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# Cardiovascular disease associated with methamphetamine use: a review

**Jared Tobolski[1] · Douglas B. Sawyer[1] · Sharon J. Song[2] · Maxwell Eyram Afari[1]**

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**Abstract**
Methamphetamine abuse is a global epidemic associated with a wide-ranging array of adverse effects on the cardiovascular system including dilated cardiomyopathy, malignant and benign arrhythmias, coronary vasospasm, and atherosclerotic coronary artery disease. While the acute behavioral manifestations of amphetamine abuse are the most easily clinically identified, cardiovascular toxicity is common in this patient population and should be considered in this setting due to its high morbidity and mortality. The specific mechanisms for amphetamine cardiotoxicity have not been fully established, but new research implicates activation of several cellular targets including Sigma-1 receptors and trace amine-associated receptor 1 (TAAR1) leading to a myriad of negative downstream effects including increased reactive oxygenating species (ROS), mitochondrial dysfunction, and modulations of intracellular calcium. Additional pathologic effects are mediated by increased circulating catecholamines, which when chronically activated have well-established adverse effects on the cardiovascular system. In this article, we present a case report followed by a current review of the epidemiology, pathophysiology, diagnosis, and treatment modalities of amphetamine-induced cardiovascular disease.

**Keywords** Methamphetamine · Cardiomyopathy · TAAR1 · Sigma-1

## Case report

A 28-year-old man with prior substance abuse history on methadone, without prior personal or family cardiac history, presented with nausea, vomiting, diarrhea, and diaphoresis. His hospital course was complicated by cardiac arrest requiring cardiopulmonary resuscitation with return of spontaneous circulation in 2 min. He was intubated for respiratory support. Lactate peaked at 8.6 mmol/L (normal range 0.5-2.0 mmol/L) and urine toxicology was positive for opiates, methadone, tetrahydrocannabinol, and amphetamine. Serum NT-pro BNP [37,250 (normal range: 0-450 pg/nL)] and troponin T [(1.04, normal range < 0.04 ng/mL)] were elevated. Initial echocardiogram revealed left ventricular ejection fraction (LVEF) of 10-15% with severe global hypokinesis. He was hemodynamically supported with dobutamine 5 mcg/kg/min and norepinephrine 0.8 mcg/kg/min. Endomyocardial biopsy revealed findings of cardiomyopathy and ischemic changes without evidence of myocarditis (Fig. 1). Cardiac MRI revealed severe biventricular dysfunction without late gadolinium enhancement. Patient endorsed methamphetamine use prior to presentation which raised our suspicion for methamphetamine-induced cardiomyopathy, but was unwilling to clarify his burden of use or route of administration. He was discharged on a guideline-directed heart failure regimen of sacubitril-valsartan 24-26 mg daily, carvedilol 3.125 mg twice daily, empagliflozin 10 mg once daily, and spironolactone 25 mg once daily along with 40 mg of daily furosemide as a maintenance diuretic. He was instructed to follow up with addiction medicine and psychiatry as an outpatient. A 1-month follow-up echocardiogram showed improved LVEF of 55%.

## Introduction

While much mainstream medical literature and media attention is given to the worldwide opiate epidemic, methamphetamine poses an equally morbid and widely used drug of

✉ Maxwell Eyram Afari
maxieafari@yahoo.co.uk

[1] Cardiac Service Line, Maine Medical Center, 22 Bramhall Street, Portland, ME 04102, USA

