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Chemical cardiomyopathies: the negative effects of medications and nonprescribed drugs on the heart.

Vincent M Figueredo
Thomas Jefferson University, FigueredoV@einstein.edu

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CHEMICAL CARDIOMYOPATHIES: THE NEGATIVE EFFECTS OF MEDICATIONS AND NON-PRESCRIBED DRUGS ON THE HEART

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Vincent M. Figueredo, MD FACC FAHA FASE

Einstein Institute for Heart and Vascular Health, Albert Einstein Medical Center, and Jefferson Medical College, Philadelphia, PA

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Address correspondence to: Vincent M. Figueredo, MD

Einstein Institute for Heart and Vascular Health

5501 Old York Road, Levy 3232

Philadelphia, PA 19141

TEL: 215-456-8819

FAX: 215-456-3533

E-mail: figueredov@einstein.edu

ABSTRACT

The heart is a target of injury for many chemical compounds, both medically prescribed and not. Pathophysiological mechanisms underlying development of chemical-induced cardiomyopathies vary depending on the inciting agent, and can include: direct toxic effects, neurohormonal activation, altered calcium homeostasis, and oxidative stress (Figures 1 and 2). A partial listing of chemicals and drugs implicated in cardiomyopathy can be found in Table 1. The purpose of this paper is to discuss examples of medication and non-prescribed drug-induced cardiomyopathies and to review their pathophysiological mechanisms.

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 to 10%). However because there are so many alcoholics, alcohol-induced cardiomyopathy is a major cause of nonischemic cardiomyopathy in Western societies (23 to 40%) [1-4]. Genetic predispositions have been proposed, including differences in human leukocyte antigen (HLA)-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, have also been proposed as potential triggers of alcohol-induced cardiomyopathy [5, 6].

Alcohol-induced cardiomyopathy is manifested as four chamber dilatation and low output failure. There appears to be a dose-related effect on cardiac muscle, independent of coronary artery disease, malnutrition, or vitamin deficiencies [7, 8]. As found by Fauchier et al., mortality with alcohol-induced cardiomyopathy is similar to that of nonischemic dilated cardiomyopathy with abstention (Figure 3) [9]. However, survival is poorer with continued alcohol abuse. Without abstinence, four-year mortality is close to 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, the potential pathological mechanisms underlying development of an alcohol-induced cardiomyopathy are complex and require long-standing alcohol abuse (Figure 4) [4].

Urbano-Marquez et al., found a linear correlation between total lifetime ethanol consumption and left ventricular ejection fraction in 52 alcoholic subjects [11]. Laonigro et al., recently suggested that greater than 90 g (eight drinks) per day for over five years is necessary to cause alcohol-induced cardiomyopathy [7]. Another report suggested 7 kg per kilogram body weight alcohol lifetime total was sufficient to cause alcohol-induced cardiomyopathy; in other words, approximately 7000 bottles of wine consumed by a 70 kg person [11]. In comparison, moderation, as defined by the 1995 Report to the Dietary Guidelines Committee on the Dietary Guidelines for Americans, is one drink per day for women and two 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., followed 11 patients with alcoholic cardiomyopathy over seven years and found with abstention and medical therapy, ejection fractions significantly improved, in some cases to normal levels, within one to two years [13]. More recently Nicolas et al., found in 55 alcoholics with cardiomyopathy that abstention or a significant reduction in daily ethanol intake resulted in improvements in left ventricular ejection fraction compared to those that continued to drink greater than 80 g of ethanol per day, who had a further decrease in left ventricular function [14].

The majority of alcoholics (90 to 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 diastolic dysfunction appears prior to the systolic contractile dysfunction [16]. These patients, for the most part are asymptomatic, but 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 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 is 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 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 to 12%

in men), into which alcohol distributes slowly from the blood. Additionally, women have less alcohol degrading liver enzymes, alcohol and aldehyde dehydrogenases, than men.

In summary, 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.

