HHS Public Access

Author manuscript

Drug Alcohol Depend. Author manuscript; available in PMC 2021 July 01.

Published in final edited form as:

Drug Alcohol Depend. 2020 July 01; 212: 108029. doi:10.1016/j.drugalcdep.2020.108029.

The Emergence of Cardiac Changes Following the Self-Administration of Methamphetamine

Jessica L. Freeling[a], **Lisa M. McFadden**[b]

[a]Physiology Core, Division of Basic Biomedical Sciences, University of South Dakota, Vermillion SD 57069

[b]Center for Brain and Behavioral Research, Division of Basic Biomedical Sciences, University of South Dakota, Vermillion SD 57069

Abstract

Background: Clinical observations suggest an association between methamphetamine (METH) use and cardiovascular disease, but preclinical studies are lacking. The purpose of the current study was to explore changes in left ventricular function as a potential precursor to cardiovascular disease in a rodent model of METH use.

Methods: Male rats were allowed to self-administer either METH or saline for 9 d. On the day following the 4th and 9th self-administration sessions, an echocardiogram was performed to assess left-ventricular parameters under basal conditions and following a low-dose of METH (1 mg/kg).

Results: A low challenge dose of METH resulted in subtle but statistically significant changes in cardiac function during the echocardiogram in both the METH and saline self-administering groups. Further, differences in left-ventricular parameters such as stroke volume and heart rate were observed between METH and saline groups following the 9th self-administration session. Finally, supervised machine learning correctly predicted the self-administration group assignment (saline or METH) using cardiac parameters following the 9th self-administration session.

Conclusions: The findings of the current study suggest the heart, specifically the left ventricle, is sensitive to METH. Overall, these findings and emerging clinical observations highlight the need for research to investigate the effects of METH use on the heart.

Keywords

Methamphetamine; self-administration; echocardiogram; heart; left ventricle

Corresponding Author: Lisa M. McFadden, Division of Basic Biomedical Sciences, University of South Dakota, 414 E. Clark St., Vermillion, SD 57069, Lisa.mcfadden@usd.edu, (605) 658-6346.

Contributors: Both authors assisted in: the study design; the collection, analysis and interpretation of data; and the writing of the report.

Conflict of Interest: Methamphetamine was generously supplied by the National Institute on Drug Abuse, National Institute of Health, Bethesda, MD. The authors have no further declarations of interest to disclose.

1. Introduction.

Methamphetamine (METH) users have higher incidences of cardiovascular disease (Chehab et al., 2012; Darke et al., 2018, 2017; Jafari Giv, 2017; Paratz et al., 2016). Recent epidemiology studies suggest that cardiovascular disease is the leading cause of *natural* death in METH users, and the second leading cause of death overall in METH users (Jafari Giv, 2017; Paratz et al., 2016). Of these cases, left ventricular hypertrophy and Takotsubo cardiomyopathy were among the most common types of cardiovascular disease (Darke et al., 2017; Paratz et al., 2016). However, determining a causal link between METH use and cardiovascular disease in humans is difficult, given the multitude of other factors that may be mediating this relationship (Jafari Giv, 2017). Despite clinical evidence suggesting METH use is associated with cardiovascular disease and cardiac-associated death, preclinical studies investigating the contribution of METH use to cardiac dysfunction are limited.

The self-administration of METH in rodents resembles aspects of human METH use. Extended access self-administration paradigms result in an escalation of drug intake and brain METH levels comparable to that of human METH users (Kalasinsky et al., 2001; Krasnova et al., 2013, 2010; McFadden et al., 2012; Schwendt et al., 2019). Additional similarities exist between preclinical models and human METH users in neurochemistry measures of the brain (Krasnova et al., 2013, 2010; McCann et al., 1998; McFadden et al., 2012; Schwendt et al., 2019; Volkow et al., 2001AB). Despite research investigating how METH changes the brain, little research has investigated how METH use changes the rest of the body, including the heart (Kevil et al., 2019).

A novel aspect of machine learning is its ability to predict disease states. For example, algorithms are being trained to predict cancer and heart disease from medical images (Ghorbani et al., 2020; Reddy et al., 2019). These advancements in machine learning can identify characteristics of a disease state that are discoverable by a trained human expert (Ghorbani et al., 2020). More importantly, advancements in machine learning have produced algorithms that can predict disease states and patient characteristics using subtle differences that may not be detected by human experts (Ghorbani et al., 2020). These advancements in machine learning show promise in aiding healthcare experts in identifying disease states using subtle, but predictive changes.

The current study investigated early changes in cardiovascular function following the self-administration of METH in male rats. Echocardiograms were used to assess left-ventricular function under basal conditions and following an acute low-dose challenge injection of METH. Results revealed differences in cardiovascular function including heart rate, stroke volume, and left ventricular mass between self-administration groups. Despite animals self-administering for only 9 d, machine learning was able to correctly predict the self-administration group assignment in the majority of animals based on subtle changes in the heart.

