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Authors

Bhatia, Harpreet Singh
Nishimura, Marin
Dickson, Stephen
et al.

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Clinical and echocardiographic outcomes in heart failure associated with methamphetamine use and cessation

Harpreet Singh Bhatia, **Marin Nishimura**, **Stephen Dickson**, **Eric Adler**, **Barry Greenberg**, **Isac C Thomas**

Division of Cardiovascular Medicine, Department of Medicine, University of California San Diego, La Jolla, California, USA

Abstract

Objective—Methamphetamine use is associated with systolic dysfunction, pulmonary arterial hypertension and may also be associated with diastolic dysfunction. The impact of methamphetamine cessation on methamphetamine-associated heart failure (MethHF) remains poorly characterised. We aimed to longitudinally characterise methamphetamine-associated heart failure patients with reduced (METHrEF) and preserved (METHpEF) left ventricular ejection fraction (EF), and evaluate the relationship between methamphetamine cessation and clinical outcomes.

Methods—We performed a retrospective cohort study, and reviewed medical records of patients with METHrEF, METHpEF and heart failure controls without methamphetamine use. Echocardiographic variables were recorded for up to 12 months, with clinical follow- up extending to 24 months.

Results—Among METHrEF patients (n=28, mean age 51±9 years, 82.1% male), cessation was associated with improvement in EF (+10.6±13.1%, p=0.009) and fewer heart failure admissions per year compared with continued use (median 0.0, IQR 0.0–1.0 vs median 2.0, IQR 1.0–3.0, p=0.039). METHpEF patients (n=28, mean age 50±8 years, 60.7% male) had higher baseline right ventricular systolic pressure (median 53.44, IQR 43.70–84.00 vs median 36.64, IQR 29.44–45.95, p=0.011), and lower lateral E/E' ratio (8.1±3.6 vs 11.2±4., p<0.01) compared with controls (n=32). Significant improvements in echocardiographic parameters and clinical outcomes were not observed following cessation in this group.

Correspondence to: Dr Isac C Thomas, Division of Cardiovascular Medicine, Department of Medicine, University of California San Diego, La Jolla, CA 92093-0021, USA; icthomas@health.ucsd.edu.

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Conclusions—METHrEF patients who cease methamphetamine use have significant improvement in left ventricular systolic function and fewer heart failure admissions, suggesting that METHrEF may be reversible. Echocardiographic parameters suggest that some patients with METHpEF may have pulmonary hypertension in the absence of overt signs of left ventricular diastolic dysfunction, but additional study is needed to characterise this patient cohort.

INTRODUCTION

Use of methamphetamines is a growing public health concern as methamphetamines and amphetamine-containing substances have become increasingly prevalent worldwide.[1] Many cardiovascular effects associated with methamphetamine use have been reported, including a long-documented association between methamphetamine use and heart failure (HF).[1–5] Proposed mechanisms related to cardiovascular complications include an increased catecholamine state leading to hypertension and tachycardia, coronary vasospasm and ischaemia, increased reactive oxygen species and direct myocardial toxicity.[1 2]

Many forms of cardiomyopathy have been reported with methamphetamine use, including ischaemic cardiomyopathy, hypertrophic cardiomyopathy and multiple types of stress cardiomyopathies.[2] However, methamphetamine use is most commonly associated with a dilated cardiomyopathy[3 4 6 7] with reduced left ventricular (LV) ejection fraction (EF)[8 9] and increased left ventricular and atrial dilation.[6 10 11] In small studies, cessation of methamphetamine use has been associated with improvement in EF,[5 11] New York Heart Association (NYHA) class and combined mortality and HF hospitalisation.[11]

Pulmonary arterial hypertension (PAH) has also been associated with methamphetamine use, predominantly among female patients.[10] Thus, many patients with elevated pulmonary pressure in the absence of left ventricular systolic dysfunction are often presumed to have methamphetamine-associated PAH. However, left ventricular diastolic dysfunction may also be present as a consequence of chronic methamphetamine use due to its effects on systemic haemodynamics. Prior studies have reported evidence of diastolic dysfunction with methamphetamine use, predominantly in the setting of systolic dysfunction[6 7] as well as in patients with PAH.[10] The association of methamphetamine use with diastolic dysfunction among patients with preserved LVEF has not been well-studied.

In this study, we sought to longitudinally characterise patients with methamphetamine-associated heart failure (MethHF) in comparison with patients with HF unrelated to methamphetamine use. We characterise those with reduced ejection fraction (METHrEF), the most recognised form of HF associated with methamphetamine use, and assess the association of methamphetamine cessation with echocardiographic and clinical outcomes. Additionally, we separately characterise those with preserved ejection fraction (METHpEF) and evaluate the association of methamphetamine use and cessation with diastolic function.

METHODS

Study design

We performed a retrospective cohort study at the University of California, San Diego Medical Center (UCSD) through systematic review of the electronic medical record. Patients or the public were not involved in the study design. We used a previously established database of adults over the age of 18 years with HF who were evaluated at UCSD between 1 January 2005 and 30 June 2016 based on the International Classification of Diseases (ICD)-9 codes for HF (428. xx) and/or elevated serum brain natriuretic peptide (BNP) (>999pg/mL) or N-terminal pro-brain natriuretic peptide (proBNP) (>4499pg/mL). We screened for methamphetamine use using the ICD-9 codes for amphetamine dependence (304.4) and amphetamine use (305.7). Of those who met these criteria, 100 patients with diagnosis codes for both HF and methamphetamine use as well as at least two echocardiograms were randomly selected as a sample of convenience for in-depth review. One hundred contemporaneous controls with diagnosis code for HF, no code for methamphetamine use and at least two echocardiograms were selected. Contemporaneous controls were chosen because the population of interest is substantially younger and more often male than the overall HF population, and age and sex matching would result in controls that are not representative of the overall HF population. Each case was matched to a control who was given an ICD diagnosis within 3 days of the case.