Cobalt Associated Alcohol-Induced Cardiomyopathy

'Quebec beer drinkers' cardiomyopathy' appeared as an epidemic among heavy beer drinkers in Canada in the mid-1960's [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.,

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 post synaptic receptor, resulting in increased sympathetic activation (Figure 2). 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 intra-coronary thrombus formation [5].

The clinical characteristics of cocaine cardiomyopathy are similar to other forms of dilated cardiomyopathy. Cocaine cardiomyopathy should strongly be considered in young (less than 50 years of age) males presenting with signs of adrenergic excess and heart failure or left ventricular dysfunction. Cocaine cardiomyopathy presents suddenly without a long prodrome. The electrocardiogram tends to show sinus tachycardia with frequent arrhythmias, including atrial fibrillation and ventricular tachycardia [20]. Echocardiogram demonstrates increased left ventricular mass and dysfunction. Urine testing for cocaine and its metabolite, benzoylecgonine, should be performed.

The management of cocaine cardiomyopathy is similar to other forms of dilated cardiomyopathy, except beta-blockers should be avoided initially, and benzodiazepine should be given to blunt adrenergic excess. Beta-blockers can be added later in the compliant patient who follows up and abstains. Left ventricular function can improve dramatically with abstinence from cocaine, like alcohol. Unfortunately, the rate of recidivism is high and left ventricular dysfunction and symptomatic heart failure often recurs.

Anabolic Steroid-Induced Cardiomyopathy

Anabolic/androgenic steroids mimic the effects of male steroids testosterone and dihydrotestosterone. Increased cellular protein synthesis, results in buildup of tissue (anabolism), especially in muscles. One survey found that two thirds of elite US powerlifters self-reported use of anabolic steroids to enhance performance [22]. Anabolic steroids share with endogenous steroids influences on left ventricular hypertrophic response through actions on the androgen receptor. Androgen receptors are ubiquitously expressed, found not only in skeletal muscle cells, but also on cardiac myocytes. Anabolic steroids can cause hypertension, dyslipidemia, and impaired fasting glucose [23]. Anabolic steroids can cause alterations in heart structure, including left ventricular hypertrophy and dilation, and impaired contraction and relaxation [24, 25]. Potential sequelae include hypertension, arrhythmias, heart failure, myocardial infarction, and sudden death. Side effects are dose-dependent [26].

In a recent postmortem series of 34 anabolic steroid abusers aged 20 to 45 years, twelve showed cardiac pathology including hypertrophy, myocardial and endocardial fibrosis, cardiac steatosis, myocardial coagulation necrosis, and coronary atheroma [27]. Prolonged anabolic steroid use leads to dose-dependent reversible myocardial hypertrophy, decreased inotropic capacity of the myocardium, and irreversibly reduced compliance of the left ventricle [26].

Amphetamine-Induced Cardiomyopathy

Crean and Pohl published an interesting case report of a 30-year-old female admitted to the hospital complaining of four month history of ankle swelling, increased abdominal extension, and a three-day history of shortness of breath [28]. She admitted to four years of daily amphetamine use. She initially used amphetamines to stay thin but this became a habit. Chest x-ray showed cardiomegaly, pulmonary edema, and pleural effusion. Electrocardiogram showed sinus tachycardia with left atrial enlargement and left ventricular hypertrophy with repolarization abnormality. Echocardiogram demonstrated dilated left ventricle and atrium with a left ventricular ejection fraction a 26%. After seven days of abstention and treatment, left ventricular dilation and ejection fraction showed significant improvement.

Amphetamines are related to natural occurring biogenic amines (dopamine, serotonin, catecholamines) by their phenylethylamine structure. The mechanism of the dilated cardiomyopathy is unclear, but may be adrenegically driven (Figure 2) tachycardia-induced cardiomyopathy or recurrent hypertensive crises or tachycardia leading to left ventricular failure. Abstinence and standard dilated cardiomyopathy therapy lead to functional improvement.