2. Materials and Methods.

2.1. Animals.

Adult male Sprague Dawley rats (Envigo Laboratories, postnatal d 56) were maintained on a 12:12 h light: dark cycle throughout the study. Animals were pair housed until the time of surgery, after which they were singly housed. Water was freely available throughout the experiments, and food was freely available at all times except for mild food restriction during food training. All procedures were approved by the University of South Dakota Institutional Animal Care and Use Committee, per the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

2.2. Food Training and Self-Administration.

Rats were food trained and underwent surgery as previously described (McFadden et al., 2012). Briefly, animals underwent 4–5 overnight sessions of food training (14 h each), where active lever presses resulted in the delivery of a 45 mg food pellet as previously described (Johansen & McFadden, 2017). Animals then underwent surgery to implant a jugular catheter under ketamine (100 mg/kg i.p.) and xylazine (7 mg/kg i.p.) anesthesia. Rats were given time to recover after the surgery. Flunixin meglumine (1.1 mg/kg) was given for post-surgery analgesia. Animals received daily infusions of cefazolin (1 mg/ 100 uL infusion) and heparin (6 U/ 100 uL infusion) following surgery. An infusion of methohexital sodium (10 mg/1 mL, 100 uL infused), a short-acting barbiturate, assessed the patency of catheters to ensure that the animals receive the drug i.v. (Schwendt et al., 2009), and only animals with patent catheters were retained in the study.

Rats then self-administered either saline or METH (8 h/d). Active lever presses resulted in an infusion of METH (0.12 mg/10 uL infusion) or 10 uL saline followed by a 30 s time out period. Inactive lever presses were recorded but resulted in no programmed responses. A total of 9 self-administration sessions were given.

2.3. Echocardiogram.

To assess the progressive development of early cardiovascular changes, animals underwent an echocardiogram approximately 24 h after the start of the 4^{th} and 9^{th} self-administration sessions. Animals were anesthetized with isoflurane (4%) and adjusted to 1.5% to sustain a light anesthetic plane. Standard echocardiograms were collected (VisualSonics Vevo 2100, Toronto, ON, Canada). Parasternal long-axis B-mode was utilized to identify the correct cardiac plane. The probe was then rotated to the short-axis plane, adjusted to the level of the papillary muscle, and video of B-mode and M-mode were collected. After baseline assessments, a 1 mg/kg injection of METH (i.p.) was given to assess cardiac function following a low-dose challenge, and images were acquired 10 min, 20 min, and 30 min post-injection. Intraperitoneal injection was used to allow METH to be administered without altering the plane from which the echocardiograms were recorded. From these videos, the cardiac walls were traced using VisualSonics VevoLAB 3.1.1 Software Cardiac Package by an individual blinded to treatment at each time point. Calculated output parameters included: heart rate, stroke volume, ejection fraction, left ventricular mass corrected (left ventricular mass x 0.8 to correct for shape), and diastolic left ventricular posterior wall thickness.

2.4. Data Analysis.

Data were analyzed in SAS Studio. Lever pressing and cardiac parameters were assessed at each time point using repeated-measures ANOVAs followed by Tukey's HSD posthoc analyses. Significance for these measures occurred when $p \leq 0.05$. Graphs of these measures represent the mean ± SEM.

Supervised machine learning (linear discriminate analysis) was then used to predict group assignment (METH self-administration or saline self-administration) based on average cardiac parameters. Linear discriminate analysis seeks to find a linear combination of predictor variables that best explain the dependent variable. For the algorithm to perform its best, variables that are not predictive of the dependent variable, i.e. self-administration group, need to be removed. A stepwise selection was used to select the best predictor variables of all of those captured by the echocardiogram. Specifically, predictor variable selection was determined by Wilks' lambda and the F-value of the analysis of covariance ($p_{in}<0.15$; $p_{out}<0.15$). This selection method yielded two predictor variables, left ventricular mass and diastolic left ventricular posterior wall thickness. Next, the linear discriminate analysis algorithm was trained using the two predictor variables and the self-administration group as the dependent variable. Findings were then cross-validated using leave-one-out cross-validation to determine the accuracy of the model.

3. Results.

Lever presses for METH increased over the course of the experiment while saline presses decreased (Figure 1A; Group: $F(1,12)=36.38$, $p<0.05$; Day: $F(8,96)=1.87$, ns; Group x Day: $F(8,96)=16.91$, $p<0.05$). METH intake significantly increased throughout self-administration (Figure 1B; $F(8,48)=61.35$, $p<0.05$), with intake exceeding 15 mg/kg/session on the last two days of self-administration. As expected, METH self-administration resulted in a reduction in weight gain over the course of the study (1^{st} day of self- administration: Saline- 323.57 g ± 5.32 g, METH- 319.57 g ± 3.89 g; 1^{st} ECHO: Saline- 333.14 g ± 6.06 g, METH- 305.86 g ± 2.95 g; 2^{nd} ECHO: Saline- 347.57 g ± 6.43 g, METH- 305.71 g ± 3.48 g; Group: $F(1,12)=13.08$, $p<0.05$; Day: $F(2,24)=18.19$, $p<0.05$; Group x Day: $F(2,24)=122.7$, $p<0.05$).

