Progress in Cardiovascular Diseases 52 (2010) 289–299
www.onlinepcd.com

# Alcoholic and Cocaine-Associated Cardiomyopathies

Eric H. Awtry, George J. Philippides*

*Cardiovascular Section Boston Medical Center, Boston, MA 02118, USA*
*Boston University School of Medicine, USA*

**Abstract** Alcohol and cocaine use are associated with significant cardiovascular complications, including cardiomyopathy. The pathophysiologic mechanisms underlying the development of these toxic cardiomyopathies vary depending on the inciting agent but include direct toxic effects, neurohormonal activation, altered calcium homeostasis, and oxidative stress. The typical patient with alcoholic cardiomyopathy is a long-term excessive alcohol consumer who is otherwise indistinguishable from other patients with nonischemic cardiomyopathy. The typical patient with cocaine cardiomyopathy is a young male smoker who presents with signs of adrenergic excess. Management of these patients is similar to that of patients with other forms of dilated cardiomyopathy, although β-blockers should be avoided in patients with cocaine-associated heart failure and benzodiazepines should be given in this setting to blunt adrenergic excess. Left ventricular function may improve dramatically with abstinence from alcohol or cocaine. Unfortunately, the rate of recidivism is high and left ventricular dysfunction and symptomatic heart failure often recurs. (Prog Cardiovasc Dis 2010;52:289-299)


*Keywords:* Cocaine; Alcohol; Cardiomyopathy; Heart failure; β-blockers

The excessive use of alcohol or cocaine has been associated with a variety of cardiovascular complications, and the increased prevalence of the abuse of these substances in developed societies has resulted in a significant burden of cardiovascular disease. While hypertension, chest pain, accelerated atherosclerosis, and arrhythmias are important and well-recognized effects of alcohol and/or cocaine abuse, the scope of this article will be limited to a review of the effects of these agents on the development of myocardial dysfunction, cardiomyopathy, and clinical heart failure.

Statement of Conflict of Interest: see page 298.

* Address reprint requests to George J. Philippides, MD, F.A.H.A, Associate Chair for Clinical Affairs, Assistant Professor of Medicine, Boston Medical Center 88 East Newton Street, Collamore 818 H, Cardiovascular Office Boston, MA 02118.

*E-mail address:* george.philippides@bmc.org (G.J. Philippides).

## Alcoholic cardiomyopathy

For the past several decades, a series of epidemiologic studies and meta-analyses have revealed a beneficial effect of low to moderate levels of alcohol consumption on cardiovascular risk.[1-3] These studies demonstrate that otherwise healthy moderate alcohol drinkers are less likely to develop coronary heart disease (CHD) than their nondrinking counterparts.[4] In addition, moderate alcohol consumption (compared with alcohol abstinence) is associated with reduced mortality in otherwise healthy persons and in those with established CHD, diabetes, or hypertension.[5] A variety of mechanisms have been proposed to explain the cardiovascular benefit of alcohol including alterations in the serum lipid profile (increased HDL), inhibition of platelet aggregation, improved endothelial function, reduction in clotting factors, increased endogenous fibrinolytic activity, improved glucose metabolism, and reduced inflammation.[6,7]

0033-0620/$ – see front matter 
doi:10.1016/j.pcad.2009.11.004

**Abbreviations and Acronyms**

**ACE** = angiotensin-converting enzyme

**ACM** = alcoholic cardiomyopathy

**CHD** = coronary heart disease

**EKG** = electrocardiogram

**IDCM** = idiopathic dilated cardiomyopathy

**RAS** = renin-angiotensin system

Nonetheless, enthusiasm regarding the cardioprotective effects of alcohol has been tempered by the recognition that higher levels of alcohol consumption are associated with increases in CHD risk[3] and in overall mortality[8] (Fig 1). Furthermore, long-term excessive alcohol consumption has been associated with the development of heart failure,[9-11] and heavy alcohol consumption has been identified as a leading cause of nonischemic dilated cardiomyopathy in the United States.[12]

### *Definitions*

The definition of a standard alcoholic drink varies. In general, one drink represents 0.5 to 0.6 fl oz or 12 to 14 g of alcohol. This is equivalent to 5 oz of wine, 12 oz of beer, or 1.5 oz of 80-proof distilled spirits or liquor. Moderate drinking is defined as up to 1 drink daily for women and 1 to 2 drinks daily for men. Levels of alcohol intake greater than this are usually considered heavy drinking, whereas binge drinking refers to the consumption more than a 2-hour period of more than 4 drinks for men and more than 3 drinks for women. According to the most recent statistics, greater than 50% of American adults drank alcohol at some time in the past 30 days, whereas approximately 5% of adults admit to being heavy consumers of alcohol and 15% of the population reports binge drinking.[13]

### *Relationship of mild to moderate alcohol use to heart failure*

Mild to moderate alcohol consumption has not been associated with the development of heart failure or cardiomyopathy. In fact, most studies support a beneficial effect of moderate drinking on the risk of developing heart failure and a reduction in mortality in patients with established heart failure. In the Framingham heart study, the hazard ratio for congestive heart failure was lowest among men who consumed 8 to 14 alcoholic drinks/wk (hazard ratio, 0.41) compared with those who consumed less than 1 drink/wk; a similar but statistically insignificant pattern was seen for women.[14] In the Cardiovascular Health Study, moderate alcohol consumption (7-13 drinks/wk) was associated with a 34% lower risk of congestive heart failure in patients older than 65 years.[15] Similarly, in the Physician's Health Study, moderate drinking lowered the risk of heart failure by as much as

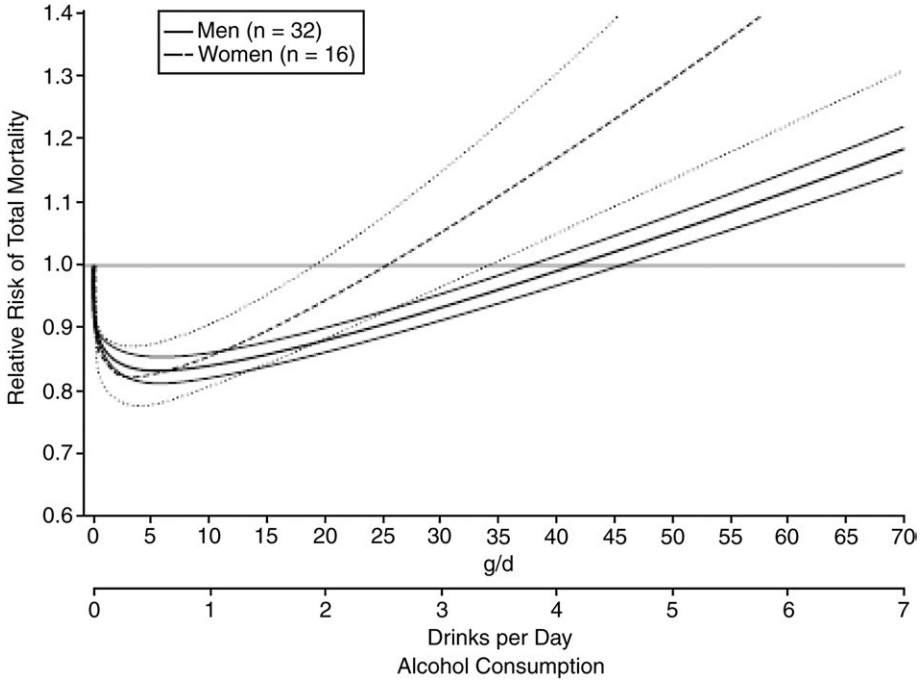


Fig 1. Relative risk of total mortality (99% confidence interval) and alcohol intake in men and women. Reprinted from Di Castelnuivo et al,[8] with permission from the publisher.

