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Systolic dysfunction in patients with methamphetamine use and heart failure with preserved ejection fraction

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Abstract

Background: We aimed to evaluate for occult systolic dysfunction and the effect of methamphetamine cessation among patients with methamphetamine use (MU) and heart failure with preserved ejection fraction (HFpEF).

Methods: A retrospective cohort of patients with HFpEF with serial echocardiograms was stratified by MU and evaluated using myocardial strain analysis on echocardiograms at baseline and 1 year to measure global longitudinal strain (GLS). Contemporaneous controls with an ICD diagnosis of HF within 3 days of an MU case were chosen.

Results: Patients with MU (n = 31) were younger (49 ± 10 vs 59 ± 16 years, $p < 0.01$) and more frequently male (55% vs 26%, $p = 0.04$) than controls (n = 23). There was no baseline difference in ejection fraction (EF) (median 66% [IQR 58,71%] vs 62% [56,69%], $p = 0.33$) or GLS (−13.0% [−16.3, −10.9%] vs −14.8% [−16.0, −11.3%], $p = 0.40$). At one-year follow-up, MU cessation (n = 15) was associated with improvement in GLS (absolute change −4.4% [−6.5, −1.7%], $p < 0.01$), while no absolute change was observed with continued MU (n = 16) (0.74% [−1.2,2.8%], $p = 0.22$) or controls without MU (−0.6% [−2.1,2.8%], $p = 0.78$). Of those with abnormal baseline GLS, normalization was observed in 46% with MU cessation, none with continued MU, and 5% of controls ($p < 0.001$). Among MU patients, improvement in GLS was associated with decreased HF admissions per year [HR 0.74 per 1% change in GLS, 95% CI 0.55,0.98, $p = 0.04$].

Conclusions: Patients with MU and HFpEF may have occult systolic dysfunction as demonstrated by abnormal GLS, and MU cessation at 1 year is associated with improvement in GLS and a reduction in risk of HF admissions.

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Declaration of Competing Interest

None.

Keywords

Methamphetamine use; Substance use; Heart failure with preserved ejection fraction; Echocardiography; Strain

1. Introduction

Methamphetamine use (MU) is increasing nationally [1], and is associated with significant adverse effects, including hypertension and tachycardia, and toxic injury to the myocardium and pulmonary vasculature. These toxicities may lead to long term heart failure and pulmonary arterial hypertension (PAH) [2–6]. Methamphetamine associated heart failure (MethHF) is most commonly characterized by a non-ischemic, dilated cardiomyopathy with reduced ejection fraction [1–3,7–9]. We have previously shown that those with MU and heart failure with reduced ejection fraction have improvement in left ventricular ejection fraction (EF) with methamphetamine cessation [10]. However, many MU patients have heart failure with preserved ejection fraction (HFpEF). The adverse effects of MU on systolic function may be overlooked by the standard echocardiographic parameter of left ventricular ejection fraction (EF), and may contribute to symptoms and poor HF outcomes. We previously showed that some patients with MU and HFpEF develop reduced LV EF with continued MU, raising the possibility of occult systolic dysfunction preceding a decline in EF [10]. The effect of MU on left ventricular (LV) systolic function in HFpEF patients is currently not well characterized.

Myocardial strain analysis by speckle tracking echocardiography is a sensitive technique for assessing LV systolic function. Strain has been demonstrated to be more accurate and reproducible over time than EF and may uncover left ventricular systolic dysfunction not captured by EF. Myocardial strain has been well studied for early detection of systolic dysfunction in patients receiving cardiotoxic chemotherapy, as well as for determining the underlying cause of HF such as in cardiac amyloidosis and hypertrophic cardiomyopathy [11]. A cross sectional study of asymptomatic participants with MU demonstrated reduced strain parameters compared with healthy controls [12], but this has not been studied in the heart failure population. Due to the toxic effect of MU on ventricular myocardium, we hypothesized that occult left ventricular systolic dysfunction may be detectable by myocardial strain analysis in patients with MU and HFpEF, and may improve with MU cessation.

