REVIEW

THE AMERICAN JOURNAL of MEDICINE®

Chemical Cardiomyopathies: The Negative Effects of Medications and Nonprescribed Drugs on the Heart

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ABSTRACT

The heart is a target of injury for many chemical compounds, both medically prescribed and not medically prescribed. Pathophysiologic mechanisms underlying the development of chemical-induced cardiomyopathies vary depending on the inciting agent, including direct toxic effects, neurohormonal activation, altered calcium homeostasis, and oxidative stress. Numerous chemicals and drugs are implicated in cardiomyopathy. This article discusses examples of medication and nonprescribed drug-induced cardiomyopathies and reviews their pathophysiologic mechanisms.

 • *The American Journal of Medicine (2011) 124, 480-488*

KEYWORDS: Alcohol; Amphetamine; Anabolic steroid; Anthracycline; Cardiomyopathy; Chloroquine; Clozapine; Cobalt; Cocaine; Doxorubicin; Ecstasy; Ephedra; Ma huang; Methylenedioxymethamphetamine; Methylphenidate

Alcohol-Induced Cardiomyopathy

Thomas Jefferson said "it is an error to consider a heavy tax on wine as a tax on luxury. On the contrary, it is a tax on the health of our citizens." However, Abraham Lincoln warned "it has long been recognized that the problems with alcohol relate not to the use of a bad thing, but to the abuse of a good thing." The Scottish physician Graham Steell wrote in 1893 "not only do I recognize alcoholism as one of the causes of muscle failure of the heart, but I find it to be comparatively a common one."

Alcoholic cardiomyopathy occurs in a minority of alcoholics (5%-10%). However, because there are so many alcoholics, alcohol-induced cardiomyopathy is a major cause of nonischemic cardiomyopathy in Western societies (23%-40%).[1-4] Genetic predispositions have been proposed, including differences in human leukocyte antigen-B8, dopamine receptors, alcohol dehydrogenase alleles, and angiotensin-converting enzyme DD genotype.[4,5] Environmental predispositions, such as simultaneous exposure to normally non-toxic levels of cobalt and arsenic, also have been proposed as potential triggers of alcohol-induced cardiomyopathy.[5,6]

Alcohol-induced cardiomyopathy is manifested as 4-chamber dilatation and low output failure. There seems to be a dose-related effect on cardiac muscle that is independent of coronary artery disease, malnutrition, or vitamin deficiencies.[7,8] As found by Fauchier et al,[9] mortality with alcohol-induced cardiomyopathy is similar to that of nonischemic dilated cardiomyopathy with abstention (Figure 1). However, survival is poorer with continued alcohol abuse. Without abstinence, 4-year mortality is approximately 50%.

Potential mechanisms underlying the toxic effects of alcohol on the myocardium include impaired mitochondrial oxidative function, altered myofilament protein synthesis, alterations in cytosolic calcium levels, oxidative stress, and apoptosis.[4,7,10] As proposed by Piano,[4] the potential pathologic mechanisms underlying the development of an alcohol-induced cardiomyopathy are complex and require long-standing alcohol abuse (Figure 2).

Urbano-Marquez et al[11] found a linear correlation between total lifetime ethanol consumption and left ventricular ejection fraction in 52 alcoholic subjects. Laonigro et al[7] recently suggested that more than 90 g (8 drinks) per day for more than 5 years is necessary to cause alcohol-induced cardiomyopathy.[7] Another report suggested an alcohol lifetime total of 7 kg per kilogram of body weight was sufficient to cause alcohol-induced cardiomyopathy; that is, approximately 7000 bottles of wine consumed by a 70-kg

Funding: None.

Conflict of Interest: None.

Authorship: The author was the sole preparer of this manuscript and is solely responsible for its content.

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doi:10.1016/j.amjmed.2010.11.031

person.[11] In comparison, moderation, as defined by the 1995 Report to the Dietary Guidelines Committee on the Dietary Guidelines for Americans, is 1 drink per day for women and 2 drinks per day for men.[12] A drink is defined as 12 ounces of beer, 5 ounces of wine, or 1.5 ounces of 80 proof distilled spirits.

Francis et al[13] followed 11 patients with alcoholic cardiomyopathy over 7 years and found with abstention and medical therapy, ejection fractions significantly improved, in some cases to normal levels, within 1 to 2 years. More recently, Nicolas et al[14] found that abstention or a significant reduction in daily ethanol intake in 55 alcoholics with cardiomyopathy resulted in improvements in left ventricular ejection fraction compared with those who continued to drink more than 80 g of ethanol per day, who had a further decrease in left ventricular function.