Ma Huang (Ephedra)-Induced Cardiomyopathy

The dietary supplement ephedra, also known as ma huang, contains two alkaloids, ephedrine and its enantiomer, pseudoephedrine. Ma Huang has been associated with stroke, myocardial infarction, sudden death, and cardiomyopathy [29, 30]. Samenuk et al., found at autopsy in seven ma huang-related cases of sudden death, three cardiomyopathies (ages 23 to 37 years old) [29]. Ma huang increases catecholamines at synaptic areas in the brain and heart and directly

stimulates alpha and beta-adrenergic receptors (Figure 2). Thus, ma huang can increase heart rate, blood pressure, cardiac output and peripheral resistance. Coronary artery spasm and proarrhythmic effects can account for acute events and death. Prolonged catecholamine excess with long-term ma huang use is one likely underlying mechanism for cardiomyopathy.

Ecstasy (3, 4-Methylenedioxymethamphetamine)-Induced Cardiomyopathy

3, 4- Methylenedioxymethamphetamine (MDMA), commonly known as ecstasy, can cause myocardial infarction, arrhythmias and cardiomyopathy [31, 32]. Animal studies have shown that repeated administration of MDMA and/or its metabolites causes eccentric left ventricular dilation and diastolic dysfunction as well as contractile dysfunction in myocytes [31, 33]. Shenouda and colleagues demonstrated MDMA-induced myocarditis with inflammatory infiltrates and areas of necrosis [33]. MDMA is metabolized to catechols that can undergo redox cycling, producing reactive oxygen and nitrogen species [34]. This suggests that potential mechanisms of MDMA-induced cardiomyopathy are related to oxidative stress, as well as catecholaminergic stimulation.

Anthracycline-Induced Cardiomyopathy

Doxorubicin (Adriamycin) has been used in oncologic practice since the late 1960s. Tumors most commonly treated with doxorubicin include breast and esophageal carcinomas, osteosarcoma, Kaposi's sarcoma, soft tissue sarcomas, Hodgkin's and non-Hodgkin's lymphomas. Unfortunately, reports of fatal cardiotoxic effects have subdued enthusiasm for

doxorubicin. Swain and colleagues found in a group of 630 patients receiving doxorubicin that congestive heart failure developed in less than 5% of patients receiving a cumulative dose of 400 mg/m^2 of body surface area, 16% at 500 mg/m^2, 26% at 550 mg/m^2, and 48% at a dose of 700 mg/m^2 (Figure 5) [35]. As shown in Figure 6, Lipshultz et al., found differences in the relationship between cumulative dose of doxorubicin and probability of depressed left ventricular contractility in female versus male patients [36].

Cardiomyopathy generally occurs within a month to a year, but may occur up to six to twenty years later [36, 37]. Risk factors for anthracycline-induced cardiomyopathy include: age greater than 70 years, diabetes, gender, hypertension, liver disease, poor nutrition, mediastinal radiotherapy, previous cardiac disease, or simultaneous administration of other anti-neoplastic agents such as cyclophosphamides, actinomycin D, bleomycin, cisplatin, and methotrexate [36-39].

The etiology of anthracycline-induced cardiomyopathy is likely multifactorial. Anthracyclines promote generation of free radicals and oxidative stress that correlates with cellular injury [38-40]. Anthracyclines are associated with a decrease in endogenous antioxidants responsible for scavenging free radicals [38-40]. Cardiac myocytes have limited capacity to deal with free radicals. Other anthracycline-induced mechanisms of cell injury may include apoptosis, elevated calcium accumulation in mitochondria, and modulation of cardiac gene expression [38-40].

Diagnosis of anthracycline-induced cardiomyopathy centers on serial echocardiography or radionuclide imaging to evaluate left ventricular ejection fraction. An example is shown in Figure 7. Invasive test such as angiography with radiolabeled anti-myosin antibody or

metaiodobenzylguanidine, or endo myocardial biopsy have high sensitivity, but increased complication risk and high expense.

Strategies have been attempted to prevent doxorubicin-induced cardiomyopathy. These include the use of doxorubicin analogues (carminomycin, detorubicin, esorubicin, marcellomycin, quelamycin, rodorubicin, epirubicin, and idarubicin) and administration of doxorubicin in combination with cardioprotective agents such as probucol [40]. These approaches have had limited success. The greatest success has been found with limitations on the amount of drug used and alternate drug delivery methods, such as continuous infusion over a six hour period rather than rapid infusion. An empirical dose limit of 500 mg/m^2 of body surface area is suggested as a strategy to minimize the risk of cardiomyopathy.