58%,[16] an effect that persisted when a subset of hypertensive subjects was evaluated.[17] Thus, it appears that moderate alcohol consumption has a beneficial effect on the risk of heart failure. Several studies have demonstrated that this effect may be limited to patients who have heart failure in the setting of an antecedent myocardial infarction, suggesting that the benefit of alcohol on heart failure risk may be mediated via a reduction in coronary artery disease.[15,16]

### *Relationship of heavy alcohol use to heart failure*

An absolute causal relationship between heavy alcohol consumption and congestive heart failure is difficult to establish and prospective data are largely lacking. In addition, some studies have shown not only no association between heavy alcohol use and cardiomyopathy but also a potential benefit.[14] Nonetheless, most data support an association, and various studies have reported a high rate of abnormal left ventricular systolic and diastolic dysfunction among patients who are heavy consumers of alcohol.[11,18-20] Furthermore, heavy alcohol use is reported in up to 40% of patients with idiopathic dilated cardiomyopathy (IDCM),[10] and patients with IDCM are significantly more likely to be heavy alcohol users than patients without cardiomyopathy.[21]

The prevalence of symptomatic alcoholic cardiomyopathy (ACM) in the population of heavy alcohol consumers is not well defined although it is probably a small minority, perhaps as low as 1% to 2%.[22] Conversely, asymptomatic ventricular dysfunction may be relatively frequent in this population. In one series of 150 asymptomatic alcoholic patients (100 men, 50 women), almost a third had echocardiographic evidence of cardiomyopathy.[23] Owing to the high prevalence of alcoholism, ACM is a leading cause of nonischemic dilated cardiomyopathy in Western societies, accounting for 21% to 36% of all cases.[21,24]

The amount and duration of alcohol consumption necessary to develop ACM is currently unknown. Although some studies have demonstrated an inverse relationship between total lifetime alcohol dose and ventricular systolic[11] and diastolic[9] functions, most studies have failed to reveal a linear dose-response relationship. Nonetheless, in general, alcoholic patients with asymptomatic ventricular dysfunction have had a daily consumption of more than 90 g of alcohol for at least 5 years.[24] Patients with symptomatic heart failure and ACM appear to have had a longer duration of heavy alcohol use compared to patients with asymptomatic ACM (>10-15 years).[11,25] It is likely that a prolonged preclinical stage of ACM exists before the development of clinical heart failure. During this preclinical stage, patients remain asymptomatic despite demonstrable abnormalities of ventricular function on echocardiography.

### *Gender considerations*

In a series of studies from an ambulatory alcohol treatment center in Spain, the incidence of echocardiographic features of cardiomyopathy in asymptomatic patients and symptomatic heart failure in patient with ACM were noted to be similar in men and women.[23,26] However, women reported lower daily alcohol consumption and a shorter duration of alcoholism,[26] and the lifetime dose of alcohol was 40% lower in women with ACM than in their male counterparts.[23] Furthermore, although women and men enjoy a similar mortality benefit with moderate alcohol consumption, the detrimental effects of higher alcohol intake are seen at lower daily doses in women than in men.[8] These data suggest a heightened sensitivity of women to the toxic myocardial effects of alcohol.

### *Pathophysiologic mechanisms of ACM*

The mechanism whereby alcohol causes myocardial injury has not been completely elucidated but is likely multifactorial (Fig 2). Chronic ACM is associated with histologic abnormalities that are similar to other forms of IDCM including alteration in myofibrillar architecture, mitochondrial abnormalities, widening of gap junctions between myocytes, alterations of the sarcoplasmic reticulum, inflammatory infiltrates, lipid deposition, and fibrosis.[27,28] Recent studies have yielded further insight into the pathophysiologic mechanisms responsible for these histologic changes.

The acute ingestion of moderate amounts of alcohol by healthy young adults results in a reduction in left ventricular end-diastolic dimension, wall stress, and systemic vascular resistance, reflecting a fall in both preload and afterload. Despite this, left ventricular contractility is also reduced suggesting that alcohol, or its metabolite, is a direct myocardial depressant.[29] Nonoxidative metabolism of alcohol results in the production of fatty acid ethyl esters. These compounds have been shown to be produced in the heart and to induce mitochondrial dysfunction through uncoupling of mitochondrial oxidative phosphorylation.[30] Such an effect results in inefficient energy production and may contribute to the myocardial dysfunction seen in ACM.

Alcohol undergoes oxidative metabolism in the liver, and to a lesser extent in the heart, through the action of alcohol dehydrogenase. This results in production of the toxic metabolite acetaldehyde, which is subsequently metabolized by the enzyme aldehyde dehydrogenase. In animal models, acetaldehyde has been shown to impair cardiac excitation-contraction coupling, inhibit the release of calcium from the sarcoplasmic reticulum,[31,32] and markedly inhibit myocardial protein synthesis.[33] These effects could contribute to depression of ventricular systolic function. Studies in transgenic rats support the hypothesis that acetaldehyde may be a mediator of ACM. Rats that overexpress alcohol

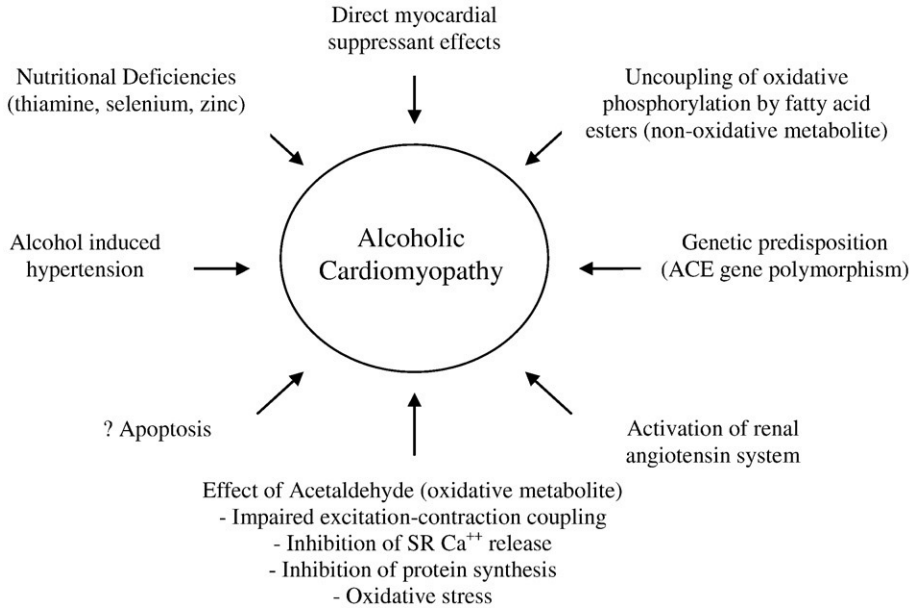


Fig 2. Potential pathophysiologic mechanisms underlying the development of alcoholic cardiomyopathy.