2. Methods

2.1. Study design

The study was approved by the UCSD Human Protections Program, conforms to the ethical guidelines of the Declaration of Helinski, and no informed consent was required. We performed a single-center retrospective cohort study using a previously established database of heart failure patients from 2005 to 2016 at University of California, San Diego Health based on International Classification of Diseases (ICD)-9 codes for heart failure (428.xx) and/or elevated serum brain natriuretic peptide (BNP) or N-terminal pro-BNP. Of

these patients, those with MU were identified based on ICD-9 codes for amphetamine dependence (304.4) and/or amphetamine use (305.7). Among these, 150 patients with multiple echocardiograms were selected for detailed manual chart review to confirm the clinical diagnoses of heart failure with preserved ejection fraction and MU. The diagnosis of heart failure with preserved ejection fraction was confirmed by documentation by a treating physician of heart failure with EF ≥ 50%, and MU was defined by positive urine toxicology testing within 3 months of baseline echocardiogram. Patients who did not meet these criteria or have available serial echocardiograms with follow up echocardiogram at 1 year (± 3 months) were excluded. Additionally, patients with a history of heart transplantation, without available follow-up urine toxicology results, or with other identified causes of heart failure (such as ischemic cardiomyopathy) or ischemic heart disease were excluded.

Patients with heart failure, as defined above, with preserved EF (≥ 50%) and no diagnosis of MU were then assessed for inclusion in the HFpEF control group. Contemporaneous controls with an ICD diagnosis of heart failure within 3 days of a patient in the MethHF cohort were selected. Contemporaneous controls rather than age-matched controls were chosen as patients with MethHF are known to be younger than the general heart failure population, and age-matching may select for controls with rarer causes of heart failure, such as genetic cardiomyopathies. Detailed manual chart review was then performed to confirm the clinical diagnosis of heart failure, and patients were excluded based on the same clinical and echocardiographic criteria listed above.

Finally, during strain analysis, patients with inadequate quality echocardiograms (defined as dropout or artifact in greater than two endocardial segments) were excluded from the study.

2.2. Data collection

Demographics, medical comorbidities (by ICD-9 codes), medication prescriptions and laboratory data were collected at baseline. Echocardiograms were performed using various echocardiography machines, with standard views and measurements in accordance with the American Society of Echocardiography (ASE) cardiac chamber quantification guidelines [13]. Measurements of LV EF and LA volume were made using the Simpson's biplane method. Preserved EF was defined as ≥ 50%. Parameters for the assessment of diastolic function including tissue doppler velocities were made in accordance with the ASE Diastolic Function guidelines [14]. For assessment of diastolic function, lateral e' velocity was used. Additional parameters included right ventricular systolic pressure (RVSP) and tricuspid annular plane systolic excursion (TAPSE). For patients with baseline MU, continued use versus cessation was determined based on urine toxicology results at 12 months. Follow-up echocardiographic data was collected at 12 months. Clinical outcomes, including emergency department (ED) visits, hospital admissions and hospital admissions with a primary heart failure diagnosis were collected for an additional 12-month follow-up after determination of methamphetamine cessation (from 12 to 24 months overall from baseline assessment). Fixed time points for data collection were chosen due to the feasibility of chart review and to maximize data capture.

2.3. Myocardial strain analysis

Myocardial strain analysis by speckle-tracking echocardiography was performed independently by four readers (HB, MN, AM, SV) trained in strain evaluation using EchoInsight v.3.2.3.5564 (Epsilon Imaging, Ann Arbor, MI, USA). Standard apical (two, three, and four-chamber) views and the parasternal short axis view at level of the mitral valve leaflet tips were used for measurement of global longitudinal strain (GLS) and global circumferential strain (GCS), respectively. Readers were blinded to MA status and clinical outcomes of each patient.