Following 4 d of self-administration, few group differences in cardiac measures were observed. METH self-administering animals had a slightly lower left ventricular mass compared to saline animals overall (Group: $F(1,12)=4.68$, $p=0.05$; Time: $F(3,36)=0.42$, ns; Group x Time: $F(3,36)=0.41$; ns). The METH challenge increased heart rate ($F(3,36)=9.51$, $p<0.05$), but no group differences were observed ($F(1,12)=0.29$, ns; Group x Time: $F(3,36)=1.39$, ns). This injection of METH also resulted in an increase in the ejection fraction ($F(3,36)=21.66$, $p<0.05$), but no differences were observed between groups (Group: $F(1,12)=0.11$, ns; Group x Time: $F(3,36)=1.41$, ns). Diastolic left ventricular posterior wall thickness did not differ by group ($F(1,12)=3.29$, $p<0.10$), but did increase following the METH challenge (Time: $F(3,36)=8.58$, $p<0.05$; Group x Time: $F(3,36)=1.04$, ns). No differences were observed in stroke volume (Group: $F(1,12)=0.23$, ns; Time: $F(3,36)=0.52$, ns; Time x Group: $F(3,36)=0.66$, ns;).

After 9 d of self-administration, group differences began to emerge. Heart rate was increased in METH self-administering animals ($F(3,12)=5.02$, $p<0.05$; Figure 2A), and the METH challenge increased heart rate in both groups (Time: $F(3,36)=14.97$, $p<0.05$), but no significant interaction occurred (Group x Time: $F(3,36)=0.03$, ns). The METH challenge increased the ejection fraction (Time: $F(3,36)=2.97$, $p<0.05$; Figure 2B), but no group differences were observed (Group: $F(1,12)=0.05$, ns; Group x Time: $F(3,36)=0.60$, ns). METH self-administering rats had reduced stroke volumes compared to saline self-administering animals (Group: $F(1,12)=5.08$, $p<0.05$; Figure 2C), but the METH challenge resulted in no significant changes (Time: $F(3,36)=0.62$, ns; Group x Time: $F(3,36)=0.60$, ns). Diastolic left ventricular posterior wall thickness did not differ (Group: $F(1,12)=0.13$, ns; Time: $F(3,36)=1.47$, ns; Group x Time : $F(3,36)=1.25$, ns). Finally, METH self-administering animals had slightly lower left ventricular mass compared to saline animals (Group: $F(1,12)=5.35$, $p<0.05$). Overall, there was no significant effect of time for the ventricular mass measure (Time: $F(3,36)=1.56$, ns), but instead mass was higher in the saline group following the drug challenge (Group x Time: $F(3,36)=2.85$, $p=0.05$).

Given group differences emerged following 9 d of self-administration, supervised machine learning was used to classify self-administration groups based on cardiac parameters averaged across time. Given the large number of measures generated by the echocardiograms, a stepwise selection method was first utilized to select the measures most predictive variables of the self-administration group. The resulting model found left ventricular mass and diastolic left ventricular posterior wall thickness were significant predictors of METH self-administration (F-statistic=9.35, $p<0,05$; Wilks' Lambda=0.37, $p<0.05$; Figure 2D). When all animals were included in this model, it correctly classified 100% of the METH self-administration rats and 85.7% of the saline self-administration rats. Moreover, cross-validation resulted in the correct classification of 100% of the METH animals and 71.4% of the saline animals.

4.1. Discussion.

Clinical reports suggest that METH use is associated with an increase in cardiovascular disease and related deaths (Chehab et al., 2012; Darke et al., 2018, 2017; Jafari Giv, 2017; Paratz et al., 2016). These clinical reports likely represent the extremes on a continuum of cardiac complications associated with long-term METH use. Understanding the early stages of METH-induced cardiac changes using non-invasive methods is important for determining the prognosis and developing effective treatments (Schürer et al., 2017). The current study sought to investigate the development of METH self-administration-induced cardiac changes. The results of the current study demonstrate an *acute* low-dose of METH robustly change cardiac function. Regardless of the self-administration group, the acute low-dose injection of METH was sufficient to increase heart rate and ejection fraction. These findings suggest that the heart is readily responsive to METH when administered in a single intraperitoneal bolus. Further, the current study suggests that subtle left ventricular alterations emerge as *chronic* METH use progresses. After 9 d of self-administration, increased heart rate and reduced stroke volumes were also observed in the METH self-administering animals compared to saline. Given the relatively short time of self-administration (9 d), it is unknown if these subtle changes will worsen if a longer duration of

self-administration was given. Further, one limitation of the current study is that animals were only subjected to a mild challenge in the form of a low dosage of METH, given intraperitoneally during the assessment of cardiac parameters. If a greater challenge was given to the animals, such as a higher intravenous dose of METH, a physical cardiac stressor, or chemical stressors such as isoproterenol, greater differences in cardiac parameters in animals with a history of METH self-administration compared to saline self-administration may be unmasked.

