

## Crystal Methamphetamine-Associated Cardiomyopathy: Tip of the Iceberg?

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### ABSTRACT

*Background.* Crystal methamphetamine has become a drug of widespread use. Previous reports describe myocardial infarction, pulmonary edema, and aortic dissection related to methamphetamine use. Cardiomyopathy due to methamphetamine exposure has been rarely described. *Methods.* We identified 1640 patients admitted in a 4-yr period with a primary or secondary diagnosis of cardiomyopathy. We excluded patients with known cause of cardiomyopathy other than substance abuse. We found 120 patients had a diagnosis of substance abuse, including 21 patients with methamphetamine use. We retrospectively reviewed the medical records of these 21 crystal methamphetamine users. *Results.* Nineteen (84%) underwent echocardiography with consistent findings of dilated cardiomyopathy and global ventricular dysfunction. Of five who had a nuclear myocardial perfusion study, none had evidence of ischemia or infarct. Of six who underwent cardiac catheterization, only one had evidence of coronary stenosis. *Conclusion.* Methamphetamine use appears to produce cardiomyopathy in some users. The pathogenesis is probably similar to that of cocaine and catecholamine-induced cardiomyopathy. Cellular, animal, and clinical data support the link between methamphetamine exposure and myocardial pathology.

*Key Words:* Dilated cardiomyopathy; Congestive heart failure; Methamphetamine; Substance abuse.

### INTRODUCTION

Methamphetamine is a potent central nervous system stimulant and a substance of widespread use. During the

past 15 yrs, its use has increased rapidly in Hawaii, the Pacific coast, and the south/midwest of the United States (1). The 2000 National Household Survey on Drug Abuse estimated that 8.8 million Americans

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used methamphetamine in their lifetime. This figure shows a marked increase from the 1994 estimate of 3.4 million (2,3).

Psychostimulant and neuropsychiatric effects of methamphetamine, including euphoria, increased energy level, irritability, paranoia, and psychosis are described in the medical literature (4,5). Although less known, methamphetamine is also linked with alterations of cardiovascular structure and function (5). We have reviewed data that strongly suggest the development of dilated cardiomyopathy in chronic methamphetamine users.

## METHOD

The study was approved by the local institutional review committee. At a tertiary care center in Honolulu, Hawaii, we (authors M.W. and T.S.) performed a review of medical records using a standard data abstraction form on patients who were discharged during the period August 1997 to August 2001, with the final ICD-9 diagnoses of cardiomyopathy (425.0–425.9) and substance abuse/dependence (304.0–305.93, excluding tobacco 305.1). We selected patients in whom methamphetamine use was confirmed either by history or positive serum or urine toxicology testing. The discharge diagnosis of cardiomyopathy was confirmed in all patients by the presence of wall motion abnormality or left ventricular ejection fraction <45% in echocardiography or nuclear myocardial perfusion scanning. We excluded those with previous or current myocardial infarction, previous or current myocarditis of any etiology, rheumatic heart disease, metastatic cancer, anthracycline therapy, symptomatic valvulopathy, the discharge diagnosis of alcohol dependence, cocaine and/or heroin use, HIV infection, current pregnancy, uncontrolled atrial or ventricular arrhythmia, and previous cardiac surgery. Authors who performed the review of medical records concurred on the final selection of patients.

## RESULTS

A total of 1640 patients (2227 discharges) were noted with the primary or secondary diagnosis of cardiomyopathy. Of these, 120 patients (143 discharges) had the concomitant diagnoses of cardiomyopathy and substance abuse. Of the 120 patients, 21 (18%) met the criteria for cardiomyopathy and methamphetamine use and had none of the exclusion criteria described above.

Their mean age was 40.8 years (range 25–57). The demographic data and clinical characteristics of this cohort are described in Table 1. The frequency of methamphetamine use was described in 52% (11 of 21) patients and it ranged from every day to every other week. The dose of methamphetamine per administration was not clearly documented in any patient. The duration of use was documented in 23% (5 of 21) and ranged from 2 to 20 years.