Treatment of anthracycline-induced cardiomyopathy is similar to that of other dilated cardiomyopathies, including angiotensin converting enzyme inhibitors, beta-blockers, diuretics, and digoxin. The only curative option is transplantation. After heart failure occurs, the prognosis is poorer with anthracycline-induced cardiomyopathy then with other dilated or ischemic cardiomyopathies. Despite dose-dependent cardiotoxic effects, doxorubicin remains in use because of efficacy in the treatment of several types of tumors.

Other Antineoplastic Drugs Causing Cardiomyopathy

Tyrosine kinase inhibitors are small molecule agents that inhibit cellular signaling involved in tumor cell angiogenesis and proliferation. Sunitinib is approved for treatment of renal cell

carcinoma and gastrointestinal stromal tumours. Varying rates of cardiac toxicity have been reported with Sunitinib, ranging as high as 11% [41].

Trastuzumab is a recombinant IgG monoclonal antibody that binds to the human epidermal growth factor receptor 2 protein (HER2) and is used for treatment of breast cancers that over expresses HER2. Trastuzumab has been found to cause heart failure and left ventricular dysfunction [42].

Chloroquine-Induced Cardiomyopathy

August and colleagues report a case of a 81 year old female with rheumatoid arthritis treated intermittently over 25 years with chloroquine (Aralen) 250 mg/day [43]. The patient was hospitalized for acute right heart failure. Physical exam found bilateral lower extremity edema and hepatomegaly. Electrocardiogram showed sinus rhythm at 58 bpm, left anterior fascicular block, and left and right ventricular hypertrophy. An echocardiogram found hypertrophic myopathy with hypokinesis, left atrial and right ventricular dilatation. On the twelfth day of admission she developed complete heart block with a ventricular escape rhythm at 30 bpm. Although a pacemaker was implanted, she died from low output syndrome on the sixteenth day of hospitalization.

Chloroquine and derivates (e.g., hydroxychloroquine) treat rheumatoid arthritis, sarcoidosis, systemic lupus erythematous, and malaria,. Cardiotoxic effects include conduction disturbances such as bundle branch blocks and complete heart block, and biventricular hypertrophy with restrictive cardiomyopathy, several of which were found in the aforementioned case [43].

Chloroquine inhibits lysosomal hydrolases, decreasing digestive efficacy of phagocytic cells. Chloroquine is known to affect lysosomal membranes of other cells, especially skeletal and cardiac myocytes Vacuolated cardiomyocytes due to intra-lysosomal accumulations of lipids and curvilinear structures have been observed [43].

Clozapine Myocarditis and Cardiomyopathy

Clozapine (Clozaril, FazaClo) is only approved for treatment-resistant schizophrenia. Numerous cases of myocarditis have occurred; some fatal [44-46]. Post-marketing experience suggests there is an increased risk of myocarditis, occurring most commonly within the first two months of treatment. Cardiomyopathy has also been reported; generally occurring later in treatment and in some cases fatal [45]. Tachycardia is a common side effect of clozapine treatment (25% of users), especially during dose titration in early treatment. It is essential that patients with persistent tachycardia at rest, especially in first two months of clozapine treatment, are closely observed for other signs and symptoms of myocarditis and cardiomyopathy [45].

Methylphenidate-Induced Cardiomyopathy

Several cases of methylphenidate (Ritalin, Concerta, Metadate or Methylin) cardiomyopathy, including two from Norway in patients of 17 and 18 years of age, have been reported [47, 48]. A 2006 United States Food and Drug Administration report ordered a black box warning placed on drugs treating attention-deficit hyperactivity disorder (ADHD) due to various cardiovascular side effects, including cardiomyopathy [49]. While the mechanism is not completely understood,

methylphenidate does have a central nervous system stimulating action similar to amphetamines. Methylphenidate alters myocardial ultra-structure in rats [50].

