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# Methamphetamine-Associated Pulmonary Arterial Hypertension Is Associated With Worse Right Ventricular Function Than Idiopathic Pulmonary Arterial Hypertension: A Matched Study

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## Abstract

**Background:** Methamphetamine is increasingly recognized as a cause of pulmonary arterial hypertension (PAH). This study examines whether non-invasively measured metrics of right heart function, right atrial (RA) and right ventricular (RV) strain, are more impaired in methamphetamine-associated PAH (MA-PAH) compared with idiopathic PAH (IPAH).

**Methods:** A retrospective cohort analysis of 51 patients with MA-PAH matched for mean pulmonary artery pressure (mPAP) with 51 patients with IPAH followed at the pulmonary hypertension clinic at the University of Utah was performed. Invasive hemodynamics and echocardiographic measures of right heart function, including RA strain and RV free wall strain, were compared.

**Results:** Compared to the matched IPAH group, MA-PAH patients had lower cardiac index ($2.04 \pm 0.84$ vs. $2.52 \pm 1.07$ L/min/m$^2$, $p = 0.016$) and higher pulmonary vascular resistance (PVR; $11.8 \pm 6.8$ vs. $8.9 \pm 4.8$ Wood units, $p = 0.018$). The MA-PAH group had larger RA maximal and minimal volume, lower RA reservoir strain ($26.4 \pm 11.7$ vs. $33.4 \pm 14.8$ %, $p = 0.011$), more significant RV chamber dilation, and lower fractional area change (FAC; $21.1 \pm 11.1$ % vs. $34.5 \pm 11.8$ %, $p < 0.001$), compared to the IPAH group. RV e' was lower in MA-PAH ($6.5 \pm 2.8$ cm/s vs. $8.3 \pm 4.3$ cm/s, $p = 0.021$), suggesting worse RV diastolic function and RV free wall strain was significantly more reduced compared to patients with I-PAH ($17.0 \pm 6.5$ vs. $22.3 \pm 7.2$ %, $p < 0.001$). There were no differences in 5-year survival ($p = 0.26$), 6MW distance including stratification for males and females ($p = 0.249$ in females, $p = 0.279$ in males), and rehospitalization rates within 5 years of diagnosis ($p = 0.70$).

**Discussion:** Despite a similar mPAP, patients with MA-PAH had more RA dilation, RV dilation, lower RV systolic/diastolic function, and worse RA and RV mechanics as assessed by strain compared to patients with I-PAH. Our findings suggest that,

**Abbreviations:** I-PAH, idiopathic pulmonary arterial hypertension; MA-PAH, methamphetamine-associated pulmonary arterial hypertension; PPH, pre-capillary pulmonary hypertension; RAP, right atrial pressure.

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in addition to causing remodeling of the pulmonary vasculature, methamphetamine may have a direct cardiotoxic effect on the right heart.

## 1 | Introduction

Pulmonary arterial hypertension (PAH) is a progressive disease characterized by pulmonary vascular remodeling and eventual right heart failure, hemodynamic instability, and death. Although numerous known risk factors are linked to PAH development, methamphetamine-associated PAH (MA-PAH) is increasingly recognized for its distinct impact on patient risk stratification due to emerging evidence indicating notable disparities in functional class, morbidity, and mortality [1]. Moreover, methamphetamine use is rapidly increasing across the country, and understanding the distinct clinical features of MA-PAH, including echocardiographic characteristics, is paramount to guiding management.

Methamphetamine is a profoundly addictive substance that has witnessed a significant surge in use in the United States, rising by 43% between 2015 and 2019, with non-injection methamphetamine use disorder escalating by a staggering 105% during this same period [2]. Methamphetamine has only recently been considered an independent risk factor for PAH, with studies in idiopathic PAH (I-PAH) patients demonstrating a ten-fold association with stimulant use compared to PAH patients with known risk factors [3, 4]. Although the means by which methamphetamine use leads to PAH is unclear, proposed mechanisms include direct pulmonary toxicity and vascular damage, oxidative stress, dysregulation among pulmonary vasodilators and vasoconstrictors, and reduced activity of CES1, a serine esterase implicated in drug metabolism [5–7].