Inter-observer agreement for GLS and GCS was assessed in a test cohort of ten patients with each of the four readers performing an independent analysis on baseline and follow up echocardiograms (n = 20). The mean standard deviation for strain measurements by the four readers for each study was 0.98% for GLS and 2.23% for GCS; Spearman correlation coefficients were 0.94 for GLS and 0.95 for GCS. Strain analysis was then performed on the remaining echocardiograms in the full cohort, divided among the four readers. Normal values for strain measurements are not well established; in a meta-analysis, normal GLS was −15.9% to −22.1% with mean of −19.7%, and normal GCS was −20.9% to −27.8% with a mean of −23.3% [15]. For dichotomous analyses, normal GLS was defined as ≤ −18%, the value used in our clinical laboratory, and normal GCS was defined as ≤ −20%, the lower end of normal in the previously referenced meta-analysis.

2.4. Statistical analysis

Data is presented as number (frequency) for categorical variables and mean ± standard deviation or median [interquartile range] for continuous variables with normal or skewed distributions, respectively. For categorical variables, the chi square test was used for statistical comparison. For continuous baseline variables, unpaired student's *t*-test was used for normally distributed variables, and the Mann-Whitney *U* test or Kruskall-Wallis test were used for skewed distributions. For comparison of continuous variables at baseline and follow-up, paired student's *t*-test was used for normally distributed variables, and the Wilcoxon signed-rank test was used for skewed variables.

In an exploratory analysis, the relationship between change in GLS and clinical outcomes among patients with MU was evaluated using negative binomial regression. Each model adjusted for age, sex, and history of hypertension at baseline and clinical outcomes evaluated were ED visits per year, hospital admissions per year and HF admissions per year.

A two-tailed p-value of <0.05 was considered statistically significant. Statistical analysis was performed using SPSS Statistics version 26.0 (IBM Corporation, Armonk, NY, USA).

3. Results

After evaluating 335 patients with ICD diagnoses for HF, a final cohort of 54 patients with HFpEF (including MU patients with contemporaneous controls) was selected for analysis after application of exclusion criteria. The study cohort was comprised of 31 patients with MU at baseline and 23 control patients. MU patients were younger (49 ± 10 years vs 59 ± 16 years, p = 0.006), and more often male (54.8% vs. 26.1%, p = 0.04), with lower prevalence

of hypertension (38.7% vs. 69.6%, p = 0.03). The MU group had more White and fewer Hispanic participants. Baseline NT-proBNP was significantly higher in the MU group (2395 [1131–4282] pg/mL vs 915 [553–1663] pg/mL, p = 0.045, Table 1). However, NT-proBNP was only available at baseline in a limited set of participants (24 in the MU group, 12 in the control group). BNP levels were also available for some participants (10 in the MU group, 7 in the control group), and were not different between groups (196.50 pg/mL, IQR 122.00–457.25 pg/mL) than the non-MU group (252.00 pg/mL, IQR 178.00, 392.00 pg/mL, p = 0.60 for comparison).

At baseline, EF was not significantly different between the MU and control patients (66.0% [58.0, 71.0%] vs 62.0% [56.0, 69.0%], p = 0.33). Baseline GLS was abnormal in both groups, but not significantly different between groups (−13.0% [−16.3, −10.9%] vs −14.8% [−16.0, −11.3%], p = 0.40). The control group had larger left atrial volume index (30.0 [34.5, 48.0] mL/m^2 vs. 21.5 [13.0, 36.5] mL/m^2, p = 0.034), as well as higher E/E' ratio (11.2 [7.3, 14.1] vs 6.2 [4.4, 9.6], p = 0.004, Table 1). In contrast, the MU group had higher TR velocity (3.6 [3.0, 4.5] m/s vs 2.8 [2.5, 3.5] m/s, p = 0.006). Rates of mineralocorticoid receptor antagonists (MRA) and loop diuretics did not differ between the MU and control groups (10.0% vs 13.0%, p = 1.00 and 33.3% vs 30.4%, p = 0.823, respectively).

