

Toxic Cardiomyopathies: Alcohol, Amphetamines, and Anabolic Steroids

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Abstract

Toxic cardiomyopathies include those caused by drug abuse, as well as chemotherapy agents. This review addresses cardiomyopathies induced by alcoholism, amphetamines, and anabolic steroids, focusing on their pathophysiology, clinical presentation, treatment, and prognosis. Alcoholic cardiomyopathy is frequent and predominates in males. It is dose-dependent, with a probable genetic predisposition. Women are susceptible at lower doses of alcohol intake. The disease ranges from a subclinical asymptomatic form to the typical form of dilated cardiomyopathy with systolic dysfunction and heart failure with reduced ejection fraction (HFrEF). Diagnosis is based on history and exclusion of other etiologies. Treatment is similar to other forms of heart failure, and prognosis depends on cessation of alcoholism. The use of amphetamines has increased, as has the incidence of secondary cardiomyopathy. The majority of patients are young and male. The pathophysiology is multifactorial. Diagnosis is based on history. During the acute phase, there is adrenergic hyperactivity. Treatment is similar to other etiologies of HFrEF. Not infrequently, patients progress to cardiogenic shock and require circulatory support and indication for heart transplantation. Cardiomyopathy secondary to use of anabolic steroids usually occurs in young men. Anabolic steroids have a direct or indirect impact on the cardiovascular system, through their risk factors. Presentation can range from asymptomatic to cardiogenic shock. It is imperative to discontinue anabolic steroid use and institute guidelines-based therapies, usually with reverse remodeling and favorable prognosis.

Introduction

Toxic or chemical cardiomyopathies comprise a group of secondary diseases that affect the myocardium through

different mechanisms. This group includes cardiomyopathies caused by the abuse of licit and illicit drugs and drugs commonly used in clinical practice. In this review, we will emphasize cardiomyopathies induced by alcoholism, use of amphetamines, and anabolic steroids.

Alcoholic cardiomyopathy

Concepts and history

Ethyl alcohol, also known as ethanol or simply “alcohol”, is the most consumed drug in the history of humanity.¹ Alcohol consumption is currently high, with a global distribution, and there are signs that consumption has increased among young people and adults, especially during the COVID-19 pandemic.²⁻⁴ The acute and chronic effects of alcohol on different organs are characteristics that make excessive consumption harmful to health. High and prolonged consumption mainly affects the liver, which is the organ responsible for metabolizing alcohol; the gastrointestinal system; the central and peripheral nervous system; and the cardiovascular system. The effects of alcohol on the heart can lead, in the final stages, to a phenotype of dilated cardiomyopathy, with impaired left ventricular (LV) systolic function and heart failure (HF), a condition known as alcoholic cardiomyopathy.

Alcoholic cardiomyopathy was first described in 1877, and the term “alcoholic heart disease” was coined by William Mackenzie, in his treatise *Study of the Pulse*, in 1902.^{5,6} According to epidemiological data, alcoholic cardiomyopathy represents one of the main non-ischemic etiologies of HF in the western world.⁶ The development of alcoholic cardiomyopathy seems to be related to the amount of alcohol ingested daily and the duration of the period of alcohol abuse. Although the exact amount and time of abuse are not well determined, consumption above 80 g/day, for at least 5 years, is associated with an increased risk of developing cardiomyopathy.⁶ Table 1 displays the volumes of different types of alcoholic beverages equivalent to a standard dose of alcohol, according to the World Health Organization.⁷ A standard dose is the unit of measurement that defines the amount of pure ethanol contained in alcoholic beverages. It is equivalent, in general, to the same amount of alcohol and corresponds to different volumes, depending on the alcoholic strength of the beverage.

Keywords

Alcoholic Cardiomyopathy; Amphetamines; Anabolic Agents; Substance-Related Disorders.

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Table 1 – Standard dose of alcohol according to the World Health Organization (WHO)

Organ	Beer	Wine	Distilled spirits	Standard dose (pure alcohol)
WHO	330 mL	100 mL	30 mL	10 to 12 g

**Considering the alcohol content of beer as 4%, wine as 12%, and distilled spirits as 40%. Source: World Health Organization.⁷*

Epidemiology

In reference centers for the treatment of alcoholism, the prevalence of alcoholic cardiomyopathy ranges from 21% to 32% of cardiomyopathies, but it may be higher in populations with an elevated prevalence of alcoholism.⁵⁻⁸ There is evidence that many patients may have subclinical heart disease. In one study, necropsy of patients with alcoholism revealed signs of cardiomyopathy in patients without clinical manifestations of heart disease.^{5,9}