While the effect of METH exposure on the brain and neurological system are widely studied, less is known about how METH effects the peripheral and central cardiovascular system. METH use resulted in increased blood pressure, acute vasospasm, and atherosclerosis, suggesting that METH has effects on the peripheral vasculature (Blaker et al., 2016; Kaye et al., 2008; Lv et al., 2016; Kevil et al., 2019). Preclinical studies have also shown that METH-induced endothelial nitric oxide synthase activation and endothelin-1 release leads to potent vasoconstriction (Seo et al., 2016). Further, chronic METH users are less responsive to the vasodilatation effects of nitroglycerine (Navaei et al., 2016). In addition to these vascular effects, direct effects of METH on the heart can occur through the remodeling of the cardiac tissue itself (Islam et al., 1995; Yu et al., 2002). For example, acute METH exposure inhibits cardiac contractile function (Turdi et al., 2009). Contractile function is an important factor that influences stroke volume (Yu et al., 2002), and this measure was altered in the current study. Further, chronic METH use has been shown to induce apoptosis through cardiac-specific apoptotic pathways (Liou et al., 2013). A principal route of cardiac cell loss may involve systemic catecholamine toxicity (Kevil et al., 2019; Silman et al., 2015). Sustained norepinephrine release leads to hypertrophy and cell death of cardiomyocytes (Jain et al., 2015). Further, these effects were blocked by the non-selective β-adrenergic receptor antagonist, propranolol. Stimulating cardiac adrenergic receptors are known to increase heart rate (Leenen et al., 2007), and heart rate was altered in the current study. These studies suggest that METH acts directly on the heart through catecholamine receptors, which may influence the development of cardiovascular disease (Kevil et al., 2019; Silman et al., 2015). The acute physiological adaptation found in the current study may represent early cardiac changes that may increase the risk of developing more severe cardiac diseases. Future studies are necessary to fully elucidate how these changes in the heart interact with changes in the peripheral vascular to promote cardiovascular diseases following METH use.

These differences following METH self-administration may contribute to the development of later diseases such as Takotsubo syndrome or dilated cardiomyopathy. Takotsubo syndrome, especially the reverse phenotype, has been observed in human METH users (Chehab et al., 2012; Jafari Giv, 2017; Voskoboinik et al., 2016). These users tend to have a shorter duration of use (Jafari Giv, 2017; Voskoboinik et al., 2016). Although Takotsubo syndrome is not well understood, excessive catecholamine release and stress are thought to contribute to some cases (Chehab et al., 2012; Pelliccia et al., 2017). Indeed, the ability of METH to release catecholamines and stress hormones has been well established (Chehab et al., 2012; Zuloaga et al., 2014). In mice, 1 mg/kg injection of METH, caused a significant increase in plasma corticosterone 30 min after the injection (Zuloaga et al., 2014). Of note, METH users with Takotsubo syndrome have a greater chance of recovery from ventricular

dilation (Voskoboinik et al., 2016). Although Takotsubo syndrome associated with METH use is reversible, Voskoboinik and colleagues speculate that chronic catecholamine-induced myocardial stunning from METH use may increase the chances of developing other cardiovascular diseases which have irreversible damage (2016). Preclinical studies have found that METH use can activate cardiac-specific apoptotic pathways (Liou et al., 2013). Further, chronically elevated catecholamine levels can lead to an increase in fibrosis and hypertrophy (Laks et al., 1973). The apoptosis and fibrosis may contribute to the development of more severe cardiac diseases associated with METH use, including left-ventricular cardiomyopathy. With longer drug use, it is speculated that differences in cardiac parameters between METH and saline self-administering animals may become more pronounced and persistent, and perhaps contribute to more severe cardiovascular diseases.

Echocardiograms are commonly used to assess cardiac function in humans. Developing algorithms to predict drug use could aid physicians in determining drug use history in patients. Recent advancements in machine learning have driven the development of algorithms to assist medical professionals in identifying disease states from subtle differences (Ghorbani et al., 2020). These algorithms could potentially allow medical professionals to reliably identify disease states and direct patients to needed treatments earlier before the disease progresses. The results of the current study suggest that even after the short period of METH use, cardiac parameter differences predicted drug self-administration group. However, the specificity of these changes to METH versus other drugs or cardiac conditions was not investigated and remains a limitation of this study. The resulting methods could be applied to develop similar algorithms using clinical data to detect METH usage. Indeed, using transthoracic echocardiograms, Wei and colleagues (2018) were able to predict METH abusers with preserved left ventricular ejection fraction from that of healthy control subjects. Moreover, Ghorbani and colleagues were able to develop algorithms of echocardiograms that could detect specific characteristics about the patient, such as weight, gender, and height, as well as cardiac disease states such as a atrial dilation and ventricle hypertrophy (2020). Given the availability of this non-invasive technology in hospitals, further developing these methods may provide essential information on the cardiovascular impact of drug use and aid health care professionals in identifying drug use. Therefore with further development of these algorithms, we propose that early-stage detection of METH use with a common clinically available tool such as ultrasound combined with the predictive nature of machine learning can provide a valuable potential resource for addressing the METH epidemic by helping medical professionals identify and direct patients to treatment before more severe cardiomyopathies develop.

