Title

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Journal

Journal of the American Heart Association: Cardiovascular and Cerebrovascular Disease, 13(7)

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Publication Date

2024-04-02

DOI

10.1161/JAHA.123.033667

Journal of the American Heart Association

ORIGINAL RESEARCH

Cardiomyopathy in Patients With Acute Ischemic Stroke and Methamphetamine Use: Relevance for Cardioembolic Stroke and Outcome

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BACKGROUND: Methamphetamine use has emerged as a major risk factor for cardiovascular and cerebrovascular disease in young adults. The aim of this study was to investigate a possible association of methamphetamine use with cardioembolic stroke.

METHODS AND RESULTS: We performed a retrospective study of patients with acute ischemic stroke admitted at our medical center between 2019 and 2022. All patients were screened for methamphetamine use and cardiomyopathy, defined as left ventricular ejection fraction ≤45%. Among 938 consecutive patients, 46 (4.9%) were identified as using methamphetamine. Compared with the nonmethamphetamine group (n=892), the methamphetamine group was significantly younger (52.8±9.6 versus 69.7±15.2 years; $P<0.001$), included more men (78.3% versus 52.8%; $P<0.001$), and had a significantly higher rate of cardiomyopathy (30.4% versus 14.0%; $P<0.01$). They were also less likely to have a history of atrial fibrillation (8.7% versus 33.4%; $P<0.01$) or hyperlipidemia (28.3% versus 51.7%; $P<0.01$). Compared with patients with cardiomyopathy without methamphetamine use, the patients with cardiomyopathy with methamphetamine use had significantly lower left ventricular ejection fraction (26.0±9.59% versus 32.47±9.52%; $P<0.01$) but better functional outcome at 3 months, likely attributable to significantly younger age and fewer comorbidities. In the logistic regression model of clinical variables, methamphetamine-associated cardiomyopathy was found to be significantly associated with cardioembolic stroke (odds ratio, 1.79 [95% CI, 1.04–3.06]; $P<0.05$).

CONCLUSIONS: We demonstrate that methamphetamine use is significantly associated with cardiomyopathy and cardioembolic stroke in young adults.

Key Words: cardioembolic stroke ■ cardiomyopathy ■ functional outcome ■ methamphetamine use

Methamphetamine is a synthetic psychostimulant with high dependence liability.[1,2] Methamphetamine use has emerged as a major risk factor for acute ischemic stroke (AIS) in young adults worldwide in recent years.[3–12]

The mechanisms by which methamphetamine causes acute ischemic stroke are unclear. Case studies and forensic analysis showed cerebral vasoconstriction, atherosclerotic stenoses, arterial dissection, vasculitis, and small-vessel disease in patients with methamphetamine-associated stroke.[2,6,8,12,13] Methamphetamine use was also shown to produce a dose-dependent elevation of blood pressure and chronic hypertension.[14,15] Hypertension,

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This article was sent to Kori S. Zachrison, MD, MSc, Associate Editor, for review by expert referees, editorial decision, and final disposition.

Preprint posted on MedRxiv, November 23, 2023. doi: https://doi.org/10.1101/2023.11.22.23298930.

For Sources of Funding and Disclosures, see page 6.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Patients with acute ischemic stroke and methamphetamine use are significantly younger, more likely men, and associated with higher risk of cardiomyopathy compared with patients with acute ischemic stroke and no methamphetamine use.
- Patients with methamphetamine use and cardiomyopathy have significantly lower left ventricular ejection fraction than patients with cardiomyopathy and no methamphetamine use.
- Methamphetamine use is significantly associated with cardiomyopathy and cardioembolic stroke.

What Are the Clinical Implications?

- Methamphetamine use may cause cardioembolic stroke in young adults.
- Health care providers and the public should be aware of the risk of cardiomyopathy and cardioembolic stroke from methamphetamine use.

Nonstandard Abbreviations and Acronyms

AIS	acute ischemic stroke

vasoconstriction, and vascular toxicity were postulated as major mechanisms of ischemic stroke.[13]

Methamphetamine use also induces sympathetic activation, cardiovascular injury, and dilated cardiomyopathy with significantly reduced left ventricular ejection fraction (LVEF).[16,17] Compared with nonusers, methamphetamine users have more severe dilated cardiomyopathy on echocardiography.[18] Methamphetamine use has been increasingly identified as a major cause of cardiomyopathy and cardiac death in young adults.[19–21]

There were isolated case reports on methamphetamine-associated cardiomyopathy and cardioembolic stroke.[22,23] In a case series of methamphetamine-associated cardiomyopathy, one-third of the patients were found to have intraventricular thrombi on endomyocardial biopsy,[19] suggesting a possible mechanism of cardioembolic stroke.