Retrospective analyses suggest that individuals with MA-PAH exhibit worse functional class and prognosis compared to other types of precapillary pulmonary hypertension (PPH). In their study of 1830 patients enrolled in a PAH Biobank, Charoenpong et al. found that the mPAP and PVR of individuals with MA-PAH were higher than those in the CTD-PAH population (though not significantly different from I-PAH) [8]. Data from the Pulmonary Hypertension Association Registry has shown that MA-PAH patients have a lower cardiac index than those with I-PAH and are more likely to be hospitalized, with worse functional status overall [9]. A prospective cohort study of patients with MA-PAH and I-PAH presenting to the Stanford University Pulmonary Hypertension Program found that those with MA-PAH reported more advanced heart failure symptoms [1]. Ramirez et al. found evidence to suggest that, despite therapy, the 5-year survival in those with MA-PAH is lower, along with worse functional status and exercise tolerance [10]. Despite some variability in findings amongst the different populations studied, the evidence overall underscores a trend toward higher risk hemodynamics, as well as worse right heart function, functional status, and prognosis in individuals with MA-PAH.

Echocardiography is an integral non-invasive screening tool for pulmonary hypertension, and is also used to evaluate prognosis and monitor therapeutic efficacy in PAH [11]. Multiple studies have demonstrated the utility of right atrial (RA) mechanics, including RA ejection fraction, RA emptying fraction, RA size, and right ventricular (RV) outflow tract velocity-time integral to establish prognostic implications in PPH [12–14]. More recent work has investigated the role of RA and RV strain by speckle-tracking echocardiography in PPH for their use in risk stratification and prognostication [15, 16]. Echocardiographic strain is an assessment of the distortion of the myocardium during contraction and provides valuable information about subclinical myocardial dysfunction. In PPH patients, RA strain has been shown to be more significantly reduced as compared to controls, associated with clinical worsening, and an independent predictor of 5-year mortality [15, 17–19]. RA and RV strain have also been shown to become impaired in PPH before a detectable decline in RVEF, indicating subclinical right heart dysfunction [16].

Prior work has demonstrated the importance of right heart strain in the detection of subclinical right heart dysfunction and prognostication in PPH. In this study, we asked whether echocardiographic measures of right heart function, including right heart strain, could provide insight into the mechanism of the poorer prognosis described in individuals with MA-PAH compared to I-PAH.

## 2 | Methods

The University of Utah Institutional Review Board approved all aspects of this study.

### 2.1 | Patient Population

Individuals diagnosed with pulmonary hypertension and previously followed at the University of Utah Pulmonary Hypertension Program were retrospectively captured in a program-specific registry between August 2020 and December 2021. A matched design was used to remove the confounding impact of PA pressure on right heart function, since elevated PA pressure represents an increased RV afterload and leads to right heart strain and failure [20]. In this study, we retrospectively enrolled 51 patients with MA-PAH matched by mean pulmonary artery pressure (mPAP) with another 51 patients with I-PAH. PAH was defined as mPAP of >20 mmHg and a pulmonary capillary wedge pressure (PCWP) of less than or equal to 18 mmHg by right heart catheterization [3]. These criteria for enrollment in the registry were based on a prior diagnosis using criteria similar to the Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL) registry or a new diagnosis based on recent guidelines [21, 22]. Systematic screening for substance use was performed for all patients, and clinical and demographic data were collected through interviews and structured questionnaires, including age, sex, race, substance use history, medical comorbidities, WHO functional class, and medications. MA-PAH was diagnosed as PAH in the setting of

significant methamphetamine exposure by history or structured questionnaire. The patient with I-PAH had a negative methamphetamine exposure history with no other identifiable causes of pulmonary hypertension. The earliest recorded diagnosis in the cohort was June 10, 2002. The mean follow-up duration from the time of diagnosis was 54.8 months (SD = 35.2 months). To evaluate 5-year survival, follow-up durations longer than 5 years were truncated at 60 months, resulting in a mean follow-up of 44.5 months (SD = 17.3 months). Mortality data were collected through 2023 by chart review, publicly available obituaries, or social media.