The prevalence of alcoholic cardiomyopathy is higher in men, due to the greater prevalence of alcoholism in the male sex.⁵ However, women reach a higher maximum alcohol concentration than men for the same amount of alcohol ingested. This is probably due to the greater proportion of body water in men and the greater proportion of body fat in women. Moreover, women have a lower quantity of enzymes that metabolize alcohol. As a result, women may develop alcoholic cardiomyopathy earlier and with lower daily intakes of alcohol compared to men.^{5,10}

Pathophysiology

The benefit-harm ratio of alcohol in relation to the cardiovascular system remains rather controversial.⁶ Initial studies suggested cardiovascular benefits with the ingestion of moderate doses, but recent studies have suggested that even small amounts can be harmful.¹¹ The recent literature predominantly shows that the harm is dose-dependent; nonetheless, moderate alcohol consumption should not be recommended to obtain cardiovascular benefits. There is concrete evidence that alcohol can have a toxic effect on cardiomyocytes^{6,12} through different mechanisms, as shown in Figure 1. Acute consumption of large amounts of alcohol can lead to inflammation and myocardial injury, detected by troponin elevations.¹³ Cardiac arrhythmias may occur, especially atrial fibrillation, in a situation known as “holiday heart syndrome”. Chronic alcohol abuse can lead to myocyte hypertrophy, apoptosis, necrosis, dysfunction of intracellular structures, changes in contractile proteins and calcium homeostasis, mitochondrial degeneration, and myocardial fibrosis. As a result, an initial phenotype of myocardial hypertrophy is observed, with evolution to dilated cardiomyopathy.⁶

Although the effects of alcohol on the myocardium are proven, there seems to be a genetic predisposition for the development of alcoholic cardiomyopathy.^{14,15} In one study, sequencing of genes related to dilated cardiomyopathy performed in 141 patients with alcoholic cardiomyopathy, 716 patients with dilated cardiomyopathy of other etiologies, and 445 healthy controls revealed that patients with alcoholic cardiomyopathy had more pathogenic variants in genes

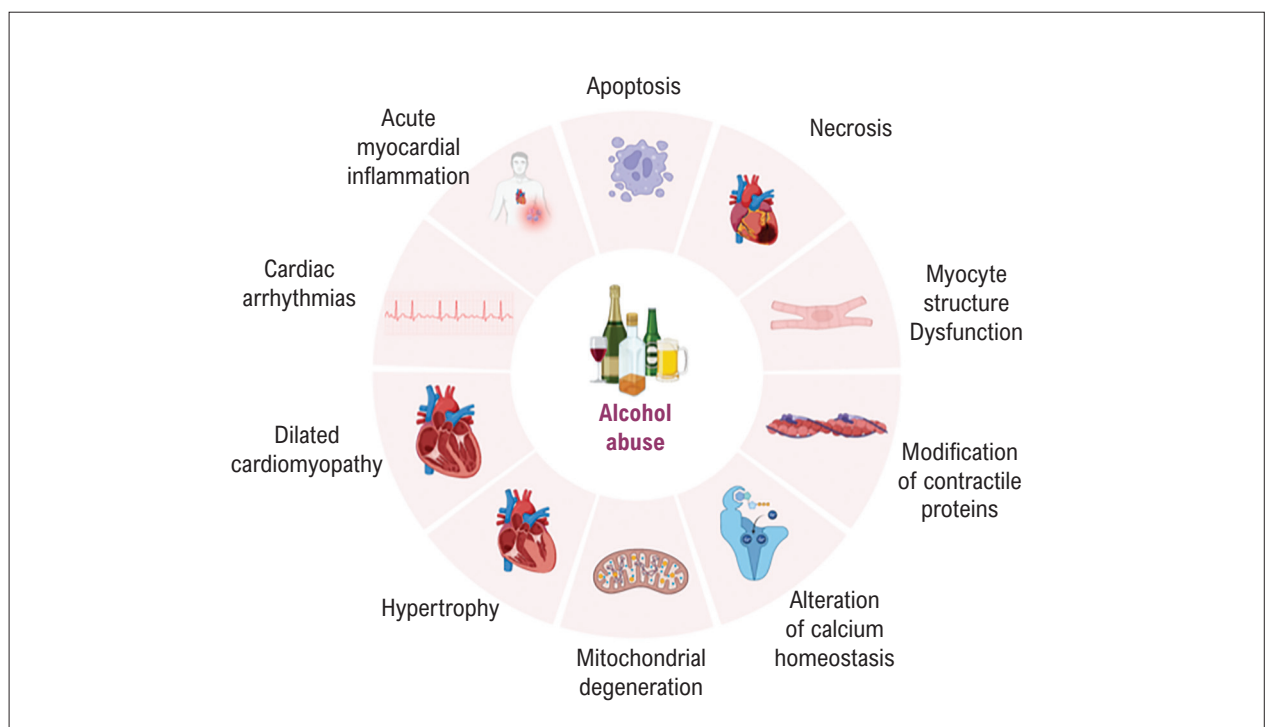


Figure 1 – The deleterious effects of alcohol on the myocardium. Source: Figure created by the author, using, BioRender.com, with permission.