After this initial screen of 200 patients, the analytical sample was selected by performing a detailed chart review of the medical record to confirm clinical diagnoses of HF as well as methamphetamine use. Methamphetamine use was confirmed by urine toxicology results positive for methamphetamine at the time of the initial echocardiogram. The diagnosis of HF was confirmed by physician documentation of HF and a treatment plan. Patients were designated as MethHF if they had physician documentation of the diagnosis of MethHF and the absence of other identified causes of HF. Patients were enrolled at first presentation in the database regardless of initial visit location as long as echocardiogram and, for the methamphetamine use group, urine toxicology results were available. Patients were excluded if they did not meet the above criteria or received a heart transplant or left ventricular assist device prior to inclusion; if transplant or left ventricular assist device placement occurred during the study period, follow-up was censored at that time point.

Data collection

For all patients, data on demographics, medical comorbidities, history of HF admission and NYHA class, use of other substances, nearest laboratory data (within 4 weeks of study entry), medication prescriptions and baseline electrocardiograms were collected. Medication prescriptions were based on documentation in the medical record; if non-compliance with a medication was documented, it was not counted. Data from baseline echocardiograms on left ventricular size and function (systolic and diastolic), left atrial size, left ventricular thrombi, right ventricular systolic pressure (RVSP), tricuspid annular plane systolic excursion (TAPSE) and valvular disease were collected. Echocardiographic data were also collected at 6-month and 12-month follow-up. Urine toxicology results were collected every 6 months, up to 24 months. Fixed time points for data collection were chosen

for feasibility of chart review and to maximise capture of echocardiographic and clinical variables. Methamphetamine cessation was determined by follow-up urine toxicology, and defined as a negative test nearest to the conclusion of the initial 12-month follow-up period. The duration of 12 months for the initial follow-up was chosen to allow sufficient time to demonstrate methamphetamine cessation after study inclusion. Clinical outcomes were collected from months 12 through 24 and included emergency department (ED) visits, hospital admissions, HF admissions, death and medication prescriptions.

Statistical analysis

Subjects with reduced EF (HFrEF, EF <50%) and preserved EF (HFpEF, EF ≥50%) were compared separately. For baseline demographics and echocardiographic characteristics, continuous variables were compared using the Student's t-test for two groups or analysis of variance for more than two groups, and categorical variables were compared using the χ^2 test. Mann-Whitney U test was used to compare continuous variables with skewed distributions. Changes in echocardiographic characteristics over serial echocardiograms were compared using paired t-tests. The McNemar test was used to compare presence of valvular disease in serial echocardiograms. ED visits, hospital admissions and HF admissions were reported as per year, and compared using the Kruskal-Wallis test with pairwise comparison and Bonferroni correction for multiple hypothesis testing for comparison of methamphetamine cessation versus continued use; adjusted p values to be interpreted at the same significance level of 0.05 are presented. Categorical clinical outcomes were compared using the χ^2 test including medication prescriptions, LV thrombi and deaths.

In a post hoc exploratory analysis, Poisson regression was performed to compare clinical outcomes between methamphetamine continued use and cessation groups to explore how confounding variables may affect results. Two models were created for multivariable adjustment: model 1 included age, sex and race/ethnicity; model 2 included model 1 variables as well as history of diabetes mellitus, hypertension, ischaemic heart disease, atrial fibrillation/flutter, chronic kidney disease, endocarditis and alcohol abuse. Model 1 was chosen as a base model to limit the number of variables due to limited sample size. Statistical analysis was performed using SPSS Statistics V.26.0 (IBM, Armonk, New York, USA).

RESULTS

Study population

After manual chart review and confirmation of study eligibility, the final sample included 51 patients with HF with reduced EF (28 with methamphetamine use and 23 controls) and 60 patients with HF with preserved EF (28 with methamphetamine use and 32 controls). Among the METHrEF patients, 14 demonstrated continued methamphetamine use, while 14 demonstrated methamphetamine cessation at 1 year. Among the METHpEF patients, 15 demonstrated continued methamphetamine use, while 13 demonstrated methamphetamine cessation at 1 year (figure 1).

Heart failure with reduced ejection fraction

Baseline characteristics for patients with HF with reduced EF are shown in table 1. Patients with METHrEF were on average younger (51±9 vs 60±13 years, p<0.01) and more often male (82.1% vs 52.2%, p=0.022) than controls. Compared with controls, METHrEF patients had higher rates of endocarditis and substance use. METHrEF had lower EF (30.2±9.2% vs 36.0±10.0%, p=0.036, table 1) and numerically worse left ventricular dilation compared with controls at baseline. There were no statistically significant differences in other echocardiographic parameters at baseline. HF medication prescriptions did not differ significantly between the METHrEF and control groups at baseline or over follow-up. There was no difference in age between the METHrEF continued use and cessation groups (51±6 vs 51±12 years, p=0.968).

