30,31] but, most data, and more recent studies in particular, refute this and have shown normal ejection fraction and fractional shortening,[32,35] suggesting that decreases in cardiac output may be more specifically related to differential reductions in heart rate in the starved patient as opposed to those who are just underweight. This is supported by a recent evaluation of the effect of starvation on rat contractility. Stroke volume in the starved rats was not lower than that in underweight rats that were not starved; however, bradycardia was more severe in the starved rats. This explained the difference seen in cardiac output between the groups in their study.[63] Atrial function in anorexia nervosa unfortunately has not been studied enough for adequate comments.

In summary, decreases in left ventricular mass and remodelling of the myocardium resulting in dimensional changes occur in anorexia nervosa, but it is unclear about the mechanisms leading to these changes. Furthermore, these structural changes are not directly related to cardiac dysfunction. Contractility can be impacted by starvation and nutrient insufficiency as well as toxicity and other co-morbid conditions, but without these insults decreases in cardiac output seem to be most dependent upon the bradycardia seen along with the starvation associated with anorexia nervosa. Refeeding, or correction of nutritional deficiencies, leads to normalisation of reduced left ventricular mass, regional wall movement abnormalities, and decreased cardiac output.[64–68]

Valve abnormalities

Mitral valve prolapse is a known, common cardiac complication of anorexia nervosa. Prevalence rates vary from 33 to 66%,[69] compared with only 0.6 to 2.4% in the general population[70] and up to 5% in children.[71] Usually, only mild regurgitation is found; however, it is a potential cause of chest pain and palpitations, which if symptomatic may be treated

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with beta blockers.[72] Mitral valve prolapse is reversible with nutritional rehabilitation.[35,40,64]

As there are no definitive associated electrocardiogram changes, it is usually diagnosed by the characteristic mid-systolic click, perhaps associated with a late-systolic murmur, best heard at the apex of the heart. In anorexia nervosa, mitral valve prolapse has been postulated to be associated with loss of ventricular mass found with low weight combined with sparing of the valvular support tissues, resulting in a relative redundancy of the valve itself;[69] however, Oflaz et al, evaluated the impact of body mass index and duration of illness on rates of mitral valve prolapse in their cohort of 40 young adult females with anorexia nervosa and found no association. This suggests that more than just low body weight may be necessary to develop mitral valve prolapse in this population.[33]

Pericardial effusion

Pericardial effusion is an area of increased interest within anorexia nervosa. Pericardial effusion has turned out to be a relatively common finding with prevalence rates varying widely from 15 to 71%;[16,73–75] newer studies suggest that approximately one-third may be the expected rate.[29,33] It is almost always silent, and refeeding leads to remission, but the temporal course has not yet been elucidated.[29,73] There have been two cases reported in the literature of cardiac tamponade in anorexia nervosa requiring surgical intervention by pericardiocentesis[76] or creation of a surgical window[77] and two other cases where pericardiocentesis was performed pre-emptively because of the risk of imminent tamponade.[78]

Predicting patients with anorexia nervosa who are most at risk for pericardial effusion has proven to be difficult. In the only study to examine the subtypes of anorexia nervosa, no differences in prevalence were noted based on restricting compared with binge/purge subtype.[29] Most studies have suggested a relation to low body mass index,[16,29,73,75,79] significant weight loss,[75] and duration of illness,[74] but recent studies have not been as consistent.[29,33] In a recent study of 173 adolescents with anorexia nervosa, Kastner et al[29] showed an association with low body mass index, but this was a small effect size ($n^2 = 0.034$), and Oflaz et al,[33] in a cross-sectional study of 40 female patients with anorexia nervosa, found no relation to body mass index at all. Absolute amount of weight loss of >25lbs was linked to the presence of pericardial effusion by Docx et al[75] in a large study of 128 patients, but this has not consistently been found.