4.2 Conclusions.

The findings of the current study suggest that the heart is readily responsive to METH even at low doses. Further, METH self-administration can lead to changes in the heart that can be utilized to differentiate between drug and saline self-administering animals. Recent studies suggest that METH use in the United States is on the rise (Jahal et al., 2018; Winkelman et al., 2018). The alterations in the heart induced by METH use combined with aging may put METH users at a higher risk of cardiovascular disease (Darke et al., 2017). Utilizing

preclinical models to study the development of METH-related cardiovascular disorders may be an important factor in understanding the impact of METH use on overall health.

Role of Funding Source:

This research was supported by the National Institutes of Health [grant numbers DA036012 & DA033674]. The funding sources played no further role in the study.

References.

Blaker AL, Northrop NA, & Yamamoto B, 2016 Peripheral Influences of Methamphetamine Neurotoxicity. In Stimulants, Club and Dissociative Drugs, Hallucinogens, Steroids, Inhalants and International Aspects. 2, 309–319. doi: 10.1016/B978-0-12-800212-4.00030-3.

Chehab O, Ioannou A, Sawhney A, Rice A, Dubrey S, 2012 Reverse Takotsubo Cardiomyopathy and cardiogenic shock associated with methamphetamine consumption. J. Emerg. Med 53, e81–e83. doi: 10.1016/j.jemermed.2017.06.027.

Darke S, Duflou J, Kaye S, 2017 Prevalence and nature of cardiovascular disease in methamphetamine-related death: A national study. Drug Alcohol Depend. 179, 174–179. doi: 10.1016/j.drugalcdep.2017.07.001. [PubMed: 28787694]

Darke S, Duflou J, Lappin J, Kaye S, 2018 Clinical and autopsy characteristics of fatal methamphetamine toxicity in Australia. J. Forensic Sci 63, 1466–1471. doi: 10.1111/1556-4029.13710. [PubMed: 29193063]

Ghorbani A, Ouyang D, Abid A, He B, Chen JH, Harrington RA, Liang DH, Ashley EA, Zou JY, 2020 Deep learning interpretation of echocardiograms. NPJ Digit Med. 3, 10. doi: 10.1038/s41746-019-0216-8. eCollection 2020. [PubMed: 31993508]

Jafari Giv M, 2017 Exposure to amphetamines leads to development of amphetamine type stimulants associated cardiomyopathy (ATSAC). Cardiovasc. Toxicol 17, 13–24. doi: 10.1007/s12012-016-9385-8. [PubMed: 27663745]

Islam MN, Kuroki H, Hongcheng B, Ogura Y, Kawaguchi N, Onishi S, Wakasugi C, 1995 Cardiac lesions and their reversibility after long term administration of methamphetamine. Forensic Sci Int. 75, 29–43. doi: 10.1016/0379-0738(95)01765-b. [PubMed: 7590547]

Jalal H, Buchanich JM, Roberts MS, Balmert LC, Zhang K, Burke DS, 2018 Changing dynamics of the drug overdose epidemic in the United States from 1979 through 2016. Science. 361, pii: eaau1184. doi: 10.1126/science.aau1184. [PubMed: 30237320]

Johansen A, McFadden LM, 2017 The neurochemical consequences of methamphetamine self-administration in male and female rats. Drug Alcohol Depend. 178, 70–74. doi: 10.1016/j.drugalcdep.2017.04.011. [PubMed: 28645061]

Kalasinsky KS, Bosy TZ, Schmunk GA, Reiber G, Anthony RM, Furukawa Y, Guttman M, Kish SJ, 2001 Regional distribution of methamphetamine in autopsied brain of chronic human methamphetamine users. Forensic Sci. Int 116, 163–169. [PubMed: 11182268]

Kaye S, Darke S, Duflou J, McKetin R, 2008 Methamphetamine-related fatalities in Australia: demographics, circumstances, toxicology and major organ pathology. Addiction. 103, 1353–1360. doi: 10.1111/j.1360-0443.2008.02231.x. [PubMed: 18855825]

Kevil CG, Goeders NE, Woolard MD, Bhuiyan MS, Dominic P, Kolluru GK, Arnold CL, Traylor JG, Orr AW, 2019 Methamphetamine use and cardiovascular disease. Arterioscler. Thromb. Vasc. Biol 39, 1739–1746. doi: 10.1161/ATVBAHA.119.312461. [PubMed: 31433698]