[2] Spectrum Healthcare Partners, South Portland, ME 04106, USA

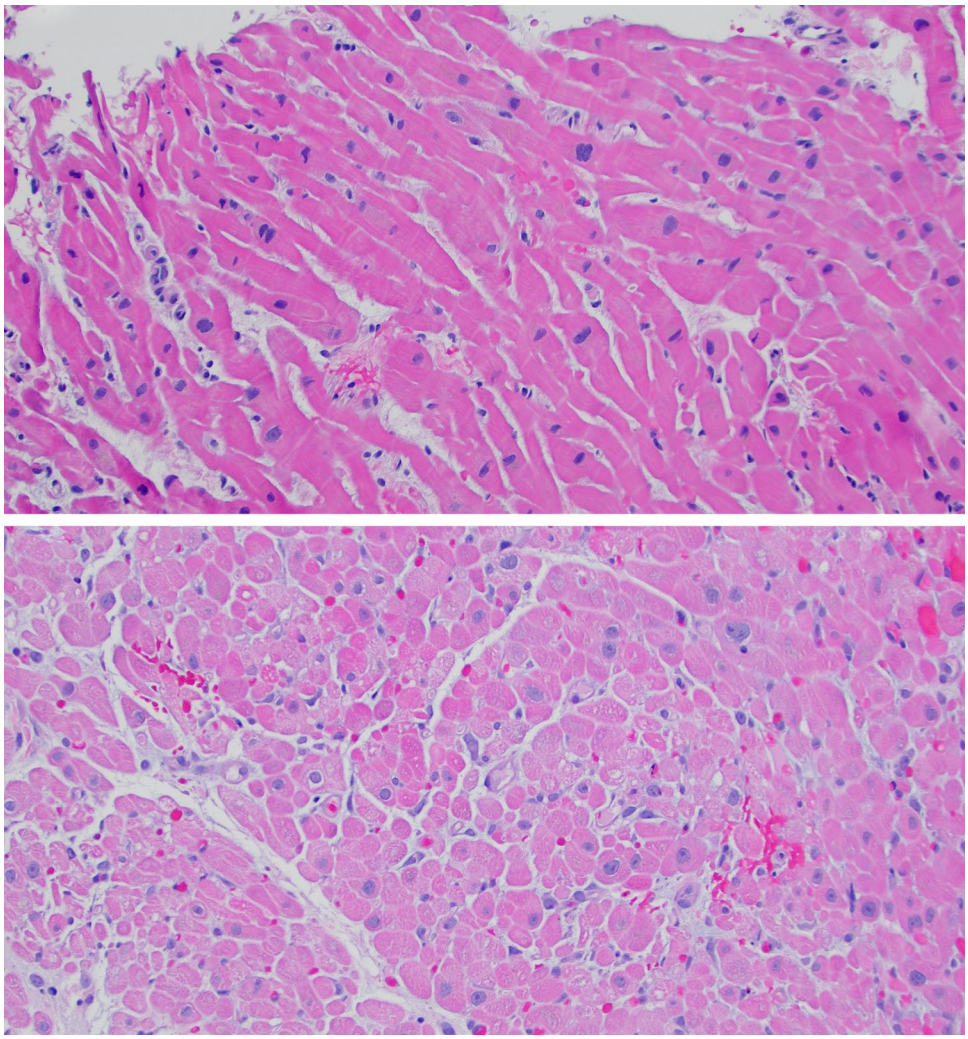

**Fig. 1** Endomyocardial biopsy of patient with cardiomyopathy and cardiogenic shock. The first image shows myocardial fiber hypertrophy with scattered enlarged and occasionally binucleated nuclei. The second image also shows enlarged and atypical nuclei, as well as degenerative cytoplasmic vacuolar changes, suggestive of ischemic damage. H&E stain, 20×

abuse. Synthesized originally in Japan in the late nineteenth century, methamphetamine was used as a stimulant for German soldiers during World War II to promote extended periods of wakefulness, and emerged as a drug of abuse due to its euphoric effects and role in appetite suppression [1–3]. Methamphetamine is abused on a mass scale, noted to be second only to marijuana across the globe among recreational drugs [3]. In some countries, methamphetamine surpasses opiates and serves as the number one drug of abuse [4].