related to the development of dilated cardiomyopathy, such as the TTNtv variant, than healthy controls.¹⁵ The frequency of pathogenic variants was similar between alcoholic cardiomyopathy and non-alcoholic dilated cardiomyopathy. The left ventricular ejection fraction (LVEF) of patients with dilated cardiomyopathy with TTNtv and excessive alcohol intake was 8.7% lower than that of patients without TTNtv or excessive alcohol intake. However, patients with alcoholic cardiomyopathy and TTNtv did not differ from those without TTNtv in response to HF treatment. Additional robust studies are needed to further clarify the role of genetics.

Other environmental factors, in conjunction with alcohol, could contribute to the development of cardiomyopathy. Both alcohol and its metabolites, such as acetaldehyde, are proven to be toxic to the myocardium.⁶ Other factors possibly involved (albeit without definitive proof) in the genesis of alcoholic cardiomyopathy include malnutrition, thiamine deficiency, electrolyte deficiency, and selenium deficiency.⁶ A hypothesis raised by German researchers related the presence of antifoam additives present in beer, such as arsenic and cobalt, to the development of alcoholic cardiomyopathy.⁶ This hypothesis gained strength with the case of “Quebec beer-drinkers cardiomyopathy”. In the 1960s, there was an epidemic of cardiomyopathies in Canada, in heavy beer drinkers. The phenotype was that of a dilated cardiomyopathy, but it had a peculiar characteristic, namely, purplish skin coloration and high initial mortality rate (42%). Furthermore, pericardial effusion and low-output HF were common. This cardiomyopathy disappeared when breweries discontinued the practice of adding cobalt to beer to stabilize foam formation.⁵

Natural history and clinical presentation

The natural history is not completely understood due to the absence of cohorts with long follow-up, initial asymptomatic period, and social issues, which lead individuals to hide their alcoholism problem in the early stages. In the final phase, we have a pattern of dilated cardiomyopathy, with LV systolic dysfunction. The progression of the disease from the normal cardiac phase to the dilated phase is still not well understood. Some studies suggest an initial phase with a hypertrophy phenotype and diastolic dysfunction.^{16,17} In fact, diastolic dysfunction is found in about 30% of cases of patients with a history of chronic alcohol abuse, in the absence of systolic dysfunction or LV hypertrophy, correlating with the duration and amount of alcohol consumed.^{6,17} However, other authors found ventricular dilation as an earlier alteration.¹⁸

Patients may be asymptomatic at an early stage. Unfortunately, the symptoms appear at an advanced stage of cardiac injury. The symptoms and signs are the same as the classic ones for HF, and they do not differ from HF of other etiologies. Cardiac symptoms may be accompanied by signs of liver impairment, malnutrition, and neurological disorders.^{5,6}

Diagnosis and prognosis

To date, there is no typical clinical or histological aspect of alcoholic cardiomyopathy. Diagnosis is basically by exclusion, based on clinical history. A history of chronic alcohol abuse

in the absence of other etiologies of dilated cardiomyopathy suggests diagnosis of alcoholic cardiomyopathy.^{5,6} Chest radiography findings are the same as in other causes of cardiomyopathy, such as cardiomegaly, pulmonary congestion, and pleural effusion.⁶ The electrocardiogram is also not typical and may contain ST-segment and T-wave changes, low voltage in the presence of extensive fibrosis, bundle branch blocks, and cardiac arrhythmias. Biomarkers such as natriuretic peptides and high sensitivity troponins may be elevated and should be interpreted in the same way as for other HF etiologies. Echocardiography can contribute to the exclusion of other causes of HF and define the phenotypic pattern of LV hypertrophy, dilatation, diastolic dysfunction, or systolic dysfunction, which may precede the onset of symptoms. Cardiac magnetic resonance imaging may show areas of delayed enhancement, indicating myocardial fibrosis (Figure 2). Although there is no specific pattern of alcoholic cardiomyopathy on cardiac resonance imaging, it can be useful to exclude other etiologies. Improvement of cardiac function with alcohol abstinence strengthens the diagnosis of alcoholic cardiomyopathy.