Krasnova IN, Chiflikyan M, Justinova Z, McCoy MT, Ladenheim B, Jayanthi S, Quintero C, Brannock C, Barnes C, Adair JE, Lehrmann E, Kobeissy FH, Gold MS, Becker KG, Goldberg SR, Cadet JL, 2013 CREB phosphorylation regulates striatal transcriptional responses in the self-administration model of methamphetamine addiction in the rat. Neurobiol. Dis 58, 132–143. doi: 10.1016/j.nbd.2013.05.009. [PubMed: 23726845]

Krasnova IN, Justinova Z, Ladenheim B, Jayanthi S, McCoy MT, Barnes C, Warner JE, Goldberg SR, Cadet JL, 2010 Methamphetamine self-administration is associated with persistent biochemical

alterations in striatal and cortical dopaminergic terminals in the rat. PLoS One. 5, e8790. doi: 10.1371/journal.pone.0008790. [PubMed: 20098750]

Leenen FH, Fourney A, Coletta E, White R 2007 Effects of hypertension on cardiovascular responses to epinephrine in humans. Am J Physiol Heart Circ Physiol. 292, H3025–H3031. DOI: 10.1152/ajpheart.01200.2006. [PubMed: 17307999]

Laks MM, Morady F, Swan HJ, 1973 Myocardial hypertrophy produced by chronic infusion of subhypertensive doses of norepinephrine in the dog. Chest. 64, 75–78. DOI: 10.1378/chest.64.1.75. [PubMed: 4268685]

Liou CM, Tsai SC, Kuo CH, Williams T, Ting H, Lee SD, 2014 Chronic methamphetamine exposure induces cardiac fas-dependent and mitochondria-dependent apoptosis. Cardiovasc Toxicol. 14, 134–144. doi: 10.1007/s12012-013-9237-8. [PubMed: 24307234]

Lv D, Zhang M, Jin X, Zhao J, Han B, Su H, Zhang J, Zhang X, Ren W, He J, 2016 The body mass index, blood pressure, and fasting blood glucose in patients with methamphetamine dependence. Medicine (Baltimore). 95, e3152. doi: 10.1097/MD.0000000000003152. [PubMed: 27015198]

McCann UD, Wong DF, Yokoi F, Villemagne V, Dannals RF, Ricaurte GA, 1998 Reduced striatal dopamine transporter density in abstinent methamphetamine and methcathinone users: Evidence from positron emission tomography studies with [11C]WIN-35,428. J. Neurosci 18, 8417–8422. [PubMed: 9763484]

McFadden LM, Hadlock GC, Allen SC, Vieira-Brock PL, Stout KA, Ellis JD, Hoonakker AJ, Andrenyak DM, Nielsen SM, Wilkins DG, Hanson GR, Fleckenstein AE, 2012 Methamphetamine self-administration causes persistent striatal dopaminergic alterations and mitigates the deficits caused by a subsequent methamphetamine exposure. J. Pharmacol. Exp. Ther 340, 295–303. doi: 10.1124/jpet.111.188433. [PubMed: 22034657]

Nabaei G, Oveisgharan S, Ghorbani A, Fatehi F, 2016 Impaired arterial smooth muscle cell vasodilatory function in methamphetamine users. J Neurol Sci. 370, 107–111. doi: 10.1016/j.jns.2016.09.027. [PubMed: 27772737]

Neeki MM, Kulczycki M, Toy J, Dong F, Lee C, Borger R, Adigopula S, 2016 Frequency of methamphetamine use as a major contributor toward the severity of cardiomyopathy in adults ≤50 years. Am. J. Cardiol 118, 585–589. doi: 10.1016/j.amjcard.2016.05.057. [PubMed: 27374605]

Paratz ED, Cunningham NJ, MacIsaac AI, 2016 The cardiac complications of methamphetamines. Heart Lung Circ. 25, 325–332. doi: 10.1016/j.hlc.2015.10.019. [PubMed: 26706652]

Pelliccia F, Kaski JC, Crea F, Camici PG, 2017 Pathophysiology of Takotsubo Syndrome. Circulation. 135, 2426–2441. doi: 10.1161/CIRCULATIONAHA.116.027121. [PubMed: 28606950]

Reddy UJ, Ramana Reddy BV, Reddy BE, 2019 Categorization & Recognition of Lung Tumor Using Machine Learning Representations. Curr Med Imaging Rev. 15, 405–413. doi: 10.2174/1573405614666180212162727. [PubMed: 31989910]

Seo JW, Jones SM, Hostetter TA, Iliff JJ, West GA, 2016 Methamphetamine induces the release of endothelin. J Neurosci Res. 94, 170–178. doi: 10.1002/jnr.23697. [PubMed: 26568405]

Sliman S, Waalen J & Shaw D, 2015 Methamphetamine-Associated Congestive Heart Failure: Increasing Prevalence and Relationship of Clinical Outcomes to Continued Use or Abstinence. Cardiovasc Toxicol. 16, 381–389. Doi: 10.1007/s12012-015-9350-y.