The aim of this study was to investigate the prevalence of cardiomyopathy in patients with acute ischemic stroke and methamphetamine use, and its association with cardioembolic stroke and functional outcome.

METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request.

This is a retrospective cohort study. The study protocol was approved by the University of California, Irvine, Institutional Review Board and the Ethics Committee. Informed consents were waived because of the retrospective study design and minimal harm to the patients. All methods in the study were performed in accordance with the relevant guidelines and regulations.

Study Population

Consecutive patients with AIS admitted at the University of California, Irvine, Medical Center from January 1, 2019 to December 30, 2022 were screened for the study. The patient list was generated by searching the Vizient Clinical Database using *the International Classification of Diseases, Tenth Revision* (*ICD-10*), codes for ischemic stroke or cerebral infarction as a primary or secondary discharge diagnosis. Vizient contains data from >97% of US academic medical centers, including ours.[24] The following information was collected from the Vizient database and independent chart review from our electronic medical record system EPIC: age, sex, race and ethnicity, medical history, home medications, social history, including smoking and recreational drug use, National Institutes of Health Stroke Scale scores, urine drug screen results, low-density lipoprotein cholesterol levels, echocardiogram results, length of stay in the intensive care unit and hospital, and functional outcome with modified Rankin Scale scores at 3 months. All patients underwent standard diagnostic evaluation and treatment per American Heart Association/American Stroke Association guidelines.[25]

On the basis of the history of methamphetamine use and urine drug screen, patients were divided into methamphetamine and nonmethamphetamine groups. The urine drug screen was performed using the EMIT II Plus Amphetamines Assay (Beckman Coulter, Inc) with a sensitivity and specificity of 94.3% and 93.3%, respectively.[26] Cardiomyopathy was defined with reduced LVEF to ≤45% on clinical echocardiography report.[18]

Statistical Analysis

Continuous variables with normal distribution were described by mean±SD. Nonnormal variables were reported as median (interquartile range). Categorical variables were expressed by counts with percentages. Baseline characteristics and functional outcome at 3 months, as determined by modified Rankin Scale

score, were compared between methamphetamine and nonmethamphetamine groups by the Student *t* test for continuous variables and χ^2 or Fisher exact test for categorical variables. Logistic regression model was performed using data from all study subjects to identify independent predictors of cardioembolic stroke. Statistical analyses were performed using SAS software. A 2-tailed value of $P<0.05$ was considered statistically significant.

RESULTS

A total of 973 consecutive patients were admitted for AIS during the study period (Figure). Thirty-five patients were excluded from the study because of incomplete data, lack of echocardiogram, use of cocaine, or lost to follow-up. Among the remaining 938 patients, 46 (4.9%) were identified as having a history of methamphetamine use or positive urine drug screen.

In the methamphetamine group (n=46), 14 patients (30.4%) were found to have cardiomyopathy on clinical echocardiogram report. In contrast, 125 patients (14%) in the nonmethamphetamine group were noted to have cardiomyopathy.

The basic characteristics of the methamphetamine and nonmethamphetamine groups were shown in Table 1. Compared with the nonmethamphetamine group (n=892), the patients in the methamphetamine group were significantly younger (52.8±9.6 versus 69.7±15.2 years; $P<0.001$) and more likely men (78.3% versus 52.8%; $P<0.001$). They were less likely to have a history of atrial fibrillation (8.7% versus 33.4%; $P<0.01$), hyperlipidemia (29.8% versus 51.7%; $P<0.01$), or statin use (30.4% versus 47.0%; $P<0.05$) but more likely to have a history of smoking (95.7% versus 24.8%; $P<0.001$), heart failure (37.0% versus 22.9%; $P<0.05$), or cardiomyopathy (30.4% versus 14.0%; $P<0.01$). Although there was a significant difference in the mechanism of stroke between the 2 groups, there were no significant differences between the 2 groups in race or ethnicity, history of hypertension, diabetes, obesity, the use of antiplatelet or anticoagulation medications, initial National Institutes of Health Stroke Scale scores, low-density lipoprotein cholesterol levels, echocardiogram findings of patent foramen ovale or left ventricular thrombus, length of stay in the intensive care unit or hospital, good functional outcome (modified Rankin Scale score, 0–2), and mortality at 3 months.