At 1-year follow-up, methamphetamine cessation was associated with improvement in EF in absolute terms (10.6±13.1%, p=0.009), which was similar to improvement in controls (10.8±12.6%, p<0.001). Those with continued use demonstrated no change in EF (figure 2). Additionally, more patients in the METHrEF cessation and control groups demonstrated improvement in EF by at least 10% (n=18, 78.6% cessation vs n=17, 73.9% control vs n=2, 14.3% continued use, p<0.01). Methamphetamine cessation was also associated with significant improvement in LA volume index (-8.83±12.199mL/m^2, p=0.029) while continued use was associated with no change. Change in other echocardiographic parameters were not statistically significantly different over follow-up (table 2).

Clinical outcomes from 12 to 24 months (1 year after last echo and determination of methamphetamine cessation) are shown in table 3. Patients with METHrEF and continued use had similar rates of ED visits per year, more hospital admissions and significantly more HF admissions per year compared with those with methamphetamine cessation in unadjusted analyses. The increased risk of HF admissions per year in the METHrEF continued use group compared with cessation remained significant after multivariable adjustment for potential confounding variables (online supplemental table 1). There were no deaths observed. Of the 28 METHrEF patients included in the study, urine toxicology results at 24 months were available for 19 of them. Of those in the cessation group, three (37.5%) had a urine toxicology result at some point in follow-up between 1 and 2 years that was positive.

Heart failure with preserved ejection fraction

At baseline, patients with METHpEF were younger (50±8 vs 60±16 years, p=0.007, table 4), and more often white (78.6% vs 41.9%, p=0.033 for race/ethnicity overall) than controls. Medical comorbidities were similar between these two groups, and alcohol abuse (14.3% vs 0.0%, p=0.042) was more common among METHpEF patients. There was no significant difference in loop diuretic or mineralcorticoid receptor antagonist prescriptions at baseline between METHpEF patients and controls. There was no difference in age between the METHpEF continued use and cessation groups (49±7 vs 51±11 years, p=0.550).

The METHpEF group had higher baseline TR velocity (3.45±1.08 m/s vs 2.90±0.68 m/s, p=0.042) and RVSP (median 53.44, IQR 43.70–84.00 vs median 36.64, IQR 29.44–45.95,

p=0.011), as well as a lower TAPSE/RVSP ratio than controls. In addition, METHpEF patients had higher lateral E' (10.0±3.8 cm/s vs 7.9±2.2 cm/s, p=0.021) and lower E/E' ratio (8.1±3.6 vs 11.2±4.4, p=0.007) than controls. Other baseline echocardiographic characteristics were similar between METHpEF and controls (table 4).

Over follow-up, the METHpEF cessation group demonstrated increased LA volume index and lateral E/E' ratio. The METHpEF continued use group demonstrated decreased RVSP over follow-up. There were no other significant changes in several echocardiographic parameters among the groups. Among those with continued methamphetamine use, 26.7% developed HFrEF, compared with 7.7% in the cessation group and 12.5% in the control group (p=0.316, table 5).

Clinical outcomes from 12 to 24 months (1 year after last echo and determination of methamphetamine cessation) are shown in table 6. There were no significant differences in ED visits per year, hospital admissions per year or HF admissions per year between the METHpEF continued use and METHpEF cessation groups in unadjusted analyses. After multivariable adjustment, in model 1, there was a significantly increased risk for ED visits per year, hospital admissions per year and HF admissions per year in the METHpEF continued use group compared with cessation. In model 2, only hospital admissions per year remained significant (online supplemental table 2). There was no statistically significant difference in deaths among the METHpEF continued use, cessation and control groups in follow-up (one death in each group, p=0.796). Of the 28 METHPEF patients included in the study, urine toxicology results at 24 months were available for 15 of them. Of those in the cessation group, three (42.9%) had a urine toxicology result at some point in follow-up between 1 and 2 years that was positive.

DISCUSSION

MethHF is increasing in prevalence nationally, and a better understanding of patient and disease characteristics, as well as potential targets for intervention, is needed. Patients with METHrEF, despite being younger, demonstrated evidence of more severe disease at baseline than controls both by echocardiographic characteristics and clinical outcomes. Methamphetamine cessation over follow-up was associated with significant improvement in echocardiographic parameters and clinical outcomes, with improvements that paralleled the control group. This suggests that with cessation of methamphetamines, METHrEF patients may have a clinical course similar to other HF patients. However, ED visits, hospital admissions and HF admissions remained more common among the methamphetamine cessation group when compared with controls, suggesting that while echocardiographic parameters may be reversed to a degree with methamphetamine cessation, significant residual risk of clinical HF remains. Medical therapy did not appear to account for disparities in outcomes as medication prescriptions did not differ significantly between groups, although adherence to prescribed medical therapy was not certain in this study.