Schürer S, Klingel K, Sandri M, Majunke N, Besler C, Kandolf R, Lurz P, Luck M, Hertel P, Schuler G, Linke A, Mangner N, 2017 Clinical characteristics, histopathological features, and clinical outcome of methamphetamine-associated cardiomyopathy. JACC Heart Fail. 5, 435–445. doi: 10.1016/j.jchf.2017.02.017. [PubMed: 28571597]

Schwendt M, Rocha A, See RE, Pacchioni AM, McGinty JF, Kalivas PW, 2009 Extended methamphetamine self-administration in rats results in a selective reduction of dopamine transporter levels in the prefrontal cortex and dorsal striatum not accompanied by marked monoaminergic depletion. J. Pharmacol. Exp. Ther 331, 555–562. doi: 10.1124/jpet.109.155770. [PubMed: 19648469]

Turdi S, Schamber RM, Roe ND, Chew HG Jr., Culver B, Ren J, 2009 Acute methamphetamine exposure inhibits cardiac contractile function. Toxicol Lett. 189, 152–158. doi: 10.1016/j.toxlet.2009.05.015. Epub 2009 May 27. [PubMed: 19481142]

Volkow ND, Chang L, Wang GJ, Fowler JS, Franceschi D, Sedler M, Gatley SJ, Miller E, Hitzemann R, Ding YS, et al., 2001A Loss of dopamine transporters in methamphetamine abusers recovers with protracted abstinence. J. Neurosci 21, 9414–9418. [PubMed: 11717374]

Volkow ND, Chang L, Wang GJ, Fowler JS, Ding YS, Sedler M, Logan J, Franceschi D, Gatley J, Hitzemann R, Gifford A, Wong C, Pappas N, 2001B Low level of brain dopamine D2 receptors in methamphetamine abusers: association with metabolism in the orbitofrontal cortex. Am. J. Psychiatry 158, 2015–2021. doi: 10.1176/appi.ajp.158.12.2015. [PubMed: 11729018]

Voskoboinik A, Ihle JF, Bloom JE, Kaye DM, 2016 Methamphetamine-associated cardiomyopathy: Patterns and predictors of recovery. Intern. Med. J 46, 723–727. doi: 10.1111/imj.13050. [PubMed: 26929061]

Wei GL, Zheng XZ, Chen KQ, Shi YY, Wang LY, Tan XY, 2018 Coronary sinus flow is reduced in methamphetamine abusers: A transthoracic echocardiographic study, Int. J. Cardiovasc. Imaging 34, 1889–1894. doi: 10.1007/s10554-018-1417-y. [PubMed: 30032415]

Winkelman TNA, Admon LK, Jennings L, Shippee ND, Richardson CR, Bart G, 2018 Evaluation of amphetamine-related hospitalizations and associated clinical outcomes and costs in the United States. JAMA Netw. Open 1, e183758. doi:10.1001/jamanetworkopen.2018.3758. [PubMed: 30646256]

Yu Q, Montes S, Larson DF, Watson RR, 2002 Effects of chronic methamphetamine exposure on heart function in uninfected and retrovirus-infected mice. Life Sci. 71, 953–965. DOI: 10.1016/s0024-3205(02)01769-1. [PubMed: 12084392]

Zuloaga DG, Johnson LA, Agam M, Raber J, 2014 Sex differences in activation of the hypothalamic-pituitary-adrenal axis by methamphetamine. J. Neurochem 129, 495–508. doi: 10.1111/jnc.12651. [PubMed: 24400874]

Highlights:

- 1 mg/kg of methamphetamine robustly changed left ventricular measurements
- Methamphetamine self-administration leads to alterations in cardiac parameters
- These subtle cardiac alterations were predictive of self-administration group assignment

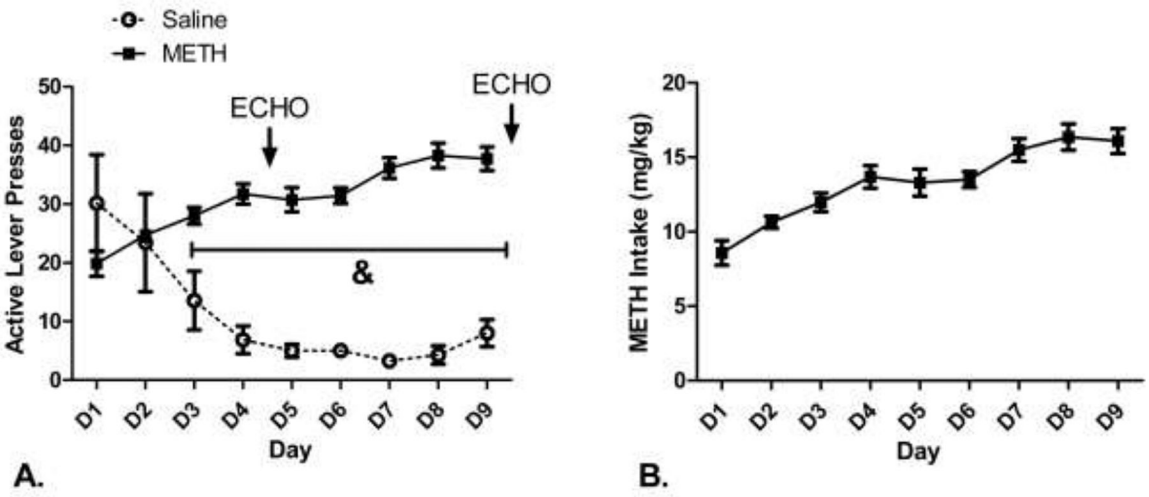

Figure 1.