Alcoholic cardiomyopathy appears to have better prognosis than idiopathic dilated cardiomyopathy.¹⁹ Evolution depends substantially on abstinence from alcohol.^{17,20} We suggest observation of the clinical cases presented below, with their different evolutions, according to whether they ceased or continued alcohol consumption.

One study observed improved cardiac function in patients who were completely abstinent or who reduced their alcohol consumption to < 60 g of alcohol per day. On the other hand, cardiac function deteriorated in most patients who did not change their alcohol consumption pattern.²⁰ In one of the largest cohorts of patients with alcoholic cardiomyopathy, one third of patients died or required heart transplantation; one third showed disease stability; and one third showed recovery of heart function.¹⁹ Predictors of severe cardiac events were absence of prescription of beta-blockers, atrial fibrillation, and QRS width > 120 ms.

Treatment

Abstinence from alcohol is the mainstay of treatment for alcoholic cardiomyopathy.^{5,6,17,20} It may be necessary to use medications that reduce alcohol compulsion.^{21,22} In services specialized in controlling alcohol abuse, complete abstinence is achieved in 50% to 60% of cases.³ HF syndrome should be treated in the same way as in other etiologies.^{5,6} Thus, beta-blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, spironolactone, and diuretics are indicated in cases of congestion. Digoxin can be used as a second line of treatment. New drugs such as sacubitril/valsartan and SGLT2 inhibitors, although not specifically tested in the context of cardiomyopathies, appear to be beneficial.^{23,24} In the PARADIGM-HF study,²³ which compared sacubitril/valsartan with enalapril, 158 patients had alcoholic cardiomyopathy, and the benefits were similar to other etiologies. In relation to SGLT2 inhibitors, empagliflozin has been shown to

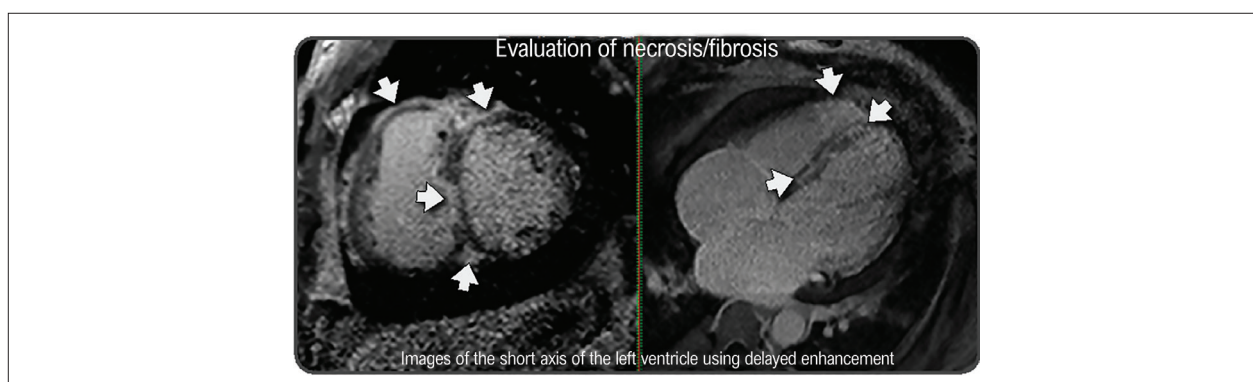


Figure 2 – Cardiac magnetic resonance imaging of a patient with alcoholic cardiomyopathy and stage D heart failure. Note the presence of delayed enhancement (arrows) indicating extensive fibrosis. Source: Author's collection.

reduce alcohol-induced myocardial injury by inhibiting mitochondrial apoptosis.²⁴

Patients with nutritional deficiencies may need to correct these abnormalities, with replacement of vitamins and administration of minerals such as selenium and zinc.⁵

Clinical case 1

A 53-year-old male patient had stage C HF of alcoholic etiology. In 2015, the patient was hospitalized 3 times during a 6-month period for decompensated HF, with New York Heart Association (NYHA) functional class IV. The electrocardiogram after initial treatment showed sinus rhythm, heart rate of 88 bpm, incomplete left bundle branch block, and first-degree atrioventricular block (Figure 3). At that moment, the patient was already using carvedilol at a maximum dose. The echocardiogram showed severe LV systolic dysfunction, with LVEF of 15%, calculated by Simpson's method (Figure 4). At the first outpatient visit, NT-proBNP was 2800 pg/mL. The patient was able to achieve complete abstinence from alcohol. He was medicated with carvedilol, reaching the maximum dose without complications; enalapril maleate 10 mg every 12 hours; spironolactone 25 mg/day; and furosemide, with higher initial doses, later reduced to 40 mg/day. As the patient's heart rate remained 88 bpm, despite the maximum dose of carvedilol, ivabradine 5 mg every 12 hours was started. He had a favorable evolution, with adequate heart rate control, improvement in functional class, improvement in dyspnea, and regression of edema in the lower limbs, with no hospitalizations during the following 4 years. There was a decrease in NT-proBNP to 1200 pg/mL after 6 months and to 450 pg/mL at one year. An echocardiogram performed in 2019, 4 years after treatment, showed improvement in LV myocardial function, with LVEF of 41%. The patient is currently in NYHA functional class II.