Follow-up echocardiograms at 1 year were compared to baseline echocardiograms, stratified by MU status based on urine toxicology at 1 year (MU continued use, MU cessation, and no MU controls). EF did not differ at follow-up compared with baseline within any of the groups. However, more patients in the MU continued use group developed abnormal EF in follow-up than in the cessation or control groups (37.5% vs 0.0% vs 13.0%, p = 0.016). Heart rate did not differ among the individual groups when comparing baseline to follow-up (Table 2). Medical management with MRAs and loop diuretics did not differ significantly between the MU continued use and MU cessation groups at baseline (0.0% vs 20.0%, p = 0.224, and 33.3% vs 33.0%, p = 1.000, respectively) or at one year (0.0% vs 0.0% and 62.5% vs 72.7%, p = 1.000).

GLS improved significantly at follow-up compared with baseline with MU cessation (−17.2% [−20.0, −13.9%] vs −13.0% [−16.0, −11.1%], p = 0.006). MU cessation was associated with absolute change in GLS of −4.4% [−6.5, −1.7%, p = 0.008], while GLS did not change significantly in the continued MU group (0.74% [−1.2,2.8%], p = 0.215) or control group (−0.6% [−2.1,2.8%], p = 0.783) over follow-up (Fig. 1). Additionally, GLS was not different between groups at baseline, but was significantly different between groups in follow-up (−11.6% [−14.5, −9.2%] MU continued vs −17.2% [−20.0, −13.9%] MU cessation vs −14.6% [−16.7, −11.8%] controls, p = 0.001, Table 2]. Of those with abnormal baseline GLS, normalization was noted in no patients with continued MU, 6 (46.2%) patients with MU cessation, and 1 (4.8%) control (p < 0.001, Table 2). A non-significant trend towards improving GCS was seen in the MU cessation group in contrast to worsening in the MU continued use group and no change in the control group. Additionally, there were significantly fewer patients with abnormal GCS in the cessation group compared with the continued use and control groups, respectively (20.0% vs 73.3% vs 33.3%, p = 0.008, Table 2).

The results for negative binomial regression models for clinical outcomes are shown in Table 3. Among methamphetamine users, in a model adjusting for age, sex, and history of hypertension (all of which were significantly different between groups as in Table 1), a 1% absolute decrease (improvement) in GLS at follow-up was associated with a HR for HF admissions per year of 0.74 (95% CI 0.55, 0.98, p = 0.04). There were also non-statistically significant trends towards reduction in ED admissions per year (p = 0.12) and hospitalizations per year (p = 0.11). Few deaths were observed over the follow-up period (3 in the continued MU group, 1 in the MU cessation group, 1 in the control group, p = 0.14).

4. Discussion

In this retrospective cohort study of patients with MU and HFpEF, patients with MU have reduced GLS, despite preserved EF, providing evidence of occult systolic dysfunction in this population. Continued MU is associated with worsened GLS, and cessation of MU is associated with improvement in GLS, providing evidence of an adverse effect of MU on LV systolic function among patients with HFpEF. Improvement in GLS was also associated with a reduction in HF admissions in this cohort. These results are consistent with the notion that systolic dysfunction in these patients is pathophysiologically related to MU, and is reversible, which translates to improved clinical outcomes with abstinence.