The self-administration of METH and saline. A. METH self-administering animals increased active lever presses throughout self-administration while saline animals rapidly extinguished lever pressing. B. This resulted in an escalation of METH intake over the course of self-administration. &p<0.05 METH vs. Saline.

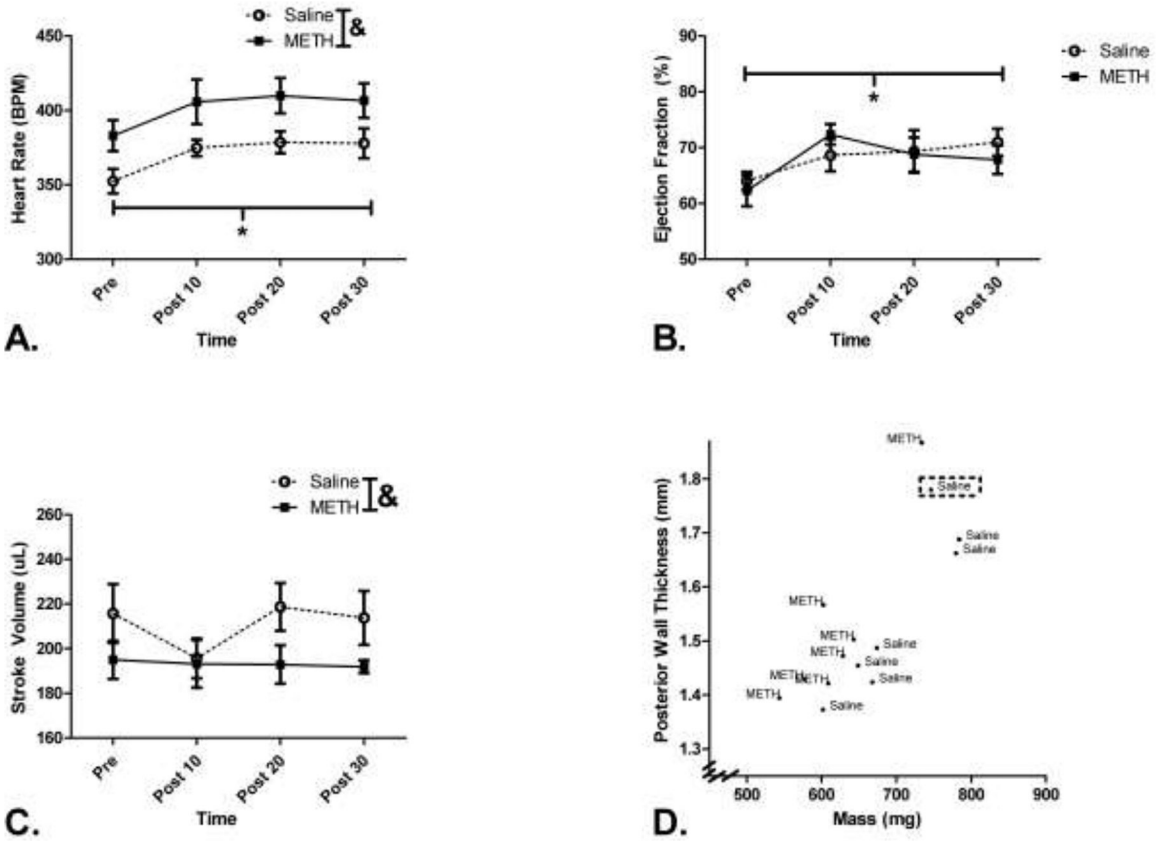

Figure 2.

Echocardiogram measures as assessed on the day following the 9th self-administration. Basal cardiac parameters were assessed followed by a 1 mg/kg injection of METH. Cardiac parameters were then reassessed every 10 min after the injection. A. METH self-administering animals had elevated heart rates compared to saline animals, but both groups' heart rate increased following the METH challenge. B. Ejection fraction increased following the METH challenge in both groups. C. METH self-administering animals had reduced stroke volumes compared to saline self-administering animals. D. A scatter plot of average left ventricular volume versus average diastolic left ventricular posterior wall thickness following 9 d of self-administration. Linear discriminate analysis was performed using these parameters and cross-validated to predict group assignment. The animal that was misclassified during the training of the linear discriminate analysis is outlined with dashed markers. & $p<0.05$ METH vs. Saline. *$p<0.05$ Pre vs. Post 10, Post 20, Post 30.