dehydrogenase develop increased acetaldehyde levels in response to alcohol ingestion and develop glucose intolerance, cardiac hypertrophy, and contractile dysfunction.[34] Furthermore, transgenic mice that overexpress aldehyde dehydrogenase have reduced levels of acetaldehyde after chronic alcohol ingestion and do not develop the alcohol-induced cardiac hypertrophy, reduced fractional shortening, or impaired calcium homeostasis seen in wild type mice.[35] In addition, acetaldehyde dehydrogenase overexpression attenuates alcohol-induced myocardial fibrosis, apoptosis, and oxidative stress, effects that may to be mediated, at least in part, through reversal of alcohol-induced abnormal activation or up-regulation of signaling proteins.

Activation of the renin-angiotensin system (RAS) has also been proposed as a possible contributor to the development of ACM. In a study by Cheng et al,[36] 22 dogs were given alcohol, alcohol plus irbesartan, or placebo for 6 months, and cardiac function and the RAS were serially evaluated. Alcohol ingestion was associated with sustained activation of the RAS, increased expression of angiotensin II type 1 receptors in the left ventricle, and a progressive decline in measures of ventricular function, effects that were prevented by coadministration of the angiotensin receptor blocking agent. Polymorphisms of the angiotensin-converting enzyme (ACE) gene may impart a genetic vulnerability to ACM. In a case-control study of men who are long-term alcohol users, those with symptomatic ACM were much more likely to have ACE gene alleles associated with higher circulating levels of ACE and angiotensin II than were subjects with normal ventricular function (50% vs 7%, respectively).[37] These findings suggests a possible role of the RAS in the pathogenesis of ACM.

Several other factors may contribute to the development of ACM. Nutritional abnormalities are common among alcohol individuals. Thiamine or selenium deficiency can result in beriberi and Keshan disease, respectively, and may produce a cardiomyopathy independent of the effects of alcohol. Zinc deficiency is a common feature of alcoholism and animal models suggest that zinc deficiency may contribute to the cardiac fibrosis seen in ACM through its effects on collagen deposition and degradation.[38] Cobalt was previously used as a foaming agent in beer but was found to be associated with the development of large pericardial effusions and low-output heart failure ("beer-drinkers' heart").[39] This condition is now mainly of historical interest.

### *Presentation/diagnosis*

The clinical characteristics of patients with ACM are similar to those of patients with other forms of dilated cardiomyopathy,[10,40] although patients with ACM are more likely to be male and more likely to be smokers.[40] The severity and duration of presenting symptoms do not distinguish between these forms of cardiomyopathy,[10,40] and physical examination findings are similar in the absence of cirrhosis. It is worthwhile noting that the assessment of right-sided heart failure may be difficult in the face of advanced alcoholism when cirrhosis is present. In this regard, estimation of the jugular venous pressure may help distinguish whether ascites and edema reflect heart failure (elevated jugular venous pressure) or cirrhosis (normal or low jugular venous pressure).

Although abnormal liver function tests, elevated mean red cell corpuscular volume, thrombocytopenia, and coagulopathy may suggest alcohol abuse, there is currently no diagnostic test that can differentiate ACM from other forms of IDCM, and echocardiographic and invasive hemodynamic parameters are similar in these 2 populations. Thus, the diagnosis is presumed on the basis of a history of long-term heavy alcohol consumption and the absence of other identifiable causes of cardiomyopathy. In this regard, it is essential that physicians consider the diagnosis of ACM in patients presenting with heart failure and obtain a through alcohol history.[41] In addition, a search for other potential causes should be undertaken including an ischemic evaluation for all patients with atherosclerotic risk factors, symptoms of coronary artery disease, or evidence of prior myocardial infarction on electrocardiogram (EKG) or echocardiogram.

Echocardiographically, ACM is characterized by dilatation of the ventricles, increased LV mass, normal or reduced left ventricular wall thickness, and ventricular dysfunction[24]; however, the presence of these individual abnormalities depends on the clinical stage and severity of the disease. Echocardiographic studies in long-term alcohol users without symptoms of heart failure have demonstrated increased left ventricular wall thickness and mass without ventricular dilatation,[11,18] as well as abnormalities in diastolic function including prolonged isovolumic relaxation time, longer deceleration time, and reversal of early and late diastolic filling velocities.[9,42] These abnormalities likely reflect a preclinical stage of ACM. Most studies in asymptomatic patients demonstrate no difference in ventricular systolic function between alcoholic patients and nonalcoholic controls; however, patients with ACM and heart failure routinely have depressed ventricular systolic function.[26] Autopsy studies suggest that there is a nonlinear U-shaped relationship between alcohol consumption and both LV and RV sizes. Light, moderate, and even heavy alcohol consumption are associated with a decrease in ventricular size; only with very heavy alcohol consumption (>180 g/d) was an increase in ventricular size noted.[43]

### *Prognosis*

There are conflicting reports regarding whether ACM portends a better prognosis than other forms of nonischemic dilated cardiomyopathy. In a retrospective analysis of 23 patients with ACM and 52 patients with IDCM who had similar symptom severity, ejection fraction, and ventricular size, the 1-, 5-, and 10-year survival was significantly greater in patients with ACM.[44] In contrast, data from a prospective multicenter registry demonstrated that 7-year transplant-free survival was significantly lower in patients with ACM than in patients with IDCM, irrespective of whether abstinence from alcohol occurred.[10] In a larger prospective study of 134 patients with dilated cardiomyopathy, 50 of whom had ACM, there was no difference in mortality between patients with ACM