Clinical case 2

A 42-year-old male patient with HF and a history of chronic alcoholism had been using alcohol heavily since the age of 20 years. At the first visit to the outpatient clinic, he was in NYHA functional class IV, with orthopnea, lower limb edema (+++/4+), pathological jugular swelling, hepatomegaly,

and moderate ascites. The electrocardiogram showed sinus rhythm, QRS axis shifted to the left, and discrete Q waves in DII, DIII, and aVF. He had a previous coronary angiography with epicardial coronary arteries free of obstructive lesions. Echocardiogram showed LV diastolic and systolic diameters of 63 mm and 57 mm, respectively, with LVEF of 21%. His NT-proBNP was 8426 pg/mL. He was medicated with carvedilol, reaching the maximum dose of 25 mg every 12 hours; enalapril maleate 10 mg every 12 hours; spironolactone 25 mg/day; and furosemide. There was an improvement in functional class and regression of lower limb edema. The patient evolved favorably during 6 months, in NYHA functional class II, and NT-proBNP dropped to 3900 pg/mL. In a consultation during the ninth month of follow-up, he showed a worsening of the condition, with worsening of functional class and return of the lower limb edema. His family reported poor adherence to treatment due to a relapse in excessive alcohol consumption. He evolved with refractory HF, having been hospitalized, and died during this hospitalization.

Amphetamine-induced cardiomyopathy

Introduction

Amphetamines are synthetic drugs that act directly on the central nervous system, stimulating its activity. Examples of amphetamines are methamphetamine and methylenedioxymethamphetamine, also known as MDMA or "ecstasy". The use of these stimulant drugs has increased in recent years.²⁵ An estimated 34 million people used amphetamines in 2020, representing 0.7% of the global population. Record amounts of amphetamine were seized globally in 2020, dominated by methamphetamine, in addition to the significant increase in the number of people being treated for methamphetamine-related disorders in North America in the past years.²⁶

Cardiovascular complications are the main causes of death, and they have been found in up to 75% of patients who abuse methamphetamine.²⁷ They include malignant arterial hypertension, arrhythmias, aortic dissection, myocardial infarction secondary to vasospasm, stroke, and cardiomyopathy.²⁸

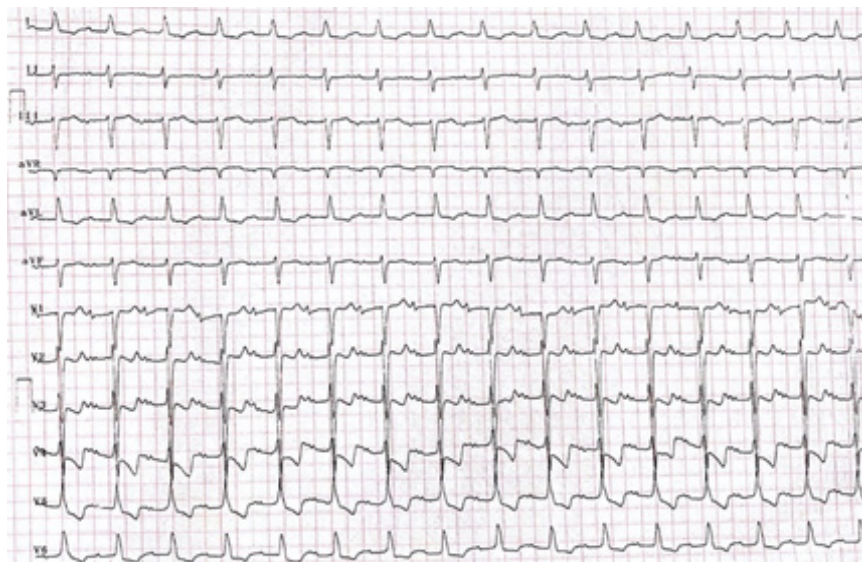


Figure 3 – Electrocardiogram of a patient with alcoholic cardiomyopathy and stage C heart failure, showing sinus rhythm, heart rate of 88 bpm, incomplete left bundle branch block, and first-degree atrioventricular block. At the time, the patient was already receiving medication for heart failure, including a maximum dose of carvedilol. Source: Author's collection.