We compared the clinical characteristics of patients with cardiomyopathy with and without methamphetamine use in Table 2. The patients with cardiomyopathy with methamphetamine use (n=14) remained significantly younger (52.4±9.5 versus 70.9±15.4 years; $P<0.001$) and more likely smokers (100% versus 23.2%; $P<0.001$) than those without methamphetamine use (n=125). The patients with cardiomyopathy with methamphetamine use were also found to have significantly lower LVEF (26.0±9.6% versus 32.5±9.5%; $P<0.01$) than those without methamphetamine use. In contrast, the patients with cardiomyopathy without methamphetamine use had significantly higher rates of hypertension, hyperlipidemia, and atrial fibrillation than those with methamphetamine use.

Despite significantly lower LVEF in the patients with cardiomyopathy with methamphetamine use, they had significantly higher rate of favorable functional outcomes (modified Rankin Scale score, 0–2) at 3 months after AIS than the patients without methamphetamine

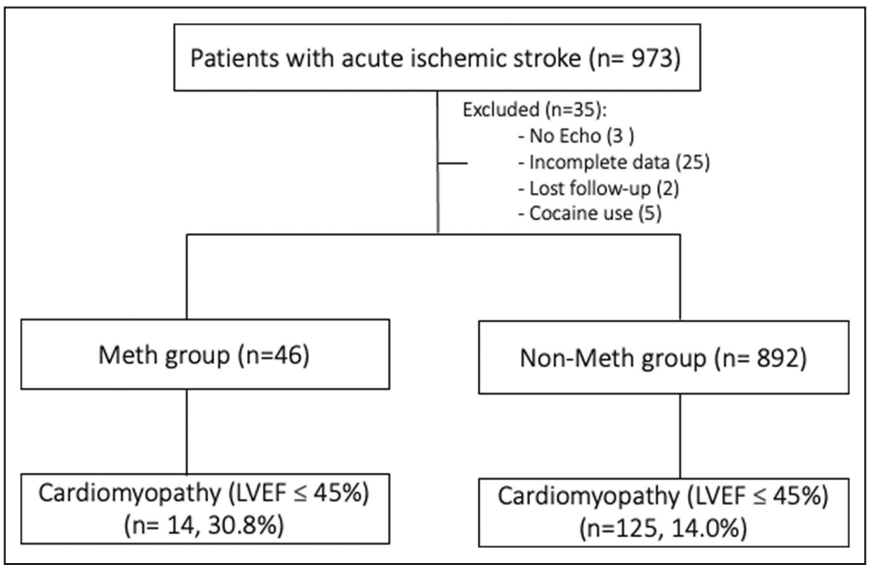

Figure. Study flowchart.
Echo indicates echocardiography; LVEF, left ventricular ejection fraction; and Meth, methamphetamine.

Table 1. Demographics and Clinical Characteristics Between Methamphetamine Group and Nonmethamphetamine Group

Variables	Methamphetamine group	Nonmethamphetamine group	*P* value
No.	46	892	
Age, y	52.8±9.6	69.7±15.2	<0.001
Male sex	36 (78.3)	471 (52.8)	<0.001
Race or ethnicity			
White	20 (43.5)	272 (30.5)	0.1285
Hispanic	8 (17.0)	131 (14.7)	
Black	8 (17.0)	197 (20.1)	
Asian	6 (12.8)	243 (27.2)	
Other	4 (8.5)	49 (5.5)	
Hypertension	42 (91.5)	771 (86.4)	0.32
Diabetes	18 (39.1)	400 (44.8)	0.78
Hyperlipidemia	13 (29.8)	461 (51.7)	<0.01
Atrial fibrillation	4 (8.7)	300 (33.4)	<0.01
Heart failure	17 (36.2)	204 (22.9)	<0.05
Obesity (BMI >30 kg/m^2)	22 (46.8)	317 (35.5)	0.12
Smoking	45 (95.7)	221 (24.8)	<0.001
Antiplatelet use	11 (23.9)	260 (28.1)	0.5415
Anticoagulant use	2 (4.4)	134 (14.5)	0.0536
Statin use	14 (30.4)	436 (47.0)	<0.05
Initial NIHSS score	8.9±8.2	10.3±8.6	0.29
LDL cholesterol, mg/dL	84.0±31.7	89.6±41.9	0.37
Echocardiographic findings			
LVEF ≤45%	14 (31.1)	125 (13.2)	<0.01
Positive PFO	3 (6.5)	81 (9.1)	0.53
Thrombosis	4 (8.7)	78 (8.7)	0.96
Mechanism of stroke			
Large-artery disease	9 (19.6)	290 (32.5)	<0.05
Cardioembolism	20 (43.5)	408 (45.7)	
Small-vessel disease	12 (26.1)	92 (10.3)	
Other causes	5 (10.6)	125 (14.0)	
ICU LOS, d, median (IQR)	3.0 (2.0–7.0)	3.0 (1.0–5.0)	0.5271
Hospital LOS, d, median (IQR)	4.5 (2.0–8.0)	4.0 (2.0–7.0)	0.4179
mRS score 0–2 at 3 mo	28 (60.9)	517 (58.0)	0.2668
Mortality at 3 mo	4 (8.7)	171 (19.2)	0.0753