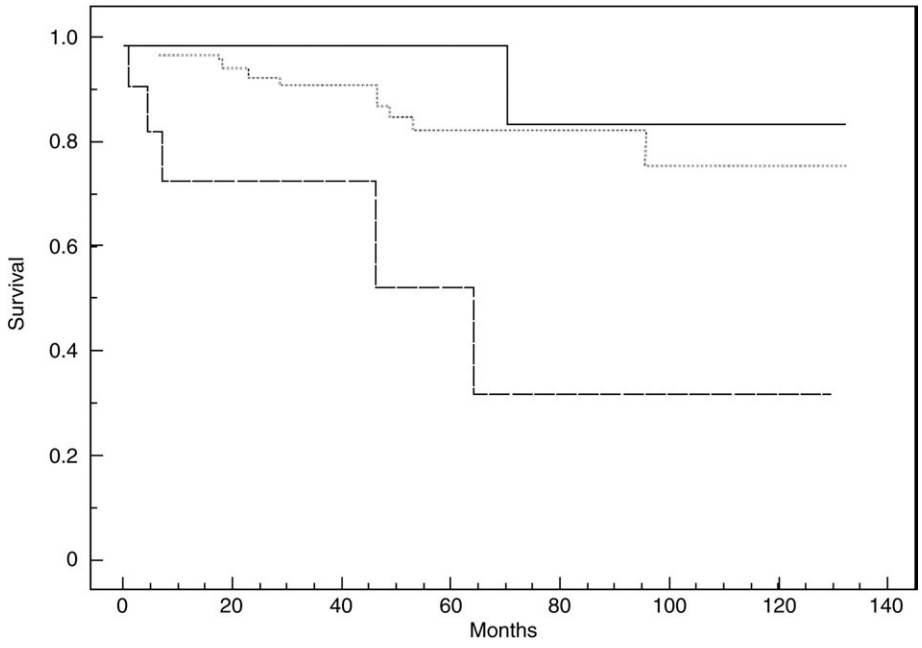


Fig 3. Survival curves of cardiac deaths in patients with alcoholic dilated cardiomyopathy (with [——] and without [– – –] abstinence) and idiopathic dilated cardiomyopathy (···). Idiopathic dilated cardiomyopathy vs alcoholic dilated cardiomyopathy with abstinence, $P$ = not significant; idiopathic dilated cardiomyopathy vs alcoholic dilated cardiomyopathy without abstinence, $P$ = .002; alcoholic dilated cardiomyopathy with abstinence vs alcoholic dilated cardiomyopathy without abstinence, $P$ = .003. Reprinted from Fauchier et al,[3] with permission from the publisher.

and IDCM at a mean follow-up of 4 years, and the lack of abstinence during follow-up was an independent predictor of cardiac death[40] (Fig 3). This later finding was also seen in an earlier study investigating the natural history of ACM, which also found that a shorter duration of symptoms preceding the diagnosis of ACM was associated with better long-term outcome.[45]

### *Treatment*

There are no specific guidelines regarding the treatment of alcoholic cardiomyopathy. In general, treatment is similar to that of patients with other forms of nonischemic dilated cardiomyopathy.[46] The ACE inhibitors or angiotensin receptor blocking agents have theoretical benefit in ACM (see prior section regarding pathophysiologic mechanisms) and should be considered even in asymptomatic patients with only mild systolic dysfunction. As with other forms of IDCM, $\beta$-blocker therapy should be instituted in patients with systolic dysfunction, irrespective of symptoms. However, in patients with ACM, a thorough substance abuse history should be taken as polysubstance use is frequent, and $\beta$-blocker therapy may be problematic in the face of concomitant cocaine use (see below). Other medications including diuretics and digoxin should be used for symptoms control, based on published guidelines.[46] Alcoholic patients often have poor dietary habits; nutritional deficiencies and electrolyte abnormalities should be assessed and corrected.

### *The issue of abstinence*

An essential part of the therapy for ACM is a reduction in alcohol consumption. Early studies have demonstrated reversibility of ventricular dysfunction and improved mortality with alcohol cessation,[40,45,47] and most physicians continue to encourage complete abstinence in this setting. Nonetheless, data suggest that a reduction in consumption may have equivalent benefit. In a prospective cohort study of 55 alcoholic men who had been drinking at least 100 g of alcohol daily for at least 10 years,[48] patients who abstained from alcohol had a significant improvement in ejection fraction from 39% to 52% at 1 year of follow-up. Patients who drank 20 to 60 g of alcohol daily had similar improvements in ejection fraction (37%-50%), whereas patients who continued to drink heavily (>80 g/d) had a deterioration in ventricular function (40%-36%). Importantly, 10 patients died during 4 years of follow-up, all of whom continued to drink heavily. In the Studies of Left Ventricular Dysfunction,[49] a subset of 2594 patients who were light-to-moderate drinkers (1-14 drinks/wk) were compared with 3719 patients who were nondrinkers. All patients had an ejection fraction of 35% or less. Mortality rates with significantly lower among the light-to-moderate drinkers (7.2 vs 9.4 deaths/100 person-years; $P < .001$), an effect that was limited to the patients with ischemic cardiomyopathy. Among patients with IDCM, light-to-moderate drinking had neither a harmful nor beneficial effect on mortality.

### *Summary*

Although moderate alcohol consumption appears to be associated with beneficial effects on the risk of cardiovascular disease, heavy alcohol use may result in the development of a dilated cardiomyopathy, manifesting as either asymptomatic ventricular dysfunction or symptomatic congestive heart failure. The diagnosis is usually one of exclusion but occurs in the setting of excessive and long-standing alcohol abuse. Treatment of ACM is similar to that of other forms of dilated cardiomyopathy. Complete abstinence or a significant reduction in alcohol consumption is a mandatory component of long-term management.

## Cocaine cardiomyopathy

Cocaine is one of the most commonly used illicit drugs in the United States. According to the 2005 National Survey on Drug Use and Health, 34 million Americans, roughly 14% of the population 12 years or older, have tried cocaine at least once.[50] The widespread abuse of this potent and addictive drug has resulted in a large number of cardiovascular complications including chest pain, myocardial ischemia, myocardial infarction, life-threatening arrhythmias, aortic dissection, and stroke.

### *Epidemiology*

The exact incidence of cocaine cardiomyopathy is unknown and likely underreported. The medical literature to date consists mostly of case reports[51] describing young men with a history of cocaine abuse and reversible cardiomyopathy. In one review of 1278 cases of dilated cardiomyopathy patients at Johns Hopkins, only 10 cases were related to cocaine use. In a study of 84 asymptomatic apparently healthy cocaine users, left ventricular systolic dysfunction was diagnosed in 6 (7%) by radionuclide angiography performed 2 weeks after cocaine use.[52]

### *Pathophysiology*

The exact mechanism by which cocaine abuse causes cardiomyopathy is not fully understood. Furthermore, the amount and duration of cocaine use necessary to develop cocaine cardiomyopathy is currently unclear. Several pharmacologic effects of cocaine appear to be directly and indirectly related to its toxic myocardial actions.