### 2.2 | Hemodynamic Data

Hemodynamic data were obtained from the initial right heart catheterization performed at or near the time of diagnosis, including PA systolic pressure, PA diastolic pressure, mPAP, and cardiac index measured by the Fick method. Pulmonary vascular resistance (PVR) was calculated as (mPAP-RA pressure [RAP])/cardiac output. RV stroke work index (RVSWI) was calculated as (stroke volume/body surface area) × (mPAP-RAP) × 0.0136 [23, 24]. Pulmonary artery pulsatility index (PAPI) was calculated as (PA systolic pressure − PA diastolic pressure)/RAP [25].

### 2.3 | Transthoracic Echocardiography

Echocardiographic data were collected from transthoracic echocardiograms performed closest to the time of right heart catheterization (MA-PAH 1.93 ± 1.67 years vs. I-PAH 1.22 ± 0.99 years after RHC). Left ventricular end-diastolic volume (LVEDV), end-systolic volume (LVESV), and ejection fraction (LVEF) were calculated using modified biplane Simpson's method. Left ventricular outflow tract velocity-time integral (LVOT VTI) was assessed from the apical 3 or 5 chamber view using pulsed-wave Doppler [26]. RA volume, RA ejection fraction, RV area, and fractional area change (FAC) were quantified from the RV-focused apical 4-chamber views. Additional measurements such as tricuspid annular plane systolic excursion (TAPSE) and tissue Doppler early peak diastolic wave (e'), late diastolic wave (a'), and systolic wave (a') were also obtained. Peak velocity of tricuspid regurgitation was measured from the parasternal short-axis view, RV-inflow view, or apical 4-chamber view using continuous-wave Doppler. RV outflow tract (RVOT) diameter was measured from the parasternal short-axis view at the level of the pulmonic valve. RV outflow tract time-velocity integral (RVOT VTI) was assessed from the parasternal short-axis view using pulsed-wave Doppler [27].

### 2.4 | Deformation Analysis

2D images for strain analysis were acquired at a frame rate of 50–90 Hz. RV free wall strain and RA reservoir strain were analyzed by two trained physicians (E.O. and D.Y.L.) using TomTec Arena, TTA 2.41 (TomTec, Unterschleissheim, Germany). RV free wall strain was analyzed from the RV focused apical 4-chamber view using AutoStrain RV Package, and the RA reservoir strain was obtained from the RA focused apical 4-chamber view using AutoStrain left atrial (LA) Package. RA strain was calculated using the beginning of the QRS wave (atrial end systole) as the zero-reference point, with the total magnitude of the strain curve corresponding to the reservoir strain. Because of coexisting atrial arrhythmia in some study patients, only the reservoir strain was analyzed. While RA reservoir strain is generally reported as a positive value and the RV free wall strain is reported as a negative value, in this study, the strain values were presented as absolute values for easier interpretation.

### 2.5 | Statistics

All analyses were performed using STATA 14 (StataCorp LP, College Station, Texas). Descriptive statistics were performed on patient demographics, hemodynamics, conventional echocardiographic, and strain parameters stratified by the category of PAH. Continuous variables are presented as mean ± standard deviation, and categorical variables as the total number and percentage. Comparison of continuous variables was performed using a *t*-test, and comparison of categorical variables was performed using the Chi-square test or Fisher's exact test as appropriate. The association between strain and hemodynamic parameters was examined by Pearson's correlation. Kaplan-Meier curves were generated and stratified by PAH group with a maximal 5-year follow-up. The Cox proportional hazards regression technique was used to evaluate the risk of MA-PAH on all-cause mortality, adjusting for age and sex. A test of the proportional hazards, a required assumption of Cox regression, was performed for each covariate and globally using a formal significance test based on the unscaled and scaled Schoenfeld residuals [28]. Inter-observer variability was performed on RV free wall strain and RA reservoir strain using intra-class correlation and coefficients of variation. A two-tailed p-value of $< 0.05$ was considered statistically significant.

## 3 | Results

Altogether 102 PAH patients were included in the study, 51 individuals with MA-PAH and 51 with I-PAH, with an average mPAP of 49.5 ± 13.3 mmHg. Patients with MA-PAH were younger at diagnosis, more likely to be male, and had a history of tobacco use (Table 1). Treatment with PAH specific therapy was similar between groups (Supporting Material, S1). Despite similar mPAP, MA-PAH patients had lower cardiac index (2.04 ± 0.84 vs. 2.52 ± 1.07 L/min/m$^2$, $p = 0.016$) and higher PVR (11.8 ± 6.8 vs. 8.9 ± 4.8 Wood units, $p = 0.018$) on hemodynamic assessment compared to patients with IPAH (Table 1).