The majority of alcoholics (90%-95%) experience mild abnormalities in myocardial contractile function, defined in 1980 by the World Health Organization and the International Society and Federation of Cardiology as "alcoholic heart muscle disease."[15] Hearts from these alcoholics demonstrate mild left ventricular hypertrophy and mild systolic contractile dysfunction.[16,17] Data suggest that diastolic dysfunction appears before the systolic contractile dysfunction.[16] These patients for the most part are asymptomatic, but they often have resistant hypertension. Arrhythmias can occur, including atrial fibrillation with acute intoxication (holiday heart) and malignant ventricular arrhythmias with withdrawal.[18]

The clinical characteristics of alcohol-induced cardiomyopathy are similar to other dilated cardiomyopathies. Currently, there are no diagnostic tests to differentiate alcohol-induced cardiomyopathy from other forms of dilated cardiomyopathies. There are no specific guidelines regarding the treatment of alcohol-induced cardiomyopathy. Generally recommended are angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, beta-blockers, diuretics, and digoxin for symptoms. Also recommended are correcting nutritional deficiencies and electrolyte abnormalities, and, of course, abstinence.

The echocardiographic features of alcohol-induced cardiomyopathy are similar in men and women. However, women report lower daily alcohol consumption and a shorter duration of alcohol abuse, with a lifetime alcohol dose approximately 40% lower than that of men.[11] Women have a significantly higher maximum blood alcohol concentration than men when they consume a comparable amount of alcohol. This is due to several factors. First, body composition of women differs from men. Men have a larger proportion of body water than women into which the alcohol can distribute. Women have a larger proportion of body fat (33% compared with 12% in men), into which alcohol distributes slowly from the blood. Also, women have fewer alcohol-degrading liver enzymes, alcohol and aldehyde dehydrogenases, than men.

Although moderate alcohol consumption may be associated with beneficial effects against cardiovascular disease,[19] alcohol abuse can result in dilated cardiomyopathy. "Alcohol heart muscle disease" manifests as asymptomatic systolic and diastolic ventricular dysfunction in the majority of alcoholics. However, a minority experience symptomatic congestive heart failure symptoms. Diagnosis is one of exclusion, but occurs in the setting of excessive and long-standing alcohol abuse.

CLINICAL SIGNIFICANCE

- The heart is a target of injury for many chemical compounds, both medically prescribed and not medically prescribed.
- Pathophysiologic mechanisms underlying the development of chemical-induced cardiomyopathies include direct toxic effects on myocyte structure and function, pathologic increases in sympathetic activation, and myocyte oxidative stress.
- In the event that a patient is experiencing a chemical-induced cardiomyopathy, early recognition of signs and symptoms may reverse myocardial damage and save lives.

Cobalt-Associated Alcohol-Induced Cardiomyopathy

"Quebec beer drinkers' cardiomyopathy" appeared as an epidemic among heavy beer drinkers in Canada in the mid-1960s.[6] The cardiomyopathy resembled typical dilated cardiomyopathy, except for purplish skin coloration and a high early mortality rate (42%). It was associated with development of a large pericardial effusion and low output heart failure. Quebec beer drinkers' cardiomyopathy disappeared when Canadian brewers discontinued their new practice of adding minute quantities of cobalt to beer to stabilize the foam head.

Cocaine Cardiomyopathy

Cocaine is associated with multiple cardiovascular complications, including chest pain, myocardial ischemia/infarction, arrhythmias, aortic dissection, and stroke.[20] Felker et al[21] reported cocaine use as a rare cause of cardiomyopathy, with 10 cases found among 1278 cases of dilated cardiomyopathy at Johns Hopkins Hospital.[21]

Cocaine blocks reuptake of dopamine and neuroepinephrine at the postsynaptic receptor, resulting in increased sympathetic activation (Figure 3). The mechanisms underlying cocaine cardiomyopathy are not fully understood but are thought to include sympathomimetic effects, increased calcium flux, enhanced oxidative stress, and promotion of intracoronary thrombus formation.[5]

The clinical characteristics of cocaine cardiomyopathy are similar to other forms of dilated cardiomyopathy. Cocaine cardiomyopathy should be strongly considered in young men (age < 50 years) presenting with signs of adren-