Conclusions

The heart is a target of injury for many chemical compounds, both medically prescribed and not. Pathophysiological mechanisms underlying development of chemical-induced cardiomyopathies vary depending on the inciting agent. Alcohol abuse can have direct toxic effects on myocyte structure and function. Cocaine, amphetamines and substituted amphetamines (e.g., ecstasy and ma huang) cause pathological increases in sympathetic activation. Anthracyclines produce myocyte oxidative stress. Whether prescribed or not, discussions with patients regarding the potential risk of cardiomyopathy are necessary. In the rare event that a patient is experiencing a chemical-induced cardiomyopathy, early recognition of signs and symptoms may reverse myocardial damage and save lives.

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Table 1: Medications, non-prescribed drugs and chemicals implicated in cardiomyopathy.

Figure Legends:

1. Potential mechanisms involved in chemical-induced cardiomyopathies.

2. Effects of various drugs on the presynaptic axon terminal and postsynaptic cells in the heart. Left: normal functioning dopamine transporter (DAT; as well as norepinephrine and serotonin transporters) and vesicular monoamine transporter (VMAT) in the presynaptic axon terminal, and dopamine uptake in the postsynaptic cell. Center: cocaine, a transporter antagonist, increases extracellular dopamine (and neuroepinephrine) by binding to DAT and blocking neurotransmitter uptake. Right: amphetamine and substituted amphetamines, including methamphetamine, methylphenidate (Ritalin), methylenedioxymethamphetamine (ecstasy), and ephedra (ma huang), reverse the action of the DAT and VMAT, increasing neurotransmitter available in the synapse.

3. Survival curves of cardiac deaths in patients with alcoholic dilated cardiomyopathy (with (—) and without (– –) abstinence) and idiopathic dilated cardiomyopathy (· ·). Idiopathic dilated cardiomyopathy versus alcoholic dilated cardiomyopathy with abstinence, P=ns; idiopathic dilated cardiomyopathy versus alcoholic dilated cardiomyopathy without abstinence, *P*=0·002; alcoholic dilated cardiomyopathy with abstinence versus alcoholic dilated cardiomyopathy without abstinence, P=0·003. Reprinted with permission from Fauchier L, Babuty D, Poret P, et al.: Comparison of long-term outcome of alcoholic and idiopathic dilated cardiomyopathy. Eur Heart J 2000; 21(4): 306-14.

4. Proposed hypothetical schema for the pathogenesis of alcohol-induced cardiomyopathy. gms = grams; NE = norepinephrine. Reprinted with permission from Piano MR: Alcoholic cardiomyopathy: incidence, clinical characteristics, and pathophysiology. Chest 2002; 121(5): 1638-50.

5. Cumulative doxorubicin dose at onset (on study or off study) of doxorubicin-related congestive heart failure in 630 patients who were randomized to receive a doxorubicin-containing regimen plus placebo. Reprinted with permission from Swain SM, Whaley FS, Ewer MS: Congestive heart failure in patients treated with doxorubicin: a retrospective analysis of three trials. Cancer 2003; 97(11): 2869-79.

6. Probability of depressed left ventricular contractility as a function of the cumulative dose of doxorubicin in female and male patients. Reprinted with permission from Lipshultz SE, Lipsitz SR, Mone SM, et al.: Female sex and drug dose as risk factors for late cardiotoxic effects of doxorubicin therapy for childhood cancer. N Engl J Med 1995; 332(26): 1738-43.

7. Technetium-99m-pertechnetate multigated acquisition scans (MUGA) in a 47 year old female with breast cancer treated with doxorubicin. The top scan was performed prior to initiation of doxorubicin and cyclophosphamide therapy in September 2009. The left ventricular ejection fraction (LVEF = (LV end-diastolic counts minus LV end-systolic counts)/LV end-diastolic counts X 100) was calculated at 60%. The bottom scan was performed in March 2010 after treatment with a total doxorubicin dose of 451 mg/m^2. LVEF was calculated at 28%. White arrows point to left ventricle during end-diastole and end-systole.