In echocardiographic analyses, the MA-PAH group had more advanced right heart remodeling, including larger RA volume, larger RV volume, and lower RV FAC (Table 2). This group also had lower RV e', suggesting worse RV diastolic function ($p = 0.021$). RA reservoir strain was lower in individuals with MA-PAH (26.4 ± 11.7 vs. 33.4 ± 14.8 %, $p = 0.011$), as was absolute RV free wall strain (17.0 ± 6.5 vs. 22.3 ± 7.2 %, $p < 0.001$), suggesting worse right heart function than the I-PAH group despite similar mPAP. The RA reservoir strain was negatively correlated with invasively measured RAP. The absolute RV free wall strain is positively correlated with the invasive measures of right heart function

**TABLE 1** | Baseline characteristics between methamphetamine-associated pulmonary arterial hypertension (MA-PAH) and idiopathic pulmonary arterial hypertension (IPAH).

| Patient characteristics | Meth-APAH $N = 51$ | IPAH $N = 51$ | *p* value |
|---|---|---|---|
| Age, years | 46.6 ± 10.5 | 55.5 ± 14.7 | <0.001 |
| Male sex, *n* (%) | 27 (53) | 10 (20) | <0.001 |
| Body mass index, kg/m$^2$ | 28.5 ± 7.1 | 30.0 ± 6.3 | 0.252 |
| Race, *n* (%) | | | |
| White/Caucasian | 46 (90) | 45 (88) | 0.109 |
| Hispanic/Latino | 2 (4) | 0 | |
| African American | 1 (2) | 1 (2) | |
| Asian | 1 (2) | 0 | |
| Other | 1 (2) | 5 (10) | |
| Smoking, *n* (%) | 43 (84) | 15 (29) | <0.001 |
| **WHO-FC at diagnosis, *n* (%)*** | | | 0.804 |
| I | 3 (8) | 2 (7) | |
| II | 10 (26) | 10 (32) | |
| II | 18 (46) | 11 (35) | |
| IV | 8 (20) | 8 (26) | |
| **Hemodynamic data** | | | |
| RAP, mmHg | 10.6 ± 5.4 | 10.7 ± 5.2 | 0.925 |
| RVEDP, mmHg | 15.2 ± 7.5 | 13.9 ± 5.7 | 0.386 |
| Mean PAP, mmHg | 49.5 ± 13.3 | 49.5 ± 13.2 | — |
| PCWP, mmHg | 11.7 ± 5.7 | 11.4 ± 4.4 | 0.779 |
| RVSWI, mmHg | 13.9 ± 6.7 | 15.2 ± 5.6 | 0.329 |
| PAPI | 5.1 ± 4.3 | 5.3 ± 3.7 | 0.764 |
| Cardiac output, L/min | 3.91 ± 1.63 | 4.76 ± 1.88 | 0.021 |
| Cardiac index, L/min/m$^2$ | 2.04 ± 0.84 | 2.52 ± 1.07 | 0.016 |
| PVR, wood units | 11.8 ± 6.8 | 8.9 ± 4.8 | 0.018 |

Abbreviations: PAH, pulmonary arterial hypertension; PAP, pulmonary arterial pressure; PAPI, pulmonary artery pulsatility index; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RVEDP, right ventricular end-diastolic pressure; RVSWI, right ventricular stroke.

PAPi, cardiac index, and RVSWI, and negatively correlated with PVR, as expected (Table 3).