#### *Promotion of intracoronary thrombus formation*

Cocaine ingestion stimulates platelet hyperaggregability and increased thromboxane production, often in the

setting of coronary vasospasm. These physiologic effects promote acute intracoronary thrombus formation and myocardial ischemic events and account, in part, for the increased incidence of myocardial infarction noted in cocaine users. Acute coronary ischemia and extensive or recurrent myocardial infarction also contribute to the left ventricular dysfunction and cardiomyopathy associated with cocaine abuse. However, many cocaine abusers with severe regional or global left ventricular dysfunction do not have a clear history of obstructive coronary disease or myocardial infarction. In one study, 33 patients with a history of cocaine abuse and with cardiac symptoms underwent coronary angiography. Eighteen patients (55%) had left ventricular dysfunction defined as an ejection fraction less than 50%, whereas only 12 patients had coronary artery disease and regional wall motion abnormalities. Of interest, 6 patients exhibited diffuse left ventricular dysfunction with nonobstructive coronary anatomy.[53] These findings suggest that myocardial dysfunction can result from transient ischemic insults, perhaps in the setting of vasospasm or spontaneous coronary thrombosis. Alternatively, it is likely that nonischemic mechanisms of myocyte injury may also contribute.

*Sympathomimetic effects*

The physiologic effects of cocaine are predominantly mediated by inhibition of the reuptake of norepinephrine and dopamine at the presynaptic adrenergic terminals, leading to an accumulation of catecholamines at the postsynaptic receptor sites. Cocaine may also amplify the release of catecholamines from the both the central nervous system and the adrenal medulla. Thus, cocaine acts as a powerful sympathomimetic agent. Stimulation of the $\beta$-adrenergic receptors in myocardial tissue results in increased contractility and heart rate, whereas stimulation of the $\alpha$-adrenergic receptors in coronary and peripheral arteries results in increased coronary resistance, decreased coronary blood flow, elevated blood pressure, and increased myocardial wall stress.

Animal studies suggest that the increased wall stress seen in acute cocaine intoxication plays an important role in the acute depression of left ventricular function. Mehta and colleagues examined LV function in 30 sedated closed-chest dogs after cocaine infusion. Ejection-phase indices of left ventricular function were reduced by cocaine, but the effects were attributable to increased wall stress not to reduced contractility.[54,55]

Pathologic studies have revealed contraction band necrosis in the hearts of patients with cocaine cardiomyopathy and those with pheochromocytoma. These pathologic similarities suggest that chronic catecholamine stimulation may play a role in the development of cocaine cardiomyopathy.[56] Autopsy results from 40 cocaine using patients who died traumatic deaths suggest that cocaine may also exert direct toxic effects on the myocardium, resulting in myocardial inflammation, interstitial fibrosis, ventricular dilation, and clinical heart failure.[57]

*Increased calcium flux into smooth muscle cells*

$\beta$-Adrenergic stimulation causes increased calcium influx into myocardial cells. Immediately, the increased intracellular calcium concentration results in increased force of contraction; however, chronically high calcium concentrations may ultimately impair myofilament responsiveness and depress left ventricular performance.

*Enhanced oxidative stress*

Animal experiments suggest that cocaine-induced oxidative stress may play a role in the development of cardiomyopathy. In a study by Isabelle et al,[58] Wistar rats were injected with cocaine to produce left ventricular dysfunction. Administration of nicotinamide adenine dinucleotide phosphate and xanthine oxidase inhibitors, which may prevent the excess production of reactive oxygen species, prevented cocaine-induced cardiomyopathy.

## *Presentation/diagnosis*

*Patient characteristics*

The clinical characteristics of patients with cocaine cardiomyopathy are similar to those of patients with other forms of dilated cardiomyopathy. Case reports of patients presenting to emergency departments with cocaine-associated chest pain reveal that most patients were young (mean, 38-44 years), male ( 87%), and were active smokers (84-91%).[59,60] Thus, cocaine cardiomyopathy should be strongly considered in relatively young (<50 years old) male patients who present with heart failure or LV dysfunction. It should also be considered in older patients (>50 years) without a clear etiology of ventricular dysfunction.

## *History/presenting symptoms*

The symptoms of cocaine cardiomyopathy often present suddenly without a long prodrome but are otherwise very similar to those of patients with other types of heart failure. Dyspnea, diaphoresis, anxiety, palpitations, dizziness, and nausea are particularly common presenting complaints in patients who abuse cocaine.[61] Ischemic stroke secondary to cardiogenic emboli and temporally related to cocaine abuse has also been reported in young adults with cocaine cardiomyopathy.[62]

Establishing a history of cocaine use is essential in confirming the diagnosis and guiding therapy. A history of cocaine use should preferentially be obtained by self-reporting and direct questioning of the patient. However, when the patient is unable or unwilling to communicate this information and the clinical suspicion is high, the presence of cocaine abuse should be investigated further by testing urine for cocaine and its metabolites.

### *Physical examination*

The physical findings of cocaine cardiomyopathy are generally similar to those found in patients with other forms of heart failure with a few notable exceptions. Firstly, cocaine cardiomyopathy generally presents more acutely and findings of chronic heart failure, such as pedal edema, are less common. Secondly, patients presenting with symptoms of heart failure after acute cocaine intoxication usually demonstrate signs of increased adrenergic tone including hypertension (systolic blood pressures > 200 mm Hg are common), sinus tachycardia, atrial and ventricular ectopy, atrial fibrillation, fever (especially after cocaine associated seizure), acute delirium, disorientation, agitation, and paranoia (especially if polysubstance use occurs). Ventricular tachycardia is not uncommon. Thirdly, patients with cocaine cardiomyopathy often demonstrate overt evidence of drug abuse including needle tracks and scars from intravenous injection, and nasal septal irritation or perforation from intranasal cocaine use.

### *Laboratory evaluation*

The laboratory evaluation for patients with suspected cocaine cardiomyopathy is similar to that for patients with other forms of heart failure with a few additions. A qualitative immunoassay test for cocaine and its metabolite in the urine should be ordered because many patients with acute heart failure present soon after cocaine use. Benzoylecgonine is the most commonly tested cocaine metabolite in the United States[63] and can generally be detected in the urine for 24 to 48 hours after cocaine use; however, it may remain detectable for several weeks in long-term users or those ingesting large quantities (up to 10 g/d).[64] Because many patients who abuse cocaine abuse other illicit drugs concurrently, a toxicology screen for other ingestions should be considered as well. Patients who abuse cocaine and other intravenous drugs are at increased risk for endocarditis. Blood cultures should be drawn as soon as possible in all patients with fever or signs and symptoms of infection.

### *Electrocardiogram*

The EKG is often abnormal in patients with cocaine cardiomyopathy and cocaine-associated chest pain. Sinus tachycardia is the most frequent EKG abnormality. Because many of these patients are young males, early repolarization abnormalities are also common. In a study of patients with cocaine-associated chest pain, Gitter and colleagues[65] found an early repolarization pattern in 32%, a left ventricular hypertrophy pattern in 16%, and a normal EKG in only 32% of patients. Arrhythmias, including atrial fibrillation and ventricular tachycardia, are not uncommon. It is prudent to place patients presenting with acute heart failure on continuous telemetry monitoring until their condition has been stabilized.