After acute intoxication, cardiovascular disease is noted to be the leading cause of death in methamphetamine users [5–7]. The cardiac effects of methamphetamine range from benign tachycardia to malignant arrhythmias and cardiovascular collapse. For the purpose of this review, we will summarize current knowledge pertaining to the epidemiology, clinical manifestations, postulated mechanisms, and treatment of methamphetamine-associated cardiovascular pathology.

## Epidemiology

Methamphetamine abuse constitutes a global epidemic with recent studies estimating approximately 51 million users worldwide between the ages of 15 and 64 [3]. In the USA alone, the National Surveys on Drug Use and Health reports between 2015 and 2018 an estimated prevalence of methamphetamine use of 6.6 per 1000 people, with frequent use encompassing 200 days or more in 27.3% of reported cases [8]. Between 2008 and 2018, age-adjusted methamphetamine-associated heart failure (MethHF) hospitalizations increased by 585% in California in the USA. A total of 42,565 patients were hospitalized with MethHF in California and the annual inflation-adjusted cost of care increased from $41.5 million to $390.2 million within the specified time period [9]. Socioeconomic disparities, such as lower attainment of formal education and low annual household income (< $50,000 annually), have been associated with abuse potential [8]. Healthcare disparities such as insurance status (Medicaid and no insurance),

co-occurring substance use, and mental illness have also been associated with increased risk for methamphetamine abuse.

A retrospective review of 9491 veterans with heart failure found that 4.5% had associated methamphetamine use history [10]. The incidence of MethHF doubled from 3.4 to 6.7% from 2005 to 2015 in veterans. Veterans with MethHF were younger (61 versus 72 years), more likely to be depressed, homeless or unemployed, and with comorbid post-traumatic stress disorder [10]. These trends are disturbing and highlight the need for more attention to prevention and treatment of methamphetamine use disorder.

## Clinical presentation and clinical course

The clinical presentation of acute methamphetamine abuse depends on chronicity of use and level of intoxication, but generally presents with a myriad of neurologic manifestations including agitation and insomnia, as well as psychomotor symptoms including excessive speech and motor hyperactivity [11]. On physical examination, other non-cardiac signs include track marks from injection site, diaphoresis, and xerostomia with tooth decay.

Cardiovascular manifestations of methamphetamine toxicity include dilated cardiomyopathy, atherosclerotic coronary artery disease, malignant hypertension, ventricular and supraventricular arrhythmias, coronary vasospasm, heart failure, cardiogenic shock, and sudden cardiac death.

Methamphetamine-induced heart failure frequently presents with dilated cardiomyopathy and global left ventricular dysfunction [12], which can progress to fatal cardiogenic shock [13]. One proposed mechanism for cardiac dysfunction is similar to stress cardiomyopathy in the setting of catecholaminergic overload [14], although there are direct myocardial effects of methamphetamines that have also been described. Coronary angiography performed in patients presenting with acute methamphetamine intoxication and acute ST-segment myocardial infarction have demonstrated thrombolysis in myocardial infarction (TIMI) I flow without obstructive epicardial coronary artery disease, suggesting coronary vasospasm and microvascular dysfunction [15]. Methamphetamine has been shown to prolong QTc intervals, theoretically raising the risk of early-after depolarizations and torsade de pointes [16]. Table 1 highlights the acute and chronic cardiac manifestations of methamphetamine compared with other drugs of abuse.

## Pathophysiology and molecular mechanism

While the physiology behind the euphoric effects of methamphetamine is relatively well understood, the toxic effects are less delineated. The euphoria is thought to be secondary