There were 10 deaths at the end of the 5-year follow-up, including 2 (4%) in the MA-PAH group and 8 (16%) in the IPAH group. We did not observe a significant difference in all-cause mortality between the two groups (Table 4, Figure 1). Five-year hospitalization rates for PAH-related admissions were similar between the two groups ($p = 0.7$) (Supporting Material, S2). Six Minute Walk (6MW) Testing distances were also similar between the two groups, even when stratified by sex. Interestingly, there appeared to be a trend in 6MWT with women improving their 6MW

**TABLE 2** | Echo parameters between methamphetamine-associated pulmonary arterial hypertension (meth-PAH) and idiopathic pulmonary arterial hypertension (IPAH).

| | MA-PAH $N = 46$ | IPAH $N = 51$ | *p* value |
|---|---|---|---|
| Heart rate, bpm | 80 ± 14 | 78 ± 13 | 0.396 |
| **Right atrium (RA)** | | | |
| RA max volume, mL | 93.7 ± 46.1 | 75.4 ± 34.8 | 0.029 |
| RA min volume, mL | 55.8 ± 40.6 | 41.3 ± 30.2 | 0.048 |
| RA ejection fraction, % | 43.5 ± 15.4 | 48.4 ± 16.9 | 0.138 |
| **Right ventricle (RV)** | | | |
| RV diastolic area, cm$^2$ | 32.8 ± 7.7 | 26.2 ± 6.9 | <0.001 |
| RV systolic area, cm$^2$ | 25.9 ± 7.1 | 17.4 ± 6.2 | <0.001 |
| RV FAC, % | 21.1 ± 11.1 | 34.5 ± 11.8 | <0.001 |
| TAPSE, mm | 20.3 ± 6.0 | 19.5 ± 5.2 | 0.478 |
| RV s', cm/s | 12.4 ± 3.5 | 11.8 ± 3.1 | 0.426 |
| RV e', cm/s | 6.5 ± 2.8 | 8.3 ± 4.3 | 0.021 |
| RV a', cm/s | 13.6 ± 5.4 | 13.7 ± 5.7 | 0.899 |
| TR velocity, m/s | 3.65 ± 0.85 | 3.23 ± 0.83 | 0.017 |
| RVOT VTI, cm | 14.3 ± 5.3 | 15.0 ± 4.9 | 0.482 |
| RVOT stroke volume, ml | 87.7 ± 43.6 | 82.5 ± 34.8 | 0.510 |
| **Left ventricle (LV)** | | | |
| LVOT VTI, cm | 18.8 ± 5.6 | 21.8 ± 4.8 | 0.008 |
| LVOT stroke volume, mL | 56.1 ± 18.4 | 62.1 ± 16.4 | 0.089 |
| LV ejection fraction, % | 60.6 ± 12.6 | 62.8 ± 7.9 | 0.360 |
| **Strain** | | | |
| RA reservoir strain, % | 26.4 ± 11.7 | 33.4 ± 14.8 | 0.011 |
| RV free wall strain, % | 17.0 ± 6.5 | 22.3 ± 7.2 | <0.001 |

Abbreviations: a', tissue Doppler early diastolic wave; e', tissue Doppler early peak diastolic wave; FAC, fractional area change; LVOT, left ventricular outflow tract; s', tissue Doppler systolic wave; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation; VTI, time-velocity integral.

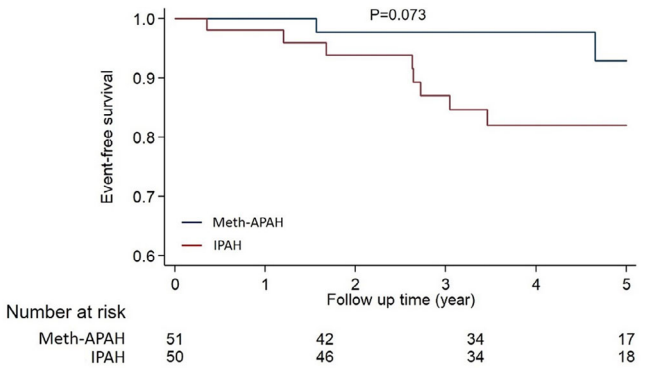


**FIGURE 1** | Kaplan-Meier curves comparing overall death between methamphetamine-associated pulmonary arterial hypertension (MA-PAH) and idiopathic pulmonary arterial hypertension (IPAH).