METHpEF patients demonstrated more severe HF at baseline compared with controls as evidenced by worse pro-BNP, despite being younger. METHpEF has typically been presumed to be due to PAH. However, in a prior study of 20 patients with

methamphetamine-associated PAH who underwent right heart catheterisation, three patients (all male) had significantly elevated left-sided filling pressures.[10] The METHpEF group had higher TR velocity, RVSP and lower TAPSE/RVSP ratio (a proposed measure of right ventricular dysfunction)[12] than controls. Controls, on the other hand, had higher LA volume index, lower E' velocities and higher E/E' ratios. Taken together, these findings may suggest that PAH, rather than left ventricular diastolic dysfunction, may be the aetiology of symptoms in these patients. We did not observe a reduction in TR velocity and RVSP among the methamphetamine cessation group, nor did we observe improvements in clinical outcomes associated with cessation in our main analysis. However, the cessation group had a trend towards increases in LA volume index and E/E' ratio over follow-up, which may suggest that left sided filling pressures increased as a result of methamphetamine cessation, perhaps as a result of lower pulmonary vascular resistance. Thus, methamphetamine cessation among patients with PAH may unmask a component of LV diastolic dysfunction when LV preload from the right side increases. Also of note, some patients in the METHpEF group with continued use developed reduced EF over follow-up, suggesting that methamphetamine may induce occult LV systolic dysfunction in some that becomes apparent with a reduction in LVEF over time. Further study is needed to draw more definitive conclusions.

Our study has several strengths. A relatively broad population of MethHF patients was included while prior studies have focused on younger patients, those with depressed LVEF only or specific types of cardiomyopathy. Data were primarily collected by detailed chart review, allowing for better adjudication of patient characteristics and outcomes. There was no difference in guideline-directed medical therapy among the HFrEF patients, suggesting that the effects we observed were in fact due to the presence or absence of methamphetamine use. Additionally, methamphetamine use was defined objectively by urine toxicology results.

Our study also has limitations. It was conducted as a retrospective chart review, which is subject to inherent biases and limitations. Patients were included in the study at first presentation with echocardiographic and urine toxicology data, and as such we could not establish all cases as new diagnoses of HF. Fixed time points for data collection were chosen for feasibility and to maximise capture of important variables, which may result in unequal time from methamphetamine cessation to follow-up echo across patients. Urine toxicology results may not represent long-term methamphetamine use patterns. As such, the final echocardiogram was collected at the time of determination of methamphetamine cessation, rather than at an interval postces sation as a high rate of methamphetamine relapse was expected. In fact, there was a high rate of recurrent methamphetamine use, which likely biased our results towards the null. Documentation of medication prescriptions was collected but actual use of medications could not be confirmed. In our exploratory analyses, clinical outcomes were adjusted for multiple confounders between the groups without significant change in the results, but these models should not be considered confirmatory and should be interpreted with caution as the small sample size limits the applicability of regression analysis. By selecting patients with serial echocardiograms, patients who died or were lost to follow-up were not included. Many methamphetamine users were likely enrolled during ED visits or hospitalisation, limiting comparisons to HF patients in the outpatient setting.

In conclusion, our study demonstrates that patients with METHrEF have more severe disease than controls as evidenced by worsened LV function and NYHA class at baseline despite a younger population. However, METHrEF patients who cease methamphetamine use had significant improvement in LV function and fewer HF admissions, lending support to a causal relationship between methamphetamine use and HF, and suggesting that METHrEF may be reversible. These findings emphasise the importance of efforts focused on methamphetamine cessation. There was evidence of clinically worse HF among those with METHpEF compared with controls, as well as the suggestion that the underlying aetiology for HF may in fact be PAH. However, more study is needed, and may include other echocardiographic modalities, such as myocardial strain, to better evaluate for occult abnormalities in LV function.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Data availability statement

Data are available on reasonable request. Not applicable.

REFERENCES

1. Won S, Hong RA, Shohet RV, et al. Methamphetamine-Associated cardiomyopathy. Clin Cardiol 2013;36:737–42. [PubMed: 24037954]
2. Paratz ED, Cunningham NJ, MacIsaac AI. The cardiac complications of Methamphetamines. Heart Lung Circ 2016;25:325–32. [PubMed: 26706652]
3. Hong R, Matsuyama E, Nur K. Cardiomyopathy associated with the smoking of crystal methamphetamine. JAMA 1991;265:1152–4. [PubMed: 1996001]
4. Jacobs LJ. Reversible dilated cardiomyopathy induced by methamphetamine. Clin Cardiol 1989;12:725–7. [PubMed: 2612079]
5. Sliman S, Waalen J, Shaw D. Methamphetamine- Associated congestive heart failure: increasing prevalence and relationship of clinical outcomes to continued use or abstinence. Cardiovasc Toxicol 2016;16:381–9. [PubMed: 26661075]
6. Ito H, Yeo K-K, Wijetunga M, et al. A comparison of echocardiographic findings in young adults with cardiomyopathy: with and without a history of methamphetamine abuse. Clin Cardiol 2009;32:E18–22.
7. Richards JR, Harms BN, Kelly A, et al. Methamphetamine use and heart failure: prevalence, risk factors, and predictors. Am J Emerg Med 2018;36:1423–8. [PubMed: 29307766]
8. Yeo K-K, Wijetunga M, Ito H, et al. The association of methamphetamine use and cardiomyopathy in young patients. Am J Med 2007;120:165–71. [PubMed: 17275458]
9. Neeki MM, Kulczycki M, Toy J, et al. Frequency of Methamphetamine Use as a Major Contributor Toward the Severity of Cardiomyopathy in Adults ≤50 Years. Am J Cardiol 2016;118:585–9. [PubMed: 27374605]
10. Zhao SX, Kwong C, Swaminathan A, et al. Clinical Characteristics and Outcome of Methamphetamine-Associated Pulmonary Arterial Hypertension and Dilated Cardiomyopathy. JACC Heart Fail 2018;6:209–18. [PubMed: 29496022]

11. Schürer S, Klingel K, Sandri M, et al. Clinical characteristics, histopathological features, and clinical outcome of methamphetamine- associated cardiomyopathy. JACC Heart Fail 2017;5:435–45. [PubMed: 28571597]

12. Huston JH, Maron BA, French J, et al. Association of mild echocardiographic pulmonary hypertension with mortality and right ventricular function. JAMA Cardiol 2019;4:1112. [PubMed: 31532457]

Key messages

What is already known on this subject?