**Table 1** Acute and chronic cardiac manifestations of common drugs of abuse

| Drug of abuse | Acute cardiovascular toxicity | Chronic cardiovascular toxicity |
|---|---|---|
| Amphetamines | -Sympathetic hyperactivation (increased myocardial O2 demand, hypertensive crisis)<br>-Cardiomyopathy/heart failure/cardiogenic shock<br>-Prolonged QTc<br>-Arrhythmias<br>-Sudden cardiac death | -Cardiomyopathy<br>-Heart failure (with reduced or preserved left ventricular systolic function) |
| Alcohol | -Arrhythmias (notably tachycardia, atrial fibrillation)<br>-Cardiopulmonary arrest, secondary to respiratory depression and metabolic disturbances | -Cardiomyopathy<br>-Heart failure (classically with reduced left ventricular systolic function) |
| Cocaine | -Hypertensive crisis<br>-Acute vasoconstriction/vasospasm<br>-Acute myocardial infarction<br>-Increased myocardial O2 demand<br>-Sudden cardiac death<br>-Cerebrovascular accident | -Cardiomyopathy<br>-Heart failure (with reduced or preserved left ventricular systolic function)<br>-Atherosclerotic coronary artery disease |
| Tobacco | | - Atherosclerotic coronary artery disease<br>-Cerebrovascular accident<br>-Aortic dissection/aneurysm<br>-Congestive heart failure |
| Opiates | -Cardiopulmonary arrest<br>-Infective endocarditis | |

to increased dopamine availability in the synaptic clefts of the mesolimbic nervous system, which is facilitated by methamphetamine's methyl group enhancing lipophilicity, resulting in increased blood–brain barrier penetration [17]. Methamphetamine dysregulates monoamine regulation through the disruption of intracellular storage vesicles containing monoamines, inducing dopamine efflux into the synaptic cleft, and downregulation of dopamine active transporters (DAT) [18, 19].

The mechanisms of the cardiovascular effects of methamphetamine are multifactorial and include intra and extracellular signaling, upregulation of reactive oxygenating species, and mitochondrial dysregulation via catecholamine-dependent and independent mechanisms [2, 3, 20, 21]. Methamphetamine effects on catecholamine release and metabolism increase catecholamine levels, which can cause direct myocardial injury, stimulate hypertrophy via myocyte adrenergic receptor activation, increase oxygen free radical generation, cause mitochondrial dysfunction, and impair intracellular calcium hemostasis [7, 21, 22]. Furthermore, catecholamine increases blood pressure, heart rate, and vasospasm, all of which promote cardiac ischemia which can exacerbate contractile dysfunction [20].

The proposed mechanisms of action for methamphetamine to trigger arrhythmias include the inhibition of potassium current and L-type calcium, which has been demonstrated in a murine model [23], and through the stimulation of cardiac structural changes causing electrical remodeling, which can manifest by QTc prolongation. In a postmortem analysis of methamphetamine-related deaths in Australia, coronary artery atherosclerosis was detected in 54% of decedents [24] while severe coronary artery disease was present in 19% [25]. The production of reactive oxygen species and reactive nitrogen species, from a direct effect of methamphetamine on mitochondria, has been implicated as the potential mechanism of atherogenesis [26].

The mechanism behind vascular effects of methamphetamine is complicated due to the complex regulation of baseline vascular tone that involves a complex array of interworking mechanisms involving vaso-modulating factors such as nitric oxide, prostacyclin, angiotensin II, and adrenergic compounds [3]. In a mouse model, TAAR1 was implicated in methamphetamine-related effects that has the potential to promote methamphetamine use [27], thus making TAAR1 a potential target for therapeutic intervention. One of the mechanisms of methamphetamine-induced vasoconstriction is through the release of endothelin-1 [28] or TAAR1 signaling [29]. TAAR1-dependent vasoconstriction has been proposed to be mediated by phenylethylamine-specific receptors [30].

New research has demonstrated involvement of Sigma-1 receptor in methamphetamine toxicity, which results in dysregulated modulation of intracellular signaling affecting overall cellular homeostasis through mechanisms such as cellular calcium and gene transcription regulation [31, 32]. Sigma-1 receptor is a chaperone protein associated with the endoplasmic reticulum predominantly in the central nervous system, but is also heavily expressed elsewhere, including cardiac tissue [33]. Some studies demonstrate a relationship between Sigma-1 and DAT [34]. One proposed mechanism of calcium modulation is through the interaction of Sigma-1 receptor and inositol-1,4,5-triphosphate which regulates calcium storage in the endoplasmic reticulum [33].