Data are given as mean±SD or number (percentage), unless otherwise indicated. *P*<0.05 was considered statistically significant.

BMI indicates body mass index; ICU, intensive care unit; IQR, interquartile range; LDL, low-density lipoprotein; LOS, length of stay; LVEF, left ventricular ejection fraction; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; and PFO, patent foramen ovale.

use (64.3% versus 35.2%; *P*<0.05), likely attributable to significantly younger age and fewer comorbidities.

Baseline characteristics and clinical variables from all subjects of the study (n=938) were further analyzed in a logistic regression model to identify the association of clinical variables with cardioembolic stroke. As shown in Table 3, atrial fibrillation, heart failure, female sex, and methamphetamine-associated cardiomyopathy were found to be significantly associated with cardioembolic stroke. Atrial fibrillation was the most significant risk factor for cardioembolic stroke in this single-center retrospective study (odds ratio [OR], 20.72 [95% CI, 13.68–31.38]; *P*<0.0001). Multivariate analysis after adjustment for other clinical variables showed that methamphetamine-associated cardiomyopathy remained significantly associated with cardioembolic stroke (OR, 1.79 [95% CI, 1.04–3.06]; *P*<0.05).

DISCUSSION

Our results demonstrate that methamphetamine use was seen in 4.9% of the patients with AIS at our medical centers. Compared with patients with AIS without methamphetamine use, patients with methamphetamine use were significantly younger and more likely men. They were less likely to have atrial fibrillation

Table 2. Characteristics of Patients With Cardiomyopathy With and Without Methamphetamine Use

Variable	Patients with cardiomyopathy with methamphetamine use	Patients with cardiomyopathy without methamphetamine use	*P* value
No.	14	125	—
Age, y	52.4±9.5	70.9±15.4	<0.001
Male sex	11 (78.6)	79 (63.2)	0.25
Race or ethnicity			
White	5 (35.7)	43 (34.4)	0.6242
Hispanic	4 (28.6)	24 (19.2)	
Black	1 (7.1)	19 (15.2)	
Asian	2 (14.3)	30 (24.0)	
Other	2 (14.3)	9 (7.2)	
Hypertension	12 (85.7)	124 (99.2)	<0.01
Diabetes	5 (35.7)	54 (43.2)	0.59
Hyperlipidemia	3 (21.4)	62 (49.6)	<0.05
Atrial fibrillation	2 (14.3)	62 (49.6)	<0.05
Heart failure	12 (85.7)	98 (78.4)	0.52
Obesity (BMI >30 kg/m^2)	6 (42.9)	46 (36.8)	0.66
Smoking	14 (100)	29 (23.2)	<0.001
Initial NIHSS score	10.7±8.2	13.8±8.6	0.10
LDL cholesterol, mg/dL	77.9±23.7	81.9±45.3	0.38
Echocardiographic findings			
LVEF, %	26.0±9.6	32.5±9.5	<0.01
Positive PFO	2 (14.3)	8 (6.4)	0.28
Thrombosis	4 (28.6)	24 (19.2)	0.41
Mechanism of stroke			
Large-artery disease	0 (0.0)	23 (18.4)	0.2615
Cardioembolism	13 (92.9)	91 (72.8)	
Small-vessel disease	1 (7.1)	5 (4.0)	
Other causes	1 (7.1)	7 (5.6)	
mRS score 0–2 at 3 mo	9 (64.3)	44 (35.2)	<0.05
Mortality at 3 mo	2 (14.3)	43 (34.4)	0.13

Data are given as mean±SD or number (percentage). *P*<0.05 was considered statistically significant.

BMI indicates body mass index; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; and PFO, patent foramen ovale.

but highly associated with cardiomyopathy and propensity for cardioembolic stroke. The patients with methamphetamine-associated cardiomyopathy had better functional outcome at 3 months after stroke than those without methamphetamine use, possibly attributable to significantly younger age and fewer comorbidities, such as atrial fibrillation and hyperlipidemia.