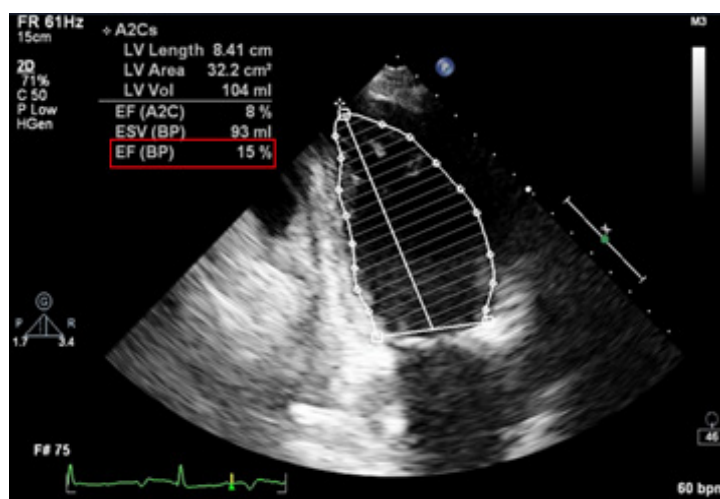


Figure 4 – Transthoracic echocardiogram of a patient with alcoholic cardiomyopathy and stage C heart failure. Source: Author's collection.

The incidence of methamphetamine-induced heart disease has increased from 1.8% to 5.6%. These patients tend to be younger, and the majority are male.²⁹

Pathophysiology

The pathophysiology of methamphetamine-associated cardiomyopathy is multifactorial, with direct and indirect myocardial damage characterized by increased production of free radicals promoting oxidative stress, cellular apoptosis,

mitochondrial dysfunction, alteration of gene expression and intracellular defects in calcium homeostasis.³⁰ Figure 5 summarizes some pathophysiological mechanisms for the development of methamphetamine-induced heart disease.

Diagnosis

The clinical picture of patients generally presents with signs and symptoms of heart failure with reduced ejection fraction (HFrEF). One study analyzed the clinical

characteristics of patients with methamphetamine-induced heart disease and found a young population, with a mean age of 30.3 years, that was 93% male. Eighty-three percent were in NYHA functional class III or IV. Other signs and symptoms included angina pectoris, palpitations, cough, and hemoptysis. The study reported 1 episode of cardiogenic shock, 1 case of infective endocarditis, and 1 patient with stroke. The majority of the patients used other illicit drugs associated with methamphetamine, such as marijuana, heroin and cocaine.³¹

The main electrocardiographic findings were tachyarrhythmias. Additionally, other findings were described, such as deviation of the electrical axis to the right, T wave inversion in the lateral wall, pulmonale P wave, LV hypertrophy, prolongation of the QT interval, among others.³²

Regarding biomarkers, BNP and NT-proBNP are generally elevated in this population and related to the severity of HFrEF. Ventricular dysfunction is the most evident alteration on the echocardiogram, often with very severe LV dysfunction and dilation. Another finding is dilation of the left atrium and right ventricle. Ventricular function may also be impaired. Some patients have shown thrombi in the ventricles, and pericardial and pleural effusion may be common, with a frequency measured between 40% and 50% of cases.³¹

Comparing the echocardiographic findings of young adults with other dilated cardiomyopathies, patients with methamphetamine-induced heart disease had a significantly

larger left atrium and right ventricle, lower LVEF, and higher frequency of mitral regurgitation.³³

There is no consensus on the diagnostic criteria for amphetamine-induced cardiomyopathy. Young patients with a clinical picture of HFrEF and history of drug abuse should have a urine analysis for screening. An assessment of the coronary arteries should be performed to rule out atherosclerotic coronary artery disease, and cardiac magnetic resonance imaging can also be useful to rule out other etiologies such as deposit diseases, myocarditis, amyloidosis, and others.³⁴

Treatment

In the acute phase of intoxication, patients have exacerbated adrenergic activation, which may be associated with a hypertensive crisis. Benzodiazepines can attenuate agitation and sympathetic stimulation.³⁵ Patients in cardiogenic shock may require some short-term mechanical circulatory support as a bridge to decision or recovery. Optimized therapy for HFrEF should be administered to chronic patients, as recommended in the guidelines.³⁶ Seeing that the incidence of thrombotic complications is common in these patients, anticoagulation should be performed, but there is no consensus on its timing.³⁴

These patients are not candidates for heart transplantation until they have been abstinent for 6 months.³⁷ They may, however, be candidates for a long-term device as a bridge to candidacy until the abstinence period has been completed.