Modulation of Sigma-1 receptor activity has been associated with myocardial disease. Mice lacking Sigma-1 receptor expression due to genetic disruption of expression develop progressive cardiac dysfunction associated with ventricular dilatation and myocardial fibrosis [35]. Similarly, in mice exposed to methamphetamine, cardiac hypertrophy, fibrotic remodeling, and mitochondrial dysfunction are the pathological hallmarks [32]. Inhibiting Sigma-1 receptor results in the inactivation of the cyclic adenosine monophosphate response element-binding protein (CREB), and decreased expression of mitochondrial fission 1 protein (FIS1), which ultimately alters mitochondrial dynamics and function [32]. Activation of Sigma-1 receptor has been explored as a therapeutic strategy for cardioprotection. For example, the selective serotonin reuptake inhibitor class of antidepressants are known activators of Sigma-1 receptor, and treatment of rodents with selective serotonin reuptake inhibitors is cardioprotective against pressure overload-induced heart failure [36]. Figure 2 shows various receptors implicated in the pathogenesis of MethHF.

## Diagnostic workup

A high index of clinical suspicion is needed to diagnose MethHF, since there is no single diagnostic tool utilized. Clinical symptoms listed above, especially non-cardiac signs such as track marks, tooth decay, and psychomotor symptoms, should raise suspicion [20, 37]. Table 2 shows common diagnostic tools utilized in the diagnosis of MethHF.

## Treatment

Since treatment options specifically tailored to methamphetamine-induced cardiomyopathy are not available, current management is limited to interventions that promote abstinence from methamphetamine and comorbid drugs of abuse, as well as use of standard heart failure therapies. Public health policies targeting those who are vulnerable to methamphetamine are imperative. This may require psychosocial strategies which target risk factors for methamphetamine use such as low income, unemployment, and other socioeconomic disadvantage. The importance of the patients discontinuing methamphetamine use cannot be overstated,

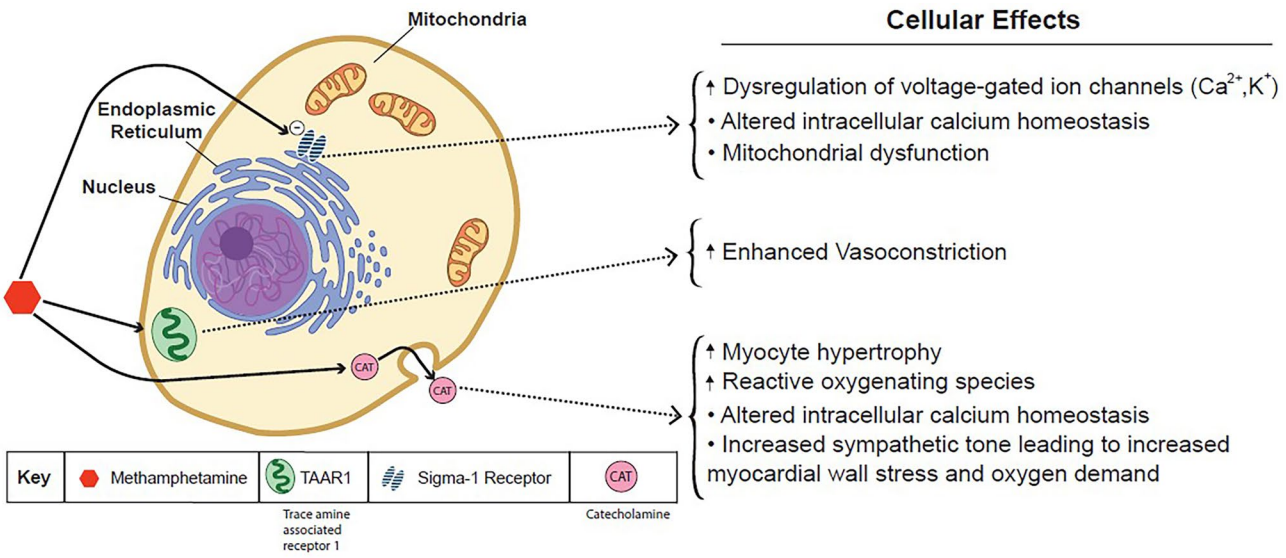


**Fig. 2** Intracellular mechanisms of methamphetamine toxicity as it pertains to the cardiovascular system (Adobe Illustrator)