Our study corroborates previous reports on the younger and male predominance in patients with methamphetamine-associated cardiomyopathy[10,27–29] and stroke.[11,12] Public education and government policies are needed to increase the awareness of the major health concerns of methamphetamine use and the socioeconomic burden of methamphetamine-associated disabilities.[20,21]

The mechanisms of methamphetamine-associated cardioembolic stroke remain unclear but are likely multifactorial. Methamphetamine may cause vasoconstriction, atherosclerotic disease, cardiac arrhythmias, and cardiomyopathy.[30] It was also shown to promote myocardial structural or electrical remodeling, such as increased ventricular fibrosis, inflammation, or myocyte function.[17,31,32] This remodeling of cardiac tissue following methamphetamine exposure promotes dilated cardiomyopathy and the susceptibility to cardiac arrhythmia and heart failure.[17,30] It has been theorized that heart failure, a clinically significant reduction in LVEF associated with progressive left ventricular dilatation and cardiac remodeling, will have a heightened risk for cardioembolic stroke.[33] Our study corroborated findings from previous reports that methamphetamine users have significantly lower LVEF than nonusers.[17,20,28,29] Methamphetamine-associated nonischemic cardiomyopathy can be reversible, and

Table 3. Logistic Regression Model of Clinical Variables and Risk of Cardioembolic Stroke

Variable	OR of cardioembolic stroke	95% CI	*P* value
Age	1.00	0.99–1.01	0.9020
Sex (female vs male)	1.61	1.15–2.27	<0.01
Hypertension (yes vs no)	0.97	0.58–1.64	0.974
Diabetes (yes vs no)	0.89	0.63–1.25	0.887
Hyperlipidemia (yes vs no)	0.89	0.63–1.26	0.889
Heart failure (yes vs no)	2.62	1.67–4.12	<0.0001
AF (yes vs no)	20.72	13.68–31.38	<0.0001
Methamphetamine use and cardiomyopathy (yes vs no)	1.79	1.04–3.06	<0.05

AF indicates atrial fibrillation; and OR, odds ratio.

methamphetamine cessation is associated with improvement in functional status.[10,23,33]

Currently, there are only isolated case reports suggesting the association between cardiomyopathy and cardioembolic stroke in patients with methamphetamine use.[22,23]

We have previously reported on methamphetamine use increasing the risk of cerebral small-vessel disease in young patients with AIS.[12] That study also found a high percentage (34%) of cardioembolic stroke in patients with methamphetamine use. This study demonstrated that 92.9% of patients with methamphetamine-associated cardiomyopathy had cardioembolic stroke, suggesting cardiomyopathy as the possible mechanism of cardioembolic stroke. To our knowledge, we are the first study to demonstrate methamphetamine-associated cardiomyopathy and the propensity of cardioembolic stroke.

Methamphetamine-associated cardiomyopathy/heart failure is increasingly recognized as the leading cause of hospitalization or death in methamphetamine users.[19–21,30] Recent studies showed that hospitalizations for methamphetamine-related heart failure increased nearly 6 to 12 times over the past decade.[21,34] It is therefore imperative to further investigate the risk of methamphetamine-associated cardioembolic stroke.

Our study has a few limitations. First, it is a retrospective study with a relatively small sample size of an ethnically diverse patient population in southern California. The results may not be generalizable. Second, our data supported a significant association between methamphetamine use and cardioembolic stroke but could not establish a causal relationship. Third, there was no information on the route, frequency, and duration of methamphetamine use. We also did not have long-term follow-up data beyond 3 months. Last, alcohol use and other cardiac comorbidities could be confounding factors that cannot be ruled out in this retrospective study. Further large sample size studies are warranted to adjust for confounding factors and to establish the temporal relationship between methamphetamine-associated cardiomyopathy and cardioembolic stroke.

CONCLUSIONS

In conclusion, our study demonstrates that methamphetamine use is significantly associated with cardiomyopathy and cardioembolic stroke in young adults.

ARTICLE INFORMATION

Received November 22, 2023; accepted March 1, 2024.

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Acknowledgments

Author contributions: Dr Lee contributed to data acquisition, statistical analysis, data interpretation, and drafting the manuscript. Dr Liu contributed to statistical analysis and verification. H. Blackwill and D. Stradling contributed to data acquisition. Dr Shafie contributed to data interpretation and manuscript revision. Dr Yu contributed to study design, data interpretation, drafting, and finalizing the manuscript.

Sources of Funding

Dr Lee is supported by the Republic of Korea for this research project.

Disclosures

None.

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