Other associations between pericardial effusion and anorexia nervosa noted in the literature also have either conflicting data or have not been replicated in other studies but have included increased length of hospitalisation[29] and relation to specific lab abnormalities such as decreased levels of free triiodothyronine, sodium,[16] and insulin-like growth factor-1[75] or increased levels of plasma-derived brain natriuretic peptide.[76,80]

Electrocardiogram changes and rhythm complications

Sinus bradycardia is the most common arrhythmia found in anorexia nervosa.[81] It is caused by an increased degree of vagal tone and a concomitant decrease in sympathetic modulation.[30] Although the exact reason for the transition to heightened vagal tone is not known, the presumption is that it can be ascribed to a physiological adaptation to a lowering of the metabolic rate as a consequence of malnutrition and caloric restriction.[82] Indeed, sympathetic tone is known to increase, with a concomitant reduction in vagal tone, as weight restoration occurs.[83] Sinus bradycardia becomes more pronounced in concert with a lowering of the body mass index and with a longer duration of the disease.[84] As the bradycardia becomes more marked, a junctional escape rhythm may develop as well as a sinoatrial or atrioventricular block.[85] Of note, the junctional escape rhythm can be extinguished with mild amounts of exercise even when the escape rhythm is extremely slow.[86]

Thus, the typical resting vital signs of a patient with anorexia nervosa include a low heart rate, hypothermia, and hypotension with systolic blood pressure values of 70 and 80mmHg commonly noted. Therefore, the finding of a "normal" resting heart rate of 80 or 90mmHg is indeed abnormal for this population, especially for the more severe segment of patients with anorexia nervosa who have body mass indices <14. Consideration of secondary concerning aetiologies for this relative "tachycardia" might include incipient heart failure, refeeding syndrome, anaemia or another concomitant acute medical illness,[87] or heightened anxiety related to refeeding. This concern is of greatest importance early on in the weight restoration process because that is when these patients are at the highest risk for the dangerous refeeding syndrome to occur.

There have been a number of case reports of postural orthostatic tachycardia syndrome described in anorexia nervosa.[88] It is, however, not clear whether this is of any true causal relationship, because large swings in pulse rate can logically be expected due to the aforementioned reduction in left ventricular mass and stroke volume, which necessitates a major rise in the standing heart rate, and that associated with even minimal degrees of exertion.

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Therefore, at a minimum, resting bradycardia and hypotension should not be treated with medicines to raise the pulse or systolic blood pressure, as these are expected physiological adaptations to starvation and weight loss. Moreover, they both will progressively revert to normal as consistent adequate nutritional rehabilitation ensues, and hypothermia ceases to be found.

In a related manner, the electrocardiogram may demonstrate right-axis deviation in some patients with anorexia nervosa.[38] This also is attributable to the reduction in left ventricular mass.[89] Low voltage may also be noted on the electrocardiogram, due to either a reduction in ventricular mass or due to the recently described incidence of pericardial effusions, which accompany the more severe cases of anorexia nervosa.

An additional finding on the electrocardiograms of patients with anorexia nervosa is that of QT dispersion. This is defined by the maximum inter-lead variability in the QT interval between the leads with the longest and shortest QT intervals. The abnormally increased QT dispersion is a maker of ventricular excitability and may be a root cause for the increased risk of sudden cardiac death in anorexia nervosa patients.[37] Studies have demonstrated increased QT dispersion in patients with moderately severe anorexia nervosa versus controls as a repolarisation abnormality.[15] Interestingly, QT dispersion inversely correlates with resting metabolic rate and as refeeding progresses in anorexia nervosa, and as this metabolic rate increases QT dispersion reduces.[90]

In a related manner, another potential cause for the increased propensity towards sudden cardiac death in anorexia nervosa, notwithstanding the young age of these patients, is the issue of heart rate variability, a marker of autonomic function. There have been a number of studies that have attempted to look at this issue in anorexia nervosa. Although there are hints that these patients may have reduced heart rate variability, results are disparate making conclusions a bit tenuous.[91] It does seem likely that there is an evolution from predominantly parasympathetic tone to sympathetic dominant, as the patient weight restores or progresses from acute to chronic.[92,93]

Nevertheless, what has become increasingly clear is that the long-held belief that QT prolongation is inherent to anorexia nervosa does not seem to be correct.[94] Thus, when QT prolongation is detected in a patient with anorexia nervosa, it should not summarily be ascribed to anorexia nervosa, but rather an assiduous search for secondary causes should be pursued, including electrolyte aberrations and medication side effects.[95,96] The causal association of QT interval prolongation in anorexia nervosa with an increased risk of sudden cardiac death is no longer supported in the literature.

Conclusion

In summary, anorexia nervosa is unfortunately associated with an excessive mortality rate, even though it typically affects the young population. There are a litany of medical complications of anorexia nervosa that likely contribute to this guarded prognosis. These complications related to the cardiovascular system have long been felt to be impactful in this regard as the aforementioned text has described. Increased awareness and enquiry in this regard will help achieve more successful treatment outcomes for patients afflicted by anorexia nervosa.

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Conflicts of Interest

None.

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