The investigational modalities during hospitalization included two-dimensional and Doppler echocardiography in 91% (19 of 21), nuclear myocardial perfusion imaging in 24% (5 of 21), and coronary angiography in 29% (6 of 21). The results of the imaging modalities are summarized in Table 2. The mean left ventricular ejection fraction was 25% (range 9–50). None of the patients underwent endomyocardial biopsies. Three of 21 had serological studies to rule out viral myocarditis and all three had negative serology. None of the patients died during index hospitalization. Upon discharge 81% of the patients (17 of 21) were started on angiotensin converting enzyme inhibitors, 76% (16 of 21) on diuretics, 48% (10 of 21) on digoxin, and 43% (9 of 21) on beta adrenergic receptor blockers.

**Table 1.** Characteristics of 21 patients with methamphetamine use and cardiomyopathy.

Characteristic	(n = 21)	%
<45 years	14	67
Men	19	90
Ethnicity		
Hawaiian	8	38
Filipino	8	38
Caucasian	2	10
Japanese	2	10
Cardiac risk factors		
Hypertension	11	52
Tobacco use	8	38
Dyslipidemia	1	5
Diabetes mellitus	5	23
Principal symptom		
Dyspnea	14	67
NYHA class IV	2	10
NYHA class III	8	38
NYHA class II	4	19
Chest pain	2	10
Syncope	2	10
Mode of methamphetamine administration		
Smoking	19	90
Not documented	2	10
Admitted current use of methamphetamine	20	95

**Table 2.** Investigational modalities and findings.

Echocardiography ( <i>n</i> = 19)		
Left ventricular diastolic dimension >5.5 cm	16	84%
Left atrial dimension >4.2 cm	16	84%
Right ventricular dimension >1.9 cm	12	63%
Global hypokinesis	18	95%
Nuclear myocardial perfusion study ( <i>n</i> = 5)		
Evidence of ischemia or infarct	0	0%
Left heart catheterization ( <i>n</i> = 6)		
No evidence of coronary stenosis <sup>a</sup>	5	83%
Coronary stenosis	1 <sup>b</sup>	17%

<sup>a</sup>Defined as absence of epicardial coronary artery stenosis >50% of luminal diameter.

<sup>b</sup>One patient had 80% stenosis in the proximal left anterior descending artery.

## DISCUSSION

The predominant finding in our study was the occurrence of dilated cardiomyopathy and congestive heart failure in the apparent absence of occlusive coronary artery disease, among the chronic methamphetamine users.

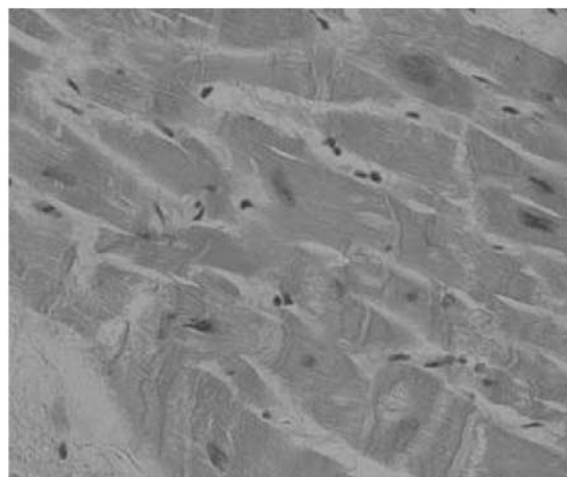
Methamphetamine represents the fastest growing drug threat in the United States today (3). It is a synthetic amine belonging to the amphetamine class of drugs. It can be smoked, snorted, injected, or ingested (5). In Hawaii, the volatile and smokable form is commonly abused and known as “ice,” named for its appearance of clear, large chunky crystals. The physiological effects of amphetamine-related compounds are attributed to the enhanced release of catecholamines from nerve terminals and adrenal medulla, leading to the stimulation of central and peripheral alpha and beta adrenergic receptors. These compounds may also have a direct stimulating effect on end organs (6). The most common cardiovascular manifestations of amphetamine-related compounds include chest pain, tachycardia, and hypertension (7–15). At higher doses tachyarrhythmias may occur (16,17). Amphetamines are also linked with coronary artery disease, myocardial ischemia and infarction (18–28), acute pulmonary edema (29,30), necrotizing vasculitis (31–33), endocarditis (32,34), pulmonary hypertension (35), acute aortic dissection (28,36), ischemic stroke (37), cerebrovascular hemorrhage (28,32,34,38–40), acute rhabdomyolysis, (41,42) and sudden cardiac death (32,35,43). Anecdotal clinical reports in living patients have previously described the presence of cardiomyopathy and suggested a plausible role of amphetamine analogues in the development of structural alterations of myocardium (22,44–49). Autopsy studies have demon-