Outcomes

It has been reported that HF secondary to methamphetamine use is a more severe form of cardiomyopathy, with severely reduced LVEF and a more dilated LV,³⁸ in addition to a greater association with hospital readmission. One study reported 57% readmission at least once during a mean follow-up of 17.7 months, most within 3 months of discharge.³⁹ Predictors of rehospitalizations for HF included reduction in LVEF, elevated systolic pulmonary artery pressure, stroke, and mood or anxiety disorders.⁴⁰

The likelihood of recovering heart function and improving symptoms was significantly higher in patients who discontinued methamphetamine abuse, with a lower incidence of death, non-fatal stroke, and hospital readmissions for HF.³¹

Anabolic steroid-induced cardiomyopathy

Introduction

Anabolic steroids are drugs that are chemically and pharmacologically related to testosterone; their main effect is the development of muscle mass. The term anabolic refers to a hormone or substance capable of enhancing the growth of tissues, such as skeletal muscle.⁴¹ Testosterone was biochemically described and synthesized in the early 1930s, and a series of synthetic variations have been produced since then. The use of testosterone or other anabolic steroids by athletes began in the 1940s to 1950s, and it has grown considerably. Current data show that the use of

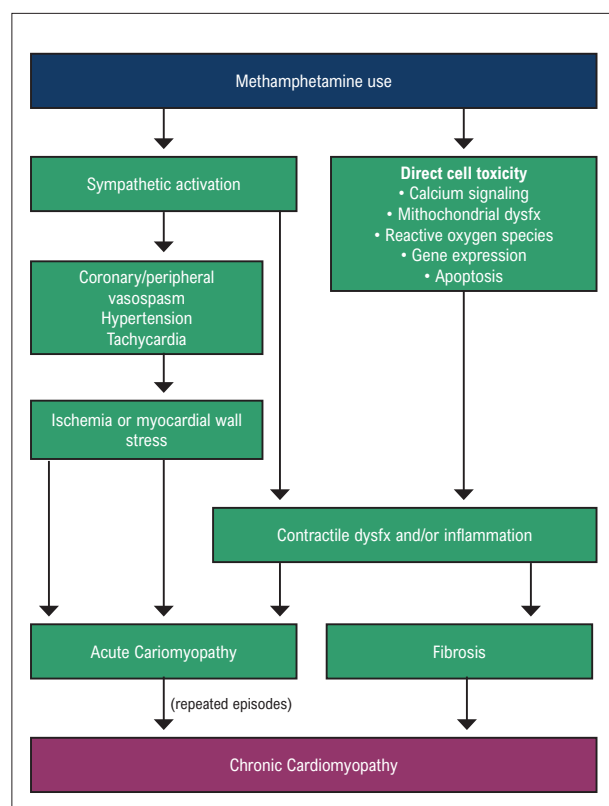


Figure 5 – Physiopathology of amphetamine-induced cardiomyopathy. dysfx: dysfunction. Source: Adapted from Reddy et al³⁰