Methamphetamine use is associated with PAH, and HF symptoms in patients with preserved left ventricular ejection fraction are often attributed to PAH, particularly when there is evidence of elevated pulmonary artery pressures in the absence of signs of significant left ventricular diastolic dysfunction. However, MU may lead to diastolic dysfunction or occult systolic dysfunction through direct cardiotoxicity or adverse hemodynamic conditions including hypertension and tachycardia. We previously reported that echocardiograms in a similar population of patients with MU and HFpEF frequently showed pulmonary hypertension without significant diastolic dysfunction, but some patients developed a reduced LV ejection fraction with continued MU over follow-up, raising the possibility of pre-existing occult systolic dysfunction [10]. The present study demonstrates that patients with MU and HFpEF have evidence of occult systolic dysfunction by strain imaging, which improves with MU cessation. These findings suggest that MU may have toxic effects on the LV myocardium that are detectable by strain imaging before overt reductions in LV ejection fraction develop, and that these toxic effects may impact the risk of HF hospitalization.

While the change in GCS with methamphetamine cessation was not significant, there were trends towards worsening GCS in the continued MU group and improvement in the cessation MU group with no change in the control group. These non-significant results may be due to GCS being a less robust marker than GLS, including the greater amount of tissue assessed with GLS and greater reproducibility of GLS [16]. Additionally, a significantly higher percentage of those with continued MU had abnormal GCS in follow-up.

Further study is needed to confirm these findings prospectively. In particular, our study was not able to address specific details regarding methamphetamine use beyond whether or not urine toxicology was positive. A future prospective study may address methamphetamine use with more granularity, such as the relevance of different types of methamphetamines,

route of administration, and duration of administration and how these relate to the development of occult systolic dysfunction and the potential for improvement with methamphetamine cessation.

This is the first study to our knowledge to assess myocardial strain in patients with MU and HF, and to provide evidence of systolic dysfunction in those with HFpEF. The significant improvement in GLS seen in the cessation group is also reflected in a trend towards improvement in GCS. The control group remained constant in terms of both GLS and GCS, which suggests that the improvement in strain observed is related to MU cessation. Additionally, MU was assessed objectively by urine toxicology testing. Incomplete data regarding loading conditions was available, but no difference was seen in heart rate between the groups at baseline or follow-up. Additionally, NT-proBNP levels in the subset where data was available were higher among MU participants compared with controls at baseline, but BNP levels, where available, were not significantly different. While higher NT-proBNP levels in the MU group may reflect greater disease severity on presentation, this did not appear to affect baseline echocardiographic measures as GLS was not significantly different between groups at baseline.

There are also limitations to our study. We collected a small cohort due to the need for serial echocardiograms of sufficient quality for myocardial analysis with concurrent urine toxicology results. Given its observational nature, our results are subject to confounding. For example, continued methamphetamine use may be associated with other factors that negatively impact outcomes, such as less consistent outpatient follow-up. The use of a longitudinal study design, comparing patients to themselves in terms of echocardiographic parameters, however, reduces confounding. Age matching was not performed due to concern that this would lead to selection for rarer types of HF in the control group as those with MethHF tend to be younger and more often male. The observational nature of our study also makes it subject to missing data. For example, limited data was available for baseline NT-proBNP levels. We also believe this was partially due to the transition over time from BNP to NT-proBNP measurements, as some participants had BNP levels measured, while others had NT-proBNP. Hemodynamic loading conditions can affect strain measurements; while no difference was seen in heart rate at follow-up compared with baseline, blood pressure measurements were not available for most patients.

5. Conclusions

In summary, patients with MU and HFpEF have evidence of occult left ventricular systolic dysfunction. Additionally, MU cessation is associated with significant improvement in left ventricular myocardial strain in HFpEF patients, and improvement in strain translates to improvement in clinical outcomes. These findings suggest potential benefits of MU screening and cessation among patients with HFpEF.