- Methamphetamine use is associated with heart failure and pulmonary hypertension.
- Small studies have suggested that heart failure with reduced ejection fraction may be reversible with cessation of methamphetamine use.
- Diastolic dysfunction may be associated with methamphetamine use, but is not well studied.

What might this study add?

- Methamphetamine cessation is associated with significant improvement in both echocardiographic parameters and clinical outcomes, including left ventricular ejection fraction, and heart failure admissions.
- Echocardiographic parameters suggest that those methamphetamine users characterised as having heart failure with preserved ejection fraction may be more likely to have pulmonary arterial hypertension than diastolic dysfunction.

How might this impact on clinical practice?

- This study demonstrates the importance of treating methamphetamine use in patients with heart failure with reduced ejection fraction, which may lead to improvement in left ventricular systolic function and a decrease in hospital and heart failure admissions.

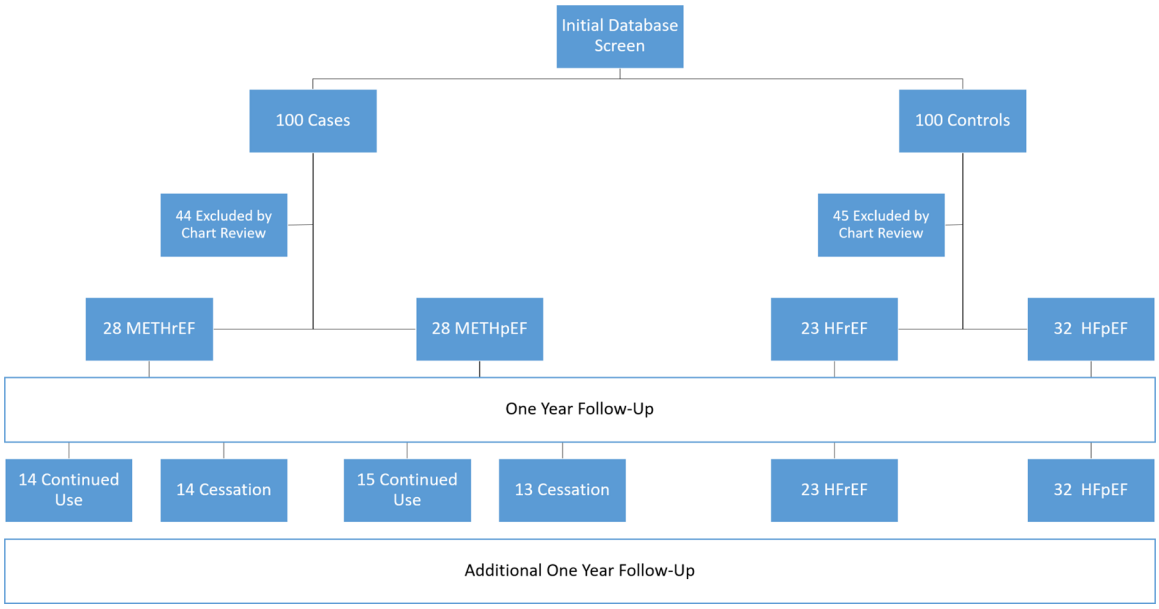

Figure 1.

Study screening and enrolment. HFpEF. heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; METHpEF, methamphetamine-associated heart failure patients with preserved ejection fraction; METHrEF, methamphetamine- associated heart failure patients with reduced ejection fraction.