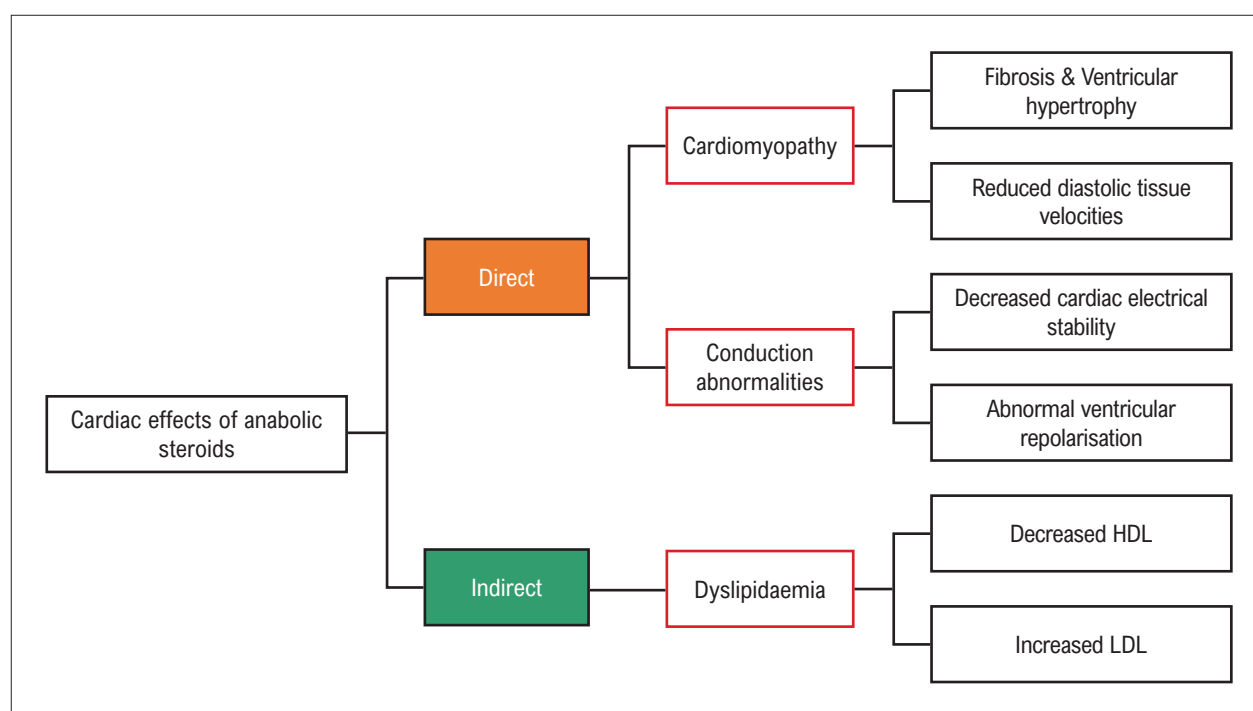


Figure 6 – Effects of anabolic steroids on the cardiovascular system. Source: Adapted from Milevski SV.

anabolic steroids is not restricted to bodybuilders or high-performance athletes. In addition to competitive athletes, use among non-athletes is growing, with a higher prevalence observed in males.^{41,42} It is estimated that around 4 million people use anabolic steroids in the United States alone.⁴³ In Brazil, a study revealed that the prevalence of anabolic steroid use may vary from 2.1% to 31.6%, depending on the cohort studied; these higher numbers were obtained in a study carried out among students and teachers of physical education.⁴⁴ Athletes and non-athletes use anabolic steroids in order to improve their performance and increase strength and muscle mass, but these substances can cause adverse effects in different organs and tissues, including the central nervous system, liver, and cardiovascular system.^{45,46} The pattern of use varies greatly in different groups, depending on the type of substance used, routes of administration, dosages, cyclic patterns, duration, and association with other drugs.

Effects on the cardiovascular system

Numerous case reports have been described associating the use of anabolic steroids with cardiovascular events, such as myocardial infarction, stroke, and death. Furthermore, data have been reported demonstrating increased blood pressure levels, changes in the lipid profile with increased total cholesterol and LDL-cholesterol and reduced HDL-cholesterol levels, LV hypertrophy, and systolic and diastolic ventricular dysfunction. Prolonged use of anabolic steroids may also result in increased peripheral vascular resistance, dose-dependent ventricular hypertrophy, and worsening of myocardial

contractility.^{41,42,45,46} Figure 6 displays a summary of the effects of anabolic steroids on the cardiovascular system.⁴⁷

Pathophysiology

The mechanisms responsible for the negative effects on the cardiovascular system are still not very well understood. Direct damage to myocytes and endothelial cells, reduced intracellular calcium levels, and an increase in apoptosis factors have been described as possible mechanisms. It has also been suggested that anabolic steroids have a negative effect on the system of vasodilation related to nitric oxide, contributing to the occurrence of vasoconstriction and increased peripheral vascular resistance.^{42,46,48}

Among the cases of healthy young athletes who had adverse effects as consequences of anabolic steroid abuse, the most frequent cardiovascular events include acute myocardial infarction, sudden death, atrial fibrillation, ventricular fibrillation, and the development of dilated cardiomyopathy.^{45,48}

Treatment and prevention of anabolic steroid-induced cardiomyopathy

Abuse of anabolic steroids can cause cardiomyopathy and lead to severe LV systolic dysfunction. Fortunately, in most cases it is possible to reverse the dysfunction, at least partially, after discontinuing the use of anabolic steroids.⁴⁵ The treatment of patients who present with HF due to anabolic steroids must follow the current recommendations of the guidelines.³⁶ The knowledge of the cardiovascular risks associated with the use of

these substances is essential to diagnostic suspicion and adequate treatment. In cases of heart disease related to anabolic steroids, it is fundamental to discontinue the use of the substance in order to reverse the condition. Therefore, efforts must be made to educate health professionals, especially physical education teachers, and the population as a whole regarding the harmful effects of using these substances and reinforce that the best way to avoid complications is to refrain from using anabolic steroids inappropriately, without medical indication.

Author Contributions

Conception and design of the research, Acquisition of data, Analysis and interpretation of the data AND Critical revision of the manuscript for important intellectual content: Villacorta H, Avila MS, Souza GEC, Savaris SL, Braga GA, Martins WA; Writing of the manuscript: Villacorta H, Avila MS, Souza GEC, Savaris SL, Braga GA.

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