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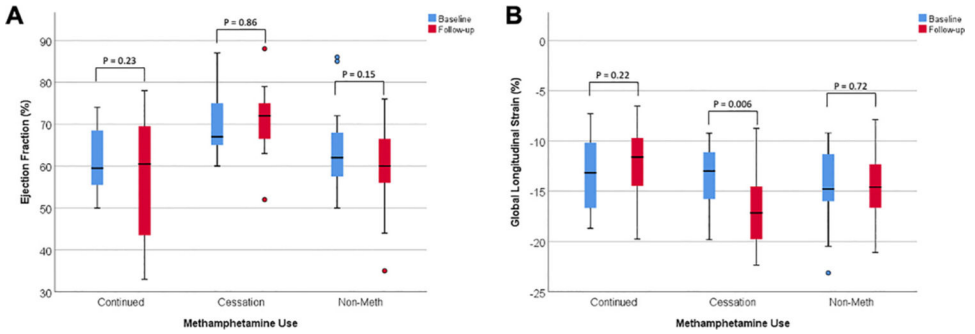

Fig. 1.

Ejection fraction (A) and global longitudinal strain (B) at baseline and follow-up stratified by methamphetamine use.

Follow-up denotes measurements at 1-year. Methamphetamine use status was determined by urine toxicology at 1 year.

Table 1

Baseline characteristics of study population stratified by methamphetamine use.

	MU (n = 31)	Non-MU Controls (n = 23)	p value
Age (years)	49 ± 10	59 ± 16	0.006
Male, n (%)	17 (54.8)	6 (26.1)	0.035
Race (%)			0.139
Asian	1 (3.2)	0 (0.0)	
Black or African American	3 (9.7)	4 (17.4)	
Hispanic or Latino	5 (16.1)	7 (30.4)	
White	22 (71.0)	10 (43.5)	
Other or more than one race	0 (0.0)	2 (8.7)	
Hypertension (%)	12 (38.7)	16 (69.6)	0.025
Diabetes Mellitus (%)	4 (12.9)	7 (30.4)	0.173
Atrial fibrillation/flutter (%)	4 (12.9)	8 (34.8)	0.096
Cerebrovascular Accident (%)	4 (12.9)	4 (17.4)	0.711
Chronic Kidney Disease (%)	5 (16.1)	6 (26.1)	0.369
History of Endocarditis (%)	2 (6.5)	3 (13.0)	0.640
Mood Disorders (%)	7 (22.6)	1 (4.3)	0.119
Alcohol abuse (%)	1 (3.2)	0 (0.0)	1.000
Opioid abuse (%)	5 (16.1)	1 (4.3)	0.224
Cocaine use (%)	2 (6.5)	0 (0.0)	0.502
NYHA Class	3.0 [2.8, 3.0] (n = 10)	2.0 [1.0, 3.0]	0.056
Echocardiographic Data			
GLS (%)	−13.0 [−16.3, −10.9]	−14.8 [−16.0, −11.3]	0.396
GCS (%)	−20.5 [−25.8, −15.5]	−21.5 [−27.0, −15.8]	0.774
LVEF (%)	66.0 [58.0, 71.0]	62.0 [56.0, 69.0]	0.327
LVEDD (cm)	4.1 ± 0.7	4.6 ± 0.9	0.045
LVESD (cm)	2.5 ± 0.8	3.0 ± 0.8	0.032
LA Volume Index (mL/m^2)	21.5 [13.0, 36.5]	30.0 [34.5, 48.0]	0.034
E' (lateral, cm/s)	9.00 [7.00, 12.00]	7.9 [6.0, 9.3)	0.132
E/E' (lateral)	6.20 [4.41, 9.62]	11.2 [7.3, 14.1)	0.004
RVSP (mm Hg)	64.0 [48.0, 91.7]	39.1 [30.0, 52.6]	0.002
TAPSE (cm)	1.7 ± 0.5 (n = 23)	2.0 ± 0.7	0.164
Lab Studies			
Sodium (mmol/L)	137 ± 3	138 ± 4	0.582
Creatinine (mg/dL)	0.98 [0.81, 1.15]	0.93 [0.67, 1.08]	0.386
NT-proBNP (pg/mL)	2395 [1131, 4282] (n = 24)	915 [553, 1664] (n = 12)	0.045

Values are presented as mean ± standard deviation, n (%) or median [IQR]. BNP = brain natriuretic peptide, EF = ejection fraction, GCS = global circumferential strain, GLS = global longitudinal strain, HFpEF = heart failure with preserved ejection fraction, LA = left atrium, LV = left ventricle, LVEDD = left ventricular end-diastolic diameter, LVESD = left ventricular end-systolic diameter, MU = methamphetamine use, MRA = mineralocorticoid receptor antagonist, NYHA = new york heart association, RVSP = right ventricular systolic pressure, TAPSE = tricuspid annular plane systolic excursion.