strated the occurrence of cardiomyopathy in patients with methamphetamine-related deaths (28,32,34). Histological analysis of myocardial tissue from methamphetamine users has shown the presence of contraction band necrosis, which usually is an indicator of catecholamine toxicity and a recognized feature in the hearts of cocaine abusers (5,28,50–54).

Several experimental studies have shown the development of myocyte atrophy, hypertrophy, contraction bands, patchy cellular infiltration, eosinophilic degeneration, cellular edema, myocytolysis, fibrosis, and vacuolization when animals and cultured myocytes are exposed to methamphetamine (52,55–59). The accompanying ultra structural features include sarcolemmal injury, mitochondrial degeneration, myofibrillar hypercontraction, and loss of myofilaments (55,57,60,61).

The plausible mechanisms for the development of dilated cardiomyopathy in chronic methamphetamine users include recurrent coronary artery spasm, small vessel disease, or diffuse myocardial toxicity due to repeated stimulation of alpha and beta-adrenergic receptors in the heart. Thus, the adverse pathogenetic role of adrenergic receptor stimulation in this setting is likely similar to that of cocaine and catecholamine-induced cardiomyopathy.

The myocardial pathology induced by amphetamine analogues may be reversible with timely intervention (49). However, with chronic administration, amphetamines may lead to altered molecular phenotypes and permanent ultra structural changes causing myocyte contractile dysfunction, ventricular remodeling, and hemodynamic derangement.



**Figure 1.** Contraction band necrosis in a myocardial histology specimen of a methamphetamine user. Source: Courtesy Steven B. Karch, MD, Assistant Medical Examiner, City and County of San Francisco.



## LIMITATIONS

This study has several limitations. It is a single center, retrospective case series and did not have a control group. Consequently the results may not be generalizable. It is possible that the younger age groups are over-represented in the study cohort as the threshold for toxicology screening tends to be low when a young patient presents to the hospital with cardiac manifestations. On the other hand, our study may underestimate the overall prevalence of methamphetamine use, as it was dependent on the documentation of drug abuse by the clinician. The quantitation of methamphetamine exposure was not feasible due to insufficient documentation. The observational study format does not rule out potentially undiagnosed conditions such as myocarditis, confounders such as contaminants, or other comorbidities. Therefore, an etiological relationship between methamphetamine exposure and the development of dilated cardiomyopathy cannot be irrefutably established. In addition, the patients were not followed up prospectively and data on long-term prognosis are not known.

## CONCLUSION

Dilated cardiomyopathy is observed in some patients who use methamphetamine. Cellular, animal, and clinical data suggest a plausible causative link between chronic methamphetamine exposure and the development of myocardial pathology. The optimal management strategy for this patient group is not well defined. In view of the contemporary growth of methamphetamine abuse across the United States, further studies are warranted to delineate this association and define treatment options.

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