### *Echocardiogram*

Cocaine abusers have a higher left ventricular mass index compared to nonusers (mean, 103 g/m$^2$ vs 77 g/m$^2$) and are more likely to exhibit increased thickness of the posterior wall (>1.2 cm in 44% of users, compared to 11% of nonusers). However, it is difficult to discern cocaine cardiomyopathy from other forms of heart failure by echocardiographic images alone.[66]

### *Acute therapeutic strategies*

No randomized placebo-controlled trials regarding therapies to improve outcomes in patients with cocaine cardiomyopathy have been published. Recommendations regarding treatment are based on animal studies, autopsy studies, case reports, and published American Heart Association scientific statements on the management of

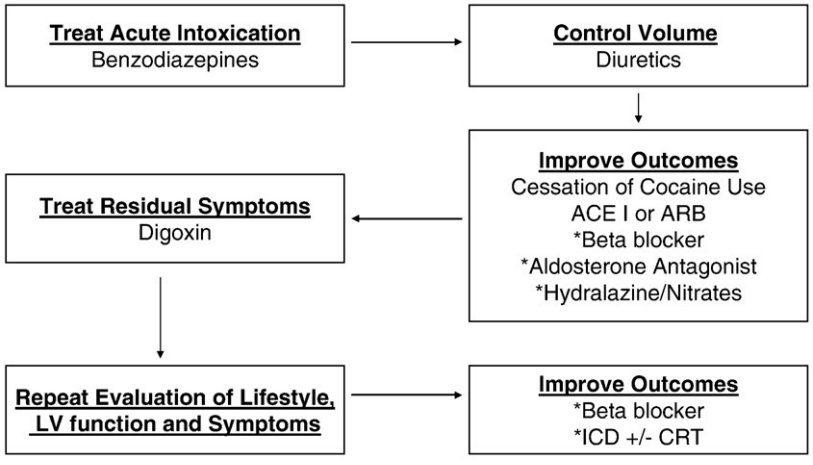


Fig 4. An algorithm for the management of cocaine associated cardiomyopathy. *In selected patients.

heart failure, cocaine-associated chest pain, and myocardial infarction[46,67] (Fig 4). Patients with cocaine cardiomyopathy should generally be treated similarly to those with other forms of heart failure, again, with notable exceptions discussed below.

*Benzodiazepines*

Unlike patients with cardiomyopathy and without history of cocaine use, patients with cocaine cardiomyopathy who present with hypertension should be treated with benzodiazepines.

Animal studies suggest that the sympathomimetic effects of cocaine administration, such as tachycardia and hypertension, are robust in conscious animals and significantly blunted in animals treated with general anesthesia or benzodiazepines. In essence, the cardiovascular manifestations of cocaine intoxication are only fully expressed when the central nervous system is active.[68]

These experimental findings are relevant for the treatment of patients with cardiac disease. As previously noted, patients who use cocaine and present to the hospital with cardiac symptoms often demonstrate signs of central nervous system hyperactivity and adrenergic excess. The neuropsychiatric symptoms of acute cocaine toxicity are closely tied to the cardiac manifestations of heart failure. Aggressively treating neuropsychiatric symptoms by blunting central nervous system stimulation helps to treat cocaine-associated heart failure. Therefore, patients with heart failure and signs of acute cocaine intoxication should be treated with intravenous benzodiazepines to achieve sedation. Relief of anxiety will often adequately control hypertension and tachycardia. When sedation alone is ineffective, other antihypertensive agents can be used as per established clinical guidelines.

*β-Blockers*

β-Blockers are strongly recommended for patients with heart failure unrelated to cocaine use. In this population, β-blocker administration lessens the symptoms of heart failure, decreases the risk for hospitalization, and most importantly, improves survival. The American College of Cardiology/American Heart Association heart failure guidelines state that that treatment with β-blocking agents "should be initiated as soon as left ventricular dysfunction is diagnosed."[46] However, in patients who abuse cocaine, β-blockers should not be administered in the acute phase of therapy.[69] In the setting of recent cocaine use, β-receptor blockade leaves the α-adrenergic receptors unopposed and can result in coronary vasoconstriction, significant elevations in blood pressure, and increased left ventricular wall stress.[70]

Carvedilol, which has been well studied in the general heart failure population, is theoretically more attractive than selective β-blockers in the cocaine using population because it has both α- and β-adrenergic antagonistic effects. However, it has not been studied in the population of patients with cocaine cardiomyopathy.

***Discharge planning/long-term therapy***

Absolute cessation of cocaine use should be a primary goal in the long-term management of these patients. In many case reports, patients have shown significant improvement in left ventricular function and clinical course after the cessation of cocaine use. In addition, left ventricular dysfunction and clinical heart failure can recur if the patient returns to cocaine abuse.[51] Patients must be told in no uncertain terms that continued cocaine use greatly increases their risk of having a life-threatening cardiovascular complication, such as heart failure, myocardial infarction, stroke, and sudden death and that absolute cessation is the most effective method to avoid these events.

Unfortunately, there are few well-studied and established treatment strategies for cocaine addiction, and the rate of recidivism is high. In a study of patients with cocaine-associated chest pain, 60% of patients admitted to using cocaine again within 1 year of their initial presentation.[71] The authors recommend that all resources available in the inpatient and outpatient setting be considered, including hospitalization for detoxification (especially if other drugs are being abused concurrently), psychiatric consultation to evaluate the need for pharmacotherapy and psychotherapy, and individual and group drug counseling.

Consultation with a cardiologist during the hospitalization is strongly recommended to help guide short-term management, outline a diagnostic strategy, and formulate discharge planning. Chronic pharmacotherapy in patients with cocaine cardiomyopathy is similar to that recommended for patients with other forms of heart failure. Diuretics, ACE inhibitors, angiotensin receptor antagonists, vasodilators, and digoxin should be prescribed as recommended by published evidence-based guidelines.[46]

There is one important exception. β-Blockers should not be routinely prescribed postdischarge. The decision to discharge a patient with cocaine cardiomyopathy on a β-blocker is a difficult one. On the one hand, long-term β-blocker therapy has been shown to be very beneficial in patients with cardiomyopathy who do not use cocaine. However, the high rate of recidivism and the theoretical risk of provoking hypertensive and ischemic events by the concomitant use of cocaine and β-blockers argues against this strategy. The authors feel that the final advice offered in the American Heart Association guidelines for the management of cocaine-associated chest pain also pertains to patients with cocaine cardiomyopathy:

"This decision should be individualized on the basis of careful risk-benefit assessment and after counseling the patient about the potential negative interactions between recurrent cocaine use and β-blockade."[67]

Finally, all patients should be seen by a cardiologist and primary care physician on a regular basis after discharge to help guide future management and support the patient in their efforts to abstain from using cocaine. The authors recommend that repeat noninvasive testing be performed several months after discharge to evaluate the response of left ventricular function to medical therapy and cocaine cessation. The decision to prescribe $\beta$-blockers can also be revisited after LV function is reassessed, and the patient's commitment to abstain from cocaine use and comply with a therapeutic strategy is reevaluated.