Table 2

Left ventricular function in serial echocardiograms stratified by methamphetamine use at 1 year.

	MU continued use (n = 16)	MU cessation (n = 15)	Non-MU controls (n = 23)	P (between groups)
Heart Rate				
Baseline (BPM)	89.0 [75.0, 98.8]	89.0 [81.8, 99.5]	78.0 [72.0, 95.0]	0.208
Follow-up (BPM)	87.0 [77.0, 97.5]	85.0 [71.8, 100.8]	76.0 [64.8, 96.5]	0.431
p value (baseline vs. f/u)	0.756	0.258	0.153	
Ejection Fraction (EF)				
Baseline (%)	59.5 [55.3, 68.8]	67.0 [65.0, 77.0]	62.0 [56.0, 69.0]	0.004
Follow-up (%)	60.5 [43.3, 69.8]	72.0 [65.0, 76.0]	60.0 [54.0, 67.0]	0.023
p value (baseline vs. f/u)	0.233	0.861	0.166	
Abnormal, n (%)	6 (37.5)	0 (0.0)	3 (13.0)	0.016
Global Longitudinal Strain (GLS)				
Baseline (%)	−13.2 [−16.8, −9.8]	−13.0 [−16.0, −11.1]	−14.8 [−16.0, −11.3]	0.663
Abnormal, n (%)	14 (87.5)	13 (86.7)	21 (91.3)	0.886
Follow-up (%)	−11.6 [−14.5, −9.2]	−17.2 [−20.0, −13.9]	−14.6 [−16.7, −11.8]	0.001
p value (baseline vs. f/u)	0.215	0.006	0.715	
Abnormal, n (%)	15 (93.8)	8 (53.3)	21 (91.3)	0.004
Abnormal to Normal, n (%)	0 (0.0)	6 (46.2)	1 (4.8)	<0.001
Global Circumferential Strain (GCS)				
Baseline (%)	−20.0 [−25.0, −16.0]	−21.0 [−28.0, −14.0]	−21.5 [−27.0, −15.8]	0.931
Abnormal, n (%)	7 (46.7)	7 (46.7)	9 (40.9)	0.918
Follow-up (%)	−17.0 [−19.5, −13.5]	−24.0 [−27.5, −20.0]	−22.0 [−27.0, −17.0]	0.032
p value (baseline vs. f/u)	0.107	0.176	0.779	
Abnormal, n (%)	11 (73.3)	3 (20.0)	7 (33.3)	0.008

Values are presented as mean ± standard deviation, n (%) or median [IQR]. Continued methamphetamine use or cessation determined by urine toxicology at 1 year. BPM = beats per minute, f/u = follow-up. Other abbreviations as listed in Table 1.

Table 3

Clinical Outcomes Associated with Improvement in Global Longitudinal Strain among Patients with MU and HFpEF.

	IRR (95% CI) for GLS	P
ED Visits / Year	0.83 [0.71, 1.04]	0.12
Hospitalizations / Year	0.85 [0.70, 1.04]	0.11
HF Admissions / Year	0.74 [0.55, 0.98]	0.04

Results are presented for outcomes from 12 to 24 months from baseline. Negative binomial regression model variables are age + sex + hypertension + GLS. ED = emergency department, GLS = global longitudinal strain, HF = heart failure, IRR = Incidence rate ratio.