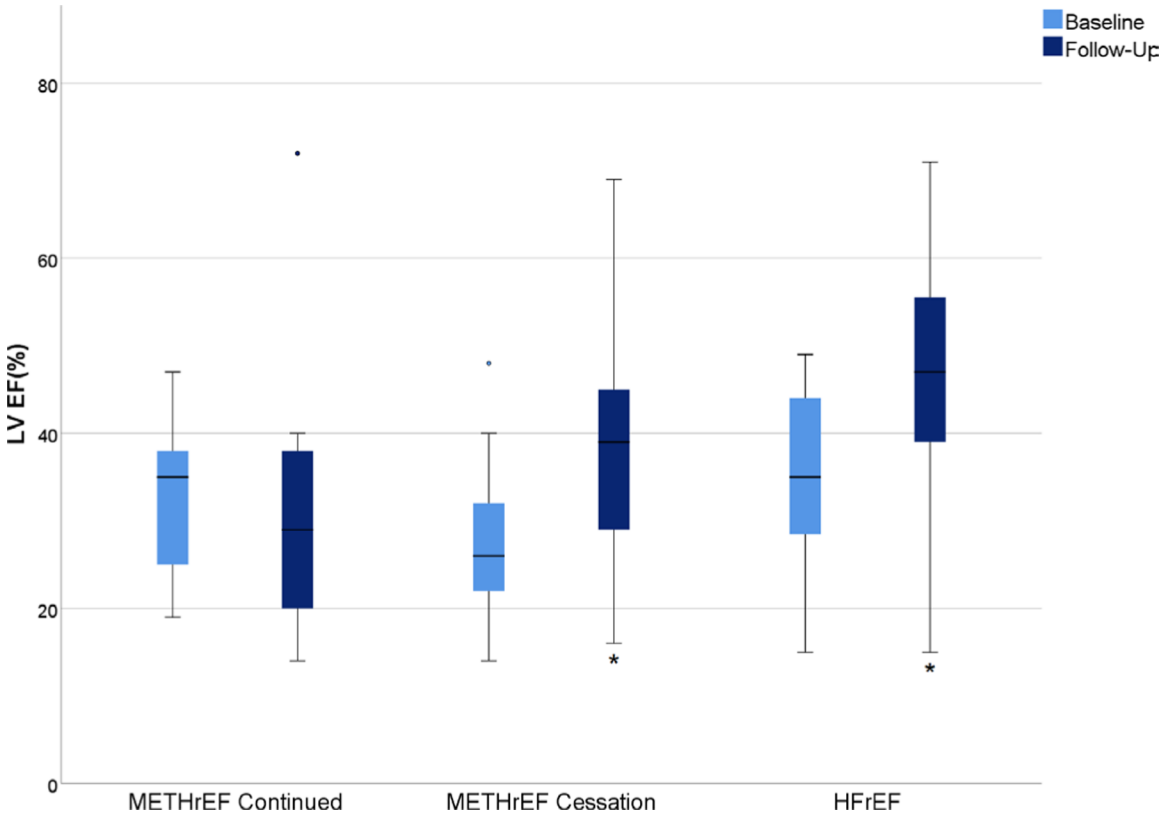

Figure 2.

Change in echocardiographic parameters among patients with reduced ejection fraction stratified by methamphetamine use status over 1-year follow-up period. Dots represent outliers. *P<0.05. P values for baseline vs follow-up: METHrEF continued, p=0.616; METHrEF cessation, p=0.009; HFrEF controls, p=0.0005. EF, ejection fraction; HFrEF, heart failure with reduced ejection fraction without methamphetamine use; METHrEF, methamphetamine-associated heart failure with reduced ejection fraction.

Table 1

Characteristics of heart failure with reduced ejection fraction study population at baseline

	METHrEF (n=28)	HFrEF controls (n=23)	P value
Age (years)	51±9	60±13	0.005 *
Male, n (%)	23 (82.1)	12 (52.2)	0.022
Race, n (%)			0.349
Asian	2 (7.1)	0 (0.0)	
Black or African-American	7 (25.0)	2 (8.7)	
Hispanic or Latino	6 (21.4)	7 (30.4)	
White	12 (42.9)	13 (56.5)	
Other or more than one race	1 (3.6)	1 (4.3)	
Hypertension, n (%)	19 (67.9)	19 (82.6)	0.229
Diabetes mellitus, n (%)	14 (50.0)	6 (26.1)	0.082
Ischaemic heart disease, n (%)	19 (64.3)	10 (43.5)	0.137
Atrial fibrillation/flutter, n (%)	8 (28.6)	12 (52.2)	0.086
Cerebrovascular accident, n (%)	4 (14.3)	4 (17.4)	0.762
Chronic kidney disease, n (%)	7 (25.0)	9 (39.1)	0.279
History of endocarditis, n (%)	3 (10.7)	0 (0.0)	0.106
Alcohol abuse, n (%)	4 (14.3)	2 (8.7)	0.538
Opioid abuse, n (%)	1 (3.6)	1 (4.3)	0.887
Cocaine use, n (%)	0 (0.0)	0 (0.0)	N/A
NYHA class	2.9±0.7	2.1±0.8	0.001 *
Echocardiographic data			
LVEF (%)	30.2±9.2	36.0±10.0	0.036 *
LVEDD (cm)	5.89±0.89	5.44±0.75	0.058 *
LA volume index (mL/m^2)	Median 44.0, IQR 35.5–50.0	Median 40.0, IQR 30.0–51.0	0.440 †
TR velocity (m/s)	2.92±0.58	2.73±0.36	0.199 *
Moderate or severe TR, n (%)	7 (25.0)	6 (26.1)	0.929
Moderate or severe MR, n (%)	9 (28.6)	5 (21.7)	0.577
Medication prescriptions			
Loop diuretics, n (%)	11 (39.3)	7 (30.4)	0.510
ACE/ARB, n (%)	14 (50.0)	13 (56.5)	0.642
Beta-blocker, n (%)	14 (50.0)	10 (43.5)	0.642
MRA, n (%)	3 (10.7)	5 (21.7)	0.281
Lab studies			
Sodium (mmol/L)	138±4	139±3	0.284 *
Creatinine (mg/dL)	Median 0.96, IQR 0.79–1.13	Median 0.87, IQR 0.66–1.21	0.256 †
BNP (pg/mL)	Median 573, IQR 276–1722 (n=18)	Median 424, IQR 263–892 (n=17)	0.351 †
Pro-BNP (pg/mL)	Median 4827, IQR 1842 – 6595 (n=19)	Median 2898, IQR 1723 – 5124 (n=11)	0.471 †

* Student's t-test used.

[†]Mann-Whitney U test used.

ARB, angiotensin-receptor blocker; BNP, brain natriuretic peptide; EF, ejection fraction; HFrEF, heart failure with reduced ejection fraction without methamphetamine use; LA, left atrium; LV, left ventricle; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; METHrEF, methamphetamine-associated heart failure with reduced ejection fraction; MR, mitral regurgitation; MRA, mineralocorticoid receptor antagonist; N/A, not available; NYHA, New York Heart Association; TR, tricuspid regurgitation.