## Statement of Conflict of Interest

All authors declare that there are no conflicts of interest.

## References


1. Coate D: Moderate drinking and coronary heart disease mortality: evidence from NHANES I and the NHANES I Follow-up. Am J Public Health 1993;83:888-890.
2. Kannel WB, Ellison RC: Alcohol and coronary heart disease: the evidence for a protective effect. Clin Chim Acta 1996;246:59-76.
3. Corrao G, Rubbiati L, Bagnardi V, et al: Alcohol and coronary heart disease: a meta-analysis. Addiction 2000;95:1505-1523.
4. Mukamal KJ, Chiuve SE, Rimm EB: Alcohol consumption and risk for coronary heart disease in men with healthy lifestyles. Arch Intern Med 2006;166:2145-2150.
5. Rimm EB, Moats C: Alcohol and coronary heart disease: drinking patterns and mediators of effect. Ann Epidemiol 2007;17:S3-S7.
6. Collins MA, Neafsey EJ, Mukamal KJ, et al: Alcohol in moderation, cardioprotection, and neuroprotection: epidemiological considerations and mechanistic studies. Alcohol Clin Exp Res 2009;33: 206-219.
7. Agarwal DP: Cardiovascular effects of light-moderate consumption of alcohol: A review of putative mechanism. Alcohol and Alcoholism 2002;37:409-415.
8. Di Castelnuovo A, Costanzo S, Bagnardi V, et al: Alcohol dosing and total mortality in men and women: an updated meta-analysis of 34 prospective studies. Arch Intern Med 2006;166:2437-2445.
9. Lazarevic' AM, Nakatani S, Nes kovic AN, et al: Early changes in left ventricular function in chronic asymptomatic alcoholics: relation to the duration of heavy drinking. J Am Coll Cardiol 2000;35: 1599-1606.
10. Gavazzi A, De Maria R, Parolini M, et al, on behalf of the Italian Multicenter Cardiomyopathy Study Group (SPIC): Alcohol abuse and dilated cardiomyopathy in men. Am J Cardiol 2000;85: 1114-1118.
11. Urbano-Marquez A, Estruch R, Navarro-Lopez F, et al: The effects of alcoholism on skeletal and cardiac muscle. N Engl J Med 1989; 320:409-415.
12. Vital and Health Statistics. Hyattsville, MD: U.S. Department of Health and Human Services. Centers for Disease Control and Prevention 1995;13.
13. Centers for Disease Control and Prevention (CDC): Behavioral Risk Factor Surveillance System Survey Data. Atlanta, Georgia: U.S: Department of Health and Human Services, Centers for Disease Control and Prevention; 2008.
14. Walsh CR, Larson MG, Evans JC, et al: Alcohol consumption and risk for congestive heart failure in the Framingham Heart Study. Ann Intern Med 2002;136:181-191.
15. Bryson CL, Mukamal KJ, Mittleman MA, et al: The association of alcohol consumption and incident heart failure. The Cardiovascular Health Study. J Am Coll Cardiol 2006;48:305-311.
16. Djousse L, Gaziano JM: Alcohol consumption and risk of heart failure in the Physician's Health Study I. Circulation 2007;115:34-39.
17. Djousse L, Gaziano JM: Alcohol consumption and heart failure in hypertensive US male physicians. Am J Cardiol 2008;102: 593-597.
18. Kupari M, Koskinen P, Suokas A: Left ventricular size, mass and function in relation to the duration and quantity of heavy drinking in alcoholics. Am J Cardiol 1991;67:274-279.
19. Bertolet BD, Freund G, Martin CA, et al: Unrecognized left ventricular dysfunction in an apparently healthy alcohol abuse population. Drug Alcohol Depend 1991;28:113-119.
20. Darcy M, Bland JM, Leech G, et al: Preclinical left ventricular abnormalities in alcoholics are independent of nutritional status, cirrhosis, and cigarette smoking. Lancet 1985;1:1122-1125.
21. McKenna CJ, Codd MB, McCann HA, et al: Alcohol consumption and idiopathic dilated cardiomyopathy: a case control study. Am Heart J 1998;135:833-837.
22. Dancy M, Maxwell JD: Alcohol and dilated cardiomyopathy. Alcohol Alcohol 1986;21:185-198.
23. Urbano-Marquez A, Estruch R, Fernanez-Sola J, et al: The greater risk of alcoholic cardiomyopathy and myopathy in women compared with men. JAMA 1995;274:149-154.
24. Piano MR: Alcoholic cardiomyopathy: Incidence, clinical characteristics, and pathophysiology. Chest 2002;121:1638-1650.
25. Matthews EC, Gradin JM, Henry WL, et al: Echocardiographic abnormalities in chronic alcoholics with and without overt congestive heart failure. Am J Cardiol 1981;47:570-578.
26. Fernández-Solà J, Estruch R, Nicolás J, et al: Comparison of Alcoholic Cardiomyopathy in Women Versus Men. Am J Cardiol 1997;80:481-485.
27. Hibbs RG, Ferrans VJ, Black WC, et al: Alcoholic cardiomyopathy. An electron microscopic study. Am Heart J 1965;69:766-779.
28. Ferrans VJ, Hibbs RG, Weilbaecher DG, et al: Alcoholic cardiomyopathy. A histochemical study. Am Heart J 1965;69:748-765.
29. Lang RM, Borow KM, Neumann A, et al: Adverse effects of acute alcohol ingestion in young adults. Ann Intern Med 1985;102:742-747.
30. Lang LG, Sobel BE: Mitochondrial dysfunction induced by fatty acid ethyl esters, myocardial metabolites of alcohol. J Clin Invest 1983; 72:724-731.
31. Brown RA, Jefferson L, Sudan N, et al: Acetaldehyde depresses myocardial contraction and cardiac myocyte shortening in spontaneously hypertensive rats: role of intracellular $Ca^{2+}$. Cell Mol Biol 1999;45:453-465.
32. Ren J, Davidoff AJ, Brown RA, et al: Acetaldehyde depresses shortening and intracellular $Ca2^{+}$transients in adult rat ventricular myocytes. Cell Mol Biol 1997;43:825-834.
33. Schreiber SS, Oratz M, Rothschild MA: Alcoholic cardiomyopathy: the effect of ethanol and acetaldehyde on cardiac protein synthesis. Recent Adv Stud Cardiac Struct Metab 1975;7:431-442.
34. Li S, Ren J: Cardiac overexpression of alcohol dehydrogenase exacerbates chronic ethanol ingestion-included myocardial dysfunction and hypertrophy: role of insulin signaling and ER stress. J Mol Cell Cardiol 2008;44:992-1001.
35. Doser TA, Turdi S, Thomas T, et al: Transgenic overexpression of aldehyde dehydrogenase-2 rescues chronic alcohol intake-induced myocardial hypertrophy and contractile dysfunction. Circulation 2009;119:1941-1949.
36. Cheng CP, Cheng HJ, Cunningham C, et al: Angiotensin II type 1 receptor blockade prevents alcoholic cardiomyopathy. Circulation 2006;114:226-236.
37. Fernandez-Sola J, Nicolas JM, Oriola J, et al: Angiotensin-converting enzyme gene polymorphism is associated with