as data suggests abstaining from methamphetamine is the most important predictor in reversing the cardiomyopathy [4, 38]. Current pharmacologic therapeutics designed to curb addiction include bupropion and modafinil [38]. Addiction rehabilitation should be recommended to methamphetamine users.

The mainstay of therapy in the acute setting is targeted towards the specific end-organ clinical manifestations of acute intoxication, including managing agitation, decompensated heart failure, coronary vasospasm, and hypertensive emergency. With regard to hypertensive emergency, it is generally recommended to first initiate alpha blockade prior to beta-adrenergic receptor blockade, with the concern of impeded alpha constriction due to the adrenergic properties of methamphetamine, similar to cocaine toxicity [1].

Heart failure treatment should be initiated in accordance with current guidelines. In symptomatic patients with heart failure with reduced ejection fraction as a result of methamphetamine toxicity, current guideline therapies include neurohormonal blockade with a beta-adrenergic receptor blocker (metoprolol succinate, carvedilol, or bisoprolol), an angiotensin-converting enzyme inhibitor (ACEI), angiotensin receptor blocker or an angiotensin receptor-neprolysin inhibitor (ARNi), mineralocorticoid receptor antagonist, and a sodium-glucose cotransporter 2 (SGLT-2) inhibitor [23, 39]. In the case of patients with advanced heart failure, referral for transplant or mechanical circulatory support devices is often impeded by psychosocial complications and substance abuse frequently associated with patients abusing amphetamines.

**Table 2** Common diagnostic tools used in diagnosing methamphetamine cardiac toxicity

| Diagnostic test | Findings |
|---|---|
| Urine toxicology | Positive for methamphetamine |
| Creatinine kinase | Rule out rhabdomyolysis |
| Biomarkers | (NT-pro) BNP and troponin I or T may be elevated—reflecting heart failure or acute coronary syndrome |
| Lactate | Marker of hypoperfusion |
| Electrocardiogram | Tachyarrhythmia, ischemic ST changes, QTc prolongation, left ventricular hypertrophy |
| Echocardiogram | Reduced systolic function, left ventricular dilation, stress pattern of cardiomyopathy, enlarged atria, intracardiac thrombus |
| Cardiac MRI | Late gadolinium enhancement/fibrosis burden is a poor prognosticator |
| Right heart catheterization | Biventricular dysfunction, pulmonary hypertension |
| Coronary angiogram | Rule out obstructive coronary artery disease, vasospasm |
| Endomyocardial biopsy | Degree of fibrosis is a poor prognostic marker |

One future direction that shows promise in animal models is the use of anti-methamphetamine monoclonal antibodies which have been demonstrated to reduce acute locomotor toxicity and have a protective effect against both cardiovascular and neurologic toxicity [23, 40]. Additionally, preliminary research suggests the partial dopamine and serotonin agonist aripiprazole, commonly used now in the management of cognitive decline, may reduce acute stimulant properties of methamphetamine [23, 41].

## Conclusion

Methamphetamine abuse confers significant global morbidity and mortality. Cardiovascular complications from methamphetamine have dire public health consequences including a profound economic impact. Resources should be dedicated to promoting methamphetamine cessation and rehabilitation. While modern research has given some insight into the specific mechanisms behind methamphetamine toxicity, continued research into mitigating the addictive use patterns and specific pharmacological targets are needed.

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### Declarations

**Competing interests** The authors declare no competing interests.

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