Table 2

Change in echocardiographic characteristics of HF patients with reduced ejection fraction over 1-year follow-up stratified by methamphetamine use status

	METHrEF continued use (n=14)	METHrEF cessation (n=14)	HFrEF controls (n=23)
LVEF absolute change (%)	−1.7±12.5	10.6±13.1	10.8±12.6
P value (baseline vs f/u)	0.616	0.009	0.0005
LVEDD absolute change (cm)	0.05±0.70	−0.14±0.63	−0.25±0.45
P value (baseline vs f/u)	0.813	0.432	0.015
LA volume index absolute change (mL/m^2)	2.41±13.77	−8.83±12.19	−7.53±9.78
P value (baseline vs f/u)	0.524	0.029	0.004
TR velocity absolute change (m/s)	0.12±0.71	−0.23±0.58	−0.13±0.55
P value (baseline vs f/u)	0.601	0.236	0.305
Moderate or severe MR, n (%)	4 (28.6)	1 (7.7)	2 (9.5)
P value (baseline vs f/u)	0.687	0.063	0.375
Moderate or severe TR, n (%)	6 (42.9)	2 (14.3)	4 (17.4)
P value (baseline vs f/u)	0.687	1.000	0.687

EF, ejection fraction; f/u, follow up; HFrEF, heart failure with reduced ejection fraction without methamphetamine use; LA, left atrium; LV, left ventricle; LVEDD, left ventricular end-diastolic dimension; METHrEF, methamphetamine-associated heart failure with reduced ejection fraction; MR, mitral regurgitation; TR, tricuspid regurgitation.

Table 3

Clinical outcomes of HF patients with reduced ejection fraction from 12 to 24 months, stratified by methamphetamine use status at 1 year

	METHrEF continued use (n=12)	METHrEF cessation (n=12)	METHrEF p value*	HFrEF controls (n=18)	Overall p value
Average ED visits/year	3.75 (median 3.00, IQR 2.00–4.00)	3.58 (median 2.50, IQR 0.00–7.75)	N/A	2.00 (median 1.00, IQR 0.00–4.00)	0.248
Average hospital admissions/year	2.83 (median 2.00, IQR 2.00–3.00)	1.42 (median 1.00, IQR 0.00–2.75)	0.087	0.56 (median 0.00, IQR 0.00–1.00)	0.001
Average heart failure admissions/year	2.33 (median 2.00, IQR 1.00–3.00)	0.67 (median 0.00, IQR 0.00–1.00)	0.039	0.28 (median 0.00, IQR 0.00–0.00)	0.001

* Denotes adjustment with Bonferroni correction for multiple tests to be interpreted with a significance level of 0.05, N/A denotes comparison not performed due to non-significant overall p value.

ED, emergency department; HFrEF, heart failure with reduced ejection fraction without methamphetamine use; METHrEF, methamphetamine-associated heart failure with reduced ejection fraction.

Table 4

Characteristics of HF study population with preserved ejection fraction at baseline

	METHpEF (n=28)	HFpEF controls (n=32)	P value
Age (years)	50±8	60±16	0.007*
Male, n (%)	17 (60.7)	12 (37.5)	0.073
Race, n (%)			0.033
Asian	0 (0.0)	0 (0.0)	
Black or African-American	3 (10.7)	8 (25.8)	
Hispanic or Latino	3 (10.7)	8 (28.8)	
White	22 (78.6)	13 (41.9)	
Other or more than one race	0 (0.0)	2 (6.5)	
Hypertension, n (%)	18 (64.3)	23 (71.9)	0.528
Diabetes mellitus, n (%)	7 (25.0)	11 (34.4)	0.429
Ischaemic heart disease, n (%)	7 (25.0)	6 (18.8)	0.558
Atrial fibrillation/flutter, n (%)	7 (25.0)	8 (25.0)	1.000
Cerebrovascular accident, n (%)	5 (17.9)	5 (15.6)	0.817
Chronic kidney disease, n (%)	8 (28.6)	7 (21.9)	0.550
History of endocarditis, n (%)	2 (7.1)	3 (9.4)	1.000
Alcohol abuse, n (%)	4 (14.3)	0 (0.0)	0.042
Opioid abuse, n (%)	4 (14.3)	1 (3.1)	0.923
Cocaine abuse, n (%)	0.0 (0.0)	0.0 (0.0)	N/A
Echocardiographic data			
LVEF (%)	66.2±8.2	62.1±9.7	0.086*
LVEDD (cm)	4.42±0.77	4.53±0.81	0.591*
LA volume index (mL/m^2)	Median 30.7, IQR 14.0–37.0 (n=24)	Median 29.5, IQR 26.0–45.0 (n=26)	0.214†
TR velocity (m/s)	3.45±1.08 (n=23)	2.90±0.68 (n=26)	0.042*
E’ (lateral, cm/s)	9.95±3.79 (n=25)	7.88±2.15 (n=28)	0.021*
E’ (medial, cm/s)	8.32±4.28 (n=24)	5.91±1.78 (n=28)	0.015*
E/E’ (lateral)	8.08±3.56 (n=25)	11.23±4.43 (n=27)	0.007*
RVSP (mm Hg)	Median 53.44, IQR 43.70–84.00 (n=21)	Median 36.64, IQR 29.44–45.95 (n=25)	0.011†
TAPSE (cm)	2.00±0.57 (n=24)	2.07±0.69 (n=26)	0.678*
TAPSE/RVSP ratio (mm/mm Hg)	0.39±0.24 (n=20)	0.55±0.23 (n=23)	0.025*
Moderate or severe TR, n (%)	7 (25.0)	4 (12.5)	0.318
Moderate or severe MR, n (%)	2 (7.1)	0 (0.0)	0.214
NYHA class	2.5±0.8 (n=16)	2.1±0.9	0.163
Medication prescriptions			
Loop diuretics, n (%)	11 (39.3)	12 (37.5)	0.887
MRA, n (%)	3 (10.7)	4 (12.5)	1.000
Lab studies			
Sodium (mmol/L)	137±4	138±4	0.510*