vulnerability to alcoholic cardiomyopathy. Ann Intern Med 2002; 137:321-326.
38. Wang L, Zhuo Z, Saari J, et al: Alcohol-induced myocardial fibrosis in metallothionein-null mice. Prevention by zinc supplementation. Am J Pathol 2005;167:337-344.
39. Kesteloot H, Roelandt J, Willems J, et al: An inquiry into the role of cobalt in the heart disease of chronic beer drinkers. Circulation 1968; 37:854-864.
40. Fauchier L, Babuty D, Poret P, et al: Comparison of long-term outcome of alcoholic and idiopathic dilated cardiomyopathy. Eur Heart J 2000;21:306-314.
41. Skotzko CE, Vrinceanu A, Krueger L, et al: Alcohol use and congestive heart failure: indicence, importance, and approaches to improve history taking. Heart Fail Rev 2009;14:51-55.
42. Kupari M, Koskinen P, Suokas A, et al: Left ventricular filling impairment in asymptomatic chronic alcoholics. Am J Cardiol 1990; 66:1473-1477.
43. Kanjander OA, Laippala P, Savolainen V, et al: Dose dependent but non-linear effects of alcohol on the left and right ventricle. Heart 2001;86:417-423.
44. Prazak P, Pfisterer M, Osswald S, et al: Differences in disease progression in congestive heart failure due to alcoholic as compared to idiopathic dilated cardiomyopathy. Eur Heart J 1996;17:251-257.
45. Demakis JG, Proskey A, Rahimtoola DH, et al: The natural course of alcoholic cardiomyopathy. Ann Intern Med 1974;80:293-297.
46. Hunt SA, Abraham WT, Chin MH, et al: Focused update incorporated into the ACC/AHA 2005 guidelines for the diagnosis and management of heart failure in adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2009;119:e391-e479.
47. Guillo P, Mansourati J, Maheu B, et al: Long term prognosis of patients with alcoholic cardiomyopathy and severe heart failure after total abstinence. Am J Cardiol 1997;79:1276-1278.
48. Nicolas JM, Fernandez-Sola J, Estruch R, et al: The effect of controlled drinking in alcoholic cardiomyopathy. Ann Intern Med 2002;136:192-200.
49. Cooper HA, Exner DV, Domanski MJ: Light-to-moderate alcohol consumption and prognosis in patients with left ventricular systolic dysfunction. J Am Coll Cardiol 2000;35:1753-1759.
50. US Department of Health and Human Services: Substance Abuse and Mental Health Services Administration. Results from the 2005 National Survey on Drug Use and Health: National Findings. September 2006.
51. Willens H, Chakko S, Kessler K: Cardiovascular manifestations of cocaine abuse. A case of recurrent dilated cardiomyopathy. Chest 1994;106:594-600.
52. Felker G, Hu W, Hare J: The spectrum of dilated cardiomyopathy. The Johns Hopkins experience with 1,278 patients. Medicine 1999; 78:270-283.
53. Bertolet B, Freund G, Martin D: Unrecognized left ventricular dysfunction in an apparently healthy cocaine abuse population. Clin Cardiol 1990;13:323-328.
54. Kloner RA, Hale S, Alker K, et al: The effects of acute and chronic cocaine use on the heart. Circulation 1992;85:407-419.
55. Mehta P, Grainger R, Lust R, et al: Effect of cocaine on left ventricular function: Relation to increased wall stress and persistence after treatment. Circulation 1995;91:3002-3009.
56. Tazelaar H, Karch S, Stephens B: Cocaine and the heart. Hum Pathol 1987;18:195-199.
57. Virmani R, Robinowitz M, Smialek J, et al: Cardiovascular effects of cocaine: an autopsy study of 40 patients. Am Heart J 1989;117: 1928-1929.
58. Isabelle M, Vergeade A, Mortiz F, et al: NADPH oxidase inhibition prevents cocaine-induced up-regulation of xanthine oxidoreductase and cardiac dysfunction. J Mol Cell Cardiol 2007; 42:326-332.
59. Hollander J, Hoffman R, Burstein J, et al: Cocaine-associated myocardial infarction. Mortality and complications. Cocaine-Associated Myocardial Infarction Study Group. Arch Intern Med 1995; 155:1081-1086.
60. Mittleman M, Mintzer D, Maclure M, et al: Triggering of myocardial infarction by cocaine. Circulation 1999;99:2737-2741.
61. Mccord J, Brody S, Slovis C, et al: Cocaine-related medical problems: consecutive series of 233 patients. Am J Med 1990;88: 325-331.
62. Sauer C: Recurrent embolic stroke and cocaine-related cardiomyopathy. Stroke 1991;22:1203-1205.
63. Preston K, Epstein D, Cone E, et al: Assessment of cocaine use with quantitative urinalysis and estimation of new uses. Addiction 1997; 92:717-727.
64. Weiss R, Gawin F: Protracted elimination of cocaine metabolites in long-term high dose cocaine abusers. Am J Med 1988;85: 879-880.
65. Gitter M, Goldsmith S, Dunbar D, et al: Cocaine and chest pain: clinical features and outcomes of patients hospitalized to rule out myocardial infarction. Ann Intern Med 1991;115:277-282.
66. Brickner M, Willard J, Eichorn E, et al: Left ventricular hypertrophy associated with chronic cocaine abuse. Circulation 1991;84: 1130-1135.
67. McCord J, Jneid J, Hollander J: Management of cocaine-associated chest pain and myocardial infarction. A scientific statement from the American Heart Association Acute Cardiac Care committee of the Council on Clinical Cardiology. Circulation 2008;117: 1897-1907.
68. Wilkerson R: Cardiovascular effects of cocaine in conscious dogs: importance of fully functional autonomic and central nervous systems. J Pharmacol Exp Ther 1988;246:466-471.
69. 2005 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 2005;112(suppl IV):IV-126-IV-132.
70. Rappolt R, Gay G, Inaba D, et al: Propranolol in cocaine toxicity. Lancet 1976;2:640-641.
71. Hollander J, Hoffman R, Gennis P, et al: Cocaine-associated chest pain: one year follow-up. Acad Emerg Med 1995;2:179-181.