**TABLE 3** | Correlation between strain parameters and hemodynamic study parameters.

| | RA reservoir strain | | RV free wall strain | |
|---|---|---|---|---|
| | **Pearson correlation** | ***p* value** | **Pearson correlation** | ***p* value** |
| ***Hemodynamic*** | | | | |
| RAP | **−0.233** | **0.023** | −0.137 | 0.185 |
| PAPI | 0.202 | 0.050 | **0.209** | **0.042** |
| PVR | −0.192 | 0.067 | **−0.350** | **0.001** |
| Cardiac index | 0.158 | 0.132 | **0.341** | **0.001** |
| RVSWI | 0.143 | 0.199 | **0.255** | **0.021** |

Abbreviations: PAH, pulmonary arterial hypertension; PAP, pulmonary arterial pressure; PAPI, pulmonary artery pulsatility index; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RVEDP, right ventricular end-diastolic pressure; RVSWI, right ventricular stroke.

**TABLE 4** | Hazard ratio and 95% confidence interval (CI) for pulmonary arterial hypertension (meth-PAH) on all-cause death.

| | **Hazard ratio (95% CI)** | ***p* value** |
|---|---|---|
| MA-PAH | 0.357 (0.059–2.145) | 0.260 |
| Age at diagnosis | 1.043 (0.992–1.097) | 0.097 |
| Male sex | 1.529 (0.387–6.039) | 0.544 |

distance between their first and last visit, regardless of etiology of PAH, although this did not meet significance (Supporting Material, S3 and S4).

We found low variability in the intra-observer analysis of RA reservoir strain and RV FWS (Supporting Material, S5).

## 4 | Discussion

Previous studies have indicated that elevated RAP and echocardiographic assessment of RV and RA strain are associated with poor prognosis in PPH. Additionally, individuals with MA-PAH have been shown to have a worse prognosis than those with I-PAH. In this study, we hypothesized that this poorer prognosis might be accounted for by decreased right heart function and showed that echocardiographic measures of right heart function are more impaired in those with MA-PAH compared to I-PAH.

Although invasive measures of right heart function, such as RVSWI and PAPi, were not statistically significantly different between the MA-PAH and I-PAH groups, RV FWS was correlated with these measures, suggesting that non-invasively measured RV FWS may be a more sensitive method of detecting subclinical right heart dysfunction. Similarly, while RAP was not statistically different between groups. RA reservoir strain, which correlated with RAP, was more abnormal in those with MA-PAH.

These echocardiographic measures of right heart function were more abnormal in the MA-PAH group despite a similar afterload, or mPAP, to the I-PAH group. This finding is suggestive of increased RV-pulmonary arterial (RV-PA) uncoupling in those with MA-PAH, which may be secondary to direct cardiotoxic effects of methamphetamine [29].

Although our findings suggest that MA-PAH patients had worse right heart function at the time of diagnosis, this was not associated with worse survival at 5 years, 6MWT, or rehospitalization rates in our analysis. This contrasts with the findings of Ramirez et al., who reported lower 5-year survival in MA-PAH patients despite PH-specific therapy [1, 10]. The lack of statistical significance in these functional parameters in our study may be attributed to a smaller sample size and difficulties ascertaining accurate death or hospitalization data, as many patients utilize various health systems to attain care.

### 4.1 | Limitations

Several limitations in this analysis should be noted. The RA strain analysis was conducted using the LA-specific strain package within TomTec, as no RA-specific strain package is currently available. This was addressed by selecting the RA-focused view from the 4-chamber window, allowing the software to track similarly to the LA. Despite using the RA-focused view, manual adjustments were necessary to achieve optimal tracking, introducing the potential for human error. Additionally, the sample size and follow-up data for mortality and functional assessments were limited. The study was based at a single center and was retrospective in nature.

### 4.2 | Future Directions

Given the limited data on the differences between MA-PAH and I-PAH, future studies should focus on strain analysis using a larger data pool. Additionally, these studies should examine the relationship between mortality and the severity of strain abnormalities, as well as the degree of RA and RV dysfunction.

## 5 | Conclusions

Despite the same degree of PAH, patients with MA-PAH demonstrated worse RV function by echocardiographic measurements when compared to I-PAH. Our findings suggest that the poorer prognosis of MA-PAH may be accounted for in part by direct cardiotoxicity of methamphetamine on the RA and RV in conjunction with pulmonary arterial remodeling. RA and RV strain

may serve as early indicators of remodeling not yet reflected invasively by RHC in those with MA-PAH.

## Disclosure

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## Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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**Supporting Information**

Additional supporting information can be found online in the Supporting Information section.