	METHpEF (n=28)	HFpEF controls (n=32)	P value
Creatinine (mg/dL)	Median 1.12, IQR 0.87–1.6	Median 1.00, IQR 0.77–1.14	0.183†
BNP (pg/mL)	Median 145, IQR 84–191, n=5	Median 253, IQR 181–556, n=13	0.026†
Pro-BNP (pg/mL)	Median 2414, IQR 671–6161, n=23	Median 772, IQR 492–1486, n=15	0.038†

*Student's t-test used.

†Mann-Whitney U test used.

ARB, angiotensin-receptor blocker; BNP, brain natriuretic peptide; EF, ejection fraction; HFpEF, heart failure with preserved ejection fraction without methamphetamine use; LA, left atrium; LV, left ventricle; LVEDD, left ventricular end-diastolic dimension; METHpEF, methamphetamine-associated heart failure with preserved ejection fraction; MR, mitral regurgitation; MRA, mineralocorticoid receptor antagonist; N/A, not available; NYHA, New York Heart Association; RVSP, right ventricular systolic pressure; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation.

Table 5

Change in echocardiographic characteristics of patients with HF with preserved ejection fraction over 1-year follow-up stratified by methamphetamine use status

	METHpEF continued use (n=15)	METHpEF cessation (n=13)	HFpEF controls (n=32)
LVEF absolute change (%)	−2.33±14.45	−4.92±12.71	−1.97±10.34
P value (baseline vs f/u)	0.542	0.188	0.290
Development of HFrEF, n (%)	4 (26.7)	1 (7.7)	4 (12.5)
Overall p value	0.316		
LA volume index absolute change (mL/m^2)	−3.46±9.83 (n=12)	6.15±9.52 (n=10)	3.19±10.91 (n=26)
P value (baseline vs f/u)	0.249	0.071	0.149
TR velocity absolute change (m/s)	−0.32±0.66 (n=11)	0.07±0.61 (n=9)	−0.07±0.46 (n=25)
P value (baseline vs f/u)	0.141	0.737	0.464
E/E' (lateral) absolute change	−0.05±1.84 (n=12)	3.04±5.57	0.99±5.55 (n=24)
P value (baseline vs f/u)	0.923	0.073	0.394
RVSP absolute change (mm Hg)	−16.33±21.02 (n=11)	−2.94±20.83 (n=7)	−2.39±12.07 (n=24)
P value (baseline vs f/u)	0.028	0.722	0.342
TAPSE/RVSP ratio absolute change (mm/mm Hg)	0.1±0.3 (n=10)	−0.006±0.2 (n=8)	0.02±0.3 (n=23)
P value (baseline vs f/u)	0.366	0.941	0.713
Moderate or severe MR, n (%)	0 (0.0)	0 (0.0)	2 (6.7)
P value (baseline vs f/u)	N/A	N/A	N/A
Moderate or severe TR, n (%)	2 (13.3)	4 (33.3)	4 (12.5)
P value (baseline vs f/u)	0.500	1.000	1.000

EF, ejection fraction; f/u, follow up; HFpEF, heart failure with preserved ejection fraction without methamphetamine use; HFrEF, heart failure with reduced ejection fraction; LA, left atrium; METHpEF, methamphetamine-associated heart failure with preserved ejection fraction; MR, mitral regurgitation; N/A, not available; TR, tricuspid regurgitation.

Table 6

Clinical outcomes of HF patients with preserved ejection fraction from 12 to 24 months, stratified by methamphetamine use status at 1 year

	METHpEF continued use (n=11)	METHpEF cessation (n=12)	METHpEF P value*	HFpEF controls (n=26)	Overall P value
Average ED visits/year	8.18 (median 6.00, IQR 1.00–15.00)	4.42 (median 3.00, IQR 2.00–4.75)	1.000	1.88 (median 1.00, IQR 0.00–3.00)	0.031
Average hospital admissions/year	2.82 (median 2.00, IQR 1.00–5.00)	1.67 (median 1.00, IQR 0.00–2.75)	N/A	1.12 (median 0.00, IQR 0.00–2.00)	0.084
Average heart failure admissions/year	1.55 (median 0.00, IQR 0.00–4.00)	0.33 (median 0.00, IQR 0.00–0.75)	N/A	0.42 (median 0.00, IQR 0.00–0.00)	0.117

*Denotes adjustment with Bonferroni correction for multiple tests to be interpreted with a significance level of 0.05, N/A denotes comparison not performed due to non-significant overall p value.

ED, emergency department; HFpEF, heart failure with preserved ejection fraction without methamphetamine use; METHpEF, methamphetamine-associated heart failure with preserved ejection fraction.